KRAS G12D MODULATING COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

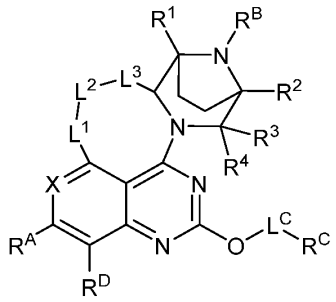
[0001] This application claims priority to U.S. provisional application no. 63/333,347, filed April 21, 2022, U.S. provisional application no. 63/353,726, filed June 20, 2022, and U.S. provisional application no. 63/386,651, filed December 8, 2022, which are incorporated herein in their entireties for all purposes.

BACKGROUND

[0002] The KRAS protein, Kirsten Rat Sarcoma 2 Viral Oncogene Homolog ("KRAS"), is a GTPase. KRAS gene mutations have been observed in a number of conditions including, for instance, pancreatic cancer, endometrial cancer, lung adenocarcinoma, colorectal cancer, rectal carcinoma, gall bladder cancer, thyroid cancer, bile duct cancer, small cell lung cancer, and non-small cell lung cancer (NSCLC). Accordingly, there is a need for compounds, pharmaceutical compositions, and methods for inhibiting KRAS (e.g., KRAS G12C and/or KRAS G12D) and treating associated cancers.

SUMMARY

[0003] In one embodiment, the present disclosure provides a compound of Formula I:



Formula I,

or a pharmaceutically acceptable salt thereof,

wherein

X is N, CH, or CR^x;

R^x is $(CH_2)_mCN$ or halo;

m is 0, 1, 2 or 3;

R^1, R^2, R^3, and R^4 are each independently H or C_1-C_3 alkyl;

L^1 is O, S, or $CR^{1a}R^{1b}$;

R^{1a} and R^{1b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{1a} and R^{1b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

L^2 is $CR^{2a}R^{2b}$;

alternatively, L^2 is O or S, and L^1 is $CR^{1a}R^{1b}$;

R^{2a} and R^{2b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{2a} and R^{2b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

alternatively, R^{1b} and R^{2b} can combine with the atoms to which they are attached to form a C_3-C_6 cycloalkyl;

L^3 is a bond or $CR^{3a}R^{3b}$;

R^{3a} and R^{3b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{3a} and R^{3b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

alternatively, R^{2b} and R^{3b} can combine with the atoms to which they are attached to form a C_3-C_6 cycloalkyl;

R^A is phenyl or naphthyl, wherein R^A is substituted with 0, 1, 2, 3, 4, or 5 R^{A2};

each R^{A2} is independently -OH, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, C_2-C_{10} alkoxyalkyl, C_1-C_6 alkyl-$N(R^{A2a})(R^{A2b})$, C_1-C_{10} thioalkyl, halo, C_1-C_6 haloalkyl, -CN, $-C(O)R^{A2a}$, $-C(O)OR^{A2a}$, $-OC(O)R^{A2a}$, $-OC(O)OR^{A2a}$, $-C(O)N(R^{A2a})(R^{A2b})$, -

$N(R^{A2a})C(O)(R^{A2b})$, $-OC(O)N(R^{A2a})(R^{A2b})$, $-N(R^{A2a})C(O)(OR^{A2b})$, oxo, $-OR^{A2a}$, $-SR^{A2a}$, $-S(O)_2R^{A2a}$, $-S(O)_2OR^{A2a}$, $-N(R^{A2a})(R^{A2b})$, $-(C_0\text{-}C_3$ alkyl)-SF_5, $-OP(O)(OR^{A2a})(OR^{A2b})$, $C_3\text{-}C_8$ cycloalkyl, $-(C_1\text{-}C_6$ alkyl)-($C_3\text{-}C_8$ cycloalkyl), 3- to 14-membered heterocyclyl, $-(C_1\text{-}C_6$ alkyl)-(3- to 14-membered heterocyclyl), $C_6\text{-}C_{14}$ aryl, $-(C_1\text{-}C_6$ alkyl)-($C_6\text{-}C_{14}$ aryl), 5- to 14-membered heteroaryl, or $-(C_1\text{-}C_6$ alkyl)-(5- to 14-membered heteroaryl), wherein each alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, and haloalkyl is substituted with 0, 1, 2, or 3 R^{A3}, and wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 R^{A4};

each R^{A2a} and R^{A2b} is independently H, $C_1\text{-}C_{10}$ alkyl, $C_1\text{-}C_6$ haloalkyl, or $C_3\text{-}C_8$ cycloalkyl;

each R^{A3} is independently halo, -CN, $-OR^{A3a}$, $-SR^{A3a}$, $-N(R^{A3a})(R^{A3b})$, $C_3\text{-}C_8$ cycloalkyl, or 5- to 14-membered heteroaryl;

each R^{A3a} and R^{A3b} is independently H, $C_1\text{-}C_{10}$ alkyl, $C_1\text{-}C_6$ haloalkyl, or $C_3\text{-}C_8$ cycloalkyl;

each R^{A4} is independently $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ hydroxyalkyl, $C_2\text{-}C_6$ alkoxyalkyl, $C_1\text{-}C_6$ haloalkyl, $C_1\text{-}C_6$ haloalkoxy, $C_1\text{-}C_6$ haloalkylthio, $C_3\text{-}C_8$ cycloalkyl, $-(C_1\text{-}C_6$ alkyl)-($C_6\text{-}C_{10}$ aryl), halo, -CN, -OH, or $-N(R^{A4a})(R^{A4b})$;

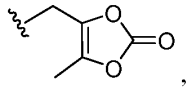
each R^{A4a} and R^{A4b} is independently H or $C_1\text{-}C_6$ alkyl;

alternatively, two R^{A2} can combine to form a $C_3\text{-}C_{10}$ cycloalkyl, $C_6\text{-}C_{10}$ aryl, a 3- to 10-membered heterocyclyl, or 5- to 14-membered heteroaryl on two adjacent atoms on R^A;

R^B is H, $-C(O)R^{B1}$, or $-C(O)OR^{B2}$;

R^{B1} is $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, $C_3\text{-}C_8$ cycloalkyl, $C_6\text{-}C_{14}$ aryl, or 5- to 14-membered heteroaryl, wherein the $C_3\text{-}C_8$ cycloalkyl, $C_6\text{-}C_{14}$ aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B1a};

R^{B2} is $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, ($C_1\text{-}C_6$ alkyl)-$OC(O)R^{B3}$, $C_3\text{-}C_8$ cycloalkyl, $C_6\text{-}C_{14}$ aryl, 5- to 14-membered heteroaryl, or

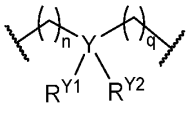


wherein the $C_3\text{-}C_8$ cycloalkyl, $C_6\text{-}C_{14}$ aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B2a};

R^{B3} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B3a};

each R^{B1a}, R^{B2a} and R^{B3a} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkoxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, oxo, -OH, -CN, or C_3-C_{10} cycloalkyl;

L^C is a bond or



;

Y is C or Si;

n is 0, 1, 2, or 3;

q is 0, 1, 2, or 3;

R^{Y1} is H or C_1-C_3 alkyl;

R^{Y2} is H or C_1-C_3 alkyl;

alternatively, R^{Y1} and R^{Y2} combine to form a C_3-C_{10} cycloalkyl or a 3- to 10-membered heterocyclyl;

R^C is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-NH_2$, $-NHR^{C1}$, $-N(R^{C1})_2$, C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein each C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-C_{14} aryl, and 3- to 14-membered heteroaryl, is substituted with 0, 1, 2, 3, or 4 R^{C3};

each R^{C1} is independently selected from C_1-C_6 alkyl;

each R^{C3} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxyalkyl, C_1-C_6 hydroxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, -(C_1-C_6 alkyl)-$N(R^{C3a})(R^{C3b})$, -CN, $-C(O)R^{C3a}$, $-C(O)OR^{C3a}$, $-C(O)N(R^{C3a})(R^{C3b})$, $-N(R^{C3a})C(O)(R^{C3b})$, $-OC(O)N(R^{C3a})(R^{C3b})$, $-N(R^{C3a})C(O)(OR^{C3b})$, $=CH_2$, $=CF_2$, oxo, $-OR^{C3a}$, $-SR^{C3a}$, $-N(R^{C3a})(R^{C3b})$, $-N_3$, SF_5, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, -(C_1-C_6 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, -(C_1-C_6

alkyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl),

wherein each alkyl is substituted with 0, 1, 2, or 3 -CN, $-C(O)OR^{C3a1}$, $-C(O)N(R^{C3a1})(R^{C3a2})$, $-N(R^{C3a1})C(O)(R^{C3a2})$, $-OC(O)N(R^{C3a1})(R^{C3a2})$, $-OR^{C3a1}$, $-SR^{C3a1}$, N_3, SF_5, or 3- to 10-membered heterocyclyl substituted with 0, 1, 2, or 3 R^{C3a2}, each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2}, each alkenyl is substituted with 0, 1, 2, or 3 halo, and each alkoxyalkyl and alkynyl is substituted with 0, 1, 2, or 3 C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl substituted with 0 or 1 C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each R^{C3a} and R^{C3b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein each aryl and heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2};

alternatively, R^{C3a} and R^{C3b} together with the N to which they are attached form a 3- to 8-membered heterocycle;

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, halo, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, -(C_1-C_3 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, -(C_1-C_3 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, -(C_1-C_3 alkyl)-(C_6-C_{10} aryl), -(C_2-C_4 alkynyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, -(C_1-C_3 alkyl)-(5- to 10-membered heteroaryl), or SF_5, wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, alkynyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 halo, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, or SF_5;

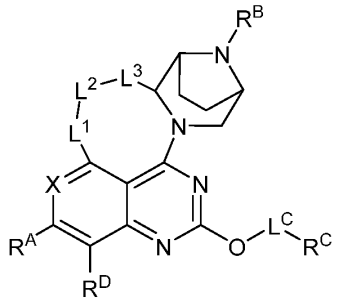
alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle;

R^D is halo;

each heterocyclyl has 1, 2, 3, or 4 heteroatoms selected from N, O, S, and Si; and

each heteroaryl has 1, 2, 3, or 4 heteroatoms selected from N, O, and S.

[0004] In one embodiment, the present disclosure provides a compound of Formula I-A:



Formula I-A,

or a pharmaceutically acceptable salt thereof, wherein

X is N, CH, or CR^x;

R^x is $(CH_2)_mCN$ or halo;

m is 0, 1, 2 or 3;

L^1 is O, S, or $CR^{1a}R^{1b}$;

R^{1a} and R^{1b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{1a} and R^{1b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

L^2 is $CR^{2a}R^{2b}$;

alternatively, L^2 is O or S, and L^1 is $CR^{1a}R^{1b}$;

R^{2a} and R^{2b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{2a} and R^{2b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

alternatively, R^{1b} and R^{2b} can combine with the atoms to which they are attached to form a C_3-C_6 cycloalkyl;

L^3 is a bond or $CR^{3a}R^{3b}$;

R^{3a} and R^{3b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{3a} and R^{3b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

alternatively, R^{2b} and R^{3b} can combine with the atoms to which they are attached to form a C_3-C_6 cycloalkyl;

R^A is phenyl or naphthyl, wherein R^A is substituted with 0, 1, 2, 3, 4, or 5 R^{A2};

each R^{A2} is independently -OH, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, C_2-C_{10} alkoxyalkyl, C_1-C_6 alkyl-$N(R^{A2a})(R^{A2b})$, C_1-C_{10} thioalkyl, halo, C_1-C_6 haloalkyl, -CN, $-C(O)R^{A2a}$, $-C(O)OR^{A2a}$, $-OC(O)R^{A2a}$, $-OC(O)OR^{A2a}$, $-C(O)N(R^{A2a})(R^{A2b})$, $-N(R^{A2a})C(O)(R^{A2b})$, $-OC(O)N(R^{A2a})(R^{A2b})$, $-N(R^{A2a})C(O)(OR^{A2b})$, oxo, $-OR^{A2a}$, $-SR^{A2a}$, $-S(O)_2R^{A2a}$, $-S(O)_2OR^{A2a}$, $-N(R^{A2a})(R^{A2b})$, -(C_0-C_3 alkyl)-SF_5, $-OP(O)(OR^{A2a})(OR^{A2b})$, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), 3- to 14-membered heterocyclyl, -(C_1-C_6 alkyl)-(3- to 14-membered heterocyclyl), C_6-C_{14} aryl, -(C_1-C_6 alkyl)-(C_6-C_{14} aryl), 5- to 14-membered heteroaryl, or -(C_1-C_6 alkyl)-(5- to 14-membered heteroaryl), wherein each alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, and haloalkyl is substituted with 0, 1, 2, or 3 R^{A3}, and wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 R^{A4};

each R^{A2a} and R^{A2b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl;

each R^{A3} is independently halo, -CN, $-OR^{A3a}$, $-SR^{A3a}$, $-N(R^{A3a})(R^{A3b})$, C_3-C_8 cycloalkyl, or 5- to 14-membered heteroaryl;

each R^{A3a} and R^{A3b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl;

each R^{A4} is independently C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 haloalkylthio, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), halo, -CN, -OH, or $-N(R^{A4a})(R^{A4b})$;

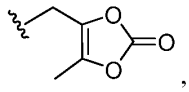
each R^{A4a} and R^{A4b} is independently H or C_1-C_6 alkyl;

alternatively, two R^{A2} can combine to form a C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, a 3- to 10-membered heterocyclyl, or 5- to 14-membered heteroaryl on two adjacent atoms on R^A;

R^B is H, $-C(O)R^{B1}$, or $-C(O)OR^{B2}$;

R^{B1} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B1a};

R^{B2} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, (C_1-C_6 alkyl)-OC(O)R^{B3}, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 14-membered heteroaryl, or



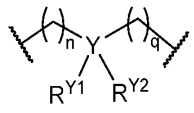
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wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B2a};

R^{B3} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B3a};

each R^{B1a}, R^{B2a} and R^{B3a} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkoxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, oxo, -OH, -CN, or C_3-C_{10} cycloalkyl;

L^C is a bond or



;

Y is C or Si;

n is 0, 1, 2, or 3;

q is 0, 1, 2, or 3;

R^{Y1} is H or C_1-C_3 alkyl;

R^{Y2} is H or C_1-C_3 alkyl;

alternatively, R^{Y1} and R^{Y2} combine to form a C_3-C_{10} cycloalkyl or a 3- to 10-membered heterocyclyl;

R^C is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -NH_2, -NHR^{C1}, -$N(R^{C1})_2$, C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-

C_{14} aryl, or 5- to 14-membered heteroaryl, wherein each C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-C_{14} aryl, and 3- to 14-membered heteroaryl, is substituted with 0, 1, 2, or 3 R^{C3};

each R^{C1} is independently selected from C_1-C_6 alkyl;

each R^{C3} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxyalkyl, C_1-C_6 hydroxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, -(C_1-C_6 alkyl)-N(R^{C3a})(R^{C3b}), -CN, -C(O)R^{C3a}, -C(O)OR^{C3a}, -C(O)N(R^{C3a})(R^{C3b}), -N(R^{C3a})C(O)(R^{C3b}), -OC(O)N(R^{C3a})(R^{C3b}), -N(R^{C3a})C(O)(OR^{C3b}), $=CH_2$, $=CF_2$, oxo, -OR^{C3a}, -SR^{C3a}, -N(R^{C3a})(R^{C3b}), $-N_3$, SF_5, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, -(C_1-C_6 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl), wherein each alkyl is substituted with 0, 1, 2, or 3 -CN, -C(O)OR^{C3a1}, -C(O)N(R^{C3a1})(R^{C3a2}), -N(R^{C3a1})C(O)(R^{C3a2}), -OC(O)N(R^{C3a1})(R^{C3a2}), -OR^{C3a1}, -SR^{C3a1}, N_3, SF_5, or 3- to 10-membered heterocyclyl substituted with 0, 1, 2, or 3 R^{C3a2}, each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2}, each alkenyl is substituted with 0, 1, 2, or 3 halo, and each alkoxyalkyl and alkynyl is substituted with 0, 1, 2, or 3 C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl substituted with 0 or 1 C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each R^{C3a} and R^{C3b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein each aryl and heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2};

alternatively, R^{C3a} and R^{C3b} together with the N to which they are attached form a 3- to 8-membered heterocycle;

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, halo, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, -(C_1-C_3 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, -(C_1-C_3 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, -(C_1-C_3 alkyl)-(C_6-C_{10} aryl), -(C_2-C_4 alkynyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, -(C_1-C_3 alkyl)-(5- to 10-membered heteroaryl), or SF_5, wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, alkynyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, 3, or 4 halo, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, or SF_5;

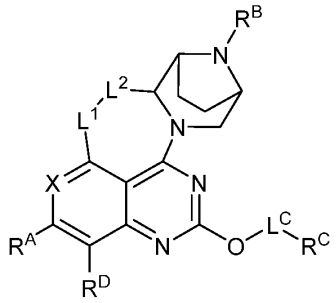
alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle;

R^D is halo;

each heterocyclyl has 1, 2, 3, or 4 heteroatoms selected from N, O, S, and Si; and

each heteroaryl has 1, 2, 3, or 4 heteroatoms selected from N, O, and S.

[0005] In one embodiment, the present disclosure provides a compound of Formula II:



Formula II,

or a pharmaceutically acceptable salt thereof, wherein

X is N, CH, or CR^x;

R^x is $(CH_2)_mCN$ or halo;

m is 0, 1, 2 or 3;

L^1 is O or $CR^{1a}R^{1b}$;

R^{1a} and R^{1b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{1a} and R^{1b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

L^2 is $CR^{2a}R^{2b}$;

R^{2a} and R^{2b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{2a} and R^{2b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

alternatively, R^{1b} and R^{2b} can combine with the atoms to which they are attached to form a C_3-C_6 cycloalkyl;

R^A is phenyl or naphthyl, wherein R^A is substituted with 0, 1, 2, 3, 4, or 5 R^{A2};

each R^{A2} is independently -OH, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, C_2-C_{10} alkoxyalkyl, C_1-C_6 alkyl-$N(R^{A2a})(R^{A2b})$, C_1-C_{10} thioalkyl, halo, C_1-C_6 haloalkyl, -CN, $-C(O)R^{A2a}$, $-C(O)OR^{A2a}$, $-OC(O)R^{A2a}$, $-OC(O)OR^{A2a}$, $-C(O)N(R^{A2a})(R^{A2b})$, $-N(R^{A2a})C(O)(R^{A2b})$, $-OC(O)N(R^{A2a})(R^{A2b})$, $-N(R^{A2a})C(O)(OR^{A2b})$, oxo, $-OR^{A2a}$, $-SR^{A2a}$, $-S(O)_2R^{A2a}$, $-S(O)_2OR^{A2a}$, $-N(R^{A2a})(R^{A2b})$, -(C_0-C_3 alkyl)-SF_5, $-OP(O)(OR^{A2a})(OR^{A2b})$, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), 3- to 14-membered heterocyclyl, -(C_1-C_6 alkyl)-(3- to 14-membered heterocyclyl), C_6-C_{14} aryl, -(C_1-C_6 alkyl)-(C_6-C_{14} aryl), 5- to 14-membered heteroaryl, or -(C_1-C_6 alkyl)-(5- to 14-membered heteroaryl), wherein each alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, and haloalkyl is substituted with 0, 1, 2, or 3 R^{A3}, and wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 R^{A4};

each R^{A2a} and R^{A2b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl;

each R^{A3} is independently halo, -CN, $-OR^{A3a}$, $-SR^{A3a}$, $-N(R^{A3a})(R^{A3b})$, C_3-C_8 cycloalkyl, or 5- to 14-membered heteroaryl;

each R^{A3a} and R^{A3b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl;

each R^{A4} is independently C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 haloalkylthio, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), halo, -CN, -OH, or $-N(R^{A4a})(R^{A4b})$;

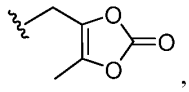
each R^{A4a} and R^{A4b} is independently H or C_1-C_6 alkyl;

alternatively, two R^{A2} can combine to form a C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, a 3- to 10-membered heterocyclyl, or 5- to 14-membered heteroaryl on two adjacent atoms on R^A;

R^B is H, $-C(O)R^{B1}$, or $-C(O)OR^{B2}$;

R^{B1} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B1a};

R^{B2} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, (C_1-C_6 alkyl)-OC(O)R^{B3}, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 14-membered heteroaryl, or



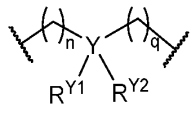
,

wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B2a};

R^{B3} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B3a};

each R^{B1a}, R^{B2a} and R^{B3a} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkoxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, oxo, -OH, -CN, or C_3-C_{10} cycloalkyl;

L^C is a bond or



;

Y is C or Si;

n is 0, 1, 2, or 3;

q is 0, 1, 2, or 3;

R^{Y1} is H or C_1-C_3 alkyl;

R^{Y2} is H or C_1-C_3 alkyl;

alternatively, R^{Y1} and R^{Y2} combine to form a C_3-C_{10} cycloalkyl or a 3- to 10-membered heterocyclyl;

R^C is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -NH_2, -NHR^{C1}, -$N(R^{C1})_2$, C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-

C_{14} aryl, or 5- to 14-membered heteroaryl, wherein each C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-C_{14} aryl, and 3- to 14-membered heteroaryl, is substituted with 0, 1, 2, or 3 R^{C3};

each R^{C1} is independently selected from C_1-C_6 alkyl;

each R^{C3} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxyalkyl, C_1-C_6 hydroxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, -(C_1-C_6 alkyl)-$N(R^{C3a})(R^{C3b})$, -CN, -$C(O)R^{C3a}$, -$C(O)OR^{C3a}$, -$C(O)N(R^{C3a})(R^{C3b})$, -$N(R^{C3a})C(O)(R^{C3b})$, -$OC(O)N(R^{C3a})(R^{C3b})$, -$N(R^{C3a})C(O)(OR^{C3b})$, $=CH_2$, $=CF_2$, oxo, -OR^{C3a}, -SR^{C3a}, -$N(R^{C3a})(R^{C3b})$, $-N_3$, SF_5, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, -(C_1-C_6 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl), wherein each alkyl is substituted with 0, 1, 2, or 3 -CN, -$C(O)OR^{C3a1}$, -$C(O)N(R^{C3a1})(R^{C3a2})$, -$N(R^{C3a1})C(O)(R^{C3a2})$, -$OC(O)N(R^{C3a1})(R^{C3a2})$, -$OR^{C3a1}$, -$SR^{C3a1}$, N_3, SF_5, or 3- to 10-membered heterocyclyl substituted with 0, 1, 2, or 3 R^{C3a2}, each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2}, each alkenyl is substituted with 0, 1, 2, or 3 halo, and each alkoxyalkyl and alkynyl is substituted with 0, 1, 2, or 3 C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl substituted with 0 or 1 C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each R^{C3a} and R^{C3b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein each aryl and heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2};

alternatively, R^{C3a} and R^{C3b} together with the N to which they are attached form a 3- to 8-membered heterocycle;

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, halo, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, -(C_1-C_3 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, -(C_1-C_3 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, -(C_1-C_3 alkyl)-(C_6-C_{10} aryl), -(C_2-C_4 alkynyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, -(C_1-C_3 alkyl)-(5- to 10-membered heteroaryl), or SF_5, wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, alkynyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, 3, or 4 halo, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, or SF_5;

alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle;

R^D is halo;

each heterocyclyl has 1, 2, 3, or 4 heteroatoms selected from N, O, S, and Si; and

each heteroaryl has 1, 2, 3, or 4 heteroatoms selected from N, O, and S.

[0006] In another embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, and a pharmaceutically acceptable excipient.

[0007] In another embodiment, the present disclosure provides a method of inhibiting KRAS G12D protein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0008] In another embodiment, the present disclosure provides a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0009] In another embodiment, the present disclosure provides a method for manufacturing a medicament for treating cancer in a subject in need thereof, characterized in that a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, is used.

[0010] In another embodiment, the present disclosure provides a method for manufacturing a medicament for inhibiting cancer metastasis in a subject in need thereof, characterized in that a compound of the present invention, or a pharmaceutically acceptable salt thereof, is used.

[0011] In another embodiment, the present disclosure provides use of the compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer in a subject.

[0012] In another embodiment, the present disclosure provides use of the compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inhibiting cancer metastasis in a subject.

[0013] In another embodiment, the present disclosure provides the compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a subject in need thereof.

[0014] In another embodiment, the present disclosure provides the compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for use in inhibiting cancer metastasis in a subject in need thereof.

[0015] In another embodiment, the present disclosure provides the compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for use in therapy.

[0016] Also disclosed herein are compounds and pharmaceutically acceptable salts thereof of sub-formulas of Formulas I, I-A, and II, such as Formula (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2).

DETAILED DESCRIPTION

I. General

[0017] The disclosure relates generally to methods and compounds, and pharmaceutically acceptable salts thereof, for inhibiting $KRAS^{G12D}$ and/or $KRAS^{G12C}$. The following description sets forth exemplary methods, parameters and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

II. Definitions

[0018] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0019] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-CONH_2$ is attached through the carbon atom. A dash at the front or end of a chemical group is a matter of convenience; chemical groups can be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line drawn through a line in a structure indicates a point of attachment of a group. Unless chemically or structurally required, no directionality is indicated or implied by the order in which a chemical group is written or named.

[0020] A squiggly line on a chemical group as shown below, for example,  indicates a point of attachment, i.e., it shows the broken bond by which the group is connected to another described group.

[0021] As used herein, "a compound of the disclosure" can mean a compound of any of the Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), and (IIb-2), or a pharmaceutically acceptable salt thereof. Similarly, the phrase "a compound of Formula (number)" means a compound of that formula and pharmaceutically acceptable salts thereof.

[0022] The prefix "C_u-C_v" indicates that the following group has from u to v carbon atoms. For example, "C_1-C_8 alkyl" indicates that the alkyl group has from 1 to 8 carbon atoms.

[0023] "Alkyl" refers to an unbranched or branched saturated hydrocarbon chain. For example, an alkyl group can have 1 to 20 carbon atoms (i.e., C_1-C_{20} alkyl), 1 to 8 carbon atoms (i.e., C_1-C_8 alkyl), 1 to 6 carbon atoms (i.e., C_1-C_6 alkyl), or 1 to 3 carbon atoms (i.e., C_1-C_3 alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (*n*-Pr, *n*-propyl, $-CH_2CH_2CH_3$), 2-propyl (*i*-Pr, *i*-propyl, $-CH(CH_3)_2$), 1-butyl (*n*-Bu, *n*-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (*i*-Bu, *i*-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (*s*-Bu, *s*-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (*t*-Bu, *t*-butyl, $-C(CH_3)_3$), 1-pentyl (*n*-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), and 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$. Other alkyl groups include, but are not limited to, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, pentadcyl, hexadecyl, heptadecyl and octadecyl.

[0024] "Alkenyl" refers to an unbranched or branched hydrocarbon chain containing at least two carbon atoms and at least one carbon-carbon double bond. As used herein, alkenyl can have from 2 to 20 carbon atoms (i.e., $C_{2\text{-}20}$ alkenyl), 2 to 8 carbon atoms (i.e., $C_{2\text{-}8}$ alkenyl), 2 to 6 carbon atoms (i.e., $C_{2\text{-}6}$ alkenyl), or 2 to 4 carbon atoms (i.e., $C_{2\text{-}4}$ alkenyl). Alkenyl can include any number of carbons, such as C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, C_{18},

C_{19}, C_{20}, or any range therein. Alkenyl groups can have any suitable number of double bonds, including, but not limited to, 1, 2, 3, 4, 5 or more. Examples of alkenyl groups include, but are not limited to, vinyl (ethenyl), propenyl, isopropenyl, 1-butenyl, 2-butenyl, isobutenyl, butadienyl, 1-pentenyl, 2-pentenyl, isopentenyl, 1,3-pentadienyl, 1,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,5-hexadienyl, 2,4-hexadienyl, or 1,3,5-hexatrienyl.

[0025] "Alkynyl" refers to an unbranched or branched hydrocarbon chain containing at least one carbon-carbon triple bond. For example, an alkynyl group can have from 2 to 20 carbon atoms (i.e., $C_{2\text{-}20}$ alkynyl), 2 to 8 carbon atoms (i.e., $C_{2\text{-}8}$ alkynyl), 2 to 6 carbon atoms (i.e., $C_{2\text{-}6}$ alkynyl), or 2 to 4 carbon atoms (i.e., $C_{2\text{-}4}$ alkynyl). The term "alkynyl" also includes those groups having one triple bond and one double bond. Examples of $C_{2\text{-}6}$alkynyl include, but are not limited to, ethynyl, prop-1-ynyl, but-1-ynyl, pent-1-ynyl, pent-4-ynyl and penta-1,4-diynyl.

[0026] "Alkoxy" means a group having the formula –O-alkyl, in which an alkyl group, as defined above, is attached to the parent molecule via an oxygen atom. The alkyl portion of an alkoxy group can have 1 to 20 carbon atoms (i.e., C_1-C_{20} alkoxy), 1 to 12 carbon atoms (i.e., C_1-C_{12} alkoxy), 1 to 8 carbon atoms (i.e., C_1-C_8 alkoxy), 1 to 6 carbon atoms (i.e., C_1-C_6 alkoxy) or 1 to 3 carbon atoms (i.e., C_1-C_3 alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy (-O-CH_3 or –OMe), ethoxy (-OCH_2CH_3 or -OEt), isopropoxy (-O-$CH(CH_3)_2$), t-butoxy (-O-$C(CH_3)_3$ or –OtBu) and the like. Other examples of suitable alkoxy groups include, but are not limited to, sec-butoxy, tert-butoxy, pentoxy, hexoxy, and the like.

[0027] "Alkoxyalkyl" refers an alkoxy group linked to an alkyl group which is linked to the remainder of the compound. Alkoxyalkyl can have any suitable number of carbon, such as from 2 to 6 ($C_{2\text{-}6}$ alkoxyalkyl), 2 to 5 ($C_{2\text{-}5}$ alkoxyalkyl), 2 to 4 ($C_{2\text{-}4}$ alkoxyalkyl), or 2 to 3 ($C_{2\text{-}3}$ alkoxyalkyl). Alkoxy and alkyl are as defined above. Examples of "alkoxyalkyl" include, but are not limited to, methoxymethyl (CH_3OCH_2-), and methoxyethyl ($CH_3OCH_2CH_2$).

[0028] "Bridged" means a ring system in which non-adjacent atoms on a ring are connected by a divalent substituent, such as an alkylenyl or heteroalkylenyl group or a single heteroatom.

[0029] "Hydroxyalkyl" refers to a hydroxy group, -OH, linked to an alkyl group which is linked to the remainder of the compound such that the alkyl group is divalent. Hydroxyalkyl can have any suitable number of carbons, such as from 1 to 8 ($C_{1\text{-}8}$ hydroxyalkyl), 1 to 6 ($C_{1\text{-}6}$ hydroxyalkyl), 2 to 6 ($C_{2\text{-}6}$ hydroxyalkyl), 2 to 4 ($C_{2\text{-}4}$ hydroxyalkyl), or 2 to 3 ($C_{2\text{-}3}$ hydroxyalkyl). Alkyl is as defined above where the alkyl is divalent.

[0030] "Halo" or "halogen" as used herein refers to fluoro (-F), chloro (-Cl), bromo (-Br) and iodo (-I).

[0031] "Haloalkyl" is an alkyl group, as defined above, in which one or more hydrogen atoms of the alkyl group is replaced with a halogen atom. The alkyl portion of a haloalkyl group can have 1 to 20 carbon atoms (i.e., C_1-C_{20} haloalkyl), 1 to 12 carbon atoms (i.e., C_1-C_{12} haloalkyl), 1 to 8 carbon atoms (i.e., C_1-C_8 haloalkyl), 1 to 6 carbon atoms (i.e., C_1-C_6 alkyl) or 1 to 3 carbon atoms (i.e., C_1-C_3 alkyl). The alkyl groups can be substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9 or more halogens. Examples of suitable haloalkyl groups include, but are not limited to, $-CF_3$, $-CHF_2$, $-CFH_2$, $-CH_2CF_3$, fluorochloromethyl, difluorochloromethyl, 1,1,1-trifluoroethyl and pentafluoroethyl.

[0032] "Haloalkoxy" refers to an alkoxy group where some or all of the hydrogen atoms are substituted with halogen atoms. As for an alkyl group, haloalkoxy groups can have any suitable number of carbon atoms, such as C_{1-6}. The alkoxy groups can be substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9 or more halogens. When all the hydrogens are replaced with a halogen, for example by fluorine, the compounds are per-substituted, for example, perfluorinated. Haloalkoxy includes, but is not limited to, trifluoromethoxy, 2,2,2,-trifluoroethoxy, perfluoroethoxy, etc.

[0033] "Thioalkyl" refers to a thio group, -SH, linked to an alkyl group which is linked to the remainder of the compound such that the alkyl group is divalent. Thioalkyl can have any suitable number of carbons, such as from 1 to 8 (C_{1-8} thioalkyl), 1 to 6 (C_{1-6} thioalkyl), 2 to 6 (C_{2-6} thioalkyl), 2 to 4 (C_{2-4} thioalkyl), or 2 to 3 (C_{2-3} thioalkyl). Alkyl is as defined above where the alkyl is divalent.

[0034] "Haloalkylthio" is an alkylthio group, as defined above, in which one or more hydrogen atoms of the alkyl group is replaced with a halogen atom. The alkyl portion of a haloalkylthio group can have 1 to 20 carbon atoms (i.e., C_1-C_{20} haloalkylthio), 1 to 12 carbon atoms (i.e., C_1-C_{12} haloalkylthio), 1 to 8 carbon atoms (i.e., C_1-C_8 haloalkylthio), 1 to 6 carbon atoms (i.e., C_1-C_6 alkylthio) or 1 to 3 carbon atoms (i.e., C_1-C_3 alkylthio). The alkylthio groups can be substituted with 1, 2, 3, 4, 5, 6, 7, 8, 9 or more halogens.

[0035] "Heteroalkyl" refers to an unbranched or branched saturated hydrocarbon chain containing from 1 to 4 heteroatoms.

[0036] "Cyanoalkyl" refers to a cyano group, -CN, linked to an alkyl group which is linked to the remainder of the compound such that the alkyl group is divalent. Cyanoalkyl can have any suitable

number of carbons, such as from 1 to 8 (C_{1-8} cyanoalkyl), 1 to 6 (C_{1-6} cyanoalkyl), 2 to 6 (C_{2-6} cyanoalkyl), 2 to 4 (C_{2-4} cyanoalkyl), or 2 to 3 (C_{2-3} cyanoalkyl). Alkyl is as defined above where the alkyl is divalent.

[0037] "Cycloalkyl" refers to a saturated or partially saturated cyclic alkyl group having a single ring or multiple rings, such as 2, 3, 4 or more, wherein the multiple rings can be fused, bridged, spiro, or any combination thereof. As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C_{3-20} cycloalkyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} cycloalkyl), 3 to 10 ring carbon atoms (i.e., C_{3-10} cycloalkyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} cycloalkyl). Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Cycloalkyl groups also include partially unsaturated ring systems containing one or more double bonds, including fused ring systems with one aromatic ring and one non-aromatic ring, but not fully aromatic ring systems.

[0038] The term "fused" refers to a ring system in which two or more rings in the system share a pair of adjacent ring atoms.

[0039] "Spiro" refers to at least two rings are linked together by one common atom. "Spiro" also refers to a ring substituent which is joined by two bonds at the same carbon atom. Examples of spiro groups include, but are not limited to, 1,1-diethylcyclopentane, dimethyl-dioxolane, and 4-benzyl-4-methylpiperidine, wherein the cyclopentane and piperidine, respectively, are the spiro substituents.

[0040] "Alkyl-cycloalkyl" refers to a radical having an alkyl component and a cycloalkyl component, where the alkyl component links the cycloalkyl component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is at least divalent, an alkylene, to link to the cycloalkyl component and to the point of attachment. In some instances, the alkyl component can be absent. The alkyl component can include any number of carbons, such as C_{1-6}, C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. The cycloalkyl component is as defined within. Exemplary alkyl-cycloalkyl groups include, but are not limited to, methyl-cyclopropyl, methyl-cyclobutyl, methyl-cyclopentyl and methyl-cyclohexyl.

[0041] "Heterocycle" or "heterocyclyl" or "heterocycloalkyl" refer to a saturated or unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen, sulfur and silicon. A heterocyclyl can be a single ring or multiple rings, such as 2, 3, 4 or more, wherein the multiple rings can be fused, bridged, spiro, or any combination thereof. As used herein, heterocyclyl has 3 to 20 ring atoms (i.e., 3 to 20 membered heterocyclyl), 3 to 12 ring

atoms (i.e., 3 to 12 membered heterocyclyl), 3 to 10 ring atoms (i.e., 3 to 10 membered heterocyclyl), 3 to 8 ring atoms (i.e., 3 to 8 membered heterocyclyl), 4 to 12 ring carbon atoms (i.e., 4 to 12 membered heterocyclyl), 4 to 8 ring atoms (i.e., 4 to 8 membered heterocyclyl), or 4 to 6 ring atoms (i.e., 4 to 6 membered heterocyclyl). Examples of heterocyclyl groups include pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, dioxolanyl, azetidinyl, and morpholinyl.

[0042] "Alkyl-heterocycloalkyl" refers to a radical having an alkyl component and a heterocycloalkyl component, where the alkyl component links the heterocycloalkyl component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is at least divalent, an alkylene, to link to the heterocycloalkyl component and to the point of attachment. The alkyl component can include any number of carbons, such as C_{0-6}, C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{1-6}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. In some instances, the alkyl component can be absent. The heterocycloalkyl component is as defined above.

[0043] "Aryl" means an aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 10 carbon atoms. Exemplary aryl groups include, but are not limited to, radicals derived from benzene (e.g., phenyl), naphthalene, anthracene, biphenyl, and the like.

[0044] "Alkyl-aryl" refers to a radical having an alkyl component and an aryl component, where the alkyl component links the aryl component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is at least divalent, an alkylene, to link to the aryl component and to the point of attachment. The alkyl component can include any number of carbons, such as C_{0-6}, C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{1-6}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. In some instances, the alkyl component can be absent. The aryl component is as defined above. Examples of alkyl-aryl groups include, but are not limited to, benzyl and ethyl-benzene.

[0045] "Heteroaryl" refers to an aromatic group, including groups having an aromatic tautomer or resonance structure, having a single ring, multiple rings, or multiple fused rings, with at least one heteroatom in the ring, i.e., one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the nitrogen or sulfur can be oxidized. Thus, the term includes rings having one or more annular O, N, S, S(O), $S(O)_2$, and N-oxide groups. The term includes rings having one or more annular C(O) groups. As used herein, heteroaryl include 5 to 20 ring atoms (i.e., 5- to 20-membered heteroaryl), 5 to 12 ring atoms (i.e., 5- to 12-membered heteroaryl), or 5 to 10 ring atoms (i.e., 5- to 10-membered heteroaryl), and 1 to 5 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and oxidized forms of the heteroatoms.

Examples of heteroaryl groups include, but are not limited to, pyridin-2(1H)-one, pyridazin-3(2H)-one, pyrimidin-4(3H)-one, quinolin-2(1H)-one, pyrimidinyl, purinyl, pyridyl, pyridazinyl, benzothiazolyl, and pyrazolyl. Heteroaryl does not encompass or overlap with aryl as defined above.

[0046] "Alkyl-heteroaryl" refers to a radical having an alkyl component and a heteroaryl component, where the alkyl component links the heteroaryl component to the point of attachment. The alkyl component is as defined above, except that the alkyl component is at least divalent, an alkylene, to link to the heteroaryl component and to the point of attachment. The alkyl component can include any number of carbons, such as C_{0-6}, C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{1-6}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6} and C_{5-6}. In some instances, the alkyl component can be absent. The heteroaryl component is as defined within.

[0047] "KRAS G12D" refers to the G12D mutation of the KRAS protein, where aspartic acid replaces glycine at amino acid position 12.

[0048] "KRAS G12D inhibitor" refers to compounds of the present disclosure, including compounds of Formulas I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), and (IIb-2). The compounds modulate or inhibit some or all of the activity of KRAS G12D.

[0049] "KRAS G12D-associated disease or disorder" refers to diseases or disorders associated with or mediated by or having a KRAS G12D mutation. Representative diseases or disorders include, but are not limited to, KRAS G12D-associated cancer.

[0050] "Oxo" refers to the group (=O) or (O).

[0051] Provided are also pharmaceutically acceptable salts, hydrates, solvates, tautomeric forms, polymorphs, and prodrugs of the compounds described herein. "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, formulations, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0052] The compounds described herein can be prepared and/or formulated as pharmaceutically acceptable salts or when appropriate as a free base. Pharmaceutically acceptable salts are non-toxic salts of a free base form of a compound that possess the desired pharmacological activity of the free base. These salts can be derived from inorganic or organic acids or bases. For example, a compound that contains a basic nitrogen can be prepared as a pharmaceutically acceptable salt by

contacting the compound with an inorganic or organic acid. Non-limiting examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, methylsulfonates, propylsulfonates, besylates, xylenesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates, and mandelates. Lists of other suitable pharmaceutically acceptable salts are found in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 21st Edition, Lippincott Wiliams and Wilkins, Philadelphia, Pa., 2006.

[0053] Examples of "pharmaceutically acceptable salts" of the compounds disclosed herein also include salts derived from an appropriate base, such as an alkali metal (for example, sodium, potassium), an alkaline earth metal (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1–C_4 alkyl). Also included are base addition salts, such as sodium or potassium salts.

[0054] Provided are also compounds described herein or pharmaceutically acceptable salts, isomers, or a mixture thereof, in which from 1 to n hydrogen atoms attached to a carbon atom can be replaced by a deuterium atom or D, in which n is the number of hydrogen atoms in the molecule. As known in the art, the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds can increase resistance to metabolism, and thus can be useful for increasing the half-life of the compounds described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof when administered to a mammal. *See,* e.g., Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," TRENDS PHARMACOL. SCI., 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

[0055] Examples of isotopes that can be incorporated into the disclosed compounds also 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. 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 Formulas I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-

2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), and (IIb-2), can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0056] The compounds of the embodiments disclosed herein, or their pharmaceutically acceptable salts can contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high-pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. Where compounds are represented in their chiral form, it is understood that the embodiment encompasses, but is not limited to, the specific diastereomerically or enantiomerically enriched form. Where chirality is not specified but is present, it is understood that the embodiment is directed to either the specific diastereomerically or enantiomerically enriched form; or a racemic or scalemic mixture of such compound(s). As used herein, "scalemic mixture" is a mixture of stereoisomers at a ratio other than 1:1.

[0057] "Racemates" refers to a mixture of enantiomers. The mixture can comprise equal or unequal amounts of each enantiomer.

[0058] "Stereoisomer" and "stereoisomers" refer to compounds that differ in the chirality of one or more stereocenters. Stereoisomers include enantiomers and diastereomers. The compounds can exist in stereoisomeric form if they possess one or more asymmetric centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Unless otherwise indicated, the description is intended to include individual stereoisomers as well as mixtures. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (*see,* e.g., Chapter 4 of ADVANCED ORGANIC CHEMISTRY, 4th ed., J. March, John Wiley & Sons, New York, 1992).

[0059] A "subject" or "patient" is meant to describe a human or vertebrate animal including a dog, cat, pocket pet, marmoset, horse, cow, pig, sheep, goat, elephant, giraffe, chicken, lion, monkey, owl, rat, squirrel, slender loris, and mouse. A "pocket pet" refers to a group of vertebrate animals capable of fitting into a commodious coat pocket such as, for example, hamsters, chinchillas, ferrets, rats, guinea pigs, gerbils, rabbits and sugar gliders.

[0060] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. A dash at the front or end of a chemical group is a matter of convenience; chemical groups can be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line drawn through a line in a structure indicates a point of attachment of a group. A dashed line indicates an optional bond. Unless chemically or structurally required, no directionality is indicated or implied by the order in which a chemical group is written or the point at which it is attached to the remainder of the molecule. For instance, the group "$-SO_2CH_2-$" is equivalent to "$-CH_2SO_2-$" and both can be connected in either direction. Similarly, an "arylalkyl" group, for example, can be attached to the remainder of the molecule at either an aryl or an alkyl portion of the group. A prefix such as "C_u-C_v" or "(C_u-C_v)" indicates that the following group has from u to v carbon atoms. For example, "$C_{1\text{-}6}$ alkyl" and "C_1-C_6 alkyl" both indicate that the alkyl group has from 1 to 6 carbon atoms.

[0061] Unless otherwise specified, the carbon atoms of the compounds of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), are intended to have a valence of four. If in some chemical structure representations, carbon atoms do not have a sufficient number of variables attached to produce a valence of four, the remaining carbon substituents needed to provide a valence of four should be assumed to be hydrogen.

[0062] "Treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired clinical results may include one or more of the following: (a) inhibiting the disease or condition (e.g., decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); (b) slowing or arresting the development of one or more clinical symptoms associated with the disease or condition (e.g., stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition, and/or preventing or delaying the spread (e.g., metastasis) of the disease or condition); and/or (c) relieving the disease, that is, causing the regression of clinical symptoms (e.g., ameliorating the disease state, providing partial or total remission of the

disease or condition, enhancing effect of another medication, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival.

[0063] The term "therapeutically effective amount," as used herein, is the amount of compound disclosed herein present in a formulation described herein that is needed to provide a desired level of drug in the secretions and tissues of the airways and lungs, or alternatively, in the bloodstream of a subject to be treated to give an anticipated physiological response or desired biological effect when such a formulation is administered by the chosen route of administration. The precise amount will depend upon numerous factors, for example the particular compound disclosed herein, the specific activity of the formulation, the delivery device employed, the physical characteristics of the formulation, its intended use, as well as subject considerations such as severity of the disease state, subject cooperation, etc., and can readily be determined by one skilled in the art based upon the information provided herein. The term "therapeutically effective amount" or "effective amount" also means amounts that eliminate or reduce the subject's viral burden and/or viral reservoir.

[0064] "Administering" refers to oral administration, administration as a suppository, topical contact, parenteral, intravenous, intraperitoneal, intramuscular, intralesional, intranasal or subcutaneous administration, intrathecal administration, or the implantation of a slow-release device e.g., a mini-osmotic pump, to the subject. The administration can be carried out according to a schedule specifying frequency of administration, dose for administration, and other factors.

[0065] "Co-administration" as used herein refers to administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more additional therapeutic agents, for example, administration of the compound disclosed herein within seconds, minutes, or hours of the administration of one or more additional therapeutic agents. For example, in some embodiments, a unit dose of a compound of the present disclosure is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound of the present disclosure within seconds or minutes. In some embodiments, a unit dose of a compound of the present disclosure is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the present disclosure. Co-administration of a compound disclosed herein

with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of each agent are present in the body of the patient.

[0066] "Subject" refers to animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In some embodiments, the subject is a human.

[0067] "Disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with a compound, pharmaceutical composition, or method provided herein. The disease may be an autoimmune, inflammatory, cancer, infectious (e.g., a viral infection), metabolic, developmental, cardiovascular, liver, intestinal, endocrine, neurological, or other disease. In some embodiments, the disease is cancer (e.g. lung cancer, ovarian cancer, osteosarcoma, bladder cancer, cervical cancer, liver cancer, kidney cancer, skin cancer (e.g., Merkel cell carcinoma), testicular cancer, leukemia, lymphoma, head and neck cancer, colorectal cancer, prostate cancer, pancreatic cancer, melanoma, breast cancer, neuroblastoma).

[0068] "Cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals, including leukemias, lymphomas, melanomas, neuroendocrine tumors, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound, pharmaceutical composition, or method provided herein include lymphoma, sarcoma, bladder cancer, bone cancer, brain tumor, cervical cancer, colon cancer, esophageal cancer, gastric cancer, head and neck cancer, kidney cancer, myeloma, thyroid cancer, leukemia, prostate cancer, breast cancer (e.g. triple negative, ER positive, ER negative, chemotherapy resistant, herceptin resistant, HER2 positive, doxorubicin resistant, tamoxifen resistant, ductal carcinoma, lobular carcinoma, primary, metastatic), ovarian cancer, pancreatic cancer, liver cancer (e.g. hepatocellular carcinoma) , lung cancer (e.g. non-small cell lung carcinoma, squamous cell lung carcinoma, adenocarcinoma, large cell lung carcinoma, small cell lung carcinoma, carcinoid, sarcoma), glioblastoma multiforme, glioma, melanoma, prostate cancer, castration-resistant prostate cancer, breast cancer, triple negative breast cancer, glioblastoma, ovarian cancer, lung cancer, squamous cell carcinoma (e.g., head, neck, or esophagus), colorectal cancer, leukemia, acute myeloid leukemia, lymphoma, B cell lymphoma, or multiple myeloma.

[0069] Additional examples include, cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, esophagus, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus or Medulloblastoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer,

rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, Paget's Disease of the Nipple, Phyllodes Tumors, Lobular Carcinoma, Ductal Carcinoma, cancer of the pancreatic stellate cells, cancer of the hepatic stellate cells, or prostate cancer.

[0070] "Leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). Exemplary leukemias that may be treated with a compound, pharmaceutical composition, or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocyte leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

[0071] "Sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound, pharmaceutical composition, or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose

sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

[0072] "Melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound, pharmaceutical composition, or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, or superficial spreading melanoma.

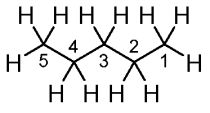
[0073] "Carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound, pharmaceutical composition, or method provided herein include, for example, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basal oid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, ductal carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniforni carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lobular carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous

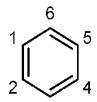
carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhous carcinoma, carcinoma scroti, signet- ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tubular carcinoma, tuberous carcinoma, verrucous carcinoma, or carcinoma villosum.

[0074] "Metastasis," "metastatic," and "metastatic cancer" can be used interchangeably and refer to the spread of a proliferative disease or disorder, e.g., cancer, from one organ or another non-adjacent organ or body part. Cancer occurs at an originating site, e.g., breast, which site is referred to as a primary tumor, e.g., primary breast cancer. Some cancer cells in the primary tumor or originating site acquire the ability to penetrate and infiltrate surrounding normal tissue in the local area and/or the ability to penetrate the walls of the lymphatic system or vascular system circulating through the system to other sites and tissues in the body. A second clinically detectable tumor formed from cancer cells of a primary tumor is referred to as a metastatic or secondary tumor. When cancer cells metastasize, the metastatic tumor and its cells are presumed to be similar to those of the original tumor. Thus, if lung cancer metastasizes to the breast, the secondary tumor at the site of the breast consists of abnormal lung cells and not abnormal breast cells. The secondary tumor in the breast is referred to a metastatic lung cancer. Thus, the phrase metastatic cancer refers to a disease in which a subject has or had a primary tumor and has one or more secondary tumors. The phrases non-metastatic cancer or subjects with cancer that is not metastatic refers to diseases in which subjects have a primary tumor but not one or more secondary tumors. For example, metastatic lung cancer refers to a disease in a subject with or with a history of a primary lung tumor and with one or more secondary tumors at a second location or multiple locations, e.g., in the breast.

[0075] "Associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g., diabetes, cancer (e.g. prostate cancer, renal cancer, metastatic cancer, melanoma, castration-resistant prostate cancer, breast cancer, triple negative breast cancer, glioblastoma, ovarian cancer, lung cancer, squamous cell carcinoma (e.g., head, neck, or esophagus), colorectal cancer, leukemia, acute myeloid leukemia, lymphoma, B cell lymphoma, or multiple myeloma)) means that the disease (e.g. lung cancer, ovarian cancer,

osteosarcoma, bladder cancer, cervical cancer, liver cancer, kidney cancer, skin cancer (e.g., Merkel cell carcinoma), testicular cancer, leukemia, lymphoma, head and neck cancer, colorectal cancer, prostate cancer, pancreatic cancer, melanoma, breast cancer, neuroblastoma) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function.

[0076] The term "adjacent carbons" as used herein refers to consecutive carbons atoms that are directly attached to each other. For example, in 

, C_1 and C_2 are adjacent carbons, C_2 and C_3 are adjacent carbons, C_3 and C_4 are adjacent carbons, and C_4 and C_5 are adjacent carbons. Similarly, in 

C_1 and C_2 are adjacent carbons, C_2 and C_3 are adjacent carbons, C_3 and C_4 are adjacent carbons, and C_4 and C_5 are adjacent carbons, C_5 and C_6 are adjacent carbons and C_6 and C_1 are adjacent carbons.

[0077] "Solvate" as used herein refers to the result of the interaction of a solvent and a compound. Solvates of salts of the compounds described herein are also provided. Hydrates of the compounds described herein are also provided.

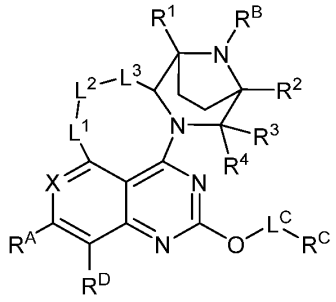
[0078] "Prodrug" as used herein refers to a derivative of a drug that upon administration to the human body is converted to the parent drug according to some chemical or enzymatic pathway.

[0079] As used herein, "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes, but is not limited to, any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and combinations thereof. The use of pharmaceutically acceptable carriers and pharmaceutically acceptable excipients for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic formulations is contemplated. Supplementary active ingredients can also be incorporated into the formulations. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

III. Compounds

[0080] Disclosed herein are, among other things, compounds of Formulas I, I-A, II, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), (II-1), (IIa), (IIa-

1), (IIb), (IIb-1), and (IIb-2). In some embodiments, the present disclosure provides a compound of Formula I:



Formula I,

or a pharmaceutically acceptable salt thereof,

wherein

X is N, CH, or CR^x;

R^x is $(CH_2)_mCN$ or halo;

m is 0, 1, 2 or 3;

R^1, R^2, R^3, and R^4 are each independently H or C_1-C_3 alkyl;

L^1 is O, S, or $CR^{1a}R^{1b}$;

R^{1a} and R^{1b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{1a} and R^{1b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

L^2 is $CR^{2a}R^{2b}$;

alternatively, L^2 is O or S, and L^1 is $CR^{1a}R^{1b}$;

R^{2a} and R^{2b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{2a} and R^{2b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

alternatively, R^{1b} and R^{2b} can combine with the atoms to which they are attached to form a C_3-C_6 cycloalkyl;

L^3 is a bond or $CR^{3a}R^{3b}$;

R^{3a} and R^{3b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{3a} and R^{3b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

alternatively, R^{2b} and R^{3b} can combine with the atoms to which they are attached to form a C_3-C_6 cycloalkyl;

R^A is phenyl or naphthyl, wherein R^A is substituted with 0, 1, 2, 3, 4, or 5 R^{A2};

each R^{A2} is independently -OH, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, C_2-C_{10} alkoxyalkyl, C_1-C_6 alkyl-$N(R^{A2a})(R^{A2b})$, C_1-C_{10} thioalkyl, halo, C_1-C_6 haloalkyl, -CN, $-C(O)R^{A2a}$, $-C(O)OR^{A2a}$, $-OC(O)R^{A2a}$, $-OC(O)OR^{A2a}$, $-C(O)N(R^{A2a})(R^{A2b})$, $-N(R^{A2a})C(O)(R^{A2b})$, $-OC(O)N(R^{A2a})(R^{A2b})$, $-N(R^{A2a})C(O)(OR^{A2b})$, oxo, $-OR^{A2a}$, $-SR^{A2a}$, $-S(O)_2R^{A2a}$, $-S(O)_2OR^{A2a}$, $-N(R^{A2a})(R^{A2b})$, -(C_0-C_3 alkyl)-SF_5, $-OP(O)(OR^{A2a})(OR^{A2b})$, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), 3- to 14-membered heterocyclyl, -(C_1-C_6 alkyl)-(3- to 14-membered heterocyclyl), C_6-C_{14} aryl, -(C_1-C_6 alkyl)-(C_6-C_{14} aryl), 5- to 14-membered heteroaryl, or -(C_1-C_6 alkyl)-(5- to 14-membered heteroaryl), wherein each alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, and haloalkyl is substituted with 0, 1, 2, or 3 R^{A3}, and wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 R^{A4};

each R^{A2a} and R^{A2b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl;

each R^{A3} is independently halo, -CN, $-OR^{A3a}$, $-SR^{A3a}$, $-N(R^{A3a})(R^{A3b})$, C_3-C_8 cycloalkyl, or 5- to 14-membered heteroaryl;

each R^{A3a} and R^{A3b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl;

each R^{A4} is independently C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 haloalkylthio, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), halo, -CN, -OH, or $-N(R^{A4a})(R^{A4b})$;

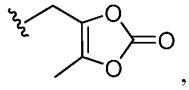
each R^{A4a} and R^{A4b} is independently H or C_1-C_6 alkyl;

alternatively, two R^{A2} can combine to form a C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, a 3- to 10-membered heterocyclyl, or 5- to 14-membered heteroaryl on two adjacent atoms on R^A;

R^B is H, -C(O)R^{B1}, or -C(O)OR^{B2};

R^{B1} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B1a};

R^{B2} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, (C_1-C_6 alkyl)-OC(O)R^{B3}, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 14-membered heteroaryl, or



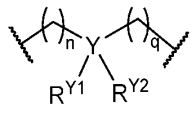
,

wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B2a};

R^{B3} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B3a};

each R^{B1a}, R^{B2a} and R^{B3a} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkoxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, oxo, -OH, -CN, or C_3-C_{10} cycloalkyl;

L^C is a bond or



;

Y is C or Si;

n is 0, 1, 2, or 3;

q is 0, 1, 2, or 3;

R^{Y1} is H or C_1-C_3 alkyl;

R^{Y2} is H or C_1-C_3 alkyl;

alternatively, R^{Y1} and R^{Y2} combine to form a C_3-C_{10} cycloalkyl or a 3- to 10-membered heterocyclyl;

R^C is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-NH_2$, $-NHR^{C1}$, $-N(R^{C1})_2$, C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein each C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-C_{14} aryl, and 3- to 14-membered heteroaryl, is substituted with 0, 1, 2, 3, or 4 R^{C3};

each R^{C1} is independently selected from C_1-C_6 alkyl;

each R^{C3} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxyalkyl, C_1-C_6 hydroxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, -(C_1-C_6 alkyl)-$N(R^{C3a})(R^{C3b})$, -CN, $-C(O)R^{C3a}$, $-C(O)OR^{C3a}$, $-C(O)N(R^{C3a})(R^{C3b})$, $-N(R^{C3a})C(O)(R^{C3b})$, $-OC(O)N(R^{C3a})(R^{C3b})$, $-N(R^{C3a})C(O)(OR^{C3b})$, $=CH_2$, $=CF_2$, oxo, $-OR^{C3a}$, $-SR^{C3a}$, $-N(R^{C3a})(R^{C3b})$, $-N_3$, SF_5, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, -(C_1-C_6 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl),
wherein each alkyl is substituted with 0, 1, 2, or 3 -CN, $-C(O)OR^{C3a1}$, $-C(O)N(R^{C3a1})(R^{C3a2})$, $-N(R^{C3a1})C(O)(R^{C3a2})$, $-OC(O)N(R^{C3a1})(R^{C3a2})$, $-OR^{C3a1}$, $-SR^{C3a1}$, N_3, SF_5, or 3- to 10-membered heterocyclyl substituted with 0, 1, 2, or 3 R^{C3a2},
each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2},
each alkenyl is substituted with 0, 1, 2, or 3 halo, and
each alkoxyalkyl and alkynyl is substituted with 0, 1, 2, or 3 C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl substituted with 0 or 1 C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each R^{C3a} and R^{C3b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein each aryl and heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2};

alternatively, R^{C3a} and R^{C3b} together with the N to which they are attached form a 3- to 8-membered heterocycle;

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, halo, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, -(C_1-C_3 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, -(C_1-C_3 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, -(C_1-C_3 alkyl)-(C_6-C_{10} aryl), -(C_2-C_4 alkynyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, -(C_1-C_3 alkyl)-(5- to 10-membered heteroaryl), or SF_5, wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, alkynyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 halo, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, or SF_5;

alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle;

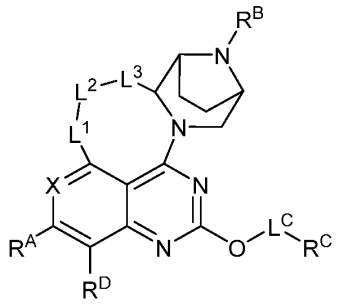
R^D is halo;

each heterocyclyl has 1, 2, 3, or 4 heteroatoms selected from N, O, S, and Si; and

each heteroaryl has 1, 2, 3, or 4 heteroatoms selected from N, O, and S.

[0081] In some embodiments, the present disclosure provides the compound of Formula I, wherein R^1, R^2, R^3, and R^4 are each independently H or methyl. In some embodiments, the present disclosure provides the compound of Formula I, wherein one of two of R^1, R^2, R^3, and R^4 are methyl. In some embodiments, the present disclosure provides the compound of Formula I, wherein R^1 and R^2 are methyl. In some embodiments, the present disclosure provides the compound of Formula I, wherein R^1, R^2, R^3, and R^4 are each H.

[0082] In some embodiments, the present disclosure provides a compound of Formula I-A:



Formula I-A,

or a pharmaceutically acceptable salt thereof, wherein

X is N, CH, or CR^x;

R^x is $(CH_2)_mCN$ or halo;

m is 0, 1, 2 or 3;

L^1 is O, S, or $CR^{1a}R^{1b}$;

R^{1a} and R^{1b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{1a} and R^{1b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

L^2 is $CR^{2a}R^{2b}$;

alternatively, L^2 is O or S, and L^1 is $CR^{1a}R^{1b}$;

R^{2a} and R^{2b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{2a} and R^{2b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

alternatively, R^{1b} and R^{2b} can combine with the atoms to which they are attached to form a C_3-C_6 cycloalkyl;

L^3 is a bond or $CR^{3a}R^{3b}$;

R^{3a} and R^{3b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{3a} and R^{3b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

alternatively, R^{2b} and R^{3b} can combine with the atoms to which they are attached to form a C_3-C_6 cycloalkyl;

R^A is phenyl or naphthyl, wherein R^A is substituted with 0, 1, 2, 3, 4, or 5 R^{A2};

each R^{A2} is independently -OH, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, C_2-C_{10} alkoxyalkyl, C_1-C_6 alkyl-$N(R^{A2a})(R^{A2b})$, C_1-C_{10} thioalkyl, halo, C_1-C_6 haloalkyl, -CN, $-C(O)R^{A2a}$, $-C(O)OR^{A2a}$, $-OC(O)R^{A2a}$, $-OC(O)OR^{A2a}$, $-C(O)N(R^{A2a})(R^{A2b})$, -

$N(R^{A2a})C(O)(R^{A2b})$, $-OC(O)N(R^{A2a})(R^{A2b})$, $-N(R^{A2a})C(O)(OR^{A2b})$, oxo, $-OR^{A2a}$, $-SR^{A2a}$, $-S(O)_2R^{A2a}$, $-S(O)_2OR^{A2a}$, $-N(R^{A2a})(R^{A2b})$, $-(C_0\text{-}C_3$ alkyl)-SF_5, $-OP(O)(OR^{A2a})(OR^{A2b})$, $C_3\text{-}C_8$ cycloalkyl, $-(C_1\text{-}C_6$ alkyl)-($C_3\text{-}C_8$ cycloalkyl), 3- to 14-membered heterocyclyl, $-(C_1\text{-}C_6$ alkyl)-(3- to 14-membered heterocyclyl), $C_6\text{-}C_{14}$ aryl, $-(C_1\text{-}C_6$ alkyl)-($C_6\text{-}C_{14}$ aryl), 5- to 14-membered heteroaryl, or $-(C_1\text{-}C_6$ alkyl)-(5- to 14-membered heteroaryl), wherein each alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, and haloalkyl is substituted with 0, 1, 2, or 3 R^{A3}, and wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 R^{A4};

each R^{A2a} and R^{A2b} is independently H, $C_1\text{-}C_{10}$ alkyl, $C_1\text{-}C_6$ haloalkyl, or $C_3\text{-}C_8$ cycloalkyl;

each R^{A3} is independently halo, -CN, $-OR^{A3a}$, $-SR^{A3a}$, $-N(R^{A3a})(R^{A3b})$, $C_3\text{-}C_8$ cycloalkyl, or 5- to 14-membered heteroaryl;

each R^{A3a} and R^{A3b} is independently H, $C_1\text{-}C_{10}$ alkyl, $C_1\text{-}C_6$ haloalkyl, or $C_3\text{-}C_8$ cycloalkyl;

each R^{A4} is independently $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ hydroxyalkyl, $C_2\text{-}C_6$ alkoxyalkyl, $C_1\text{-}C_6$ haloalkyl, $C_1\text{-}C_6$ haloalkoxy, $C_1\text{-}C_6$ haloalkylthio, $C_3\text{-}C_8$ cycloalkyl, $-(C_1\text{-}C_6$ alkyl)-($C_6\text{-}C_{10}$ aryl), halo, -CN, -OH, or $-N(R^{A4a})(R^{A4b})$;

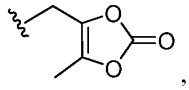
each R^{A4a} and R^{A4b} is independently H or $C_1\text{-}C_6$ alkyl;

alternatively, two R^{A2} can combine to form a $C_3\text{-}C_{10}$ cycloalkyl, $C_6\text{-}C_{10}$ aryl, a 3- to 10-membered heterocyclyl, or 5- to 14-membered heteroaryl on two adjacent atoms on R^A;

R^B is H, $-C(O)R^{B1}$, or $-C(O)OR^{B2}$;

R^{B1} is $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, $C_3\text{-}C_8$ cycloalkyl, $C_6\text{-}C_{14}$ aryl, or 5- to 14-membered heteroaryl, wherein the $C_3\text{-}C_8$ cycloalkyl, $C_6\text{-}C_{14}$ aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B1a};

R^{B2} is $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, ($C_1\text{-}C_6$ alkyl)-$OC(O)R^{B3}$, $C_3\text{-}C_8$ cycloalkyl, $C_6\text{-}C_{14}$ aryl, 5- to 14-membered heteroaryl, or



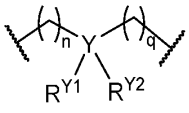
,

wherein the $C_3\text{-}C_8$ cycloalkyl, $C_6\text{-}C_{14}$ aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B2a};

R^{B3} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B3a};

each R^{B1a}, R^{B2a} and R^{B3a} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkoxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, oxo, -OH, -CN, or C_3-C_{10} cycloalkyl;

L^C is a bond or



;

Y is C or Si;

n is 0, 1, 2, or 3;

q is 0, 1, 2, or 3;

R^{Y1} is H or C_1-C_3 alkyl;

R^{Y2} is H or C_1-C_3 alkyl;

alternatively, R^{Y1} and R^{Y2} combine to form a C_3-C_{10} cycloalkyl or a 3- to 10-membered heterocyclyl;

R^C is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-NH_2$, $-NHR^{C1}$, $-N(R^{C1})_2$, C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein each C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-C_{14} aryl, and 3- to 14-membered heteroaryl, is substituted with 0, 1, 2, or 3 R^{C3};

each R^{C1} is independently selected from C_1-C_6 alkyl;

each R^{C3} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxyalkyl, C_1-C_6 hydroxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, -(C_1-C_6 alkyl)-$N(R^{C3a})(R^{C3b})$, -CN, $-C(O)R^{C3a}$, $-C(O)OR^{C3a}$, $-C(O)N(R^{C3a})(R^{C3b})$, $-N(R^{C3a})C(O)(R^{C3b})$, $-OC(O)N(R^{C3a})(R^{C3b})$, $-N(R^{C3a})C(O)(OR^{C3b})$, $=CH_2$, $=CF_2$, oxo, $-OR^{C3a}$, $-SR^{C3a}$, $-N(R^{C3a})(R^{C3b})$, $-N_3$, SF_5, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, -(C_1-C_6 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl),

wherein each alkyl is substituted with 0, 1, 2, or 3 -CN, -C(O)OR^{C3a1}, -C(O)N(R^{C3a1})(R^{C3a2}), -N(R^{C3a1})C(O)(R^{C3a2}), -OC(O)N(R^{C3a1})(R^{C3a2}), -OR^{C3a1}, -SR^{C3a1}, N_3, SF_5, or 3- to 10-membered heterocyclyl substituted with 0, 1, 2, or 3 R^{C3a2}, each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2}, each alkenyl is substituted with 0, 1, 2, or 3 halo, and each alkoxyalkyl and alkynyl is substituted with 0, 1, 2, or 3 C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl substituted with 0 or 1 C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each R^{C3a} and R^{C3b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein each aryl and heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2};

alternatively, R^{C3a} and R^{C3b} together with the N to which they are attached form a 3- to 8-membered heterocycle;

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, halo, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, -(C_1-C_3 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, -(C_1-C_3 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, -(C_1-C_3 alkyl)-(C_6-C_{10} aryl), -(C_2-C_4 alkynyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, -(C_1-C_3 alkyl)-(5- to 10-membered heteroaryl), or SF_5, wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, alkynyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, 3, or 4 halo, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, or SF_5;

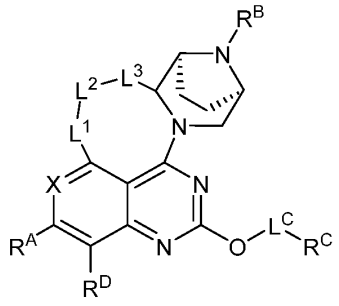
alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle;

R^D is halo;

each heterocyclyl has 1, 2, 3, or 4 heteroatoms selected from N, O, S, and Si; and

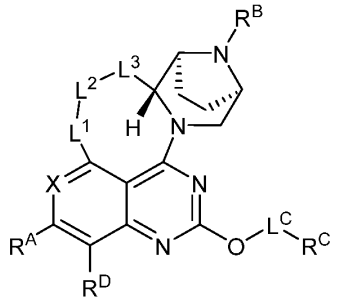
each heteroaryl has 1, 2, 3, or 4 heteroatoms selected from N, O, and S.

[0083] In some embodiments, the present disclosure provides the compound of Formula I or I-A, or a pharmaceutically acceptable salt thereof, having the structure of Formula (I-1):



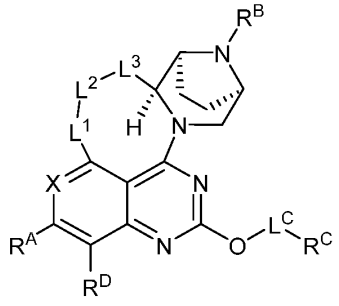
(I-1).

[0084] In some embodiments, the present disclosure provides the compound of Formula I, I-A, or I-1, or a pharmaceutically acceptable salt thereof, having the structure of Formula (I-2):



(I-2).

[0085] In some embodiments, the present disclosure provides the compound of Formula I, I-A, or I-1, or a pharmaceutically acceptable salt thereof, having the structure of Formula (I-3):

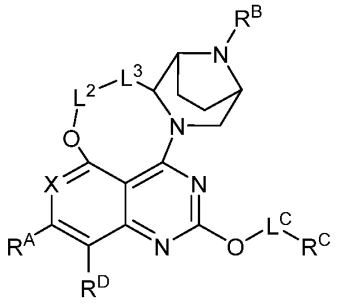


(I-3).

[0086] In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein X is N. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein X is CH. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein X is CR^x, wherein R^x is $(CH_2)_mCN$, and m is 0, 1, 2 or 3. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein X is CR^x, wherein R^x is CH_2CN. In some

embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein X is CR^x, wherein R^x is halo.

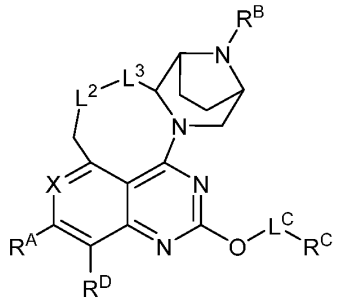
[0087] In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein L^1 is O. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ia):



(Ia).

[0088] In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein L^1 is CHR^{1b}. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein L^1 is CH_2. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein L^1 is $CH(CH_3)$. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein R^{1a} and R^{1b} are each independently H, C_1-C_3 alkyl, or halo. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is C_1-C_3 alkyl or halo. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is H or methyl. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is H. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is methyl.

[0089] In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, or I-3, or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ib):

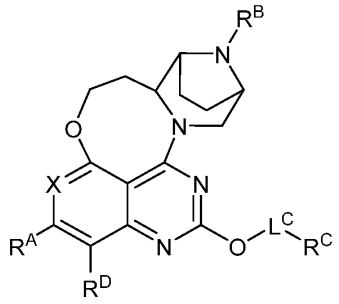


(Ib).

[0090] In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, I-3, (Ia), or (Ib), or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are each independently H, C_1-C_3 alkyl, halo, or C_1-C_6 haloalkyl. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, I-3, (Ia), or (Ib), or a pharmaceutically acceptable salt thereof, wherein L^2 is CHR^{2b}. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, I-3, (Ia), or (Ib), or a pharmaceutically acceptable salt thereof, wherein R^{2b} is H or C_1-C_3 alkyl. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, I-3, (Ia), or (Ib), or a pharmaceutically acceptable salt thereof, wherein R^{2b} is H. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, I-3, (Ia), or (Ib), or a pharmaceutically acceptable salt thereof, wherein R^{2b} is C_1-C_3 alkyl. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, I-3, (Ia), or (Ib), or a pharmaceutically acceptable salt thereof, wherein R^{2b} is methyl.

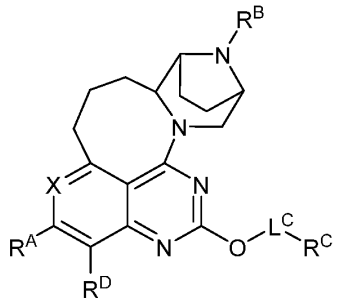
[0091] In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, I-3, (Ia), or (Ib), or a pharmaceutically acceptable salt thereof, wherein L^3 is $CR^{3a}R^{3b}$. In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, I-3, (Ia), or (Ib), or a pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{3b} are H.

[0092] In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, I-3, or (Ia), or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ia-1):



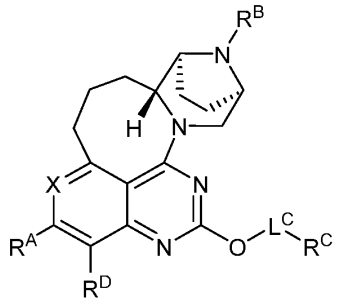
(Ia-1).

[0093] In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, I-3, or (Ib), or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ib-1):



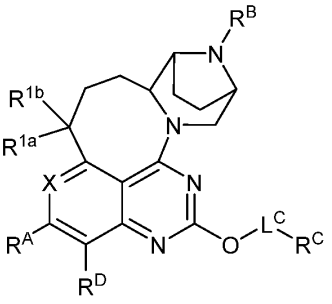
(Ib-1).

[0094] In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, I-3, Ib, or Ib-1, or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ib-2):



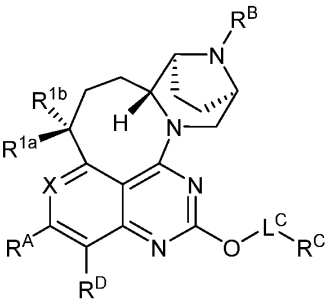
(Ib-2).

[0095] In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, I-3, Ib, or Ib-1, or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ib-3):

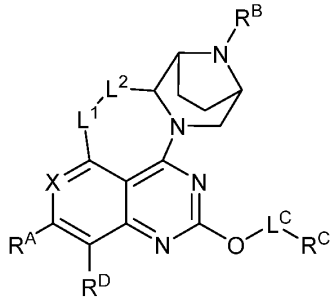


(Ib-3).

[0096] In some embodiments, the present disclosure provides the compound of Formula I, I-A, I-1, I-2, I-3, Ib, or Ib-1, or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ib-4):



[0097] (Ib-4).Disclosed herein are, among other things, compounds of Formulas II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), and (IIb-2). In some embodiments, the present disclosure provides a compound of Formula II:



Formula II,

or a pharmaceutically acceptable salt thereof, wherein

X is N, CH, or CR^x;

R^x is $(CH_2)_mCN$ or halo;

m is 0, 1, 2 or 3;

L^1 is O or $CR^{1a}R^{1b}$;

R^{1a} and R^{1b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{1a} and R^{1b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

L^2 is $CR^{2a}R^{2b}$;

R^{2a} and R^{2b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{2a} and R^{2b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

alternatively, R^{1b} and R^{2b} can combine with the atoms to which they are attached to form a C_3-C_6 cycloalkyl;

R^A is phenyl or naphthyl, wherein R^A is substituted with 0, 1, 2, 3, 4, or 5 R^{A2};

each R^{A2} is independently -OH, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, C_2-C_{10} alkoxyalkyl, C_1-C_6 alkyl-$N(R^{A2a})(R^{A2b})$, C_1-C_{10} thioalkyl, halo, C_1-C_6 haloalkyl, -CN, $-C(O)R^{A2a}$, $-C(O)OR^{A2a}$, $-OC(O)R^{A2a}$, $-OC(O)OR^{A2a}$, $-C(O)N(R^{A2a})(R^{A2b})$, $-N(R^{A2a})C(O)(R^{A2b})$, $-OC(O)N(R^{A2a})(R^{A2b})$, $-N(R^{A2a})C(O)(OR^{A2b})$, oxo, $-OR^{A2a}$, $-SR^{A2a}$, $-S(O)_2R^{A2a}$, $-S(O)_2OR^{A2a}$, $-N(R^{A2a})(R^{A2b})$, -(C_0-C_3 alkyl)-SF_5, $-OP(O)(OR^{A2a})(OR^{A2b})$, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), 3- to 14-membered heterocyclyl, -(C_1-C_6 alkyl)-(3- to 14-membered heterocyclyl), C_6-C_{14} aryl, -(C_1-C_6 alkyl)-(C_6-C_{14} aryl), 5- to 14-membered heteroaryl, or -(C_1-C_6 alkyl)-(5- to 14-membered heteroaryl), wherein each alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, and haloalkyl is substituted with 0, 1, 2, or 3 R^{A3}, and wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 R^{A4};

each R^{A2a} and R^{A2b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl;

each R^{A3} is independently halo, -CN, $-OR^{A3a}$, $-SR^{A3a}$, $-N(R^{A3a})(R^{A3b})$, C_3-C_8 cycloalkyl, or 5- to 14-membered heteroaryl;

each R^{A3a} and R^{A3b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl;

each R^{A4} is independently C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 haloalkylthio, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), halo, -CN, -OH, or -N(R^{A4a})(R^{A4b});

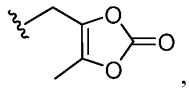
each R^{A4a} and R^{A4b} is independently H or C_1-C_6 alkyl;

alternatively, two R^{A2} can combine to form a C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, a 3- to 10-membered heterocyclyl, or 5- to 14-membered heteroaryl on two adjacent atoms on R^A;

R^B is H, -C(O)R^{B1}, or -C(O)OR^{B2};

R^{B1} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B1a};

R^{B2} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, (C_1-C_6 alkyl)-OC(O)R^{B3}, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 14-membered heteroaryl, or



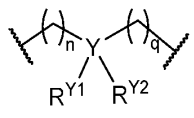
,

wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B2a};

R^{B3} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B3a};

each R^{B1a}, R^{B2a} and R^{B3a} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkoxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, oxo, -OH, -CN, or C_3-C_{10} cycloalkyl;

L^C is a bond or



;

Y is C or Si;

n is 0, 1, 2, or 3;

q is 0, 1, 2, or 3;

R^{Y1} is H or C_1-C_3 alkyl;

R^{Y2} is H or C_1-C_3 alkyl;

alternatively, R^{Y1} and R^{Y2} combine to form a C_3-C_{10} cycloalkyl or a 3- to 10-membered heterocyclyl;

R^C is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, $-NH_2$, $-NHR^{C1}$, $-N(R^{C1})_2$, C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein each C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-C_{14} aryl, and 3- to 14-membered heteroaryl, is substituted with 0, 1, 2, or 3 R^{C3};

each R^{C1} is independently selected from C_1-C_6 alkyl;

each R^{C3} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxyalkyl, C_1-C_6 hydroxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, $-(C_1$-C_6 alkyl)-$N(R^{C3a})(R^{C3b})$, -CN, $-C(O)R^{C3a}$, $-C(O)OR^{C3a}$, $-C(O)N(R^{C3a})(R^{C3b})$, $-N(R^{C3a})C(O)(R^{C3b})$, $-OC(O)N(R^{C3a})(R^{C3b})$, $-N(R^{C3a})C(O)(OR^{C3b})$, $=CH_2$, $=CF_2$, oxo, $-OR^{C3a}$, $-SR^{C3a}$, $-N(R^{C3a})(R^{C3b})$, $-N_3$, SF_5, C_3-C_8 cycloalkyl, $-(C_1$-C_6 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, $-(C_1$-C_6 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, $-(C_1$-C_6 alkyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, or $-(C_1$-C_6 alkyl)-(5- to 10-membered heteroaryl), wherein each alkyl is substituted with 0, 1, 2, or 3 -CN, $-C(O)OR^{C3a1}$, $-C(O)N(R^{C3a1})(R^{C3a2})$, $-N(R^{C3a1})C(O)(R^{C3a2})$, $-OC(O)N(R^{C3a1})(R^{C3a2})$, $-OR^{C3a1}$, $-SR^{C3a1}$, N_3, SF_5, or 3- to 10-membered heterocyclyl substituted with 0, 1, 2, or 3 R^{C3a2}, each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2}, each alkenyl is substituted with 0, 1, 2, or 3 halo, and each alkoxyalkyl and alkynyl is substituted with 0, 1, 2, or 3 C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl substituted with 0 or 1 C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each R^{C3a} and R^{C3b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein each aryl and heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2};

alternatively, R^{C3a} and R^{C3b} together with the N to which they are attached form a 3- to 8-membered heterocycle;

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, halo, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, -(C_1-C_3 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, -(C_1-C_3 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, -(C_1-C_3 alkyl)-(C_6-C_{10} aryl), -(C_2-C_4 alkynyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, -(C_1-C_3 alkyl)-(5- to 10-membered heteroaryl), or SF_5, wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, alkynyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, 3, or 4 halo, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, or SF_5;

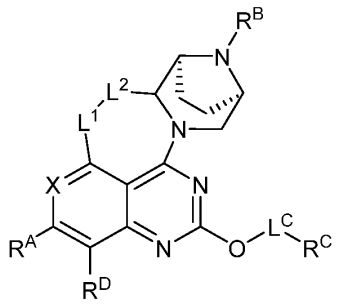
alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle;

R^D is halo;

each heterocyclyl has 1, 2, 3, or 4 heteroatoms selected from N, O, S, and Si; and

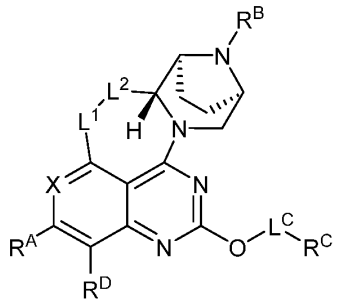
each heteroaryl has 1, 2, 3, or 4 heteroatoms selected from N, O, and S.

[0098] In some embodiments, the present disclosure provides the compound of Formula II, or a pharmaceutically acceptable salt thereof, having the structure of Formula (II-1):



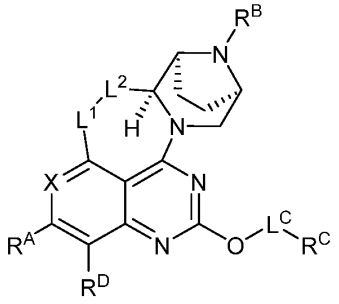
(II-1).

[0099] In some embodiments, the present disclosure provides the compound of Formula II or II-1, or a pharmaceutically acceptable salt thereof, having the structure of Formula (II-2):



(II-2).

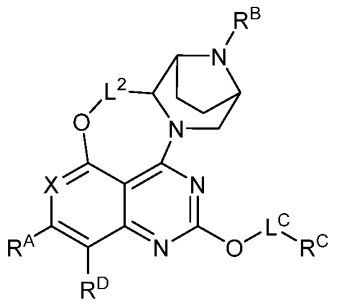
[0100] In some embodiments, the present disclosure provides the compound of Formula II or II-1, or a pharmaceutically acceptable salt thereof, having the structure of Formula (II-3):



(II-3).

[0101] In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, wherein X is N. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, wherein X is CH. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, wherein X is CR^x, wherein R^x is $(CH_2)_mCN$, and m is 0, 1, 2 or 3. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, wherein X is CR^x, wherein R^x is CH_2CN. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, wherein X is CR^x, wherein R^x is halo. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, wherein X is C-Cl.

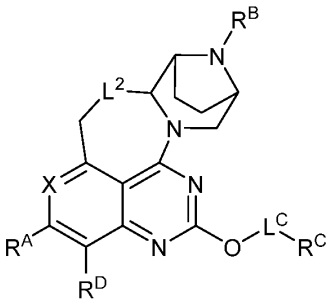
[0102] In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, wherein L^1 is O. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, having the structure of Formula (IIa):



(IIa).

[0103] In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, wherein L^1 is CHR^{1b}. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, wherein L^1 is CH_2. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, wherein L^1 is $CH(CH_3)$. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, wherein R^{1a} and R^{1b} are each independently H, C_1-C_3 alkyl, or halo. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is C_1-C_3 alkyl or halo. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is methyl.

[0104] In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, or II-3, or a pharmaceutically acceptable salt thereof, having the structure of Formula (IIb):

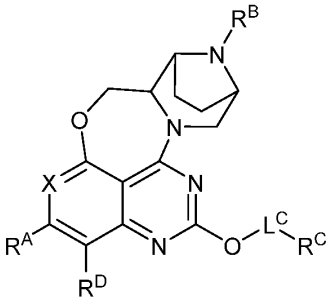


(IIb).

[0105] In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, II-3, (IIa), or (IIb), or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are each independently H, C_1-C_3 alkyl, halo, or C_1-C_6 haloalkyl. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, II-3, (IIa), or (IIb), or a pharmaceutically acceptable salt thereof, wherein L^2 is CHR^{2b}. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, II-3, (IIa), or (IIb), or a pharmaceutically acceptable salt thereof, wherein R^{2b} is H or C_1-C_3 alkyl. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, II-3, (IIa), or (IIb), or a pharmaceutically acceptable salt thereof, wherein R^{2b} is H. In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, II-3, (IIa), or (IIb), or a pharmaceutically acceptable salt thereof, wherein R^{2b} is C_1-C_3 alkyl. In some embodiments, the

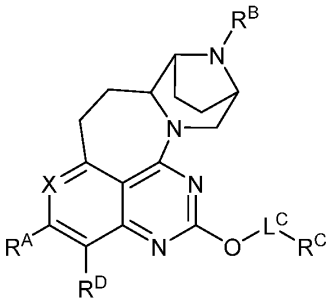
present disclosure provides the compound of Formula II, II-1, II-2, II-3, (IIa), or (IIb), or a pharmaceutically acceptable salt thereof, wherein R^{2b} is methyl.

[0106] In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, II-3, or (IIa), or a pharmaceutically acceptable salt thereof, having the structure of Formula (IIa-1):



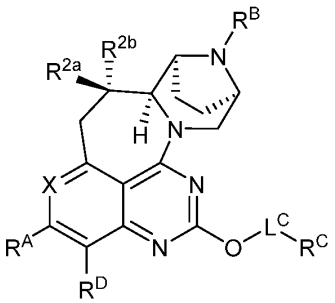
(IIa-1).

[0107] In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, II-3, or (IIb), or a pharmaceutically acceptable salt thereof, having the structure of Formula (IIb-1):



(IIb-1).

[0108] In some embodiments, the present disclosure provides the compound of Formula II, II-1, II-2, II-3, (IIa), (IIb), or (IIb-1), or a pharmaceutically acceptable salt thereof, having the structure of Formula (IIb-2):

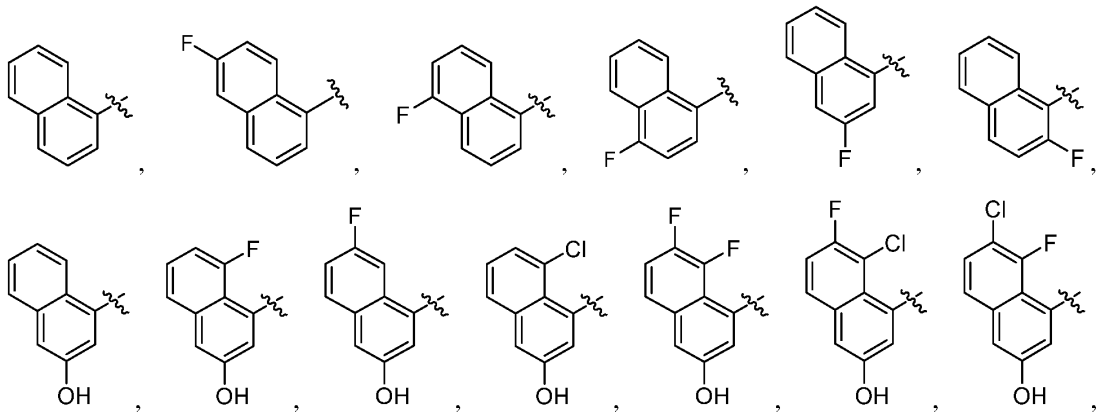


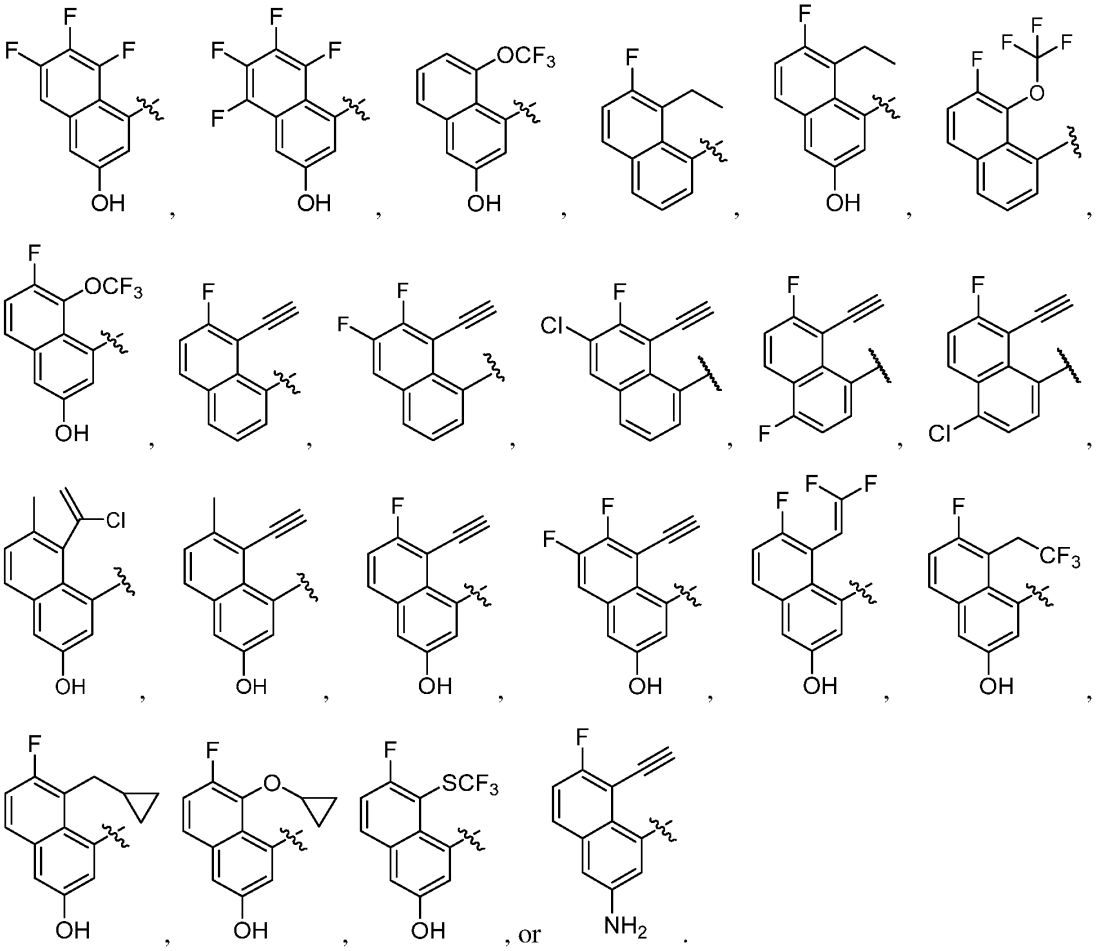
(IIb-2).

[0109] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), and (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^A is phenyl substituted with 0, 1, 2, 3, 4, or 5 R^{A2}. In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), and (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^A is naphthyl substituted with 0, 1, 2, 3, 4, or 5 R^{A2}.

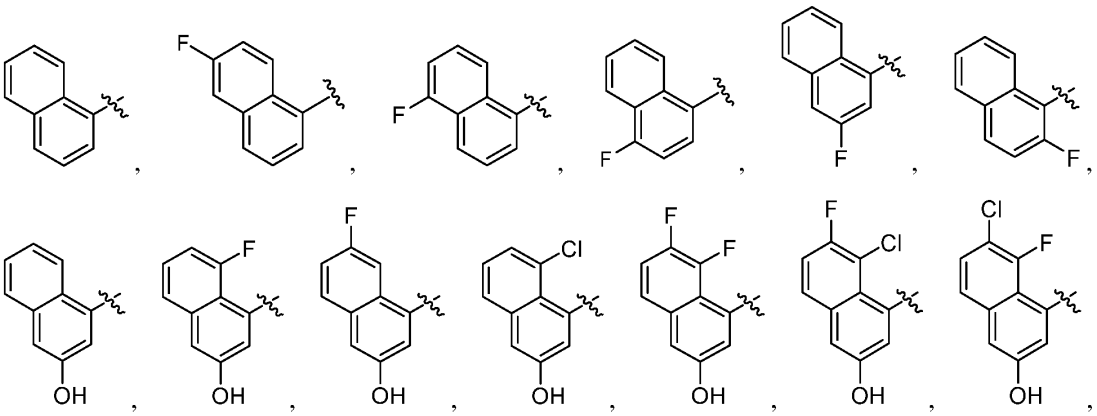
[0110] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), and (IIb-2), or a pharmaceutically acceptable salt thereof, wherein each R^{A2} is independently C_1-C_6 alkyl, -OH, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo, C_1-C_6 haloalkyl, -OR^{A2a}, -SR^{A2a}, or -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), wherein each alkenyl is substituted with 0, 1, 2, or 3 R^{A3}; each R^{A2a} is independently C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl; and each R^{A3} is independently halo. In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), and (IIb-2), or a pharmaceutically acceptable salt thereof, wherein each R^{A2} is independently Me, -OH, , -C(Cl)=CH_2, -CH=CHF_2, -C≡CH, F, Cl, -CH_2CF_3, -OCF_3, -O-cyclopropyl, -SCF_3, or –CH_2-cyclopropyl.

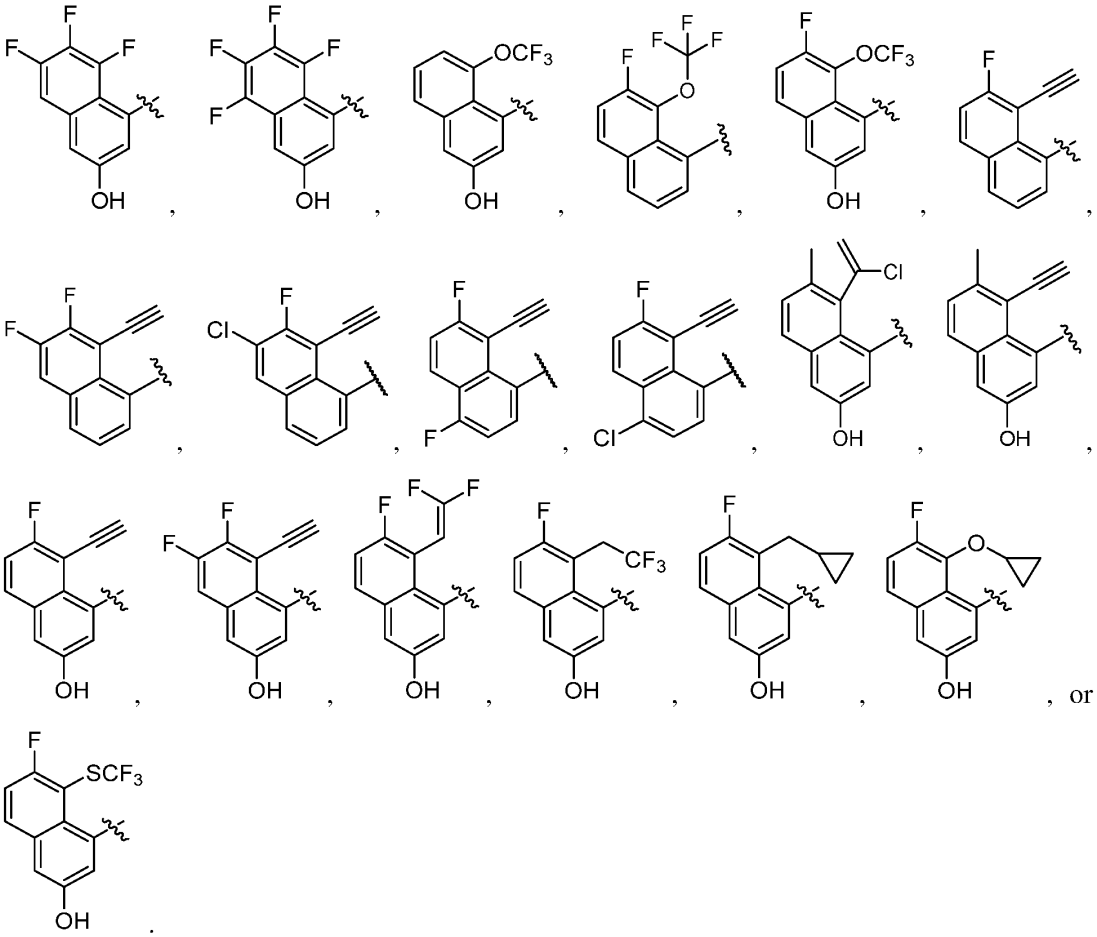
[0111] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), and (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^A is



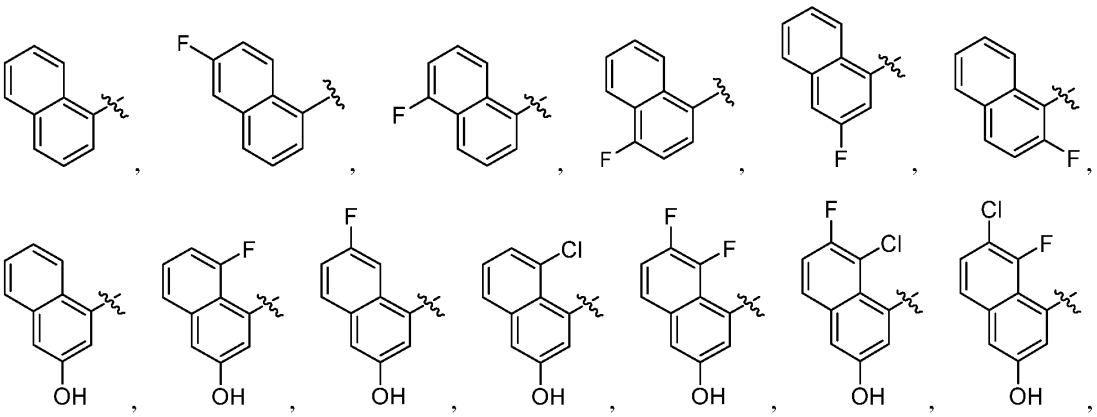


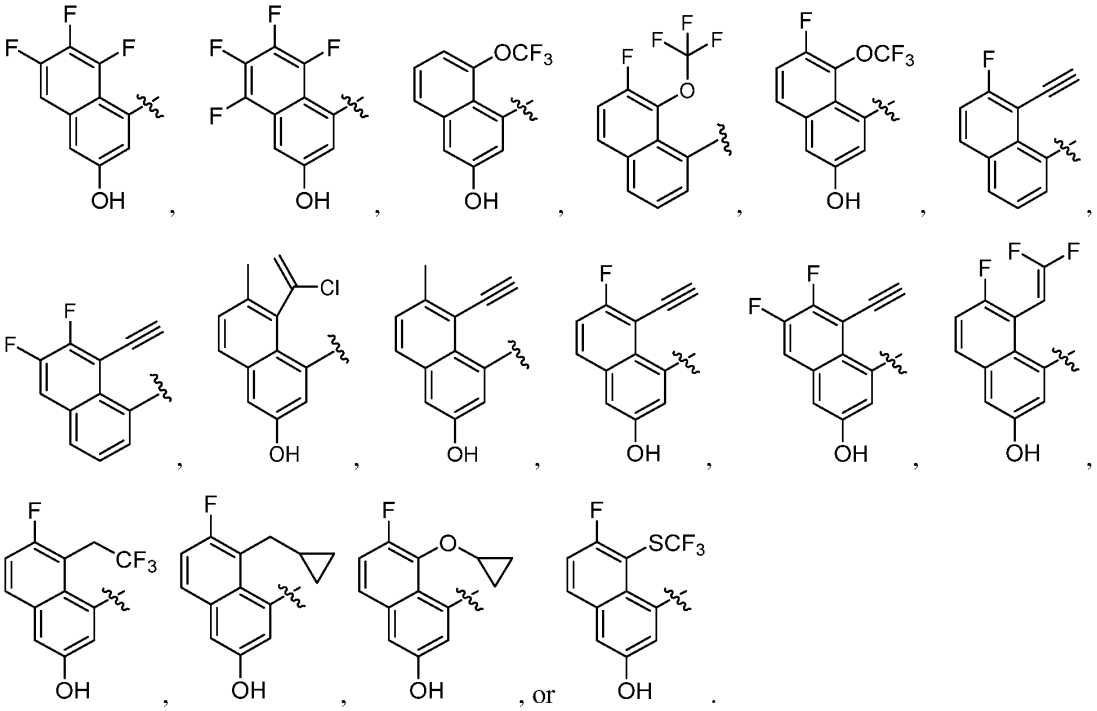
[0112] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), and (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^A is



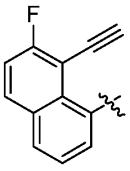


[0113] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^A is





[0114] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^A is



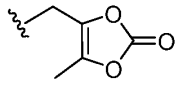
[0115] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^B is H.

[0116] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein

R^B is $-C(O)R^{B1}$, or $-C(O)OR^{B2}$;

R^{B1} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B1a};

R^{B2} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, (C_1-C_6 alkyl)-OC(O)R^{B3}, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 14-membered heteroaryl, or



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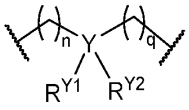
wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B2a};

R^{B3} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B3a}; and

each R^{B1a}, R^{B2a} and R^{B3a} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkoxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, oxo, -OH, -CN, or C_3-C_{10} cycloalkyl.

[0117] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein L^C is a bond.

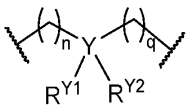
[0118] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein L^C is



;

Y is C or Si; n is 0 or 1; q is 0 or 1; R^{Y1} is H or C_1-C_3 alkyl; and R^{Y2} is H or C_1-C_3 alkyl; alternatively, R^{Y1} and R^{Y2} combine to form a C_3-C_6 cycloalkyl.

[0119] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein L^C is



;

Y is C or Si; n is 0 or 1; q is 0 or 1; R^{Y1} is H or Me; and R^{Y2} is H or Me; alternatively, R^{Y1} and R^{Y2} combine to form a cyclopropyl.

[0120] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein

R^C is 3- to 14-membered heterocyclyl, substituted with 0, 1, 2, or 3 R^{C3};

each R^{C3} is independently C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, $=CH_2$, $-OR^{C3a}$, or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl), wherein each alkyl is substituted with 1-OC(O)N(R^{C3a1})(R^{C3a2}), -OR^{C3a1}, or N_3;

each R^{C3a} is independently C_1-C_6 haloalkyl; and

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl wherein each aryl or heteroaryl, is substituted with 0, 1, 2, 3, or 4 halo, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, or SF_5;

alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle.

[0121] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein

R^C is 3- to 14-membered heterocyclyl, substituted with 0, 1, 2, or 3 R^{C3};

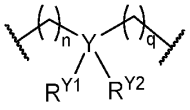
each R^{C3} is independently C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, $=CH_2$, $-OR^{C3a}$, or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl), wherein each alkyl is substituted with 1-OC(O)N(R^{C3a1})(R^{C3a2}), -OR^{C3a1}, or N_3;

each R^{C3a} is independently C_1-C_6 haloalkyl; and

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, C_1-C_6 haloalkyl, or C_6-C_{10} aryl, wherein each aryl, is substituted with 1 SF_5;

alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle.

[0122] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein L^C is



;

Y is C; n is 0; q is 0; R^{Y1} is H; and R^{Y2} H. In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein L^C is $–CH_2-$.

[0123] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein

R^C is 8- to 14-membered heterocyclyl, is substituted with 0, 1, 2, or 3 R^{C3};

each R^{C3} is independently C_1-C_6 alkyl, halo, $=CH_2$, $-OR^{C3a}$, or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl),

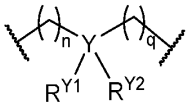
wherein each alkyl is substituted with 1 $-OC(O)N(R^{C3a1})(R^{C3a2})$, $-OR^{C3a1}$, or N_3;

each R^{C3a} is independently C_1-C_6 haloalkyl; and

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, C_1-C_6 haloalkyl, or C_6-C_{10} aryl, wherein each aryl is substituted with 1 SF_5;

alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle.

[0124] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein L^C is



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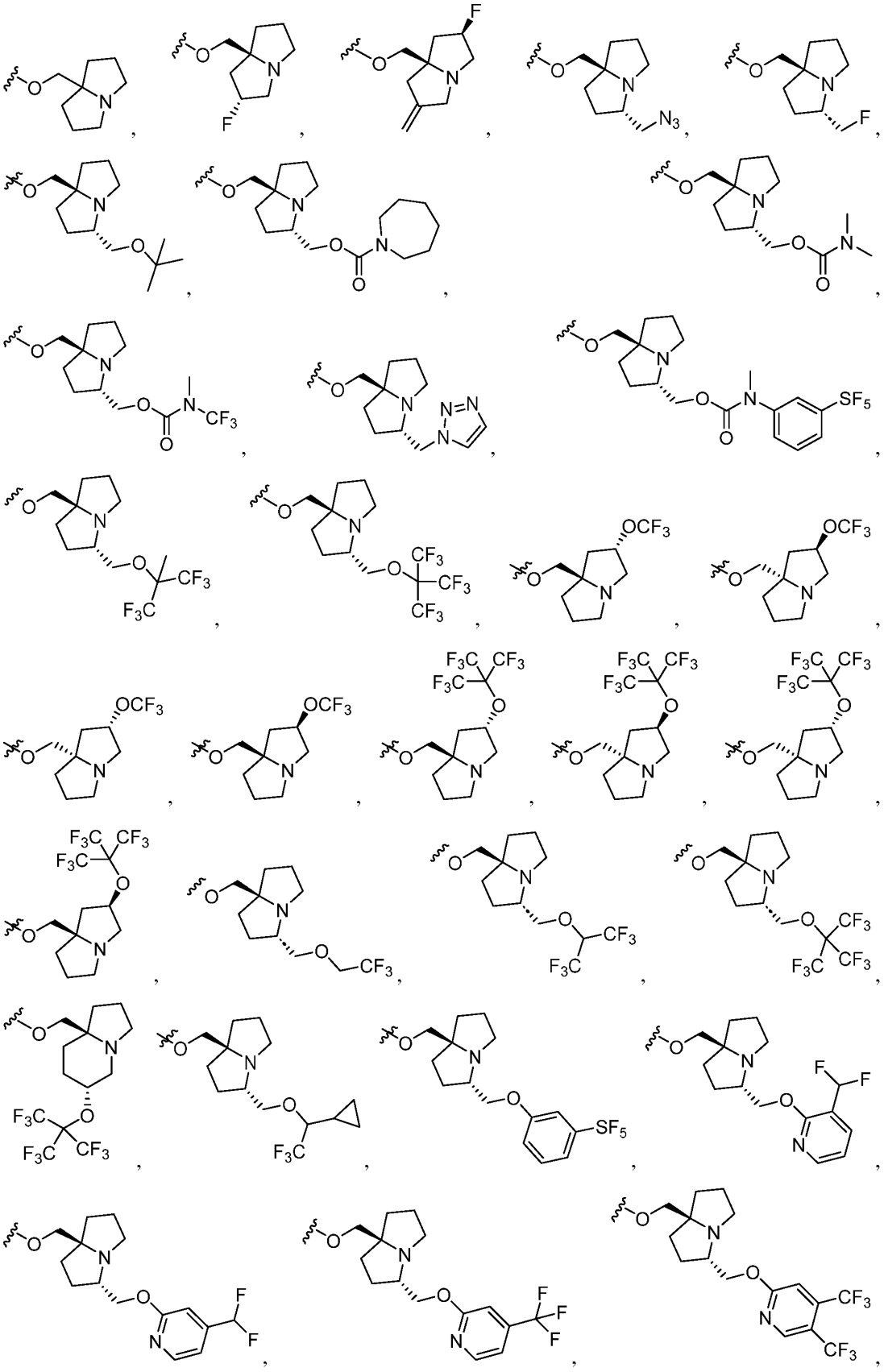
Y is C or Si; n is 1; q is 1; R^{Y1} is Me; and R^{Y2} is Me; alternatively, R^{Y1} and R^{Y2} combine to form a cyclopropyl. In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb),

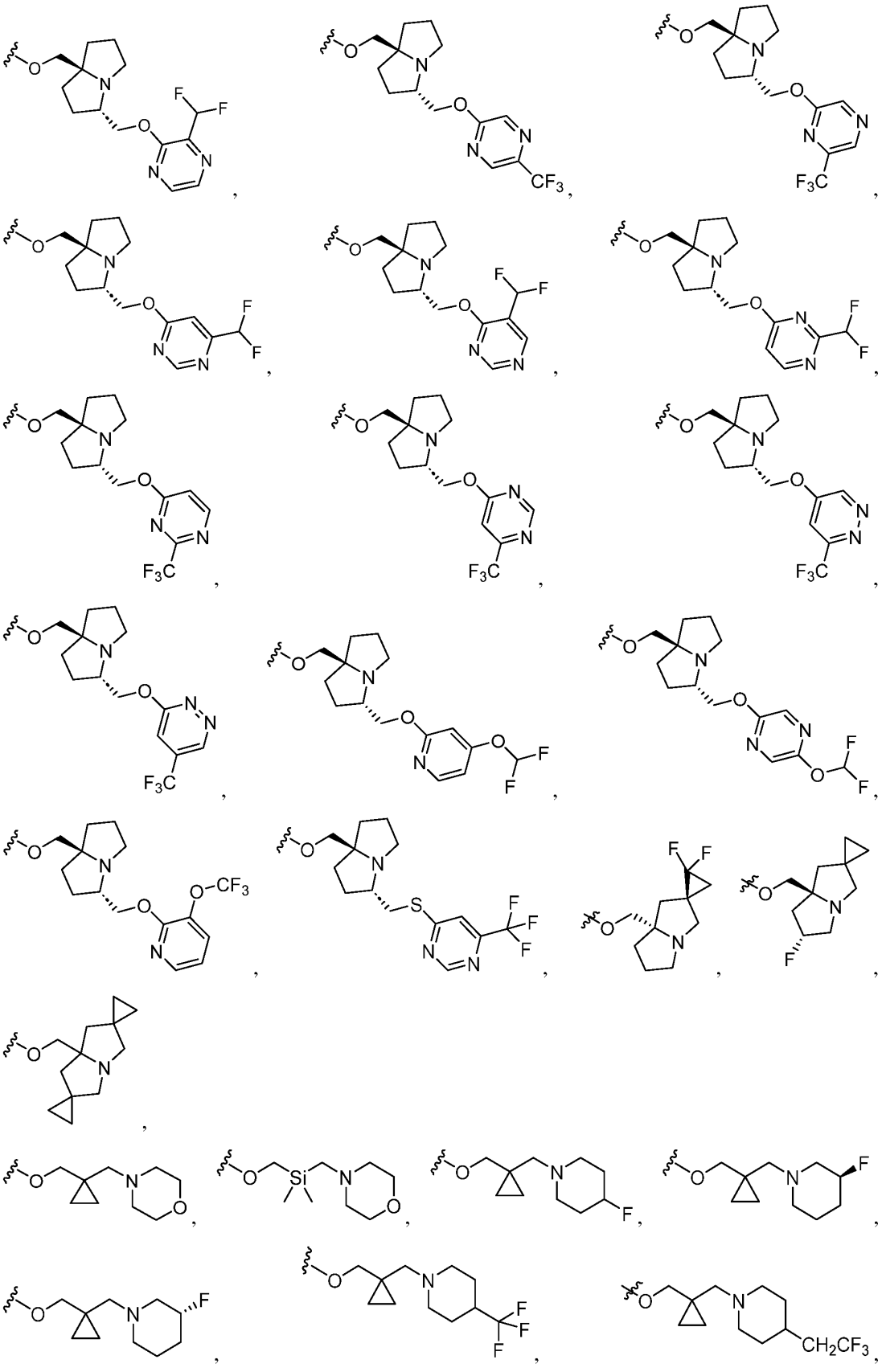
(IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^C is 3- to 7-membered heterocyclyl, substituted with 0, 1, or 2 R^{C3}; and each R^{C3} is independently halo or C_1-C_6 haloalkyl.

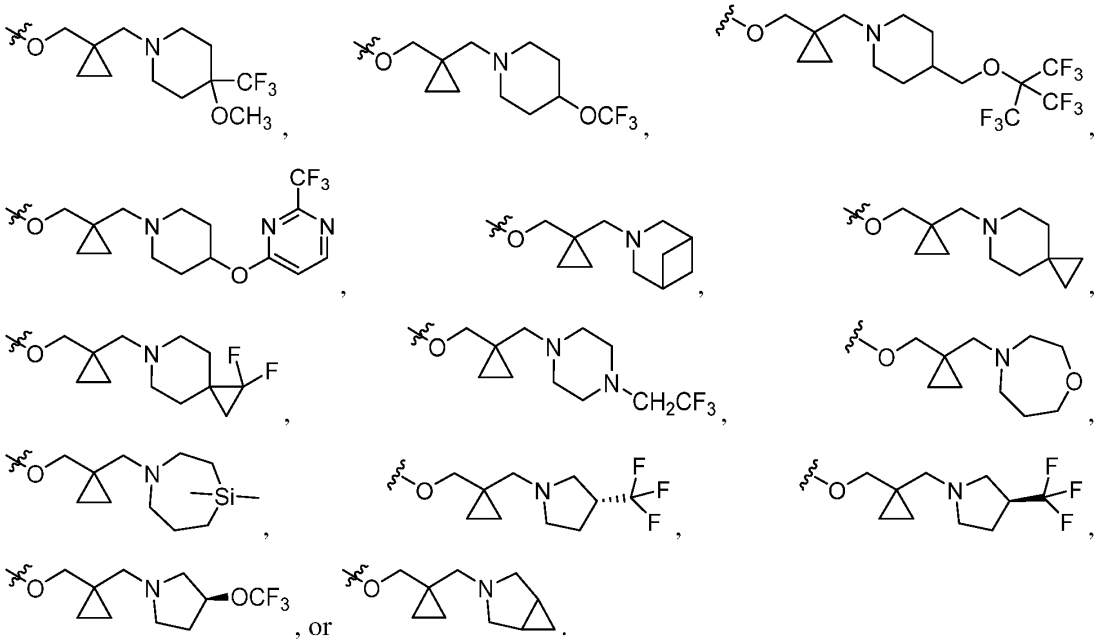
[0125] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^{1b} is H or methyl; R^{C3} is -CH_2OR^{C3a1} or F; and R^{C3a1} is 5- to 6-membered heteroaryl substituted with one halo or C_1-C_2 haloalkyl. In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^{1b} is H or methyl; and R^{C3} is F. In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^{1b} is H or methyl; R^{C3} is -CH_2OR^{C3a1}; and R^{C3a1} is 6-membered heteroaryl substituted with one C_1 haloalkyl. In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^{1b} is H or methyl; R^{C3} is -CH_2OR^{C3a1}; and R^{C3a1} is pyridazine, pyrimidine, or pyrazine, wherein the pyridazine, pyrimidine, or pyrazine is substituted with one CF_3.

[0126] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein L^C is –CH_2-; R^C is 3- to 14-membered heterocyclyl substituted with 1 R^{C3}; R^{C3} is C_1-C_6 alkyl substituted with one -OR^{C3a1} or -SR^{C3a1}; and R^{C3a1} is 5- to 10-membered heteroaryl substituted with 0, 1, or 2 C_1-C_3 haloalkyl or C_1-C_3 haloalkoxy. In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein L^C is –CH_2-; R^C is 4- to 8-membered heterocyclyl substituted with 1 R^{C3}; R^{C3} is -CH_2OR^{C3a1}; and R^{C3a1} is a pyrimidine, wherein the pyrimidine is substituted with 1 trifluoromethyl group.

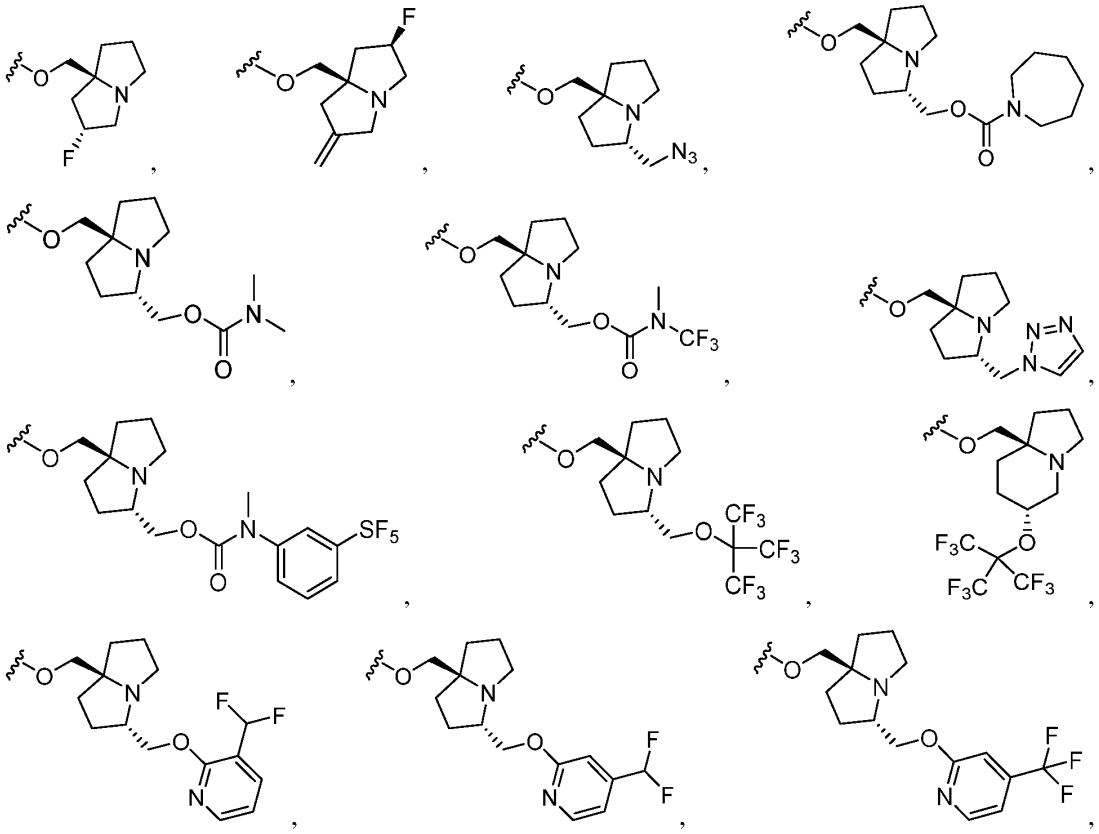
[0127] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein the –O-L^C-R^C moiety is

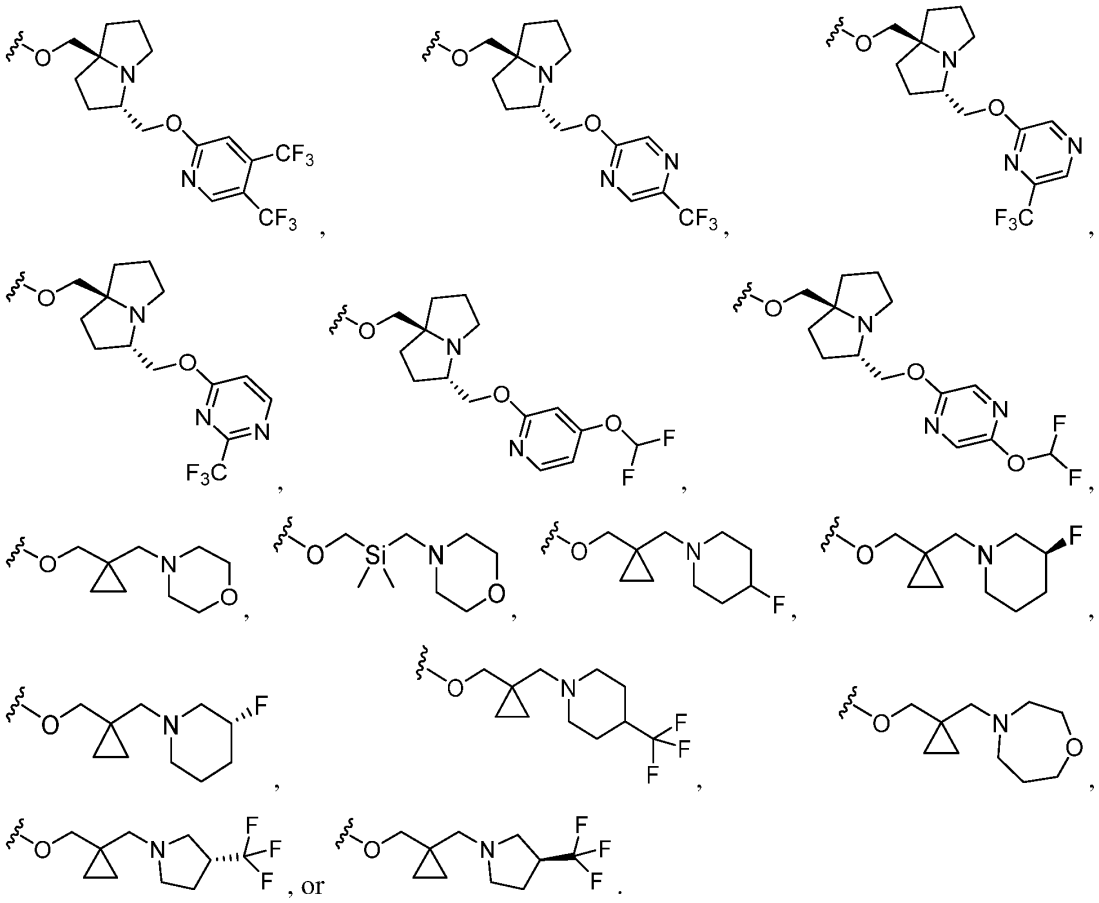




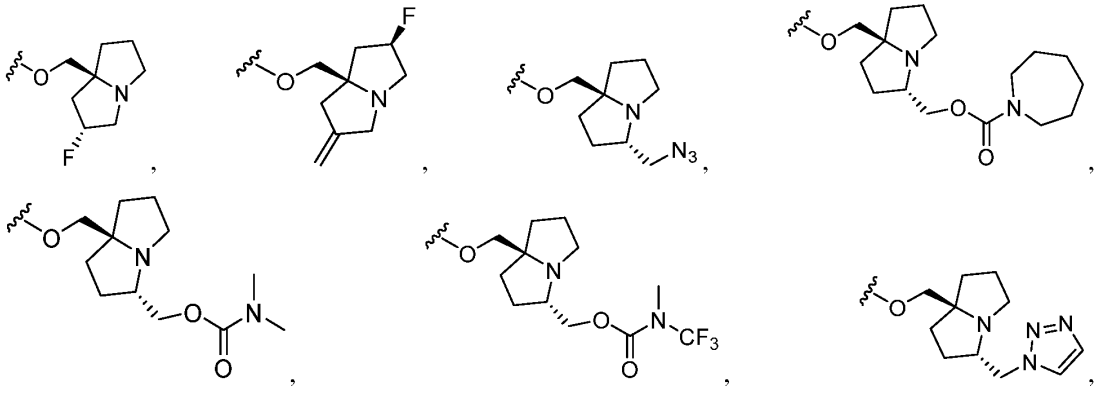


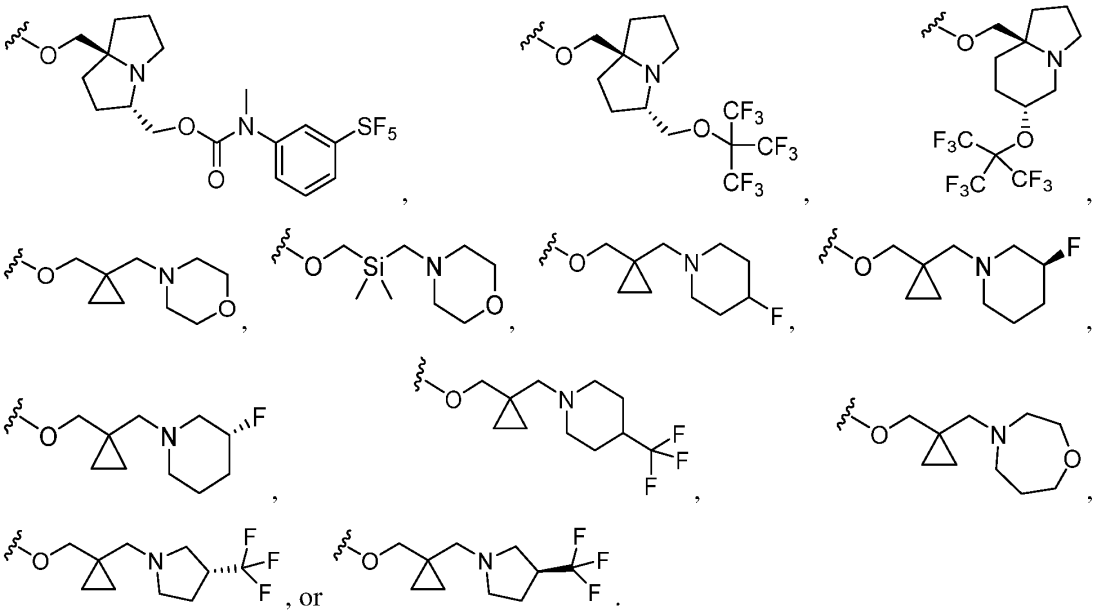
[0128] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein the –O-L^C-R^C moiety is



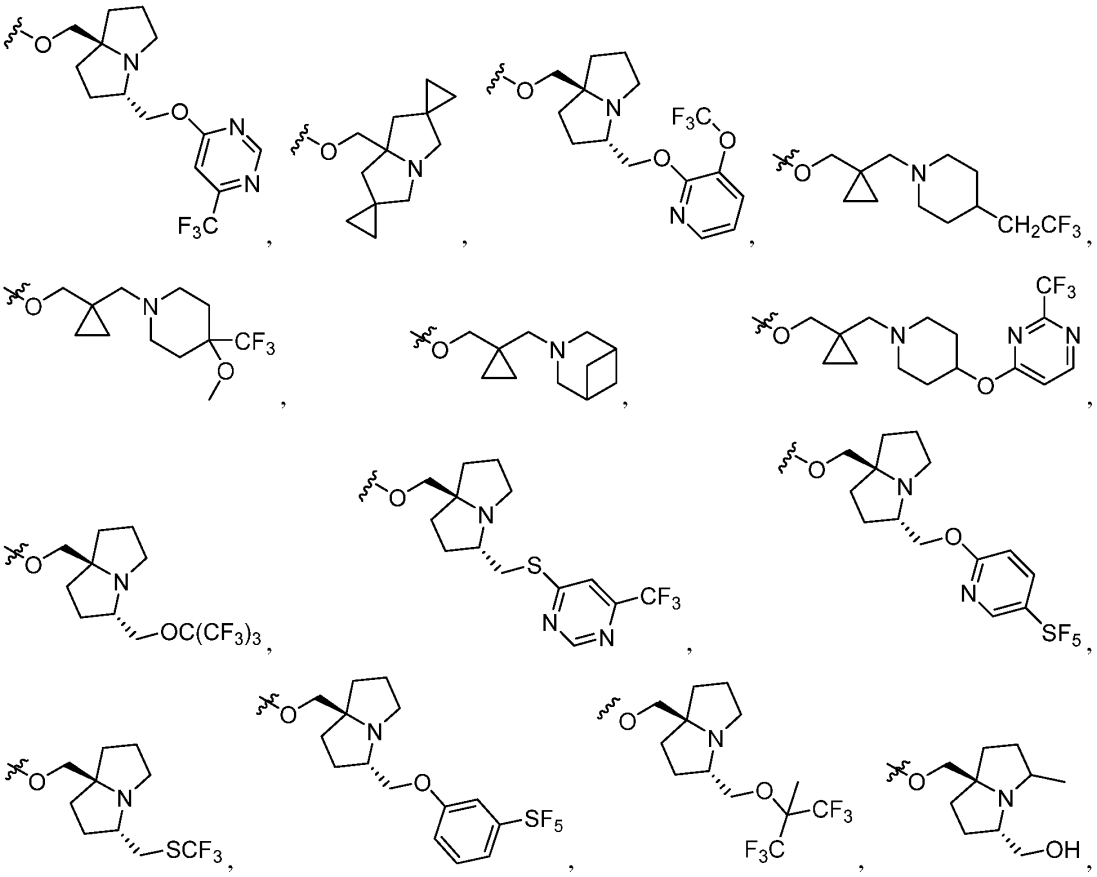


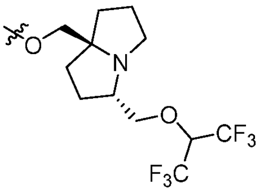
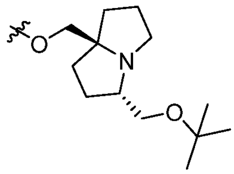
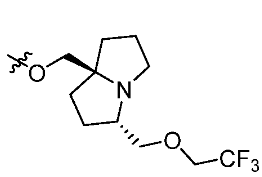
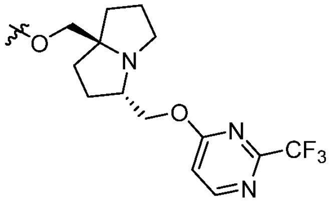
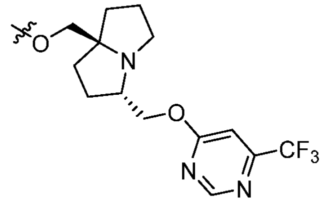
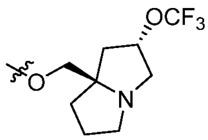
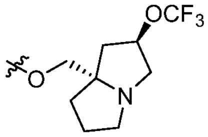
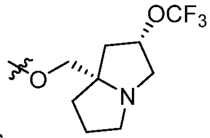
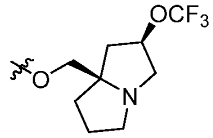
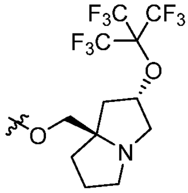
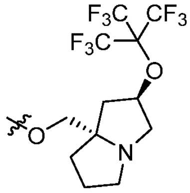
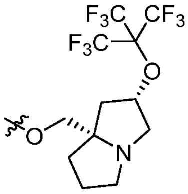
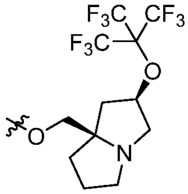
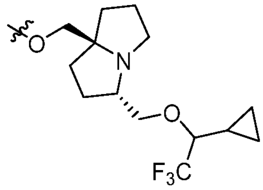
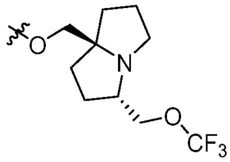
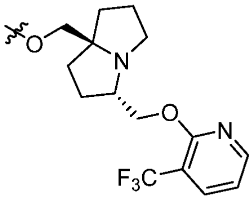
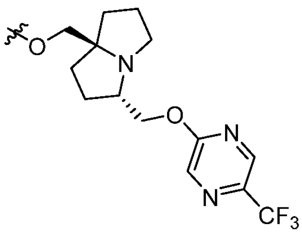
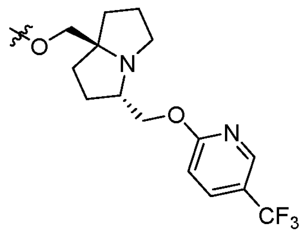
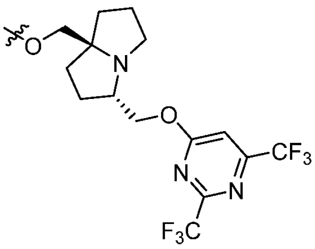
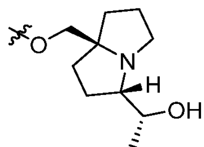
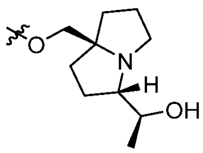
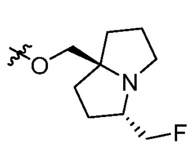
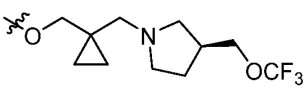
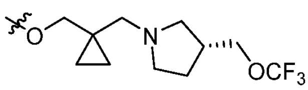
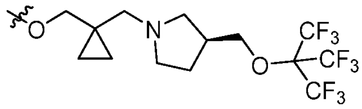
[0129] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein the –O-L^C-R^C moiety is

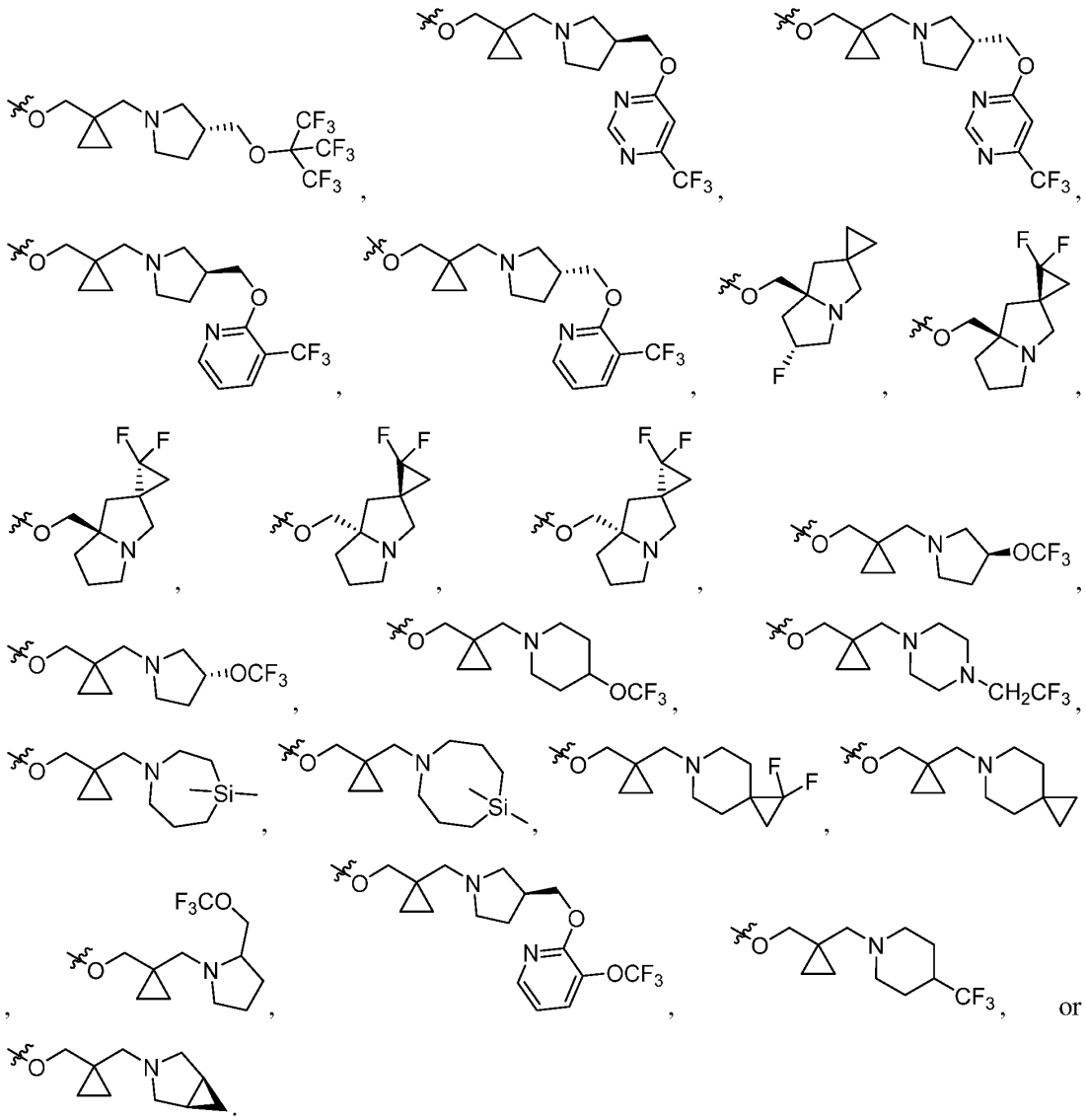




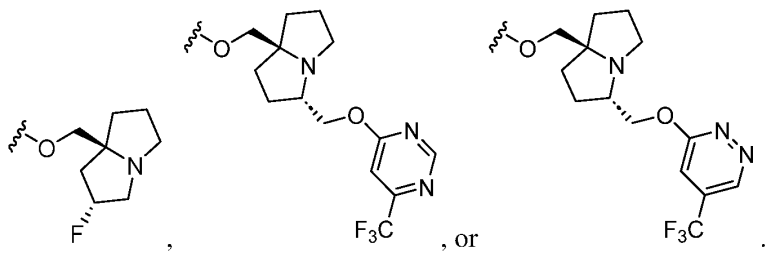
[0130] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein the –O-L^C-R^C moiety is



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[0131] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein the –O-L^C-R^C moiety is



[0132] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^D is F or Cl. In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^D is F.

[0133] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), or (I-3), or a pharmaceutically acceptable salt thereof, wherein

X is N, CH, or CR^x;

R^x is halo;

L^1 is O or $CR^{1a}R^{1b}$;

R^{1a} and R^{1b} are each independently H, C_1-C_3 alkyl, or halo;

L^2 is $CR^{2a}R^{2b}$;

R^{2a} and R^{2b} are each independently H, C_1-C_3 alkyl, C_1-C_6 haloalkyl, or C_3-C_6 cycloalkyl;

L^3 is a bond or $CR^{3a}R^{3b}$;

R^{3a} and R^{3b} are each independently H or C_1-C_3 alkyl;

R^1, R^2, R^3, and R^4 are each H;

R^A is naphthyl, wherein R^A is substituted with 0, 1, 2, 3, 4, or 5 R^{A2};

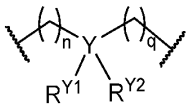
each R^{A2} is independently -OH, C_1-C_3 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, halo, C_1-C_6 haloalkyl, $-OR^{A2a}$, $-SR^{A2a}$, $-N(R^{A2a})(R^{A2b})$, or -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), wherein each alkyl, alkenyl, alkynyl, alkoxy, and haloalkyl is substituted with 0, 1, 2, or 3 R^{A3};

each R^{A2a} and R^{A2b} is independently H, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl;

each R^{A3} is independently halo;

R^B is H;

L^C is a bond or



;

Y is C or Si;

n is 0 or 1;

q is 0 or 1;

R^{Y1} is H or C_1-C_3 alkyl;

R^{Y2} is H or C_1-C_3 alkyl;

alternatively, R^{Y1} and R^{Y2} combine to form a C_3-C_8 cycloalkyl;

R^C is 3- to 14-membered heterocyclyl, wherein each 3- to 14-membered heterocyclyl is substituted with 0, 1, 2, 3, or 4 R^{C3};

each R^{C3} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxyalkyl, halo, C_1-C_6 haloalkyl, $=CH_2$, $-OR^{C3a}$, wherein each alkyl is substituted with 0, 1, 2, or 3 -$OC(O)N(R^{C3a1})(R^{C3a2})$, $-OR^{C3a1}$, $-SR^{C3a1}$, or N_3;

R^{C3a} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, or 5- to 10-membered heteroaryl, wherein the heteroaryl is substituted with 1 R^{C3a2};

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is substituted with 1 or 2 halo, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, or SF_5;

alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle; and

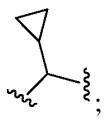
R^D is F.

[0134] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), or (I-3), or a pharmaceutically acceptable salt thereof, wherein

X is N, CH, or C-Cl;

L^1 is O, CH_2, $CHCH_3$, $CHCH_2CH_3$, CHF, or CF_2;

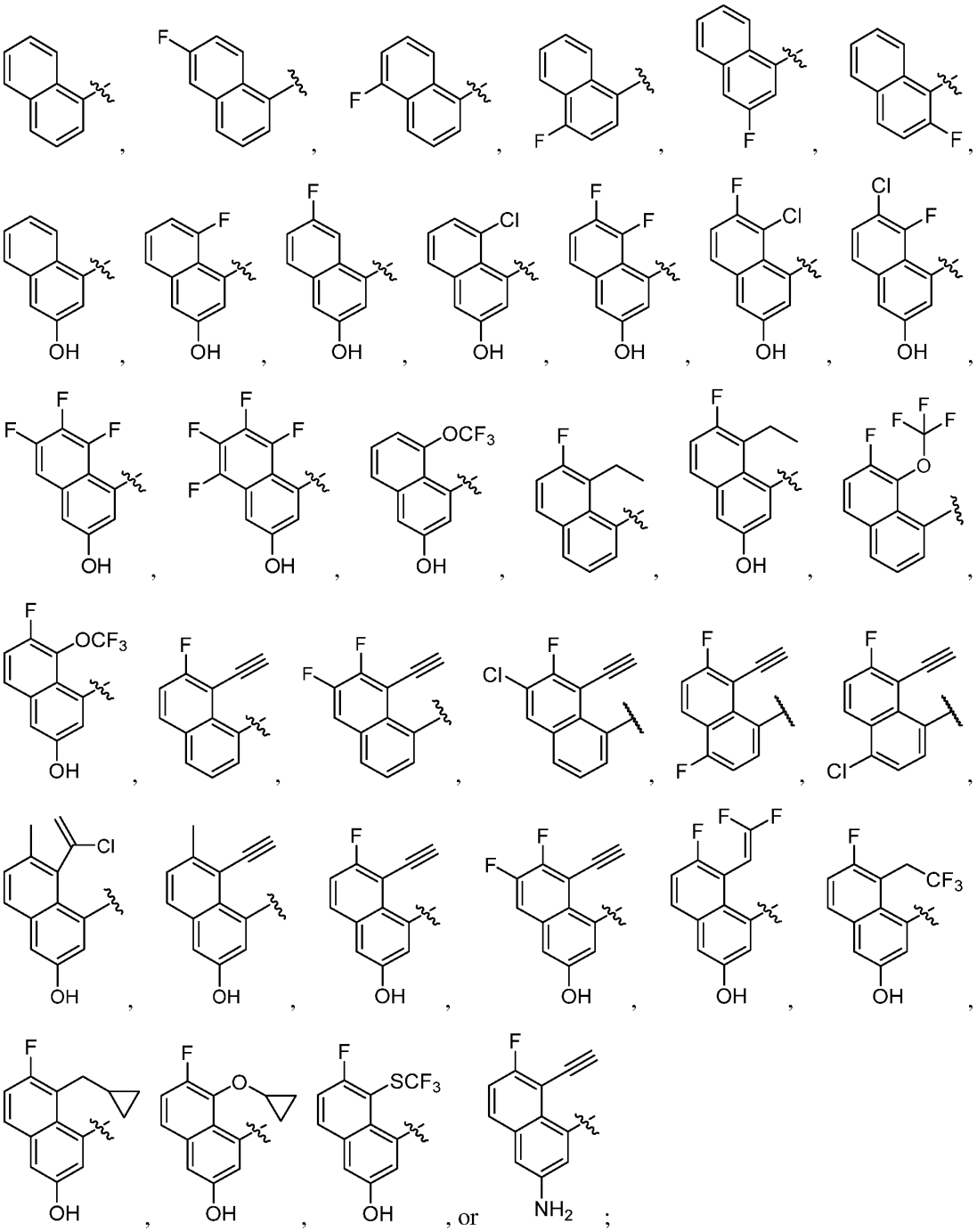
L^2 is CH_2, $CHCH_3$, $CHCH_2CH_3$, $CHCHF_2$, or

 ;

L^3 is a bond, CH_2, or $CHCH_3$;

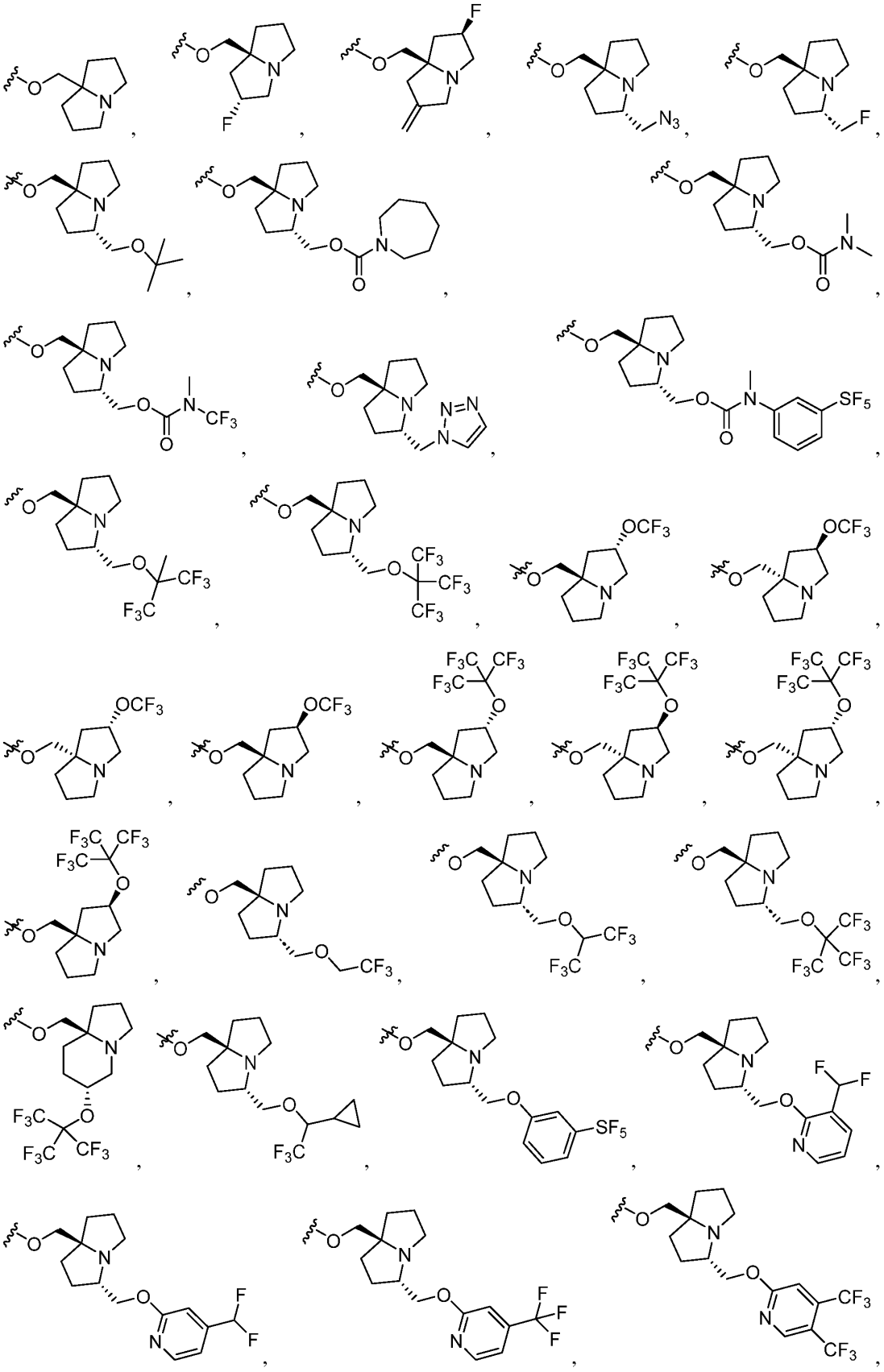
R^1, R^2, R^3, and R^4 are each H;

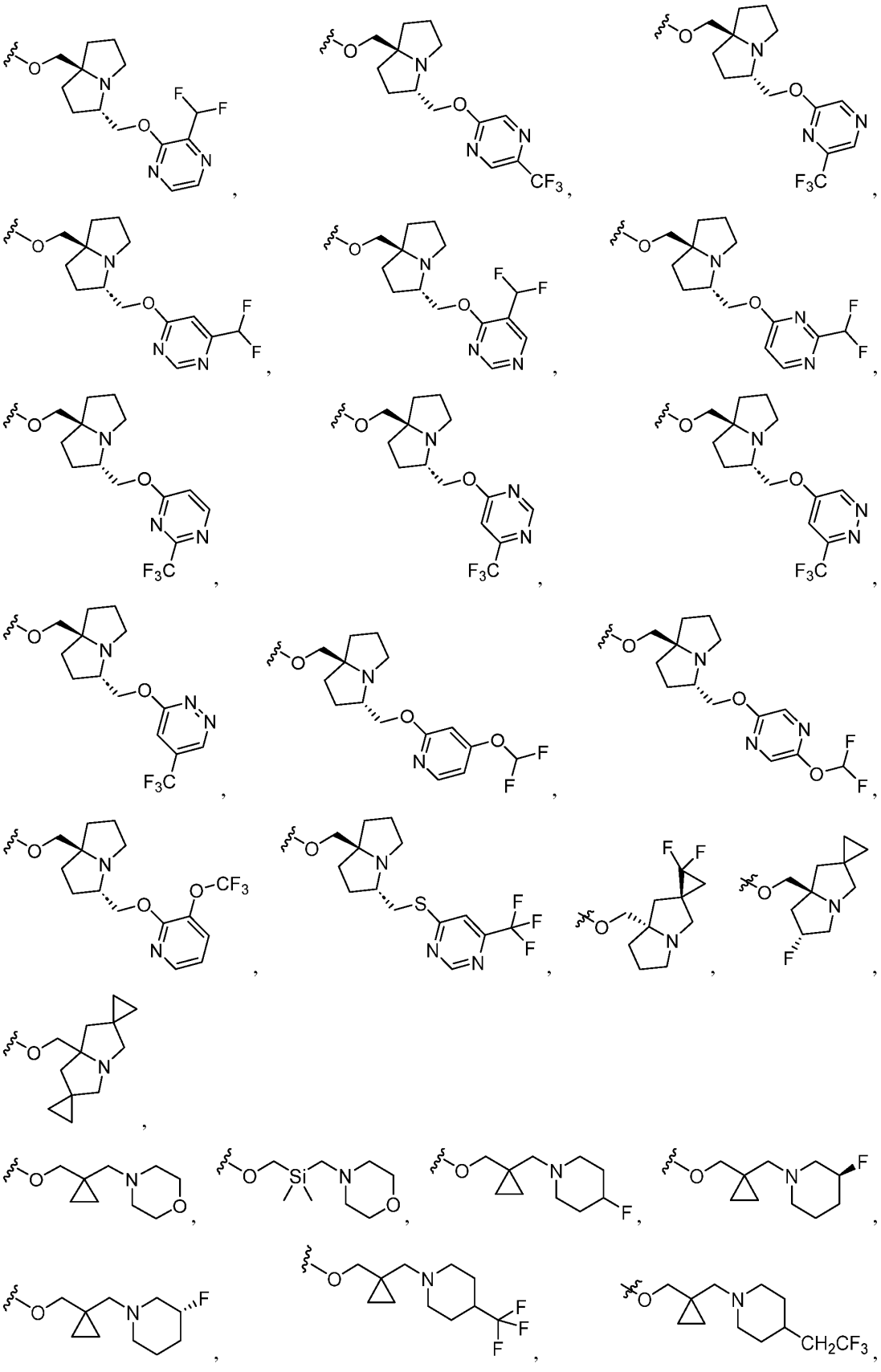
R^A is

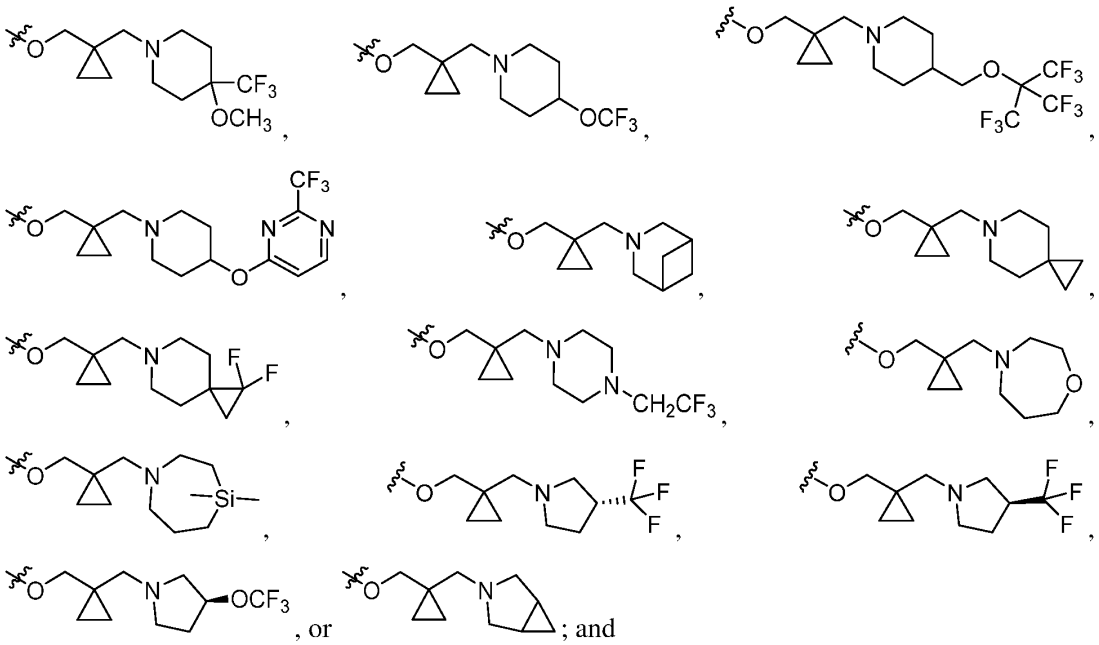


R^B is H;

the –O-L^C-R^C moiety is





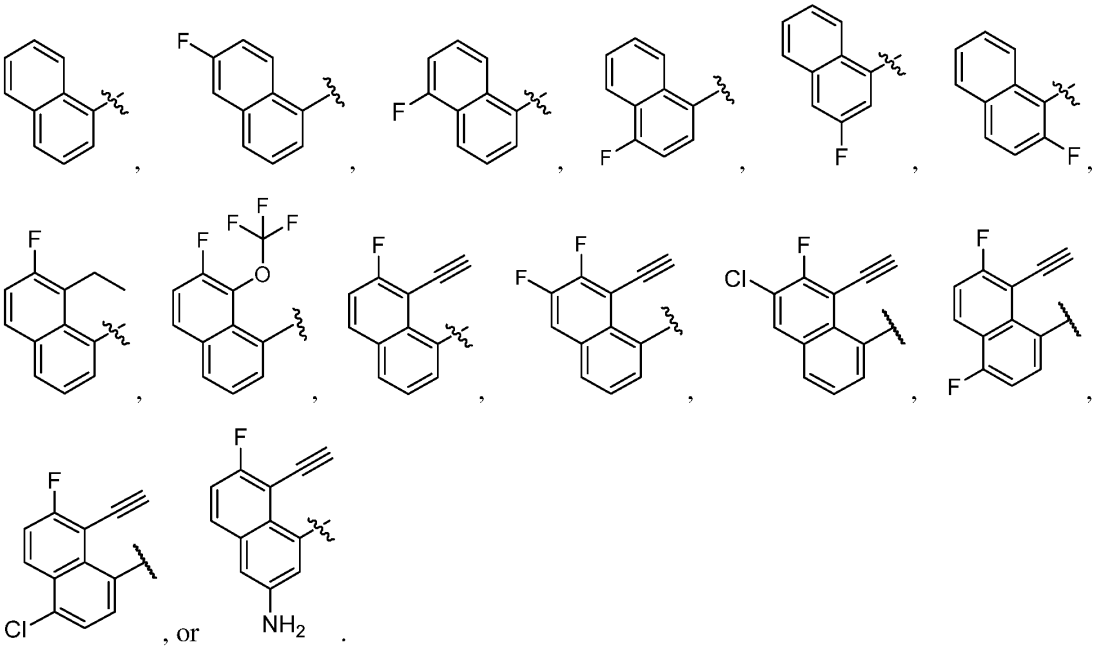


R^D is F.

[0135] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein L^1 is CH_2, $CHCH_3$, $CHCH_2CH_3$, CHF, or CF_2.

[0136] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein L^3 is CH_2 or $CHCH_3$.

[0137] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein R^A is



[0138] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), or (I-3), or a pharmaceutically acceptable salt thereof, wherein

X is N;

R^1, R^2, R^3, and R^4 are each H;

L^1 is $CR^{1a}R^{1b}$;

R^{1a} and R^{1b} are each independently H or C_1-C_3 alkyl;

L^2 is $CR^{2a}R^{2b}$;

R^{2a} and R^{2b} are each H;

L^3 is $CR^{3a}R^{3b}$;

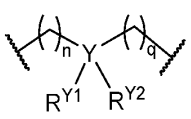
R^{3a} and R^{3b} are each H;

R^A is naphthyl, wherein R^A is substituted with 2 R^{A2};

each R^{A2} is independently C_2-C_6 alkynyl or halo;

R^B is H;

L^C is



;

Y is C;

n is 0;

q is 0;

R^{Y1} is H;

R^{Y2} is H;

R^C is 3- to 14-membered heterocyclyl, wherein the 3- to 14-membered heterocyclyl is substituted with 1 R^{C3};

R^{C3} is C_1-C_6 alkyl, halo, or C_1-C_6 haloalkyl, wherein the alkyl is substituted with 1 -OR^{C3a1};

R^{C3a1} is 5- to 10-membered heteroaryl, wherein the heteroaryl is substituted with 1 C_1-C_3 haloalkyl; and

R^D is F.

[0139] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), or (I-3), or a pharmaceutically acceptable salt thereof, wherein

X is N;

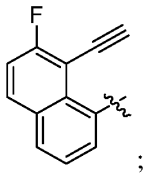
R^1, R^2, R^3, and R^4 are each H;

L^1 is CH_2 or $CHCH_3$;

L^2 is CH_2;

L^3 is CH_2;

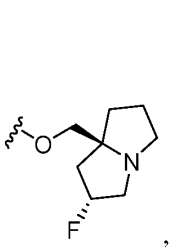
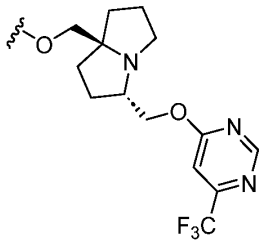
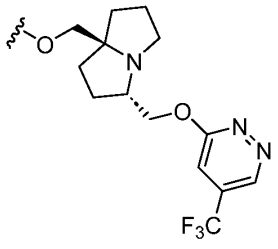
R^A is



;

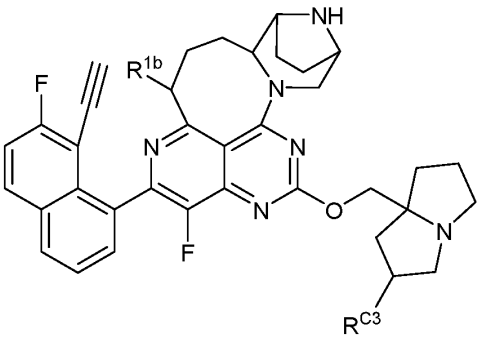
R^B is H;

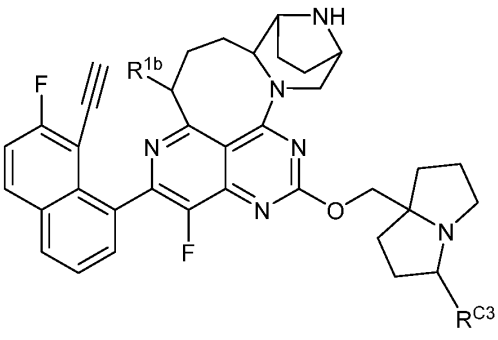
the -O-L^C-R^C moiety is


,

, or

; and

R^D is F.

[0140] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein the compound has the structure of Formula (Ib-5) or Formula (Ib-6):


(Ib-5),


(Ib-6),

wherein

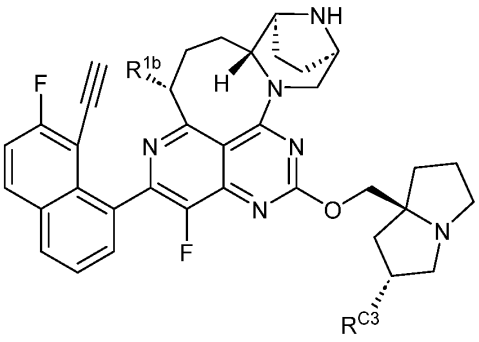
R^{1b} is H or methyl;

R^{C3} is $-CH_2OR^{C3a1}$ or F; and

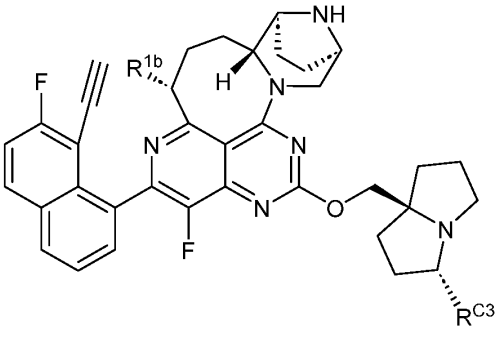
R^{C3a1} is 5- to 6-membered heteroaryl substituted with one halo or C_1-C_2 haloalkyl.

[0141] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-

1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein the compound has the structure of Formula (Ib-7) or Formula (Ib-8):



(Ib-7),



(Ib-8),

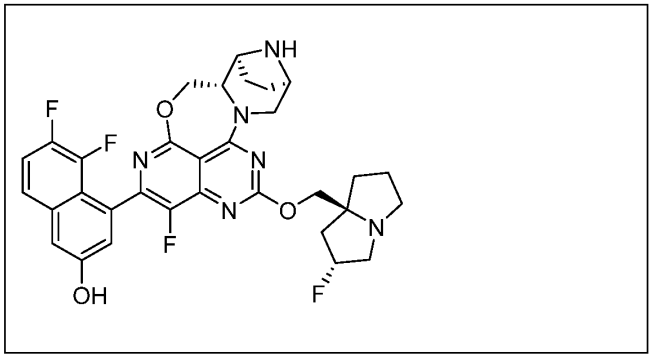
wherein

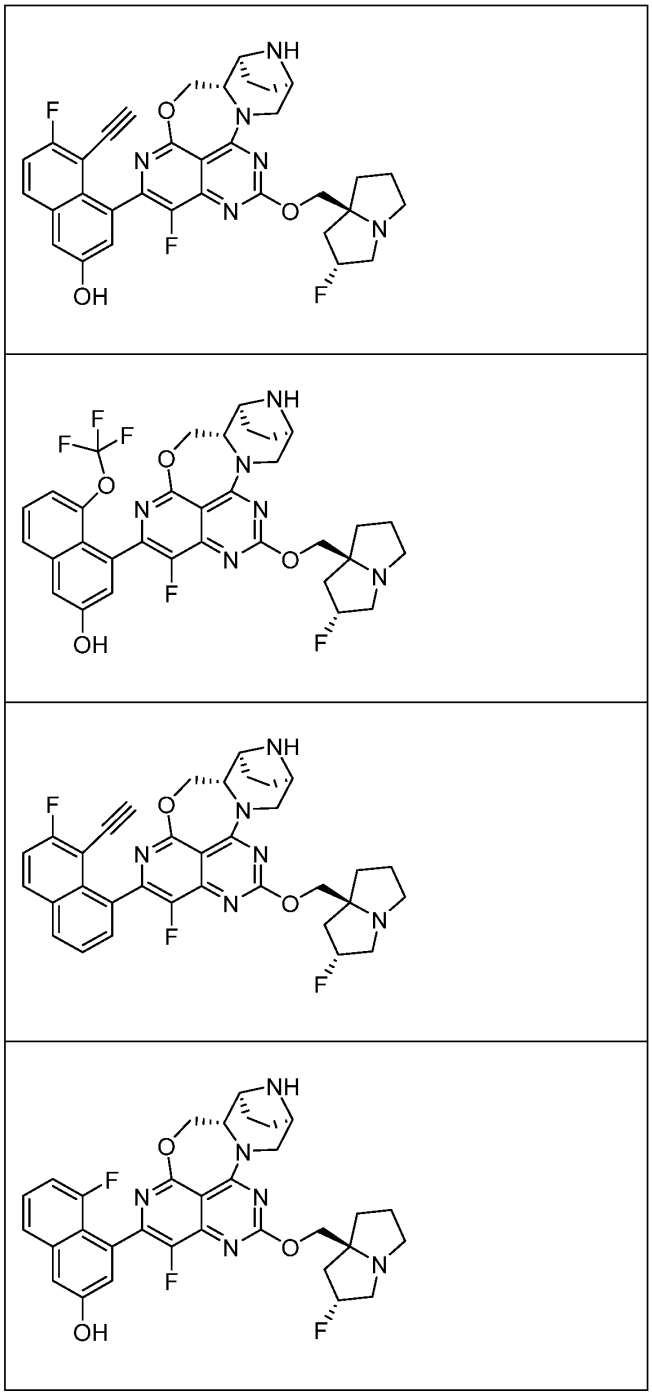
R^{1b} is H or methyl;

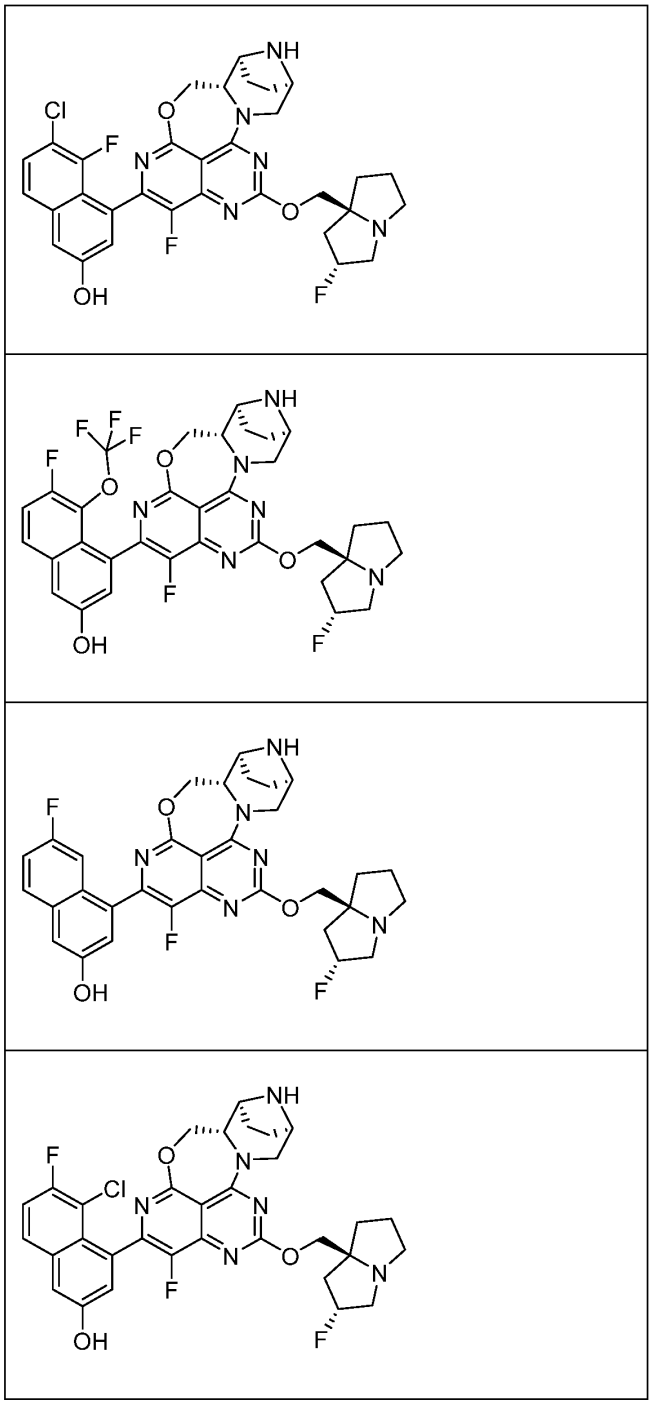
R^{C3} is $-CH_2OR^{C3a1}$ or F; and

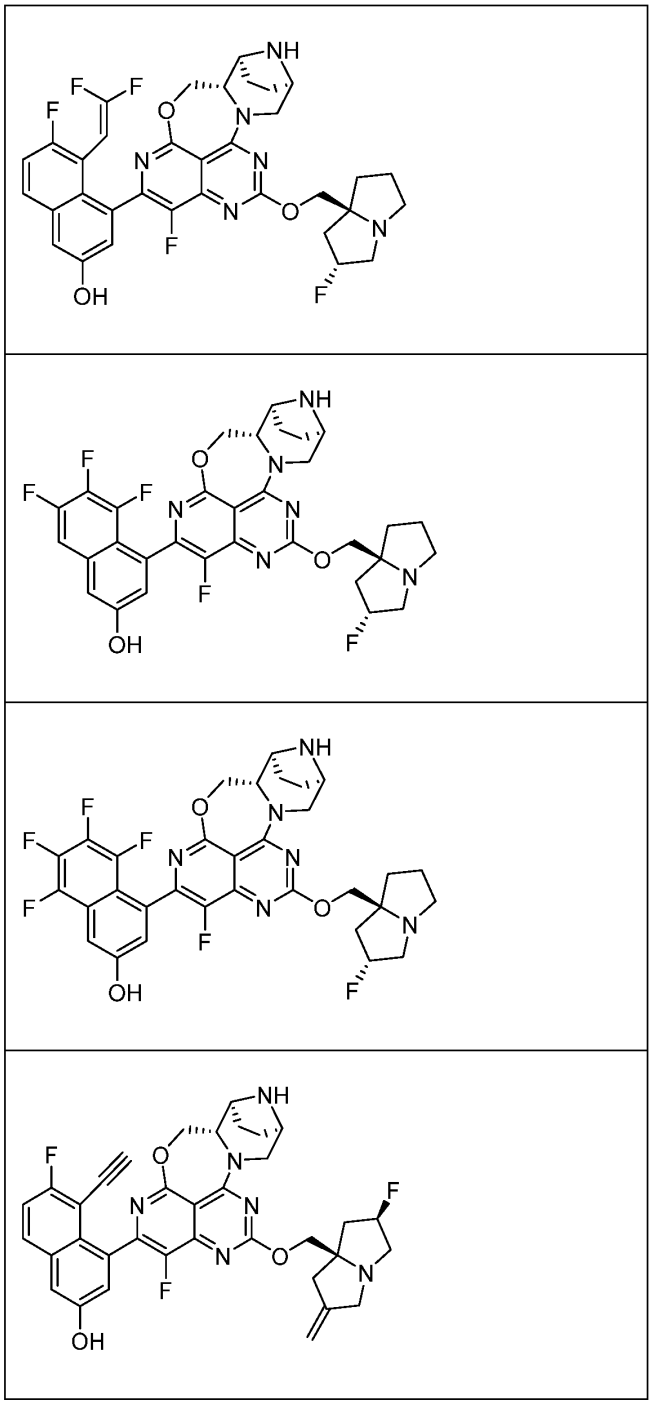
R^{C3a1} is 5- to 6-membered heteroaryl substituted with one halo or C_1-C_2 haloalkyl.

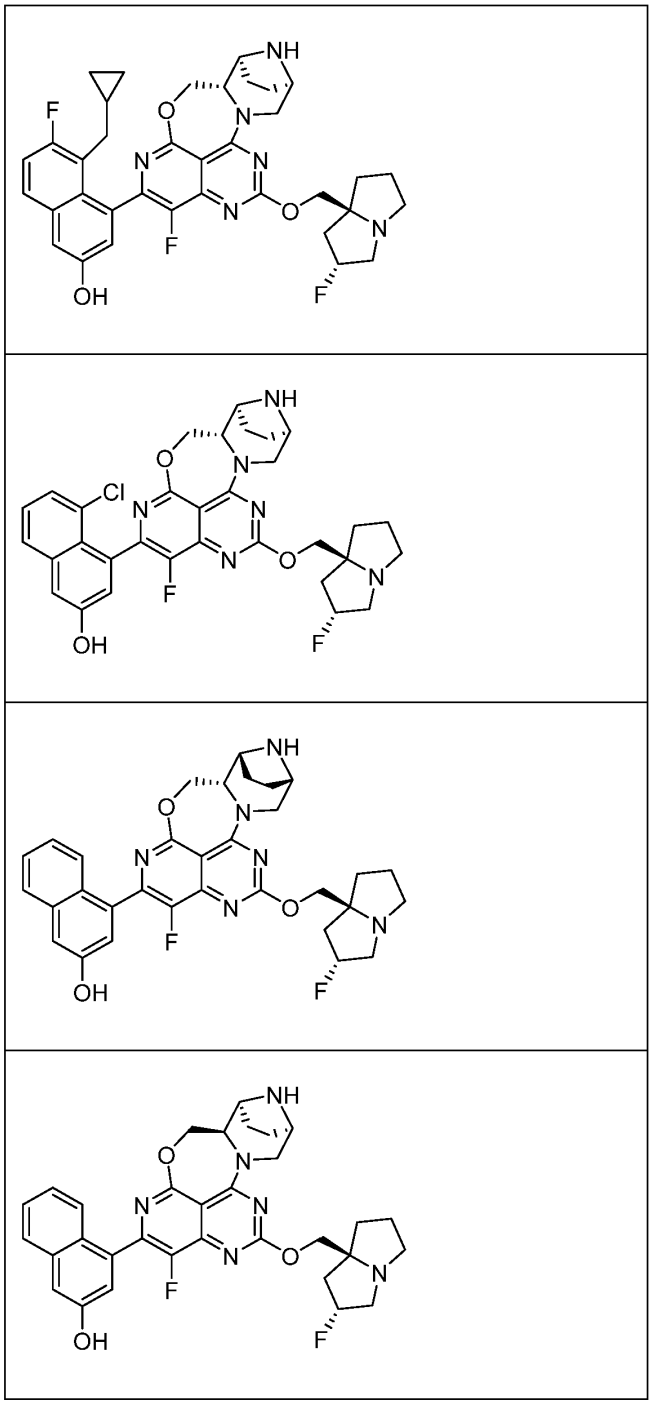
[0142] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein the compound has the structure:

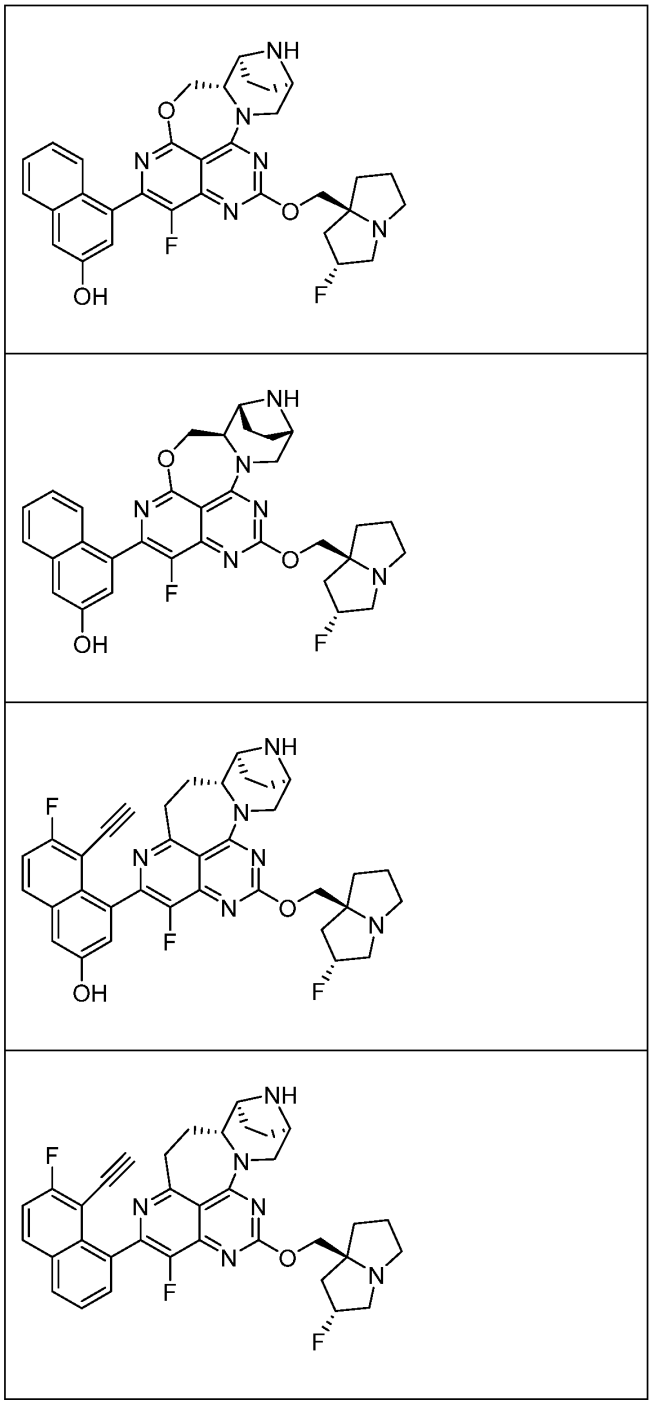


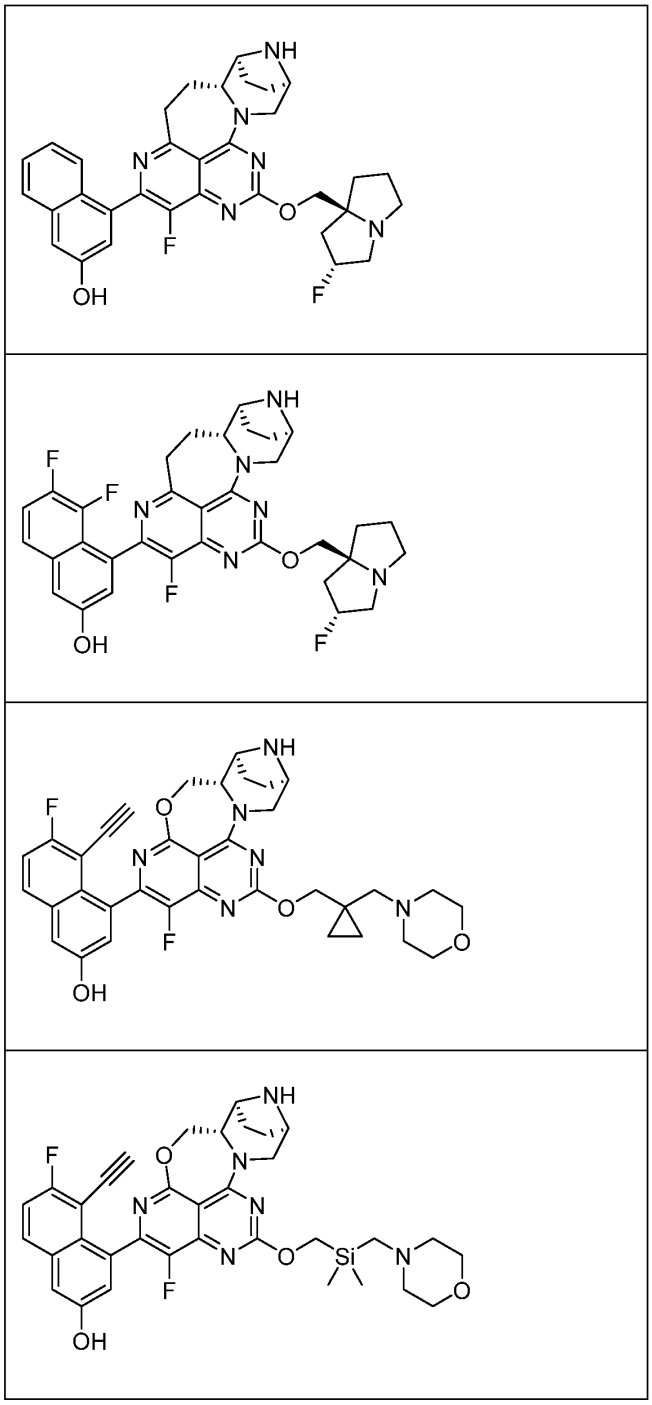


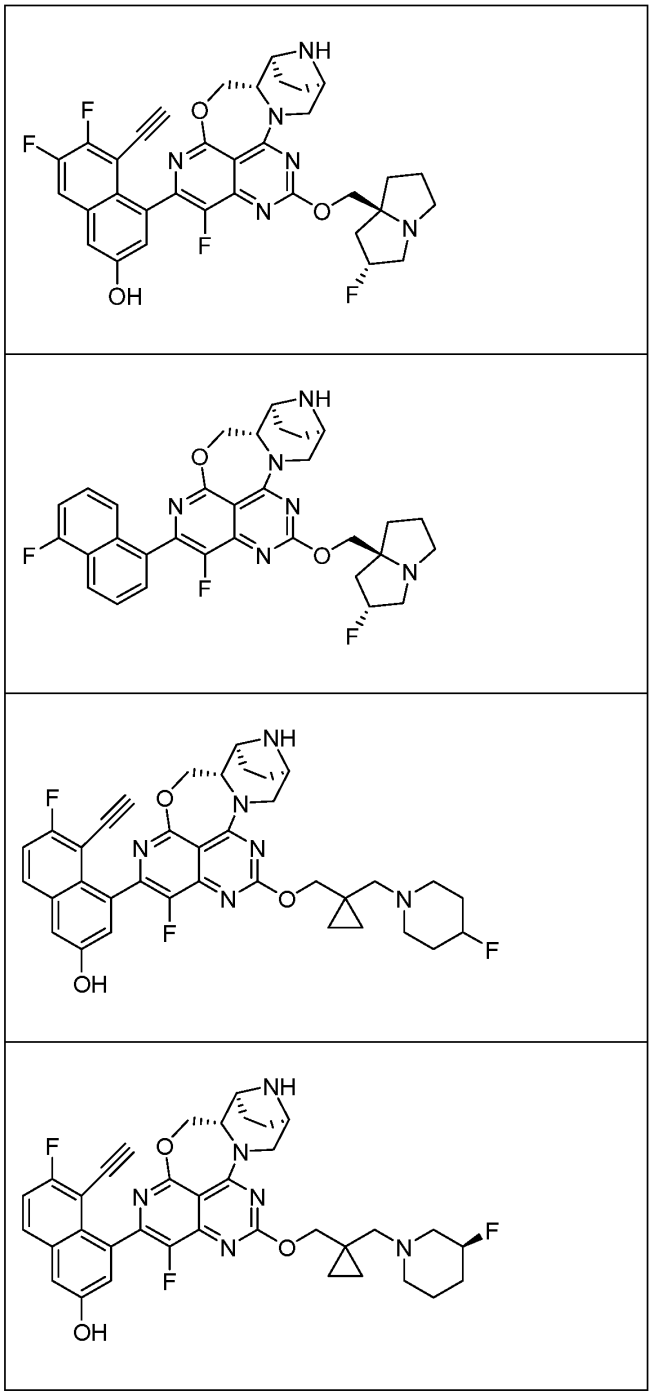


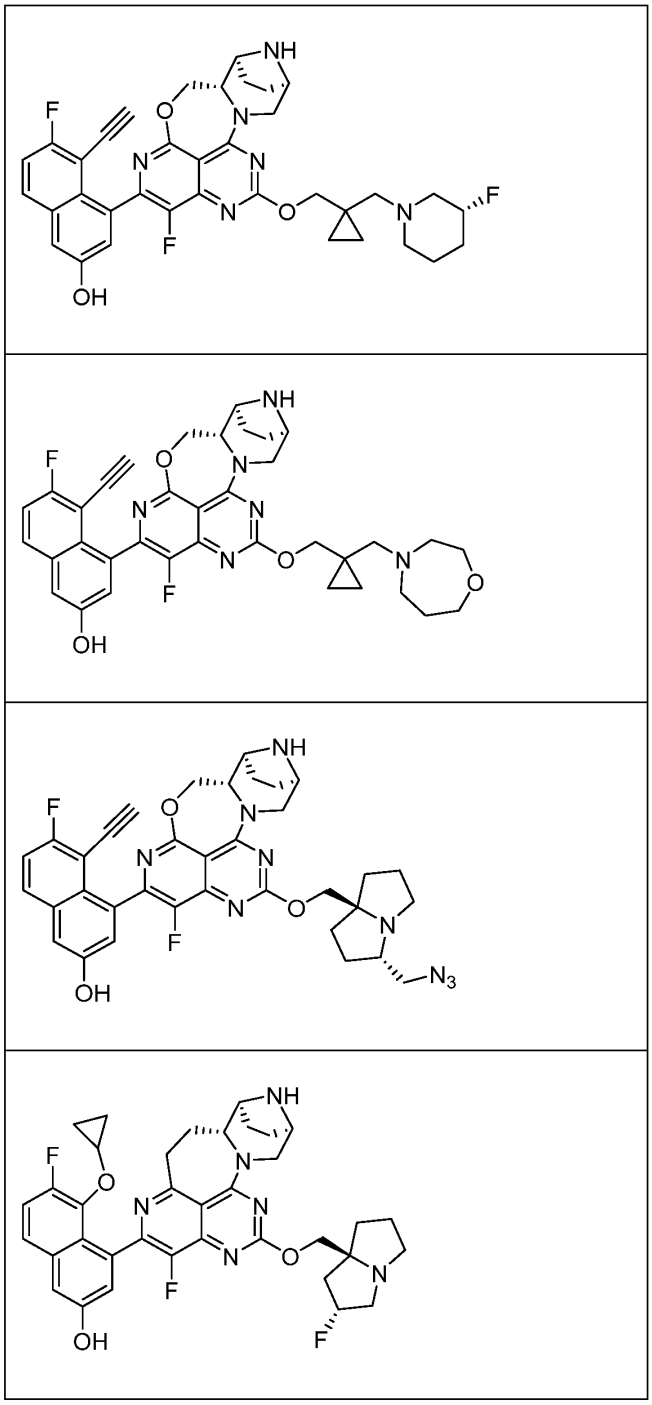


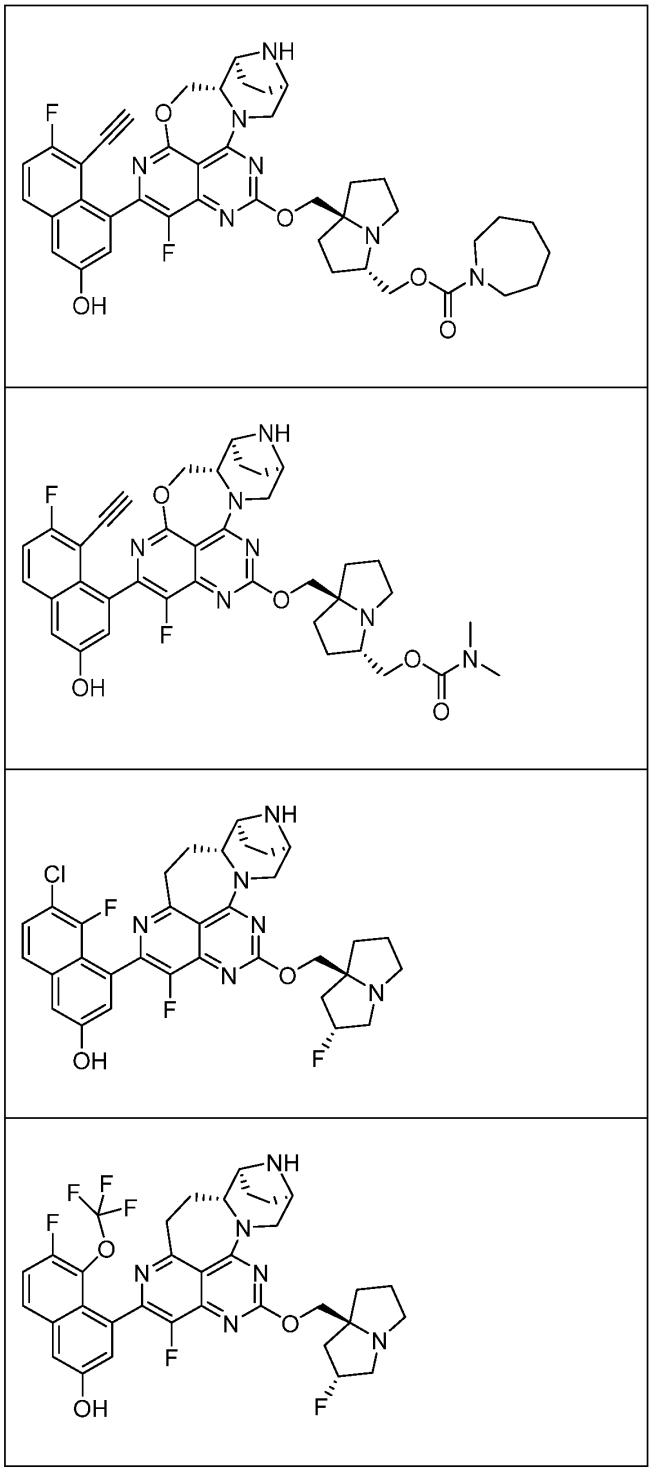


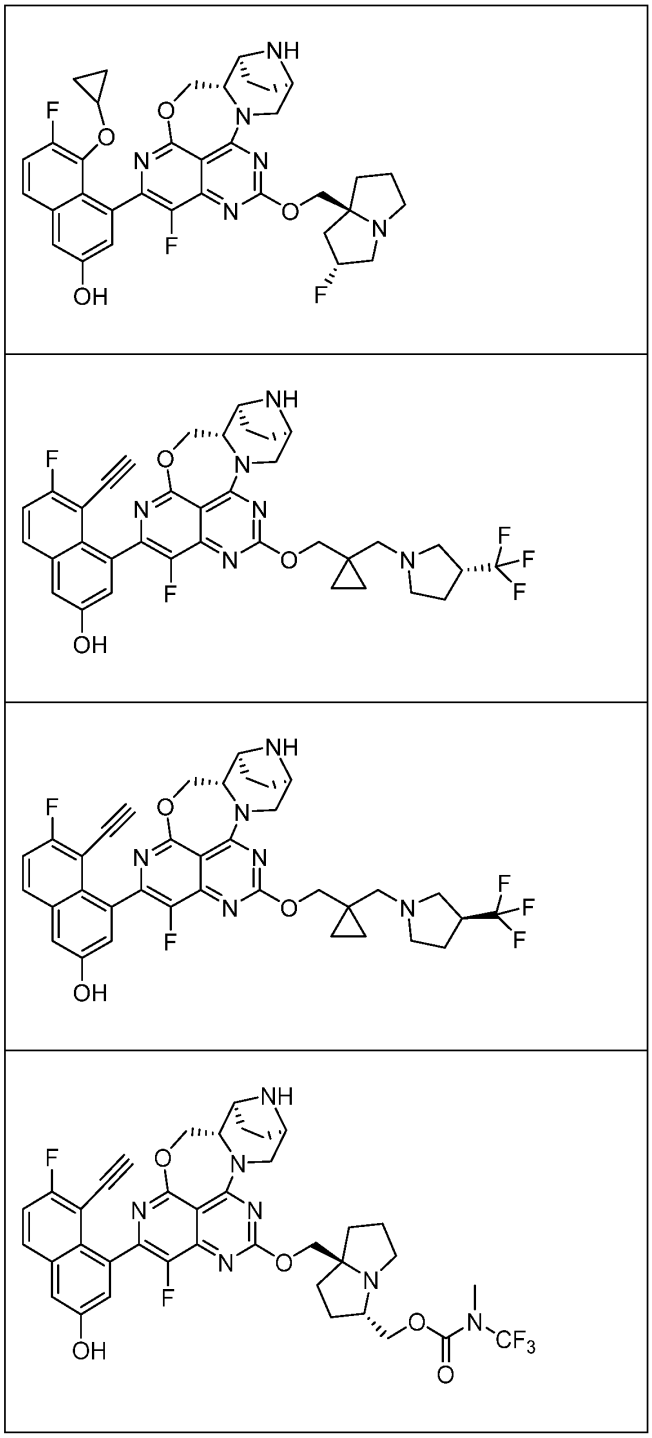


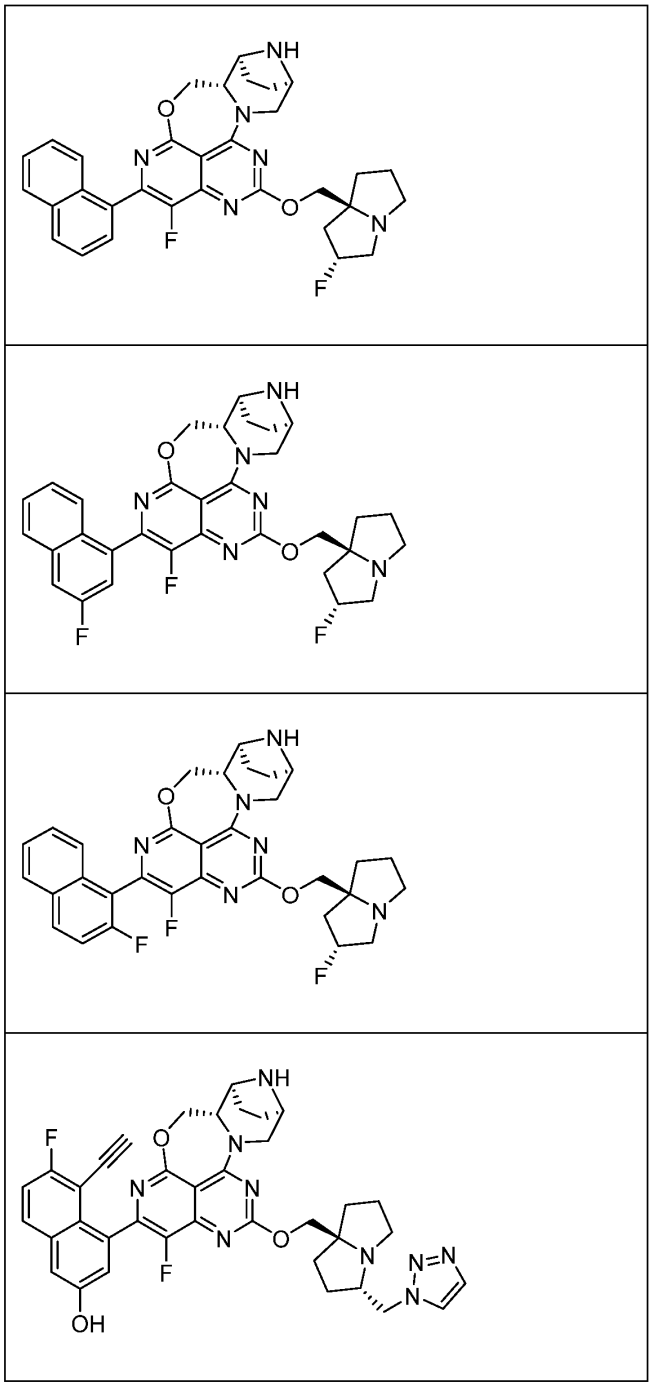


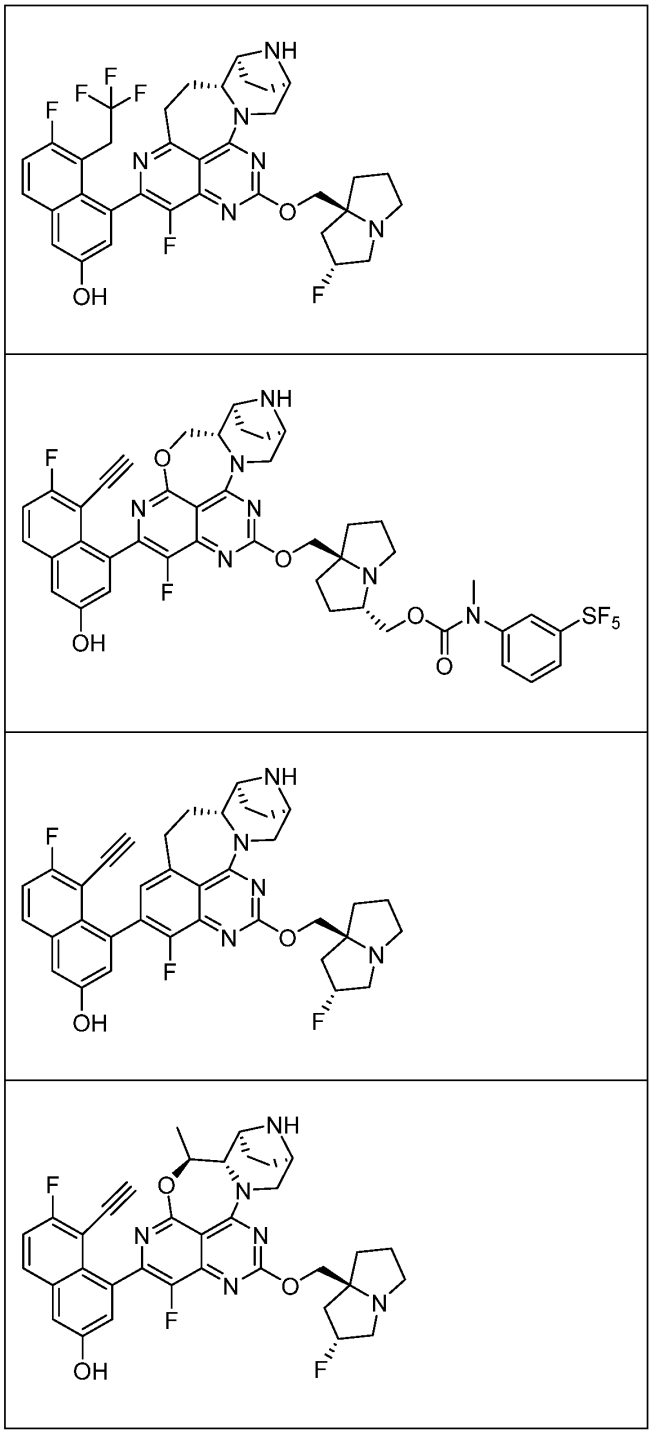


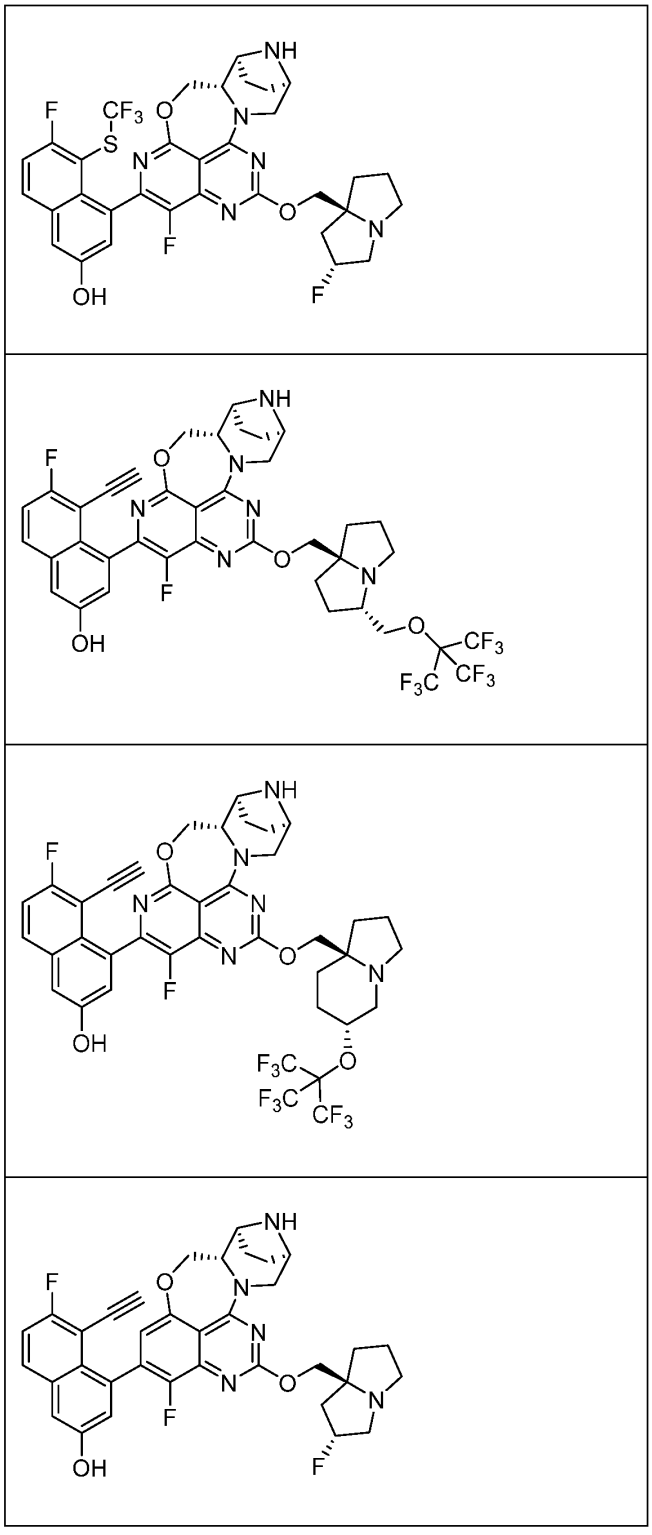


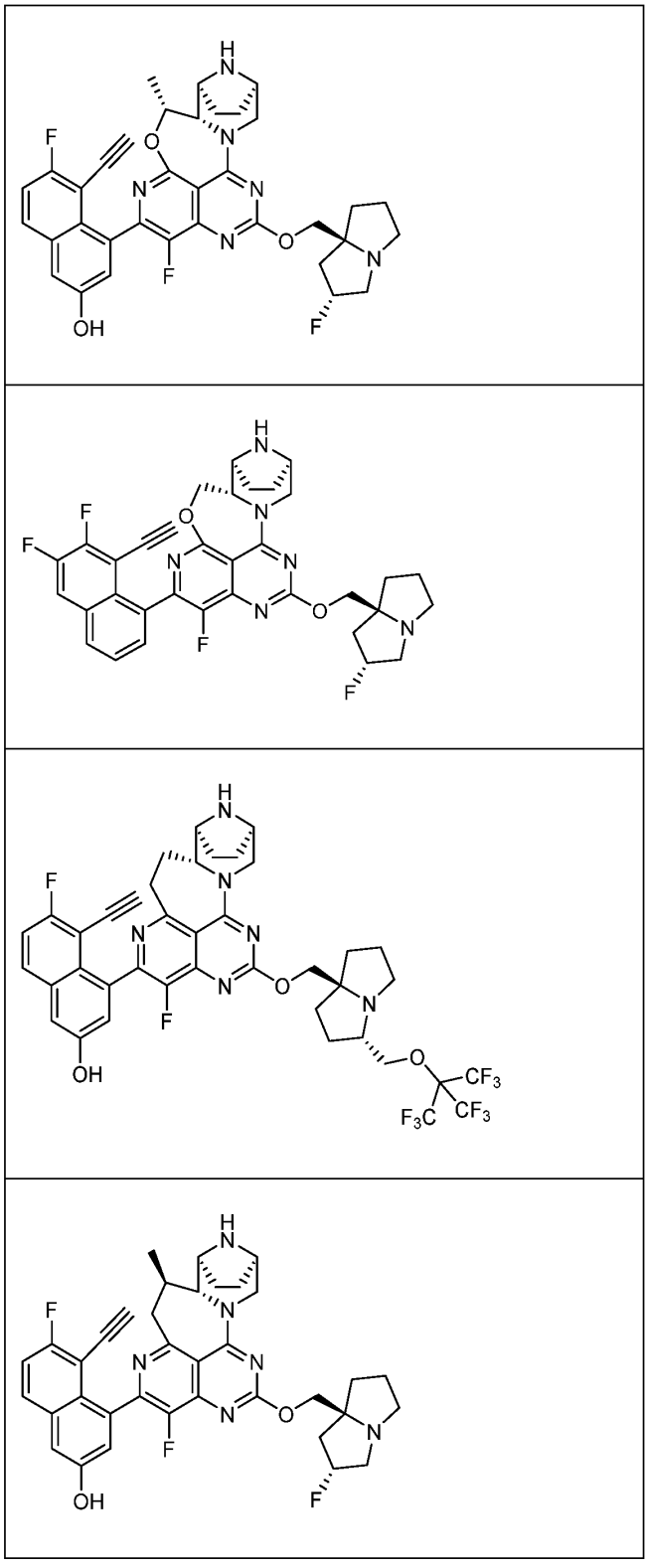


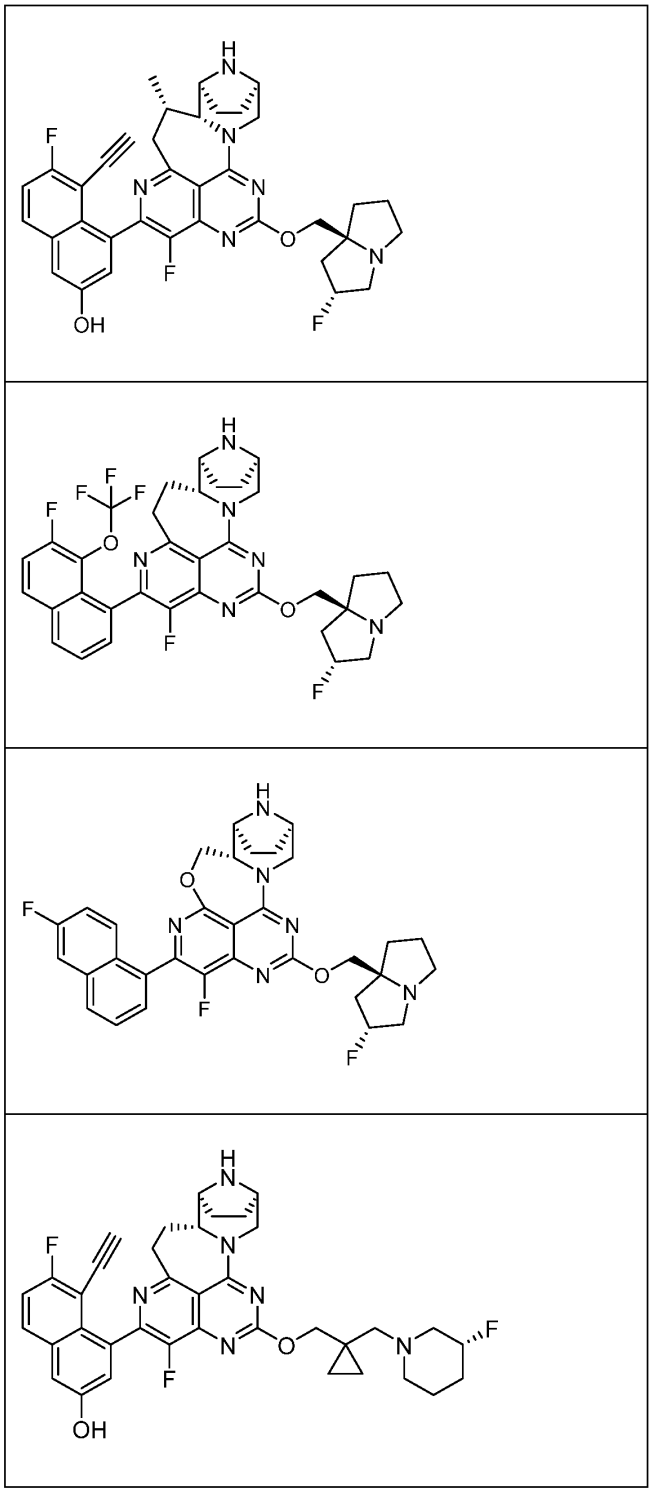


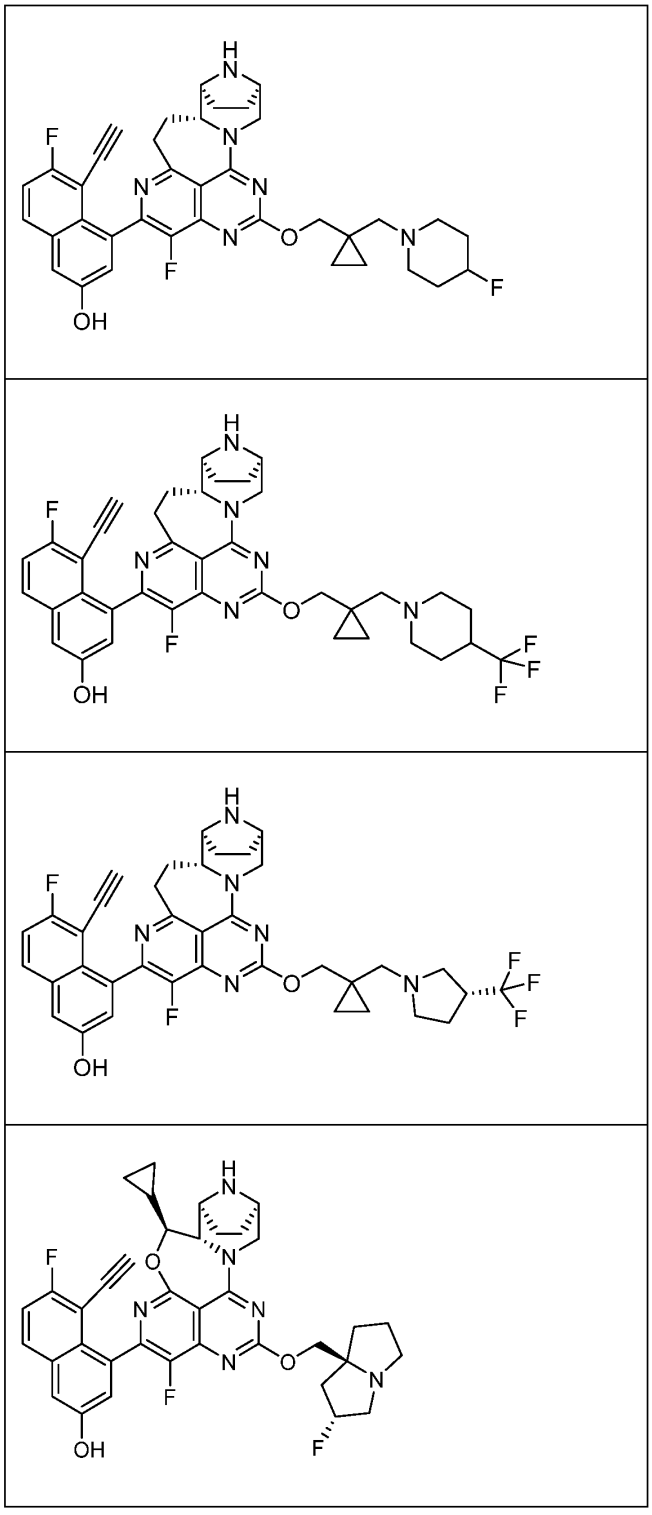


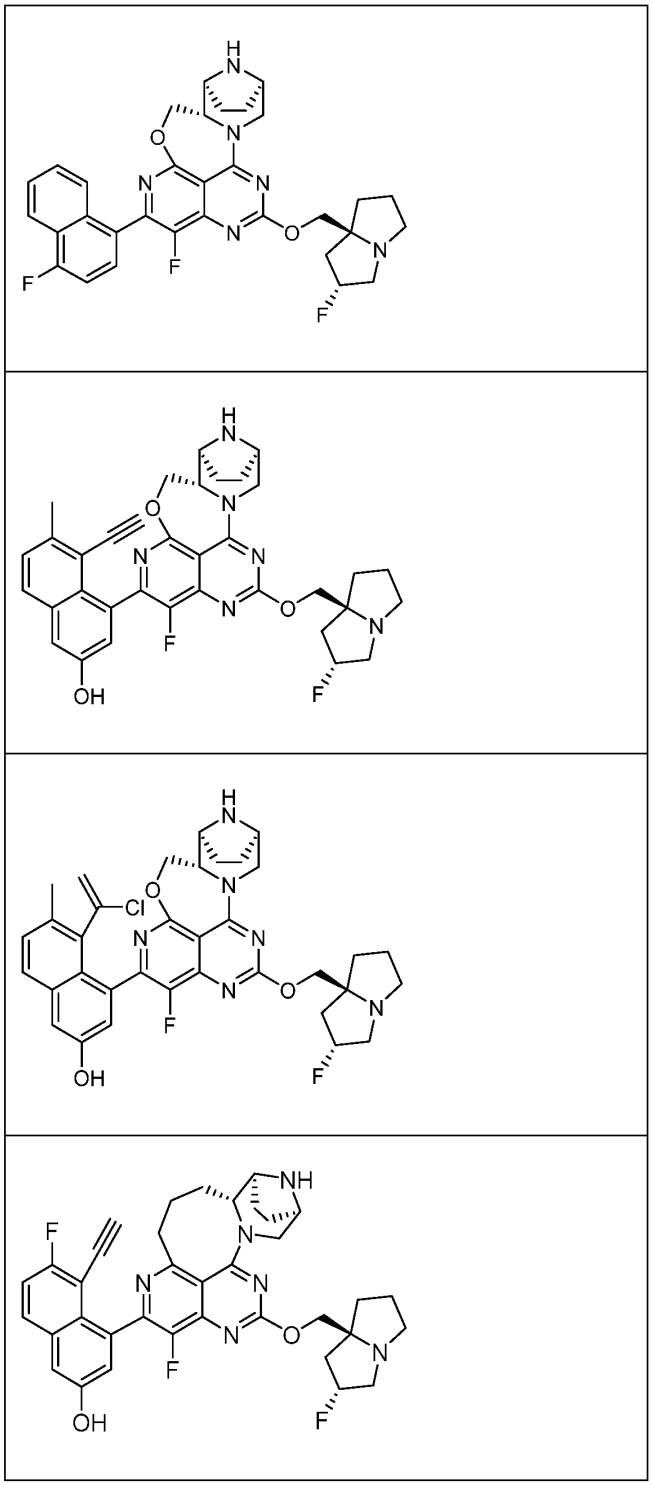


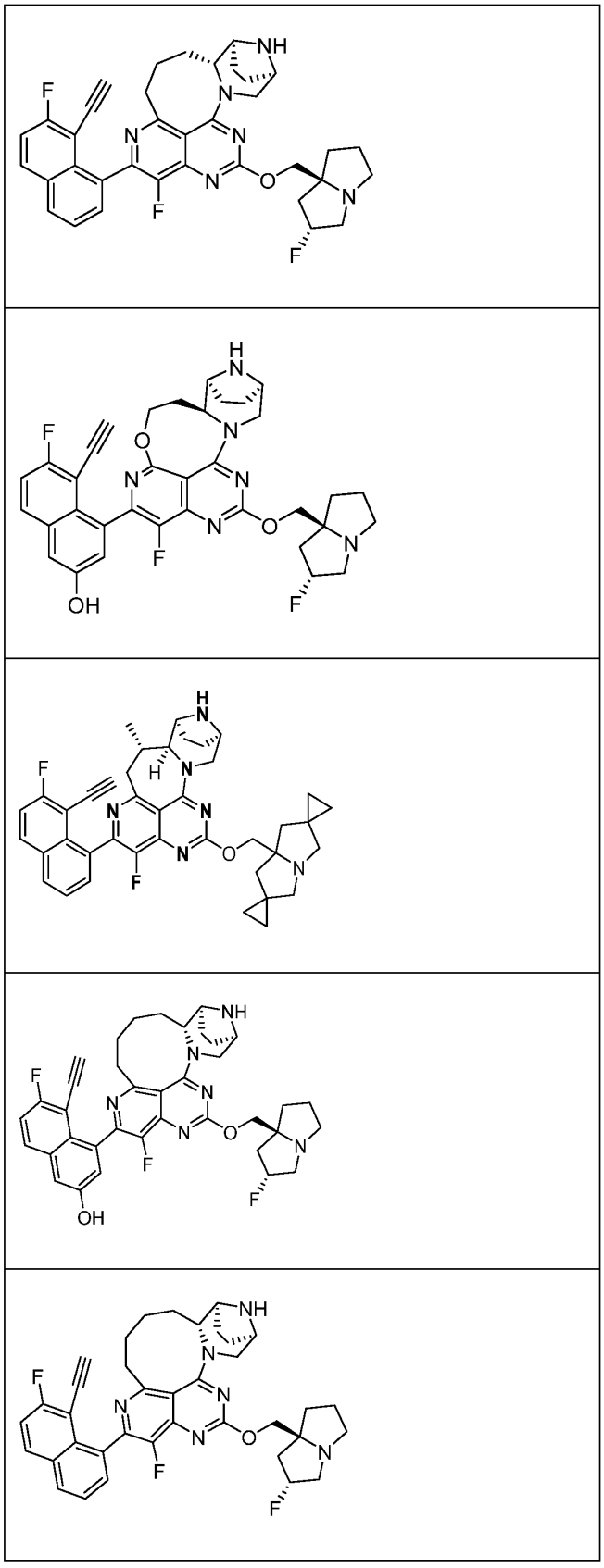


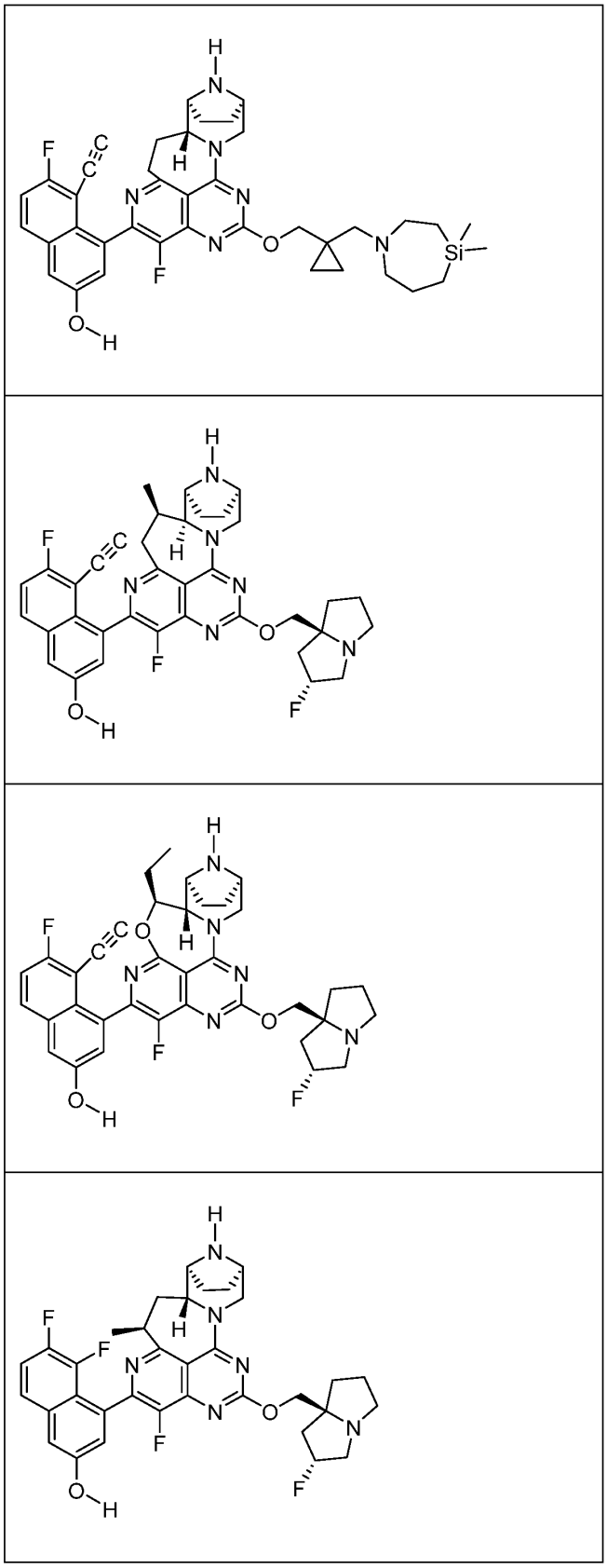


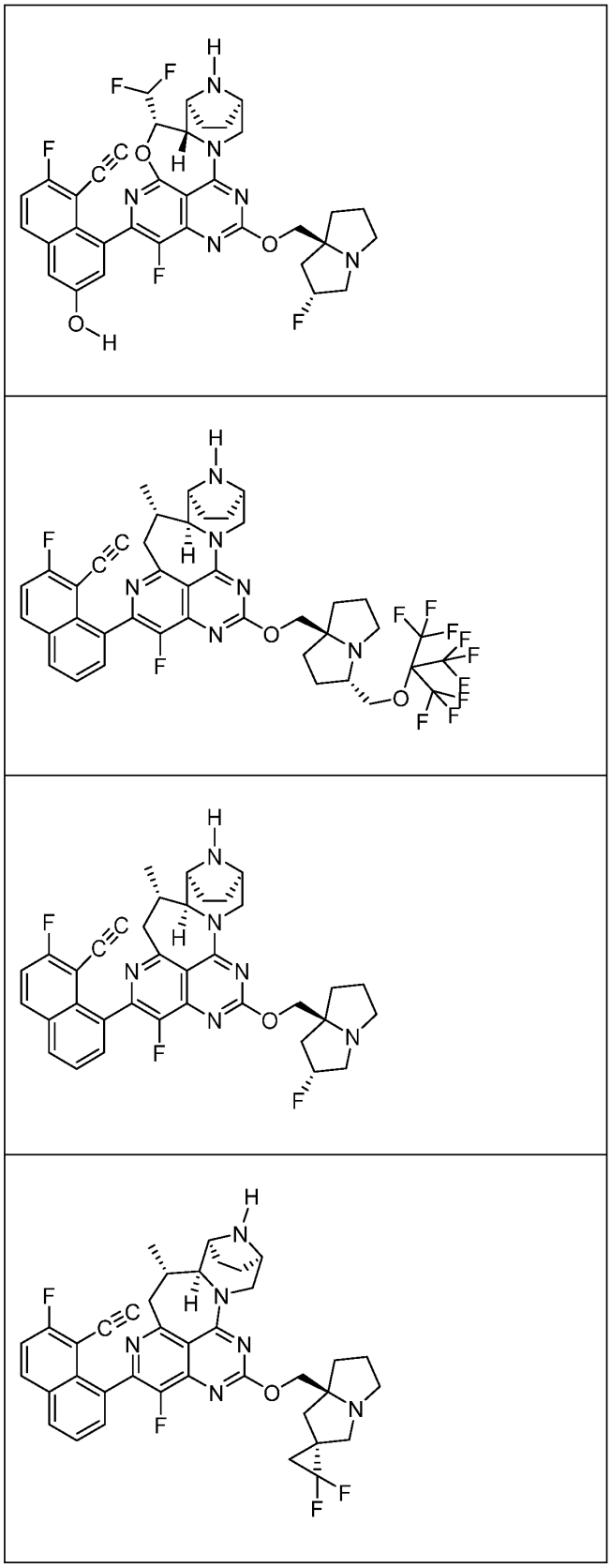


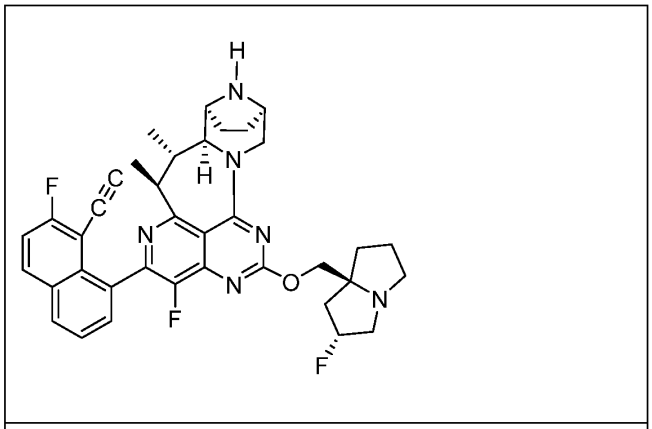


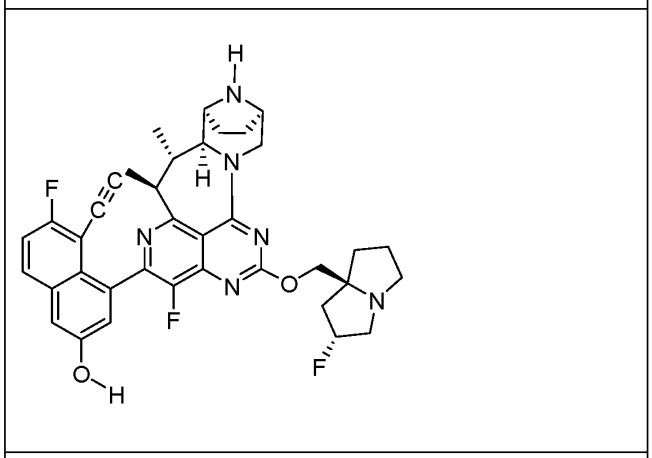


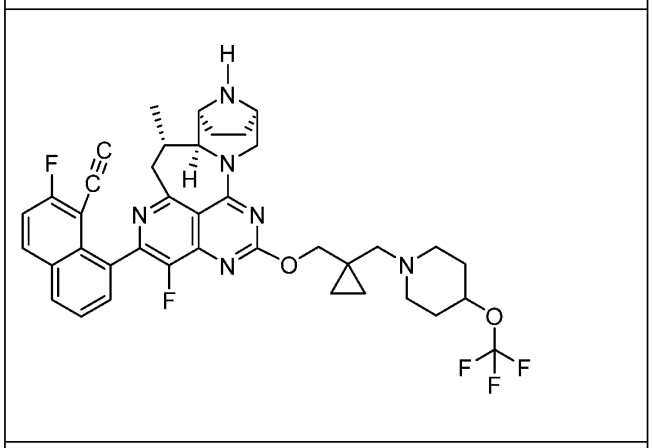


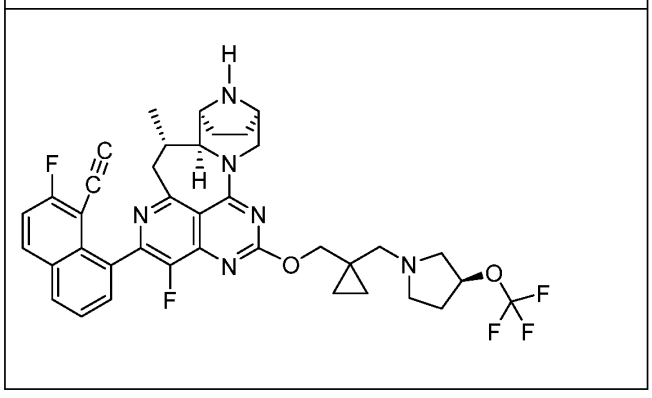


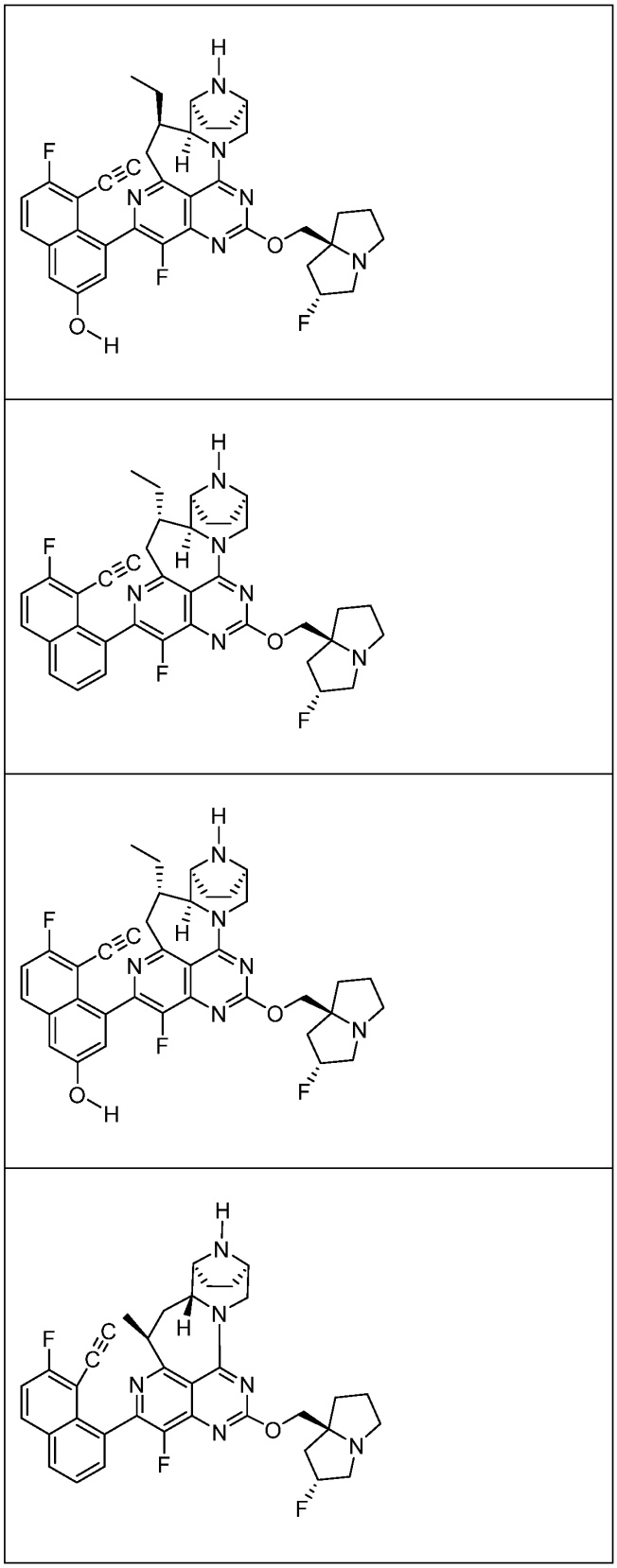


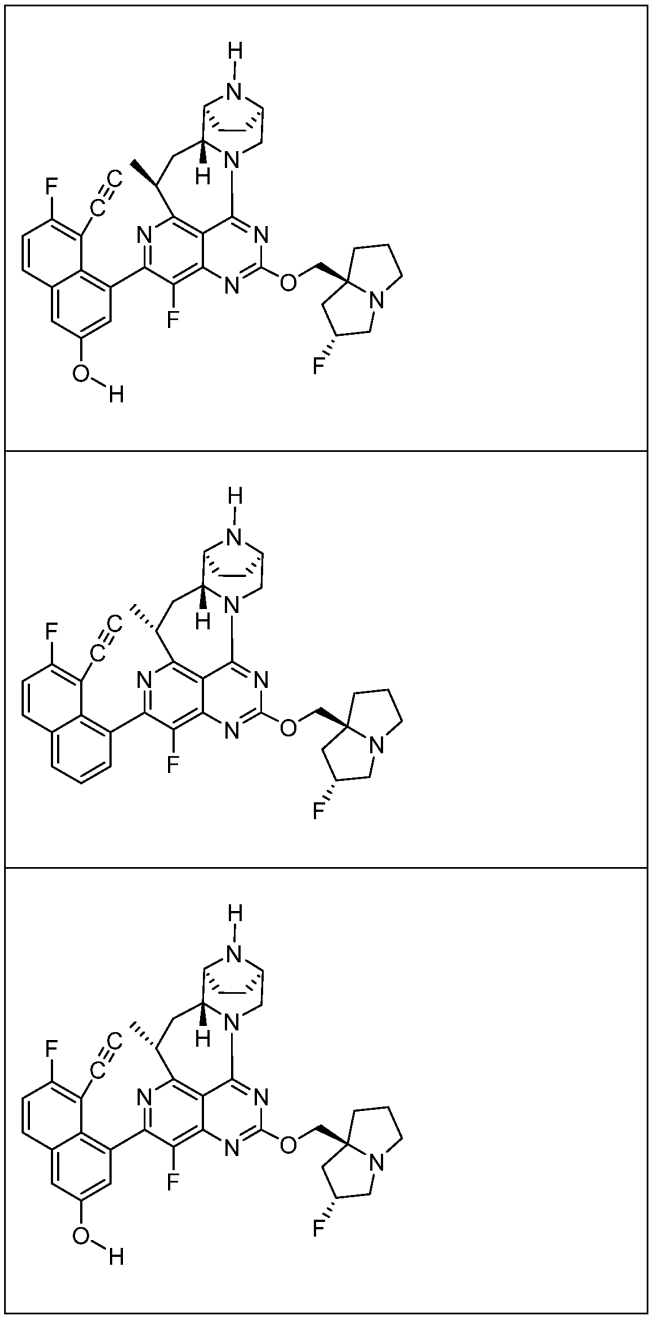


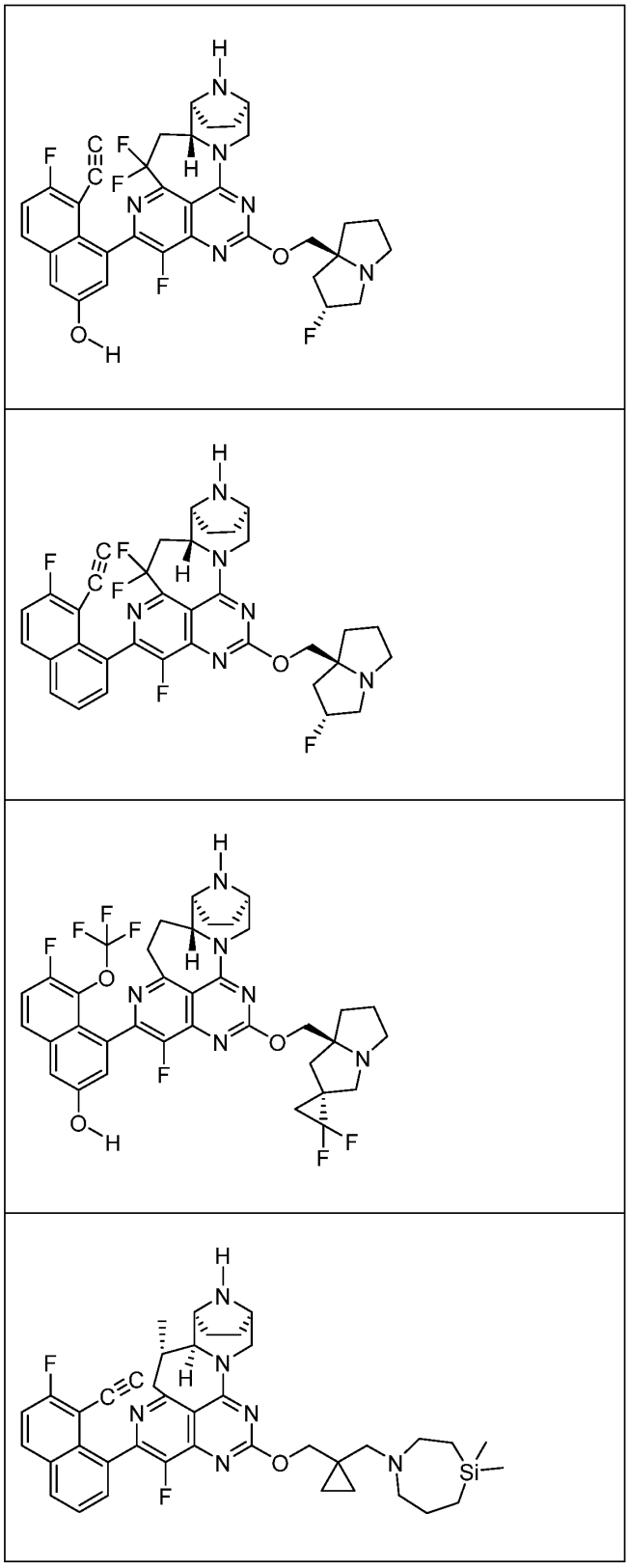


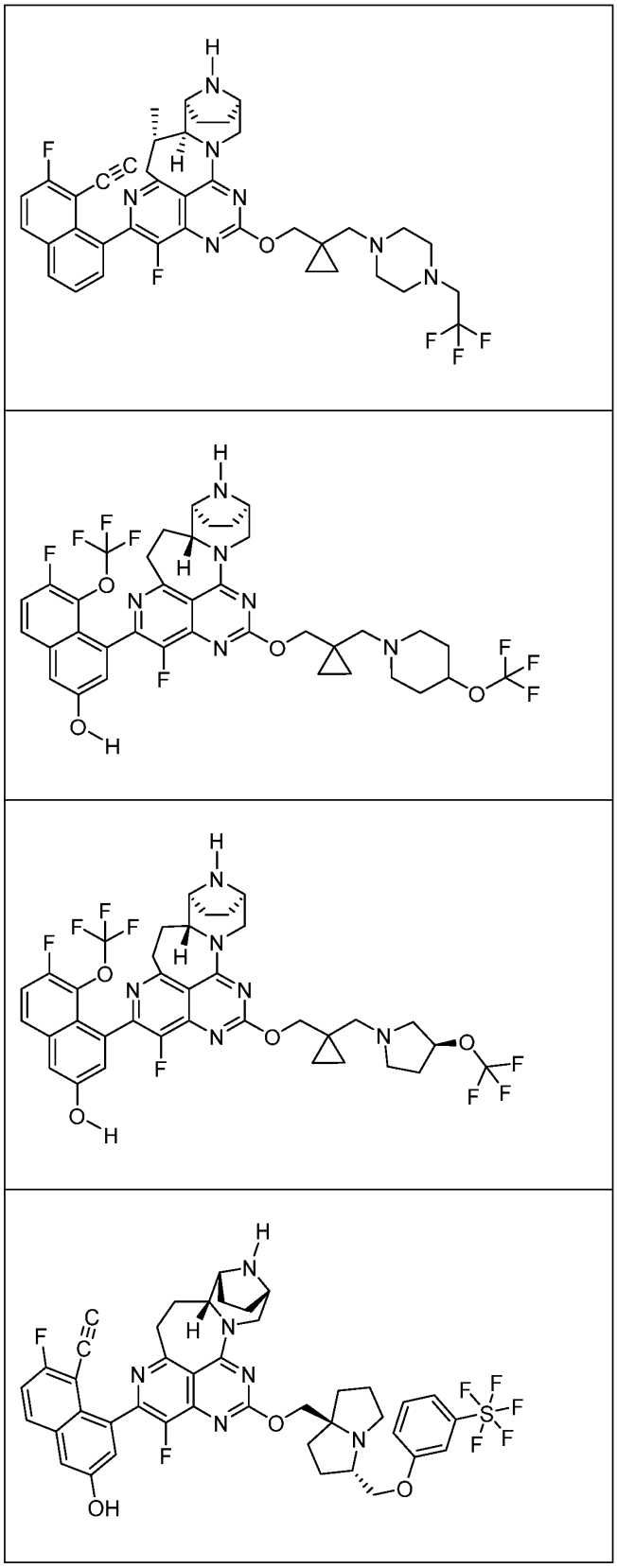


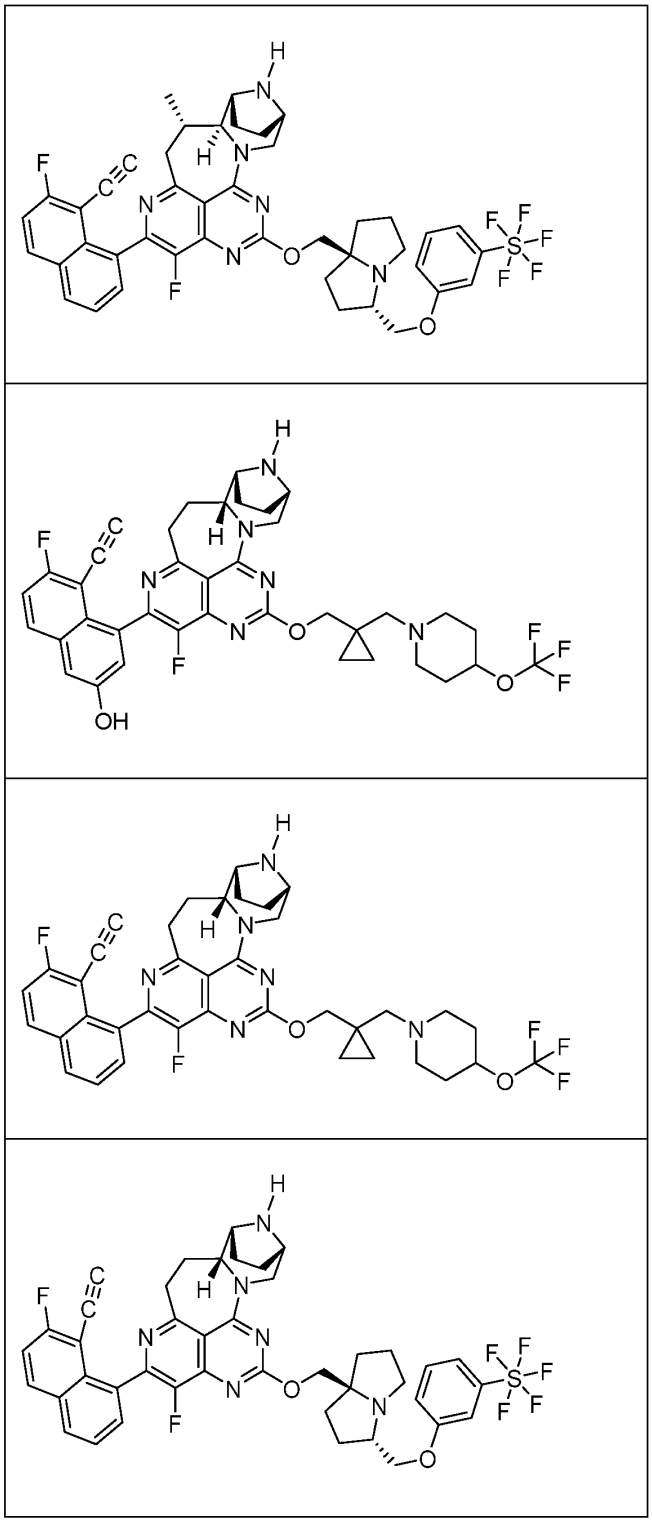


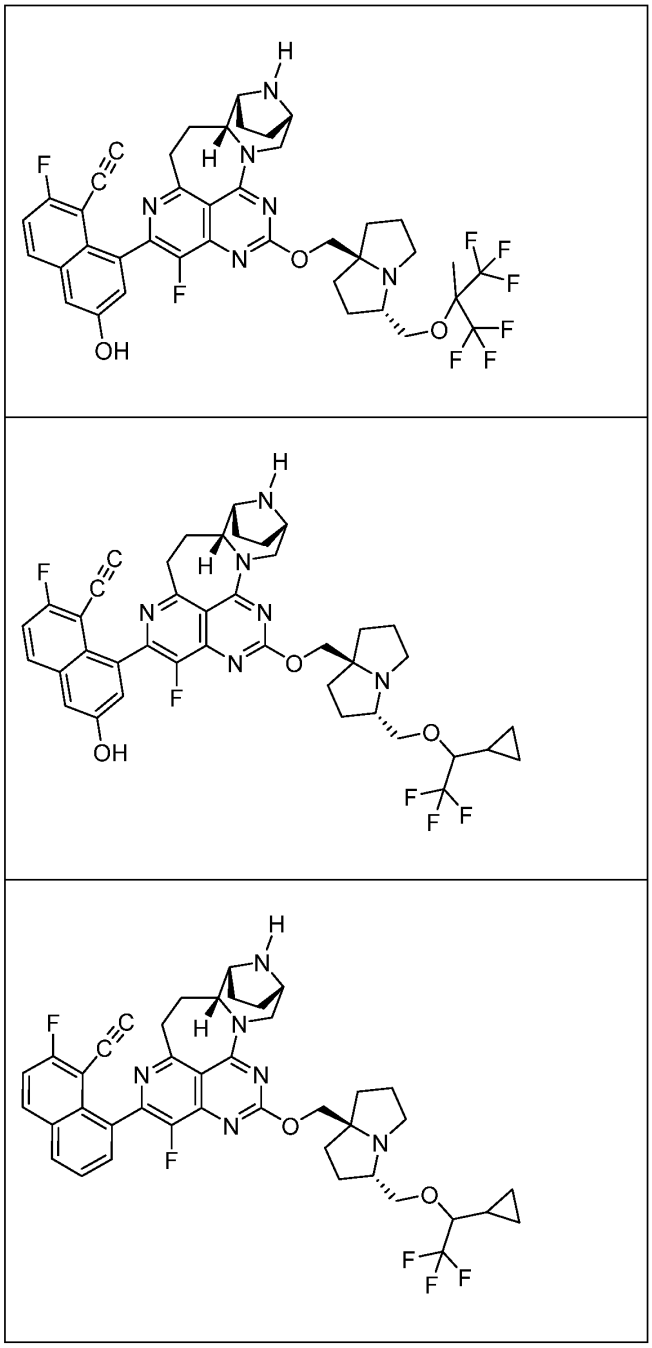


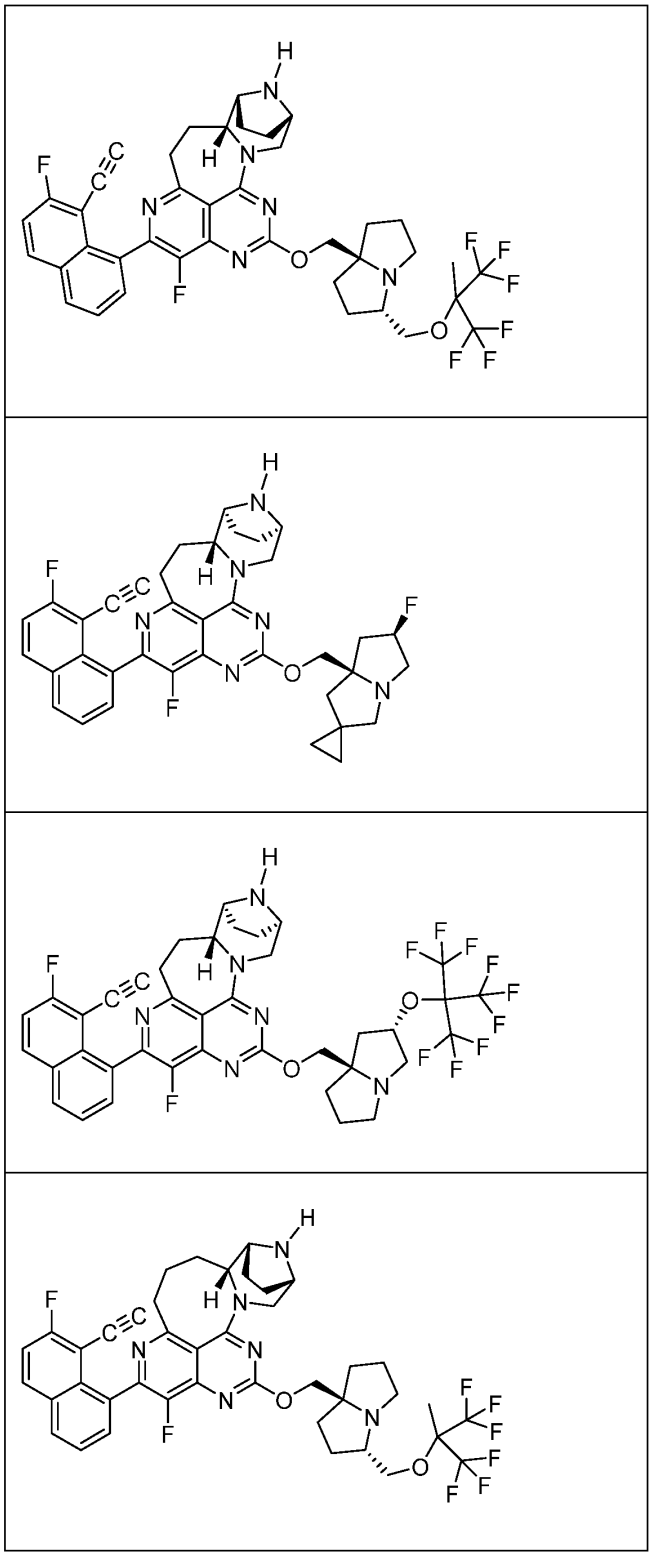


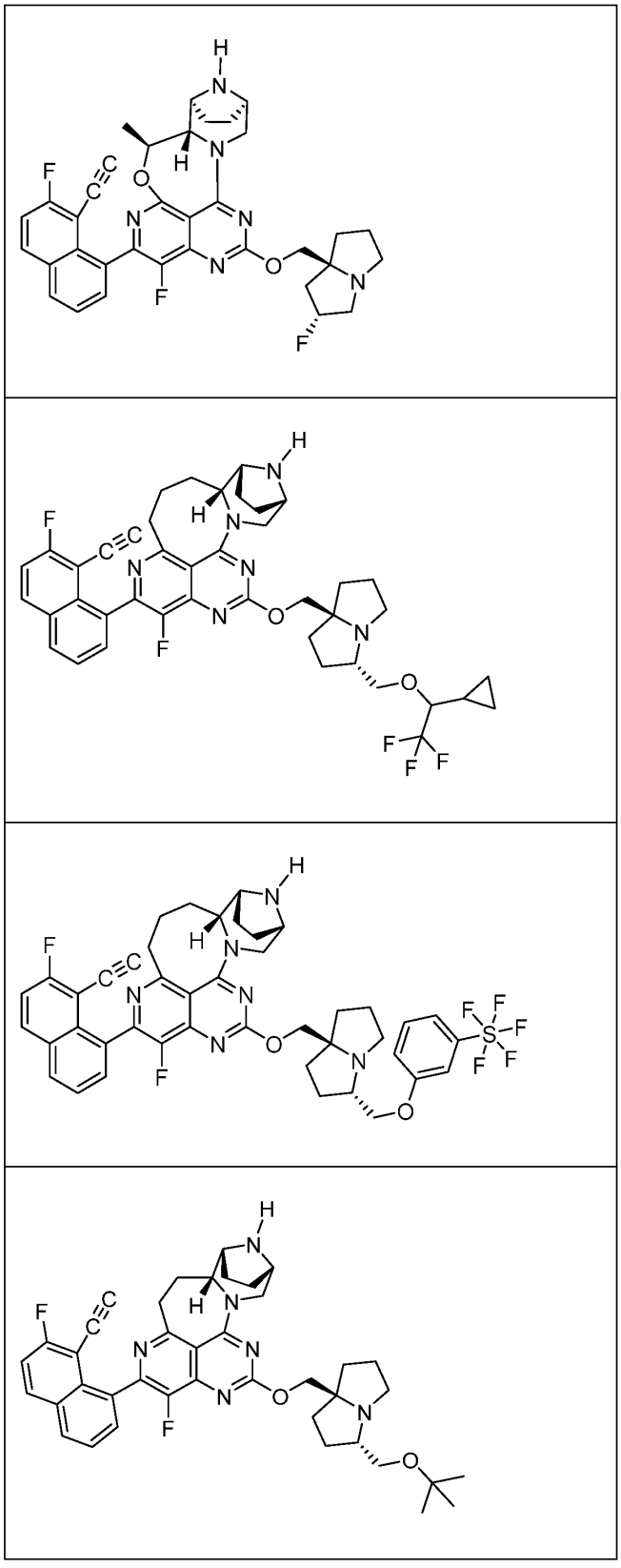


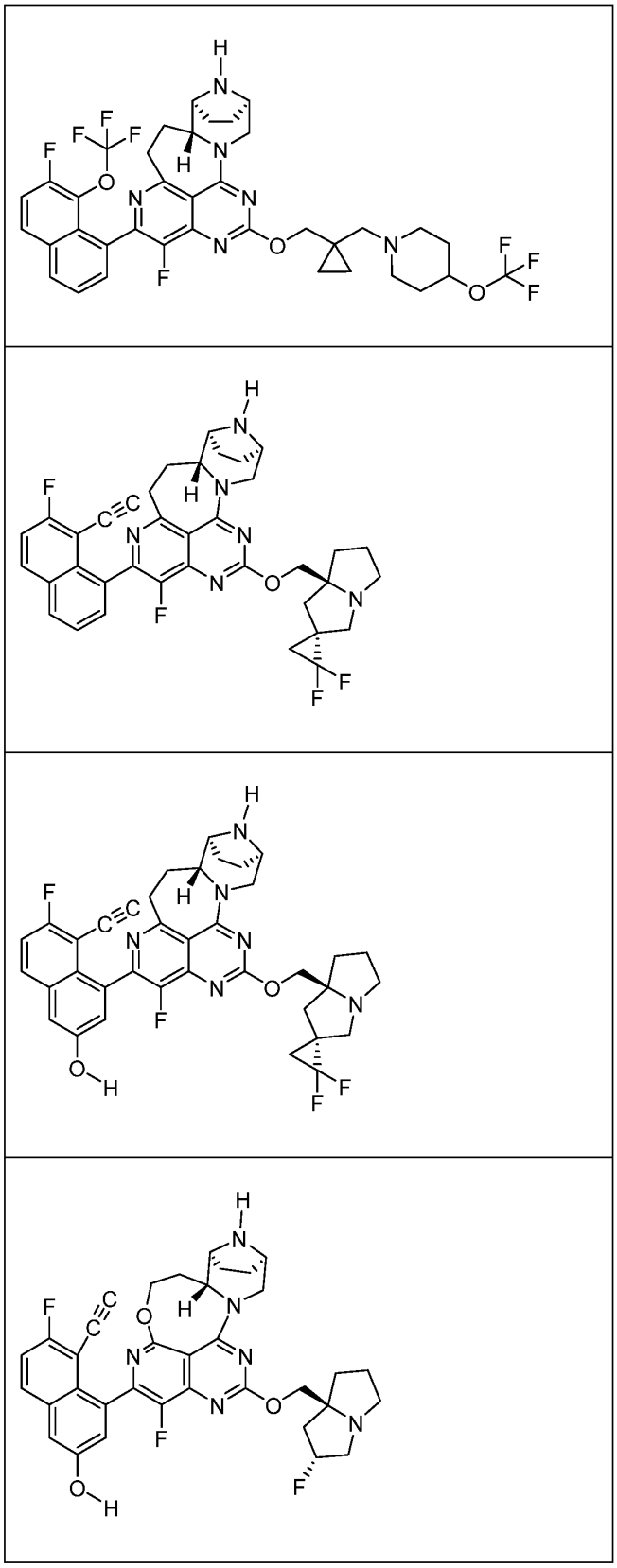


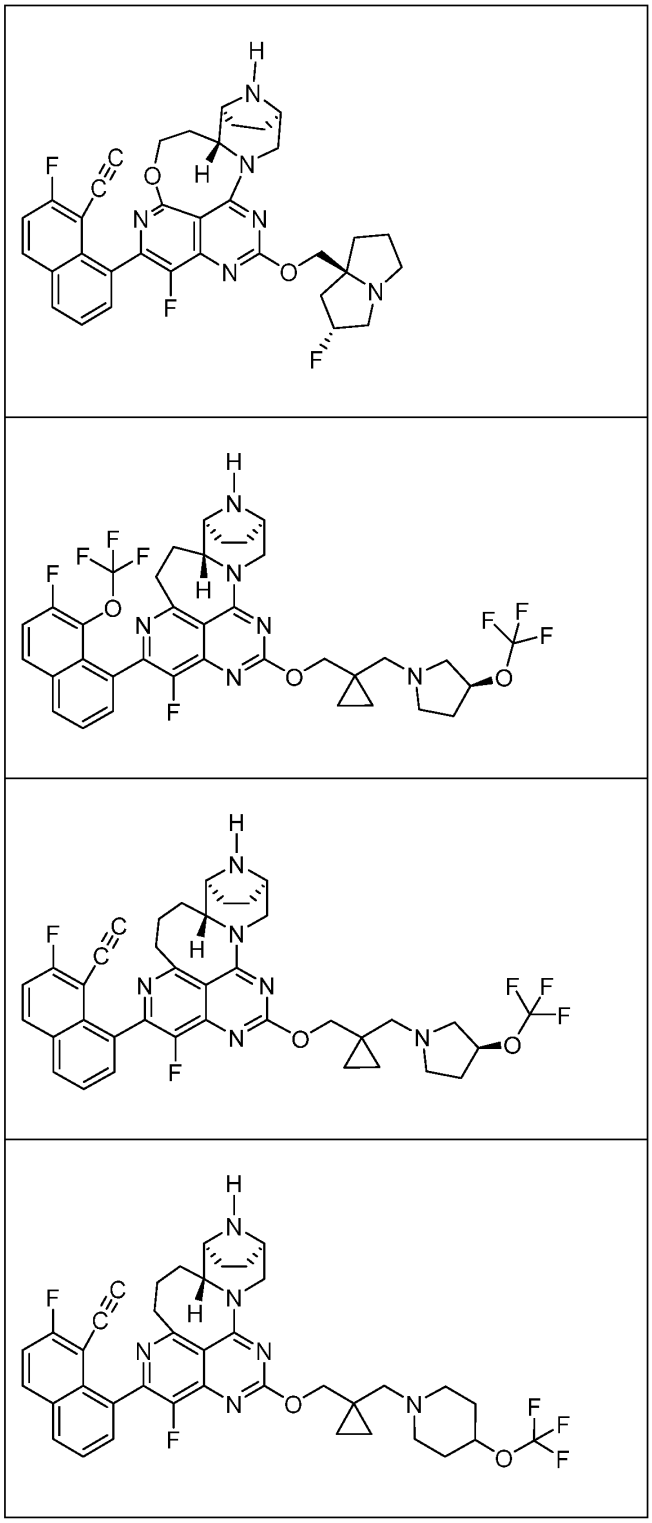


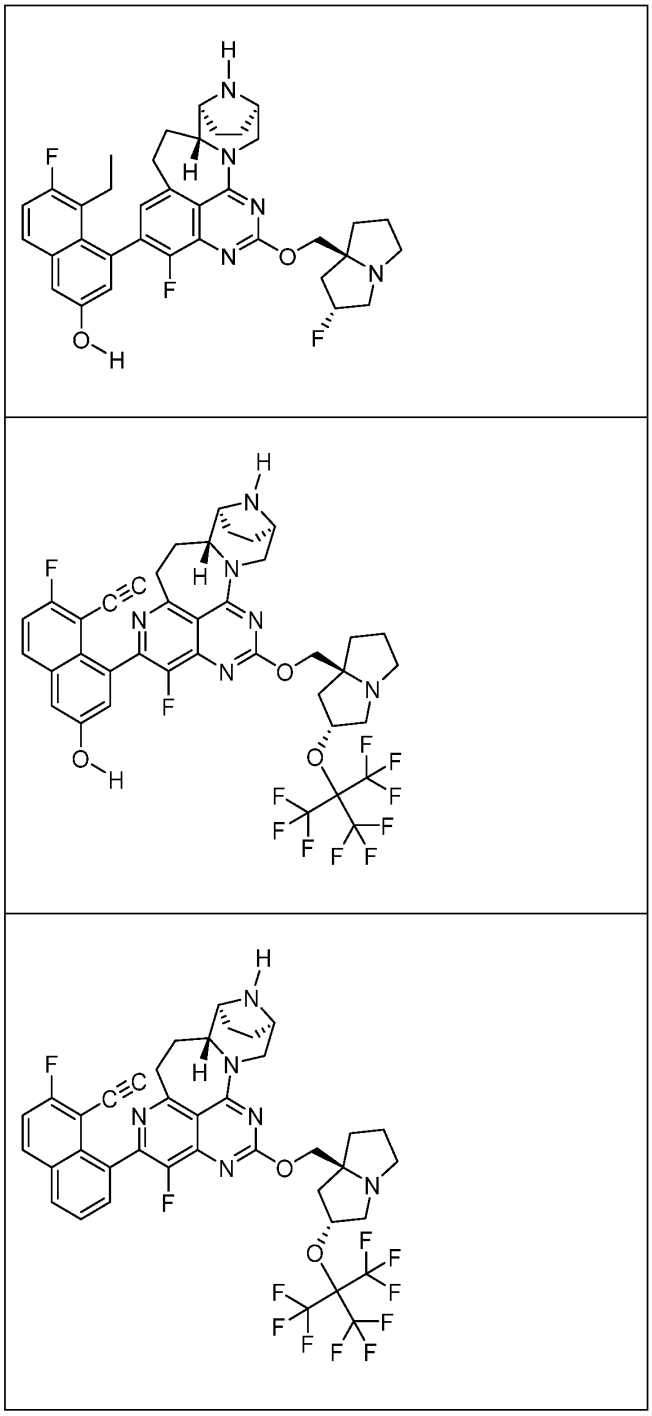


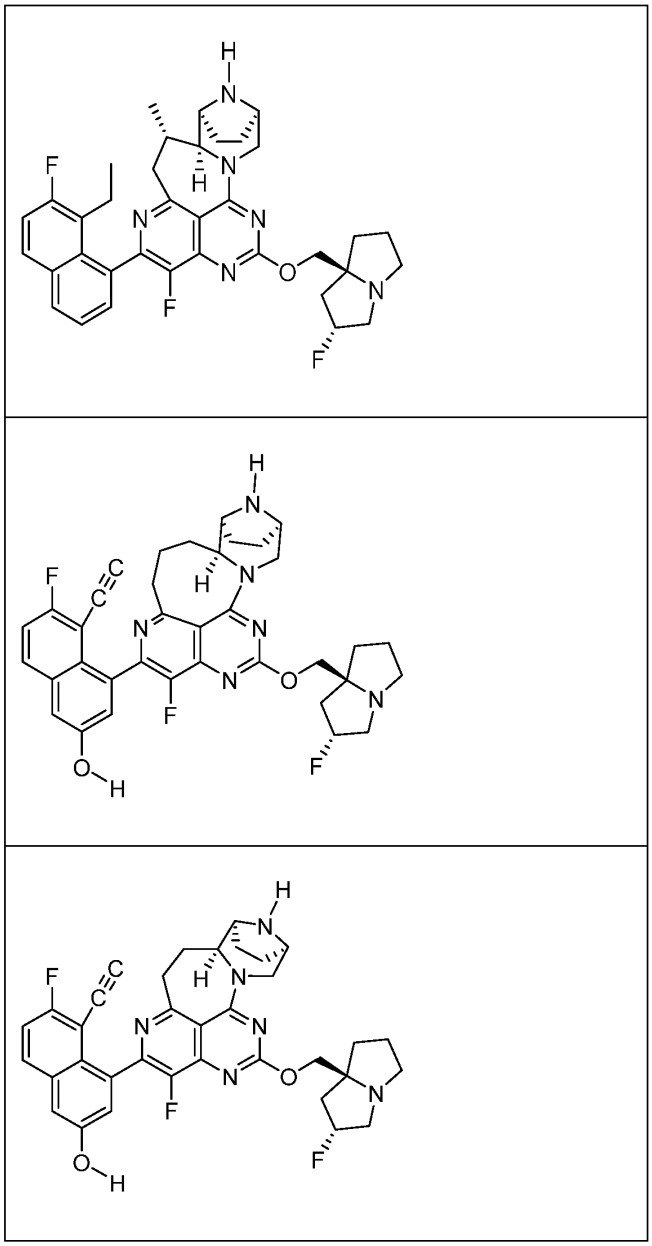


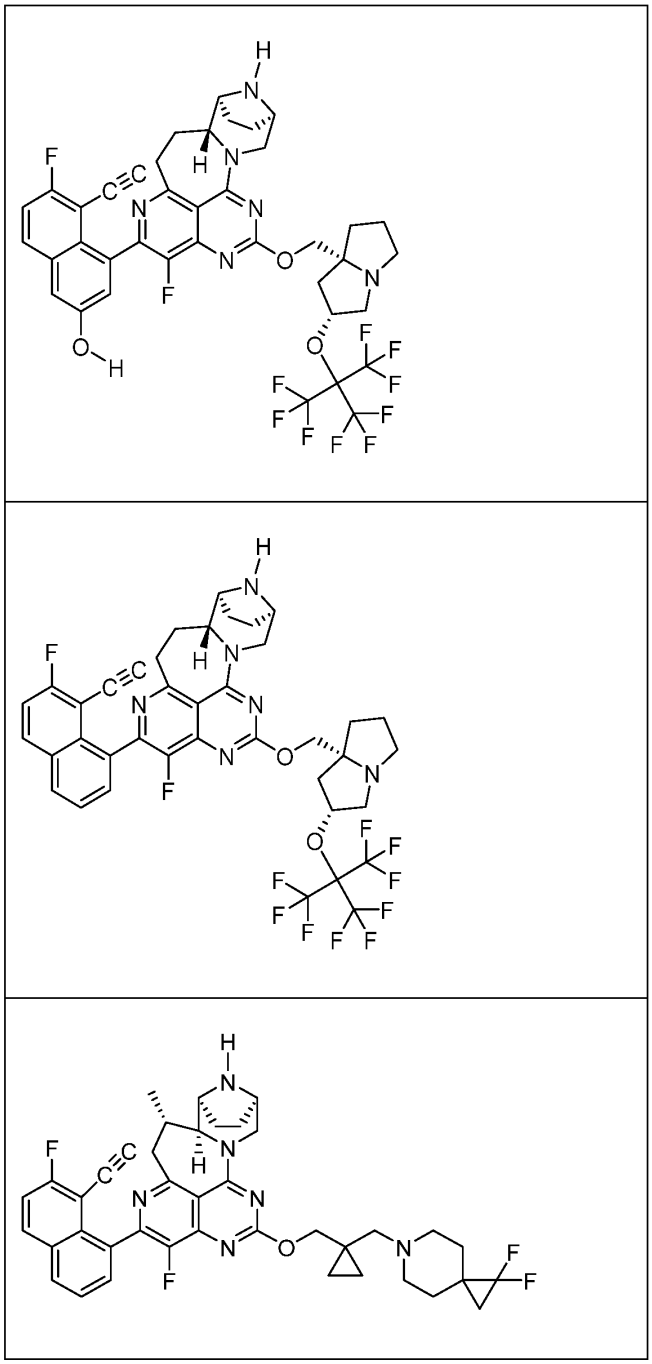


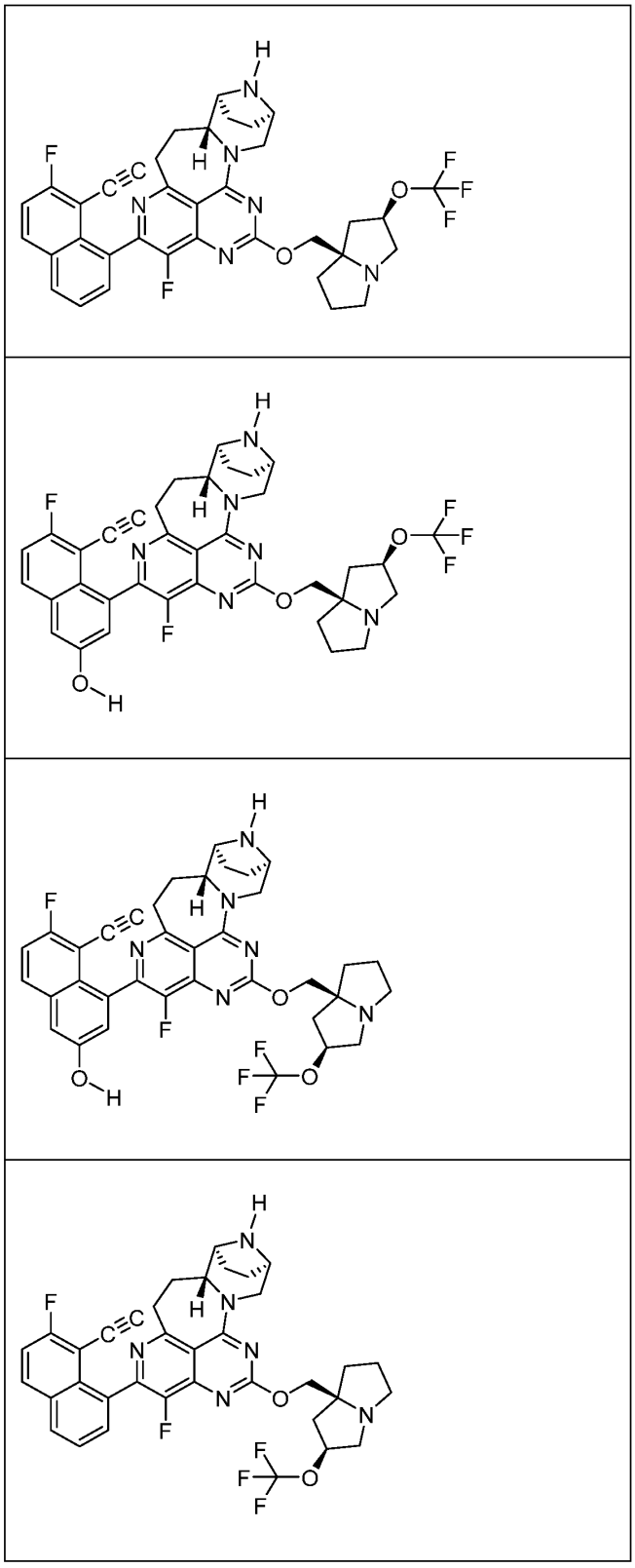


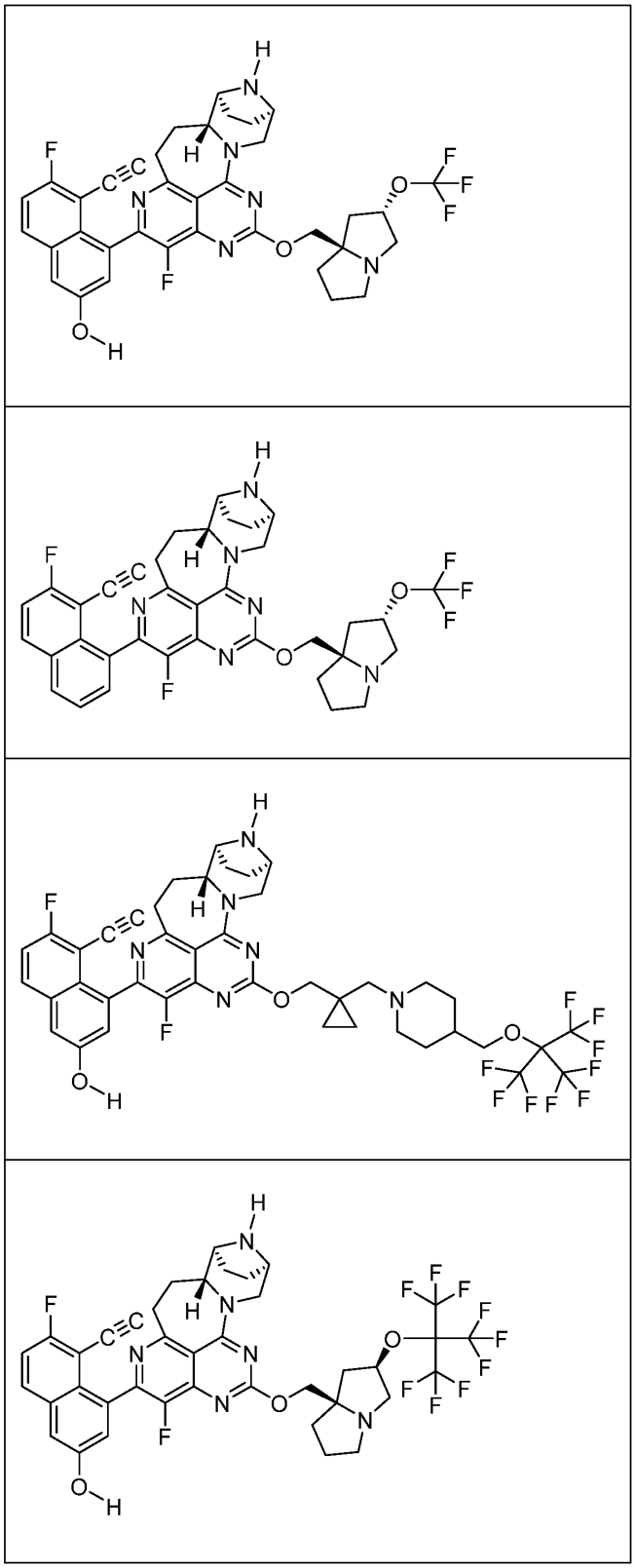


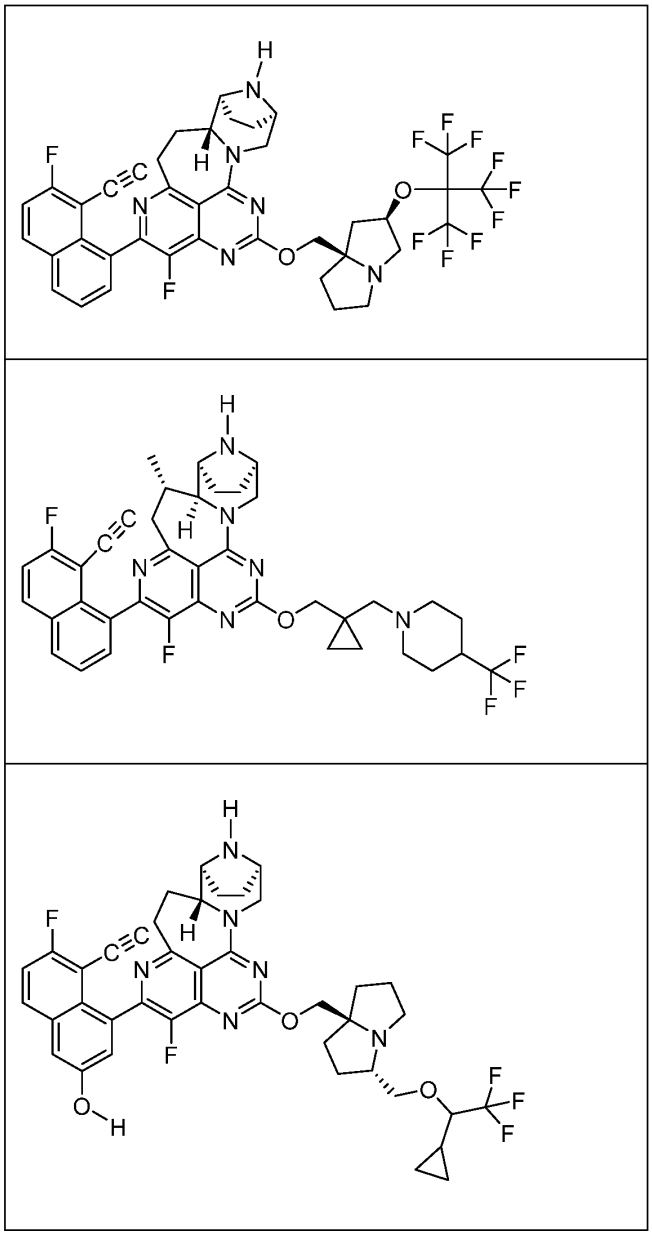


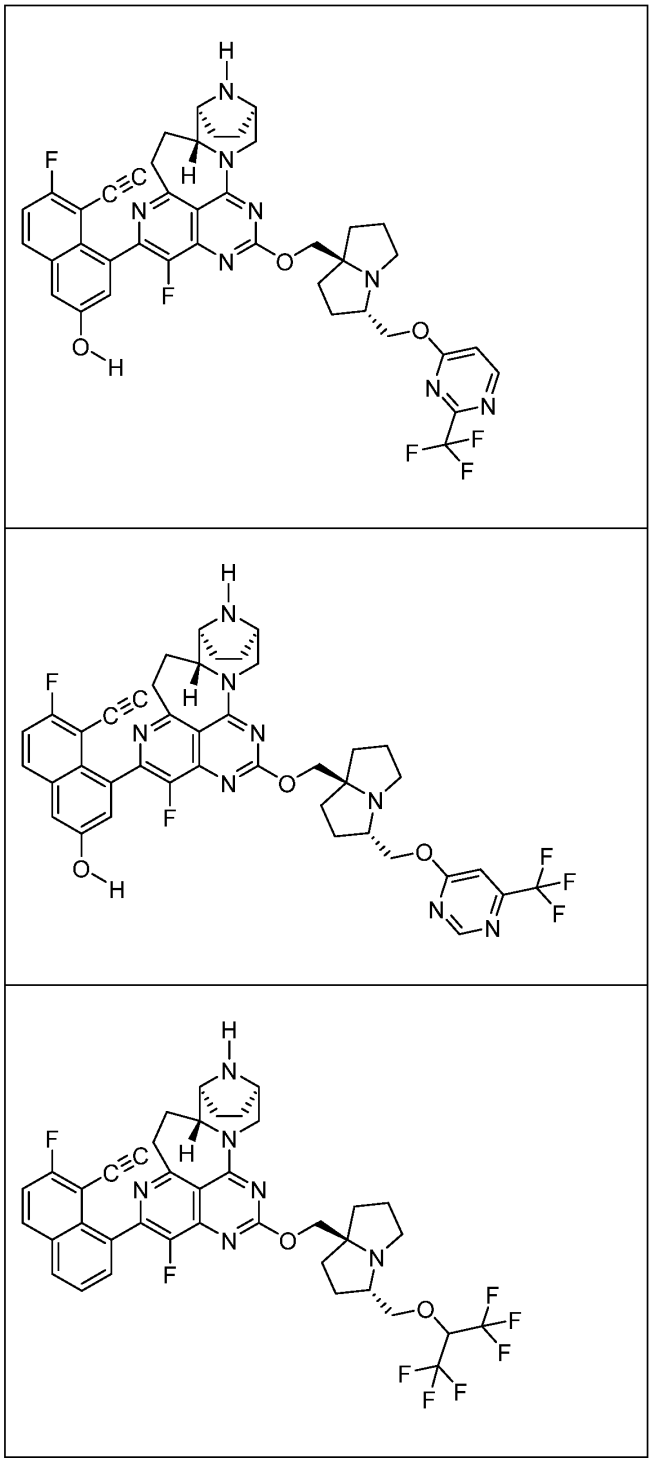


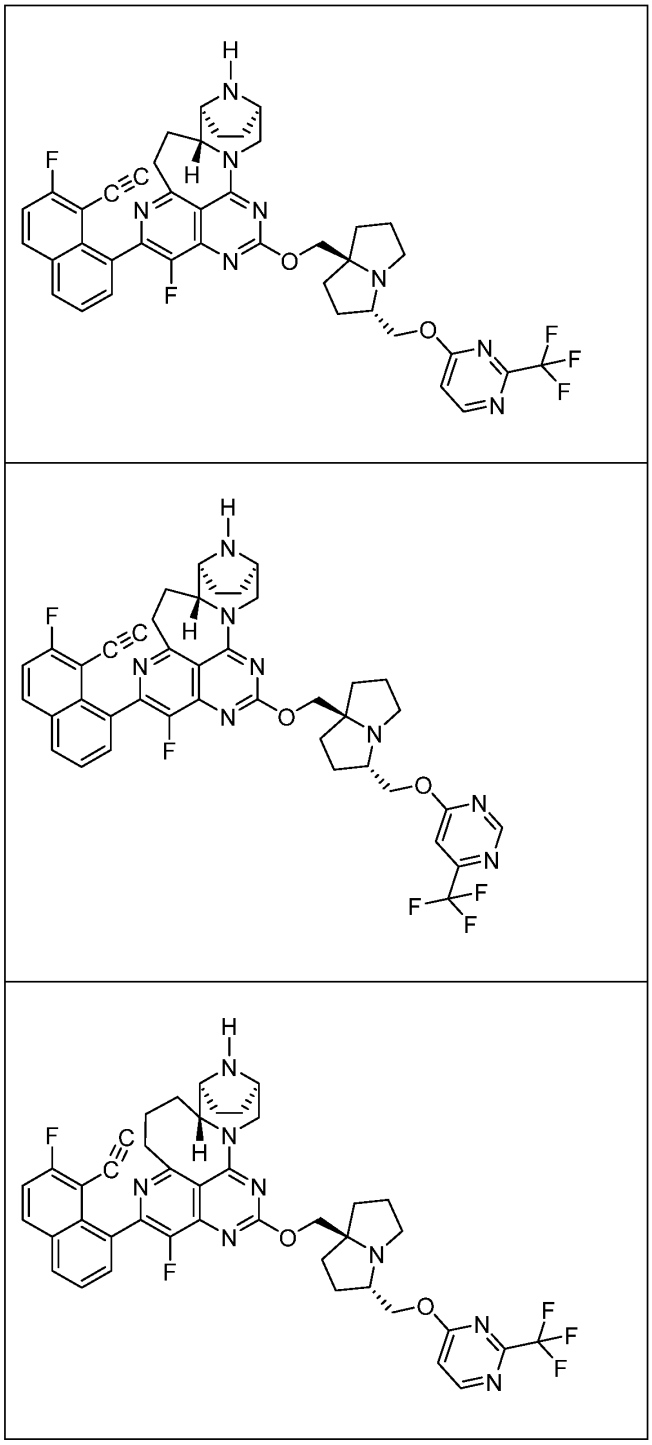


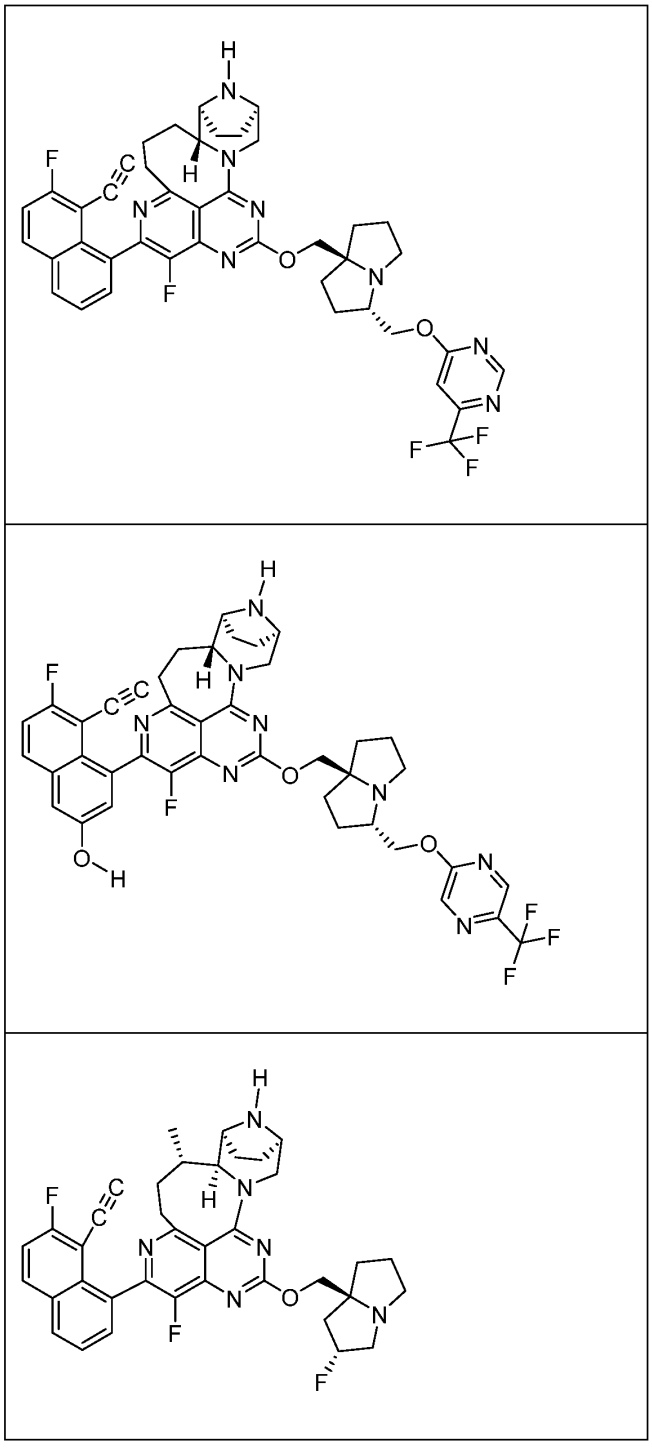


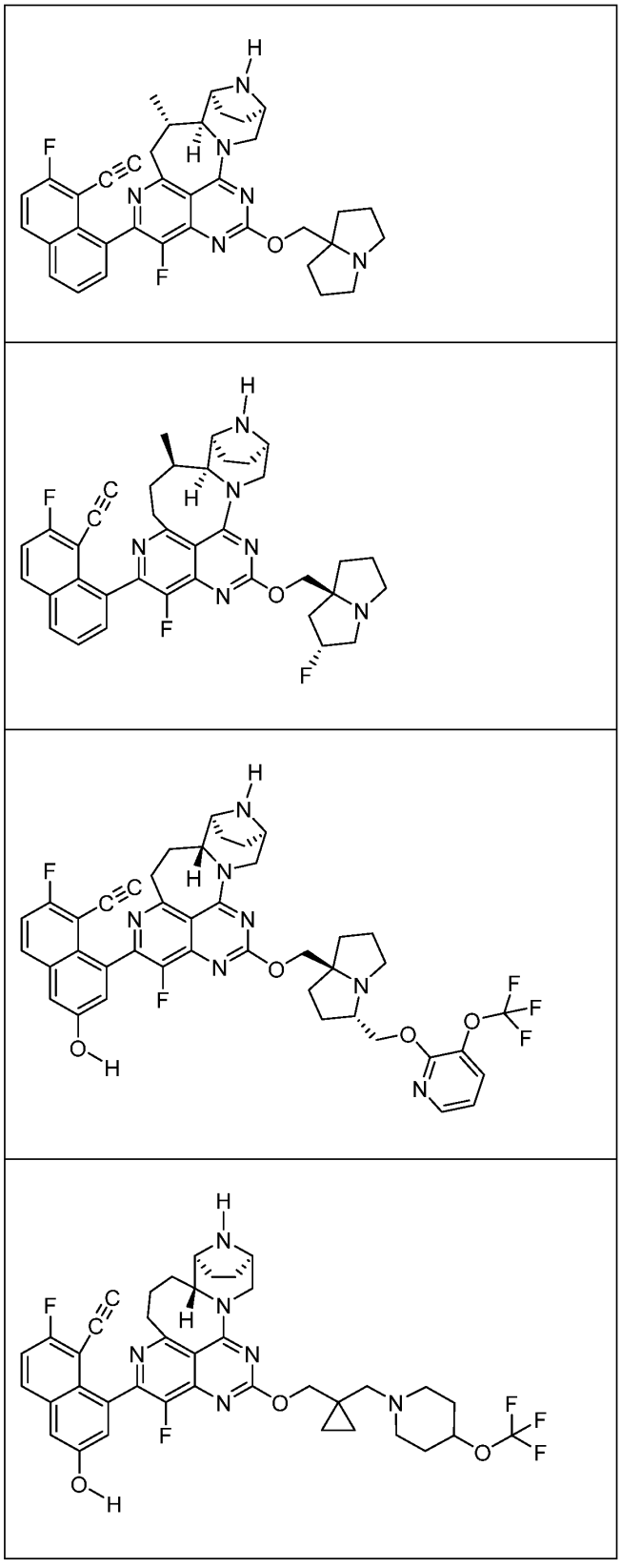


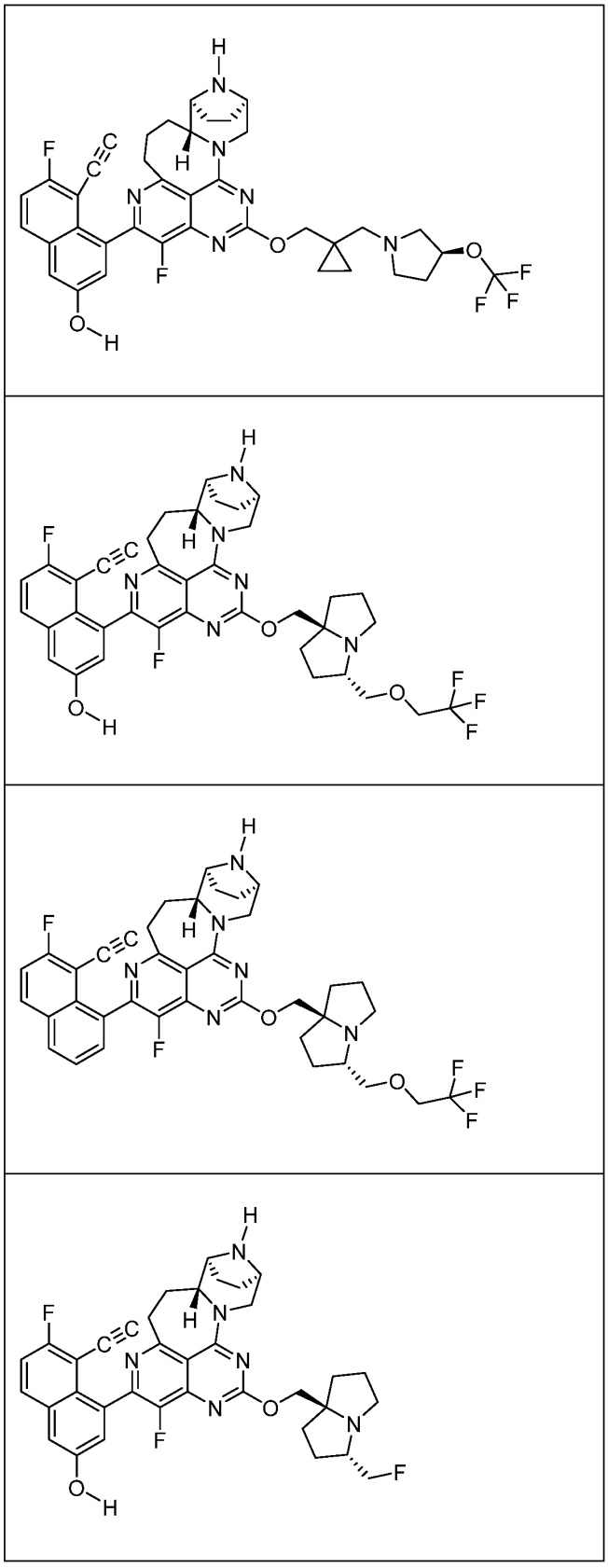


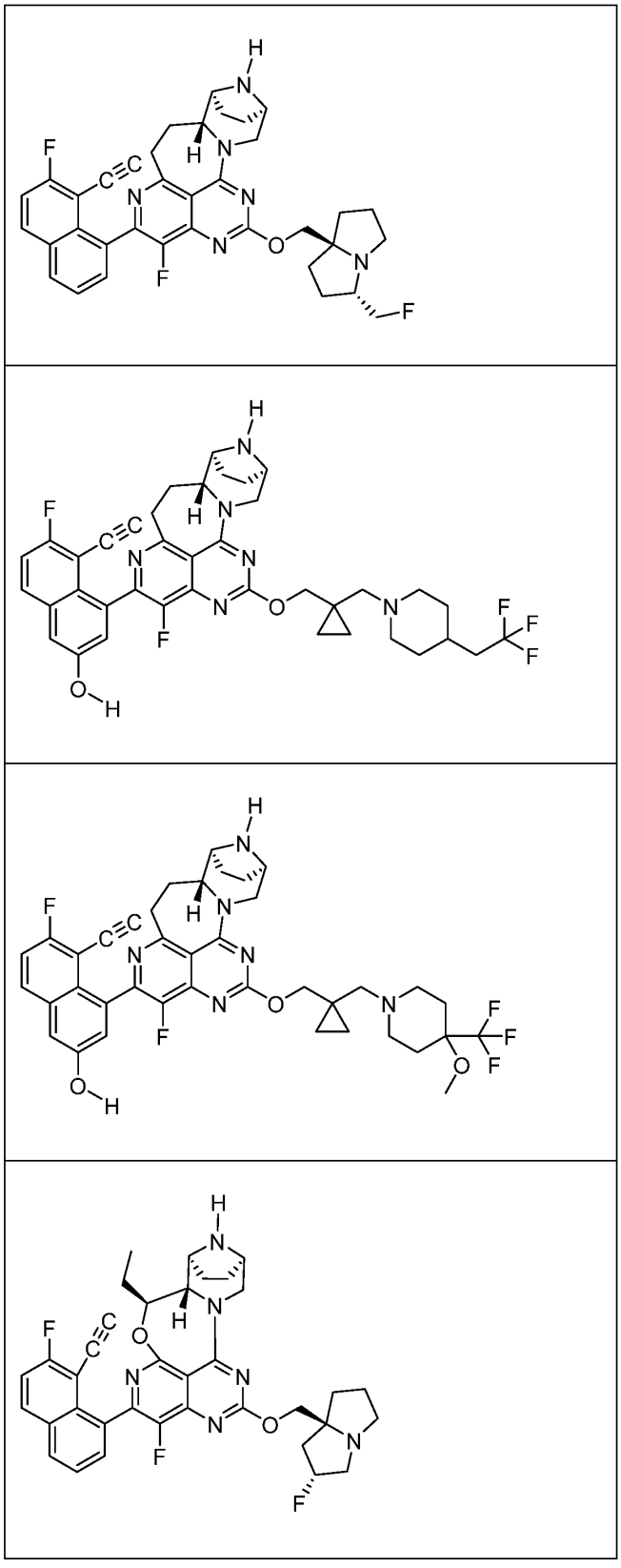


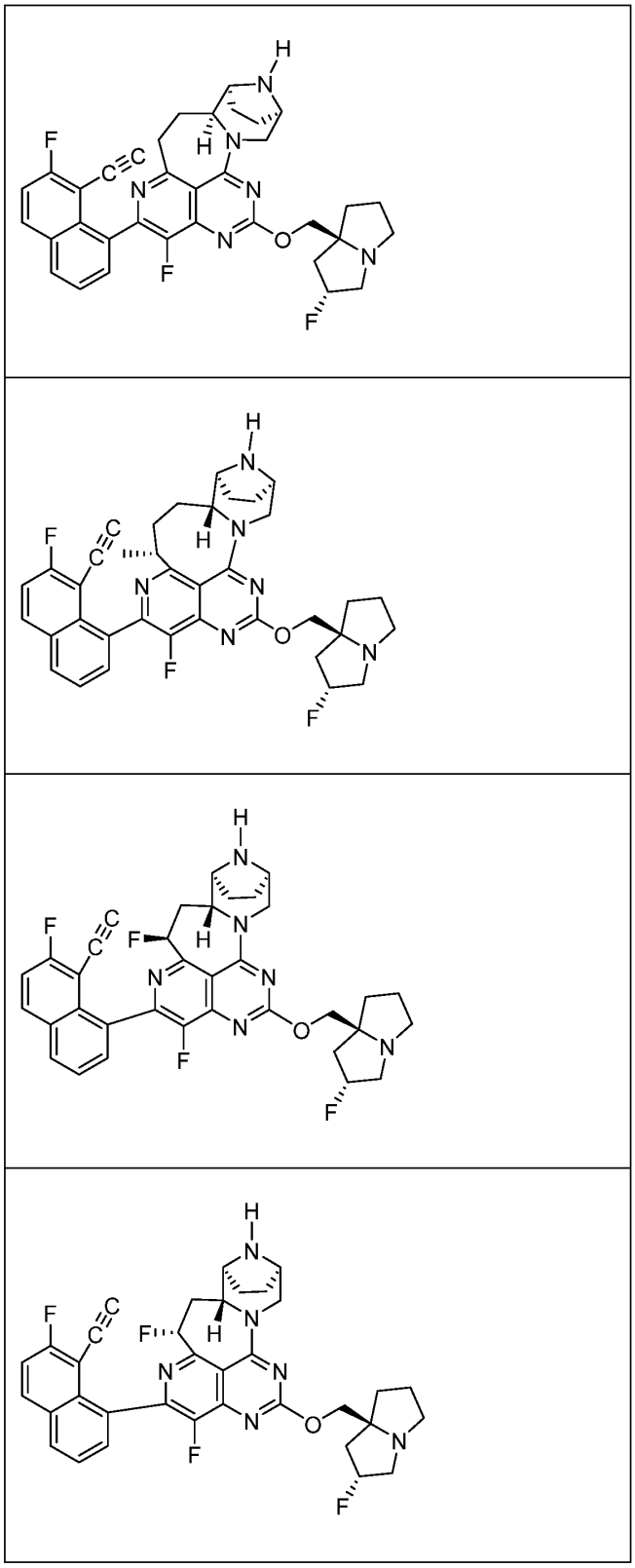


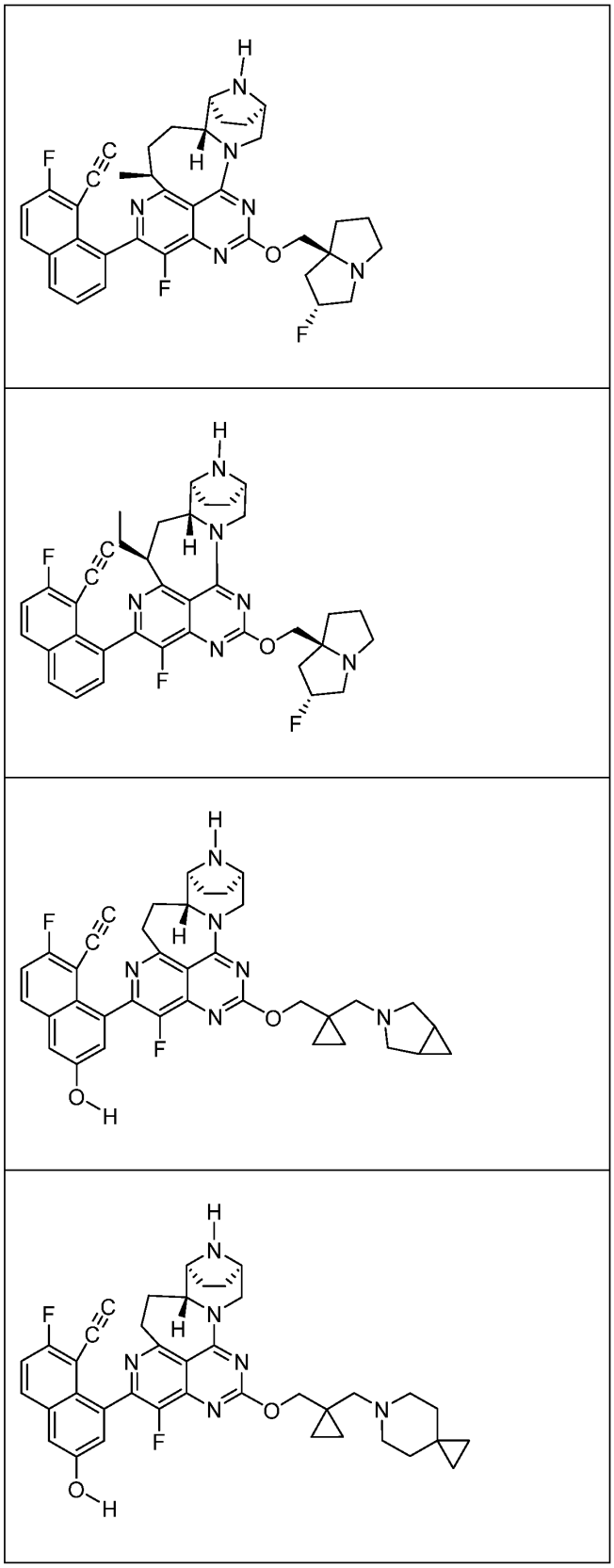


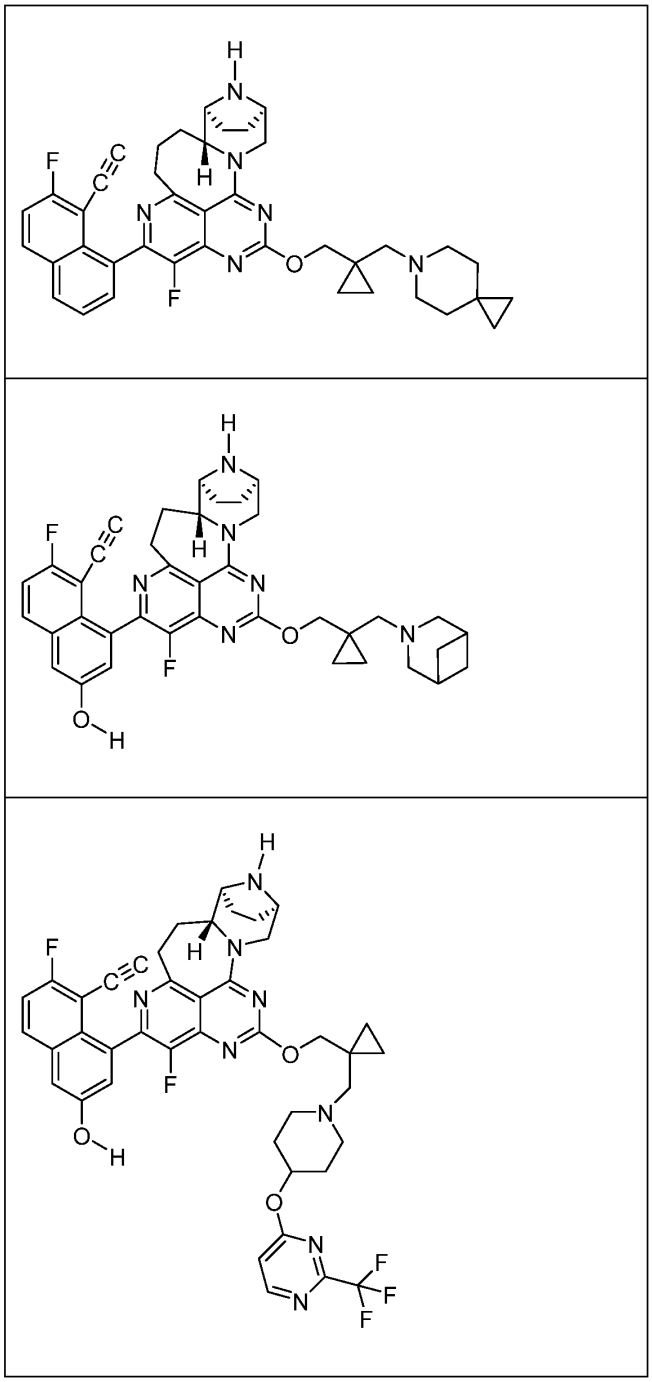


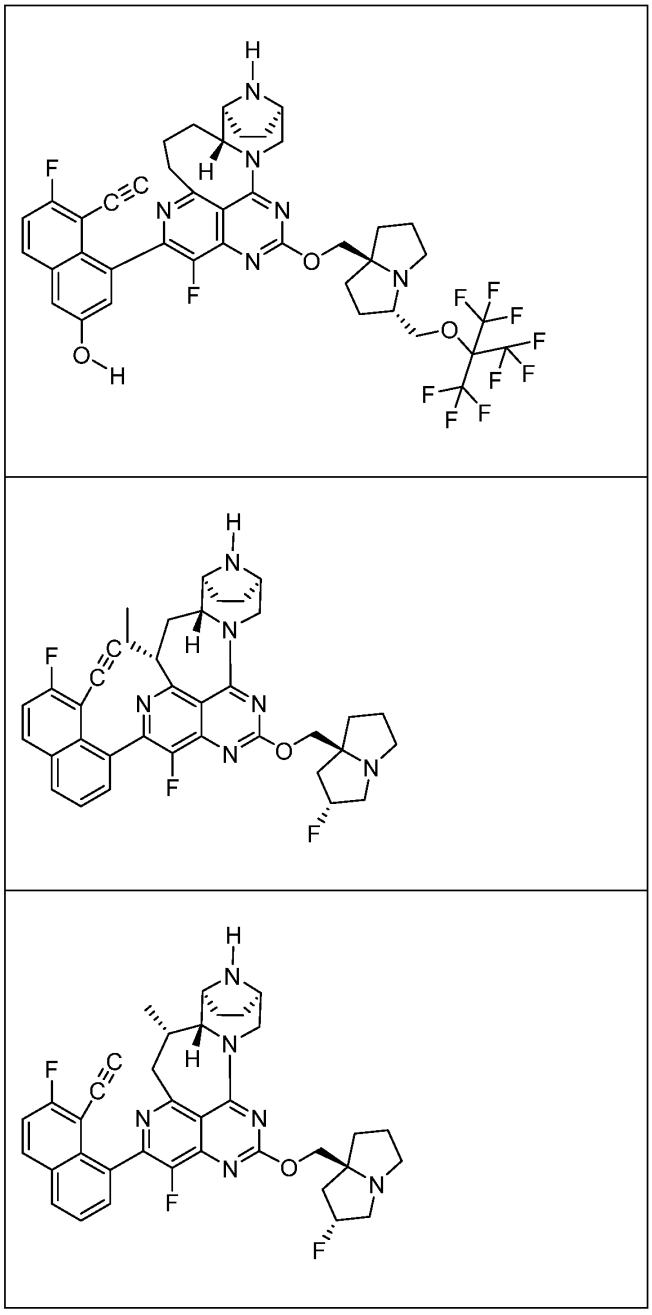


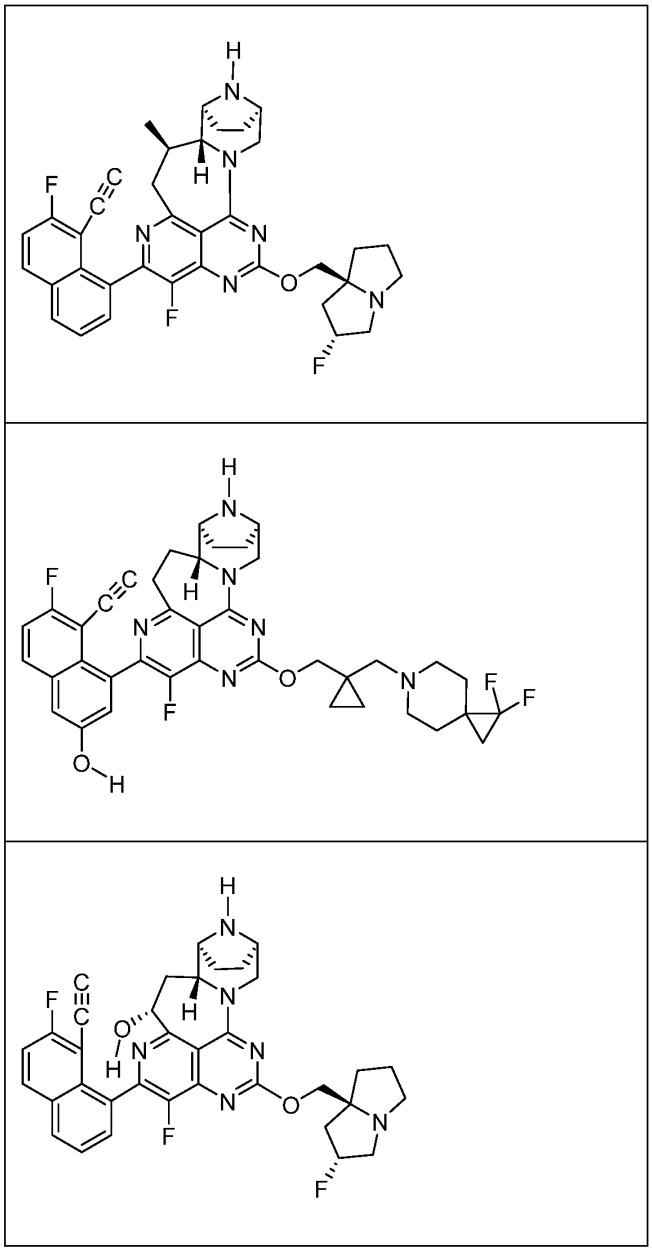


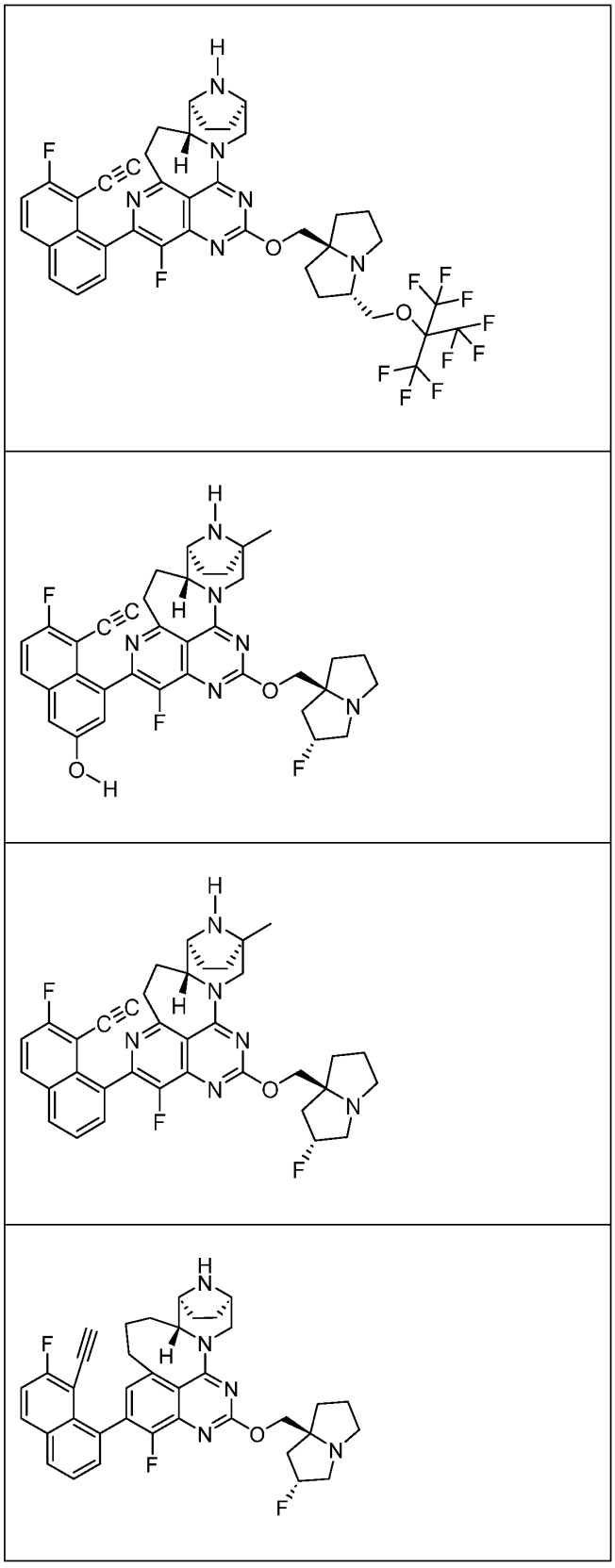


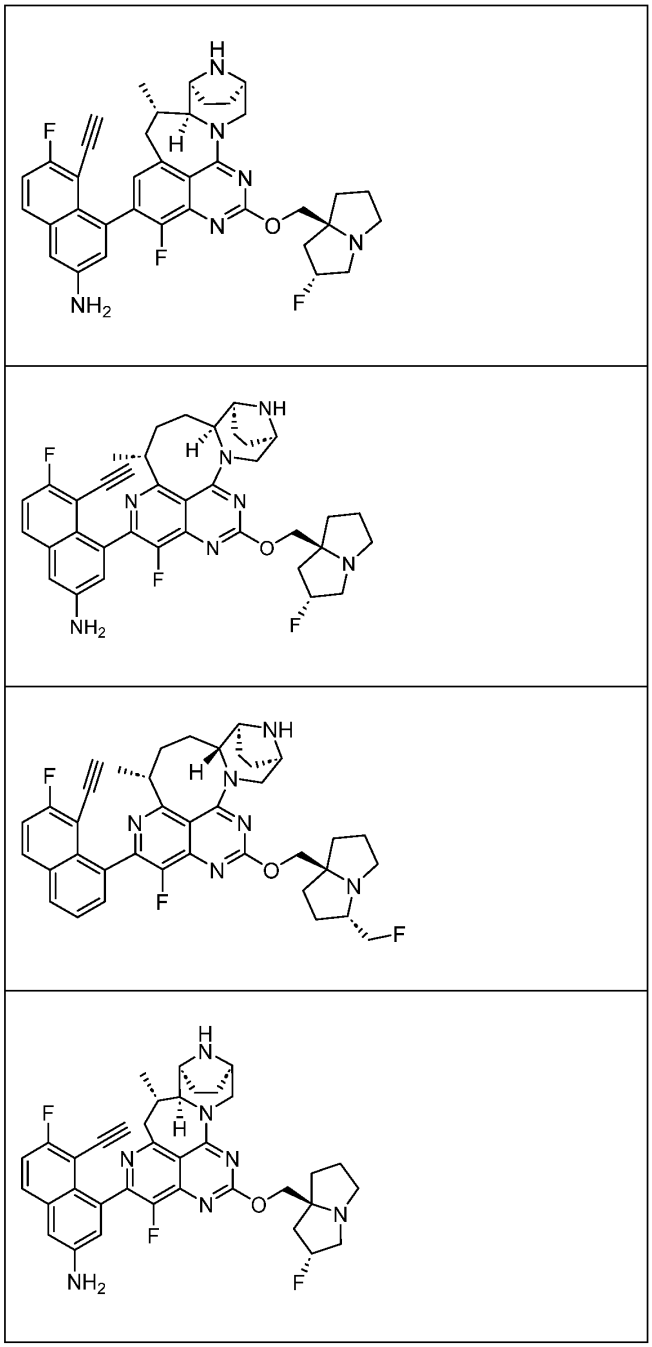


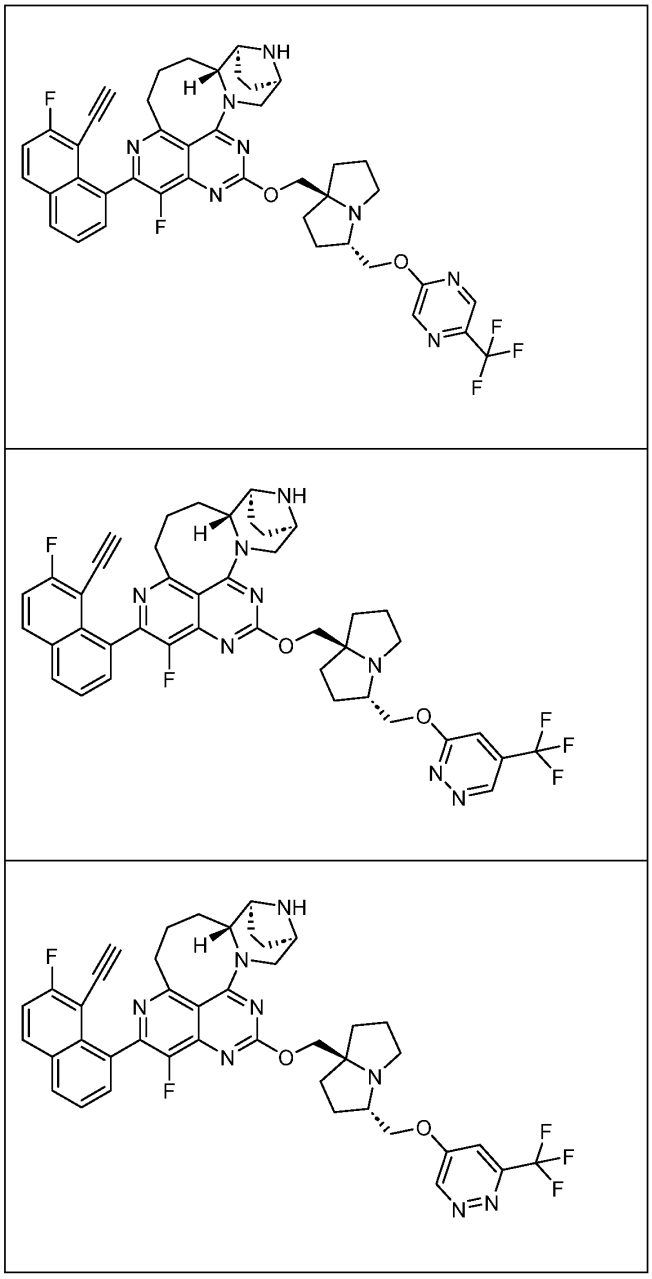


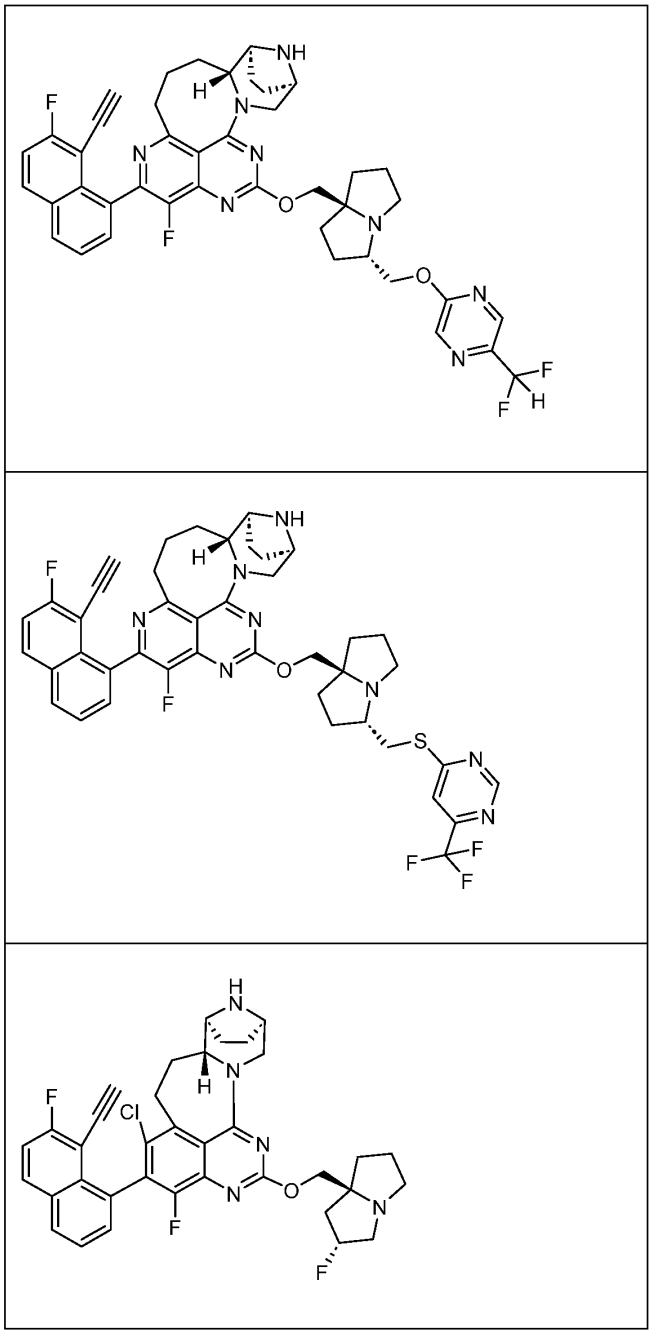


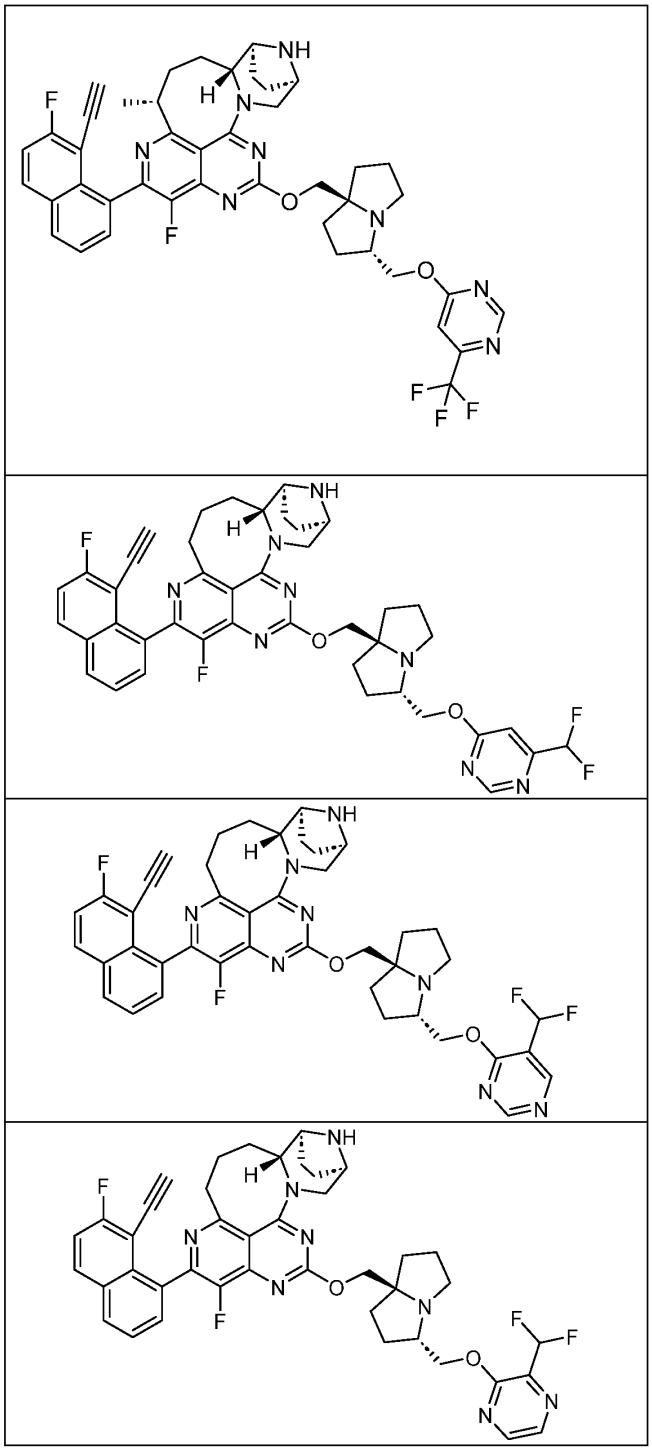


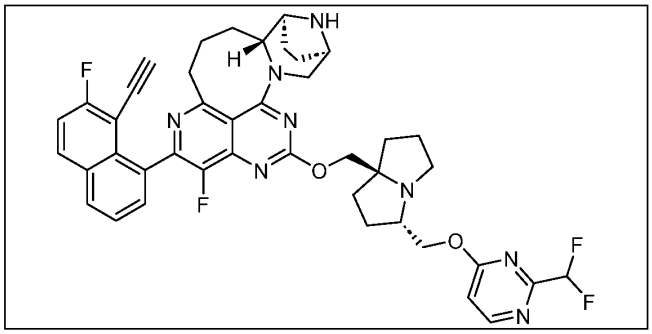




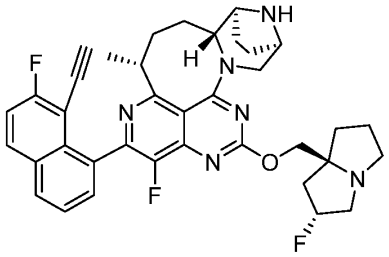






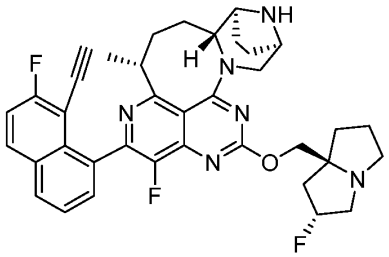


[0143] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein the compound has the structure:



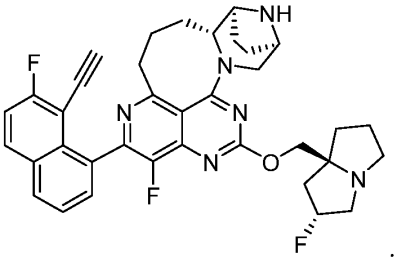
.

[0144] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), wherein the compound has the structure:

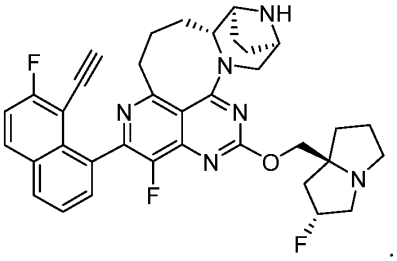


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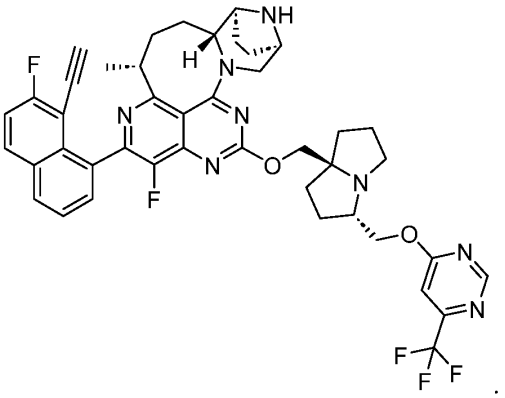
[0145] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein the compound has the structure:



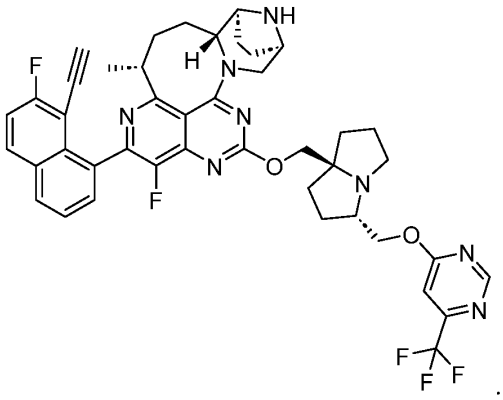
[0146] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), wherein the compound has the structure:



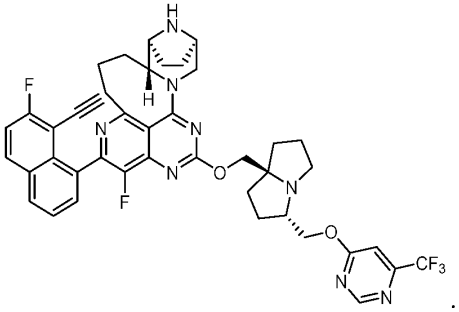
[0147] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein the compound has the structure:



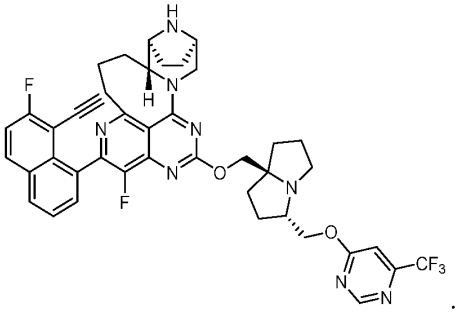
[0148] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), wherein the compound has the structure:



[0149] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein the compound has the structure:

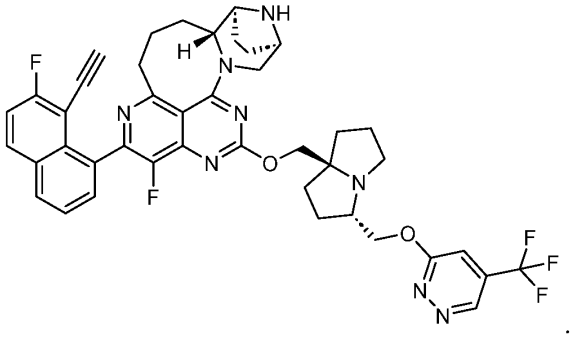


[0150] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), wherein the compound has the structure:

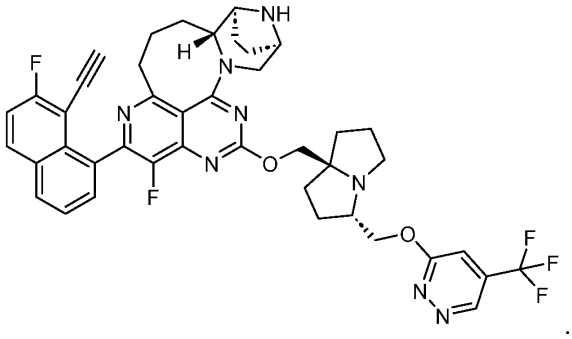


[0151] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-

1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, wherein the compound has the structure:



[0152] In some embodiments, the present disclosure provides the compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), wherein the compound has the structure:



[0153] Also falling within the scope herein are the *in vivo* metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, included are novel and unobvious compounds produced by a process comprising contacting a compound with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g., ^{14}C or ^{3}H) compound, administering it parenterally in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS or NMR analysis. In general, analysis of metabolites is done in the same way

as conventional drug metabolism studies. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds even if they possess no HSV antiviral activity of their own.

[0154] Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37°C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The prodrugs typically will be stable in the digestive system but may be substantially hydrolyzed to the parental drug in the digestive lumen, liver, lung or other metabolic organ, or within cells in general. As used herein, a prodrug is understood to be a compound that is chemically designed to efficiently liberate the parent drug after overcoming biological barriers to oral delivery.

IV. Pharmaceutical Compositions

[0155] Also disclosed herein are pharmaceutical compositions comprising a pharmaceutically effective amount of a compound of the present disclosure (e.g., a compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2),) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient. Also provided herein is a pharmaceutical composition comprising a pharmaceutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0156] The compounds disclosed herein can be formulated with conventional carriers and excipients. Tablets can contain, for instance, excipients, glidants, fillers, binders, or a combination thereof. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. Exemplary excipients include, but are not limited to, those set forth in the "HANDBOOK OF PHARMACEUTICAL EXCIPIENTS" (1986). Excipients can include, for example, ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextran, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid, and combinations thereof. In some embodiments, the formulation is basic. In some embodiments, the formulation is acidic. In some embodiments, the formulation has a neutral pH. In some embodiments, the pH of the formulations is from 2 to 11 (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, 4-5, 4-6, 4-7, 4-8, 4-9,

4-10, 4-11, 5-6, 5-7, 5-8, 5-9, 5-10, 5-11, 6-7, 6-8, 6-9, 6-10, 6-11, 7-8, 7-9, 7-10, 7-11, 8-9, 8-10, 8-11, 9-10, or 9-11).

[0157] In some embodiments, the compounds disclosed herein have pharmacokinetic properties (e.g., oral bioavailability) suitable for oral administration of the compounds. Formulations suitable for oral administration can, for instance, be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient can also be administered, for instance, as a bolus, electuary, or paste.

[0158] A tablet can be made by compression or molding, optionally with at least accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as, for instance, a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active, dispersing agent, or a combination thereof. Molded tablets can be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets can optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

[0159] For infections of the eye or other external tissues (e.g., mouth and skin), the formulations can be applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range from 0.1% to 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), from 0.2% to 15% w/w, or from 0.5% to 10% w/w. When formulated in an ointment, the active ingredients can be employed in some embodiments with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients can be formulated in a cream with an oil-in-water cream base.

[0160] In some embodiments, the aqueous phase of the cream base can include, for example, from 30% to 90% (e.g., 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%) w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. In some embodiments, the cream base can include, for instance, a compound that enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include, but are not limited to, dimethyl sulfoxide and related analogs. In some embodiments, the cream or emulsion does not include water.

[0161] The oily phase of the emulsions can be constituted from known ingredients in a known manner. In some embodiments, the phase comprises merely an emulsifier (otherwise known as an emulgent). In some embodiments, the phase comprises a mixture of at least one emulsifier with a fat, an oil, or a combination thereof. In some embodiments, a hydrophilic emulsifier is included together with a lipophilic emulsifier that acts as a stabilizer. Together, the emulsifier(s) with or without stabilizer(s) can make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base that can form the oily dispersed phase of the cream formulations.

[0162] Emulgents and emulsion stabilizers suitable for use in the formulation can include, but are not limited to, TWEEN® 60, TWEEN® 80, SPAN® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate, sodium lauryl sulfate, and combinations thereof.

[0163] The choice of suitable oils or fats for the formulation can be based on achieving the desired cosmetic properties. In some embodiments, the cream can be a non-greasy, non-staining, and washable product with suitable consistency to avoid leakage from tubes or other containers. In some embodiments, esters can be included, such as, for example, straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate, a blend of branched chain esters known as CRODAMOL® CAP, or a combination thereof. In some embodiments, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be included.

[0164] In some embodiments, the compounds disclosed herein are administered alone. In some embodiments, the compounds disclosed herein are administered in pharmaceutical compositions. In some embodiments, the pharmaceutical compositions are for veterinary use. In some embodiments, the pharmaceutical compositions are for human use. In some embodiments, the pharmaceutical compositions disclosed herein include at least one additional therapeutic agent. In some embodiments, the pharmaceutical compositions disclosed herein include one or more additional therapeutic agent. In some embodiments, the one or more additional therapeutic agents is independently a chemotherapeutic agent, an immunotherapeutic agent, a hormonal agent, an anti-hormonal agent, a targeted therapy agent, or an anti-angiogenesis agent.

[0165] Pharmaceutical compositions disclosed herein can be in any form suitable for the intended method of administration. The pharmaceutical compositions disclosed herein can be presented in unit dosage form and can be prepared by any of the methods well known in the art of pharmacy.

Exemplary techniques and formulations can be found, for instance, in REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Publishing Co., Easton, PA). Such methods can include the step of bringing into association a compound disclosed herein with the carrier that constitutes at least accessory ingredients. In general, the formulations can be prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0166] When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, solutions, syrups or elixirs can be prepared. Formulations intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such formulations can contain at least agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients can be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets can be uncoated or can be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax can be employed.

[0167] Formulations for oral use can be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin, or olive oil.

[0168] Aqueous suspensions can contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients can include, for instance, a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally-occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester

derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension can also contain, for example, at least preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents, one or more sweetening agents (such as sucrose or saccharin), or combinations thereof. Further non-limiting examples of suspending agents include cyclodextrin. In some embodiments, the suspending agent is sulfobutyl ether beta-cyclodextrin (SEB-beta-CD), for example CAPTISOL®.

[0169] Oil suspensions can be formulated by suspending the active ingredient in a vegetable oil (e.g., arachis oil, olive oil, sesame oil, coconut oil, or a combination thereof), a mineral oil such as liquid paraffin, or a combination thereof. The oral suspensions can contain, for instance, a thickening agent, such as beeswax, hard paraffin, cetyl alcohol, or a combination thereof. In some embodiments, sweetening agents, such as those set forth above, and/or flavoring agents, are added to provide a palatable oral preparation. In some embodiments, the formulations disclosed herein are preserved by the addition of an antioxidant such as ascorbic acid.

[0170] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water can provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, a preservative, and combinations thereof. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

[0171] The pharmaceutical compositions can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally-occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion can also contain sweetening and flavoring agents. Syrups and elixirs can be formulated with sweetening agents, such as for instance, glycerol, sorbitol or sucrose. Such formulations can also contain, for instance, a demulcent, a preservative, a flavoring, a coloring agent, or a combination thereof.

[0172] The pharmaceutical compositions can be in the form of a sterile injectable or intravenous preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable or intravenous preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally

acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils can be employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. Among the acceptable vehicles and solvents that can be employed include, but are not limited to, water, Ringer's solution isotonic sodium chloride solution, and hypertonic sodium chloride solution.

[0173] The amount of active ingredient that can be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans can contain approximately 1 mg to 2000 mg of active material compounded with an appropriate and convenient amount of carrier material, which can vary from 5% to 95% of the total formulations (weight:weight). For example, a time-release formulation intended for oral administration to humans can contain approximately 1 mg to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material, which can vary from 5% to 95% of the total formulations (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion can contain from 3 μg to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of 30 mL/hr can occur.

[0174] Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. In some embodiments, the compounds disclosed herein are included in the pharmaceutical compositions disclosed herein in a concentration of 0.5% to 20% (e.g., 0.5% to 10%, 1.5% w/w).

[0175] Formulations suitable for topical administration in the mouth include lozenges can comprise an active ingredient (i.e., a compound disclosed herein and/or additional therapeutic agents) in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0176] Formulations for rectal administration can be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0177] Formulations suitable for vaginal administration can be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0178] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions that can contain anti-oxidants, buffers, bacteriostats and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions that can include suspending agents and thickening agents.

[0179] The formulations can be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately before use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit-dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

[0180] It should be understood that in addition to the ingredients particularly mentioned above the formulations can include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration can include flavoring agents.

[0181] Further provided are veterinary formulations comprising a compound disclosed herein together with a veterinary carrier therefor.

[0182] Veterinary carriers are materials useful for the purpose of administering the formulation and can be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary formulations can be administered orally, parenterally, or by any other desired route.

[0183] Compounds herein are used to provide controlled release pharmaceutical compositions containing as active ingredient one or more of the compounds ("controlled release formulations") in which the release of the active ingredient can be controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

[0184] Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical composition, and will be

determined by the clinician using conventional dose escalation studies. In some embodiments, the effective dose is from 0.0001 to 100 mg/kg body weight per day; for instance, from 10 to 30 mg/kg body weight per day; from 15 to 25 mg/kg body weight per day; from 10 to 15 mg/kg body weight per day; or from 20 to 30 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight can range from 1 mg to 2000 mg (e.g., from 5 mg to 500 mg, from 500 mg to 1000 mg, from 1000 mg to 1500 mg, from 1500 mg to 2000 mg), and can take the form of single or multiple doses. For example, the daily candidate dose for an adult human of approximately 70 kg body weight can range from 1 mg to 1000 mg (e.g., from 5 mg to 500 mg), and can take the form of single or multiple doses.

V. Kits

[0185] Also provided herein are kits that includes a compound disclosed herein or a pharmaceutically acceptable salt thereof. In some embodiments the kits described herein can comprise a label and/or instructions for use of the compound in the treatment of a disease or condition in a subject (e.g., human) in need thereof. In some embodiments, the disease or condition is viral infection.

[0186] In some embodiments, the kit can also comprise one or more additional therapeutic agents and/or instructions for use of additional therapeutic agents in combination with the compound disclosed herein in the treatment of the disease or condition in a subject (e.g., human) in need thereof.

[0187] In some embodiments, the kits provided herein comprise individual dose units of a compound as described herein, or a pharmaceutically acceptable salt, racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph, amorphous form, hydrate or solvate thereof. Examples of individual dosage units can include pills, tablets, capsules, prefilled syringes or syringe cartridges, IV bags, inhalers, nebulizers etc., each comprising a therapeutically effective amount of the compound in question, or a pharmaceutically acceptable salt, racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph, amorphous form, hydrate or solvate thereof. In some embodiments, the kit can contain a single dosage unit and in others multiple dosage units are present, such as the number of dosage units required for a specified regimen or period.

[0188] Also provided are articles of manufacture that include a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof; and a container. In some embodiments, the container of the article of manufacture is a vial, jar,

ampoule, preloaded syringe, blister package, tin, can, bottle, box, an intravenous bag, an inhaler, or a nebulizer.

VI. Administration

[0189] One or more of the compounds of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the route may vary with for example the condition of the recipient. An advantage of the compounds herein is that they are orally bioavailable and can be dosed orally.

[0190] The compounds of the present disclosure (also referred to herein as the active ingredients), can be administered by any route appropriate to the condition to be treated.

[0191] Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the route may vary with for example the condition of the recipient. An advantage of certain compounds disclosed herein is that they are orally bioavailable and can be dosed orally.

[0192] A compound of the present disclosure may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer. In some embodiments, the compound is administered on a daily or intermittent schedule for the duration of the individual's life.

[0193] The dosage or dosing frequency of a compound of the present disclosure may be adjusted over the course of the treatment, based on the judgment of the administering physician.

[0194] The compound may be administered to an individual (e.g., a human) in an effective amount. In some embodiments, the compound is administered once daily.

[0195] The compound can be administered by any useful route and means, such as by oral or parenteral (e.g., intravenous) administration. Therapeutically effective amounts of the compound may include from about 0.00001 mg/kg body weight per day to about 10 mg/kg body weight per

day, such as from about 0.0001 mg/kg body weight per day to about 10 mg/kg body weight per day, or such as from about 0.001 mg/kg body weight per day to about 1 mg/kg body weight per day, or such as from about 0.01 mg/kg body weight per day to about 1 mg/kg body weight per day, or such as from about 0.05 mg/kg body weight per day to about 0.5 mg/kg body weight per day, or such as from about 0.3 mg to about 30 mg per day, or such as from about 30 mg to about 300 mg per day.

[0196] A compound of the present disclosure may be combined with one or more additional therapeutic agents in any dosage amount of the compound of the present disclosure (e.g., from about 1 mg to about 1000 mg of compound). Therapeutically effective amounts may include from about 1 mg per dose to about 1000 mg per dose, such as from about 50 mg per dose to about 500 mg per dose, or such as from about 100 mg per dose to about 400 mg per dose, or such as from about 150 mg per dose to about 350 mg per dose, or such as from about 200 mg per dose to about 300 mg per dose. Other therapeutically effective amounts of the compound of the present disclosure are about 100, about 125, about 150, about 175, about 200, about 225, about 250, about 275, about 300, about 325, about 350, about 375, about 400, about 425, about 450, about 475, or about 500 mg per dose. Other therapeutically effective amounts of the compound of the present disclosure are about 100 mg per dose, or about 125, about 150, about 175, about 200, about 225, about 250, about 275, about 300, about 325, about 350, about 375, about 400, about 425, about 450, or about 500 mg per dose. A single dose can be administered hourly, daily, or weekly. For example, a single dose can be administered once about every 1 hour, about 2, about 3, about 4, about 6, about 8, about 12, about 16 or once about every 24 hours. A single dose can also be administered once about every 1 day, about 2, about 3, about 4, about 5, about 6, or once about every 7 days. A single dose can also be administered once about every 1 week, about 2, about 3, or once about every 4 weeks. In some embodiments, a single dose can be administered once about every week. A single dose can also be administered once about every month.

[0197] Other therapeutically effective amounts of the compound of the present disclosure are about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, or about 100 mg per dose.

[0198] The frequency of dosage of the compound of the present disclosure can be determined by the needs of the individual patient and can be, for example, once per day or twice, or more times, per day. Administration of the compound continues for as long as necessary to treat the disease or condition. For example, a compound can be administered to a human having cancer for a period

of from about 20 days to about 180 days or, for example, for a period of from about 20 days to about 90 days or, for example, for a period of from about 30 days to about 60 days.

[0199] Administration can be intermittent, with a period of several or more days during which a patient receives a daily dose of the compound of the present disclosure followed by a period of several or more days during which a patient does not receive a daily dose of the compound. For example, a patient can receive a dose of the compound every other day, or three times per week. Again by way of example, a patient can receive a dose of the compound each day for a period of from about 1 to about 14 days, followed by a period of about 7 to about 21 days during which the patient does not receive a dose of the compound, followed by a subsequent period (e.g., from about 1 to about 14 days) during which the patient again receives a daily dose of the compound. Alternating periods of administration of the compound, followed by non-administration of the compound, can be repeated as clinically required to treat the patient.

[0200] In some embodiments, pharmaceutical compositions comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents, and a pharmaceutically acceptable excipient are provided.

[0201] In some embodiments, kits comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents are provided.

[0202] In some embodiments, a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four or more additional therapeutic agents. In some embodiments, a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, is combined with two additional therapeutic agents. In some embodiments, a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, is combined with three additional therapeutic agents. In some embodiments, a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, is combined with four additional therapeutic agents. The one, two, three, four or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents.

[0203] In some embodiments, when a compound of the present disclosure is combined with one or more additional therapeutic agents as described herein, the components of the composition are

administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

[0204] In some embodiments, a compound of the present disclosure is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a patient, for example as a solid dosage form for oral administration.

[0205] In some embodiments, a compound of the present disclosure is co-administered with one or more additional therapeutic agents.

[0206] In order to prolong the effect of a compound of the present disclosure, it is often desirable to slow the absorption of a compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending a compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of a compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping a compound in liposomes or microemulsions that are compatible with body tissues.

VII. Methods of Use

[0207] The disclosure further relates to the use of compounds disclosed herein for the treatment and/or prophylaxis of diseases and/or conditions through inhibition of KRAS G12D and/or G12C. Further, the present disclosure relates to the use of said compounds for the preparation of a medicament for the treatment and/or prophylaxis of cancer.

[0208] Medicaments as referred to herein can be prepared by conventional processes, including the combination of a compound according to the present disclosure and a pharmaceutically acceptable carrier.

[0209] In some embodiments, provided herein is a method of inhibiting KRAS G12D protein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a

pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2).

[0210] In some embodiments, provided herein is treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2).

[0211] In some embodiments, provided herein is a method of treating and/or preventing a cancer.

[0212] In some embodiments, provided herein is a method of treating and/or preventing a KRAS G12D-associated cancer.

[0213] In some embodiments, provided herein is a method of reducing the proliferation of a cell comprising contacting the cell with a compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2).

[0214] In some embodiments, the KRAS G12D associated disease or condition includes cancer. In some embodiments, the cancer is a hematological cancer. In some embodiments, the cancer includes a solid tumor. In some embodiments, the cancer includes a malignant tumor. In some embodiments the cancer includes a metastatic cancer. In some embodiments, the cancer is resistant or refractory to one or more anticancer therapies. In some embodiments, greater than about 50% of the cancer cells detectably express one or more cell surface immune checkpoint receptors (*e.g.*, so-called "hot" cancer or tumor). In some embodiments, greater than about 1% and less than about 50% of the cancer cells detectably express one or more cell surface immune checkpoint receptors (*e.g.*, so called "warm" cancer or tumor). In some embodiments, less than about 1% of the cancer cells detectably express one or more cell surface immune checkpoint receptors (*e.g.*, so called "cold" cancer or tumor).

[0215] In some embodiments, the KRAS G12D associated disease or condition is a hematological cancer, *e.g.*, a leukemia (*e.g.*, Acute Myelogenous Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), B-cell ALL, Myelodysplastic Syndrome (MDS), myeloproliferative disease

(MPD), Chronic Myelogenous Leukemia (CML), Chronic Lymphocytic Leukemia (CLL), undifferentiated leukemia), a lymphoma (*e.g.*, small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), follicular lymphoma (FL), T-cell lymphoma, B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), marginal zone lymphoma (MZL), Waldestrom's macroglobulinemia (WM)) and/or a myeloma (*e.g.*, multiple myeloma (MM)).

[0216] In some embodiments, the KRAS G12D associated disease or condition is an epithelial tumor (*e.g.*, a carcinoma, a squamous cell carcinoma, a basal cell carcinoma, a squamous intraepithelial neoplasia), a glandular tumor (*e.g.*, an adenocarcinoma, an adenoma, an adenomyoma), a mesenchymal or soft tissue tumor (*e.g.*, a sarcoma, a rhabdomyosarcoma, a leiomyosarcoma, a liposarcoma, a fibrosarcoma, a dermatofibrosarcoma, a neurofibrosarcoma, a fibrous histiocytoma, an angiosarcoma, an angiomyxoma, a leiomyoma, a chondroma, a chondrosarcoma, an alveolar soft-part sarcoma, an epithelioid hemangioendothelioma, a Spitz tumor, a synovial sarcoma), or a lymphoma.

[0217] In some embodiments, the KRAS G12D associated disease or condition includes a solid tumor in or arising from a tissue or organ, such as:

- bone (*e.g.*, adamantinoma, aneurysmal bone cysts, angiosarcoma, chondroblastoma, chondroma, chondromyxoid fibroma, chondrosarcoma, chordoma, dedifferentiated chondrosarcoma, enchondroma, epithelioid hemangioendothelioma, fibrous dysplasia of the bone, giant cell tumor of bone, haemangiomas and related lesions, osteoblastoma, osteochondroma, osteosarcoma, osteoid osteoma, osteoma, periosteal chondroma, Desmoid tumor, Ewing sarcoma);
- lips and oral cavity (*e.g.*, odontogenic ameloblastoma, oral leukoplakia, oral squamous cell carcinoma, primary oral mucosal melanoma); salivary glands (*e.g.*, pleomorphic salivary gland adenoma, salivary gland adenoid cystic carcinoma, salivary gland mucoepidermoid carcinoma, salivary gland Warthin's tumors);
- esophagus (*e.g.*, Barrett's esophagus, dysplasia and adenocarcinoma);
- gastrointestinal tract, including stomach (*e.g.*, gastric adenocarcinoma, primary gastric lymphoma, gastrointestinal stromal tumors (GISTs), metastatic deposits, gastric carcinoids, gastric sarcomas, neuroendocrine carcinoma, gastric primary squamous cell carcinoma, gastric adenoacanthomas), intestines and smooth muscle (*e.g.*, intravenous leiomyomatosis), colon (*e.g.*, colorectal adenocarcinoma), rectum, anus;

- pancreas (*e.g.*, serous neoplasms, including microcystic or macrocystic serous cystadenoma, solid serous cystadenoma, Von Hippel-Landau (VHL)-associated serous cystic neoplasm, serous cystadenocarcinoma; mucinous cystic neoplasms (MCN), intraductal papillary mucinous neoplasms (IPMN), intraductal oncocytic papillary neoplasms (IOPN), intraductal tubular neoplasms, cystic acinar neoplasms, including acinar cell cystadenoma, acinar cell cystadenocarcinoma, pancreatic adenocarcinoma, invasive pancreatic ductal adenocarcinomas, including tubular adenocarcinoma, adenosquamous carcinoma, colloid carcinoma, medullary carcinoma, hepatoid carcinoma, signet ring cell carcinoma, undifferentiated carcinoma, undifferentiated carcinoma with osteoclast-like giant cells, acinar cell carcinoma, neuroendocrine neoplasms, neuroendocrine microadenoma, neuroendocrine tumors (NET), neuroendocrine carcinoma (NEC), including small cell or large cell NEC, insulinoma, gastrinoma, glucagonoma, serotonin-producing NET, somatostatinoma, VIPoma, solid-pseudopapillary neoplasms (SPN), pancreatoblastoma);
- gall bladder (*e.g.* carcinoma of the gallbladder and extrahepatic bile ducts, intrahepatic cholangiocarcinoma);
- neuro-endocrine (*e.g.*, adrenal cortical carcinoma, carcinoid tumors, phaeochromocytoma, pituitary adenomas);
- thyroid (*e.g.*, anaplastic (undifferentiated) carcinoma, medullary carcinoma, oncocytic tumors, papillary carcinoma, adenocarcinoma);
- liver (*e.g.*, adenoma, combined hepatocellular and cholangiocarcinoma, fibrolamellar carcinoma, hepatoblastoma, hepatocellular carcinoma, mesenchymal, nested stromal epithelial tumor, undifferentiated carcinoma; hepatocellular carcinoma, intrahepatic cholangiocarcinoma, bile duct cystadenocarcinoma, epithelioid hemangioendothelioma, angiosarcoma, embryonal sarcoma, rhabdomyosarcoma, solitary fibrous tumor, teratoma, York sac tumor, carcinosarcoma, rhabdoid tumor);
- kidney (*e.g.*, ALK-rearranged renal cell carcinoma, chromophobe renal cell carcinoma, clear cell renal cell carcinoma, clear cell sarcoma, metanephric adenoma, metanephric adenofibroma, mucinous tubular and spindle cell carcinoma, nephroma, nephroblastoma (Wilms tumor), papillary adenoma, papillary renal cell carcinoma, renal oncocytoma, renal cell carcinoma, succinate dehydrogenase-deficient renal cell carcinoma, collecting duct carcinoma);

- breast (*e.g.*, invasive ductal carcinoma, including without limitation, acinic cell carcinoma, adenoid cystic carcinoma, apocrine carcinoma, cribriform carcinoma, glycogen-rich/clear cell, inflammatory carcinoma, lipid-rich carcinoma, medullary carcinoma, metaplastic carcinoma, micropapillary carcinoma, mucinous carcinoma, neuroendocrine carcinoma, oncocytic carcinoma, papillary carcinoma, sebaceous carcinoma, secretory breast carcinoma, tubular carcinoma; lobular carcinoma, including without limitation, pleomorphic carcinoma, signet ring cell carcinoma;
- peritoneum (*e.g.*, mesothelioma; primary peritoneal cancer);
- female sex organ tissues, including ovary (*e.g.*, choriocarcinoma, epithelial tumors, germ cell tumors, sex cord-stromal tumors), Fallopian tubes (*e.g.*, serous adenocarcinoma, mucinous adenocarcinoma, endometrioid adenocarcinoma, clear cell adenocarcinoma, transitional cell carcinoma, squamous cell carcinoma, undifferentiated carcinoma, Müllerian tumors, adenosarcoma, leiomyosarcoma, teratoma, germ cell tumors, choriocarcinoma, trophoblastic tumors), uterus (*e.g.*, carcinoma of the cervix, endometrial polyps, endometrial hyperplasia, intraepithelial carcinoma (EIC), endometrial carcinoma (*e.g.*, endometrioid carcinoma, serous carcinoma, clear cell carcinoma, mucinous carcinoma, squamous cell carcinoma, transitional carcinoma, small cell carcinoma, undifferentiated carcinoma, mesenchymal neoplasia), leiomyoma (*e.g.*, endometrial stromal nodule, leiomyosarcoma, endometrial stromal sarcoma (ESS), mesenchymal tumors), mixed epithelial and mesenchymal tumors (*e.g.*, adenofibroma, carcinofibroma, adenosarcoma, carcinosarcoma (malignant mixed mesodermal sarcoma - MMMT)), endometrial stromal tumors, endometrial malignant mullerian mixed tumors, gestational trophoblastic tumors (partial hydatiform mole, complete hydatiform mole, invasive hydatiform mole, placental site tumor)), vulva, vagina;
- male sex organ tissues, including prostate, testis (*e.g.*, germ cell tumors, spermatocytic seminoma), penis;
- bladder (*e.g.*, squamous cell carcinoma, urothelial carcinoma, bladder urothelial carcinoma);
- brain, (*e.g.*, gliomas (*e.g.*, astrocytomas, including non-infiltrating, low-grade, anaplastic, glioblastomas; oligodendrogliomas, ependymomas), meningiomas, gangliogliomas, schwannomas (neurilemmomas), craniopharyngiomas, chordomas, Non-Hodgkin lymphomas (NHLs), indolent non-Hodgkin's lymphoma (iNHL), refractory iNHL, pituitary tumors;

- eye (*e.g.*, retinoma, retinoblastoma, ocular melanoma, posterior uveal melanoma, iris hamartoma);
- head and neck (*e.g.*, nasopharyngeal carcinoma, Endolymphatic Sac Tumor (ELST), epidermoid carcinoma, laryngeal cancers including squamous cell carcinoma (SCC) (*e.g.*, glottic carcinoma, supraglottic carcinoma, subglottic carcinoma, transglottic carcinoma), carcinoma *in situ*, verrucous, spindle cell and basaloid SCC, undifferentiated carcinoma, laryngeal adenocarcinoma, adenoid cystic carcinoma, neuroendocrine carcinomas, laryngeal sarcoma), head and neck paragangliomas (*e.g.*, carotid body, jugulotympanic, vagal);
- thymus (*e.g.*, thymoma);
- heart (*e.g.*, cardiac myxoma);
- lung (*e.g.*, small cell carcinoma (SCLC), non-small cell lung carcinoma (NSCLC), including squamous cell carcinoma (SCC), adenocarcinoma and large cell carcinoma, carcinoids (typical or atypical), carcinosarcomas, pulmonary blastomas, giant cell carcinomas, spindle cell carcinomas, pleuropulmonary blastoma);
- lymph (*e.g.*, lymphomas, including Hodgkin's lymphoma, non-Hodgkin's lymphoma (NHL), indolent non-Hodgkin's lymphoma (iNHL), refractory iNHL, Epstein-Barr virus (EBV)-associated lymphoproliferative diseases, including B cell lymphomas and T cell lymphomas (*e.g.*, Burkitt lymphoma; large B cell lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, indolent B-cell lymphoma, low grade B cell lymphoma, fibrin-associated diffuse large cell lymphoma; primary effusion lymphoma; plasmablastic lymphoma; extranodal NK/T cell lymphoma, nasal type; peripheral T cell lymphoma, cutaneous T cell lymphoma, angioimmunoblastic T cell lymphoma; follicular T cell lymphoma; systemic T cell lymphoma), lymphangioleiomyomatosis);
- central nervous system (CNS) (*e.g.*, gliomas including astrocytic tumors (*e.g.*, pilocytic astrocytoma, pilomyxoid astrocytoma, subependymal giant cell astrocytoma, pleomorphic xanthoastrocytoma, diffuse astrocytoma, fibrillary astrocytoma, gemistocytic astrocytoma, protoplasmic astrocytoma, anaplastic astrocytoma, glioblastoma (*e.g.*, giant cell glioblastoma, gliosarcoma, glioblastoma multiforme) and gliomatosis cerebri), oligodendroglial tumors (*e.g.*, oligodendroglioma, anaplastic oligodendroglioma), oligoastrocytic tumors (*e.g.*, oligoastrocytoma, anaplastic oligoastrocytoma), ependymal tumors (*e.g.*, subependymom, myxopapillary

ependymoma, ependymomas (*e.g.*, cellular, papillary, clear cell, tanycytic), anaplastic ependymoma), optic nerve glioma, and non-gliomas (*e.g.*, choroid plexus tumors, neuronal and mixed neuronal-glial tumors, pineal region tumors, embryonal tumors, medulloblastoma, meningeal tumors, primary CNS lymphomas, germ cell tumors, Pituitary adenomas, cranial and paraspinal nerve tumors, stellar region tumors); neurofibroma, meningioma, peripheral nerve sheath tumors, peripheral neuroblastic tumors (including without limitation neuroblastoma, ganglioneuroblastoma, ganglioneuroma), trisomy 19 ependymoma);

- neuroendocrine tissues (*e.g.*, paraganglionic system including adrenal medulla (pheochromocytomas) and extra-adrenal paraganglia ((extra-adrenal) paragangliomas);
- skin (*e.g.*, clear cell hidradenoma, cutaneous benign fibrous histiocytomas, cylindroma, hidradenoma, melanoma (including cutaneous melanoma, mucosal melanoma), pilomatricoma, Spitz tumors); and
- soft tissues (*e.g.*, aggressive angiomyxoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, angiofibroma, angiomatoid fibrous histiocytoma, synovial sarcoma, biphasic synovial sarcoma, clear cell sarcoma, dermatofibrosarcoma protuberans, desmoid-type fibromatosis, small round cell tumor, desmoplastic small round cell tumor, elastofibroma, embryonal rhabdomyosarcoma, Ewing's tumors/primitive neurectodermal tumors (PNET), extraskeletal myxoid chondrosarcoma, extraskeletal osteosarcoma, paraspinal sarcoma, inflammatory myofibroblastic tumor, lipoblastoma, lipoma, chondroid lipoma, liposarcoma / malignant lipomatous tumors, liposarcoma, myxoid liposarcoma, fibromyxoid sarcoma, lymphangioleiomyoma, malignant myoepithelioma, malignant melanoma of soft parts, myoepithelial carcinoma, myoepithelioma, myxoinflammatory fibroblastic sarcoma, undifferentiated sarcoma, pericytoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), soft tissue leiomyosarcoma, undifferentiated sarcoma, well-differentiated liposarcoma.

[0218] In some embodiments, the KRAS G12D associated disease or condition is a cancer selected from a lung cancer, a colorectal cancer, a breast cancer, a prostate cancer, a cervical cancer, a pancreatic cancer and a head and neck cancer. In some embodiments, the cancer is metastatic.

[0219] In some embodiments, the KRAS G12D associated disease or condition is a cancer selected from non-small lung cancer (NSCLC), melanoma, triple-negative breast cancer (TNBC),

nasopharyngeal cancer (NPC), microsatellite stable colorectal cancer (mssCRC), thymoma, and gastrointestinal stromal tumor (GIST). In some embodiments, the cancer is metastatic.

[0220] In some embodiments, the KRAS G12D associated disease or condition is a cancer of pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, uterine cancer, gastric cancer, bile duct cancer, testicular cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft tissue sarcoma, non-small cell lung cancer, small-cell lung cancer, myelodysplastic syndrome, thyroid cancer, or colon cancer.

[0221] In some embodiments, the KRAS G12D associated disease or condition is a cancer of pancreatic cancer, colorectal cancer, non-small cell lung cancer, endometrial cancer, uterine endometrical carcinoma, cholangio carcinoma, testicular germ cell cancer, cervical squamous carcinoma, or myelodysplastic syndrome.

[0222] In some embodiments, the cancer is or myelodysplastic syndrome. In some embodiments, the cancer is high risk myelodysplastic syndrome or low risk myelodysplastic syndrome. In some embodiments, the cancer is high risk myelodysplastic syndrome . In some embodiments, the cancer is high risk myelodysplastic syndrome .

[0223] In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is non-small cell lung cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is endometrial cancer. In some embodiments, the cancer is uterine endometrical carcinoma. In some embodiments, the cancer is testicular germ cell cancer. In some embodiments, the cancer is cervical squamous carcinoma. In some embodiments, the cancer is cholangio carcinoma.

[0224] The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

[0225] When treating or preventing a KRAS G12D associated disease or condition for which compounds of the present disclosure are indicated, generally satisfactory results are obtained when the compounds of the present disclosure are administered at a daily dosage of from about 0.1 milligram to about 300 milligram per kilogram of animal body weight. In some embodiments, the compounds of the present disclosure are given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage

is from about 1 milligram to about 1000 milligrams, or from about 1 milligram to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.1 milligrams to about 200 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response. In some embodiments, the total daily dosage is from about 1 milligram to about 900 milligrams, about 1 milligram to about 800 milligrams, about 1 milligram to about 700 milligrams, about 1 milligram to about 600 milligrams, about 1 milligram to about 400 milligrams, about 1 milligram to about 300 milligrams, about 1 milligram to about 200 milligrams, about 1 milligram to about 100 milligrams, about 1 milligram to about 50 milligrams, about 1 milligram to about 20 milligram, or about 1 milligram to about 10 milligrams.

[0226] The compounds of the present application or the compositions thereof may be administered once, twice, three, or four times daily, using any suitable mode described above. Also, administration or treatment with the compounds may be continued for a number of days; for example, commonly treatment would continue for at least 7 days, 14 days, or 28 days, for one cycle of treatment. Treatment cycles are frequently alternated with resting periods of about 1 to 28 days, commonly about 7 days or about 14 days, between cycles. The treatment cycles, in other embodiments, may also be continuous.

[0227] In some embodiments, the methods provided herein comprise administering to the subject an initial daily dose of about 1 to 800 mg of a compound described herein and increasing the dose by increments until clinical efficacy is achieved. Increments of about 5, 10, 25, 50, or 100 mg can be used to increase the dose. The dosage can be increased daily, every other day, twice per week, or once per week.

[0228] In some embodiments, the compound or pharmaceutically acceptable salt thereof of the present disclosure is administered in combination with one or more additional therapeutic agent or therapeutic modality.

[0229] In some embodiments, the present disclosure provides the pharmaceutical composition or the method wherein the one or more more additional therapeutic agent or additional therapeutic modality comprises one, two, three, or four additional therapeutic agents and/or therapeutic modalities.

[0230] In some embodiments, the present disclosure provides the pharmaceutical composition or the method wherein the additional therapeutic agent or therapeutic modalities are selected from an immune checkpoint modulator, an antibody-drug conjugate (ADC), an antiapoptotic agent, a targeted anticancer therapeutic, a chemotherapeutic agent, surgery, or radiation therapy.

[0231] In some embodiments, the present disclosure provides the pharmaceutical composition or the method wherein the immune checkpoint modulator is selected from an anti-PD-(L)1 antibody, an anti-TIGIT antibody, an anti-CTLA4 antibody, an anti-CCR8 antibody, an anti-TREM1 antibody, an anti-TREM2 antibody, a CD47 inhibitor, a DGKα inhibitor, an HPK1 inhibitor, a FLT3 agonist, an adenosine receptor antagonist, a CD39 inhibitor, a CD73 inhibitor, an IL-2 variant (IL-2v), and a CAR-T cell therapy.

[0232] In some embodiments, the present disclosure provides the pharmaceutical composition or the method wherein the anti-PD-(L)1 antibody is selected from pembrolizumab, nivolumab, cemiplimab, pidilizumab, spartalizumab, atezolizumab, avelumab, durvalumab, cosibelimab, sasanlimab, tislelizumab, retifanlimab, balstilimab, toripalimab, cetrelimab, genolimzumab, prolgolimab, lodapolimab, camrelizumab, budigalimab, avelumab, dostarlimab, envafolimab, sintilimab, and zimberelimab.

[0233] In some embodiments, the present disclosure provides the pharmaceutical composition or the method wherein the anti-TIGIT antibody is selected from tiragolumab, vibostolimab, domvanalimab, AB308, AK127, BMS-986207, and etigilimab.

[0234] In some embodiments, the present disclosure provides the pharmaceutical composition or the method wherein the anti-CTLA4 antibody is selected from ipilimumab, tremelimumab, and zalifrelimab.

[0235] In some embodiments, the present disclosure provides the pharmaceutical composition or the method wherein the CD47 inhibitor is selected from magrolimab, letaplimab, lemzoparlimab, AL-008, RRx-001, CTX-5861, FSI-189 (GS-0189), ES-004, BI-765063, ADU1805, CC-95251, and Q-1801.

[0236] In some embodiments, the present disclosure provides the pharmaceutical composition or the method wherein the adenosine receptor antagonist is etrumadenant (AB928), taminadenant, TT-10, TT-4, or M1069.

[0237] In some embodiments, the present disclosure provides the pharmaceutical composition or the method wherein the CD39 inhibitor is TTX-030.

[0238] In some embodiments, the present disclosure provides the pharmaceutical composition or the method wherein the CD73 inhibitor is quemliclustat (AB680), uliledlimab, mupadolimab, ORIC-533, ATG-037, PT-199, AK131, NZV930, BMS-986179, or oleclumab.

[0239] In some embodiments, the present disclosure provides the pharmaceutical composition or the method wherein the IL-2v is aldesleukin (Proleukin), bempegaldesleukin (NKTR-214), nemvaleukin alfa (ALKS-4230), THOR-202 (SAR-444245), BNT-151, ANV-419, XTX-202, RG-6279 (RO-7284755), NL-201, STK-012, SHR-1916, or GS-4528.

[0240] In some embodiments, the present disclosure provides the pharmaceutical composition or the method wherein the ADC is selected from sacituzumab govitecan, datopotamab deruxtecan, enfortumab vedotin, and trastuzumab deruxtecan.

[0241] In some embodiments, the present disclosure provides the pharmaceutical composition or the method wherein the additional therapeutic agent is selected from idealisib, sacituzumab govitecan, magrolimab, GS-0189, GS-3583, zimberelimab, GS-4224, GS-9716, GS-6451, GS-1811 (JTX-1811), quemliclustat (AB680), etrumadenant (AB928), domvanalimab, AB308, PY159, PY314, AGEN-1223, AGEN-2373, axicabtagene ciloleucel and brexucabtagene autoleucel.

[0242] In some embodiments, the method includes administering one or more additional therapeutic agents. The one or more additional therapeutic agents can be one or more therapuetic agents as described below. In some embodiments, the one or more additional therapeutic agents is independently a chemotherapeutic agent, an immunotherapeutic agent, a hormonal agent, an anti-hormonal agent, a targeted therapy agent, or an anti-angiogenesis agent.

[0243] In some embodiments, the one or more additional therapeutic agents includes therapeutic agents used to treat high risk myelodysplastic syndrome (HR MDS), low risk myelodyplastic syndrome (LR MDS), colorectal cancer, non-small cell lung cancer (NSCLC), pancreatic cancer, or endometrial cancer. In some embodiments, the one or more additional therapeutic agents includes therapeutic agents used to treat high risk myelodysplastic syndrome (HR MDS). In some embodiments, the one or more additional therapeutic agents includes azacitidine (Vidaza®), decitabine (Dacogen®), lenalidomide (Revlimid®), cytarabine, idarubicin, daunorubicin, cytarabine + daunorubicin, cytarabine + idarubicin, pevonedistat, venetoclax, sabatolimab, guadecitabine, rigosertib, ivosidenib, enasidenib, selinexor, BGB324, DSP-7888, or SNS-301.

[0244] In some embodiments, the one or more additional therapeutic agents includes therapeutic agents used to treat low risk myelodyplastic syndrome (LR MDS). In some embodiments, the one or more additional therapeutic agents includes lenalidomide, azacytidine, roxadustat, luspatercept, imetelstat, LB-100, or rigosertib.

[0245] In some embodiments, the one or more additional therapeutic agents includes therapeutic agents used to treat colorectal cancer. In some embodiments, the one or more additional therapeutic agents includes bevacizumab, capecitabine, cetuximab, fluorouracil, irinotecan, leucovorin, oxaliplatin, panitumumab, ziv-aflibercept, bevacizumab (Avastin®), leucovorin, 5-FU, oxaliplatin (FOLFOX), pembrolizumab (Keytruda®), FOLFIRI, regorafenib (Stivarga®), aflibercept (Zaltrap®), cetuximab (Erbitux®), Lonsurf (Orcantas®), XELOX, FOLFOXIRI, bevacizumab + leucovorin + 5-FU + oxaliplatin (FOLFOX), bevacizumab + FOLFIRI, bevacizumab + FOLFOX, aflibercept + FOLFIRI, cetuximab + FOLFIRI, bevacizumab + XELOX, bevacizumab + FOLFOXIRI, binimetinib + encorafenib + cetuximab, trametinib + dabrafenib + panitumumab, trastuzumab + pertuzumab, napabucasin + FOLFIRI + bevacizumab, or nivolumab + ipilimumab.

[0246] In some embodiments, the one or more additional therapeutic agents includes therapeutic agents used to treat non-small cell lung cancer (NSCLC). In some embodiments, the one or more additional therapeutic agents includes afatinib, albumin-bound paclitaxel, alectinib, atezolizumab, bevacizumab, bevacizumab, cabozantinib, carboplatin, cisplatin, crizotinib, dabrafenib, docetaxel, erlotinib, etoposide, gemcitabine, nivolumab, paclitaxel, pembrolizumab, pemetrexed, ramucirumab, trametinib, trastuzumab, vandetanib, vemurafenib, vinblastine, vinorelbine, alectinib (Alecensa®), dabrafenib (Tafinlar®), trametinib (Mekinist®), osimertinib (Tagrisso®), entrectinib (Tarceva®), crizotinib (Xalkori®), pembrolizumab (Keytruda®), carboplatin, pemetrexed (Alimta®), nab-paclitaxel (Abraxane®), ramucirumab (Cyramza®), docetaxel, bevacizumab (Avastin®), brigatinib, gemcitabine, cisplatin, afatinib (Gilotrif®), nivolumab (Opdivo®), gefitinib (Iressa®), dabrafenib + trametinib, pembrolizumab + carboplatin + pemetrexed, pembrolizumab + carboplatin + nab-paclitaxel, ramucirumab + docetaxel, bevacizumab + carboplatin + pemetrexed, pembrolizumab + pemetrexed + carboplatin, cisplatin + pemetrexed, bevacizumab + carboplatin + nab-paclitaxel, cisplatin + gemcitabine, nivolumab + docetaxel, carboplatin + pemetrexed, carboplatin + nab-paclitaxel, or pemetrexed + cisplatin + carboplatin, datopotamab deruxtecan (DS-1062), trastuzumab deruxtecan (Enhertu®), enfortumab vedotin (Padcev®), durvalumab, canakinumab, cemiplimab, nogapendekin alfa, avelumab, tiragolumab, domvanalimab, vibostolimab, ociperlimab, datopotamab deruxtecan + pembrolizumab, datopotamab deruxtecan + durvalumab, durvalumab + tremelimumab, pembrolizumab + lenvatinib + pemetrexed, pembrolizumab + olaparib, nogapendekin alfa (N-803) + pembrolizumab, tiragolumab + atezolizumab, vibostolimab + pembrolizumab, or ociperlimab + tislelizumab.

[0247] In some embodiments, the one or more additional therapeutic agents includes therapeutic agents used to treat pancreatic cancer. In some embodiments, the one or more additional therapeutic agents includes 5-FU, leucovorin, oxaliplatin, irinotecan, gemcitabine, nab-paclitaxel (Abraxane®), FOLFIRINOX, 5-FU + leucovorin + oxaliplatin + irinotecan, 5-FU + nanoliposomal irinotecan, leucovorin + nanoliposomal irinotecan, or gemcitabine + nab-paclitaxel.

[0248] In some embodiments, the one or more additional therapeutic agents includes therapeutic agents used to treat endometrial cancer. In some embodiments, the one or more additional therapeutic agents includes carboplatin, paclitaxel, cisplatin, doxorubicin, ifosfamide, progesterone, anastrozole (Arimidex®), letrozole (Femara®), exemestane (Aromasin®), pembrolizumab (Keytruda®), lenvatinib (Lenvima®), or dostarlimab (Jemperli®).

[0249] In some embodiments, the one or more additional therapeutic agents is independently SNS-301, 5-FU + leucovorin + oxaliplatin + irinotecan, 5-FU + nanoliposomal irinotecan, 5-FU, afatinib (Gilotrif®), aflibercept (Zaltrap®), aflibercept + FOLFIRI, albumin-bound paclitaxel, alectinib (Alecensa®), anastrozole (Arimidex®), atezolizumab, avelumab, azacitidine (Vidaza®), bevacizumab (Avastin®), bevacizumab + carboplatin + nab-paclitaxel, bevacizumab + carboplatin + pemetrexed, bevacizumab + FOLFIRI, bevacizumab + FOLFOX, bevacizumab + FOLFOXIRI, bevacizumab + leucovorin + 5-FU + oxaliplatin (FOLFOX), bevacizumab + XELOX, bevacizumab, BGB324, binimetinib + encorafenib + cetuximab, brigatinib, cabozantinib, canakinumab, capecitabine, carboplatin + nab-paclitaxel, carboplatin + pemetrexed, carboplatin, cemiplimab, cetuximab (Erbitux®), cetuximab + FOLFIRI, cisplatin + gemcitabine, cisplatin + pemetrexed, cisplatin, crizotinib (Xalkori®), cytarabine + daunorubicin, cytarabine + idarubicin, cytarabine, dabrafenib (Tafinlar®), dabrafenib + trametinib, datopotamab deruxtecan (DS-1062), datopotamab deruxtecan + durvalumab, datopotamab deruxtecan + pembrolizumab, daunorubicin, decitabine (Dacogen®), docetaxel, domvanalimab, dostarlimab (Jemperli®), doxorubicin, DSP-7888, durvalumab + tremelimumab, durvalumab, enasidenib, enfortumab vedotin (Padcev®), entrectinib (Tarceva®), erlotinib, etoposide, exemestane (Aromasin®), fluorouracil, FOLFIRI, FOLFIRINOX, FOLFOXIRI, gefitinib (Iressa®), gemcitabine + nab-paclitaxel, gemcitabine, guadecitabine, idarubicin, ifosfamide, imetelstat, irinotecan, ivosidenib, LB-100, lenalidomide (Revlimid®), lenalidomide, lenvatinib (Lenvima®), letrozole (Femara®), leucovorin + nanoliposomal irinotecan, leucovorin, Lonsurf (Orcantas®), luspatercept, nab-paclitaxel (Abraxane®), napabucasin + FOLFIRI + bevacizumab, nivolumab (Opdivo®), nivolumab + docetaxel, nivolumab + ipilimumab, nogapendekin alfa (N-803) + pembrolizumab, nogapendekin alfa, ociperlimab + tislelizumab, ociperlimab, osimertinib (Tagrisso®), oxaliplatin (FOLFOX), paclitaxel, panitumumab, pembrolizumab (Keytruda®), pembrolizumab + carboplatin

+ nab-paclitaxel, pembrolizumab + carboplatin + pemetrexed, pembrolizumab + lenvatinib + pemetrexed, pembrolizumab + olaparib, pembrolizumab + pemetrexed + carboplatin, pemetrexed (Alimta®), pemetrexed + cisplatin + carboplatin, pevonedistat, progesterone, ramucirumab (Cyramza®), ramucirumab + docetaxel, regorafenib (Stivarga®), rigosertib, roxadustat, sabatolimab, selinexor, tiragolumab + atezolizumab, tiragolumab, trametinib (Mekinist®), trametinib + dabrafenib + panitumumab, trastuzumab + pertuzumab, trastuzumab deruxtecan (Enhertu®), trastuzumab, vandetanib, vemurafenib, venetoclax, vibostolimab + pembrolizumab, vibostolimab, vinblastine, vinorelbine, XELOX, or ziv-aflibercept.

[0250] In another embodiment, the present disclosure provides a method for manufacturing a medicament for treating cancer in a subject in need thereof, characterized in that a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, is used.

[0251] In another embodiment, the present disclosure provides a method for manufacturing a medicament for inhibiting cancer metastasis in a subject in need thereof, characterized in that a compound of the present invention, or a pharmaceutically acceptable salt thereof, is used.

[0252] In another embodiment, the present disclosure provides use of the compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer in a subject.

[0253] In another embodiment, the present disclosure provides use of the compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inhibiting cancer metastasis in a subject.

[0254] In another embodiment, the present disclosure provides the compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a subject in need thereof.

[0255] In another embodiment, the present disclosure provides the compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for use in inhibiting cancer metastasis in a subject in need thereof.

[0256] In another embodiment, the present disclosure provides the compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for use in therapy.

VIII. Combination Therapy

[0257] In some embodiments, a compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), provided herein, or pharmaceutically acceptable salt thereof, is administered in combination with one or more additional therapeutic agents to treat or prevent a disease or condition disclosed herein. In some embodiments, the one or more additional therapeutic agents are one, two, three, or four additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are one additional therapeutic agent. In some embodiments, the one or more additional therapeutic agents are two additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are three additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are four additional therapeutic agents.

[0258] In some embodiments, the pharmaceutical compositions provided herein have a compound of Formula I, I-A, (I-1), (I-2), (I-3), (Ia), (Ia-1), (Ib), (Ib-1), (Ib-2), (Ib-3), (Ib-4), (Ib-5), (Ib-6), (Ib-7), (Ib-8), II, (II-1), (IIa), (IIa-1), (IIb), (IIb-1), or (IIb-2), provided herein, or pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are one, two, three, or four additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are one additional therapeutic agent. In some embodiments, the one or more additional therapeutic agents are two additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are three additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents are four additional therapeutic agents.

[0259] In some embodiments the additional therapeutic agent includes, e.g., an inhibitory immune checkpoint blocker or inhibitor, a stimulatory immune checkpoint stimulator, agonist or activator, a chemotherapeutic agent, an anti-cancer agent, a radiotherapeutic agent, an anti-neoplastic agent, an anti-proliferation agent, an anti-angiogenic agent, an anti-inflammatory agent, an immunotherapeutic agent, a therapeutic antigen-binding molecule (e.g., a mono- and multi-specific antibody, or fragment thereof, in any format, such as DART®, Duobody®, BiTE®, BiKE, TriKE, XmAb®, TandAb®, scFv, Fab, Fab derivative), a bi-specific antibody, a non-immunoglobulin antibody mimetic (e.g., including adnectin, affibody, affilin, affimer, affitin, alphabody, anticalin, peptide aptamer, armadillo repeat protein (ARM), atrimer, avimer, designed ankyrin repeat protein (DARPin®), fynomer, knottin, Kunitz domain peptide, monobody, and nanoCLAMPs), an antibody-drug conjugate (ADC), antibody-peptide conjugate), an oncolytic virus, a gene modifier or editor, a cell comprising a chimeric antigen receptor (CAR), e.g.,

including a T-cell immunotherapeutic agent, an NK-cell immunotherapeutic agent, or a macrophage immunotherapeutic agent, a cell comprising an engineered T-cell receptor (TCR-T), or any combination thereof.

Illustrative Targets

[0260] In some embodiments, the one or more additional therapeutic agents include, e.g., an inhibitor, agonist, antagonist, ligand, modulator, stimulator, blocker, activator or suppressor of a target (e.g., polypeptide or polynucleotide), such as: 2'-5'-oligoadenylate synthetase (OAS1; NCBI Gene ID: 4938); 5'-3' exoribonuclease 1 (XRN1; NCBI Gene ID: 54464); 5'-nucleotidase ecto (NT5E, CD73; NCBI Gene ID: 4907); ABL proto-oncogene 1, non-receptor tyrosine kinase (ABL1, BCR-ABL, c-ABL, v-ABL; NCBI Gene ID: 25); absent in melanoma 2 (AIM2; NCBI Gene ID: 9447); acetyl-CoA acyltransferase 2 (ACAA2; NCBI Gene ID: 10499); acid phosphatase 3 (ACP3; NCBI Gene ID: 55); adenosine deaminase (ADA, ADA1; NCBI Gene ID: 100); adenosine receptors (e.g., ADORA1 (A1), ADORA2A (A2a, A2AR), ADORA2B (A2b, A2BR), ADORA3 (A3); NCBI Gene IDs: 134, 135, 136, 137); AKT serine/threonine kinase 1 (AKT1, AKT, PKB; NCBI Gene ID: 207); alanyl aminopeptidase, membrane (ANPEP, CD13; NCBI Gene ID: 290); ALK receptor tyrosine kinase (ALK, CD242; NCBI Gene ID: 238); alpha fetoprotein (AFP; NCBI Gene ID: 174); amine oxidase copper containing (e.g., AOC1 (DAO1), AOC2, AOC3 (VAP1); NCBI Gene IDs: 26, 314, 8639); androgen receptor (AR; NCBI Gene ID: 367); angiopoietins (ANGPT1, ANGPT2; NCBI Gene IDs: 284, 285); angiotensin II receptor type 1 (AGTR1; NCBI Gene ID: 185); angiotensinogen (AGT; NCBI Gene ID: 183); apolipoprotein A1 (APOA1; NCBI Gene ID: 335); apoptosis inducing factor mitochondria associated 1 (AIFM1, AIF; NCBI Gene ID: 9131); arachidonate 5-lipoxygenase (ALOX5; NCBI Gene ID: 240); asparaginase (ASPG; NCBI Gene ID: 374569); asteroid homolog 1 (ASTE1; NCBI Gene ID: 28990); ATM serine/threonine kinase (ATM; NCBI Gene ID: 472); ATP binding cassette subfamily B member 1 (ABCB1, CD243, GP170; NCBI Gene ID: 5243); ATP-dependent Clp-protease (CLPP; NCBI Gene ID: 8192); ATR serine/threonine kinase (ATR; NCBI Gene ID: 545); AXL receptor tyrosine kinase (AXL; NCBI Gene ID: 558); B and T lymphocyte associated (BTLA, CD272; NCBI Gene ID: 151888); baculoviral IAP repeat containing proteins (BIRC2 (cIAP1), BIRC3 (cIAP2), XIAP (BIRC4, IAP3), BIRC5 (survivin); NCBI Gene IDs: 329, 330, 331, 332); basigin (Ok blood group) (BSG, CD147; NCBI Gene ID: 682); B-cell lymphoma 2 (BCL2; NCBI Gene ID: 596); BCL2 binding component 3 (BBC3, PUMA; NCBI Gene ID: 27113); BCL2 like (e.g., BCL2L1 (Bcl-x), BCL2L2 (BIM); Bcl-x; NCBI Gene IDs: 598, 10018); beta 3-adrenergic receptor (ADRB3; NCBI Gene ID: 155); bone gamma-carboxyglutamate protein (BGLAP; NCBI Gene ID: 632); bone morphogenetic protein-10 ligand (BMP10; NCBI

Gene ID: 27302); bradykinin receptors (e.g., BDKRB1, BDKRB2; NCBI Gene IDs: 623, 624); B-RAF (BRAF; NCBI Gene ID: 273); breakpoint cluster region (BCR; NCBI Gene ID: 613); bromodomain and external domain (BET) bromodomain containing proteins (e.g., BRD2, BRD3, BRD4, BRDT; NCBI Gene IDs: 6046, 8019, 23476, 676); Bruton's tyrosine kinase (BTK; NCBI Gene ID: 695); cadherins (e.g., CDH3 (p-cadherin), CDH6 (k-cadherin); NCBI Gene IDs: 1001, 1004); cancer/testis antigens (e.g., CTAG1A, CTAG1B, CTAG2; NCBI Gene IDs: 1485, 30848, 246100); cannabinoid receptors (e.g., CNR1 (CB1), CNR2 (CB2); NCBI Gene IDs: 1268, 1269); carbohydrate sulfotransferase 15 (CHST15; NCBI Gene ID: 51363); carbonic anhydrases (e.g., CA1, CA2, CA3, CA4, CA5A, CA5B, CA6, CA7, CA8, CA9, CA10, CA11, CA12, CA13, CA14; NCBI Gene IDs: 759, 760, 761, 762, 763, 765, 766, 767, 768, 770, 771, 11238, 23632, 56934, 377677); carcinoembryonic antigen related cell adhesion molecules (e.g., CEACAM3 (CD66d), CEACAM5 (CD66e), CEACAM6 (CD66c); NCBI Gene IDs: 1048, 1084, 4680); casein kinases (e.g., CSNK1A1 (CK1), CSNK2A1 (CK2); NCBI Gene IDs: 1452, 1457); caspases (e.g., CASP3, CASP7, CASP8; NCBI Gene IDs: 836, 840, 841, 864); catenin beta 1 (CTNNB1; NCBI Gene ID: 1499); cathepsin G (CTSG; NCBI Gene ID: 1511); Cbl proto-oncogene B (CBLB, Cbl-b; NCBI Gene ID: 868); C-C motif chemokine ligand 21 (CCL21; NCBI Gene ID: 6366); C-C motif chemokine receptor 2 (CCR2; NCBI Gene ID: 729230); C-C motif chemokine receptors (e.g., CCR3 (CD193), CCR4 (CD194), CCR5 (CD195), CCR8 (CDw198); NCBI Gene IDs: 1232, 1233, 1234, 1237); CCAAT enhancer binding protein alpha (CEBPA, CEBP; NCBI Gene ID: 1050); cell adhesion molecule 1 (CADM1; NCBI Gene ID: 23705); cell division cycle 7 (CDC7; NCBI Gene ID: 8317); cellular communication network factor 2 (CCN2; NCBI Gene ID: 1490); cereblon (CRBN; NCBI Gene ID: 51185); checkpoint kinases (e.g., CHEK1 (CHK1), CHEK2 (CHK2); NCBI Gene IDs: 1111, 11200); cholecystokinin B receptor (CCKBR; NCBI Gene ID: 887); chorionic somatomammotropin hormone 1 (CSH1; NCBI Gene ID: 1442); claudins (e.g., CLDN6, CLDN18; NCBI Gene IDs: 9074, 51208); cluster of differentiation markers (e.g., CD1A, CD1C, CD1D, CD1E, CD2, CD3 alpha (TRA), CD beta (TRB), CD gamma (TRG), CD delta (TRD), CD4, CD8A, CD8B, CD19, CD20 (MS4A1), CD22, CD24, CD25 (IL2RA, TCGFR), CD28, CD33 (SIGLEC3), CD37, CD38, CD39 (ENTPD1), CD40 (TNFRSF5), CD44 (MIC4, PGP1), CD47 (IAP), CD48 (BLAST1), CD52, CD55 (DAF), CD58 (LFA3), CD74,CD79a, CD79b, CD80 (B7-1), CD84, CD86 (B7-2), CD96 (TACTILE), CD99 (MIC2), CD115 (CSF1R), CD116 (GMCSFR, CSF2RA), CD122 (IL2RB), CD123 (IL3RA), CD128 (IL8R1), CD132 (IL2RG), CD135 (FLT3), CD137 (TNFRSF9, 4-1BB), CD142 (TF, TFA), CD152 (CTLA4), CD160, CD182 (IL8R2), CD193 (CCR3), CD194 (CCR4), CD195 (CCR5), CD207, CD221 (IGF1R), CD222 (IGF2R), CD223 (LAG3), CD226 (DNAM1), CD244, CD247, CD248, CD276 (B7-H3), CD331 (FGFR1), CD332 (FGFR2), CD333 (FGFR3), CD334 (FGFR4); NCBI Gene

IDs: 909, 911, 912, 913, 914, 919, 920, 923, 925, 926, 930, 931, 933, 940, 941, 942, 945, 951, 952, 953, 958,960, 961, 962, 965, 972, 973, 974, 1043, 1232, 1233, 1234, 1237, 1436, 1438, 1493, 1604, 2152, 2260, 2261, 2263, 2322, 3480, 3482, 3559, 3560, 3561, 3563, 3577, 3579, 3604, 3902, 4267, 6955, 6957, 6964, 6965, 8832, 10666, 11126, 50489, 51744, 80381, 100133941); clusterin (CLU; NCBI Gene ID: 1191); coagulation factors (e.g., F7, FXA, ; NCBI Gene IDs: 2155, 2159); collagen type IV alpha chains (e.g., COL4A1, COL4A2, COL4A3, COL4A4, COL4A5; NCBI Gene IDs: 1282, 1284, 1285, 1286, 1287); collectin subfamily member 10 (COLEC10; NCBI Gene ID: 10584); colony stimulating factors (e.g., CSF1 (MCSF), CSF2 (GMCSF), CSF3 (GCSF); NCBI Gene IDs: 1435, 1437, 1440); complement factors (e.g., C3, C5; NCBI Gene IDs: 718, 727); COP9 signalosome subunit 5 (COPS5; NCBI Gene ID: 10987); C-type lectin domain family member (e.g., CLEC4C (CD303), CLEC9A (CD370), CLEC12A (CD371); CD371; NCBI Gene ID: 160364, 170482, 283420); C-X-C motif chemokine ligand 12 (CXCL12; NCBI Gene ID: 6387); C-X-C motif chemokine receptors (CXCR1 (IL8R1, CD128), CXCR2 (IL8R2, CD182), CXCR3 (CD182, CD183, IP-10R), CXCR4 (CD184); NCBI Gene ID: 2833, 3577, 3579, 7852); cyclin D1 (CCND1, BCL1; NCBI Gene ID: 595); cyclin dependent kinases (e.g., CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, CDK12; NCBI Gene ID: 983, 1017, 1018, 1019, 1020, 1021, 1022, 1024, 1025, 8558, 51755); cyclin G1 (CCNG1; NCBI Gene ID: 900); cytochrome P450 family members (e.g., CYP2D6, CYP3A4, CYP11A1, CYP11B2, CYP17A1, CYP19A1, CYP51A1; NCBI Gene IDs: 1565, 1576, 1583, 1585, 1586, 1588, 1595); cytochrome P450 oxidoreductase (POR; NCBI Gene ID: 5447); cytokine inducible SH2 containing protein (CISH; NCBI Gene ID: 1154); cytotoxic T-lymphocyte associated protein 4 (CTLA4, CD152; NCBI Gene ID: 1493); DEAD-box helicases (e.g., DDX5, DDX6, DDX58; NCBI Gene IDs: 1655, 1656, 23586); delta like canonical Notch ligands (e.g., DLL3, DLL4; NCBI Gene IDs: 10683, 54567); diablo IAP-binding mitochondrial protein (DIABLO, SMAC; NCBI Gene ID: 56616); diacylglycerol kinases (e.g., DGKA, DGKZ; NCBI Gene IDs: 1606, 8525); dickkopf WNT signaling pathway inhibitors (e.g., DKK1, DKK3; NCBI Gene ID: 22943, 27122); dihydrofolate reductase (DHFR; NCBI Gene ID: 1719); dihydropyrimidine dehydrogenase (DPYD; NCBI Gene ID: 1806); dipeptidyl peptidase 4 (DPP4; NCBI Gene ID: 1803); discoidin domain receptor tyrosine kinases (e.g., DDR1 (CD167), DDR2; CD167; NCBI Gene ID: 780, 4921); DNA dependent protein kinase (PRKDC; NCBI Gene ID: 5591); DNA topoisomerases (e.g., TOP1, TOP2A, TOP2B, TOP3A, TOP3B; NCBI Gene ID: 7150, 7153, 7155, 7156, 8940); dopachrome tautomerase (DCT; NCBI Gene ID: 1638); dopamine receptor D2 (DRD2; NCBI Gene ID: 1318); DOT1 like histone lysine methyltransferase (DOT1L; NCBI Gene ID: 84444); ectonucleotide pyrophosphatase/ phosphodiesterase 3 (ENPP3, CD203c; NCBI Gene ID: 5169); EMAP like 4 (EML4; NCBI Gene ID: 27436); endoglin (ENG; NCBI

Gene ID: 2022); endoplasmic reticulum aminopeptidases (e.g., ERAP1, ERAP2; NCBI Gene ID: 51752, 64167); enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2; NCBI Gene ID: 2146); ephrin receptors (e.g., EPHA1, EPHA2EPHA3, EPHA4, EPHA5, EPHA7, EPHB4; NCBIGene ID:1969, 2041, 2042, 2043, 2044, 2045, 2050); ephrins (e.g., EFNA1, EFNA4, EFNB2; NCBI Gene ID: 1942, 1945, 1948); epidermal growth factor receptors (e.g., ERBB1 (HER1, EGFR), ERBB1 variant III (EGFRvIII), ERBB2 (HER2, NEU, CD340), ERBB3 (HER3), ERBB4 (HER4); NCBI Gene ID: 1956, 2064, 2065, 2066); epithelial cell adhesion molecule (EPCAM; NCBI Gene ID: 4072); epithelial mitogen (EPGN; NCBI Gene ID: 255324); eukaryotic translation elongation factors (e.g., EEF1A2, EEF2; NCBI Gene ID: 1917, 1938); eukaryotic translation initiation factors (e.g., EIF4A1, EIF5A; NCBI Gene ID: 1973, 1984); exportin-1 (XPO1; NCBI Gene ID: 7514); farnesoid X receptor (NR1H4, FXR; NCBI Gene ID: 9971); Fas ligand (FASLG, FASL, CD95L, CD178, TNFSF6; NCBI Gene ID: 356); fatty acid amide hydrolase (FAAH; NCBI Gene ID: 2166); fatty acid synthase (FASN; FAS; NCBI Gene ID: 2194); Fc fragment of Ig receptors (e.g., FCER1A, FCGRT, FCGR3A (CD16); NCBI Gene IDs: 2205, 2214, 2217); Fc receptor like 5 (FCRL5, CD307; NCBI Gene ID: 83416); fibroblast activation protein alpha (FAP; NCBI Gene ID: 2191); fibroblast growth factor receptors (e.g., FGFR1 (CD331), FGFR2 (CD332), FGFR3 (CD333), FGFR4 (CD334); NCBI Gene IDs: 2260, 2261, 2263, 2264); fibroblast growth factors (e.g., FGF1 (FGF alpha), FGF2 (FGF beta), FGF4, FGF5; NCBI Gene IDs: 2246, 2247, 2249, 2250); fibronectin 1 (FN1, MSF; NCBI Gene ID: 2335); fms related receptor tyrosine kinases (e.g., FLT1 (VEGFR1), FLT3 (STK1, CD135), FLT4 (VEGFR2); NCBI Gene IDs: 2321, 2322, 2324); fms related receptor tyrosine kinase 3 ligand (FLT3LG; NCBI Gene ID: 2323); focal adhesion kinase 2 (PTK2, FAK1; NCBI Gene ID: 5747); folate hydrolase 1 (FOLH1, PSMA; NCBI Gene ID: 2346); folate receptor 1 (FOLR1; NCBI Gene ID: 2348); forkhead box protein M1 (FOXM1; NCBI Gene ID: 2305); FURIN (FURIN, PACE; NCBI Gene ID: 5045); FYN tyrosine kinase (FYN, SYN; NCBI Gene ID: 2534); galectins (e.g., LGALS3, LGALS8 (PCTA1), LGALS9; NCBI Gene ID: 3958, 3964, 3965); glucocorticoid receptor (NR3C1, GR; NCBI Gene ID: 2908); glucuronidase beta (GUSB; NCBI Gene ID: 2990); glutamate metabotropic receptor 1 (GRM1; NCBI Gene ID: 2911); glutaminase (GLS; NCBI Gene ID: 2744); glutathione S-transferase Pi (GSTP1; NCBI Gene ID: 2950); glycogen synthase kinase 3 beta (GSK3B; NCBI Gene ID: 2932); glypican 3 (GPC3; NCBI Gene ID: 2719); gonadotropin releasing hormone 1 (GNRH1; NCBI Gene ID: 2796); gonadotropin releasing hormone receptor (GNRHR; NCBI Gene ID: 2798); GPNMB glycoprotein nmb (GPNMB, osteoactivin; NCBI Gene ID: 10457); growth differentiation factor 2 (GDF2, BMP9; NCBI Gene ID: 2658); growth factor receptor-bound protein 2 (GRB2, ASH; NCBI Gene ID: 2885); guanylate cyclase 2C (GUCY2C, STAR, MECIL, MUCIL, NCBI Gene ID: 2984); H19 imprinted

maternally expressed transcript (H19; NCBI Gene ID: 283120); HCK proto-oncogene, Src family tyrosine kinase (HCK; NCBI Gene ID: 3055); heat shock proteins (e.g., HSPA5 (HSP70, BIP, GRP78), HSPB1 (HSP27), HSP90B1 (GP96); NCBI Gene IDs: 3309, 3315, 7184); heme oxygenases (e.g., HMOX1 (HO1), HMOX2 (HO1); NCBI Gene ID: 3162, 3163); heparanase (HPSE; NCBI Gene ID: 10855); hepatitis A virus cellular receptor 2 (HAVCR2, TIM3, CD366; NCBI Gene ID: 84868); hepatocyte growth factor (HGF; NCBI Gene ID: 3082); HERV-H LTR-associating 2 (HHLA2, B7-H7; NCBI Gene ID: 11148); histamine receptor H2 (HRH2; NCBI Gene ID: 3274); histone deacetylases (e.g., HDAC1, HDAC7, HDAC9; NCBI Gene ID: 3065, 9734, 51564); HRas proto-oncogene, GTPase (HRAS; NCBI Gene ID: 3265); hypoxia-inducible factors (e.g., HIF1A, HIF2A (EPAS1); NCBI Gene IDs: 2034, 3091); I-Kappa-B kinase (IKK beta; NCBI Gene IDs: 3551, 3553); IKAROS family zinc fingers (IKZF1 (LYF1), IKZF3; NCBI Gene ID: 10320, 22806); immunoglobulin superfamily member 11 (IGSF11; NCBI Gene ID: 152404); indoleamine 2,3-dioxygenases (e.g., IDO1, IDO2; NCBI Gene IDs: 3620, 169355); inducible T cell costimulator (ICOS, CD278; NCBI Gene ID: 29851); inducible T cell costimulator ligand (ICOSLG, B7-H2; NCBI Gene ID: 23308); insulin like growth factor receptors (e.g., IGF1R, IGF2R; NCBI Gene ID: 3480, 3482); insulin like growth factors (e.g., IGF1, IGF2; NCBI Gene IDs: 3479, 3481); insulin receptor (INSR, CD220; NCBI Gene ID: 3643); integrin subunits (e.g., ITGA5 (CD49e), ITGAV (CD51), ITGB1 (CD29), ITGB2 (CD18, LFA1, MAC1), ITGB7; NCBI Gene IDs: 3678, 3685, 3688, 3695, 3698); intercellular adhesion molecule 1 (ICAM1, CD54; NCBI Gene ID: 3383); interleukin 1 receptor associated kinase 4 (IRAK4; NCBI Gene ID: 51135); interleukin receptors (e.g., IL2RA (TCGFR, CD25), IL2RB (CD122), IL2RG (CD132), IL3RA, IL6R, IL13RA2 (CD213A2), IL22RA1; NCBI Gene IDs: 3598, 3559, 3560, 3561, 3563, 3570, 58985); interleukins (e.g., IL1A, IL1B, IL2, IL3, IL6 (HGF), IL7, IL8 (CXCL8), IL10 (TGIF), IL12A, IL12B, IL15, IL17A (CTLA8), IL18, IL23A, IL24, IL-29 (IFNL1); NCBI Gene IDs: 3552, 3553, 3558, 3562, 3565, 3569, 3574, 3586, 3592, 3593, 3600, 3605, 3606, 11009, 51561, 282618); isocitrate dehydrogenases (NADP(+)1) (e.g., IDH1, IDH2; NCBI Gene IDs: 3417, 3418); Janus kinases (e.g., JAK1, JAK2, JAK3; NCBI Gene IDs: 3716, 3717, 3718); kallikrein related peptidase 3 (KLK3; NCBI Gene ID: 354); killer cell immunoglobulin like receptor, Ig domains and long cytoplasmic tails (e.g., KIR2DL1 (CD158A), KIR2DL2 (CD158B1), KIR2DL3 (CD158B), KIR2DL4 (CD158D), KIR2DL5A (CD158F), KIR2DL5B, KIR3DL1 (CD158E1), KIR3DL2 (CD158K), KIR3DP1 (CD158c), KIR2DS2 (CD158J); NCBI Gene IDs: 3802, 3803, 3804, 3805, 3811, 3812, 57292, 553128, 548594, 100132285); killer cell lectin like receptors (e.g., KLRC1 (CD159A), KLRC2 (CD159c), KLRC3, KLRRC4, KLRD1 (CD94), KLRG1, KLRK1 (NKG2D, CD314); NCBI Gene IDs: 3821, 3822, 3823, 3824, 8302, 10219, 22914); kinase insert domain receptor (KDR, CD309, VEGFR2; NCBI

Gene ID: 3791); kinesin family member 11 (KIF11; NCBI Gene ID: 3832); KiSS-1 metastasis suppressor (KISS1; NCBI Gene ID: 3814); KIT proto-oncogene, receptor tyrosine kinase (KIT, C-KIT, CD117; NCBI Gene ID: 3815); KRAS proto-oncogene, GTPase (KRAS; NCBI Gene ID: 3845); lactotransferrin (LTF; NCBI Gene ID: 4057); LCK proto-oncogene, Src family tyrosine kinase (LCK; NCBI Gene ID: 3932); LDL receptor related protein 1 (LRP1, CD91, IGFBP3R; NCBI Gene ID: 4035); leucine rich repeat containing 15 (LRRC15; NCBI Gene ID: 131578); leukocyte immunoglobulin like receptors (e.g., LILRB1 (ILT2, CD85J), LILRB2 (ILT4, CD85D); NCBI Gene ID: 10288, 10859); leukotriene A4 hydrolase (LTA4H; NCBI Gene ID: 4048); linker for activation of T-cells (LAT; NCBI Gene ID: 27040); luteinizing hormone/choriogonadotropin receptor (LHCGR; NCBI Gene ID: 3973); LY6/PLAUR domain containing 3 (LYPD3; NCBI Gene ID: 27076); lymphocyte activating 3 (LAG3; CD223; NCBI Gene ID: 3902); lymphocyte antigens (e.g., LY9 (CD229), LY75 (CD205); NCBI Gene IDs: 4063, 17076); LYN proto-oncogene, Src family tyrosine kinase (LYN; NCBI Gene ID: 4067); lypmphocyte cytosolic protein 2 (LCP2; NCBI Gene ID: 3937); lysine demethylase 1A (KDM1A; NCBI Gene ID: 23028); lysophosphatidic acid receptor 1 (LPAR1, EDG2, LPA1, GPR26; NCBI Gene ID: 1902); lysyl oxidase (LOX; NCBI Gene ID: 4015); lysyl oxidase like 2 (LOXL2; NCBI Gene ID: 4017); macrophage migration inhibitory factor (MIF, GIF; NCBI Gene ID: 4282); macrophage stimulating 1 receptor (MST1R, CD136; NCBI Gene ID: 4486); MAGE family members (e.g., MAGEA1, MAGEA2, MAGEA2B, MAGEA3, MAGEA4, MAGEA5, MAGEA6, MAGEA10,MAGEA11, MAGEC1, MAGEC2,MAGED1, MAGED2; NCBI Gene IDs: 4100, 4101, 4102, 4103, 4104, 4105, 4109, 4110, 9500, 9947, 10916, 51438, 266740); major histocompatibility complexes (e.g., HLA-A, HLA-E, HLA-F, HLA-G; NCBI Gene IDs: 3105, 3133, 3134, 3135); major vault protein (MVP, VAULT1; NCBI Gene ID: 9961); MALT1 paracaspase (MALT1; NCBI Gene ID: 10892); MAPK activated protein kinase 2 (MAPKAPK2; NCBI Gene ID: 9261); MAPK interacting serine/threonine kinases (e.g., MKNK1, MKNK2; NCBI Gene IDs: 2872, 8569); matrix metallopeptidases (e.g., MMP1, MMP2, MMP3, MMP7, MMP8, MMP9, MMP10, MMP11, MMP12, MMP13, MMP14, MMP15, MMP16, MMP17, MMP19, MMP20, MMP21,MMP24, MMP25, MMP26, MMP27, MMP28; NCBI Gene IDs: 4312, 4313, 4314, 4316, 4317, 4318, 4319, 4320, 4321, 4322, 4323, 4324, 4325, 4326, 4327, 9313, 10893, 56547, 64066, 64386, 79148, 118856); MCL1 apoptosis regulator, BCL2 family member (MCL1; NCBI Gene ID: 4170); MDM2 proto-oncogene (MDM2; NCBI Gene ID: 4193); MDM4 regulator of p53 (MDM4; BMFS6; NCBI Gene ID: 4194); mechanistic target of rapamycin kinase (MTOR, FRAP1; NCBI Gene ID: 2475); melan-A (MLANA; NCBI Gene ID: 2315); melanocortin receptors (MC1R, MC2R; NCBI Gene IDs: 4157, 4148); MER proto-oncogene, tyrosine kinase (MERTK; NCBI Gene ID: 10461); mesothelin (MSLN; NCBI Gene

ID: 10232); MET proto-oncogene, receptor tyrosine kinase (MET, c-Met, HGFR; NCBI Gene ID: 4233); methionyl aminopeptidase 2 (METAP2, MAP2; NCBI Gene ID: 10988); MHC class I polypeptide-related sequences (e.g., MICA, MICB; NCBI Gene IDs: 4277, 100507436); mitogen activated protein kinases (e.g., MAPK1 (ERK2), MAPK3 (ERK1), MAPK8 (JNK1), MAPK9 (JNK2), MAPK10 (JNK3), MAPK11 (p38 beta), MAPK12; NCBI Gene IDs: 5594, 5595, 5599, 5600, 5601, 5602, 819251); mitogen-activated protein kinase kinase kinases (e.g., MAP3K5 (ASK1), MAP3K8 (TPL2, AURA2); NCBI Gene IDs: 4217, 1326); mitogen-activated protein kinase kinase kinase kinase 1 (MAP4K1, HPK1; NCBI Gene ID: 11184); mitogen-activated protein kinase kinases (e.g., MAP2K1 (MEK1), MAP2K2 (MEK2), MAP2K7 (MEK7); NCBI Gene IDs: 5604, 5605, 5609); MPL proto-oncogene, thrombopoietin receptor (MPL; NCBI Gene ID: 4352); mucins (e.g., MUC1 (including splice variants thereof (e.g., including MUC1/A, C, D, X, Y, Z and REP)), MUC5AC, MUC16 (CA125); NCBI Gene IDs: 4582, 4586, 94025); MYC proto-oncogene, bHLH transcription factor (MYC; NCBI Gene ID: 4609); myostatin (MSTN, GDF8; NCBI Gene ID: 2660); myristoylated alanine rich protein kinase C substrate (MARCKS; NCBI Gene ID: 4082); natriuretic peptide receptor 3 (NPR3; NCBI Gene ID: 4883); natural killer cell cytotoxicity receptor 3 ligand 1 (NCR3LG1, B7-H6; NCBI Gene ID: 374383); necdin, MAGE family member (NDN; NCBI Gene ID: 4692); nectin cell adhesion molecules (e.g., NECTIN2 (CD112, PVRL2), NECTIN4 (PVRL4); NCBI Gene IDs: 5819, 81607); neural cell adhesion molecule 1 (NCAM1, CD56; NCBI Gene ID: 4684); neuropilins (e.g., NRP1 (CD304, VEGF165R), NRP2 (VEGF165R2); NCBI Gene IDs: 8828, 8829); neurotrophic receptor tyrosine kinases (e.g., NTRK1 (TRKA), NTRK2 (TRKB), NTRK3 (TRKC); NCBI Gene IDs: 4914, 4915, 4916); NFKB activating protein (NKAP; NCBI Gene ID: 79576); NIMA related kinase 9 (NEK9; NCBI Gene ID: 91754); NLR family pyrin domain containing 3 (NLRP3, NALP3; NCBI Gene ID: 114548); notch receptors (e.g., NOTCH1, NOTCH2, NOTCH3, NOTCH4; NCBI Gene IDs: 4851, 4853, 4854, 4855); NRAS proto-oncogene, GTPase (NRAS; NCBI Gene ID: 4893); nuclear factor kappa B (NFKB1, NFKB2; NCBI Gene IDs: 4790, 4791); nuclear factor, erythroid 2 like 2 (NFE2L2; NRF2; NCBI Gene ID: 4780); nuclear receptor subfamily 4 group A member 1 (NR4A1; NCBI Gene ID: 3164); nucleolin (NCL; NCBI Gene ID: 4691); nucleophosmin 1 (NPM1; NCBI Gene ID: 4869); nucleotide binding oligomerization domain containing 2 (NOD2; NCBI Gene ID: 64127); nudix hydrolase 1 (NUDT1; NCBI Gene ID: 4521); O-6-methylguanine-DNA methyltransferase (MGMT; NCBI Gene ID: 4255); opioid receptor delta 1 (OPRD1; NCBI Gene ID: 4985); ornithine decarboxylase 1 (ODC1; NCBI Gene ID: 4953); oxoglutarate dehydrogenase (OGDH; NCBI Gene ID: 4967); parathyroid hormone (PTH; NCBI Gene ID: 5741); PD-L1 (CD274; NCBI Gene ID: 29126); periostin (POSTN; NCBI Gene ID: 10631); peroxisome proliferator activated receptors (e.g., PPARA (PPAR alpha), PPARD (PPAR delta),

PPARG (PPAR gamma); NCBI Gene IDs: 5465, 5467, 5468); phosphatase and tensin homolog (PTEN; NCBI Gene ID: 5728); phosphatidylinositol-4,5-bisphosphate 3-kinases (PIK3CA (PI3K alpha), PIK3CB (PI3K beta), PIK3CD (PI3K delta), PIK3CG (PI3K gamma); NCBI Gene IDs: 5290, 5291, 5293, 5294); phospholipases (e.g., PLA2G1B, PLA2G2A, PLA2G2D, PLA2G3, PLA2G4A, PLA2G5, PLA2G7, PLA2G10, PLA2G12A, PLA2G12B, PLA2G15; NCBI Gene IDs: 5319, 5320, 5321, 5322, 7941, 8399, 50487, 23659, 26279, 81579, 84647); Pim proto-oncogene, serine/threonine kinases (e.g., PIM1, PIM2, PIM3; NCBI Gene IDs: 5292, 11040, 415116); placenta growth factor (PGF; NCBI Gene ID: 5228); plasminogen activator, urokinase (PLAU, u-PA, ATF; NCBI Gene ID: 5328); platelet derived growth factor receptors (e.g., PDGFRA (CD140A, PDGFR2), FDGFRB (CD140B, PDGFR1); NCBI Gene IDs: 5156, 5159); plexin B1 (PLXNB1; NCBI Gene ID: 5364); poliovirus receptor (PVR) cell adhesion molecule (PVR, CD155; NCBI Gene ID: 5817); polo like kinase 1 (PLK1; NCBI Gene ID: 5347); poly(ADP-ribose) polymerases (e.g., PARP1, PARP2, PARP3; NCBI Gene IDs: 142, 10038, 10039); polycomb protein EED (EED; NCBI Gene ID: 8726); porcupine O-acyltransferase (PORCN; NCBI Gene ID: 64840); PRAME nuclear receptor transcriptional regulator (PRAME; NCBI Gene ID: 23532); premelanosome protein (PMEL; NCBI Gene ID: 6490); progesterone receptor (PGR; NCBI Gene ID: 5241); programmed cell death 1 (PDCD1, PD-1, CD279; NCBI Gene ID: 5133); programmed cell death 1 ligand 2 (PDCD1LG2, CD273, PD-L2; NCBI Gene ID: 80380); prominin 1 (PROM1, CD133; NCBI Gene ID: 8842); promyelocytic leukemia (PML; NCBI Gene ID: 5371); prosaposin (PSAP; NCBI Gene ID: 5660); prostaglandin E receptor 4 (PTGER4; NCBI Gene ID: 5734); prostaglandin E synthase (PTGES; NCBI Gene ID: 9536); prostaglandin-endoperoxide synthases (PTGS1 (COX1), PTGS2 (COX2); NCBI Gene ID: 5742, 5743); proteasome 20S subunit beta 9 (PSMB9; NCBI Gene ID: 5698); protein arginine methyltransferases (e.g., PRMT1, PRMT5; NCBI Gene ID: 3276, 10419); protein kinase N3 (PKN3; NCBI Gene ID: 29941); protein phosphatase 2A (PPP2CA; NCBI Gene ID: 5515); protein tyrosine kinase 7 (inactive) (PTK7; NCBI Gene ID: 5754); protein tyrosine phosphatase receptors (PTPRB (PTPB), PTPRC (CD45R); NCBI Gene ID: 5787, 5788); prothymosin alpha (PTMA; NCBI Gene ID: 5757); purine nucleoside phosphorylase (PNP; NCBI Gene ID: 4860); purinergic receptor P2X 7 (P2RX7; NCBI Gene ID: 5027); PVR related immunoglobulin domain containing (PVRIG, CD112R; NCBI Gene ID: 79037); Raf-1 proto-oncogene, serine/threonine kinase (RAF1, c-Raf; NCBI Gene ID: 5894); RAR-related orphan receptor gamma (RORC; NCBI Gene ID: 6097); ras homolog family member C (RHOC); NCBI Gene ID: 389); Ras homolog, mTORC1 binding (RHEB; NCBI Gene ID: 6009); RB transcriptional corepressor 1 (RB1; NCBI Gene ID: 5925); receptor-interacting serine/threonine protein kinase 1 (RIPK1; NCBI Gene ID: 8737); ret proto-oncogene (RET; NCBI Gene ID: 5979); retinoic acid early transcripts (e.g.,

RAET1E, RAET1G, RAET1L; NCBI Gene IDs: 135250, 154064, 353091); retinoic acid receptors alpha (e.g., RARA, RARG; NCBI Gene IDs: 5914, 5916); retinoid X receptors (e.g., RXRA, RXRB, RXRG; NCBI Gene IDs: 6256, 6257, 6258); Rho associated coiled-coil containing protein kinases (e.g., ROCK1, ROCK2; NCBI Gene IDs: 6093, 9475); ribosomal protein S6 kinase B1 (RPS6KB1, S6K-beta 1; NCBI Gene ID: 6198); ring finger protein 128 (RNF128, GRAIL; NCBI Gene ID: 79589); ROS proto-oncogene 1, receptor tyrosine kinase (ROS1; NCBI Gene ID: 6098); roundabout guidance receptor 4 (ROBO4; NCBI Gene ID: 54538); RUNX family transcription factor 3 (RUNX3; NCBI Gene ID: 864); S100 calcium binding protein A9 (S100A9; NCBI Gene ID: 6280); secreted frizzled related protein 2 (SFRP2; NCBI Gene ID: 6423); secreted phosphoprotein 1 (SPP1; NCBI Gene ID: 6696); secretoglobin family 1A member 1 (SCGB1A1; NCBI Gene ID: 7356); selectins (e.g., SELE, SELL (CD62L), SELP (CD62); NCBI Gene IDs: 6401, 6402, 6403); semaphorin 4D (SEMA4D; CD100; NCBI Gene ID: 10507); sialic acid binding Ig like lectins (SIGLEC7 (CD328), SIGLEC9 (CD329), SIGLEC10; NCBI Gene ID: 27036, 27180, 89790); signal regulatory protein alpha (SIRPA, CD172A; NCBI Gene ID: 140885); signal transducer and activator of transcription (e.g., STAT1, STAT3, STAT5A, STAT5B ; NCBI Gene IDs: 6772, 6774, 6776, 6777); sirtuin-3 (SIRT3; NCBI Gene ID: 23410); signaling lymphocytic activation molecule (SLAM) family members (e.g., SLAMF1 (CD150), SLAMF6 (CD352), SLAMF7 (CD319), SLAMF8 (CD353), SLAMF9; NCBI Gene IDs: 56833, 57823, 89886, 114836); SLIT and NTRK like family member 6 (SLITRK6; NCBI Gene ID: 84189); smoothened, frizzled class receptor (SMO; NCBI Gene ID: 6608); soluble epoxide hydrolase 2 (EPHX2; NCBI Gene ID: 2053); solute carrier family members (e.g., SLC3A2 (CD98), SLC5A5, SLC6A2, SLC10A3, SLC34A2, SLC39A6, SLC43A2 (LAT4), SLC44A4; NCBI Gene IDs: 6520, 6528, 6530, 8273, 10568, 25800, 80736, 124935); somatostatin receptors (e.g., SSTR1, SSTR2, SSTR3, SSTR4, SSTR5; NCBI Gene IDs: 6751, 6752, 6753, 6754, 6755); sonic hedgehog signaling molecule (SHH; NCBI Gene ID: 6469); Sp1 transcription factor (SP1; NCBI Gene ID: 6667); sphingosine kinases (e.g., SPHK1, SPHK2; NCBI Gene IDs: 8877, 56848); sphingosine-1-phosphate receptor 1 (S1PR1, CD363; NCBI Gene ID: 1901); spleen associated tyrosine kinase (SYK; NCBI Gene ID: 6850); splicing factor 3B factor 1 (SF3B1; NCBI Gene ID: 23451); SRC proto-oncogene, non-receptor tyrosine kinase (SRC; NCBI Gene ID: 6714); stabilin 1 (STAB1, CLEVER-1; NCBI Gene ID: 23166); STEAP family member 1 (STEAP1; NCBI Gene ID: 26872); steroid sulfatase (STS; NCBI Gene ID: 412); stimulator of interferon response cGAMP interactor 1 (STING1; NCBI Gene ID: 340061); superoxide dismutase 1 (SOD1, ALS1; NCBI Gene ID: 6647); suppressors of cytokine signaling (SOCS1 (CISH1), SOCS3 (CISH3); NCBI Gene ID: 8651, 9021); synapsin 3 (SYN3; NCBI Gene ID: 8224); syndecan 1 (SDC1, CD138, syndecan; NCBI Gene ID: 6382); synuclein alpha (SNCA,

PARK1; NCBI Gene ID: 6622); T cell immunoglobulin and mucin domain containing 4 (TIMD4, SMUCKLER; NCBI Gene ID: 91937); T cell immunoreceptor with Ig and ITIM domains (TIGIT; NCBI Gene ID: 201633); tachykinin receptors (e.g., TACR1, TACR3; NCBI Gene ID: 6869, 6870); TANK binding kinase 1 (TBK1; NCBI Gene ID: 29110); tankyrase (TNKS; NCBI Gene ID: 8658); TATA-box binding protein associated factor, RNA polymerase I subunit B (TAF1B; NCBI Gene ID: 9014); T-box transcription factor T (TBXT; NCBI Gene ID: 6862); TCDD inducible poly(ADP-ribose) polymerase (TIPARP, PAPR7; NCBI Gene ID: 25976); tec protein tyrosine kinase (TEC; NCBI Gene ID: 7006); TEK receptor tyrosine kinase (TEK, CD202B, TIE2; NCBI Gene ID: 7010); telomerase reverse transcriptase (TERT; NCBI Gene ID: 7015); tenascin C (TNC; NCBI Gene ID: 3371); three prime repair exonucleases (e.g., TREX1, TREX2; NCBI Gene ID: 11277, 11219); thrombomodulin (THBD, CD141; NCBI Gene ID: 7056); thymidine kinases (e.g., TK1, TK2; NCBI Gene IDs: 7083, 7084); thymidine phosphorylase (TYMP; NCBI Gene ID: 1890); thymidylate synthase (TYMS; NCBI Gene ID: 7298); thyroid hormone receptor (THRA, THRB; NCBI Gene IDs: 7606, 7608); thyroid stimulating hormone receptor (TSHR; NCBI Gene ID: 7253); TNF superfamily members (e.g., TNFSF4 (OX40L, CD252),TNFSF5 (CD40L), TNFSF7 (CD70), TNFSF8 (CD153, CD30L), TNFSF9 (4-1BB-L, CD137L), TNFSF10 (TRAIL, CD253, APO2L), TNFSF11 (CD254, RANKL2, TRANCE), TNFSF13 (APRIL, CD256, TRAIL2), TNFSF13b (BAFF, BLYS, CD257), TNFSF14 (CD258, LIGHT), TNFSF18 (GITRL); NCBI Gene IDs: 944, 959, 970, 7292, 8600, 8740, 8741, 8743, 8744, 8995); toll like receptors (e.g., TLR1 (CD281), TLR2 (CD282), TLR3 (CD283), TLR4 (CD284), TLR5, TLR6 (CD286), TLR7, TLR8 (CD288), TLR9 (CD289), TLR10 (CD290); NCBI Gene IDs: 7096, 7097, 7098, 7099, 10333, 51284, 51311, 54106, 81793); transferrin (TF; NCBI Gene ID: 7018); transferrin receptor (TFRC, CD71; NCBI Gene ID: 7037); transforming growth factors (e.g., TGFA, TGFB1; NCBI Gene ID: 7039, 7040); transforming growth factor receptors (e.g., TGFBR1, TGFBR2, TGFBR3; NCBI Gene ID: 7046, 7048, 7049); transforming protein E7 (E7; NCBI Gene ID: 1489079); transglutaminase 5 (TGM5; NCBI Gene ID: 9333); transient receptor potential cation channel subfamily V member 1 (TRPV1, VR1; NCBI Gene ID: 7442); transmembrane and immunoglobulin domain containing 2 (TMIGD2, CD28H, IGPR1; NCBI Gene ID: 126259); triggering receptors expressed on myeloid cells (e.g., TREM1 (CD354), TREM2; NCBI Gene ID: 54209, 54210); trophinin (TRO, MAGED3; NCBI Gene ID: 7216); trophoblast glycoprotein (TPBG; NCBI Gene ID: 7162); tryptophan 2,3-dioxygenase (TDO2; NCBI Gene ID: 6999); tryptophan hydroxylases (e.g., TPH1, TPH2; NCBI Gene ID: 7166, 121278); tumor associated calcium signal transducer 2 (TACSTD2, TROP2, EGP1; NCBI Gene ID: 4070); tumor necrosis factor (TNF; NCBI Gene ID: 7124); tumor necrosis factor (TNF) receptor superfamily members (e.g., TNFRSF1A (CD120a), TNFRSF1B (CD120b), TNFRSF4

(OX40), TNFRSF5 (CD40),TNFRSF6 (CD95, FAS receptor), TNFRSF7 (CD27), TNFRSF8 (CD30), TNFRSF9 (CD137, 4-1BB), TNFRSF10A (CD261), TNFRSF10B (TRAIL, DR5, CD262), TNFRSF10C, TNFRSF10D, TNFRSF11A, TNFRSF11B (OPG), TNFRSF12A, TNFRSF13B, TNFR13C (, CD268, BAFFR), TNFRSF14 (CD270, LIGHTR), TNFRSF16, TNFRSF17 (CD269, BCMA), TNFRSF18 (GITR, CD357), TNFRSF19, TNFRSF21, TNFRSF25, ; NCBI Gene IDs: 355, 608, 939, 943, 958, 3604, 4804, 4982, 7132, 7133, 7293, 8718, 8764, 8784, 8792, 8793, 8794, 8795, 8797, 23495, 27242, 51330, 55504); tumor protein p53 (TP53; NCBI Gene ID: 7157); tumor suppressor 2, mitochondrial calcium regulator (TUSC2; NCBI Gene ID: 11334); TYRO3 protein tyrosine kinase (TYRO3; BYK; NCBI Gene ID: 7301); tyrosinase (TYR; NCBI Gene ID: 7299); tyrosine hydroxylase (TH; NCBI Gene ID: 7054); tyrosine kinase with immunoglobulin like and EGF like domains 1 (e.g., TIE1, TIE1; NCBI Gene ID: 7075); tyrosine-protein phosphatase non-receptor type 11 (PTPN11, SHP2; NCBI Gene ID: 5781); ubiquitin conjugating enzyme E2 I (UBE2I, UBC9; NCBI Gene ID: 7329); ubiquitin C-terminal hydrolase L5 (UCHL5; NCBI Gene ID: 51377); ubiquitin specific peptidase 7 (USP7; NCBI Gene ID: 7874); ubiquitin-like modifier activating enzyme 1 (UBA1; NCBI Gene ID: 7317); UL16 binding proteins (e.g., ULBP1, ULBP2, ULBP3; NCBI Gene ID: 79465, 80328, 80328); valosin-containing protein (VCP, CDC48; NCBI Gene ID: 7415); vascular cell adhesion molecule 1 (VCAM1, CD106; NCBI Gene ID: 7412); vascular endothelial growth factors (e.g., VEGFA, VEGFB; NCBI Gene ID: 7422, 7423); vimentin (VIM; NCBI Gene ID: 7431); vitamin D receptor (VDR; NCBI Gene ID: 7421); V-set domain containing T cell activation inhibitor 1 (VTCN1, B7-H4; NCBI Gene ID: 79679); V-set immunoregulatory receptor (VSIR, VISTA, B7-H5; NCBI Gene ID: 64115); WEE1 G2 checkpoint kinase (WEE1; NCBI Gene ID: 7465); WRN RecQ like helicase (WRN; RECQ3; NCBI Gene ID: 7486); WT1 transcription factor (WT1; NCBI Gene ID: 7490); WW domain containing transcription regulator 1 (WWTR1; TAZ; NCBI Gene ID: 25937); X-C motif chemokine ligand 1 (XCL1, ATAC; NCBI Gene ID: 6375); X-C motif chemokine receptor 1 (XCR1, GPR5, CCXCR1; NCBI Gene ID: 2829); Yes1 associated transcriptional regulator (YAP1; NCBI Gene ID: 10413); zeta chain associated protein kinase 70 (ZAP70; NCBI Gene ID: 7535).

[0261] In some embodiments, the one or more additional therapeutic agents include, e.g., an agent targeting 5'-nucleotidase ecto (NT5E or CD73; NCBI Gene ID: 4907); adenosine A_{2A} receptor (ADORA2A; NCBI Gene ID: 135); adenosine A_{2B} receptor (ADORA2B; NCBI Gene ID: 136); C-C motif chemokine receptor 8 (CCR8, CDw198; NCBI Gene ID: 1237); cytokine inducible SH2 containing protein (CISH; NCBI Gene ID: 1154); diacylglycerol kinase alpha (DGKA, DAGK, DAGK1 or DGK-alpha; NCBI Gene ID: 1606); fms like tyrosine kinase 3 (FLT3, CD135;

NCBI Gene ID: 2322); integrin associated protein (IAP, CD47; NCBI Gene ID: 961); interleukine-2 (IL2; NCBI Gene ID:3558); interleukine 2 receptor (IL2RA, IL2RB, IL2RG; NCBI Gene IDs: 3559, 3560, 3561); Kirsten rat sarcoma virus (KRAS; NCBI Gene ID: 3845; including mutations, such as KRAS G12C or G12D); mitogen-activated protein kinase kinase kinase kinase 1 (MAP4K1) (also called Hematopoietic Progenitor Kinase 1 (HPK1), NCBI Gene ID: 11184); myeloid cell leukemia sequence 1 apoptosis regulator (MCL1; NCBI Gene ID: 4170); phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta (PIK3CD; NCBI Gene ID: 5293); programmed death-ligand 1 (PD-L1, CD274; NCBI Gene ID 29126); programmed cell death protein 1 (PD-1, CD279; NCBI Gene ID: 5133); proto-oncogen c-KIT (KIT, CD117; NCBI Gene ID: 3815); signal-regulatory protein alpha (SIRPA, CD172A; NCBI Gene ID: 140885); TCDD inducible poly(ADP-ribose) polymerase (TIPARP, PARP7; NCBI Gene ID: 25976); T cell immunoreceptor with Ig and ITIM domains (TIGIT; NCBI Gene ID: 201633); triggering receptor expressed on myeloid cells 1 (TREM1; NCBI Gene ID: 54210); triggering receptor expressed on myeloid cells 2 (TREM2; NCBI Gene ID: 54209); tumor-associated calcium signal transducer 2 (TACSTD2, TROP2, EGP1; NCBI Gene ID: 4070); tumor necrosis factor receptor superfamily, member 4 (TNFRSF4, CD134, OX40; NCBI Gene ID:7293); tumor necrosis factor receptor superfamily, member 9 (TNFRSF9, 4-1BB, CD137; NCBI Gene ID: 3604); tumor necrosis factor receptor superfamily, member 18 (TNFRSF18, CD357, GITR; NCBI Gene ID: 8784); WRN RecQ like helicase (WRN; NCBI Gene ID: 7486); zinc finger protein Helios (IKZF2; NCBI Gene ID: 22807).

Illustrative Mechanisms of Action

Immune Checkpoint Modulators

[0262] In some embodiments a compound provided herein is administered with one or more blockers or inhibitors of inhibitory immune checkpoint proteins or receptors and/or with one or more stimulators, activators or agonists of one or more stimulatory immune checkpoint proteins or receptors. Blockade or inhibition of inhibitory immune checkpoints can positively regulate T-cell or NK cell activation and prevent immune escape of cancer cells within the tumor microenvironment. Activation or stimulation of stimulatory immune check points can augment the effect of immune checkpoint inhibitors in cancer therapeutics. In some embodiments, the immune checkpoint proteins or receptors regulate T cell responses (*e.g.*, reviewed in Xu, *et al.*, *J Exp Clin Cancer Res.* (2018) 37:110). In some embodiments, the immune checkpoint proteins or receptors regulate NK cell responses (*e.g.*, reviewed in Davis, *et al.*, *Semin Immunol.* (2017) 31:64–75 and Chiossone, *et al.*, *Nat Rev Immunol.* (2018) 18(11):671-688). Inhibition of

regulatory T-cells (Treg) or Treg depletion can alleviate their suppression of antitumor immune responses and have anticancer effects (*e.g.*, reviewed in Plitas and Rudensky, *Annu. Rev. Cancer Biol.* (2020) 4:459-77; Tanaka and Sakaguchi, *Eur. J. Immunol.* (2019) 49:1140-1146).

[0263] Examples of immune checkpoint proteins or receptors include CD27 (NCBI Gene ID: 939), CD70 (NCBI Gene ID: 970); CD40 (NCBI Gene ID: 958), CD40LG (NCBI Gene ID: 959); CD47 (NCBI Gene ID: 961), SIRPA (NCBI Gene ID: 140885); CD48 (SLAMF2; NCBI Gene ID: 962), transmembrane and immunoglobulin domain containing 2 (TMIGD2, CD28H; NCBI Gene ID: 126259), CD84 (LY9B, SLAMF5; NCBI Gene ID: 8832), CD96 (NCBI Gene ID: 10225), CD160 (NCBI Gene ID: 11126), MS4A1 (CD20; NCBI Gene ID: 931), CD244 (SLAMF4; NCBI Gene ID: 51744); CD276 (B7H3; NCBI Gene ID: 80381); V-set domain containing T cell activation inhibitor 1 (VTCN1, B7H4); V-set immunoregulatory receptor (VSIR, B7H5, VISTA; NCBI Gene ID: 64115); immunoglobulin superfamily member 11 (IGSF11, VSIG3; NCBI Gene ID: 152404); natural killer cell cytotoxicity receptor 3 ligand 1 (NCR3LG1, B7H6; NCBI Gene ID: 374383); HERV-H LTR-associating 2 (HHLA2, B7H7; NCBI Gene ID: 11148); inducible T cell co-stimulator (ICOS, CD278; NCBI Gene ID: 29851); inducible T cell co-stimulator ligand (ICOSLG, B7H2; NCBI Gene ID: 23308); TNF receptor superfamily member 4 (TNFRSF4, OX40; NCBI Gene ID: 7293); TNF superfamily member 4 (TNFSF4, OX40L; NCBI Gene ID: 7292); TNFRSF8 (CD30; NCBI Gene ID: 943), TNFSF8 (CD30L; NCBI Gene ID: 944); TNFRSF10A (CD261, DR4, TRAILR1; NCBI Gene ID: 8797), TNFRSF9 (CD137; NCBI Gene ID: 3604), TNFSF9 (CD137L; NCBI Gene ID: 8744); TNFRSF10B (CD262, DR5, TRAILR2; NCBI Gene ID: 8795), TNFRSF10 (TRAIL; NCBI Gene ID: 8743); TNFRSF14 (HVEM, CD270; NCBI Gene ID: 8764), TNFSF14 (HVEML; NCBI Gene ID: 8740); CD272 (B and T lymphocyte associated (BTLA); NCBI Gene ID: 151888); TNFRSF17 (BCMA, CD269; NCBI Gene ID: 608), TNFSF13B (BAFF; NCBI Gene ID: 10673); TNFRSF18 (GITR; NCBI Gene ID: 8784), TNFSF18 (GITRL; NCBI Gene ID: 8995); MHC class I polypeptide-related sequence A (MICA; NCBI Gene ID: 100507436); MHC class I polypeptide-related sequence B (MICB; NCBI Gene ID: 4277); CD274 (CD274, PDL1, PD-L1; NCBI Gene ID: 29126); programmed cell death 1 (PDCD1, PD1, PD-1; NCBI Gene ID: 5133); cytotoxic T-lymphocyte associated protein 4 (CTLA4, CD152; NCBI Gene ID: 1493); CD80 (B7-1; NCBI Gene ID: 941), CD28 (NCBI Gene ID: 940); nectin cell adhesion molecule 2 (NECTIN2, CD112; NCBI Gene ID: 5819); CD226 (DNAM-1; NCBI Gene ID: 10666); Poliovirus receptor (PVR) cell adhesion molecule (PVR, CD155; NCBI Gene ID: 5817); PVR related immunoglobulin domain containing (PVRIG, CD112R; NCBI Gene ID: 79037); T cell immunoreceptor with Ig and ITIM domains (TIGIT; NCBI Gene ID: 201633); T cell immunoglobulin and mucin domain

containing 4 (TIMD4; TIM4; NCBI Gene ID: 91937); hepatitis A virus cellular receptor 2 (HAVCR2, TIMD3, TIM3; NCBI Gene ID: 84868); galectin 9 (LGALS9; NCBI Gene ID: 3965); lymphocyte activating 3 (LAG3, CD223; NCBI Gene ID: 3902); signaling lymphocytic activation molecule family member 1 (SLAMF1, SLAM, CD150; NCBI Gene ID: 6504); lymphocyte antigen 9 (LY9, CD229, SLAMF3; NCBI Gene ID: 4063); SLAM family member 6 (SLAMF6, CD352; NCBI Gene ID: 114836); SLAM family member 7 (SLAMF7, CD319; NCBI Gene ID: 57823); UL16 binding protein 1 (ULBP1; NCBI Gene ID: 80329); UL16 binding protein 2 (ULBP2; NCBI Gene ID: 80328); UL16 binding protein 3 (ULBP3; NCBI Gene ID: 79465); retinoic acid early transcript 1E (RAET1E; ULBP4; NCBI Gene ID: 135250); retinoic acid early transcript 1G (RAET1G; ULBP5; NCBI Gene ID: 353091); retinoic acid early transcript 1L (RAET1L; ULBP6; NCBI Gene ID: 154064); killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 1 (KIR, CD158E1; NCBI Gene ID: 3811, *e.g.*, lirilumab (IPH-2102, IPH-4102)); killer cell lectin like receptor C1 (KLRC1, NKG2A, CD159A; NCBI Gene ID: 3821); killer cell lectin like receptor K1 (KLRK1, NKG2D, CD314; NCBI Gene ID: 22914); killer cell lectin like receptor C2 (KLRC2, CD159c, NKG2C; NCBI Gene ID: 3822); killer cell lectin like receptor C3 (KLRC3, NKG2E; NCBI Gene ID: 3823); killer cell lectin like receptor C4 (KLRC4, NKG2F; NCBI Gene ID: 8302); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 1 (KIR2DL1; NCBI Gene ID: 3802); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 2 (KIR2DL2; NCBI Gene ID: 3803); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 3 (KIR2DL3; NCBI Gene ID: 3804); killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 1 (KIR3DL1); killer cell lectin like receptor D1 (KLRD1; NCBI Gene ID: 3824); killer cell lectin like receptor G1 (KLRG1; CLEC15A, MAFA, 2F1; NCBI Gene ID: 10219); sialic acid binding Ig like lectin 7 (SIGLEC7; NCBI Gene ID: 27036); and sialic acid binding Ig like lectin 9 (SIGLEC9; NCBI Gene ID: 27180).

[0264] In some embodiments a compound provided herein is administered with one or more blockers or inhibitors of one or more T-cell inhibitory immune checkpoint proteins or receptors. Illustrative T-cell inhibitory immune checkpoint proteins or receptors include CD274 (CD274, PDL1, PD-L1); programmed cell death 1 ligand 2 (PDCD1LG2, PD-L2, CD273); programmed cell death 1 (PDCD1, PD1, PD-1); cytotoxic T-lymphocyte associated protein 4 (CTLA4, CD152); CD276 (B7H3); V-set domain containing T cell activation inhibitor 1 (VTCN1, B7H4); V-set immunoregulatory receptor (VSIR, B7H5, VISTA); immunoglobulin superfamily member 11 (IGSF11, VSIG3); TNFRSF14 (HVEM, CD270), TNFSF14 (HVEML); CD272 (B and T lymphocyte associated (BTLA)); PVR related immunoglobulin domain containing (PVRIG,

CD112R); T cell immunoreceptor with Ig and ITIM domains (TIGIT); lymphocyte activating 3 (LAG3, CD223); hepatitis A virus cellular receptor 2 (HAVCR2, TIMD3, TIM3); galectin 9 (LGALS9); killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 1 (KIR, CD158E1); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 1 (KIR2DL1); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 2 (KIR2DL2); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 3 (KIR2DL3); and killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 1 (KIR3DL1). In some embodiments, the compound provided herein is administered with one or more agonist or activators of one or more T-cell stimulatory immune checkpoint proteins or receptors. Illustrative T-cell stimulatory immune checkpoint proteins or receptors include without limitation CD27, CD70; CD40, CD40LG; inducible T cell costimulator (ICOS, CD278); inducible T cell costimulator ligand (ICOSLG, B7H2); TNF receptor superfamily member 4 (TNFRSF4, OX40); TNF superfamily member 4 (TNFSF4, OX40L); TNFRSF9 (CD137), TNFSF9 (CD137L); TNFRSF18 (GITR), TNFSF18 (GITRL); CD80 (B7-1), CD28; nectin cell adhesion molecule 2 (NECTIN2, CD112); CD226 (DNAM-1); CD244 (2B4, SLAMF4), Poliovirus receptor (PVR) cell adhesion molecule (PVR, CD155). *See, e.g.*, Xu, *et al.*, *J Exp Clin Cancer Res.* (2018) 37:110.

[0265] In some embodiments the compound provided herein is administered with one or more blockers or inhibitors of one or more NK-cell inhibitory immune checkpoint proteins or receptors. Illustrative NK-cell inhibitory immune checkpoint proteins or receptors include killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 1 (KIR, CD158E1); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 1 (KIR2DL1); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 2 (KIR2DL2); killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 3 (KIR2DL3); killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 1 (KIR3DL1); killer cell lectin like receptor C1 (KLRC1, NKG2A, CD159A); killer cell lectin like receptor D1 (KLRD1, CD94), killer cell lectin like receptor G1 (KLRG1; CLEC15A, MAFA, 2F1); sialic acid binding Ig like lectin 7 (SIGLEC7); and sialic acid binding Ig like lectin 9 (SIGLEC9). In some embodiments the compound provided herein is administered with one or more agonist or activators of one or more NK-cell stimulatory immune checkpoint proteins or receptors. Illustrative NK-cell stimulatory immune checkpoint proteins or receptors include CD16, CD226 (DNAM-1); CD244 (2B4, SLAMF4); killer cell lectin like receptor K1 (KLRK1, NKG2D, CD314); SLAM family member 7 (SLAMF7). *See, e.g.*, Davis, *et al.*, *Semin Immunol.* (2017)

31:64–75; Fang, *et al.*, *Semin Immunol.* (2017) 31:37-54; and Chiossone, *et al.*, *Nat Rev Immunol.* (2018) 18(11):671-688.

[0266] In some embodiments the one or more immune checkpoint inhibitors comprises a proteinaceous (*e.g.*, antibody or fragment thereof, or antibody mimetic) inhibitor of PD-L1 (CD274), PD-1 (PDCD1), CTLA4, or TIGIT. In some embodiments the one or more immune checkpoint inhibitors comprises a small organic molecule inhibitor of PD-L1 (CD274), PD-1 (PDCD1), CTLA4, or TIGIT. In some embodiments the one or more immune checkpoint inhibitors comprises a proteinaceous (*e.g.*, antibody or fragment thereof, or antibody mimetic) inhibitor of LAG3.

[0267] Examples of inhibitors of CTLA4 that can be co-administered include ipilimumab, tremelimumab, BMS-986218, AGEN1181, zalifrelimab (AGEN1884), BMS-986249, MK-1308, REGN-4659, ADU-1604, CS-1002 (ipilimumab biosimilar), BCD-145, APL-509, JS-007, BA-3071, ONC-392, AGEN-2041, HBM-4003, JHL-1155, KN-044, CG-0161, ATOR-1144, PBI-5D3H5, BPI-002, as well as multi-specific inhibitors FPT-155 (CTLA4/PD-L1/CD28), PF-06936308 (PD-1/ CTLA4), MGD-019 (PD-1/CTLA4), KN-046 (PD-1/CTLA4), MEDI-5752 (CTLA4/PD-1), XmAb-20717 (PD-1/CTLA4), and AK-104 (CTLA4/PD-1).

[0268] Examples of inhibitors of PD-L1 (CD274) or PD-1 (PDCD1) that can be co-administered include pembrolizumab, nivolumab, cemiplimab, pidilizumab, AMP-224, MEDI0680 (AMP-514), spartalizumab, atezolizumab, avelumab, durvalumab, BMS-936559, cosibelimab (CK-301), sasanlimab (PF-06801591), tislelizumab (BGB-A317), GLS-010 (WBP-3055), AK-103 (HX-008), AK-105, CS-1003, HLX-10, retifanlimab (MGA-012), BI-754091, balstilimab (AGEN-2034), AMG-404, toripalimab (JS-001), cetrelimab (JNJ-63723283), genolimzumab (CBT-501), LZM-009, prolgolimab (BCD-100), lodapolimab (LY-3300054), SHR-1201, camrelizumab (SHR-1210), Sym-021, budigalimab (ABBV-181), PD1-PIK, BAT-1306, avelumab (MSB0010718C), CX-072, CBT-502, dostarlimab (TSR-042), MSB-2311, JTX-4014, BGB-A333, SHR-1316, CS-1001 (WBP-3155, envafolimab (KN-035), sintilimab (IBI-308), HLX-20, KL-A167, STI-A1014, STI-A1015 (IMC-001), BCD-135, FAZ-053, TQB-2450, MDX1105-01, GS-4224, GS-4416, INCB086550, MAX10181, zimberelimab (AB122), spartalizumab (PDR-001), and compounds disclosed in WO2018195321, WO2020014643, WO2019160882, or WO2018195321, as well as multi-specific inhibitors FPT-155 (CTLA4/PD-L1/CD28), PF-06936308 (PD-1/ CTLA4), MGD-013 (PD-1/LAG-3), FS-118 (LAG-3/PD-L1), RO-7247669 (PD-1/LAG-3), MGD-019 (PD-1/CTLA4), KN-046 (PD-1/CTLA4), MEDI-5752 (CTLA4/PD-1), RO-7121661 (PD-1/TIM-3), RG7769 (PD-1/TIM-3), TAK-252 (PD-1/OX40L), XmAb-20717

(PD-1/CTLA4), AK-104 (CTLA4/PD-1), FS-118 (LAG-3/PD-L1), FPT-155 (CTLA4/PD-L1/CD28), GEN-1046 (PD-L1/4-1BB), bintrafusp alpha (M7824; PD-L1/TGFβ-EC domain), CA-170 (PD-L1/VISTA), CDX-527 (CD27/PD-L1), LY-3415244 (TIM3/PDL1), and INBRX-105 (4-1BB/PDL1). In some embodiments the PD-L1 inhibitor is a small molecule inhibitor, such as CA-170, GS-4224, GS-4416 and lazertinib (GNS-1480; PD-L1/EGFR).

[0269] Examples of inhibitors of TIGIT that can be co-administered include tiragolumab (RG-6058), vibostolimab, domvanalimab, domvanalimab (AB154), AB308, BMS-986207, AGEN-1307, COM-902, or etigilimab.

[0270] Examples of inhibitors of LAG3 that can be co-administered include leramilimab (LAG525).

[0271] Inhibition of regulatory T-cell (Treg) activity or Treg depletion can alleviate their suppression of antitumor immune responses and have anticancer effects. *See*, *e.g.*, Plitas and Rudensky, *Annu. Rev. Cancer Biol.* (2020) 4:459-77; Tanaka and Sakaguchi, *Eur. J. Immunol.* (2019) 49:1140-1146. In some embodiments, an compound provided herein is administered with one or more inhibitors of Treg activity or a Treg depleting agent. Treg inhibition or depletion can augment the effect of immune checkpoint inhibitors in cancer therapeutics.

[0272] In some embodiments an compound provided herein is administered with one or more Treg inhibitors. In some embodiments the Treg inhibitor can suppress the migration of Tregs into the tumor microenvironment. In some embodiments Treg inhibitor can reduce the immunosuppressive function of Tregs. In some embodiments, the Treg inhibitor can modulate the cellular phenotype and induce production of proinflammatory cytokines. Exemplary Treg inhibitors include without limitation, CCR4 (NCBI Gene ID: 1233) antagonists and degraders of Ikaros zinc-finger proteins (e.g., Ikaros (IKZF1; NCBI Gene ID: 10320), Helios (IKZF2; NCBI Gene ID: 22807), Aiolos (IKZF3; NCBI Gene ID: 22806), and Eos (IKZF4; NCBI Gene ID: 64375).

[0273] Examples of Helios degraders that can be co-administered include without limitation I-57 (Novartis) and compounds disclosed in WO2019038717, WO2020012334, WO20200117759, and WO2021101919.

[0274] In some embodiments an compound provided herein is administered with one or more Treg depleting agents. In some embodiments the Treg depleting agent is an antibody. In some embodiments the Treg depleting antibody has antibody-dependent cytotoxic (ADCC) activity. In

some embodiments, the Treg depleting antibody is Fc-engineered to possess an enhanced ADCC activity. In some embodiments the Treg depleting antibody is an antibody-drug conjugate (ADC). Illustrative targets for Treg depleting agents include without limitation CD25 (IL2RA; NCBI Gene ID: 3559), CTLA4 (CD152; NCBI Gene ID: 1493); GITR (TNFRSF18; NCBI Gene ID: 8784); 4-1BB (CD137; NCBI Gene ID: 3604), OX-40 (CD134; NCBI Gene ID: 7293), LAG3 (CD223; NCBI Gene ID: 3902), TIGIT (NCBI Gene ID: 201633), CCR4 (NCBI Gene ID: 1233), and CCR8 (NCBI Gene ID: 1237).

[0275] In some embodiments the Treg inhibitor or Treg depleting agent that can be co-administered comprises an antibody or antigen-binding fragment thereof that selectively binds to a cell surface receptor selected from the group consisting of C-C motif chemokine receptor 4 (CCR4), C-C motif chemokine receptor 7 (CCR7), C-C motif chemokine receptor 8 (CCR8), C-X-C motif chemokine receptor 4 (CXCR4; CD184), TNFRSF4 (OX40), TNFRSF18 (GITR, CD357), TNFRSF9 (4-1BB, CD137), cytotoxic T-lymphocyte associated protein 4 (CTLA4, CD152), programmed cell death 1 (PDCD1, PD-1), Sialyl Lewis x (CD15s), CD27, ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1; CD39), protein tyrosine phosphatase receptor type C (PTPRC; CD45), neural cell adhesion molecule 1 (NCAM1; CD56), selectin L (SELL; CD62L), integrin subunit alpha E (ITGAE; CD103), interleukin 7 receptor (IL7R; CD127), CD40 ligand (CD40LG; CD154), folate receptor alpha (FOLR1), folate receptor beta (FOLR2), leucine rich repeat containing 32 (LRRC32; GARP), IKAROS family zinc finger 2 (IKZF2; HELIOS), inducible T cell costimulatory (ICOS; CD278), lymphocyte activating 3 (LAG3; CD223), transforming growth factor beta 1 (TGFB1), hepatitis A virus cellular receptor 2 (HAVCR2; CD366; TIM3), T cell immunoreceptor with Ig and ITIM domains (TIGIT), TNF receptor superfamily member 1B (CD120b; TNFR2), IL2RA (CD25) or a combination thereof.

[0276] Examples of Treg depleting anti-CCR8 antibodies that can be administered include without limitation JTX-1811 (GS-1811) (Jounce Therapeutics, Gilead Sciences), BMS-986340 (Bristol Meyers Squibb), S-531011 (Shionogi), FPA157 (Five Prime Therapeutics), SRF-114 (Surface Oncology), HBM1022 (Harbor BioMed), IO-1 (Oncurious), and antibodies disclosed in WO2021163064, WO2020138489, and WO2021152186.

[0277] Examples of Treg depleting anti-CCR4 antibodies that can be administered include mogamulizumab.

[0278] Inhibiting, depleting, or reprogramming of non-stimulatory myeloid cells in the tumor microenvironment can enhance anti-cancer immune responses (*see*, *e.g.*, Binnewies *et al.*, *Nat. Med.* (2018) 24(5): 541-550; WO2016049641). Illustrative targets for depleting or

reprogramming non-stimmulatory myeloid cells include triggering receptors expressed on myeloid cells, TREM-1 (CD354, NCBI Gene ID: 54210) and TREM-2 (NCBI Gene ID: 54209). In some embodiments an compound provided herein is administered with one or more myeloid cell depleting or reprogramming agents, such as an anti-TREM-1 antibody (e.g. PY159; antibodies disclosed in WO2019032624) or an anti-TREM-2 antibody (*e.g.*, PY314; antibodies disclosed in WO2019118513).

Cluster of Differentiation Agonists or Activators

[0279] In some embodiments, the compound provided herein is administered with agents targeting a cluster of differentiation (CD) marker. Exemplary CD marker targeting agents that can be co-administered include without limitation A6, AD-IL24, neratinib, tucatinib (ONT 380), mobocertinib (TAK-788), tesevatinib, trastuzumab (HERCEPTIN®), trastuzumab biosimimar (HLX-02), margetuximab, BAT-8001, pertuzumab (Perjeta), pegfilgrastim, RG6264, zanidatamab (ZW25), cavatak, AIC-100, tagraxofusp (SL-401), HLA-A2402/HLA-A0201 restricted epitope peptide vaccine, dasatinib, imatinib, nilotinib, sorafenib, lenvatinib mesylate, ofranergene obadenovec, cabozantinib malate, AL-8326, ZLJ-33, KBP-7018, sunitinib malate, pazopanib derivatives, AGX-73, rebastinib, NMS-088, lucitanib hydrochloride, midostaurin, cediranib, dovitinib, sitravatinib, tivozanib, masitinib, regorafenib, olverembatinib dimesylate (HQP-1351), cabozantinib, ponatinib, and famitinib L-malate, CX-2029 (ABBV-2029), SCB-313, CA-170, COM-701, CDX-301, GS-3583, asunercept (APG-101), APO-010, and compounds disclosed in WO2016196388, WO2016033570, WO2015157386, WO199203459, WO199221766, WO2004080462, WO2005020921, WO2006009755, WO2007078034, WO2007092403, WO2007127317, WO2008005877, WO2012154480, WO2014100620, WO2014039714, WO2015134536, WO2017167182, WO2018112136, WO2018112140, WO2019155067, WO2020076105, PCT/US2019/063091, WO19173692, WO2016179517, WO2017096179, WO2017096182, WO2017096281, WO2018089628, WO2017096179, WO2018089628, WO2018195321, WO2020014643, WO2019160882, WO2018195321, WO200140307, WO2002092784, WO2007133811, WO2009046541, WO2010083253, WO2011076781, WO2013056352, WO2015138600, WO2016179399, WO2016205042, WO2017178653, WO2018026600, WO2018057669, WO2018107058, WO2018190719, WO2018210793, WO2019023347, WO2019042470, WO2019175218, WO2019183266, WO2020013170, WO2020068752, Cancer Discov. 2019 Jan 9(1):8; and Gariepy J., et al. 106th Annu Meet Am Assoc Immunologists (AAI) (May 9-13, San Diego, 2019, Abst 71.5).

[0280] In some embodiments the CD marker targeting agent that can be co-administered include small molecule inhibitors, such as PBF-1662, BLZ-945, pemigatinib (INCB-054828), rogaratinib (BAY-1163877), AZD4547, roblitinib (FGF-401), quizartinib dihydrochloride, SX-682, AZD-5069, PLX-9486, avapritinib (BLU-285), ripretinib (DCC-2618), imatinib mesylate, JSP-191, BLU-263, CD117-ADC, AZD3229, telatinib, vorolanib, GO-203-2C, AB-680, PSB-12379, PSB-12441, PSB-12425, CB-708, HM-30181A, motixafortide (BL-8040), LY2510924, burixafor (TG-0054), X4P-002, mavorixafor (X4P-001-IO), plerixafor, CTX-5861, or REGN-5678 (PSMA/CD28).

[0281] In some embodiments the CD marker targeting agent that can be co-administered include small molecule agonists, such as interleukin 2 receptor subunit gamma, eltrombopag, rintatolimod, poly-ICLC (NSC-301463), Riboxxon, Apoxxim, RIBOXXIM®, MCT-465, MCT-475, G100, PEPA-10, eftozanermin alfa (ABBV-621), E-6887, motolimod, resiquimod, selgantolimod (GS-9688), VTX-1463, NKTR-262, AST-008, CMP-001, cobitolimod, tilsotolimod, litenimod, MGN-1601, BB-006, IMO-8400, IMO-9200, agatolimod, DIMS-9054, DV-1079, lefitolimod (MGN-1703), CYT-003, and PUL-042.

[0282] In some embodiments the CD marker targeting agent that can be co-administered include antibodies, such as tafasitamab (MOR208; MorphoSys AG), Inebilizumab (MEDI-551), obinutuzumab, IGN-002, rituximab biosimilar (PF-05280586), varlilumab (CDX-1127), AFM-13 (CD16/CD30), AMG330, otlertuzumab (TRU-016), isatuximab, felzartamab (MOR-202), TAK-079, TAK573, daratumumab (DARZALEX®), TTX-030, selicrelumab (RG7876), APX-005M, ABBV-428, ABBV-927, mitazalimab (JNJ-64457107), lenziluma, alemtuzuma, emactuzumab, AMG-820, FPA-008 (cabiralizumab), PRS-343 (CD-137/Her2), AFM-13 (CD16/CD30), belantamab mafodotin (GSK-2857916), AFM26 (BCMA/CD16A), simlukafusp alfa (RG7461), urelumab, utomilumab (PF-05082566), AGEN2373, ADG-106, BT-7480, PRS-343 (CD-137/HER2), FAP-4-IBBL (4-1BB/FAP), ramucirumab, CDX-0158, CDX-0159 and FSI-174, relatlimab (ONO-4482), LAG-525, MK-4280, fianlimab (REGN-3767), INCAGN2385, encelimab (TSR-033), atipotuzumab, BrevaRex (Mab-AR-20.5), MEDI-9447 (oleclumab), CPX-006, IPH-53, BMS-986179, NZV-930, CPI-006, PAT-SC1, lirilumab (IPH-2102), lacutamab (IPH-4102), monalizumab, BAY-1834942, NEO-201 (CEACAM 5/6), Iodine (131I) apamistamab (131I-BC8 (lomab-B)), MEDI0562 (tavolixizumab), GSK-3174998, INCAGN1949, BMS-986178, GBR-8383, ABBV-368, denosumab, BION-1301, MK-4166, INCAGN-1876, TRX-518, BMS-986156, MK-1248, GWN-323, CTB-006, INBRX-109, GEN-1029, pepinemab (VX-15), vopratelimab (JTX-2011), GSK3359609, cobolimab (TSR-022),

MBG-453, INCAGN-2390, and compounds disclosed in WO 2017096179, WO2017096276, WO2017096189, and WO2018089628.

[0283] In some embodiments the CD marker targeting agent that can be co-administered include cell therapies, such as CD19-ARTEMIS, TBI-1501, CTL-119 huCART-19 T cells, 1 iso-cel, lisocabtagene maraleucel (JCAR-017), axicabtagene ciloleucel (KTE-C19, Yescarta®), axicabtagene ciloleucel (KTE-X19), US7741465, US6319494, UCART-19, tabelecleucel (EBV-CTL), T tisagenlecleucel-T (CTL019), CD19CAR-CD28-CD3zeta-EGFRt-expressing T cells, CD19/4-1BBL armored CAR T cell therapy, C-CAR-011, CIK-CAR.CD19, CD19CAR-28-zeta T cells, PCAR-019, MatchCART, DSCAR-01, IM19 CAR-T, TC-110, anti-CD19 CAR T-cell therapy (B-cell acute lymphoblastic leukemia, Universiti Kebangsaan Malaysia), anti-CD19 CAR T-cell therapy (acute lymphoblastic leukemia/Non-Hodgkin's lymphoma, University Hospital Heidelberg), anti-CD19 CAR T-cell therapy (silenced IL-6 expression, cancer, Shanghai Unicar-Therapy Bio-medicine Technology), MB-CART2019.1 (CD19/CD20), GC-197 (CD19/CD7), CLIC-1901, ET-019003, anti-CD19-STAR-T cells, AVA-001, BCMA-CD19 cCAR (CD19/APRIL), ICG-134, ICG-132 (CD19/CD20), CTA-101, WZTL-002, dual anti-CD19/anti-CD20 CAR T-cells (chronic lymphocytic leukemia/B-cell lymphomas), HY-001, ET-019002, YTB-323, GC-012 (CD19/APRIL), GC-022 (CD19/CD22), CD19CAR-CD28-CD3zeta-EGFRt-expressing Tn/mem, UCAR-011, ICTCAR-014, GC-007F, PTG-01, CC-97540, GC-007G, TC-310, GC-197, tisagenlecleucel-T, CART-19, tisagenlecleucel (CTL-019)), anti-CD20 CAR T-cell therapy (non-Hodgkin's lymphoma), MB-CART2019.1 (CD19/CD20), WZTL-002 dual anti-CD19/anti-CD20 CAR-T cells, ICG-132 (CD19/CD20), ACTR707 ATTCK-20, PBCAR-20A, LB-1905, CIK-CAR.CD33, CD33CART, dual anti-BCMA/anti-CD38 CAR T-cell therapy, CART-ddBCMA, MB-102, IM-23, JEZ-567, UCART-123, PD-1 knockout T cell therapy (esophageal cancer/NSCLC), ICTCAR-052, Tn MUC-1 CAR-T, ICTCAR-053, PD-1 knockout T cell therapy (esophageal cancer/NSCLC), AUTO-2, anti-BCMA CAR T-cell therapy, Descartes-011, anti-BCMA/anti-CD38 CAR T-cell therapy, CART-ddBCMA, BCMA-CS1 cCAR, CYAD-01 (NKG2D LIGAND MODULATOR), KD-045, PD-L1 t-haNK, BCMA-CS1 cCAR, MEDI5083, anti-CD276 CART, and therapies disclosed in WO2012079000 or WO2017049166.

Cluster of Differentiation 47 (CD47) Inhibitors

[0284] In some embodiments the compound provided herein is administered with an inhibitor of CD47 (IAP, MER6, OA3; NCBI Gene ID: 961). Examples of CD47 inhibitors include anti-CD47 mAbs (Vx-1004), anti-human CD47 mAbs (CNTO-7108), CC-90002, CC-90002-ST-001,

humanized anti-CD47 antibody or a CD47-blocking agent, NI-1701, NI-1801, RCT-1938, ALX148, SG-404, SRF-231, and TTI-621. Additional exemplary anti-CD47 antibodies include CC-90002, magrolimab (Hu5F9-G4), AO-176 (Vx-1004), letaplimab (IBI-188) (letaplimab), lemzoparlimab (TJC-4), SHR-1603, HLX-24, LQ-001, IMC-002, ZL-1201, IMM-01, B6H12, GenSci-059, TAY-018, PT-240, 1F8-GMCSF, SY-102, KD-015, ALX-148, AK-117, TTI-621, TTI-622, or compounds disclosed in WO199727873, WO199940940, WO2002092784, WO2005044857, WO2009046541, WO2010070047, WO2011143624, WO2012170250, WO2013109752, WO2013119714, WO2014087248, WO2015191861, WO2016022971, WO2016023040, WO2016024021, WO2016081423, WO2016109415, WO2016141328, WO2016188449, WO2017027422, WO2017049251, WO2017053423, WO2017121771, WO2017194634, WO2017196793, WO2017215585, WO2018075857, WO2018075960, WO2018089508, WO2018095428, WO2018137705, WO2018233575, WO2019027903, WO2019034895, WO2019042119, WO2019042285, WO2019042470, WO2019086573, WO2019108733, WO2019138367, WO2019144895, WO2019157843, WO2019179366, WO2019184912, WO2019185717, WO2019201236, WO2019238012, WO2019241732, WO2020019135, WO2020036977, WO2020043188, and WO2020009725. In some embodiments, the CD47 inhibitor is RRx-001, DSP-107, VT-1021, IMM-02, SGN-CD47M, or SIRPa-Fc-CD40L (SL-172154). In some embodiments the CD47 inhibitor is magrolimab.

[0285] In some embodiments, the CD47 inhibitor is a bispecific antibodies targeting CD47, such as IBI-322 (CD47/PD-L1), IMM-0306 (CD47/CD20), TJ-L1C4 (CD47/PD-L1), HX-009 (CD47/PD-1), PMC-122 (CD47/PD-L1), PT-217, (CD47/DLL3), IMM-26011 (CD47/FLT3), IMM-0207 (CD47/VEGF), IMM-2902 (CD47/HER2), BH29xx (CD47/PD-L1), IMM-03 (CD47/CD20), IMM-2502 (CD47/PD-L1), HMBD-004B (CD47/BCMA), HMBD-004A (CD47/CD33), TG-1801 (NI-1701), or NI-1801.

SIRPa Targeting Agents

[0286] In some embodiments the compound provided herein is administered with a SIRPa targeting agent (NCBI Gene ID: 140885; UniProt P78324). Examples of SIRPa targeting agents include SIRPa inhibitors, such as AL-008, RRx-001, and CTX-5861, and anti-SIRPa antibodies, such as FSI-189 (GS-0189), ES-004, BI-765063, ADU1805, CC-95251, Q-1801 (SIRPa/PD-L1). Additional SIRPα-targeting agents of use are described, for example, in WO200140307, WO2002092784, WO2007133811, WO2009046541, WO2010083253, WO2011076781, WO2013056352, WO2015138600, WO2016179399, WO2016205042, WO2017178653, WO2018026600, WO2018057669, WO2018107058, WO2018190719, WO2018210793,

WO2019023347, WO2019042470, WO2019175218, WO2019183266, WO2020013170 and WO2020068752.

FLT3R Agonists

[0287] In some embodiments the compound provided herein is administered with a FLT3R agonist. In some embodiments, the compound provided herein is administered with a FLT3 ligand. In some embodiments, the compound provided herein is administered with a FLT3L-Fc fusion protein, *e.g.*, as described in WO2020263830. In some embodiments the compound provided herein is administered with GS-3583 or CDX-301. In some embodiments the compound provided herein is administered with GS-3583.

TNF Receptor Superfamily (TNFRSF) Member Agonists or Activators

[0288] In some embodiments, the compound provided herein is administered with an agonist of one or more TNF receptor superfamily (TNFRSF) members, *e.g.*, an agonist of one or more of TNFRSF1A (NCBI Gene ID: 7132), TNFRSF1B (NCBI Gene ID: 7133), TNFRSF4 (OX40, CD134; NCBI Gene ID: 7293), TNFRSF5 (CD40; NCBI Gene ID: 958), TNFRSF6 (FAS, NCBI Gene ID: 355), TNFRSF7 (CD27, NCBI Gene ID: 939), TNFRSF8 (CD30, NCBI Gene ID: 943), TNFRSF9 (4-1BB, CD137, NCBI Gene ID: 3604), TNFRSF10A (CD261, DR4, TRAILR1, NCBI Gene ID: 8797), TNFRSF10B (CD262, DR5, TRAILR2, NCBI Gene ID: 8795), TNFRSF10C (CD263, TRAILR3, NCBI Gene ID: 8794), TNFRSF10D (CD264, TRAILR4, NCBI Gene ID: 8793), TNFRSF11A (CD265, RANK, NCBI Gene ID: 8792), TNFRSF11B (NCBI Gene ID: 4982), TNFRSF12A (CD266, NCBI Gene ID: 51330), TNFRSF13B (CD267, NCBI Gene ID: 23495), TNFRSF13C (CD268, NCBI Gene ID: 115650), TNFRSF16 (NGFR, CD271, NCBI Gene ID: 4804), TNFRSF17 (BCMA, CD269, NCBI Gene ID: 608), TNFRSF18 (GITR, CD357, NCBI Gene ID: 8784), TNFRSF19 (NCBI Gene ID: 55504), TNFRSF21 (CD358, DR6, NCBI Gene ID: 27242), and TNFRSF25 (DR3, NCBI Gene ID: 8718).

[0289] Example anti-TNFRSF4 (OX40) antibodies that can be co-administered include MEDI6469, MEDI6383, tavolixizumab (MEDI0562), MOXR0916, PF-04518600, RG-7888, GSK-3174998, INCAGN1949, BMS-986178, GBR-8383, ABBV-368, and those described in WO2016179517, WO2017096179, WO2017096182, WO2017096281, and WO2018089628.

[0290] Example anti-TNFRSF5 (CD40) antibodies that can be co-administered include RG7876, SEA-CD40, APX-005M, and ABBV-428.

[0291] In some embodiments, the anti-TNFRSF7 (CD27) antibody varlilumab (CDX-1127) is co-administered.

[0292] Example anti-TNFRSF9 (4-1BB, CD137) antibodies that can be co-administered include urelumab, utomilumab (PF-05082566), AGEN-2373, and ADG-106.

[0293] In some embodiments the anti-TNFRSF17 (BCMA) antibody GSK-2857916 is co-administered.

[0294] Example anti-TNFRSF18 (GITR) antibodies that can be co-administered include MEDI1873, FPA-154, INCAGN-1876, TRX-518, BMS-986156, MK-1248, GWN-323, and those described in WO2017096179, WO2017096276, WO2017096189, and WO2018089628. In some embodiments, an antibody, or fragment thereof, co-targeting TNFRSF4 (OX40) and TNFRSF18 (GITR) is co-administered. Such antibodies are described, *e.g.*, in WO2017096179 and WO2018089628.

[0295] Bi-specific antibodies targeting TNFRSF family members that can be co-administered include PRS-343 (CD-137/HER2), AFM26 (BCMA/CD16A), AFM-13 (CD16/CD30), odronextamab (REGN-1979; CD20/CD3), AMG-420 (BCMA/CD3), INHIBRX-105 (4-1BB/PDL1), FAP-4-IBBL (4-1BB/FAP), plamotamab (XmAb-13676; CD3/CD20), RG-7828 (CD20/CD3), CC-93269 (CD3/BCMA), REGN-5458 (CD3/BCMA), and IMM-0306 (CD47/CD20).

Bi-Specific T-Cell Engagers

[0296] In some embodiments compound provided herein is administered with a bi-specific T-cell engager (*e.g.*, not having an Fc) or an anti-CD3 bi-specific antibody (*e.g.*, having an Fc). Illustrative anti-CD3 bi-specific antibodies or BiTEs that can be co-administered include duvortuxizumab (JNJ-64052781; CD19/CD3), AMG-211 (CEA/CD3), AMG-160 (PSMA/CD3), RG7802 (CEA/CD3), ERY-974 (CD3/GPC3), PF-06671008 (Cadherins/CD3), APVO436 (CD123/CD3), flotetuzumab (CD123/CD3), odronextamab (REGN-1979; CD20/CD3), MCLA-117 (CD3/CLEC12A), JNJ-0819 (heme/CD3), JNJ-7564 (CD3/heme), AMG-757 (DLL3-CD3), AMG-330 (CD33/CD3), AMG-420 (BCMA/CD3), AMG-427 (FLT3/CD3), AMG-562 (CD19/CD3), AMG-596 (EGFRvIII/CD3), AMG-673 (CD33/CD3), AMG-701 (BCMA/CD3), AMG-757 (DLL3/CD3), AMG-211 (CEA/CD3), blinatumomab (CD19/CD3), huGD2-BsAb (CD3/GD2), ERY974 (GPC3/CD3), GEMoab (CD3/PSCA), RG6026 (CD20/CD3), RG6194 (HER2/CD3), PF-06863135 (BCMA/CD3), SAR440234 (CD3/CDw123), JNJ-9383 (MGD-015),

AMG-424 (CD38/CD3), tidutamab (XmAb-18087 (SSTR2/CD3)), JNJ-63709178 (CD123/CD3), MGD-007 (CD3/gpA33), MGD-009 (CD3/B7H3), IMCgp100 (CD3/gp100), XmAb-14045 (CD123/CD3), XmAb-13676 (CD3/CD20), tidutamab (XmAb-18087; SSTR2/CD3), catumaxomab (CD3/EpCAM), REGN-4018 (MUC16/CD3), mosunetuzumab (RG-7828; CD20/CD3), CC-93269 (CD3/BCMA), REGN-5458 (CD3/BCMA), GRB-1302 (CD3/Erbb2), GRB-1342 (CD38/CD3), GEM-333 (CD3/CD33). As appropriate, the anti-CD3 binding bi-specific molecules may or may not have an Fc. Illustrative bi-specific T-cell engagers that can be co-administered target CD3 and a tumor-associated antigen as described herein, including, *e.g.*, CD19 (*e.g.*, blinatumomab); CD33 (*e.g.*, AMG330); CEA (*e.g.*, MEDI-565); receptor tyrosine kinase-like orphan receptor 1 (ROR1) (Gohil, *et al.*, *Oncoimmunology*. (2017) May 17;6(7):e1326437); PD-L1 (Horn, *et al.*, *Oncotarget*. 2017 Aug 3;8(35):57964-57980); and EGFRvIII (Yang, *et al.*, *Cancer Lett*. 2017 Sep 10;403:224-230).

Bi-and Tri-Specific Natural Killer (NK)-Cell Engagers

[0297] In some embodiments the compound provided herein is administered with a bi-specific NK-cell engager (BiKE) or a tri-specific NK-cell engager (TriKE) (*e.g.*, not having an Fc) or bi-specific antibody (*e.g.*, having an Fc) against an NK cell activating receptor, *e.g.*, CD16A, C-type lectin receptors (CD94/NKG2C, NKG2D, NKG2E/H and NKG2F), natural cytotoxicity receptors (NKp30, NKp44 and NKp46), killer cell C-type lectin-like receptor (NKp65, NKp80), Fc receptor FcγR (which mediates antibody-dependent cell cytotoxicity), SLAM family receptors (*e.g.*, 2B4, SLAM6 and SLAM7), killer cell immunoglobulin-like receptors (KIR) (KIR-2DS and KIR-3DS), DNAM-1 and CD137 (41BB). Illustrative anti-CD16 bi-specific antibodies, BiKEs or TriKEs that can be co-administered include AFM26 (BCMA/CD16A) and AFM-13 (CD16/CD30). As appropriate, the anti-CD16 binding bi-specific molecules may or may not have an Fc. Illustrative bi-specific NK-cell engagers that can be co-administered target CD16 and one or more tumor-associated antigens as described herein, including, *e.g.*, CD19, CD20, CD22, CD30, CD33, CD123, EGFR, EpCAM, ganglioside GD2, HER2/neu, HLA Class II and FOLR1. BiKEs and TriKEs are described, *e.g.*, in Felices, *et al.*, *Methods Mol Biol*. (2016) 1441:333–346; Fang, *et al.*, *Semin Immunol*. (2017) 31:37-54.

MCL1 apoptosis regulator, BCL2 family member (MCL1) Inhibitors

[0298] In some embodiments the compound provided herein is administered with an inhibitor of MCL1 apoptosis regulator, BCL2 family member (MCL1, TM; EAT; MCL1L; MCL1S; Mcl-1; BCL2L3; MCL1-ES; bcl2-L-3; mcl1/EAT; NCBI Gene ID: 4170). Examples of MCL1 inhibitors include tapotoclax (AMG-176), AMG-397, S-64315, AZD-5991, 483-LM, A-1210477, UMI-77,

JKY-5-037, PRT-1419, GS-9716, and those described in WO2018183418, WO2016033486, and WO2017147410.

SHP2 Inhibitors

[0299] In some embodiments compound provided herein is administered with an inhibitor of protein tyrosine phosphatase non-receptor type 11 (PTPN11; BPTP3, CFC, JMML, METCDS, NS1, PTP-1D, PTP2C, SH-PTP2, SH-PTP3, SHP2; NCBI Gene ID: 5781). Examples of SHP2 inhibitors include TNO155 (SHP-099), RMC-4550, JAB-3068, RMC-4630, and those described in WO2018172984 and WO2017211303.

Hematopoietic Progenitor Kinase 1 (HPK1) Inhibitors and Degraders

[0300] In some embodiments, the compound provided herein is administered with an inhibitor of mitogen-activated protein kinase kinase kinase kinase 1 (MAP4K1, HPK1; NCBI Gene ID: 11184). Examples of Hematopoietic Progenitor Kinase 1 (HPK1) inhibitors include without limitation, those described in WO2020092621, WO2018183956, WO2018183964, WO2018167147, WO2018049152, WO2020092528, WO2016205942, WO2016090300, WO2018049214, WO2018049200, WO2018049191, WO2018102366, WO2018049152, and WO2016090300.

Apoptosis Signal-Regulating Kinase (ASK) Inhibitors

[0301] In some embodiments the compound provided herein is administered with an ASK inhibitor, *e.g.*, mitogen-activated protein kinase kinase kinase 5 (MAP3K5; ASK1, MAPKKK5, MEKK5; NCBI Gene ID: 4217). Examples of ASK1 inhibitors include those described in WO2011008709 (Gilead Sciences) and WO 2013112741 (Gilead Sciences).

Bruton Tyrosine Kinase (BTK) Inhibitors

[0302] In some embodiments the compound provided herein is administered with an inhibitor of Bruton tyrosine kinase (BTK, AGMX1, AT, ATK, BPK, IGHD3, IMD1, PSCTK1, XLA; NCBI Gene ID: 695). Examples of BTK inhibitors include (S)-6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7H-purin-8(9H)-one, acalabrutinib (ACP-196), zanubrutinib (BGB-3111), CB988, HM71224, ibrutinib, M-2951 (evobrutinib), M7583, tirabrutinib (ONO-4059), PRN-1008, spebrutinib (CC-292), TAK-020, vecabrutinib, ARQ-531, SHR-1459, DTRMWXHS-12, PCI-32765, and TAS-5315.

Cyclin-dependent Kinase (CDK) Inhibitors

[0303] In some embodiments the compound provided herein is administered with an inhibitor of cyclin dependent kinase 1 (CDK1, CDC2; CDC28A; P34CDC2; NCBI Gene ID: 983); cyclin dependent kinase 2 (CDK2, CDKN2; p33(CDK2); NCBI Gene ID: 1017); cyclin dependent kinase 3 (CDK3, ; NCBI Gene ID: 1018); cyclin dependent kinase 4 (CDK4, CMM3; PSK-J3; NCBI Gene ID: 1019); cyclin dependent kinase 6 (CDK6, MCPH12; PLSTIRE; NCBI Gene ID: 1021); cyclin dependent kinase 7 (CDK7, CAK; CAK1; HCAK; MO15; STK1; CDKN7; p39MO15; NCBI Gene ID: 1022), or cyclin dependent kinase 9 (CDK9, TAK; C-2k; CTK1; CDC2L4; PITALRE; NCBI Gene ID: 1025). Inhibitors of CDK 1, 2, 3, 4, 6, 7 and/or 9, include abemaciclib, alvocidib (HMR-1275, flavopiridol), AT-7519, dinaciclib, ibrance, FLX-925, LEE001, palbociclib, samuraciclib, ribociclib, rigosertib, selinexor, UCN-01, SY1365, CT-7001, SY-1365, G1T38, milciclib, trilaciclib, simurosertib hydrate (TAK931), and TG-02.

Discoidin Domain Receptor (DDR) Inhibitors

[0304] In some embodiments the compound provided herein is combined with an inhibitor of discoidin domain receptor tyrosine kinase 1 (DDR1, CAK, CD167, DDR, EDDR1, HGK2, MCK10, NEP, NTRK4, PTK3, PTK3A, RTK6, TRKE; NCBI Gene ID: 780); and/or discoidin domain receptor tyrosine kinase 2 (DDR2, MIG20a, NTRKR3, TKT, TYRO10, WRCN; NCBI Gene ID: 4921). Examples of DDR inhibitors include dasatinib and those disclosed in WO2014/047624 (Gilead Sciences), US 2009-0142345 (Takeda Pharmaceutical), US 2011-0287011 (Oncomed Pharmaceuticals), WO 2013/027802 (Chugai Pharmaceutical), and WO2013/034933 (Imperial Innovations).

Targeted E3 Ligase Ligand Conjugates

[0305] In some embodiments the compound provided herein is administered with a targeted E3 ligase ligand conjugate. Such conjugates have a target protein binding moiety and an E3 ligase binding moiety (*e.g.*, an inhibitor of apoptosis protein (IAP) (*e.g.*, XIAP, c-IAP1, c-IAP2, NIL-IAP, Bruce, and surviving) E3 ubiquitin ligase binding moiety, Von Hippel-Lindau E3 ubiquitin ligase (VHL) binding moiety, a cereblon E3 ubiquitin ligase binding moiety, mouse double minute 2 homolog (MDM2) E3 ubiquitin ligase binding moiety), and can be used to promote or increase the degradation of targeted proteins, *e.g.*, via the ubiquitin pathway. In some embodiments the targeted E3 ligase ligand conjugates comprise a targeting or binding moiety that targets or binds a protein described herein, and an E3 ligase ligand or binding moiety. In some embodiments the targeted E3 ligase ligand conjugates comprise a targeting or binding moiety that targets or binds

a protein selected from Cbl proto-oncogene B (CBLB; Cbl-b, Nbla00127, RNF56; NCBI Gene ID: 868) and hypoxia inducible factor 1 subunit alpha (HIF1A; NCBI Gene ID: 3091). In some embodiments the targeted E3 ligase ligand conjugates comprise a kinase inhibitor (*e.g.*, a small molecule kinase inhibitor, *e.g.*, of BTK and an E3 ligase ligand or binding moiety. *See*, *e.g.*, WO2018098280. In some embodiments the targeted E3 ligase ligand conjugates comprise a binding moiety targeting or binding to Interleukin-1 (IL-1) Receptor-Associated Kinase-4 (IRAK-4); Rapidly Accelerated Fibrosarcoma (RAF, such as c-RAF, A-RAF and/or B-RAF), c-Met/p38, or a BRD protein; and an E3 ligase ligand or binding moiety. *See*, *e.g.*, WO2019099926, WO2018226542, WO2018119448, WO2018223909, WO2019079701. Additional targeted E3 ligase ligand conjugates that can be co-administered are described, *e.g.*, in WO2018237026, WO2019084026, WO2019084030, WO2019067733, WO2019043217, WO2019043208, and WO2018144649.

Histone Deacetylase (HDAC) Inhibitors

[0306] In some embodiments the compound provided herein is administered with an inhibitor of a histone deacetylase, *e.g.*, histone deacetylase 9 (HDAC9, HD7, HD7b, HD9, HDAC, HDAC7, HDAC7B, HDAC9B, HDAC9FL, HDRP, MITR; Gene ID: 9734). Examples of HDAC inhibitors include abexinostat, ACY-241, AR-42, BEBT-908, belinostat, CKD-581, CS-055 (HBI-8000), CUDC-907 (fimepinostat), entinostat, givinostat, mocetinostat, panobinostat, pracinostat, quisinostat (JNJ-26481585), resminostat, ricolinostat, SHP-141, valproic acid (VAL-001), vorinostat, tinostamustine, remetinostat, and entinostat.

Indoleamine-pyrrole-2,3-dioxygenase (IDO1) inhibitors

[0307] In some embodiments the compound provided herein is administered with an inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1; NCBI Gene ID: 3620). Examples of IDO1 inhibitors include BLV-0801, epacadostat, linrodostat (F-001287, BMS-986205), GBV-1012, GBV-1028, GDC-0919, indoximod, NKTR-218, NLG-919-based vaccine, PF-06840003, pyranonaphthoquinone derivatives (SN-35837), resminostat, SBLK-200802, and shIDO-ST, EOS-200271, KHK-2455, and LY-3381916.

Janus Kinase (JAK) Inhibitors

[0308] In some embodiments, the compound provided herein is administered with an inhibitor of Janus kinase 1 (JAK1, JAK1A, JAK1B, JTK3; NCBI Gene ID: 3716); Janus kinase 2 (JAK2, JTK10, THCYT3; NCBI Gene ID: 3717); and/or Janus kinase 3 (JAK3, JAK-3, JAK3_HUMAN,

JAKL, L-JAK, LJAK; NCBI Gene ID: 3718). Examples of JAK inhibitors include AT9283, AZD1480, baricitinib, BMS-911543, fedratinib, filgotinib (GLPG0634), gandotinib (LY2784544), INCB039110 (itacitinib), lestaurtinib, momelotinib (CYT0387), ilginatinib maleate (NS-018), pacritinib (SB1518), peficitinib (ASP015K), ruxolitinib, tofacitinib (formerly tasocitinib), INCB052793, and XL019.

Lysyl Oxidase-Like Protein (LOXL) Inhibitors

[0309] In some embodiments the compound provided herein is administered with an inhibitor of a LOXL protein, *e.g.*, LOXL1 (NCBI Gene ID: 4016), LOXL2 (NCBI Gene ID: 4017), LOXL3 (NCBI Gene ID: 84695), LOXL4 (NCBI Gene ID: 84171), and/or LOX (NCBI Gene ID: 4015). Examples of LOXL2 inhibitors include the antibodies described in WO 2009017833 (Arresto Biosciences), WO 2009035791 (Arresto Biosciences), and WO 2011097513 (Gilead Biologics).

Matrix Metalloprotease (MMP) Inhibitors

[0310] In some embodiments the compound provided herein is administered with an inhibitor of a matrix metallopeptidase (MMP), *e.g.*, an inhibitor of MMP1 (NCBI Gene ID: 4312), MMP2 (NCBI Gene ID: 4313), MMP3 (NCBI Gene ID: 4314), MMP7 (NCBI Gene ID: 4316), MMP8 (NCBI Gene ID: 4317), MMP9 (NCBI Gene ID: 4318); MMP10 (NCBI Gene ID: 4319); MMP11 (NCBI Gene ID: 4320); MMP12 (NCBI Gene ID: 4321), MMP13 (NCBI Gene ID: 4322), MMP14 (NCBI Gene ID: 4323), MMP15 (NCBI Gene ID: 4324), MMP16 (NCBI Gene ID: 4325), MMP17 (NCBI Gene ID: 4326), MMP19 (NCBI Gene ID: 4327), MMP20 (NCBI Gene ID: 9313), MMP21 (NCBI Gene ID: 118856), MMP24 (NCBI Gene ID: 10893), MMP25 (NCBI Gene ID: 64386), MMP26 (NCBI Gene ID: 56547), MMP27 (NCBI Gene ID: 64066) and/or MMP28 (NCBI Gene ID: 79148). Examples of MMP9 inhibitors include marimastat (BB-2516), cipemastat (Ro 32-3555), GS-5745 (andecaliximab), and those described in WO 2012027721 (Gilead Biologics).

RAS and RAS Pathway Inhibitors

[0311] In some embodiments the compound provided herein is administered with an inhibitor of KRAS proto-oncogene, GTPase (KRAS; *a.k.a.*, NS; NS3; CFC2; RALD; K-Ras; KRAS1; KRAS2; RASK2; KI-RAS; C-K-RAS; K-RAS2A; K-RAS2B; K-RAS4A; K-RAS4B; c-Ki-ras2; NCBI Gene ID: 3845); NRAS proto-oncogene, GTPase (NRAS; *a.k.a.*, NS6; CMNS; NCMS; ALPS4; N-ras; NRAS1; NCBI Gene ID: 4893) or HRAS proto-oncogene, GTPase (HRAS; *a.k.a.*, CTLO; KRAS; HAMSV; HRAS1; KRAS2; RASH1; RASK2; Ki-Ras; p21ras; C-H-RAS; c-K-

ras; H-RASIDX; c-Ki-ras; C-BAS/HAS; C-HA-RAS1; NCBI Gene ID: 3265). The Ras inhibitors can inhibit Ras at either the polynucleotide (*e.g.*, transcriptional inhibitor) or polypeptide (*e.g.*, GTPase enzyme inhibitor) level. In some embodiments, the inhibitors target one or more proteins in the Ras pathway, *e.g.*, inhibit one or more of EGFR, Ras, Raf (A-Raf, B-Raf, C-Raf), MEK (MEK1, MEK2), ERK, PI3K, AKT and mTOR. Illustrative K-Ras inhibitors that can be co-administered include sotorasib (AMG-510), COTI-219, ARS-3248, WDB-178, BI-3406, BI-1701963, SML-8-73-1 (G12C), adagrasib (MRTX-849), ARS-1620 (G12C), SML-8-73-1 (G12C), Compound 3144 (G12D), Kobe0065/2602 (Ras GTP), RT11, MRTX-849 (G12C) and K-Ras(G12D)-selective inhibitory peptides, including KRpep-2and KRpep-2d . Illustrative *KRAS* mRNA inhibitors include anti-KRAS U1 adaptor, AZD-4785, siG12D-LODER™, and siG12D exosomes. Illustrative MEK inhibitors that can be co-administered include binimetinib, cobimetinib, PD-0325901, pimasertib, RG-7304, selumetinib, trametinib, and those described below and herein. Illustrative Raf dimer inhibitors that can be co-administered include BGB-283, HM-95573, LXH-254, LY-3009120, RG7304 and TAK-580. Illustrative ERK inhibitors that can be co-administered include LTT-462, LY-3214996, MK-8353, ravoxertinib and ulixertinib. Illustrative Ras GTPase inhibitors that can be co-administered include rigosertib. Illustrative PI3K inhibitors that can be co-administered include idelalisib (Zydelig®), alpelisib, buparlisib, pictilisib, inavolisib (RG6114), ASN-003. Illustrative AKT inhibitors that can be co-administered include capivasertib and GSK2141795. Illustrative PI3K/mTOR inhibitors that can be co-administered include dactolisib, omipalisib, voxtalisib. gedatolisib, GSK2141795, GSK-2126458, inavolisib (RG6114), sapanisertib, ME-344, sirolimus (oral nano-amorphous formulation, cancer), racemetyrosine (TYME-88 (mTOR/cytochrome P450 3A4)), temsirolimus (TORISEL®, CCI-779), CC-115, onatasertib (CC-223), SF-1126, and PQR-309 (bimiralisib). In some embodiments, Ras-driven cancers (*e.g.*, NSCLC) having CDKN2A mutations can be inhibited by co-administration of the MEK inhibitor selumetinib and the CDK4/6 inhibitor palbociclib. *See*, *e.g.*, Zhou, *et al.*, *Cancer Lett.* 2017 Nov 1;408:130-137. Also, K-RAS and mutant N-RAS can be reduced by the irreversible ERBB1/2/4 inhibitor neratinib. *See*, *e.g.*, Booth, *et al.*, *Cancer Biol Ther.* 2018 Feb 1;19(2):132-137.

Mitogen-activated Protein Kinase (MEK) Inhibitors

[0312] In some embodiments the compound provided herein is administered with an inhibitor of mitogen-activated protein kinase kinase 7 (MAP2K7, JNKK2, MAPKK7, MEK, MEK 7, MKK7, PRKMK7, SAPKK-4, SAPKK4; NCBI Gene ID: 5609). Examples of MEK inhibitors include antroquinonol, binimetinib, cobimetinib (GDC-0973, XL-518), MT-144, selumetinib (AZD6244),

sorafenib, trametinib (GSK1120212), uprosertib + trametinib, PD-0325901, pimasertib, LTT462, AS703988, CC-90003, and refametinib.

Phosphatidylinositol 3-kinase (PI3K) Inhibitors

[0313] In some embodiments compounds provided herein is administered with an inhibitor of a phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit, *e.g.*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA, CLAPO, CLOVE, CWS5, MCAP, MCM, MCMTC, PI3K, PI3K-alpha, p110-alpha; NCBI Gene ID: 5290); phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta (PIK3CB, P110BETA, PI3K, PI3KBETA, PIK3C1; NCBI Gene ID: 5291); phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma (PIK3CG, PI3CG, PI3K, PI3Kgamma, PIK3, p110gamma, p120-PI3K; Gene ID: 5494); and/or phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (PIK3CD, APDS, IMD14, P110DELTA, PI3K, p110D, NCBI Gene ID: 5293). In some embodiments the PI3K inhibitor is a pan-PI3K inhibitor. Examples of PI3K inhibitors include ACP-319, AEZA-129, AMG-319, AS252424, AZD8186, BAY 10824391, BEZ235, buparlisib (BKM120), BYL719 (alpelisib), CH5132799, copanlisib (BAY 80-6946), duvelisib, GDC-0032, GDC-0077, GDC-0941, GDC-0980, GSK2636771, GSK2269557, idelalisib (Zydelig®), INCB50465, IPI-145, IPI-443, IPI-549, KAR4141, LY294002, LY3023414, MLN1117, OXY111A, PA799, PX-866, RG7604, rigosertib, RP5090, RP6530, SRX3177, taselisib, TG100115, TGR-1202 (umbralisib), TGX221, WX-037, X-339, X-414, XL147 (SAR245408), XL499, XL756, wortmannin, ZSTK474, and the compounds described in WO2005113556 (ICOS), WO 2013/052699 (Gilead Calistoga), WO2013116562 (Gilead Calistoga), WO2014100765 (Gilead Calistoga), WO2014100767 (Gilead Calistoga), and WO2014201409 (Gilead Sciences).

Spleen Tyrosine Kinase (SYK) Inhibitors

[0314] In some embodiments the compound provided herein is administered with an inhibitor of spleen associated tyrosine kinase (SYK, p72-Syk, NCBI Gene ID: 6850). Examples of SYK inhibitors include 6-(1H-indazol-6-yl)-N-(4-morpholinophenyl)imidazo[1,2-a]pyrazin-8-amine, BAY-61-3606, cerdulatinib (PRT-062607), entospletinib, fostamatinib (R788), HMPL-523, NVP-QAB 205 AA, R112, R343, tamatinib (R406), gusacitinib (ASN-002), and those described in US8450321 (Gilead Connecticut) and US20150175616.

Toll-Like Receptor (TLR) Agonists

[0315] In some embodiments compound provided herein is administered with an agonist of a toll-like receptor (TLR), *e.g.*, an agonist of TLR1 (NCBI Gene ID: 7096), TLR2 (NCBI Gene ID: 7097), TLR3 (NCBI Gene ID: 7098), TLR4 (NCBI Gene ID: 7099), TLR5 (NCBI Gene ID: 7100), TLR6 (NCBI Gene ID: 10333), TLR7 (NCBI Gene ID: 51284), TLR8 (NCBI Gene ID: 51311), TLR9 (NCBI Gene ID: 54106), and/or TLR10 (NCBI Gene ID: 81793). Example TLR7 agonists that can be co-administered include DS-0509, GS-9620 (vesatolimod), vesatolimod analogs, LHC-165, TMX-101 (imiquimod), GSK-2245035, resiquimod, DSR-6434, DSP-3025, IMO-4200, MCT-465, MEDI-9197, 3M-051, SB-9922, 3M-052, Limtop, TMX-30X, TMX-202, RG-7863, RG-7795, BDB-001, DSP-0509, and the compounds disclosed in US20100143301 (Gilead Sciences), US20110098248 (Gilead Sciences), and US20090047249 (Gilead Sciences), US20140045849 (Janssen), US20140073642 (Janssen), WO2014056953 (Janssen), WO2014076221 (Janssen), WO2014128189 (Janssen), US20140350031 (Janssen), WO2014023813 (Janssen), US20080234251 (Array Biopharma), US20080306050 (Array Biopharma), US20100029585 (Ventirx Pharma), US20110092485 (Ventirx Pharma), US20110118235 (Ventirx Pharma), US20120082658 (Ventirx Pharma), US20120219615 (Ventirx Pharma), US20140066432 (Ventirx Pharma), US20140088085 (Ventirx Pharma), US20140275167 (Novira Therapeutics), and US20130251673 (Novira Therapeutics). An TLR7/TLR8 agonist that can be co-administered is NKTR-262. Example TLR8 agonists that can be co-administered include E-6887, IMO-4200, IMO-8400, IMO-9200, MCT-465, MEDI-9197, motolimod, resiquimod, GS-9688, VTX-1463, VTX-763, 3M-051, 3M-052, and the compounds disclosed in US20140045849 (Janssen), US20140073642 (Janssen), WO2014/056953 (Janssen), WO2014/076221 (Janssen), WO2014/128189 (Janssen), US20140350031 (Janssen), WO2014/023813 (Janssen), US20080234251 (Array Biopharma), US20080306050 (Array Biopharma), US20100029585 (Ventirx Pharma), US20110092485 (Ventirx Pharma), US20110118235 (Ventirx Pharma), US20120082658 (Ventirx Pharma), US20120219615 (Ventirx Pharma), US20140066432 (Ventirx Pharma), US20140088085 (Ventirx Pharma), US20140275167 (Novira Therapeutics), and US20130251673 (Novira Therapeutics). Example TLR9 agonists that can be co-administered include AST-008, CMP-001, IMO-2055, IMO-2125, litenimod, MGN-1601, BB-001, BB-006, IMO-3100, IMO-8400, IR-103, IMO-9200, agatolimod, DIMS-9054, DV-1079, DV-1179, AZD-1419, leftolimod (MGN-1703), CYT-003, CYT-003-QbG10 and PUL-042. Examples of TLR3 agonist include rintatolimod, poly-ICLC, RIBOXXON®, Apoxxim, RIBOXXIM®, IPH-33, MCT-465, MCT-475, and ND-1.1.

Tyrosine-kinase Inhibitors (TKIs)

[0316] In some embodiments the compound provided herein is administered with a tyrosine kinase inhibitor (TKI). TKIs may target epidermal growth factor receptors (EGFRs) and receptors for fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF). Examples of TKIs include without limitation afatinib, ARQ-087 (derazantinib), asp5878, AZD3759, AZD4547, bosutinib, brigatinib, cabozantinib, cediranib, crenolanib, dacomitinib, dasatinib, dovitinib, E-6201, erdafitinib, erlotinib, gefitinib, gilteritinib (ASP-2215), FP-1039, HM61713, icotinib, imatinib, KX2-391 (Src), lapatinib, lestaurtinib, lenvatinib, midostaurin, nintedanib, ODM-203, osimertinib (AZD-9291), ponatinib, poziotinib, quizartinib, radotinib, rociletinib, sulfatinib (HMPL-012), sunitinib, famitinib L-malate, (MAC-4), tivoanib, TH-4000, and MEDI-575 (anti-PDGFR antibody). Exemplary EGFR targeting agents include neratinib, tucatinib (ONT-380), tesevatinib, mobocertinib (TAK-788), DZD-9008, varlitinib, abivertinib (ACEA-0010), EGF816 (nazartinib), olmutinib (BI-1482694), osimertinib (AZD-9291), AMG-596 (EGFRvIII/CD3), lifirafenib (BGB-283), vectibix, lazertinib (LECLAZA®), and compounds disclosed in Booth, et al., Cancer Biol Ther. 2018 Feb 1;19(2):132-137. Antibodies targeting EGFR include without limitation modotuximab, cetuximab sarotalocan (RM-1929), seribantumab, necitumumab, depatuxizumab mafodotin (ABT-414), tomuzotuximab, depatuxizumab (ABT-806), and cetuximab.

Chemotherapeutic agents

[0317] In some embodiments the compound provided herein is administered with a chemotherapeutic agent or anti-neoplastic agent.

[0318] As used herein, the term "chemotherapeutic agent" or "chemotherapeutic" (or "chemotherapy" in the case of treatment with a chemotherapeutic agent) is meant to encompass any non-proteinaceous (*e.g.*, non-peptidic) chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include but not limited to: alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan, and piposulfan; aziridines such as benzodepa, carboquone, meturedepa, and uredepa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, and trimemylolomelamine; acetogenins, *e.g.*, bullatacin and bullatacinone; a camptothecin, including synthetic analog topotecan; bryostatin, callystatin; CC-1065, including its adozelesin, carzelesin, and bizelesin synthetic analogs; cryptophycins, particularly cryptophycin 1 and cryptophycin 8;dolastatin; duocarmycin, including the synthetic analogs KW-2189 and CBI-TMI; eleutherobin; 5-azacytidine; pancratistatin; a sarcodictyin;

spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cyclophosphamide, glufosfamide, evofosfamide, bendamustine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, and uracil mustard; nitrosoureas such as carmustine, chlorozotocin, foremustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (*e.g.*, calicheamicin, especially calicheamicin gammaII and calicheamicin phiI1), dynemicin including dynemicin A, bisphosphonates such as clodronate, an esperamicin, neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromomophores, aclacinomycins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carrninomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, and zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as demopterin, methotrexate, pteropterin, and trimetrexate; purine analogs such as cladribine, pentostatin, fludarabine, 6-mercaptopurine, thiamiprine, and thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, and floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, and testolactone; anti-adrenals such as aminoglutethimide, mitotane, and trilostane; folic acid replinishers such as frolinic acid; radiotherapeutic agents such as Radium-223; trichothecenes, especially T-2 toxin, verracurin A, roridin A, and anguidine; taxoids such as paclitaxel (TAXOL®), abraxane, docetaxel (TAXOTERE®), cabazitaxel, BIND-014, tesetaxel; sabizabulin (Veru-111); platinum analogs such as cisplatin and carboplatin, NC-6004 nanoplatin; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; hestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformthine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; leucovorin; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; losoxantrone; fluoropyrimidine; folinic acid; podophyllinic acid; 2-ethylhydrazide; procarbazine; polysaccharide-K (PSK); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; trabectedin, triaziquone; 2,2',2"-trichlorotriemylamine; urethane; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiopeta; chlorambucil; gemcitabine (GEMZAR®); 6-thioguanine; mercaptopurine; methotrexate; vinblastine; platinum; etoposide (VP-16); ifosfamide;

mitroxantrone; vancristine; vinorelbine (NAVELBINE®); novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeoloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DFMO); retinoids such as retinoic acid; capecitabine; NUC-1031; FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin); FOLFIRI (folinic acid, 5-fluorouracil, irinotecan); FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin, irinotecan), FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, oxaliplatin), and pharmaceutically acceptable salts, acids, or derivatives of any of the above. Such agents can be conjugated onto an antibody or any targeting agent described herein to create an antibody-drug conjugate (ADC) or targeted drug conjugate.

Anti-hormonal Agents

[0319] Also included in the definition of "chemotherapeutic agent" are anti-hormonal agents such as anti-estrogens and selective estrogen receptor modulators (SERMs), inhibitors of the enzyme aromatase, anti-androgens, and pharmaceutically acceptable salts, acids or derivatives of any of the above that act to regulate or inhibit hormone action on tumors.

[0320] Examples of anti-estrogens and SERMs include tamoxifen (including NOLVADEXTM), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and toremifene (FARESTON®).

[0321] Inhibitors of the enzyme aromatase regulate estrogen production in the adrenal glands. Examples include 4(5)-imidazoles, aminoglutethimide, megestrol acetate (MEGACE®), exemestane, formestane, fadrozole, vorozole (RIVISOR®), letrozole (FEMARA®), and anastrozole (ARIMIDEX®).

[0322] Examples of anti-androgens include apalutamide, abiraterone, enzalutamide, flutamide, galeterone, nilutamide, bicalutamide, leuprolide, goserelin, ODM-201, APC-100, ODM-204, enobosarm (GTX-024), darolutamide, and IONIS-AR-2.5Rx (antisense).

[0323] An example progesterone receptor antagonist includes onapristone. Additional progesterone targeting agents include TRI-CYCLEN LO (norethindrone + ethinyl estradiol), norgestimate + ethinylestradiol (Tri-Cyclen) and levonorgestrel.

Anti-Angiogenic Agents

[0324] In some embodiments the compound provided herein is administered with an anti-angiogenic agent. Anti-angiogenic agents that can be co-administered include retinoid acid and

derivatives thereof, 2-methoxyestradiol, ANGIOSTATIN®, ENDOSTATIN®, regorafenib, necuparanib, suramin, squalamine, tissue inhibitor of metalloproteinase-1, tissue inhibitor of metalloproteinase-2, plasminogen activator inhibitor-1, plasminogen activator inbibitor-2, cartilage-derived inhibitor, paclitaxel (nab-paclitaxel), platelet factor 4, protamine sulphate (clupeine), sulphated chitin derivatives (prepared from queen crab shells), sulphated polysaccharide peptidoglycan complex (sp-pg), staurosporine, modulators of matrix metabolism including proline analogs such as l-azetidine-2-carboxylic acid (LACA), cishydroxyproline, d,I-3,4-dehydroproline, thiaproline, α,α'-dipyridyl, beta-aminopropionitrile fumarate, 4-propyl-5-(4-pyridinyl)-2(3h)-oxazolone, methotrexate, mitoxantrone, heparin, interferons, 2 macroglobulin-serum, chicken inhibitor of metalloproteinase-3 (ChIMP-3), chymostatin, beta-cyclodextrin tetradecasulfate, eponemycin, fumagillin, gold sodium thiomalate, d-penicillamine, beta-1-anticollagenase-serum, alpha-2-antiplasmin, bisantrene, lobenzarit disodium, n-2-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA", thalidomide, angiostatic steroid, carboxy aminoimidazole, metalloproteinase inhibitors such as BB-94, inhibitors of S100A9 such as tasquinimod . Other anti-angiogenesis agents include antibodies, preferably monoclonal antibodies against these angiogenic growth factors: beta-FGF, alpha-FGF, FGF-5, VEGF isoforms, VEGF-C, HGF/SF, and Ang-1/Ang-2. Examples for anti-VEGFA antibodies that can be co-administered include bevacizumab, vanucizumab, faricimab, dilpacimab (ABT-165; DLL4/VEGF), or navicixizumab (OMP-305B83; DLL4/VEGF).

Anti-fibrotic Agents

[0325] In some embodiments the compound provided herein is administered with an anti-fibrotic agent. Anti-fibrotic agents that can be co-administered include the compounds such as beta-aminoproprionitrile (BAPN), as well as the compounds disclosed in US4965288 relating to inhibitors of lysyl oxidase and their use in the treatment of diseases and conditions associated with the abnormal deposition of collagen and US4997854 relating to compounds which inhibit LOX for the treatment of various pathological fibrotic states, which are herein incorporated by reference. Further exemplary inhibitors are described in US4943593 relating to compounds such as 2-isobutyl-3-fluoro-, chloro-, or bromo-allylamine, US5021456, US5059714, US5120764, US5182297, US5252608 relating to 2-(1-naphthyloxymemyl)-3-fluoroallylamine, and US 20040248871, which are herein incorporated by reference.

[0326] Exemplary anti-fibrotic agents also include the primary amines reacting with the carbonyl group of the active site of the lysyl oxidases, and more particularly those which produce, after binding with the carbonyl, a product stabilized by resonance, such as the following primary

amines: emylenemamine, hydrazine, phenylhydrazine, and their derivatives; semicarbazide and urea derivatives; aminonitriles such as BAPN or 2-nitroethylamine; unsaturated or saturated haloamines such as 2-bromo-ethylamine, 2-chloroethylamine, 2-trifluoroethylamine, 3-bromopropylamine, and p-halobenzylamines; and selenohomocysteine lactone.

[0327] Other anti-fibrotic agents are copper chelating agents penetrating or not penetrating the cells. Exemplary compounds include indirect inhibitors which block the aldehyde derivatives originating from the oxidative deamination of the lysyl and hydroxylysyl residues by the lysyl oxidases. Examples include the thiolamines, particularly D-penicillamine, and its analogs such as 2-amino-5-mercapto-5-methylhexanoic acid, D-2-amino-3-methyl-3-((2-acetamidoethyl)dithio)butanoic acid, p-2-amino-3-methyl-3-((2-aminoethyl)dithio)butanoic acid, sodium-4-((p-1-dimethyl-2-amino-2-carboxyethyl)dithio)butane sulphurate, 2-acetamidoethyl-2-acetamidoethanethiol sulphanate, and sodium-4-mercaptobutanesulphinate trihydrate.

Anti-Inflammatory Agents

[0328] In some embodiments the compound provided herein is administered with an anti-inflammatory agent. Example anti-inflammatory agents include without limitation inhibitors of one or more of arginase (ARG1 (NCBI Gene ID: 383), ARG2 (NCBI Gene ID: 384)), carbonic anhydrase (CA1 (NCBI Gene ID: 759), CA2 (NCBI Gene ID: 760), CA3 (NCBI Gene ID: 761), CA4 (NCBI Gene ID: 762), CA5A (NCBI Gene ID: 763), CA5B (NCBI Gene ID: 11238), CA6 (NCBI Gene ID: 765), CA7 (NCBI Gene ID: 766), CA8 (NCBI Gene ID: 767), CA9 (NCBI Gene ID: 768), CA10 (NCBI Gene ID: 56934), CA11 (NCBI Gene ID: 770), CA12 (NCBI Gene ID: 771), CA13 (NCBI Gene ID: 377677), CA14 (NCBI Gene ID: 23632)), prostaglandin-endoperoxide synthase 1 (PTGS1, COX-1; NCBI Gene ID: 5742), prostaglandin-endoperoxide synthase 2 (PTGS2, COX-2; NCBI Gene ID: 5743), secreted phospholipase A2, prostaglandin E synthase (PTGES, PGES; Gene ID: 9536), arachidonate 5-lipoxygenase (ALOX5, 5-LOX; NCBI Gene ID: 240), soluble epoxide hydrolase 2 (EPHX2, SEH; NCBI Gene ID: 2053) and/or mitogen-activated protein kinase kinase kinase 8 (MAP3K8, TPL2; NCBI Gene ID: 1326). In some embodiments, the inhibitor is a dual inhibitor, *e.g.*, a dual inhibitor of COX-2/COX-1, COX-2/SEH, COX-2/CA, COX-2/5-LOX.

[0329] Examples of inhibitors of prostaglandin-endoperoxide synthase 1 (PTGS1, COX-1; NCBI Gene ID: 5742) that can be co-administered include mofezolac, GLY-230, and TRK-700.

[0330] Examples of inhibitors of prostaglandin-endoperoxide synthase 2 (PTGS2, COX-2; NCBI Gene ID: 5743) that can be co-administered include diclofenac, meloxicam, parecoxib, etoricoxib,

AP-101, celecoxib, AXS-06, diclofenac potassium, DRGT-46, AAT-076, meisuoshuli, lumiracoxib, meloxicam, valdecoxib, zaltoprofen, nimesulide, anitrazafen, apricoxib, cimicoxib, deracoxib, flumizole, firocoxib, mavacoxib, NS-398, pamicogrel, parecoxib, robenacoxib, rofecoxib, rutecarpine, tilmacoxib, and zaltoprofen. Examples of dual COX1/COX2 inhibitors that can be co-administered include HP-5000, lornoxicam, ketorolac tromethamine, bromfenac sodium, ATB-346, HP-5000. Examples of dual COX-2/carbonic anhydrase (CA) inhibitors that can be co-administered include polmacoxib and imrecoxib.

[0331] Examples of inhibitors of secreted phospholipase A2, prostaglandin E synthase (PTGES, PGES; Gene ID: 9536) that can be co-administered include LY3023703, GRC 27864, and compounds described in WO2015158204, WO2013024898, WO2006063466, WO2007059610, WO2007124589, WO2010100249, WO2010034796, WO2010034797, WO2012022793, WO2012076673, WO2012076672, WO2010034798, WO2010034799, WO2012022792, WO2009103778, WO2011048004, WO2012087771, WO2012161965, WO2013118071, WO2013072825, WO2014167444, WO2009138376, WO2011023812, WO2012110860, WO2013153535, WO2009130242, WO2009146696, WO2013186692, WO2015059618, WO2016069376, WO2016069374, WO2009117985, WO2009064250, WO2009064251, WO2009082347, WO2009117987, and WO2008071173. Metformin has further been found to repress the COX2/PGE2/STAT3 axis, and can be co-administered. *See*, *e.g.*, Tong, *et al.*, *Cancer Lett.* (2017) 389:23-32; and Liu, *et al.*, *Oncotarget.* (2016) 7(19):28235-46.

[0332] Examples of inhibitors of carbonic anhydrase (*e.g.*, one or more of CA1 (NCBI Gene ID: 759), CA2 (NCBI Gene ID: 760), CA3 (NCBI Gene ID: 761), CA4 (NCBI Gene ID: 762), CA5A (NCBI Gene ID: 763), CA5B (NCBI Gene ID: 11238), CA6 (NCBI Gene ID: 765), CA7 (NCBI Gene ID: 766), CA8 (NCBI Gene ID: 767), CA9 (NCBI Gene ID: 768), CA10 (NCBI Gene ID: 56934), CA11 (NCBI Gene ID: 770), CA12 (NCBI Gene ID: 771), CA13 (NCBI Gene ID: 377677), CA14 (NCBI Gene ID: 23632)) that can be co-administered include acetazolamide, methazolamide, dorzolamide, zonisamide, brinzolamide and dichlorphenamide. A dual COX-2/CA1/CA2 inhibitor that can be co-administered includes CG100649.

[0333] Examples of inhibitors of arachidonate 5-lipoxygenase (ALOX5, 5-LOX; NCBI Gene ID: 240) that can be co-administered include meclofenamate sodium, zileuton.

[0334] Examples of inhibitors of soluble epoxide hydrolase 2 (EPHX2, SEH; NCBI Gene ID: 2053) that can be co-administered include compounds described in WO2015148954. Dual inhibitors of COX-2/SEH that can be co-administered include compounds described in

WO2012082647. Dual inhibitors of SEH and fatty acid amide hydrolase (FAAH; NCBI Gene ID: 2166) that can be co-administered include compounds described in WO2017160861.

[0335] Examples of inhibitors of mitogen-activated protein kinase kinase kinase 8 (MAP3K8, tumor progression loci-2, TPL2; NCBI Gene ID: 1326) that can be co-administered include GS-4875, GS-5290, BHM-078 and those described in WO2006124944, WO2006124692, WO2014064215, WO2018005435, Teli, *et al., J Enzyme Inhib Med Chem.* (2012) 27(4):558-70; Gangwall, *et al., Curr Top Med Chem.* (2013) 13(9):1015-35; Wu, *et al., Bioorg Med Chem Lett.* (2009) 19(13):3485-8; Kaila, *et al., Bioorg Med Chem.* (2007) 15(19):6425-42; and Hu, *et al., Bioorg Med Chem Lett.* (2011) 21(16):4758-61.

Tumor Oxygenation Agents

[0336] In some embodiments the compound provided herein is administered with an agent that promotes or increases tumor oxygenation or reoxygenation, or prevents or reduces tumor hypoxia. Illustrative agents that can be co-administered include, *e.g.*, Hypoxia inducible factor-1 alpha (HIF-1α) inhibitors, such as PT-2977, PT-2385; VEGF inhibitors, such as bevasizumab, IMC-3C5, GNR-011, tanibirumab, LYN-00101, ABT-165; and/or an oxygen carrier protein (*e.g.*, a heme nitric oxide and/or oxygen binding protein (HNOX)), such as OMX-302 and HNOX proteins described in WO2007137767, WO2007139791, WO2014107171, and WO2016149562.

Immunotherapeutic Agents

[0337] In some embodiments the compound provided herein is administered with an immunotherapeutic agent. In some embodiments the immunotherapeutic agent is an antibody. Example immunotherapeutic agents that can be co-administered include abagovomab, AB308, ABP-980, adecatumumab, afutuzumab, alemtuzumab, altumomab, amatuximab, anatumomab, arcitumomab, atezolizumab, bavituximab, bectumomab, bevacizumab, bivatuzumab, blinatumomab, brentuximab, camidanlumab, cantuzumab, catumaxomab, CC49, cetuximab, citatuzumab, cixutumumab, clivatuzumab, conatumumab, dacetuzumab, dalotuzumab, daratumumab, detumomab, dinutuximab, domvanalimab, drozitumab, duligotumab, dusigitumab, ecromeximab, elotuzumab, emibetuzumab, ensituximab, ertumaxomab, etaracizumab, farletuzumab, ficlatuzumab, figitumumab, flanvotumab, futuximab, ganitumab, gemtuzumab, girentuximab, glembatumumab, ibritumomab, igovomab, imgatuzumab, indatuximab, inotuzumab, intetumumab, ipilimumab (YERVOY®, MDX-010, BMS-734016, and MDX-101), iratumumab, labetuzumab, lexatumumab, lintuzumab, lorvotuzumab, lucatumumab, mapatumumab, matuzumab, milatuzumab, minretumomab, mitumomab, mogamulizumab,

moxetumomab, naptumomab, narnatumab, necitumumab, nimotuzumab, nofetumomab, OBI-833, obinutuzumab, ocaratuzumab, ofatumumab, olaratumab, onartuzumab, oportuzumab, oregovomab, panitumumab, parsatuzumab, pasudotox, patritumab, pemtumomab, pertuzumab, pintumomab, pritumumab, racotumomab, radretumab, ramucirumab (Cyramza®), rilotumumab, rituximab, robatumumab, samalizumab, satumomab, sibrotuzumab, siltuximab, solitomab, simtuzumab, tacatuzumab, taplitumomab, tenatumomab, teprotumumab, tigatuzumab, tositumomab, trastuzumab, tucotuzumab, ubilituximab, veltuzumab, vorsetuzumab, votumumab, zalutumumab, zimberelimab, and 3F8. Rituximab can be used for treating indolent B-cell cancers, including marginal-zone lymphoma, WM, CLL, and small lymphocytic lymphoma. A combination of rituximab and chemotherapy agents is especially effective.

[0338] The exemplified therapeutic antibodies can be further labeled or combined with a radioisotope particle such as indium-111, yttrium-90 (90Y-clivatuzumab), or iodine-131.

[0339] In some embodiments, the immunotherapeutic agent is an antibody-drug conjugate (ADC). Illustrative ADCs that can be co-administered include without limitation drug-conjugated antibodies, fragments thereof, or antibody mimetics targeting the proteins or antigens listed above and herein. Example ADCs that can be co-administered include gemtuzumab, brentuximab, belantamab (*e.g.*, belantamab mafodotin), camidanlumab (*e.g.*, camidanlumab tesirine), trastuzumab (*e.g.*, trastuzumab deruxtecan; trasuzumab emtansine), inotuzumab, glembatumumab, anetumab, mirvetuximab (*e.g.*, mirvetuximab soravtansine), depatuxizumab, vadastuximab, labetuzumab, ladiratuzumab (*e.g.*, ladiratuzumab vedotin), loncastuximab (*e.g.*, loncastuximab tesirine), sacituzumab (*e.g.*, sacituzumab govitecan), datopotamab (*e.g.*, datopotamab deruxtecan; DS-1062; Dato-DXd), patritumab (*e.g.*, patritumab deruxtecan), lifastuzumab, indusatumab, polatuzumab (*e.g.*, polatuzumab vedotin), pinatuzumab, coltuximab, upifitamab (*e.g.*, upifitamab rilsodotin), indatuximab, milatuzumab, rovalpituzumab (*e.g.*, rovalpituzumab tesirine), enfortumab (*e.g.*, enfortumab vedotin), tisotumab (*e.g.*, tisotumab vedotin), tusamitamab (*e.g.*, tusamitamab ravtansine), disitamab (*e.g.*, disitamab vedotin), telisotuzumab vedotin (ABBV-399), AGS-16C3F, ASG-22ME, AGS67E, AMG172, AMG575, BAY1129980, BAY1187982, BAY94-9343, GSK2857916, Humax-TF-ADC, IMGN289, IMGN151, IMGN529, IMGN632, IMGN853, IMGC936, LOP628, PCA062, MDX-1203 (BMS936561), MEDI-547, PF-06263507, PF-06647020, PF-06647263, PF-06664178, RG7450, RG7458, RG7598, SAR566658, SGN-CD19A, SGN-CD33A, SGN-CD70A, SGN-LIV1A, SYD985, DS-7300, XMT-1660, IMMU-130, and IMMU-140. ADCs that can be co-administered are described, *e.g.*, in Lambert, *et al.*, *Adv Ther* (2017) 34:1015–1035 and in de Goeij, *Current Opinion in Immunology* (2016) 40:14–23.

[0340] Illustrative therapeutic agents (*e.g.*, anticancer or antineoplastic agents) that can be conjugated to the drug-conjugated antibodies, fragments thereof, or antibody mimetics include without limitation monomethyl auristatin E (MMAE), monomethyl auristatin F (MMAF), a calicheamicin, ansamitocin, maytansine or an analog thereof (*e.g.*, mertansine/emtansine (DM1), ravtansine/soravtansine (DM4)), an anthracyline (*e.g.*, doxorubicin, daunorubicin, epirubicin, idarubicin), pyrrolobenzodiazepine (PBD) DNA cross-linking agent SC-DR002 (D6.5), duocarmycin, a microtubule inhibitors (MTI) (*e.g.*, a taxane, a vinca alkaloid, an epothilone), a pyrrolobenzodiazepine (PBD) or dimer thereof, a duocarmycin (A, B1, B2, C1, C2, D, SA, CC-1065), and other anticancer or anti-neoplastic agents described herein. In some embodiments, the therapeutic agent conjugated to the drug-conjugated antibody is a topoisomerase I inhibitor (*e.g.*, a camptothecin analog, such as irinotecan or its active metabolite SN38). In some embodiments, the therapeutic agents (*e.g.*, anticancer or antineoplastic agents) that can be conjugated to the drug-conjugated antibodies, fragments thereof, or antibody mimetics include an immune checkpoint inhibitor. In some embodiments the conjugated immune checkpoint inhibitor is a conjugated small molecule inhibitor of CD274 (PDL1, PD-L1), programmed cell death 1 (PDCD1, PD1, PD-1) or CTLA4. In some embodiments the conjugated small molecule inhibitor of CD274 or PDCD1 is selected from the group consisting of GS-4224, GS-4416, INCB086550 and MAX10181. In some embodiments the conjugated small molecule inhibitor of CTLA4 comprises BPI-002.

[0341] In some embodiments the ADCs that can be co-administered include an antibody targeting tumor-associated calcium signal transducer 2 (TROP-2; TACSTD2; EGP-1; NCBI Gene ID: 4070). Illustrative anti-TROP-2 antibodies include without limitation TROP2-XPAT (Amunix), BAT-8003 (Bio-Thera Solutions), TROP-2-IR700 (Chiome Bioscience), datopotamab deruxtecan (Daiichi Sankyo, AstraZeneca), GQ-1003 (Genequantum Healthcare, Samsung BioLogics), DAC-002 (Hangzhou DAC Biotech, Shanghai Junshi Biosciences), sacituzumab govitecan (Gilead Sciences), E1-3s (Immunomedics/Gilead, IBC Pharmaceuticals), TROP2-TRACTr (Janux Therapeutics), LIV-2008 (LivTech/Chiome, Yakult Honsha, Shanghai Henlius BioTech), LIV-2008b (LivTech/Chiome), anti-TROP-2a (Oncoxx), anti-TROP-2b (Oncoxx), OXG-64 (Oncoxx), OXS-55 (Oncoxx), humanized anti-Trop2-SN38 antibody conjugate (Shanghai Escugen Biotechnology, TOT Biopharma), anti-Trop2 antibody-CLB-SN-38 conjugate (Shanghai Fudan-Zhangjiang Bio-Pharmaceutical), SKB-264 (Sichuan Kelun Pharmaceutical/Klus Pharma), TROP2-Ab8 (Abmart), Trop2-IgG (Nanjing Medical University (NMU)), 90Y-DTPA-AF650 (Peking University First Hospital), hRS7-CM (SynAffix), 89Zr-DFO-AF650 (University of Wisconsin-Madison), anti-Trop2 antibody (Mediterranea Theranostic, LegoChem Biosciences), KD-065 (Nanjing KAEDI Biotech), and those described in WO2020016662 (Abmart),

WO2020249063 (Bio-Thera Solutions), US20190048095 (Bio-Thera Solutions), WO2013077458 (LivTech/Chiome), EP20110783675 (Chiome), WO2015098099 (Daiichi Sankyo), WO2017002776 (Daiichi Sankyo), WO2020130125 (Daiichi Sankyo), WO2020240467 (Daiichi Sankyo), US2021093730 (Daiichi Sankyo), US9850312 (Daiichi Sankyo), CN112321715 (Biosion), US2006193865 (Immunomedics/Gilead), WO2011068845 (Immunomedics/Gilead), US2016296633 (Immunomedics/Gilead), US2017021017 (Immunomedics/Gilead), US2017209594 (Immunomedics/Gilead), US2017274093 (Immunomedics/Gilead), US2018110772 (Immunomedics/Gilead), US2018185351 (Immunomedics/Gilead), US2018271992 (Immunomedics/Gilead), WO2018217227 (Immunomedics/Gilead), US2019248917 (Immunomedics/Gilead), CN111534585 (Immunomedics/Gilead), US2021093730 (Immunomedics/Gilead), US2021069343 (Immunomedics/Gilead), US8435539 (Immunomedics/Gilead), US8435529 (Immunomedics/Gilead), US9492566 (Immunomedics/Gilead), WO2003074566 (Gilead), WO2020257648 (Gilead), US2013039861 (Gilead), WO2014163684 (Gilead), US9427464 (LivTech/Chiome), US10501555 (Abruzzo Theranostic/Oncoxx), WO2018036428 (Sichuan Kelun Pharma), WO2013068946 (Pfizer), WO2007095749 (Roche), and WO2020094670 (SynAffix). In some embodiments, the anti-Trop-2 antibody is selected from hRS7, Trop-2-XPAT, and BAT-8003. In some embodiments, the anti-Trop-2 antibody is hRS7. In some embodiments, hRS7 is as disclosed in U.S. Pat. Nos. 7,238,785; 7,517,964 and 8,084,583, which are incorporated herein by reference. In some embodiments, the antibody-drug conjugate comprises an anti-Trop-2 antibody and an anticancer agent linked by a linker. In some embodiments, the linker includes the linkers disclosed in USPN 7,999,083. In some embodiments, the linker is CL2A. In some embodiments, the drug moiety of antibody-drug conjugate is a chemotherapeutic agent. In some embodiments, the chemotherapeutic agent is selected from doxorubcin (DOX), epirubicin, morpholinodoxorubicin (morpholino-DOX), cyanomorpholino-doxorubicin (cyanomorpholino-DOX), 2-pyrrolino-doxorubicin (2-PDOX), CPT, 10-hydroxy camptothecin, SN-38, topotecan, lurtotecan, 9-aminocamptothecin, 9-nitrocamptothecin, taxanes, geldanamycin, ansamycins, and epothilones. In some embodiments, the chemotherapeutic moiety is SN-38. In some embodiments the compound provided herein is administered with sacituzumab govitecan.

[0342] In some embodiments the ADCs that can be co-administered include an antibody targeting carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1; CD66a; NCBI Gene ID: 634). In some embodiments the CEACAM1 antibody is hMN-14 (e.g., as described in WO1996011013). In some embodiments the CEACAM1-ADC is as described in WO2010093395

(anti-CEACAM-1-CL2A-SN38). In some embodiments the compound provided herein is administered with the CEACAM1-ADC IMMU-130.

[0343] In some embodiments the ADCs that can be co-administered include an antibody targeting MHC class II cell surface receptor encoded by the human leukocyte antigen complex (HLA-DR). In some embodiments the HLA-DR antibody is hL243 (e.g., as described in WO2006094192). In some embodiments the HLA-DR-ADC is as described in WO2010093395 (anti-HLA-DR-CL2A-SN38). In some embodiments the compound provided herein is administered with the HLA-DR-ADC IMMU-140.

Cancer Gene Therapy and Cell Therapy

[0344] In some embodiments the compound provided herein is administered with a cancer gene therapy and cell therapy. Cancer gene therapies and cell therapies include the insertion of a normal gene into cancer cells to replace a mutated or altered gene; genetic modification to silence a mutated gene; genetic approaches to directly kill the cancer cells; including the infusion of immune cells designed to replace most of the patient's own immune system to enhance the immune response to cancer cells, or activate the patient's own immune system (T cells or Natural Killer cells) to kill cancer cells, or find and kill the cancer cells; genetic approaches to modify cellular activity to further alter endogenous immune responsiveness against cancer.

Cellular Therapies

[0345] In some embodiments the compound provided herein is administered with one or more cellular therapies. Illustrative cellular therapies include without limitation co-administration of one or more of a population of natural killer (NK) cells, NK-T cells, T cells, cytokine-induced killer (CIK) cells, macrophage (MAC) cells, tumor infiltrating lymphocytes (TILs) and/or dendritic cells (DCs). In some embodiments, the cellular therapy entails a T cell therapy, *e.g.*, co-administering a population of alpha/beta TCR T cells, gamma/delta TCR T cells, regulatory T (Treg) cells and/or TRuC™ T cells. In some embodiments, the cellular therapy entails a NK cell therapy, *e.g.*, co-administering NK-92 cells. As appropriate, a cellular therapy can entail the co-administration of cells that are autologous, syngeneic or allogeneic to the subject.

[0346] In some embodiments the cellular therapy entails co-administering cells comprising chimeric antigen receptors (CARs). In such therapies, a population of immune effector cells engineered to express a CAR, wherein the CAR comprises a tumor antigen-binding domain. In T

cell therapies, the T cell receptors (TCRs) are engineered to target tumor derived peptides presented on the surface of tumor cells.

[0347] With respect to the structure of a CAR, in some embodiments, the CAR comprises an antigen binding domain, a transmembrane domain, and an intracellular signaling domain. In some embodiments, the intracellular domain comprises a primary signaling domain, a costimulatory domain, or both of a primary signaling domain and a costimulatory domain. In some embodiments, the primary signaling domain comprises a functional signaling domain of one or more proteins selected from the group consisting of CD3 zeta, CD3 gamma, CD3 delta, CD3 epsilon, common FcR gamma (FCERIG), FcR beta (Fc Epsilon Rlb), CD79a, CD79b, Fcgamma RIIa, DAP10, and DAP12.

[0348] In some embodiments, the costimulatory domain comprises a functional domain of one or more proteins selected from the group consisting of CD27, CD28, 4-1BB(CD137), OX40, CD30, CD40, PD-1, ICOS, CD2, CD7, LIGHT, NKG2C, B7-H3, a ligand that specifically binds with CD83, CDS, ICAM-1, GITR, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRFI), CD160, CD19, CD4, CD8alpha, CD8beta, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, ITGAE, CD103, ITGAL, CD1A (NCBI Gene ID: 909), CD1B (NCBI Gene ID: 910), CD1C (NCBI Gene ID: 911), CD1D (NCBI Gene ID: 912), CD1E (NCBI Gene ID: 913), ITGAM, ITGAX, ITGB1, CD29, ITGB2 (CD18, LFA-1), ITGB7, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, NKp44, NKp30, NKp46, and NKG2D.

[0349] In some embodiments, the transmembrane domain comprises a transmembrane domain of a protein selected from the group consisting of the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154, KIRDS2, OX40, CD2, CD27, ICOS (CD278), 4-1BB(CD137), GITR, CD40, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), CD160, CD19, IL2R beta, IL2R gamma, IL7R, ITGA1, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD1A, CD1B, CD1C, CD1D, CD1E, ITGAE, CD103, ITGAL, ITGAM, ITGAX, ITGB1, CD29, ITGB2 (LFA-1, CD18), ITGB7, TNFR2, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (TACTILE), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME

(SLAMF8), SELPLG (CD162), LTBR, PAG/Cbp, NKp44, NKp30, NKp46, NKG2D, and NKG2C.

[0350] In some embodiments, the TCR or CAR antigen binding domain or the immunotherapeutic agent described herein (*e.g.*, monospecific or multi-specific antibody or antigen-binding fragment thereof or antibody mimetic) binds a tumor-associated antigen (TAA). In some embodiments, the tumor-associated antigen is selected from the group consisting of: CD19; CD123; CD22; CD30; CD171; CS-1 (also referred to as CD2 subset 1, CRACC, SLAMF7, CD319, and 19A24); C-type lectin-like molecule-1 (CLL-1 or CLECLI); CD33; epidermal growth factor receptor variant III (EGFRvlll); ganglioside G2 (GD2); ganglioside GD3 (αNeuSAc(2-8)αNeuSAc(2-3)βDGaip(1-4)bDGIcp(1-1)Cer); ganglioside GM3 (αNeuSAc(2-3)βDGalp(1-4)βDGlcp(1-1)Cer); TNF receptor superfamily member 17 (TNFRSF17, BCMA); Tn antigen ((Tn Ag) or (GaINAcu-Ser/Thr)); prostate-specific membrane antigen (PSMA); receptor tyrosine kinase-like orphan receptor 1 (RORI); tumor-associated glycoprotein 72 (TAG72); CD38; CD44v6; Carcinoembryonic antigen (CEA); epithelial cell adhesion molecule (EPCAM); B7H3 (CD276); KIT (CD117); interleukin-13 receptor subunit alpha-2 (IL-13Ra2 or CD213A2); mesothelin; interleukin 11 receptor alpha (IL-11Ra); prostate stem cell antigen (PSCA); protease serine 21 (Testisin or PRSS21); vascular endothelial growth factor receptor 2 (VEGFR2); Lewis(Y)antigen; CD24; platelet-derived growth factor receptor beta (PDGFR-beta); stage-specificembryonic antigen-4 (SSEA-4); CD20; delta like 3 (DLL3); folate receptor alpha; receptor tyrosine-protein kinase, ERBB2 (Her2/neu); mucin 1, cell surface associated (MUC1); epidermal growth factor receptor (EGFR); neural cell adhesion molecule (NCAM); prostase; prostatic acid phosphatase (PAP); elongation factor 2 mutated (ELF2M); ephrin B2; fibroblast activation protein alpha (FAP); insulin-like growth factor 1 receptor (IGF-I receptor), carbonic anhydrase IX (CAIX); proteasome (Prosome, Macropain) subunit, beta type, 9 (LMP2); glycoprotein 100 (gp100); oncogene fusion protein consisting of breakpoint cluster region (BCR) and Abelson murine leukemia viral oncogene homolog 1 (Abl) (bcr-abl); tyrosinase; ephrin type-A receptor 2 (EphA2); fucosyl GM1; sialyl Lewis adhesion molecule (sLe); transglutaminase 5 (TGS5); high molecular weight-melanomaassociatedantigen (HMWMAA); o-acetyl-GD2 ganglioside (OAcGD2); folate receptor beta; tumor endothelial marker 1 (TEM1/CD248); tumor endothelial marker 7-related (TEM7R); six transmembrane epithelial antigen of the prostate I (STEAP1); claudin 6 (CLDN6); thyroid stimulating hormone receptor (TSHR); G protein-coupled receptor class C group 5, member D (GPRCSD); chromosome X open reading frame 61 (CXORF61); CD97; CD179a; anaplastic lymphoma kinase (ALK); polysialic acid; placenta-specific 1 (PLAC1); hexasaccharide portion of globoH glycoceramide (GloboH); mammary gland differentiation antigen (NY-BR-1);

uroplakin 2 (UPK2); hepatitis A virus cellular receptor 1 (HAVCR1); adrenoceptor beta 3 (ADRB3); pannexin 3 (PANX3); G protein-coupled receptor 20 (GPR20); lymphocyte antigen 6 complex, locus K 9 (LY6K); olfactory receptor 51E2 (ORS IE2); TCR Gamma Alternate Reading Frame Protein (TARP); Wilms tumor protein (WT1); cancer/testis antigen 1 (NY-ESO-1); cancer/testis antigen 2 (LAGE-la); melanoma associated antigen 1 (MAGE-A1); ETS translocation-variant gene 6, located on chromosome 12p (ETV6-AML); sperm protein 17 (SPA17); X Antigen Family, Member 1A (XAGE1); angiopoietin-binding cell surface receptor 2 (Tie 2); melanoma cancer testis antigen-1 (MADCT-1); melanoma cancer testis antigen-2 (MAD-CT-2); fos-related antigen 1; tumor protein p53, (p53); p53 mutant; prostein; survivin; telomerase; prostate carcinoma tumor antigen-1 (PCTA-1 or Galectin 8), melanoma antigen recognized by T cells 1 (MelanA or MARTI); rat sarcoma (Ras) mutant; human telomerase reverse transcriptase (hTERT); sarcoma translocation breakpoints; melanoma inhibitor of apoptosis (ML-IAP); ERG (transmembrane protease, serine 2 (TMPRSS2) ETS fusion gene); N-Acetyl glucosaminyl-transferase V (NA17); paired box protein Pax-3 (PAX3); androgen receptor; cyclin B1;v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (MYCN); ras homolog family member C (RhoC); tyrosinase-related protein 2 (TRP-2); cytochrome P450 1B1(CYP IBI); CCCTC-Binding Factor (Zinc Finger Protein)-Like (BORIS or Brother of the Regulator of Imprinted Sites), squamous cell carcinoma antigen recognized by T-cells 3 (SART3); paired box protein Pax-5 (PAX5); proacrosin binding protein sp32 (OY-TES I); lymphocyte-specific protein tyrosine kinase (LCK); A kinase anchor protein 4 (AKAP-4); synovial sarcoma, X breakpoint 2 (SSX2); receptor for advanced glycation endproducts (RAGE-I); renal ubiquitous 1 (RUI); renal ubiquitous 2 (RU2); legumain; human papilloma virus E6 (HPV E6); human papilloma virus E7 (HPV E7); intestinal carboxyl esterase; heat shock protein 70-2 mutated (mut hsp70-2); CD79a; CD79b; CD72; leukocyte-associated immunoglobulin-like receptor 1 (LAIRI); Fc fragment of IgA receptor (FCAR or CD89); leukocyte immunoglobulin-like receptor subfamily A member 2 (LILRA2); CD300 molecule-like family member f (CD300LF); C-type lectin domain family 12 member A (CLEC12A); bone marrow stromal cell antigen 2 (BST2); EGF-like module containing mucin-like hormone receptor-like 2 (EMR2); lymphocyte antigen 75 (LY75); Glypican-3 (GPC3); Fc receptor-like 5 (FCRL5); and immunoglobulin lambda-like polypeptide 1 (IGLL1). In some embodiments, the target is an epitope of the tumor associated antigen presented in an MHC.

[0351] In some embodiments, the tumor antigen is selected from CD150, 5T4, ActRIIA, B7, TNF receptor superfamily member 17 (TNFRSF17, BCMA), CA-125, CCNA1, CD123, CD126, CD138, CD14, CD148, CD15, CD19, CD20, CD200, CD21, CD22, CD23, CD24, CD25, CD26,

CD261, CD262, CD30, CD33, CD362, CD37, CD38, CD4, CD40, CD40L, CD44, CD46, CD5, CD52, CD53, CD54, CD56, CD66a-d, CD74, CD8, CD80, CD92, CE7, CS-1, CSPG4, ED-B fibronectin, EGFR, EGFRvIII, EGP-2, EGP-4, EPHa2, ErbB2, ErbB3, ErbB4, FBP, HER1-HER2 in combination, HER2-HER3 in combination, HERV-K, HIV-1 envelope glycoprotein gp120, HIV-1 envelope glycoprotein gp41, HLA-DR, HM1.24, HMW-MAA, Her2, Her2/neu, IGF-1R, IL-11Ralpha, IL-13R-alpha2, IL-2, IL-22R-alpha, IL-6, IL-6R, Ia, Ii, L1-CAM, L1-cell adhesion molecule, Lewis Y, Ll-CAM, MAGE A3, MAGE-A1, MART-1, MUC1, NKG2C ligands, NKG2D Ligands, NYESO-1, OEPHa2, PIGF, PSCA, PSMA, ROR1, T101, TAC, TAG72, TIM-3, TRAIL-R1, TRAIL-R1 (DR4), TRAIL-R2 (DR5), VEGF, VEGFR2, WT-I, a G-protein coupled receptor, alphafetoprotein (AFP), an angiogenesis factor, an exogenous cognate binding molecule (ExoCBM), oncogene product, anti-folate receptor, c-Met, carcinoembryonic antigen (CEA), cyclin (D 1), ephrinB2, epithelial tumor antigen, estrogen receptor, fetal acetylcholine e receptor, folate binding protein, gp100, hepatitis B surface antigen, kappa chain, kappa light chain, kdr, lambda chain, livin, melanoma-associated antigen, mesothelin, mouse double minute 2 homolog (MDM2), mucin 16 (MUC16), mutated p53, mutated ras, necrosis antigens, oncofetal antigen, ROR2, progesterone receptor, prostate specific antigen, tEGFR, tenascin, P2-Microgiobuiin, Fc Receptor-like 5 (FcRL5).

[0352] In some embodiments, the antigen binding domain binds to an epitope of a target or tumor associated antigen (TAA) presented in a major histocompatibility complex (MHC) molecule. In some embodiments, the TAA is a cancer testis antigen. In some embodiments, the cancer testis antigen is selected from the group consisting of acrosin binding protein (ACRBP; CT23, OY-TES-1, SP32; NCBI Gene ID: 84519), alpha fetoprotein (AFP; AFPD, FETA, HPAFP; NCBI Gene ID: 174); A-kinase anchoring protein 4 (AKAP4; AKAP 82, AKAP-4, AKAP82, CT99, FSC1, HI, PRKA4, hAKAP82, p82; NCBI Gene ID: 8852), ATPase family AAA domain containing 2 (ATAD2; ANCCA, CT137, PRO2000; NCBI Gene ID: 29028), kinetochore scaffold 1 (KNL1; AF15Q14, CASC5, CT29, D40, MCPH4, PPP1R55, Spc7, hKNL-1, hSpc105; NCBI Gene ID: 57082), centrosomal protein 55 (CEP55; C10orf3, CT111, MARCH, URCC6; NCBI Gene ID: 55165), cancer/testis antigen 1A (CTAG1A; ESO1; CT6.1; LAGE-2; LAGE2A; NY-ESO-1; NCBI Gene ID: 246100), cancer/testis antigen 1B (CTAG1B; CT6.1, CTAG, CTAG1, ESO1, LAGE-2, LAGE2B, NY-ESO-1; NCBI Gene ID: 1485), cancer/testis antigen 2 (CTAG2; CAMEL, CT2, CT6.2, CT6.2a, CT6.2b, ESO2, LAGE-1, LAGE2B; NCBI Gene ID: 30848), CCCTC-binding factor like (CTCFL; BORIS, CT27, CTCF-T, HMGB1L1, dJ579F20.2; NCBI Gene ID: 140690), catenin alpha 2 (CTNNA2; CAP-R, CAPR, CDCBM9, CT114, CTNR; NCBI Gene ID: 1496), cancer/testis antigen 83 (CT83; CXorf61, KK-LC-1, KKLC1; NCBI Gene ID:

203413), cyclin A1 (CCNA1; CT146; NCBI Gene ID: 8900), DEAD-box helicase 43 (DDX43; CT13, HAGE; NCBI Gene ID: 55510), developmental pluripotency associated 2 (DPPA2; CT100, ECAT15-2, PESCRG1; NCBI Gene ID: 151871), fetal and adult testis expressed 1 (FATE1; CT43, FATE; NCBI Gene ID: 89885), FMR1 neighbor (FMR1NB; CT37, NY-SAR-35, NYSAR35; NCBI Gene ID: 158521), HORMA domain containing 1 (HORMAD1; CT46, NOHMA; NCBI Gene ID: 84072), insulin like growth factor 2 mRNA binding protein 3 (IGF2BP3; CT98, IMP-3, IMP3, KOC, KOC1, VICKZ3; NCBI Gene ID: 10643), leucine zipper protein 4 (LUZP4; CT-28, CT-8, CT28, HOM-TES-85; NCBI Gene ID: 51213), lymphocyte antigen 6 family member K (LY6K; CT97, HSJ001348, URLC10, ly-6K; NCBI Gene ID: 54742), maelstrom spermatogenic transposon silencer (MAEL; CT128, SPATA35; NCBI Gene ID: 84944), MAGE family member A1 (MAGEA1; CT1.1, MAGE1; NCBI Gene ID: 4100); MAGE family member A3 (MAGEA3; CT1.3, HIP8, HYPD, MAGE3, MAGEA6; NCBI Gene ID: 4102); MAGE family member A4 (MAGEA4; CT1.4, MAGE-41, MAGE-X2, MAGE4, MAGE4A, MAGE4B; NCBI Gene ID: 4103); MAGE family member A11 (MAGEA11; CT1.11, MAGE-11, MAGE11, MAGEA-11; NCBI Gene ID: 4110); MAGE family member C1 (MAGEC1; CT7, CT7.1; NCBI Gene ID: 9947); MAGE family member C2 (MAGEC2; CT10, HCA587, MAGEE1; NCBI Gene ID: 51438); MAGE family member D1 (MAGED1; DLXIN-1, NRAGE; NCBI Gene ID: 9500); MAGE family member D2 (MAGED2; 11B6, BARTS5, BCG-1, BCG1, HCA10, MAGE-D2; NCBI Gene ID: 10916), kinesin family member 20B (KIF20B; CT90, KRMP1, MPHOSPH1, MPP-1, MPP1; NCBI Gene ID: 9585), NUF2 component of NDC80 kinetochore complex (NUF2; CDCA1, CT106, NUF2R; NCBI Gene ID: 83540), nuclear RNA export factor 2 (NXF2; CT39, TAPL-2, TCP11X2; NCBI Gene ID: 56001), PAS domain containing repressor 1 (PASD1; CT63, CT64, OXTES1; NCBI Gene ID: 139135), PDZ binding kinase (PBK; CT84, HEL164, Nori-3, SPK, TOPK; NCBI Gene ID: 55872), piwi like RNA-mediated gene silencing 2 (PIWIL2; CT80, HILI, PIWIL1L, mili; NCBI Gene ID: 55124), preferentially expressed antigen in melanoma (PRAME; CT130, MAPE, OIP-4, OIP4; NCBI Gene ID: 23532), sperm associated antigen 9 (SPAG9; CT89, HLC-6, HLC4, HLC6, JIP-4, JIP4, JLP, PHET, PIG6; NCBI Gene ID: 9043), sperm protein associated with the nucleus, X-linked, family member A1 (SPANXA1; CT11.1, CT11.3, NAP-X, SPAN-X, SPAN-Xa, SPAN-Xb, SPANX, SPANX-A; NCBI Gene ID: 30014), SPANX family member A2 (SPANXA2; CT11.1, CT11.3, SPANX, SPANX-A, SPANX-C, SPANXA, SPANXC; NCBI Gene ID: 728712), SPANX family member C (SPANXC; CT11.3, CTp11, SPANX-C, SPANX-E, SPANXE; NCBI Gene ID: 64663), SPANX family member D (SPANXD; CT11.3, CT11.4, SPANX-C, SPANX-D, SPANX-E, SPANXC, SPANXE, dJ171K16.1; NCBI Gene ID: 64648), SSX family member 1 (SSX1; CT5.1, SSRC; NCBI Gene ID: 6756), SSX family member 2 (SSX2; CT5.2, CT5.2A,

HD21, HOM-MEL-40, SSX; NCBI Gene ID: 6757), synaptonemal complex protein 3 (SYCP3; COR1, RPRGL4, SCP3, SPGF4; NCBI Gene ID: 50511), testis expressed 14, intercellular bridge forming factor (TEX14; CT113, SPGF23; NCBI Gene ID: 56155), transcription factor Dp family member 3 (TFDP3; CT30, DP4, HCA661; NCBI Gene ID: 51270), serine protease 50 (PRSS50; CT20, TSP50; NCBI Gene ID: 29122), TTK protein kinase (TTK; CT96, ESK, MPH1, MPS1, MPS1L1, PYT; NCBI Gene ID: 7272) and zinc finger protein 165 (ZNF165; CT53, LD65, ZSCAN7; NCBI Gene ID: 7718). T cell receptors (TCRs) and TCR-like antibodies that bind to an epitope of a cancer testis antigen presented in a major histocompatibility complex (MHC) molecule are known in the art and can be used in the herein described heterodimers. Cancer testis antigens associated with neoplasia are summarized, *e.g.*, in Gibbs, *et al., Trends Cancer* 2018 Oct;4(10):701-712 and the CT database website at cta.lncc.br/index.php. Illustrative TCRs and TCR-like antibodies that bind to an epitope of NY-ESO-1 presented in an MHC are described, *e.g.*, in Stewart-Jones, *et al.*, *Proc Natl Acad Sci USA.* 2009 Apr 7;106(14):5784-8; WO2005113595, WO2006031221, WO2010106431, WO2016177339, WO2016210365, WO2017044661, WO2017076308, WO2017109496, WO2018132739, WO2019084538, WO2019162043, WO2020086158 and WO2020086647. Illustrative TCRs and TCR-like antibodies that bind to an epitope of PRAME presented in an MHC are described, *e.g.*, in WO2011062634, WO2016142783, WO2016191246, WO2018172533, WO2018234319 and WO2019109821. Illustrative TCRs and TCR-like antibodies that bind to an epitope of a MAGE variant presented in an MHC are described, *e.g.*, in WO2007032255, WO2012054825, WO2013039889, WO2013041865, WO2014118236, WO2016055785, WO2017174822, WO2017174823, WO2017174824, WO2017175006, WO2018097951, WO2018170338, WO2018225732 and WO2019204683. Illustrative TCRs and TCR-like antibodies that bind to an epitope of alpha fetoprotein (AFP) presented in an MHC are described, *e.g.*, in WO2015011450. Illustrative TCRs and TCR-like antibodies that bind to an epitope of SSX2 presented in an MHC are described, *e.g.*, in WO2020063488. Illustrative TCRs and TCR-like antibodies that bind to an epitope of KK-LC-1 (CT83) presented in an MHC are described, *e.g.*, in WO2017189254.

[0353] Examples of cell therapies include: Algenpantucel-L, Sipuleucel-T, (BPX-501) rivogenlecleucel US9089520, WO2016100236, AU-105, ACTR-087, activated allogeneic natural killer cells CNDO-109-AANK, MG-4101, AU-101, BPX-601, FATE-NK100, LFU-835 hematopoietic stem cells, Imilecleucel-T, baltaleucel-T, PNK-007, UCARTCS1, ET-1504, ET-1501, ET-1502, ET-190, CD19-ARTEMIS, ProHema, FT-1050-treated bone marrow stem cell therapy, CD4CARNK-92 cells, CryoStim, AlloStim, lentiviral transduced huCART-meso cells, CART-22 cells, EGFRt/19-28z/4-1BBL CAR T cells, autologous 4H11-28z/fIL-12/EFGRt T cell,

CCR5-SBC-728-HSPC, CAR4-1BBZ, CH-296, dnTGFbRII-NY-ESOc259T, Ad-RTS-IL-12, IMA-101, IMA-201, CARMA-0508, TT-18, CMD-501, CMD-503, CMD-504, CMD-502,CMD-601,CMD-602, and CSG-005.

[0354] In some embodiments the one or more additional co-administered therapeutic agents can be categorized by their mechanism of action, e.g., into the following groups:

- agents targeting adenosine deaminase, such as pentostatin or cladribine;
- agents targeting ATM, such as AZD1390;
- agents targeting MET, such as savolitinib, capmatinib, tepotinib, ABT-700, AG213, JNJ-38877618 (OMO-1), merestinib, HQP-8361, BMS-817378, or TAS-115;
- agents targeting mitogen-activated protein kinase, such as antroquinonol, binimetinib, cobimetinib, selumetinib, trametinib, uprosertib, mirdametinib (PD-0325901), pimasertib, refametinib, or compounds disclosed in WO2011008709, WO2013112741, WO2006124944, WO2006124692, WO2014064215, WO2018005435, Zhou, et al., Cancer Lett. 2017 Nov 1, 408:130-137, Teli, et al., J Enzyme Inhib Med Chem. (2012) 27(4):558-70; Gangwall, et al., Curr Top Med Chem. (2013) 13(9):1015-35; Wu, et al., Bioorg Med Chem Lett. (2009) 19(13):3485-8; Kaila, et al., Bioorg Med Chem. (2007) 15(19):6425-42, or Hu, et al., Bioorg Med Chem Lett. (2011) 21(16):4758-61;
- agents targeting thymidine kinase, such as aglatimagene besadenovec (ProstAtak, PancAtak, GliAtak, GMCI, or AdV-tk);
- agents targeting targeting an interleukin pathway, such as pegilodecakin (AM-0010) (pegylated IL10), CA-4948 (IRAK4 inhibitor);
- agents targeting cytochrome P450 family members, such as letrozole, anastrozole, aminoglutethimide, megestrol acetate (MEGACE®), exemestane, formestane, fadrozole, vorozole (RIVISOR®), letrozole (FEMARA®), or anastrozole (ARIMIDEX®);
- agents targeting CD73, such as a CD73 inhibitor (e.g., quemliclustat (AB680)) or an anti-CD73 antibody (e.g., oleclumab);
- agents targeting DKK3, such as MTG-201;
- agents targeting EEF1A2, such as plitidepsin;

- agents targeting EIF4A1, such as rohinitib;
- agents targeting endoglin, such as TRC105 (carotuximab);
- agents targeting exportin-1, such as eltanexor;
- agents targeting fatty acid amide hydrolase, such as compounds disclosed in WO2017160861;
- agents targeting heat shock protein 90 beta family member 1, such as anlotinib;
- agents targeting lactotransferrin, such as ruxotemitide (LTX-315);
- agents targeting lysyl oxidase, such as compounds disclosed in US4965288, US4997854, US4943593, US5021456, US5059714, US5120764, US5182297, US5252608, or US20040248871;
- agents targeting MAGE family members, such as KITE-718, MAGE-A10C796T, or MAGE-A10 TCR;
- agents targeting MDM2, such as ALRN-6924, CMG-097, milademetan monotosylate monohydrate (DS-3032b), or AMG-232;
- agents targeting MDM4, such as ALRN-6924;
- agents targeting melan-A, such as MART-1 F5 TCR engineered PBMCs;
- agents targeting mesothelin, such as CSG-MESO or TC-210;
- agents targeting METAP2, such as M8891 or APL-1202;
- agents targeting NLRP3, such as BMS-986299;
- agents targeting oxoglutarate dehydrogenase, such as devimistat (CPI-613);
- agents targeting placenta growth factor, such as aflibercept;
- agents targeting SLC10A3, such as compounds disclosed in WO2015148954, WO2012082647, or WO2017160861;

- agents targeting transforming growth factor alpha (TGFa), such as compounds disclosed in WO2019103203;
- agents targeting tumor protein p53, such as kevetrin (stimulator);
- agents targeting vascular endothelial growth factor A, such as aflibercept;
- agents targeting vascular endothelial growth factor receptor, such as fruquintinib or MP0250;
- agents targeting VISTA, such as CA-170, or HMBD-002;
- agents targeting WEE1, such as adavosertib (AZD-1775);
- small molecule inhibitors targeting ABL1, such as imatinib, rebastinib, asciminib, or ponatinib (ICLUSIG®);
- small molecule antagonists targeting adenosine receptor, such as CPI-444, AZD-4635, preladenant, etrumadenant (AB928), or PBF-509;
- small molecule inhibitors targeting arachidonate 5-lipoxygenase, such as meclofenamate sodium or zileuton;
- small molecule inhibitors targeting ATR serine/threonine kinase, such as BAY-937, ceralasertib (AZD6738), AZD6783, VX-803, or VX-970 (berzosertib);
- small molecule inhibitors targeting AXL receptor tyrosine kinase, such as bemcentinib (BGB-324), SLC-0211, or gilteritinib (Axl/Flt3);
- small molecule inhibitors targeting Bruton's tyrosine kinase (BTK), such as (S)-6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7H-purin-8(9H)-one, acalabrutinib (ACP-196), zanubrutinib (BGB-3111), CB988, poseltinib (HM71224), ibrutinib (Imbruvica), M-2951 (evobrutinib), tirabrutinib (ONO-4059), rilzabrutinib (PRN-1008), spebrutinib (CC-292), vecabrutinib, ARQ-531 (MK-1026), SHR-1459, DTRMWXHS-12, or TAS-5315;
- small molecule inhibitors targeting neurotrophic receptor tyrosine kinase such as larotrectinib, entrectinib, or selitrectinib (LOXO-195);

- small molecule inhibitors targeting ROS proto-oncogene 1, receptor tyrosine kinase, such as entrectinib, repotrectinib (TPX-0005), or lorlatinib;

- small molecule inhibitors targeting SRC proto-oncogene, non-receptor tyrosine kinase, such as VAL-201, tirbanibulin (KX2-391), or ilginatinib maleate (NS-018);

- small molecule inhibitors targeting B-cell lymphoma 2, such as navitoclax (ABT-263), venetoclax (ABT-199, RG-7601), or AT-101 (gossypol);

- small molecule inhibitors targeting bromodomain and external domain (BET) bromodomain containing protein, such as ABBV-744, INCB-054329, INCB057643, AZD-5153, ABT-767, BMS-986158, CC-90010, NHWD-870, ODM-207, ZBC246, ZEN3694, CC-95775 (FT-1101), mivebresib, BI-894999, PLX-2853, PLX-51107, CPI-0610, or GS-5829;

- small molecule inhibitors targeting carbohydrate sulfotransferase 15, such as STNM-01;

- small molecule inhibitors targeting carbonic anhydrase, such as polmacoxib, acetazolamide, or methazolamide;

- small molecule inhibitors targeting catenin beta 1, such as CWP-291, or PRI-724;

- small molecule antagonists targeting a C-C motif chemokine receptor, such as CCX-872, BMS-813160 (CCR2/CCR5) or MK-7690 (vicriviroc);

- small molecule antagonists targeting a C-X-C motif chemokine receptor (*e.g.*, CXCR4), blixafortide;

- small molecule inhibitors targeting cereblon, such as avadomide (CC-122), CC-92480, CC-90009, or iberdomide;

- small molecule inhibitors targeting checkpoint kinase 1, such as SRA737;

- small molecule inhibitors targeting a complement component, such as Imprime PGG (Biothera Pharmaceuticals);

- small molecule inhibitor targeting a C-X-C motif chemokine ligand (e.g., CXCL12), such as olaptesed pegol (NOX-A12);

- small molecule inhibitors targeting cytochrome P450 family, such as ODM-209, LAE-201, seviteronel (VT-464), CFG920, abiraterone, or abiraterone acetate;
- small molecule inhibitors targeting DEAD-box helicase 5, such as supinoxin (RX-5902);
- small molecule inhibitors targeting DGKa, e.g., such as described in WO2021130638;
- small molecule inhibitors targeting diablo IAP-binding mitochondrial protein, such as BI-891065;
- small molecule inhibitors targeting dihydrofolate reductase, such as pralatrexate or pemetrexed disodium;
- small molecule inhibitors targeting DNA dependent protein kinase, such as MSC2490484A (nedisertib), VX-984, AsiDNA (DT-01), LXS-196, or sotrastaurin;
- small molecule inhibitors targeting MARCKS, such as BIO-11006;
- small molecule inhibitors targeting RIPK1, such as GSK-3145094;
- small molecule inhibitors targeting Rho associated coiled-coil containing protein kinase, such as AT13148 or KD025;
- small molecule inhibitors targeting DNA topoisomerase, such as irinotecan, firtecan pegol, or amrubicin;
- small molecule inhibitors targeting dopamine receptor D2, such as ONC-201;
- small molecule inhibitors targeting DOT1 like histone lysine methyltransferase, such as pinometostat (EPZ-5676);
- small molecule inhibitors targeting EZH2, such as tazemetostat, CPI-1205, or PF-06821497;
- small molecule inhibitors targeting fatty acid synthase, such as TVB-2640 (Sagimet Biosciences);
- small molecule inhibitors targeting fibroblast growth factor receptor 2 (FGFR2), such as bemarituzumab (FPA144);

- small molecule inhibitors targeting focal adhesion kinase (FAK, PTK2), such as VS-4718, defactinib, or GSK2256098;
- small molecule inhibitors targeting folate receptor 1, such as pralatrexate;
- small molecule inhibitors targeting FOXM1, such as thiostrepton;
- small molecule inhibitors targeting galectin 3, such as belapectin (GR-MD-02);
- small molecule antagonists targeting glucocorticoid receptor, such as relacorilant (CORT-125134);
- small molecule inhibitors targeting glutaminase include without limitation CB-839 (telaglenastat), or bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide (BPTES);
- small molecule inhibitors targeting GNRHR, such as elagolix, relugolix, or degarelix;
- small molecule inhibitors targeting EPAS1, such as belzutifan (PT-2977 (Merck & Co.));
- small molecule inhibitors targeting isocitrate dehydrogenase (NADP(+)), such as limitation ivosidenib (AG-120), vorasidenib (AG-881) (IDH1 and IDH2), IDH-305, or enasidenib (AG-221);
- small molecule inhibitors targeting lysine demethylase 1A, such as CC-90011;
- small molecule inhibitors targeting MAPK interacting serine/threonine kinase, such as tomivosertib (eFT-508);
- small molecule inhibitors targeting notch receptor, such as AL-101 (BMS-906024);
- small molecule inhibitors targeting polo like kinase 1 (PLK1), such as volasertib or onvansertib;
- small molecule inhibitors targeting poly(ADP-ribose) polymerase (PARP), such as olaparib (MK7339), rucaparib, veliparib, talazoparib, ABT-767, pamiparib (BGB-290), fluazolepali (SHR-3162), niraparib (JNJ-64091742), stenoparib (2X-121 (e-7499)), simmiparib, IMP-4297, SC-10914, IDX-1197, HWH-340, CEP 9722, CEP-8983, E7016, 3-aminobenzamide, or CK-102;
- small molecule inhibitors targeting polycomb protein EED, such as MAK683;

- small molecule inhibitors targeting porcupine O-acyltransferase, such as WNT-974;
- small molecule inhibitors targeting prostaglandin-endoperoxide synthase, such as HP-5000, lornoxicam, ketorolac tromethamine, bromfenac sodium, otenaproxesul (ATB-346), mofezolac, GLY-230, TRK-700, diclofenac, meloxicam, parecoxib, etoricoxib, celecoxib, AXS-06, diclofenac potassium, reformulated celecoxib (DRGT-46), AAT-076, meisuoshuli, lumiracoxib, meloxicam, valdecoxib, zaltoprofen, nimesulide, anitrazafen, apricoxib, cimicoxib, deracoxib, flumizole, firocoxib, mavacoxib, pamicogrel, parecoxib, robenacoxib, rofecoxib, rutecarpine, tilmacoxib, zaltoprofen, or imrecoxib;
- small molecule inhibitors targeting protein arginine N methyltransferase, such as MS203, PF-06939999, GSK3368715, or GSK3326595;
- small molecule inhibitors targeting PTPN11, such as TNO155 (SHP-099), RMC-4550, JAB-3068, RMC-4630 (SAR442720), or compounds disclosed in WO2018172984 or WO2017211303;
- small molecule antagonist targeting retinoic acid receptor, such as tamibarotene (SY-1425);
- small molecule inhibitors targeting ribosomal protein S6 kinase B1, such as MSC2363318A;
- small molecule inhibitors targeting S100 calcium binding protein A9, such as tasquinimod;
- small molecule inhibitors targeting selectin E, such as uproleselan sodium (GMI-1271);
- small molecule inhibitors targeting SF3B1, such as H3B-8800;
- small molecule inhibitors targeting Sirtuin-3, such as YC8-02;
- small molecule inhibitors targeting SMO, such as sonidegib (Odomzo®, formerly LDE-225), vismodegib (GDC-0449), glasdegib (PF-04449913), itraconazole, or patidegib, taladegib;
- small molecule antagonists targeting somatostatin receptor, such as OPS-201;
- small molecule inhibitors targeting sphingosine kinase 2, such as opaganib (Yeliva®, ABC294640);

- small molecule inhibitors targeting STAT3, such as napabucasin (BBI-608);
- small molecule inhibitors targeting tankyrase, such as G007-LK or stenoparib (2X-121 (e-7499));
- small molecule inhibitors targeting TFGBR1, such as galunisertib, PF-06952229;
- small molecule inhibitors targeting thymidylate synthase, such as idetrexed (ONX-0801);
- small molecule inhibitors targeting tumor protein p53, such as CMG-097;
- small molecule inhibitors targeting valosin-containing protein, such as CB-5083;
- small molecule inhibitors targeting WT1, such as ombipepimut-S (DSP-7888);
- small molecule agonists targeting adenosine receptor, such as namodenoson (CF102);
- small molecule agonist(s) targeting asparaginase, such as crisantaspase (Erwinase®), GRASPA (ERY-001, ERY-ASP), calaspargase pegol, or pegaspargase;
- small molecule agonists targeting CCAAT enhancer binding protein alpha, such as MTL-501;
- small molecule agonists targeting cytochrome P450 family, such as mitotane;
- small molecule agonists targeting DExD/H-box helicase 58, such as RGT-100;
- small molecule agonists targeting GNRHR, such as leuprorelin acetate, leuprorelin acetate sustained release depot (ATRIGEL), triptorelin pamoate, or goserelin acetate;
- small molecule agonists targeting GRB2, such as prexigebersen (BP1001);
- small molecule agonists targeting NFE2L2, such as omaveloxolone (RTA-408);
- small molecule agonists targeting NOD2, such as mifamurtide (liposomal);
- small molecule agonists targeting RAR-related orphan receptor gamma, such as cintirorgon (LYC-55716);
- small molecule agonists targeting retinoic acid receptor (RAR), such as tretinoin;

- small molecule agonists targeting STING1, such as ADU-S100 (MIW-815), SB-11285, MK-1454, SR-8291, AdVCA0848, GSK-532, SYN-STING, MSA-1, SR-8291, cyclic-GAMP (cGAMP), or cyclic-di-AMP;
- small molecule agonists targeting thyroid hormone receptor beta, such as levothyroxine sodium;
- small molecule agonists targeting tumor necrosis factor, such as tasonermin;
- antisense agents targeting baculoviral IAP repeat containing 5, such as EZN-3042;
- antisense agents targeting GRB2, such as prexigebersen;
- antisense agents targeting heat shock protein 27, such as apatorsen;
- antisense agents targeting STAT3, such as danvatirsen (IONIS-STAT3-2.5Rx);
- gene therapies targeting a C-C motif chemokine receptor, such as SB-728-T;
- gene therapies targeting an interleukin, such as EGENE-001, tavokinogene telseplasmid, nogapendekin alfa (ALT-803), NKTR-255, NIZ-985 (hetIL-15), SAR441000, or MDNA-55;
- antibodies targeting claudin 18, such as claudiximab;
- antibodies targeting clusterin, such as AB-16B5;
- antibodies targeting a complement component, such as ravulizumab (ALXN-1210);
- antibodies targeting a C-X-C motif chemokine ligand, such as BMS-986253 (HuMax-Inflam);
- antibodies targeting delta like canonical Notch ligand 4 (DLL4), such as demcizumab, navicixizumab (DLL4/VEGF);
- antibodies targeting EPH receptor A3, such as fibatuzumab (KB-004);
- antibodies targeting epithelial cell adhesion molecule, such as oportuzumab monatox (VB4-845);
- antibodies targeting fibroblast growth factor, such as GAL-F2, B-701 (vofatamab);

- antibodies targeting hepatocyte growth factor, such as MP-0250;
- antibodies targeting an interleukin, such as canakinumab (ACZ885), gevokizumab (VPM087), CJM-112, guselkumab, talacotuzumab (JNJ-56022473), siltuximab, or tocilizumab;
- antibodies targeting LRRC15, such as ABBV-085 or cusatuzumab (ARGX-110);
- antibodies targeting mesothelin, such as BMS-986148, SEL-403, or anti-MSLN-MMAE;
- antibodies targeting myostatin, such as landogrozumab;
- antibodies targeting notch receptor, such as tarextumab;
- antibodies targeting TGFB1 (TGFb1), such as SAR439459, ABBV-151, NIS793, SRK-181, XOMA089, or compounds disclosed in WO2019103203;
- vaccines targeting fms related receptor tyrosine kinase, such as HLA-A2402/HLA-A0201 restricted epitope peptide vaccine;
- vaccines targeting heat shock protein 27, such as PSV-AML (PhosphoSynVax);
- vaccines targeting PD-L1, such as IO-120 + IO-103 (PD-L1/PD-L2 vaccines) or IO-103;
- vaccines targeting tumor protein p53, such as MVA-p53;
- vaccines targeting WT1, such as WT-1 analog peptide vaccine (WT1-CTL);
- cell therapies targeting baculoviral IAP repeat containing 5, such as tumor lysate/MUC1/survivin PepTivator-loaded dendritic cell vaccine;
- cell therapies targeting carbonic anhydrase, such as DC-Ad-GMCAIX;
- cell therapies targeting C-C motif chemokine receptor, such as CCR5-SBC-728-HSPC;
- cell therapies targeting folate hydrolase 1, such as CIK-CAR.PSMA or CART-PSMA-TGFβRDN;
- cell therapies targeting GSTP1, such as CPG3-CAR (GLYCAR);
- cell therapies targeting HLA-A, such as FH-MCVA2TCR or NeoTCR-P1;

- cell therapies targeting an interleukin, such as CST-101;
- cell therapies targeting KRAS, such as anti-KRAS G12D mTCR PBL;
- cell therapies targeting MET, such as anti-cMet RNA CAR T;
- cell therapies targeting MUC16, such as JCAR-020;
- cell therapies targeting PD-1, such as PD-1 knockout T cell therapy (esophageal cancer/NSCLC);
- cell therapies targeting PRAME, such as BPX-701;
- cell therapies targeting transforming protein E7, such as KITE-439;
- cell therapies targeting WT1, such as WT1-CTL, ASP-7517, or JTCR-016.

Exemplified Combination Therapies

Lymphoma or Leukemia Combination Therapy

[0355] Some chemotherapy agents are suitable for treating lymphoma or leukemia. These agents include aldesleukin, alvocidib, amifostine trihydrate, aminocamptothecin, antineoplaston A10, antineoplaston AS2-1, anti-thymocyte globulin, arsenic trioxide, Bcl-2 family protein inhibitor ABT-263, beta alethine, BMS-345541, bortezomib (VELCADE®), bortezomib (VELCADE®, PS-341), bryostatin 1, bulsulfan, campath-1H, carboplatin, carfilzomib (Kyprolis®), carmustine, caspofungin acetate, CC-5103, chlorambucil, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), cisplatin, cladribine, clofarabine, curcumin, CVP (cyclophosphamide, vincristine, and prednisone), cyclophosphamide, cyclosporine, cytarabine, denileukin diftitox, dexamethasone, docetaxel, dolastatin 10, doxorubicin, doxorubicin hydrochloride, DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide), enzastaurin, epoetin alfa, etoposide, everolimus (RAD001), FCM (fludarabine, cyclophosphamide, and mitoxantrone), FCR (fludarabine, cyclophosphamide, and rituximab), fenretinide, filgrastim, flavopiridol, fludarabine, FR (fludarabine and rituximab), geldanamycin (17 AAG), hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine), ICE (iphosphamide, carboplatin, and etoposide), ifosfamide, irinotecan hydrochloride, interferon alpha-2b, ixabepilone, lenalidomide (REVLIMID®, CC-5013), lymphokine-activated killer cells, MCP (mitoxantrone, chlorambucil, and prednisolone), melphalan, mesna, methotrexate, mitoxantrone hydrochloride, motexafin

gadolinium, mycophenolate mofetil, nelarabine, obatoclax (GX15-070), oblimersen, octreotide acetate, omega-3 fatty acids, Omr-IgG-am (WNIG, Omrix), oxaliplatin, paclitaxel, palbociclib (PD0332991), pegfilgrastim, PEGylated liposomal doxorubicin hydrochloride, perifosin, prednisolone, prednisone, recombinant flt3 ligand, recombinant human thrombopoietin, recombinant interferon alfa, recombinant interleukin-11, recombinant interleukin-12, rituximab, R-CHOP (rituximab and CHOP), R-CVP (rituximab and CVP), R-FCM (rituximab and FCM), R-ICE (rituximab and ICE), and R MCP (rituximab and MCP), R-roscovitine (seliciclib, CYC202), sargramostim, sildenafil citrate, simvastatin, sirolimus, styryl sulphones, tacrolimus, tanespimycin, temsirolimus (CCl-779), thalidomide, therapeutic allogeneic lymphocytes, thiotepa, tipifarnib, vincristine, vincristine sulfate, vinorelbine ditartrate, SAHA (suberanilohydroxamic acid, or suberoyl, anilide, and hydroxamic acid), vemurafenib (Zelboraf ®), venetoclax (ABT-199).

[0356] One modified approach is radioimmunotherapy, wherein a monoclonal antibody is combined with a radioisotope particle, such as indium-111, yttrium-90, and iodine-131. Examples of combination therapies include, but are not limited to, iodine-131 tositumomab (BEXXAR®), yttrium-90 ibritumomab tiuxetan (ZEVALIN®), and BEXXAR® with CHOP.

[0357] The abovementioned therapies can be supplemented or combined with stem cell transplantation or treatment. Therapeutic procedures include peripheral blood stem cell transplantation, autologous hematopoietic stem cell transplantation, autologous bone marrow transplantation, antibody therapy, biological therapy, enzyme inhibitor therapy, total body irradiation, infusion of stem cells, bone marrow ablation with stem cell support, in vitro-treated peripheral blood stem cell transplantation, umbilical cord blood transplantation, immunoenzyme technique, low-LET cobalt-60 gamma ray therapy, bleomycin, conventional surgery, radiation therapy, and nonmyeloablative allogeneic hematopoietic stem cell transplantation.

Non-Hodgkin's Lymphomas Combination Therapy

[0358] Treatment of non-Hodgkin's lymphomas (NHL), especially those of B cell origin, includes using monoclonal antibodies, standard chemotherapy approaches (*e.g.*, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), FCM (fludarabine, cyclophosphamide, and mitoxantrone), MCP (Mitoxantrone, Chlorambucil, Prednisolone), all optionally including rituximab (R) and the like), radioimmunotherapy, and combinations thereof, especially integration of an antibody therapy with chemotherapy.

[0359] Examples of unconjugated monoclonal antibodies for the treatment of NHL/B-cell cancers include rituximab, alemtuzumab, human or humanized anti-CD20 antibodies, lumiliximab, anti-TNF-related apoptosis-inducing ligand (anti-TRAIL), bevacizumab, galiximab, epratuzumab, SGN-40, and anti-CD74.

[0360] Examples of experimental antibody agents used in treatment of NHL/B-cell cancers include ofatumumab, ha20, PRO131921, alemtuzumab, galiximab, SGN-40, CHIR-12.12, epratuzumab, lumiliximab, apolizumab, milatuzumab, and bevacizumab.

[0361] Examples of standard regimens of chemotherapy for NHL/B-cell cancers include CHOP, FCM, CVP, MCP, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), R-FCM, R-CVP, and R MCP.

[0362] Examples of radioimmunotherapy for NHL/B-cell cancers include yttrium-90 ibritumomab tiuxetan (ZEVALIN®) and iodine-131 tositumomab (BEXXAR®).

Mantle Cell Lymphoma Combination Therapy

[0363] Therapeutic treatments for mantle cell lymphoma (MCL) include combination chemotherapies such as CHOP, hyperCVAD, and FCM. These regimens can also be supplemented with the monoclonal antibody rituximab to form combination therapies R-CHOP, hyperCVAD-R, and R-FCM. Any of the abovementioned therapies may be combined with stem cell transplantation or ICE in order to treat MCL.

[0364] An alternative approach to treating MCL is immunotherapy. One immunotherapy uses monoclonal antibodies like rituximab. Another uses cancer vaccines, such as GTOP-99, which are based on the genetic makeup of an individual patient's tumor.

[0365] A modified approach to treat MCL is radioimmunotherapy, wherein a monoclonal antibody is combined with a radioisotope particle, such as iodine-131 tositumomab (BEXXAR®) and yttrium-90 ibritumomab tiuxetan (ZEVALIN®). In another example, BEXXAR® is used in sequential treatment with CHOP.

[0366] Other approaches to treating MCL include autologous stem cell transplantation coupled with high-dose chemotherapy, administering proteasome inhibitors such as bortezomib (VELCADE® or PS-341), or administering antiangiogenesis agents such as thalidomide, especially in combination with rituximab.

[0367] Another treatment approach is administering drugs that lead to the degradation of Bcl-2 protein and increase cancer cell sensitivity to chemotherapy, such as oblimersen, in combination with other chemotherapeutic agents.

[0368] A further treatment approach includes administering mTOR inhibitors, which can lead to inhibition of cell growth and even cell death. Non-limiting examples are sirolimus, temsirolimus (TORISEL®, CCI-779), CC-115, CC-223, SF-1126, PQR-309 (bimiralisib), voxtalisib, GSK-2126458, and temsirolimus in combination with RITUXAN®, VELCADE®, or other chemotherapeutic agents.

[0369] Other recent therapies for MCL have been disclosed. Such examples include flavopiridol, palbociclib (PD0332991), R-roscovitine (selicicilib, CYC202), styryl sulphones, obatoclax (GX15-070), TRAIL, Anti-TRAIL death receptors DR4 and DR5 antibodies, temsirolimus (TORISEL®, CCl-779), everolimus (RAD001), BMS-345541, curcumin, SAHA, thalidomide, lenalidomide (REVLIMID®, CC-5013), and geldanamycin (17 AAG).

Waldenstrom's Macroglobulinemia Combination Therapy

[0370] Therapeutic agents used to treat Waldenstrom's Macroglobulinemia (WM) include aldesleukin, alemtuzumab, alvocidib, amifostine trihydrate, aminocamptothecin, antineoplaston A10, antineoplaston AS2-1, anti-thymocyte globulin, arsenic trioxide, autologous human tumor-derived HSPPC-96, Bcl-2 family protein inhibitor ABT-263, beta alethine, bortezomib (VELCADE®), bryostatin 1, busulfan, campath-1H, carboplatin, carmustine, caspofungin acetate, CC-5103, cisplatin, clofarabine, cyclophosphamide, cyclosporine, cytarabine, denileukin diftitox, dexamethasone, docetaxel, dolastatin 10, doxorubicin hydrochloride, DT-PACE, enzastaurin, epoetin alfa, epratuzumab (hLL2- anti-CD22 humanized antibody), etoposide, everolimus, fenretinide, filgrastim, fludarabine, ibrutinib, ifosfamide, indium-111 monoclonal antibody MN-14, iodine-131 tositumomab, irinotecan hydrochloride, ixabepilone, lymphokine-activated killer cells, melphalan, mesna, methotrexate, mitoxantrone hydrochloride, monoclonal antibody CD19 (such as tisagenlecleucel-T, CART-19, CTL-019), monoclonal antibody CD20, motexafin gadolinium, mycophenolate mofetil, nelarabine, oblimersen, octreotide acetate, omega-3 fatty acids, oxaliplatin, paclitaxel, pegfilgrastim, PEGylated liposomal doxorubicin hydrochloride, pentostatin, perifosine, prednisone, recombinant flt3 ligand, recombinant human thrombopoietin, recombinant interferon alfa, recombinant interleukin-11, recombinant interleukin-12, rituximab, sargramostim, sildenafil citrate (VIAGRA®), simvastatin, sirolimus, tacrolimus, tanespimycin, thalidomide, therapeutic allogeneic lymphocytes, thiotepa, tipifarnib, tositumomab, ulocuplumab, veltuzumab, vincristine sulfate, vinorelbine ditartrate, vorinostat, WT1 126-134 peptide vaccine,

WT-1 analog peptide vaccine, yttrium-90 ibritumomab tiuxetan, yttrium-90 humanized epratuzumab, and any combination thereof.

[0371] Examples of therapeutic procedures used to treat WM include peripheral blood stem cell transplantation, autologous hematopoietic stem cell transplantation, autologous bone marrow transplantation, antibody therapy, biological therapy, enzyme inhibitor therapy, total body irradiation, infusion of stem cells, bone marrow ablation with stem cell support, in vitro-treated peripheral blood stem cell transplantation, umbilical cord blood transplantation, immunoenzyme techniques, low-LET cobalt-60 gamma ray therapy, bleomycin, conventional surgery, radiation therapy, and nonmyeloablative allogeneic hematopoietic stem cell transplantation.

Diffuse Large B-cell Lymphoma (DLBCL) Combination Therapy

[0372] Therapeutic agents used to treat diffuse large B-cell lymphoma (DLBCL) include cyclophosphamide, doxorubicin, vincristine, prednisone, anti-CD20 monoclonal antibodies, etoposide, bleomycin, many of the agents listed for WM, and any combination thereof, such as ICE and RICE. In some embodiments therapeutic agents used to treat DLBCL include rituximab (Rituxan®), cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin®), prednisone, bendamustine, ifosfamide, carboplatin, etoposide, ibrutinib, polatuzumab vedotin piiq, bendamustine, copanlisib, lenalidomide (Revlimid®), dexamethasone, cytarabine, cisplatin, Yescarta®, Kymriah®, Polivy®(polatuzumab vedotin), BR (bendamustine (Treanda®), gemcitabine, oxiplatin, oxaliplatin, tafasitamab, polatuzumab, cyclophosphamide, or combinations thereof. In some embodiments therapeutic agents used to treat DLBCL include R-CHOP (rituximab + cyclophosphamide + doxorubicin hydrochloride (hydroxydaunorubicin)+ vincristine sulfate (Oncovin®), + prednisone), rituximab + bendamustine, R-ICE (Rituximab + Ifosfamide + Carboplatin + Etoposide), rituximab + lenalomide, R-DHAP (rituximab + dexamethasone + high-dose cytarabine (Ara C) + cisplatin), Polivy®(polatuzumab vedotin) +BR (bendamustine (Treanda®) and rituximab (Rituxan®), R-GemOx (Gemcitabine + oxaliplatin + rituximab), Tafa-Len (tafasitamab + lenalidomide), Tafasitamab + Revlimid®, polatuzumab+bendamustine, Gemcitabine + oxaliplatin, R-EPOCH (rituximab + etoposide phosphate + prednisone + vincristine sulfate (Oncovin®) + cyclophosphamide + doxorubicin hydrochloride (hydroxydaunorubicin)), or CHOP (cyclophosphamide + doxorubicin hydrochloride (hydroxydaunorubicin)+ vincristine sulfate (Oncovin®) + prednisone). In some embodiments therapeutic agents used to treat DLBCL include tafasitamab, glofitamab, epcoritamab, Lonca-T (loncastuximab tesirine), Debio-1562, polatuzumab, Yescarta, JCAR017, ADCT-402, brentuximab vedotin, MT-3724, odronextamab , Auto-03, Allo-501A, or TAK-007.

Chronic Lymphocytic Leukemia Combination Therapy

[0373] Therapeutic agents used to treat chronic lymphocytic leukemia (CLL) include chlorambucil, cyclophosphamide, fludarabine, pentostatin, cladribine, doxorubicin, vincristine, prednisone, prednisolone, alemtuzumab, many of the agents listed for WM, and combination chemotherapy and chemoimmunotherapy, including the following common combination regimens: CVP, R-CVP, ICE, R-ICE, FCR, and FR.

High Risk Myelodysplastic Syndrome (HR MDS) Combination Therapy

[0374] Therapeutic agents used to treat HR MDS include azacitidine (Vidaza®), decitabine (Dacogen®), lenalidomide (Revlimid®), cytarabine, idarubicin, daunorubicin, and combinations thereof. In some embodiments combinations include cytarabine + daunorubicin and cytarabine + idarubicin. In some embodiments therapeutic agents used to treat HR MDS include pevonedistat, venetoclax, sabatolimab, guadecitabine, rigosertib, ivosidenib, enasidenib, selinexor, BGB324, DSP-7888, or SNS-301.

Low Risk Myelodysplastic Syndrome (LR MDS) Combination Therapy

[0375] Therapeutic agents used to treat LR MDS include lenalidomide, azacytidine, and combinations thereof. In some embodiments therapeutic agents used to treat LR MDS include roxadustat, luspatercept, imetelstat, LB-100, or rigosertib.

High Risk Myelodysplastic Syndrome (HR MDS) Combination Therapy

[0376] Therapeutic agents used to treat HR MDS include azacitidine (Vidaza®), decitabine (Dacogen®), lenalidomide (Revlimid®), cytarabine, idarubicin, daunorubicin, and combinations thereof. In some embodiments combinations include cytarabine + daunorubicin and cytarabine + idarubicin. In some embodiments therapeutic agents used to treat HR MDS include pevonedistat, venetoclax, sabatolimab, guadecitabine, rigosertib, ivosidenib, enasidenib, selinexor, BGB324, DSP-7888, or SNS-301.

Low Risk Myelodysplastic Syndrome (LR MDS) Combination Therapy

[0377] Therapeutic agents used to treat LR MDS include lenalidomide, azacytidine, and combinations thereof. In some embodiments therapeutic agents used to treat LR MDS include roxadustat, luspatercept, imetelstat, LB-100, or rigosertib.

Acute Myeloid Leukemia (AML) Combination Therapy

[0378] Therapautic agents used to treat AML include cytarabine, idarubicin, daunorubicin, midostaurin (Rydapt®), venetoclax, azacitidine, ivasidenib, gilteritinib, enasidenib, low-dose cytarabine (LoDAC), mitoxantrone, fludarabine, granulocyte-colony stimulating factor, idarubicin, gilteritinib (Xospata®), enasidenib (Idhifa®), ivosidenib (Tibsovo®), decitabine (Dacogen®), mitoxantrone, etoposide, Gemtuzumab ozogamicin (Mylotarg®), glasdegib (Daurismo®), and combinations thereof. In some embodiments therapeutic agents used to treat AML include FLAG- Ida (fludarabine, cytarabine (Ara-C), granulocyte- colony stimulating factor (G-CSF) and idarubicin), cytarabine + idarubicin, cytarabine + daunorubicin + midostaurin, venetoclax + azacitidine, cytarabine + daunorubicin, or MEC (mitoxantrone, etoposide, and cytarabine). In some embodiments, therapeutic agents used to treat AML include pevonedistat, venetoclax, sabatolimab, eprenetapopt, or lemzoparlimab.

Multiple Myeloma (MM) Combination Therapy

[0379] Therapeutic agents used to treat MM include lenalidomide, bortezomib, dexamethasone, daratumumab (Darzalex®), pomalidomide, Cyclophosphamide, Carfilzomib (Kyprolis®), Elotuzumab (Empliciti), and combinations thereof. In some embodiments therapeutic agents used to treat MM include RVS (lenalidomide + bortezomib + dexamethasone), RevDex (lenalidomide plus dexamethasone), CYBORD (Cyclophosphamide+Bortezomib+Dexamethasone), Vel/Dex (bortezomib plus dexamethasone), or PomDex (Pomalidomide + low-dose dexamethasone). In some embodiments therapeutic agents used to treat MM include JCARH125, TAK-573, belantamab-m, ide-cel (CAR-T).

Breast Cancer Combination Therapy

[0380] Therapeutic agents used to treat breast cancer include albumin-bound paclitaxel, anastrozole, atezolizumab, capecitabine, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, epirubicin, everolimus, exemestane, fluorouracil, fulvestrant, gemcitabine, Ixabepilone, lapatinib, letrozole, methotrexate, mitoxantrone, paclitaxel, pegylated liposomal doxorubicin, pertuzumab, tamoxifen, toremifene, trastuzumab, vinorelbine, and any combinations thereof. In some embodiments therapeutic agents used to treat breast cancer (e.g., HR+/-/HER2 +/-) include trastuzumab (Herceptin®), pertuzumab (Perjeta®), docetaxel, carboplatin, palbociclib (Ibrance®), letrozole, trastuzumab emtansine (Kadcyla®), fulvestrant (Faslodex®), olaparib (Lynparza®), eribulin, tucatinib, capecitabine, lapatinib, everolimus (Afinitor®), exemestane, eribulin mesylate (Halaven®), and combinations thereof. In some embodiments therapeutic agents

used to treat breast cancer include trastuzumab + pertuzumab + docetaxel, trastuzumab + pertuzumab + docetaxel + carboplatin, palbociclib + letrozole, tucatinib + capecitabine, lapatinib + capecitabine, palbociclib + fulvestrant, or everolimus + exemestane. In some embodiments therapeutic agents used to treat breast cancer include trastuzumab deruxtecan (Enhertu®), datopotamab deruxtecan (DS-1062), enfortumab vedotin (Padcev®), balixafortide, elacestrant, or a combination thereof. In some embodiments therapeutic agents used to treat breast cancer include balixafortide + eribulin.

Triple Negative Breast Cancer (TNBC) Combination Therapy

[0381] Therapeutic agents used to treat TNBC include atezolizumab, cyclophosphamide, docetaxel, doxorubicin, epirubicin, fluorouracil, paclitaxel, and combinations thereof. In some embodiments therapeutic agents used to treat TNBC include olaparib (Lynparza®), atezolizumab (Tecentriq®), paclitaxel (Abraxane®), eribulin, bevacizumab (Avastin®), carboplatin, gemcitabine, eribulin mesylate (Halaven®), sacituzumab govitecan (Trodelvy®), pembrolizumab (Keytruda®), cisplatin, doxorubicin, epirubicin, or a combination thereof. In some embodiments therapeutic agents to treat TNBC include atezolizumab + paclitaxel, bevacizumab + paclitaxel, carboplatin + paclitaxel, carboplatin + gemcitabine, or paclitaxel + gemcitabine. In some embodiments therapeutic agents used to treat TNBC include eryaspase, capivasertib, alpelisib, rucaparib + nivolumab, atezolumab + paclitaxel + gemcitabine+ capecitabine + carboplatin, ipatasertib + paclitaxel, ladiratuzumab vedotin + pembrolimab, durvalumab + DS-8201a, trilaciclib + gemcitabine +carboplatin. In some embodiments therapeutic agents used to treat TNBC include trastuzumab deruxtecan (Enhertu®), datopotamab deruxtecan (DS-1062), enfortumab vedotin (Padcev®), balixafortide, adagloxad simolenin, nelipepimut-s (NeuVax®), nivolumab (Opdivo®), rucaparib, toripalimab (Tuoyi®), camrelizumab, capivasertib, durvalumab (Imfinzi®), and combinations thereof. In some embodiments therapeutic agents use to treat TNBC include nivolumab + rucaparib, bevacizumab (Avastin®) + chemotherapy, toripalimab + paclitaxel, toripalimab + albumin-bound paclitaxel, camrelizumab + chemotherapy, pembrolizumab + chemotherapy, balixafortide + eribulin, durvalumab + trastuzumab deruxtecan, durvalumab + paclitaxel, or capivasertib + paclitaxel.

Bladder Cancer Combination Therapy

[0382] Therapeutic agents used to treat bladder cancer include datopotamab deruxtecan (DS-1062), trastuzumab deruxtecan (Enhertu®), erdafitinib, eganelisib, lenvatinib, bempegaldesleukin (NKTR-214), or a combination thereof. In some embodiments therapeutic agents used to treat bladder cancer include eganelisib + nivolumab, pembrolizumab (Keytruda®) + enfortumab

vedotin (Padcev®), nivolumab + ipilimumab, duravalumab + tremelimumab, lenvatinib + pembrolizumab, enfortumab vedotin (Padcev®) + pembrolizumab, and bempegaldesleukin + nivolumab.

Colorectal Cancer (CRC) Combination Therapy

[0383] Therapeutic agents used to treat CRC include bevacizumab, capecitabine, cetuximab, fluorouracil, irinotecan, leucovorin, oxaliplatin, panitumumab, ziv-aflibercept, and any combinations thereof. In some embodiments therapeutic agents used to treat CRC include bevacizumab (Avastin®), leucovorin, 5-FU, oxaliplatin (FOLFOX), pembrolizumab (Keytruda®), FOLFIRI, regorafenib (Stivarga®), aflibercept (Zaltrap®), cetuximab (Erbitux®), Lonsurf (Orcantas®), XELOX, FOLFOXIRI, or a combination thereof. In some embodiments therapeutic agents used to treat CRC include bevacizumab + leucovorin + 5-FU, bevacizumab + leucovorin + 5-FU + oxaliplatin (FOLFOX), bevacizumab + FOLFIRI, bevacizumab + FOLFOX, aflibercept + FOLFIRI, cetuximab + FOLFIRI, cetuximab + FOLFOX, bevacizumab + XELOX, and bevacizumab + FOLFOXIRI. In some embodiments therapeutic agents used to treat CRC include binimetinib + encorafenib + cetuximab, trametinib + dabrafenib + panitumumab, trastuzumab + pertuzumab, napabucasin + FOLFIRI + bevacizumab, nivolumab + ipilimumab.

Esophageal and Esophagogastric Junction Cancer Combination Therapy

[0384] Therapeutic agents used to treat esophageal and esophagogastric junction cancer include capecitabine, carboplatin, cisplatin, docetaxel, epirubicin, fluoropyrimidine, fluorouracil, irinotecan, leucovorin, oxaliplatin, paclitaxel, ramucirumab, trastuzumab, and any combinations thereof. In some embodiments therapeutic agents used to treat gastroesophageal junction cancer (GEJ) include herceptin, cisplatin, 5-FU, ramicurimab, or paclitaxel. In some embodiments therapeutic agents used to treat GEJ cancer include ALX-148, AO-176, or IBI-188.

Gastric Cancer Combination Therapy

[0385] Therapeutic agents used to treat gastric cancer include capecitabine, carboplatin, cisplatin, docetaxel, epirubicin, fluoropyrimidine, fluorouracil, Irinotecan, leucovorin, mitomycin, oxaliplatin, paclitaxel, ramucirumab, trastuzumab, and any combinations thereof..

Head and Neck Cancer Combination Therapy

[0386] Therapeutic agents used to treat head & neck cancer include afatinib, bleomycin, capecitabine, carboplatin, cetuximab, cisplatin, docetaxel, fluorouracil, gemcitabine,

hydroxyurea, methotrexate, nivolumab, paclitaxel, pembrolizumab, vinorelbine, and any combinations thereof.

[0387] Therapeutic agents used to treat head and neck squamous cell carcinoma (HNSCC) include pembrolizumab, carboplatin, 5-FU, docetaxel, cetuximab (Erbitux®), cisplatin, nivolumab (Opdivo®), and combinations thereof. In some embodiments therapeutic agents used to treat HNSCC include pembrolizumab + carboplatin + 5-FU, cetuximab + cisplatin + 5-FU, cetuximab + carboplatin + 5-FU, cisplatin + 5-FU, and carboplatin + 5-FU. In some embodiments therapeutic agents used to treat HNSCC include durvalumab, durvalumab + tremelimumab, nivolumab + ipilimumab, rovaluecel, pembrolizumab, pembrolizumab + epacadostat, GSK3359609 + pembrolizumab, lenvatinib + pembrolizumab, retifanlimab, retifanlimab + enobituzumab, ADU-S100 + pembrolizumab, epacadostat + nivolumab+ ipilimumab/lirilumab.

Non-Small Cell Lung Cancer Combination Therapy

[0388] Therapeutic agents used to treat non-small cell lung cancer (NSCLC) include afatinib, albumin-bound paclitaxel, alectinib, atezolizumab, bevacizumab, bevacizumab, cabozantinib, carboplatin, cisplatin, crizotinib, dabrafenib, docetaxel, erlotinib, etoposide, gemcitabine, nivolumab, paclitaxel, pembrolizumab, pemetrexed, ramucirumab, trametinib, trastuzumab, vandetanib, vemurafenib, vinblastine, vinorelbine, and any combinations thereof. In some embodiments therapeutic agents used to treat NSCLC include alectinib (Alecensa®), dabrafenib (Tafinlar®), trametinib (Mekinist®), osimertinib (Tagrisso®), entrectinib (Tarceva®), crizotinib (Xalkori®), pembrolizumab (Keytruda®), carboplatin, pemetrexed (Alimta®), nab-paclitaxel (Abraxane®), ramucirumab (Cyramza®), docetaxel, bevacizumab (Avastin®), brigatinib, gemcitabine, cisplatin, afatinib (Gilotrif®), nivolumab (Opdivo®), gefitinib (Iressa®), and combinations thereof. In some embodiments therapeutic agents used to treat NSCLC include dabrafenib + trametinib, pembrolizumab + carboplatin + pemetrexed, pembrolizumab + carboplatin + paclitaxel, pembrolizumab + carboplatin + nab-paclitaxel, ramucirumab + docetaxel, bevacizumab + carboplatin + pemetrexed, pembrolizumab + pemetrexed + cisplatin, cisplatin + pemetrexed, bevacizumab + carboplatin + nab-paclitaxel, cisplatin + gemcitabine, nivolumab + docetaxel, nivolumab + ipilimumab, carboplatin + pemetrexed, carboplatin + nab-paclitaxel, or pemetrexed + cisplatin + carboplatin. In some embodiments therapeutic agents used to NSCLC include datopotamab deruxtecan (DS-1062), ipilimumab, trastuzumab deruxtecan (Enhertu®), enfortumab vedotin (Padcev®), durvalumab, canakinumab, cemiplimab, nogapendekin alfa, avelumab, tiragolumab, domvanalimab, vibostolimab, ociperlimab, or a combination thereof. In some embodiments therapeutic agents used to treat NSCLC include

datopotamab deruxtecan + pembrolizumab, datopotamab deruxtecan + durvalumab, durvalumab + tremelimumab, pembrolizumab + lenvatinib + pemetrexed, pembrolizumab + olaparib, nogapendekin alfa (N-803) + pembrolizumab, tiragolumab + atezolizumab, vibostolimab + pembrolizumab, or ociperlimab + tislelizumab.

Small Cell Lung Cancer Combination Therapy

[0389] Therapeutic agents used to treat small cell lung cancer (SCLC) include atezolizumab, bendamustime, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, etoposide, gemcitabine, ipillimumab, irinotecan, nivolumab, paclitaxel, temozolomide, topotecan, vincristine, vinorelbine, and any combinations thereof. In some embodiments therapeutic agents used to treat SCLC include atezolizumab, carboplatin, cisplatin, etoposide, paclitaxel, topotecan, nivolumab, durvalumab, trilaciclib, or combinations thereof. In some embodiments therapeutic agents used to treat SCLC include atezolizumab + carboplatin + etoposide, atezolizumab + carboplatin, atezolizumab + etoposide, or carboplatin + paclitaxel.

Ovarian Cancer Combination Therapy

[0390] Therapeutic agents used to treat ovarian cancer include 5-flourouracil, albumin bound paclitaxel, altretamine, anastrozole, bevacizumab, capecitabine, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, etoposide, exemestane, gemcitabine, ifosfamide, irinotecan, letrozole, leuprolide acetate, liposomal doxorubicin, megestrol acetate, melphalan, olaparib, oxaliplatin, paclitaxel, pazopanib, pemetrexed, tamoxifen, topotecan, vinorelbine, and any combinations thereof.

Pancreatic Cancer Combination Therapies

[0391] Therapeutic agents used to treat pancreatic cancer include 5-FU, leucovorin, oxaliplatin, irinotecan, gemcitabine, nab-paclitaxel (Abraxane®), FOLFIRINOX, FOLFOX, XELOX, and combinations thereof. In some embodiments therapeutic agents used to treat pancreatic cancer include 5-FU + leucovorin + oxaliplatin + irinotecan, 5-FU + nanoliposomal irinotecan, cisplatin + gemcitabine, leucovorin + nanoliposomal irinotecan, 5-FU + gemcitabine, and gemcitabine + nab-paclitaxel.

Endometrial Cancer Combination Therapies

[0392] Therapeutic treatments used to treat endometrial cancer include surgery, chemotherapy, radiation therapy, hormone therapy, targeted therapy, and immunotherapy. In some embodiments,

the therapeutic treatments include Anti-angiogenesis therapy, Mammalian target of rapamycin (mTOR) inhibitors, Targeted therapy to treat a rare type of uterine cancer.

[0393] Therapeutic agents used to treat endometrial cancer include carboplatin, paclitaxel, cisplatin, doxorubicin, ifosfamide, progesterone, anastrozole (Arimidex®), letrozole (Femara®), and exemestane (Aromasin®), pembrolizumab (Keytruda®), lenvatinib (Lenvima®), dostarlimab (Jemperli®), and combinations thereof.

Prostate Cancer Combination Therapies

[0394] Therapeutic agents used to treat prostate cancer include enzalutamide (Xtandi®), leuprolide, trifluridine, tipiracil (Lonsurf), cabazitaxel, prednisone, abiraterone (Zytiga®), docetaxel, mitoxantrone, bicalutamide, LHRH, flutamide, ADT, sabizabulin (Veru-111), and combinations thereof. In some embodiments therapeutic agents used to treat prostate cancer include enzalutamide + leuprolide, trifluridine + tipiracil (Lonsurf), cabazitaxel + prednisone, abiraterone + prednisone, docetaxel + prednisone, mitoxantrone + prednisone, bicalutamide + LHRH, flutamide + LHRH, leuprolide + flutamide , and abiraterone + prednisone + ADT.

Additional Exemplified Combination Therapies

[0395] In some embodiments the compound provided herein is administered with one or more therapeutic agents selected from a PI3K inhibitor, a Trop-2 binding agent, CD47 antagonist, a SIRPα antagonist, a FLT3R agonist, a PD-1 antagonist, a PD-L1 antagonist, an MCL1 inhibitor, a CCR8 binding agent, an HPK1 antagonist, a DGKa inhibitor, a CISH inhibitor, a PARP-7 inhibitor, a Cbl-b inhibitor, a KRAS inhibitor (*e.g.*, a KRAS G12C or G12D inhibitor), a KRAS degrader, a beta-catenin degrader, a helios degrader, a CD73 inhibitor, an adenosine receptor antagonist, a TIGIT antagonist, a TREM1 binding agent, a TREM2 binding agent, a CD137 agonist, a GITR binding agent, an OX40 binding agent, and a CAR-T cell therapy.

[0396] In some embodiments the compound provided herein is administered with one or more therapeutic agents selected from a PI3Kd inhibitor (*e.g.*, idealisib), an anti-Trop-2 antibody drug conjugate (*e.g.*, sacituzumab govitecan, datopotamab deruxtecan (DS-1062)), an anti-CD47 antibody or a CD47-blocking agent (*e.g.*, magrolimab, DSP-107, AO-176, ALX-148, letaplimab (IBI-188), lemzoparlimab, TTI-621, TTI-622), an anti-SIRPα antibody (*e.g.*, GS-0189), a FLT3L-Fc fusion protein (*e.g.*, GS-3583), an anti-PD-1 antibody (pembrolizumab, nivolumab, zimberelimab), a small molecule PD-L1 inhibitor (*e.g.*, GS-4224), an anti-PD-L1 antibody (*e.g.*, atezolizumab, avelumab), a small molecule MCL1 inhibitor (*e.g.*, GS-9716), a small molecule

HPK1 inhibitor (*e.g.*, GS-6451), a HPK1 degrader (PROTAC; *e.g.*, ARV-766), a small molecule DGKa inhibitor, a small molecule CD73 inhibitor (*e.g.*, quemliclustat (AB680)), an anti-CD73 antibody (*e.g.*, oleclumab), a dual A_{2a}/A_{2b} adenosine receptor antagonist (*e.g.*, etrumadenant (AB928)), an anti-TIGIT antibody (*e.g.*, tiragolumab, vibostolimab, domvanalimab, AB308), an anti-TREM1 antibody (*e.g.*, PY159), an anti-TREM2 antibody (*e.g.*, PY314), a CD137 agonist (*e.g.*, AGEN-2373), a GITR/OX40 binding agent (*e.g.*, AGEN-1223) and a CAR-T cell therapy (*e.g.*, axicabtagene ciloleucel, brexucabtagene autoleucel, tisagenlecleucel).

[0397] In some embodiments the compound provided herein is administered with one or more therapeutic agents selected from idealisib, sacituzumab govitecan, magrolimab, GS-0189, GS-3583, zimberelimab, GS-4224, GS-9716, GS-6451, quemliclustat (AB680), etrumadenant (AB928), domvanalimab, AB308, PY159, PY314, AGEN-1223, AGEN-2373, axicabtagene ciloleucel and brexucabtagene autoleucel.

IX. Compound Preparation

[0398] In some embodiments, the present disclosure provides processes and intermediates useful for preparing the compounds disclosed herein or pharmaceutically acceptable salts thereof.

[0399] Compounds disclosed herein can be purified by any of the means known in the art, including chromatographic means, including but not limited to high-performance liquid chromatography (HPLC), preparative thin layer chromatography, flash column chromatography, and ion exchange chromatography. Any suitable stationary phase can be used, including but not limited to, normal and reversed phases as well as ionic resins. In some embodiments, the disclosed compounds are purified via silica gel and/or alumina chromatography.

[0400] During any of the processes for preparation of the compounds provided herein, it can be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups as described in standard works, such as T. W. Greene and P. G. M. Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, 4th ed., Wiley, New York 2006. The protecting groups can be removed at a convenient subsequent stage using methods known from the art.

[0401] Exemplary chemical entities useful in methods of the embodiments will now be described by reference to illustrative synthetic schemes for their general preparation herein and the specific examples that follow. Skilled artisans will recognize that, to obtain the various compounds herein, starting materials can be suitably selected so that the ultimately desired substituents will be carried

through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it can be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that can be carried through the reaction scheme and replaced as appropriate with the desired substituent. Furthermore, one of skill in the art will recognize that the transformations shown in the schemes below can be performed in any order that is compatible with the functionality of the particular pendant groups.

[0402] The methods of the present disclosure generally provide a specific enantiomer or diastereomer as the desired product, although the stereochemistry of the enantiomer or diastereomer was not determined in all cases. When the stereochemistry of the specific stereocenter in the enantiomer or diastereomer is not determined, the compound is drawn without showing any stereochemistry at that specific stereocenter even though the compound can be substantially enantiomerically or disatereomerically pure.

[0403] Compounds disclosed herein can be prepared from commercially available reagents using the synthetic methods and reaction schemes described herein, or using other reagents and conventional methods known to persons of ordinary skill in the art. For instance, representative syntheses of compounds of the present disclosure are described in the schemes below, and the particular examples that follow.

EXAMPLES

I. Abbreviations

[0404] Certain abbreviations and acronyms are used in describing the experimental details. Although most of these would be understood by one skilled in the art, Table 1 contains a list of many of these abbreviations and acronyms.

Table 1. List of Abbreviations and Acronyms

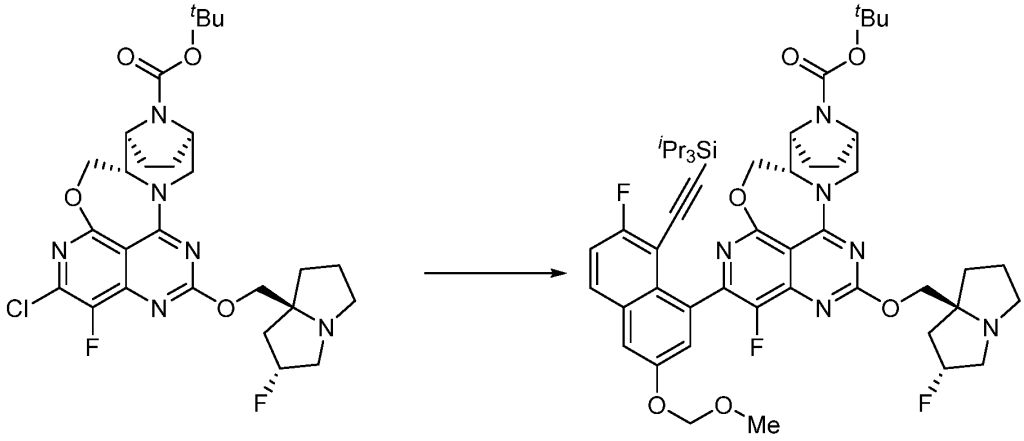
Abbreviation	Meaning
°C	degree(s) Celsius
µg or ug	microgram(s)
µL or uL	microliter(s)
µm or um	micron(s)
µmol or umol	micromole(s)
aq	aqueous
Boc	tert-butoxycarbonyl
br s	broad singlet

Cbz	benzyloxycarbonyl
d	doublet
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
ddt	doublet of doublet of triplets
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylamiopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dt	doublet of triplets
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
h	hour(s)
HATU	hexafluorophosphate azabenzotriazole tetramethyl uronium
HPLC	high-performance liquid chromatography
Hz	hertz
^{i}Pr	isopropyl
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
KOAc	potassium acetate
LAH	lithium aluminum hydride
LCMS	liquid chromatography mass spectrometry
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
M	molarity
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mm	millimeter(s)
mmol	millimole(s)
MOMO or OMOM	methoxymethoxy
NaOMe	sodium methoxide
n-BuLi	*n*-butyllithium

NMR	nuclear magnetic resonance
OSEM	2-(trimethylsilyl)ethoxymethoxy
OTf	trifluoromethanesulfonate
Piv	pivaloyl
qd	quartet of doublets
rt	room temperature
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-Butyldimethylsilyl chloride
^{t}Bu	tertbutyl
td	triplet of doublets
TES	triethylsilane
TF_2O or Tf_2O	trifluoromethanesulfonic anhydride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
tt	triplet of triplets
v/v	volume/volume
wt	weight
δ	parts per million referenced to residual non-deuterated solvent peak

II. Intermediates

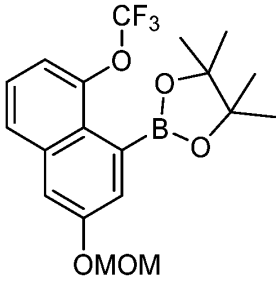
Intermediate 2-1: *tert*-butyl (5a*S*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



17-9 **2-1**

[0405] A vigorously stirred mixture of **Intermediate 17-9** (50.0 mg, 86.4 μmol), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (prepared according to WO 2021/041671) (66.4 mg, 130 μmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (9.5 mg, 13 μmol), cesium carbonate (141 mg, 432 μmol), water (0.4 mL), and 1,4-dioxane (1.0 mL) was heated to 115°C. After 90 min, the resulting mixture was cooled to room temperature, and diethyl ether (40 mL) and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (30 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified on C18 reverse phase silica gel (20% to 87% acetonitrile in water) to give **Intermediate 2-1**. LCMS: 929.5.

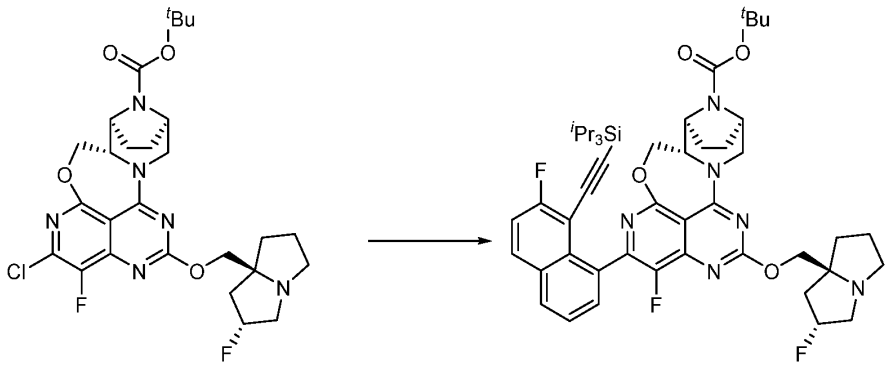
Intermediate 3-1: 2-(3-(methoxymethoxy)-8-(trifluoromethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



3-1

[0406] Intermediate 3-1 was synthesized in a manner similar to **Intermediate 5-6** using 1-bromo-3-(trifluoromethoxy)benzene instead of 4-bromo-2-chloro-1-fluorobenzene. LCMS: 367.4 $[M-CH3O]^+$.

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

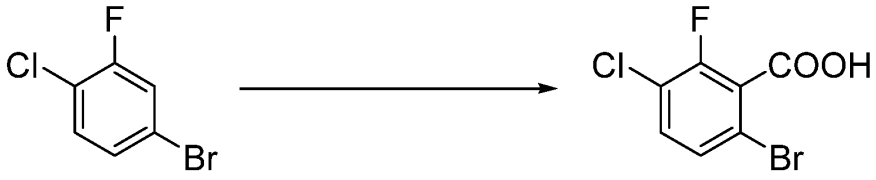


17-9 **4-1**

[0407] A vigorously stirred mixture of **Intermediate 17-9** (50.0 mg, 86.4 μmol), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (prepared according to WO 2021/041671) (58.6 mg, 130 μmol), [(di(1-adamantyl)-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate (12.6 mg, 17.3 μmol), aqueous potassium phosphate solution (1.5 M, 288 μL, 432 μmol), and tetrahydrofuran (0.5 mL) was heated to 70°C. After 80 min, the resulting mixture was cooled to room temperature,

and diethyl ether (40 mL) and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (30 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified on C18 reverse phase silica gel (20% to 87% acetonitrile in water) to give **Intermediate 4-1**. LCMS: 869.4.

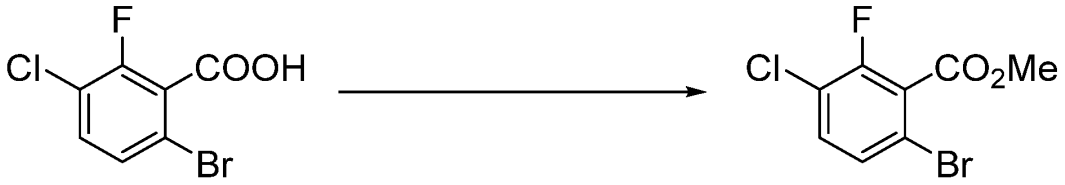
Intermediate 5-1: 6-bromo-3-chloro-2-fluorobenzoic acid



5-1

[0408] To a stirred solution of 4-bromo-2-chloro-1-fluorobenzene (10 g, 47.746 mmol) in THF (140 mL), was added LDA (2M in THF, 28.65 mL, 57.296 mmol) at -78°C and stirred at same temp for 45 min. Reaction mixture was purged with CO_2 gas for 30 min at -78°C. The resulting mixture was warmed to room temperature over 1 hour. After completion of the reaction, the reaction mixture was quenched with 2M aq. HCl (30 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with brine (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to yield **Intermediate 5-1**. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 14.44 (br s, 1H), 7.66 - 7.57 (m, 2H).

Intermediate 5-2: methyl 6-bromo-3-chloro-2-fluorobenzoate



5-1 **5-2**

[0409] To a stirred solution of **Intermediate 5-1** (8 g, 31.564 mmol) in toluene (200 mL) and MeOH (58.4 mL), was added TMS diazomethane (23.67 mL, 47.346 mmol) at room temperature. The resulting mixture was stirred at ambient temperature for 2h. After completion of the reaction, reaction mass was quenched with acetic acid (1.44 mL, 25.251 mmol) and extracted with ethyl acetate (2 x 90 mL). The combined organic layer was washed with brine (70 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to get the crude. The crude material was subjected to silica gel (100-200 mesh) column chromatography eluting with 8%-

10% ethyl acetate in petroleum ether to yield **Intermediate 5-2**. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.73 (t, *J* = 8.8 Hz, 1H), 7.64 (dd, *J* = 1.2, 8.8 Hz, 1H), 3.94 (s, 3H).

Intermediate 5-3: methyl 3-chloro-2-fluoro-6-(2-(methoxymethoxy)allyl)benzoate



5-2 5-3

[0410] To a solution of **Intermediate 5-2** (5 g, 18.693 mmol) in THF (10 mL) under stirring, was added *i*-PrMgCl•LiCl (1.3 M in THF, 14.8 mL, 19.254 mmol) at -40°C and stirred for 45 min. CuCN•2LiCl (0.93 mL, 0.935 mmol) and 2-MOMOallyl chloride (2.5 mL, 20.562 mmol) was added at -40°C. The resulting mixture was warmed to 0°C and stirred for 1.5h. After completion of the reaction, reaction mass was quenched with careful addition of saturated aqueous ammonium chloride (50 mL) followed by addition of aqueous ammonia solution (50 mL), diethyl ether (75 mL), ethyl acetate (25 mL) sequentially. The resulting mixture was filtered through celite. The organic layer was washed with brine (25 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to get the crude material which was purified by silica gel (100-200 mesh) column chromatography eluting with 12% ethyl acetate in petroleum ether to yield **Intermediate 5-3**. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.70 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 4.85 (s, 2H), 4.16 (d, *J* = 1.6 Hz, 1H), 4.02 (s, 1H), 3.87 (s, 3H), 3.52 (s, 2H), 3.20 (s, 3H).

Intermediate 5-4: 7-chloro-8-fluoro-3-(methoxymethoxy)naphthalen-1-ol



5-3 5-4

[0411] A solution of methyl **Intermediate 5-3** (2.5 g, 8.659 mmol) in 2-Me-THF (25 mL) was heated under stirring at 70°C and lithium bis(trimethylsilyl)amide (1.0 M in THF, 21.6 mL, 21.648 mmol) was added at same temperature. The resulting mixture was stirred at 70°C for 45 min. After completion of the reaction, reaction mass was quenched with citric acid (4.12 g, 21.647 mmol), diethyl ether (50 mL) and water (25 mL) were added sequentially. The organic layer was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure to get the

crude. The crude material obtained was purified by silica gel (100-200 mesh) column chromatography eluting with 15% ethyl acetate in petroleum ether to yield **Intermediate 5-4**. LCMS: 257.2.

Intermediate 5-5: 7-chloro-8-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate



5-4 **5-5**

[0412] To a solution of **Intermediate 5-4** (1.6 g, 6.233 mmol) in 2-Me-THF (44.8 mL), was added sodium bi(trimethylsilyl)amide (2 M in THF, 3.42 mL, 6.857 mmol) at 0°C and stirred for 10 min. N-phenyltrifluoromethanesulfonimide (2.45 g, 6.857 mmol) was added at 0°C and stirred at same temperature for 1h. After completion of the reaction, reaction mass was quenched with saturated aqueous sodium bicarbonate (20 mL) and added diethyl ether (75 mL) and ethyl acetate (25 mL) sequentially. The combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give **Intermediate 5-5**. LCMS: 387.1 $[M-H]^-$.

Intermediate 5-6: 2-(7-chloro-8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

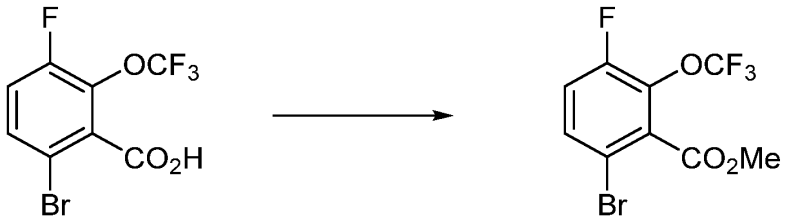


5-5 **5-6**

[0413] To a stirred solution of **Intermediate 5-5** (2.42 g, 6.233 mmol) in 1,4-dioxane (25 mL), were added 4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.37 g, 9.349 mmol) and potassium acetate (3.05 g, 31.165 mmol). Reaction mixture was degassed with argon gas for 10 min. [1,1′-Bis(diphenylphosphino) ferrocene]dichloropalladium(II) (456 mg, 0.623 mmol) was added and resulting mixture was heated to 100°C under stirring for 1.5h. After completion of the reaction, reaction mass was filtered through a pad of celite and concentrated under reduced pressure to get the crude material. The crude material was purified by silica gel (100-200 mesh)

column chromatography eluting with 10~12% ethyl acetate in petroleum ether to yield **Intermediate 5-6**. LCMS: 367.3.

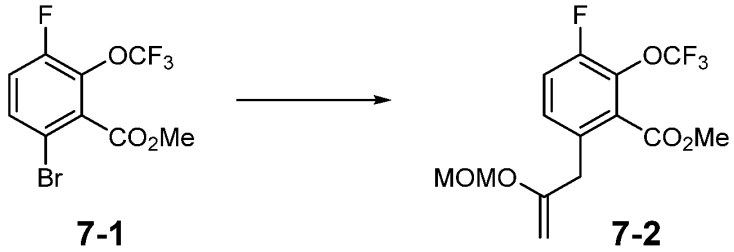
Intermediate 7-1: methyl 6-bromo-3-fluoro-2-(trifluoromethoxy)benzoate



7-1

[0414] (Trimethylsilyl)diazomethane solution (2.0 M in diethyl ether, 6.19 mL, 12.4 mmol) was added over 10 min via syringe pump to a vigorously stirred mixture of 6-bromo-3-fluoro-2-(trifluoromethoxy)benzoic acid (2.50 g, 8.25 mmol), methanol (30 mL), and toluene (70 mL) at room temperature. After 30 min, acetic acid (378 μL, 6.60 mmol) was added slowly via syringe, and the resulting mixture was concentrated under reduced pressure to give **Intermediate 7-1**. ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.85 (dd, J = 9.0, 4.3 Hz, 1H), 7.58 (dd, J = 10.0, 9.0 Hz, 1H), 4.00 (s, 3H).

Intermediate 7-2: methyl 3-fluoro-6-(2-(methoxymethoxy)allyl)-2-(trifluoromethoxy) benzoate

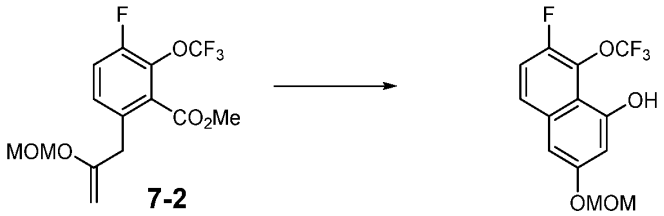


7-1 **7-2**

[0415] Isopropylmagnesium chloride lithium chloride complex solution (1.3 M in tetrahydrofuran, 6.50 mL, 8.45 mmol) was added over 5 min via syringe pump to a stirred solution of **Intermediate 7-1** (2.55 g, 8.05 mmol) in tetrahydrofuran (4.0 mL) at −40°C. After 35 min, copper(I) cyanide di(lithium chloride) complex solution (1.0 M in tetrahydrofuran, 403 μL, 400 μmol) was added via syringe. After 2 min, 3-chloro-2-(methoxymethoxy)prop-1-ene (1.15 mL, 8.86 mmol) was added over 1 min via syringe, and the resulting mixture was warmed to 10°C over 120 min. Saturated aqueous ammonium chloride solution (5 mL), aqueous ammonia solution

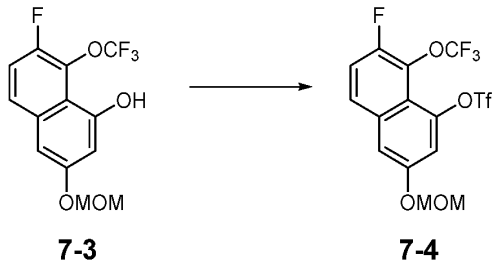
(28% wt, 15 mL), diethyl ether (100 mL), and ethyl acetate (25 mL) were added sequentially. The organic layer was washed with water (2 × 75 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 7% ethyl acetate in hexanes) to give **Intermediate 7-2**. LCMS: 339.1.

Intermediate 7-3: 7-fluoro-3-(methoxymethoxy)-8-(trifluoromethoxy)naphthalen-1-ol



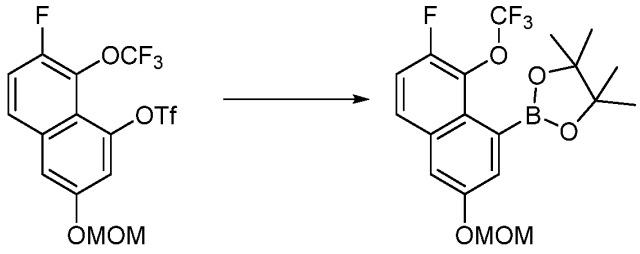
[0416] A solution of **Intermediate 7-2** (2.37 g, 7.01 mmol) in 2-methyltetrahydrofuran (30 mL) was added over 60 min via syringe pump to a vigorously stirred mixture of lithium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 17.5 mL, 18 mmol) and 2-methyltetrahydrofuran (110 mL) at 70°C. After 130 min, the resulting mixture was cooled to room temperature, acetic acid (1.20 mL, 21.0 mmol) was added via syringe, and the resulting mixture was concentrated under reduced pressure. Methanol (50 mL) and acetic acid (4.01 mL, 70.1 mmol) were added sequentially. After 20 min, the resulting mixture was concentrated under reduced pressure, and diethyl ether (200 mL), ethyl acetate (25 mL), and saturated aqueous sodium bicarbonate solution (50 mL) were added sequentially. The organic layer was washed with water (150 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 15% ethyl acetate in hexanes) to give **Intermediate 7-3**. LCMS: 307.1.

Intermediate 7-4: 7-fluoro-3-(methoxymethoxy)-8-(trifluoromethoxy)naphthalen-1-yl trifluoromethanesulfonate



[0417] Sodium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 6.33 mL, 6.33 mmol) was added over 1 min via syringe to a stirred solution of **Intermediate 7-3** (1.76 g, 5.75 mmol) in 2-methyltetrahydrofuran (15 mL) at 0°C. After 5 min, *N*-phenyl-bis(trifluoromethanesulfonimide) (2.26 g, 6.33 mmol) was added. After 40 min, diethyl ether (200 mL), ethyl acetate (25 mL), and saturated aqueous sodium bicarbonate solution (25 mL) were added sequentially. The organic layer was washed sequentially with water (200 mL) and a mixture of water and saturated aqueous sodium bicarbonate solution (4:1 v:v, 200 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure give **Intermediate 7-4**. LCMS: 439.0.

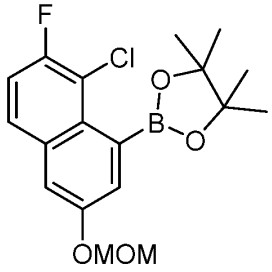
Intermediate 7-5: 2-(7-fluoro-3-(methoxymethoxy)-8-(trifluoromethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



7-4 **7-5**

[0418] A vigorously stirred mixture of **Intermediate 7-4** (2.52 g, 5.75 mmol), bis(pinacolato)diboron (2.19 g, 8.63 mmol), potassium acetate (2.82 g, 28.8 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (421 mg, 575 μmol), and 1,4-dioxane (12 mL) was heated to 100°C. After 90 min, the resulting mixture was cooled to room temperature and was filtered through celite. The filter cake was extracted with ethyl acetate (60 mL), and the combined filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 10% ethyl acetate in hexanes) to give **Intermediate 7-5**. LCMS: 417.1.

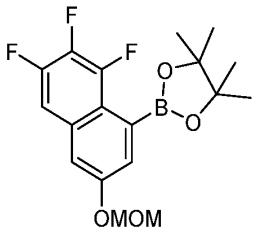
Intermediate 8-1: 2-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



8-1

[0419] Intermediate 8-1 was synthesized in a manner similar to **Intermediate 5-6** using 6-bromo-2-chloro-3-fluorobenzoic acid instead of **Intermediate 5-1**. LCMS: 367.3.

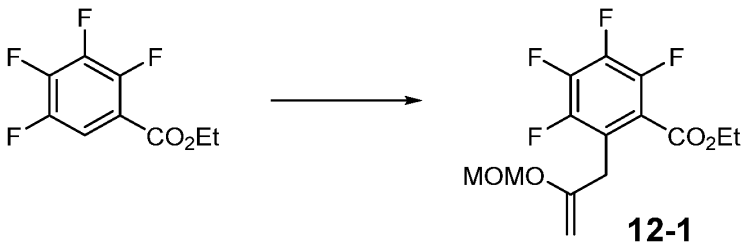
Intermediate 11-1: 4,4,5,5-tetramethyl-2-(6,7,8-trifluoro-3-(methoxymethoxy) naphthalen-1-yl)-1,3,2-dioxaborolane



11-1

[0420] Intermediate 11-1 was synthesized in a manner similar to **Intermediate 7-5** using 6-bromo-2,3,4-trifluoro-benzoic acid instead of 6-bromo-3-fluoro-2-(trifluoromethoxy)benzoic acid. LCMS: 369.1.

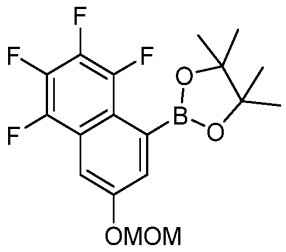
Intermediate 12-1: ethyl 2,3,4,5-tetrafluoro-6-(2-(methoxymethoxy)allyl)benzoate



12-1

[0421] 2,2,6,6-Tetramethylpiperidinylmagnesium chloride lithium chloride complex solution (1.0 M in tetrahydrofuran/toluene, 6.88 mL, 6.9 mmol) was added over 10 min via syringe pump to a vigorously stirred solution of ethyl 2,3,4,5-tetrafluorobenzoate (1.00 mL, 6.26 mmol) in tetrahydrofuran (3.5 mL) at –40°C, and the resulting mixture was warmed to –20°C. After 103 min, copper(I) cyanide di(lithium chloride) complex solution (1.0 M in tetrahydrofuran, 313 µL, 310 µmol) was added via syringe. After 1 min, 3-chloro-2-(methoxymethoxy)prop-1-ene (895 µL, 6.88 mmol) was added over 1 min via syringe, and the resulting mixture was warmed to 10°C over 95 min. The resulting mixture was warmed to room temperature. After 60 min, saturated aqueous ammonium chloride solution (10 mL), aqueous ammonia solution (28% wt, 10 mL), diethyl ether (200 mL), and ethyl acetate (25 mL) were added sequentially. The organic layer was washed with water (2 × 150 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 5% ethyl acetate in hexanes) to give **Intermediate 12-1**. LCMS: 323.1.

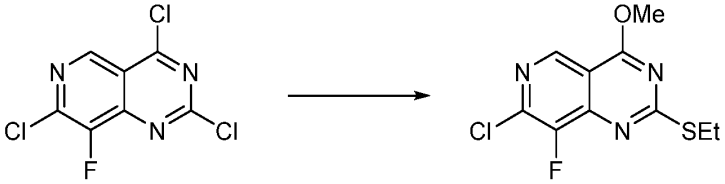
Intermediate 12-2: 4,4,5,5-tetramethyl-2-(5,6,7,8-tetrafluoro-3-(methoxymethoxy) naphthalen-1-yl)-1,3,2-dioxaborolane



12-2

[0422] Intermediate 12-2 was synthesized in a manner similar to **Intermediate 7-5** using **Intermediate 12-1** instead of **Intermediate 7-2**. ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.67 – 7.61 (m, 1H), 7.49 – 7.44 (m, 1H), 5.43 (s, 2H), 3.51 (s, 3H), 1.44 (s, 12H).

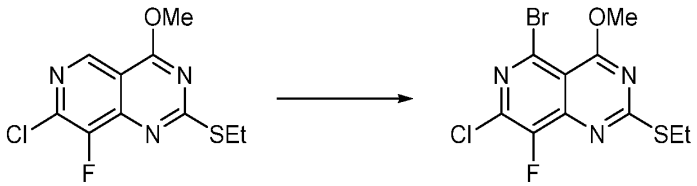
Intermediate 13-1: 7-chloro-2-(ethylthio)-8-fluoro-4-methoxypyrido[4,3-*d*]pyrimidine



13-1

[0423] Sodium methoxide solution (25% wt in methanol, 4.54 mL, 20 mmol) was added over 15 min via syringe pump to a vigorously stirred solution of 2,4,7-trichloro-8-fluoropyrido[4,3-*d*]pyrimidine (5.01 g, 19.8 mmol) in 2-methyltetrahydrofuran (70 mL) at −20°C. After 11 min, ethanethiol (4.41 mL, 59.5 mmol) was added over 1 min via syringe. After 1 min, *N*,*N*-diisopropylethylamine (11.1 mL, 63.5 mmol) was added over 2 min via syringe. After 11 min, the resulting mixture was warmed to room temperature. After 20 min, the resulting mixture was heated to 70°C. After 22 h, the resulting mixture was cooled to room temperature, and citric acid (3.0 g), diethyl ether (200 mL), and ethyl acetate (25 mL) were added sequentially. The organic layer was washed with water (200 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 11% ethyl acetate in hexanes) to give **Intermediate 13-1**. LCMS: 274.0.

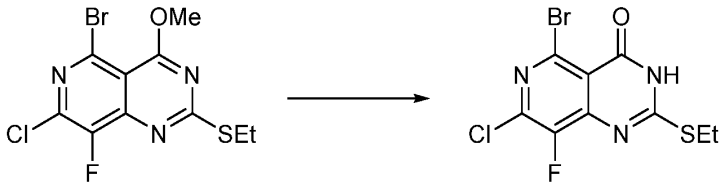
Intermediate 13-2: 5-bromo-7-chloro-2-(ethylthio)-8-fluoro-4-methoxypyrido[4,3-*d*]pyrimidine



13-1 **13-2**

[0424] 2,2,6,6-Tetramethylpiperidinylmagnesium chloride lithium chloride complex solution (1.0 M in tetrahydrofuran, 14.4 mL, 14 mmol) was added over 20 min via syringe pump to a vigorously stirred solution of **Intermediate 13-1** (1.00 g, 3.65 mmol) in tetrahydrofuran (3.0 mL) at 0°C. After 60 min, a solution of 1,2-dibromo-1,1,2,2-tetrachloroethane (4.76 g, 14.6 mmol) in tetrahydrofuran (8.0 mL) was added via syringe. After 120 min, citric acid (5.0 g), diethyl ether (200 mL), and ethyl acetate (25 mL) were added sequentially. The organic layer was washed with water (2 × 150 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 5% ethyl acetate in hexanes) to give **Intermediate 13-2**. LCMS: 351.9.

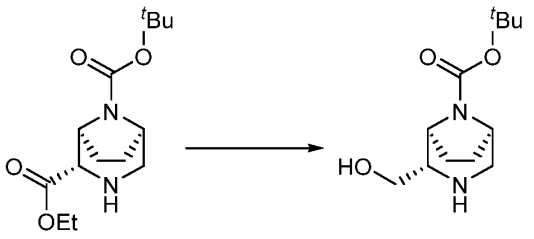
Intermediate 13-3: 5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-*d*]pyrimidin-4(3*H*)-one



13-2 **13-3**

[0425] Sodium iodide (1.90 g, 12.7 mmol) was added to a vigorously stirred solution of **Intermediate 13-2** (895 mg, 2.54 mmol) in acetic acid (12.0 mL) at room temperature, and the resulting mixture was heated to 80°C. After 2.5 h, the resulting mixture was cooled to room temperature, and ethyl acetate (100 mL) and aqueous sodium thiosulfate solution (1.0 M, 2.0 mL) were added sequentially. The organic layer was washed with water (100 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure to give **Intermediate 13-3**. LCMS: 337.9.

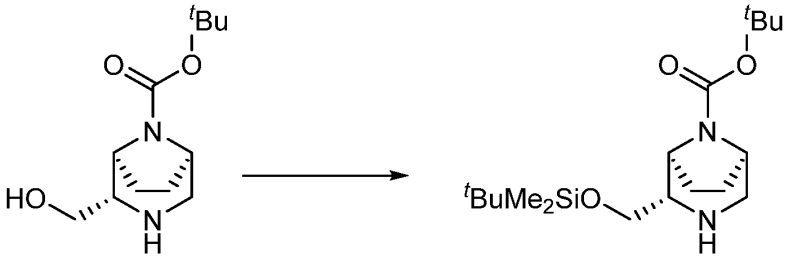
Intermediate 13-4: *tert*-butyl (1*S*,2*S*,5*R*)-2-(hydroxymethyl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate



13-4

[0426] Lithium aluminum hydride (818 mg, 21.6 mmol) was added to a vigorously stirred solution of 8-(*tert*-butyl) 2-ethyl (1*S*,2*S*,5*R*)-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate (3.07 g, 10.8 mmol) in tetrahydrofuran (60 mL) at 0°C. After 60 min, water (820 µL), aqueous sodium hydroxide solution (2.0 M, 1.53 mL), water (1.74 mL), and dichloromethane (100 mL) were added sequentially. The resulting suspension was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure to give **Intermediate 13-4**. LCMS: 243.2.

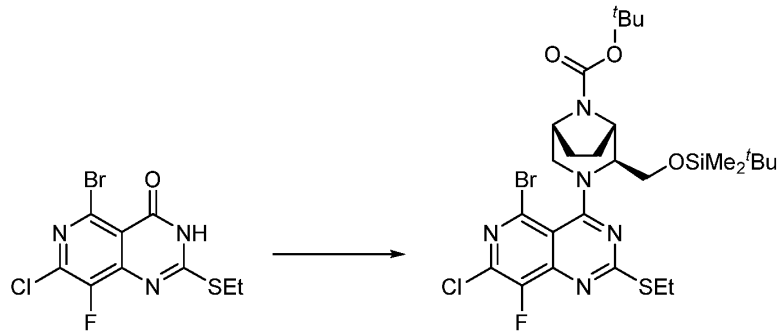
Intermediate 13-5: *tert*-butyl (1*S*,2*S*,5*R*)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



13-4 **13-5**

[0427] *tert*-Butyldimethylsilyl chloride (2.44 g, 16.2 mmol) was added to a stirred mixture of **Intermediate 13-4** (2.61 g, 10.8 mmol), 4-(dimethylamino)pyridine (132 mg, 1.08 mmol), triethylamine (3.00 mL, 21.6 mmol), and dichloromethane (70 mL) at room temperature. After 15 h, diethyl ether (200 mL) and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (150 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 70% ethyl acetate in hexanes) to give **Intermediate 13-5**. LCMS: 357.2.

Intermediate 13-6: *tert*-butyl (1*S*,2*S*,5*R*)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

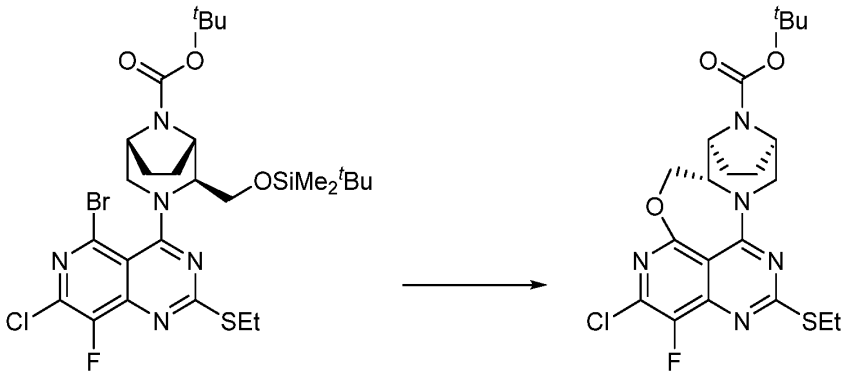


13-3 **13-6**

[0428] *N*,*N*-Diisopropylethylamine (884 μL, 5.08 mmol) was added via syringe to a mixture of **Intermediate 13-3** (839 mg, 2.48 mmol) and phosphorous(V) oxychloride (10 mL) at room temperature, and the resulting mixture was heated to 80°C. After 10 min, the resulting mixture

was cooled to room temperature and was concentrated under reduced pressure. Dichloromethane (20 mL) was added, the resulting mixture was cooled to 0°C, and *N*,*N*-diisopropylethylamine (1.33 mL, 7.61 mmol) and a solution of **Intermediate 13-5** (905 mg, 2.54 mmol) in dichloromethane (4.0 mL) were added sequentially. After 50 min, citric acid (2.0 g), diethyl ether (100 mL), and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (2 × 75 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 13% ethyl acetate in hexanes) to give **Intermediate 13-6**. LCMS: 676.1.

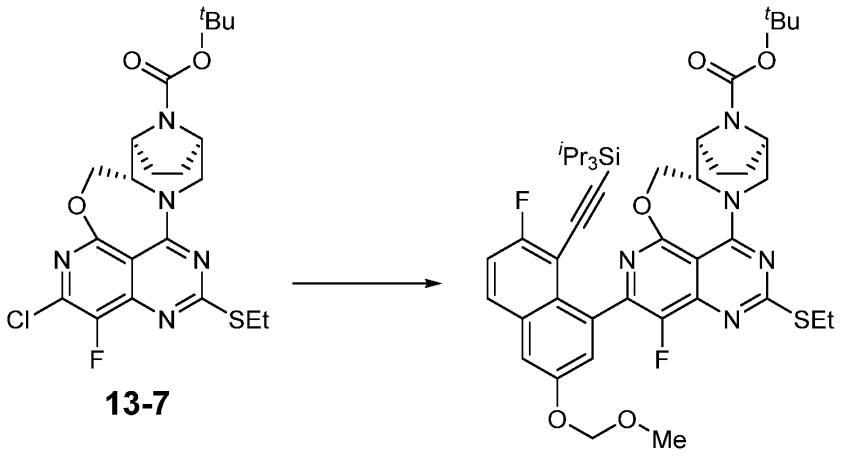
Intermediate 13-7: *tert*-butyl (5a*S*,6*S*,9*R*)-2-chloro-12-(ethylthio)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



13-6 **13-7**

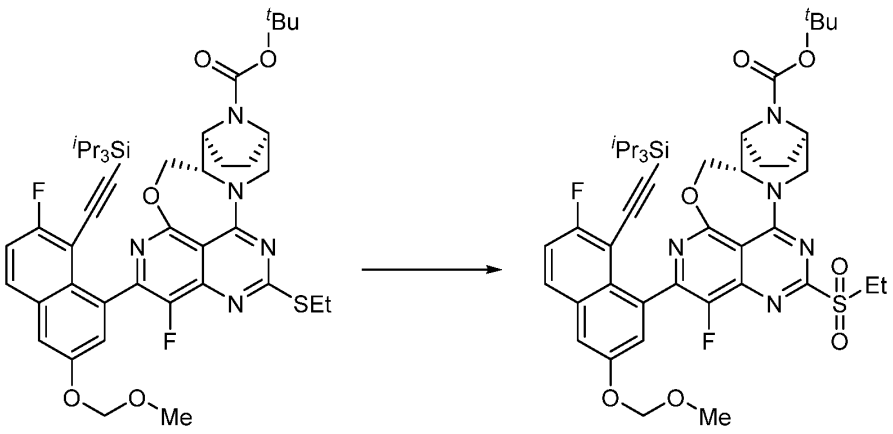
[0429] Tetrabutylammonium fluoride solution (1.0 M in tetrahydrofuran, 8.18 mL, 8.2 mmol) was added over 2 min via syringe to a stirred solution of **Intermediate 13-6** (1.39 g, 2.05 mmol) in tetrahydrofuran (110 mL) at 0°C, and the resulting mixture was warmed to room temperature. After 23 h, saturated aqueous ammonium chloride solution (20 mL) and diethyl ether (400 mL) were added sequentially. The organic layer was washed with water (2 × 400 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 35% ethyl acetate in hexanes) to give **Intermediate 13-7**. LCMS: 482.1.

Intermediate 13-8: *tert*-butyl (5a*S*,6*S*,9*R*)-12-(ethylthio)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



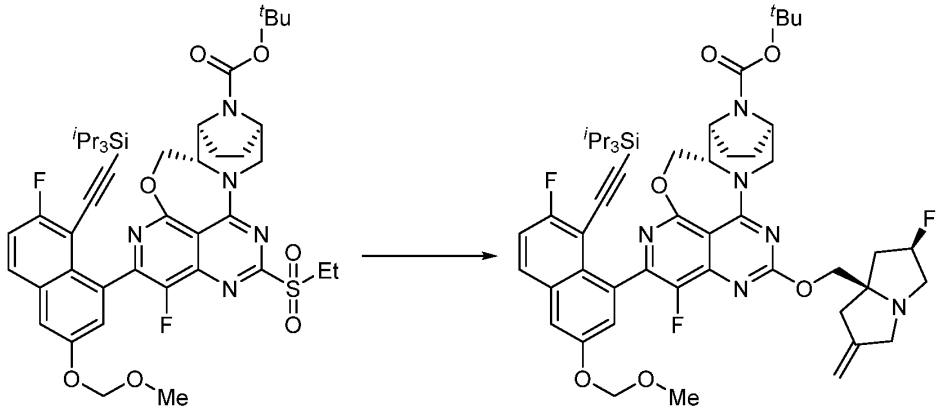
[0430] A vigorously stirred mixture of **Intermediate 13-7** (722 mg, 1.50 mmol), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (prepared according to, for instance, WO 2021/041671) (768 mg, 1.50 mmol), aqueous potassium phosphate solution (1.5 M, 4.99 mL, 7.5 mmol), [(di(1-adamantyl)-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate (218 mg, 300 μmol), and tetrahydrofuran (8.0 mL) was heated to 70°C. After 105 min, the resulting mixture was cooled to room temperature and diethyl ether (100 mL) and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (60 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 45% ethyl acetate in hexanes) to give **Intermediate 13-8**. LCMS: 832.4.

Intermediate 13-9: *tert*-butyl (5a*S*,6*S*,9*R*)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



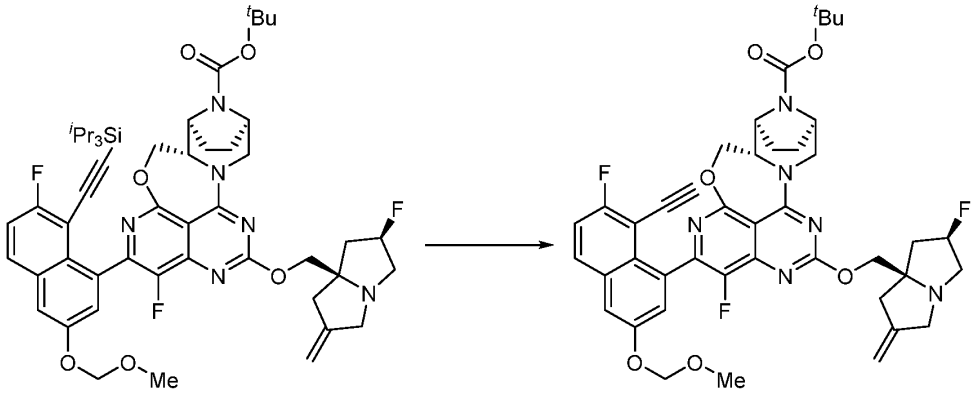
[0431] 3-Chloroperoxybenzoic acid (77% wt, 524 mg, 2.3 mmol) was added in two equal portions over 5 min to a vigorously stirred solution of **Intermediate 13-8** (884 mg, 1.06 mmol) in dichloromethane (8.0 mL) at 0°C. After 25 min, the resulting mixture was warmed to room temperature. After 60 min, diethyl ether (100 mL), ethyl acetate (20 mL), and aqueous sodium thiosulfate solution (1.0 M, 8.0 mL) were added sequentially. The organic layer was washed sequentially with water (60 mL), a mixture of water and saturated aqueous sodium bicarbonate solution (7:1 v:v, 80 mL), and water (80 mL); was dried over anhydrous magnesium sulfate; was filtered; and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 75% ethyl acetate in hexanes) to give **Intermediate 13-9**. LCMS: 864.4.

Intermediate 13-10: *tert*-butyl (5a*S*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2*R*,7a*R*)-2-fluoro-6-methylenetetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



[0432] Lithium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 46.3 μL, 46 μmol) was added over 1 min via syringe to a stirred mixture of **Intermediate 13-9** (20.0 mg, 23.1 μmol), **Intermediate 13-14** (7.9 mg, 46 μmol), and tetrahydrofuran (0.5 mL) at room temperature. After 10 min, diethyl ether (40 mL), ethyl acetate (20 mL), and saturated aqueous sodium bicarbonate solution (5 mL) were added sequentially. The organic layer was washed with water (30 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure to give **Intermediate 13-10**. LCMS: 941.4.

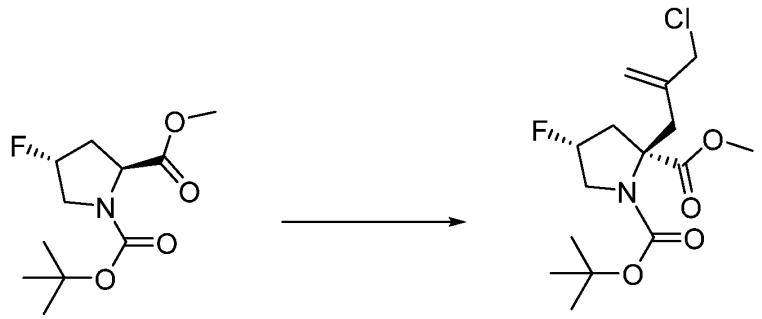
Intermediate 13-11: *tert*-butyl (5a*S*,6*S*,9*R*)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*R*)-2-fluoro-6-methylenetetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



13-10 13-11

[0433] Cesium fluoride (84.4 mg, 556 μmol) was added to a vigorously stirred solution of **Intermediate 13-10** (21.8 mg, 23.1 μmol) in *N*,*N*-dimethylformamide (0.5 mL) at room temperature. After 30 min, diethyl ether (40 mL), ethyl acetate (20 mL), and saturated aqueous sodium bicarbonate solution (10 mL) were added sequentially. The organic layer was washed with water (2 × 40 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure to give **Intermediate 13-11**. LCMS: 785.3.

Intermediate 13-12: 1-(tert-butyl) 2-methyl (2R,4R)-2-(2-(chloromethyl)allyl)-4-fluoropyrrolidine-1,2-dicarboxylate

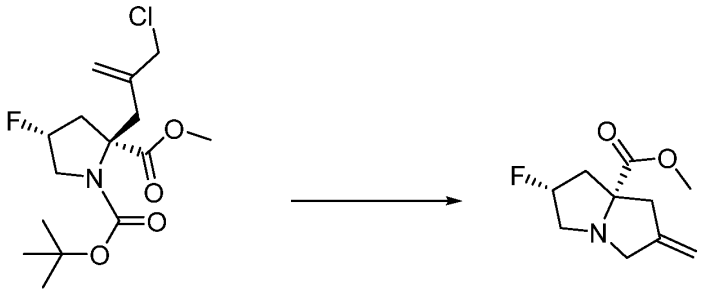


13-12

[0434] O1-tert-butyl O2-methyl (2S,4R)-4-fluoropyrrolidine-1,2-dicarboxylate (25 g, 100 mmol) and 3-chloro-2-chloromethyl-1-propene (17 mL, 160 mmol) were dissolved in tetrahydrofuran

(100 mL) in an oven dried flask under nitrogen atmosphere. The solution was cooled to -78°C and lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 120 mL, 120 mmol) was added dropwise via syringe over 20 minutes. The resulting solution was allowed to warm slowly to room temperature and was stirred for an additional 72 hours. The pH of the solution was adjusted to 2 with 2N hydrochloric acid. Brine (100 mL) was added and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using a gradient of ethyl acetate in hexanes (0% to 50%) to afford **Intermediate 13-12**. LCMS $[M+Na]^+$: 358.2.

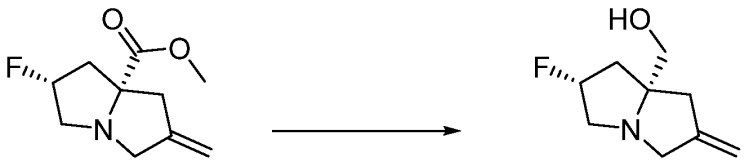
Intermediate 13-13: methyl (2R,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizine-7a(5H)-carboxylate



13-12 **13-13**

[0435] To a flask charged with **Intermediate 13-12** (22 g, 66 mmol) was added hydrogen chloride (4 M in 1,4-dioxane, 90 mL, 361 mmol) and the resulting solution was stirred at room temperature for 2 h. The solution was concentrated *in vacuo* and taken up into N,N-dimethylformamide (330 mL). Potassium iodide (1.1 g, 6.6 mmol) and potassium carbonate (27 g, 200 mmol) were added and the resulting mixture was stirred for 1h at room temperature. Brine (300 mL) was added and the pH was adjusted to 10 with saturated aqueous sodium carbonate. The mixture was extracted with dichloromethane (3 x 300 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using a gradient of methanol in dichloromethane (0 to 30%) to afford **Intermediate 13-13**. LCMS: 200.2.

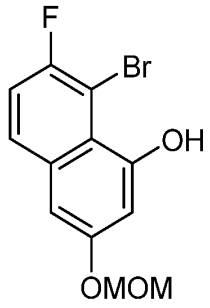
Intermediate 13-14: ((2R,7aR)-2-fluoro-6-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



13-13 **13-14**

[0436] A solution of **Intermediate 13-13** (11 g, 54 mmol) in tetrahydrofuran (40 mL) was cooled to 0°C under nitrogen atmosphere and lithium aluminum hydride (1 M in tetrahydrofuran, 108 mL, 108 mmol) was added dropwise via syringe. The resulting solution was allowed to warm to room temperature and stirred overnight. The solution was diluted with diethyl ether (40 mL) and cooled to 0°C. Water (4.1 mL) was added dropwise followed by sodium hydroxide (15% aqueous solution, 4.1 mL) and additional water (12.3 mL). The mixture was stirred vigorously at room temperature for 15 minutes. Magnesium sulfate was added and the mixture was stirred vigorously for an additional 15 minutes. The mixture was filtered, rinsing with diethyl ether, and concentrated *in vacuo* to give **Intermediate 13-14**. LCMS: 172.2.

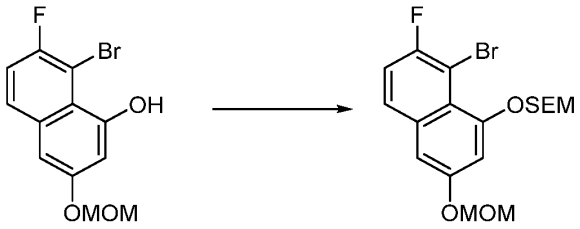
Intermediate 14-1: 8-bromo-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol



14-1

[0437] Intermediate 14-1 was synthesized in a manner similar to **Intermediate 5-6** using 2-bromo-3-fluoro-6-iodobenzoic acid instead of **Intermediate 5-1**. LCMS: 299.1 $[M-H]^-$.

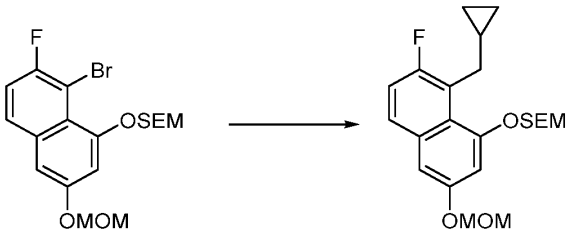
Intermediate 14-2: (2-(((8-bromo-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)oxy)methoxy)ethyl)trimethylsilane



14-1 **14-2**

[0438] (2-(Chloromethoxy)ethyl)trimethylsilane (586 μL, 3.31 mmol) was added over 3 min via syringe to a vigorously stirred mixture of **Intermediate 14-1** (949 mg, 3.15 mmol), *N*,*N*-diisopropylethylamine (1.10 mL, 6.30 mmol), and dichloromethane (3.5 mL) at 0°C. After 60 min, diethyl ether (100 ml) and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (50 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 7% ethyl acetate in hexanes) to give **Intermediate 14-2**. LCMS: 431.1.

Intermediate 14-3: (2-(((8-(cyclopropylmethyl)-7-fluoro-3-(methoxymethoxy) naphthalen-1-yl)oxy)methoxy)ethyl)trimethylsilane

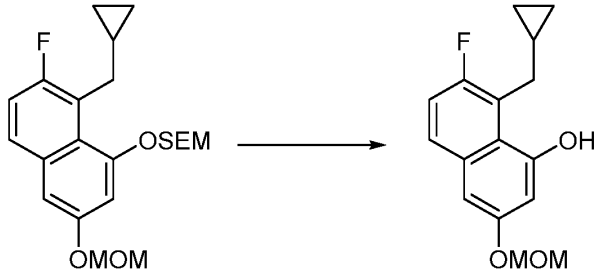


14-2 **14-3**

[0439] Isopropylmagnesium chloride lithium chloride complex solution (1.3 M in tetrahydrofuran, 297 μL, 390 μmol) was added over 1 min via syringe to a stirred solution of **Intermediate 14-2** (111 mg, 257 μmol) in tetrahydrofuran (0.40 mL) at –40°C. After 50 min, copper(I) cyanide di(lithium chloride) complex solution (1.0 M in tetrahydrofuran, 12.9 μL, 13 μmol) was added via syringe. After 1 min, (iodomethyl)cyclopropane (111 μL, 772 μmol) was added over 1 min via syringe, and the resulting mixture was warmed to room temperature. After 180 min, saturated aqueous ammonium chloride solution (2 mL), aqueous ammonia solution (28% wt, 5 mL), diethyl ether (40 mL), and ethyl acetate (20 mL) were added sequentially. The organic

layer was washed with water (35 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 10% ethyl acetate in hexanes) to give **Intermediate 14-3**. ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.67 (dd, J = 9.0, 5.8 Hz, 1H), 7.27 (t, J = 9.3 Hz, 1H), 7.12 (d, J = 2.3 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 5.51 (s, 2H), 5.31 (s, 2H), 4.01 – 3.88 (m, 2H), 3.49 (s, 3H), 3.32 – 3.18 (m, 2H), 1.41 – 1.13 (m, 1H), 1.12 – 0.97 (m, 2H), 0.38 (dt, J = 8.1, 2.8 Hz, 2H), 0.30 (t, J = 4.8 Hz, 2H), 0.04 (s, 9H).

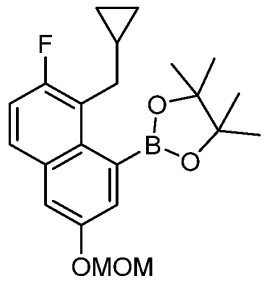
Intermediate 14-4: 8-(cyclopropylmethyl)-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol



14-3 **14-4**

[0440] Tetrabutylammonium fluoride solution (1.0 M in tetrahydrofuran, 2.58 mL, 2.6 mmol) was added via syringe to a stirred mixture of **Intermediate 14-3** (105 mg, 258 μmol) and *N*-(2-aminoethyl)acetamide (49.5 μL, 517 μmol) at room temperature, and the resulting mixture was heated to 60°C. After 60 min, the resulting mixture was cooled to room temperature, and diethyl ether (60 mL), citric acid (25 mg), and saturated aqueous ammonium chloride solution (10 mL) were added sequentially. The organic layer was washed with water (2 × 40 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 25% ethyl acetate in hexanes) to give **Intermediate 14-4**. LCMS: 275.1 $[M–H]^-$.

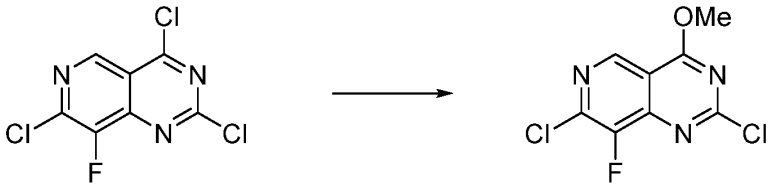
Intermediate 14-5: 2-(8-(cyclopropylmethyl)-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



14-5

[0441] Intermediate 14-5 was synthesized in a manner similar to **Intermediate 7-5** using **Intermediate 14-4** instead of **Intermediate 7-3**. LCMS: 387.2.

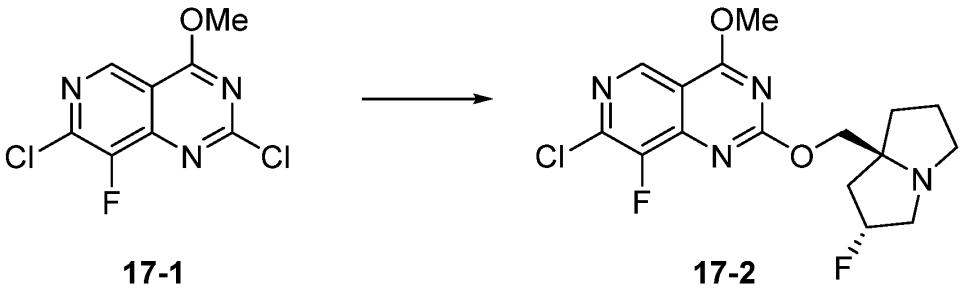
Intermediate 17-1: 2,7-dichloro-8-fluoro-4-methoxypyrido[4,3-d]pyrimidine



17-1

[0442] The solution of NaOMe (3.51 g, 25% in MeOH) was added dropwise to the solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (4.1 g, 16.2 mmol) in 2-methyltetrahydrofuran (30 mL) at -40°C. The reaction mixture was stirred at -40°C for 0.5 h. Saturated aqueous ammonium chloride solution (100 mL) was added. The mixture was extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated to give **Intermediate 17-1**. LCMS: 248.1.

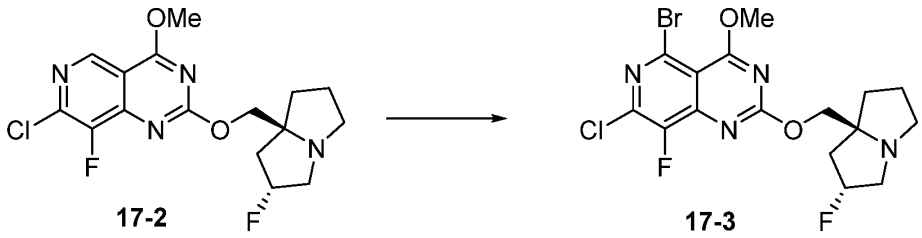
Intermediate 17-2: 2,7-dichloro-8-fluoro-4-methoxypyrido[4,3-d]pyrimidine



17-1 **17-2**

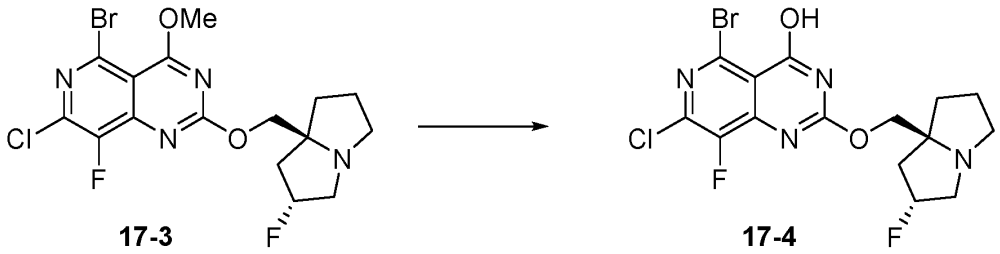
[0443] Sodium bis(trimethylsilyl)amide (1.0 M in THF, 8.47 mL) was added dropwise to the solution of [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (1.35 g, 8.47 mmol) in 2-methyltetrahydrofuran (10 mL) at 0 C. The resulting solution was stirred at 0°C for 10 min before it was transferred via a syringe to the solution of **Intermediate 17-1** (2.00 g, 8.06 mmol) in 2-methyltetrahydrofuran (20 mL) at 0°C. The mixture was stirred at 0°C for 20 min. Saturated aqueous solution of NH_4Cl (100 mL) was added. The mixture was extracted with dichloromethane (3 × 200 mL). The combined organic phase was washed with brine (200 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was crystallized in EtOAc to give the **Intermediate 17-2**. LCMS: 371.0

Intermediate 17-3: 5-bromo-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methoxypyrido[4,3-d]pyrimidine



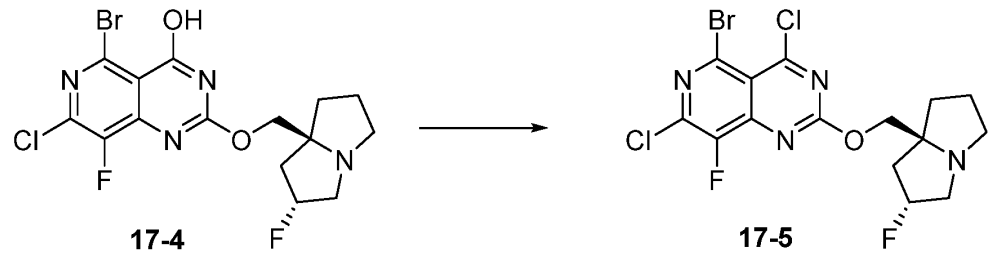
[0444] 2,2,6,6-Tetramethylpiperidinylmagnesium chloride lithium chloride complex solution (1.0 M in THF/toluene, 17.9 mL) was added dropwise to the solution of **Intermediate 17-2** (1.66 g, 4.48 mmol) in 2-methyltetrahydrofuran (15 mL) at 0°C. The resulting solution was stirred at 0°C for 0.5 h before a solution of 1,2-dibromotetrachloroethane (5.83 g, 17.9 mmol) was added dropwise at 0°C. The resulting solution was stirred at 0°C for 20 min. Saturated aqueous NH_4Cl solution (100 mL) was added to quench the reaction. The mixture was extracted with EtOAc (2 × 100 mL). The combined organic phase was washed with brine (200 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (0% to 10% methanol in dichloromethane) to give **Intermediate 17-3**. LCMS: 450.9.

Intermediate 17-4: 5-bromo-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-ol



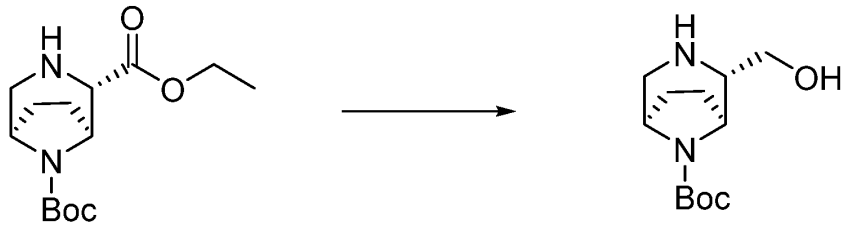
[0445] The suspension of **Intermediate 17-3** (1.58 g, 3.51 mmol) and sodium iodide (2.63 g, 17.6 mmol) in acetic acid (15 mL) was stirred at 70°C for 2 h (LCMS control) before the reaction mixture was cooled to rt. Saturated aqueous solution of sodium thiosulfate (50 mL) was added. The resulting mixture was extracted with dichloromethane (2 × 150 mL). The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (0% to 10% methanol in dichloromethane) to give **Intermediate 17-4**. LCMS: 434.9.

Intermediate 17-5: 5-bromo-4,7-dichloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine



[0446] DIPEA (0.72 mL, 4.13 mmol) was added dropwise to the solution of **Intermediate 17-4** (600 mg, 1.38 mmol) in phosphoryl chloride (8 mL) at rt and the reaction mixture was stirred at 70°C for 10 min before it was cooled to rt. The mixture was concentrated *in vacuo* to give the crude product of **Intermediate 17-5**, which was used for the next step without purification. LCMS: 454.9.

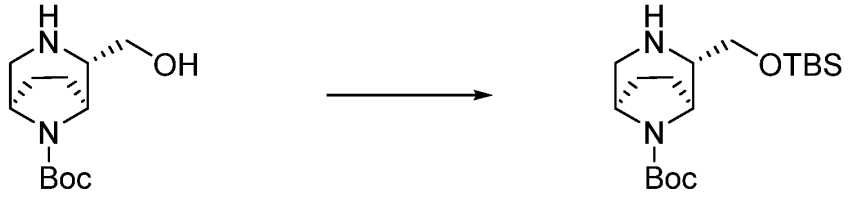
Intermediate 17-6: tert-butyl (1S,2S,5R)-2-(hydroxymethyl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate



17-6

[0447] Lithium aluminum hydride (1.0 M in THF, 2.64 mL) was added dropwise to the solution of 8-(tert-butyl) 2-ethyl (1S,2S,5R)-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate in dry THF at 0°C. The reaction mixture was stirred at 0°C for 2 h before it was quenched with 2 M NaOH solution (250 mL). The mixture was extracted with DCM (2 × 200 mL). The combined organic phase was washed with brine (200 mL), dried with Na_2SO_4, and concentrated *in vacuo* to give the **Intermediate 17-6**. LCMS: 243.2.

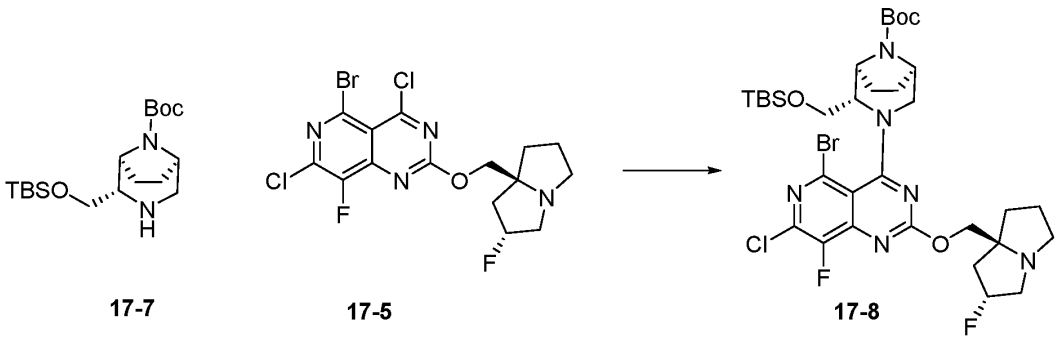
Intermediate 17-7: tert-butyl (1S,2S,5R)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



17-6 **17-7**

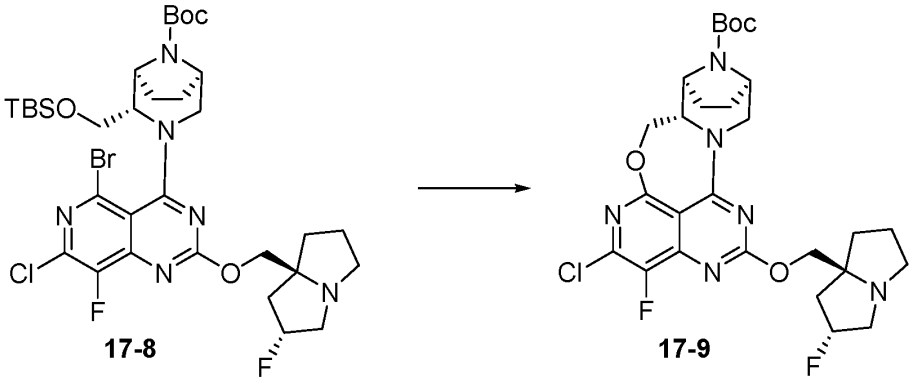
[0448] Triethylamine (0.185 mL, 1.28 mmol) was added dropwise to the mixture of **Intermediate 17-6** (155 mg, 0.640 mmol) and TBSCl (115 mg, 0.763 mmol) in DCM at rt. The reaction mixture was stirred at rt for 12 h before concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (0% to 10% methanol in dichloromethane) to give **Intermediate 17-7**. LCMS: 357.3.

Intermediate 17-8: tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



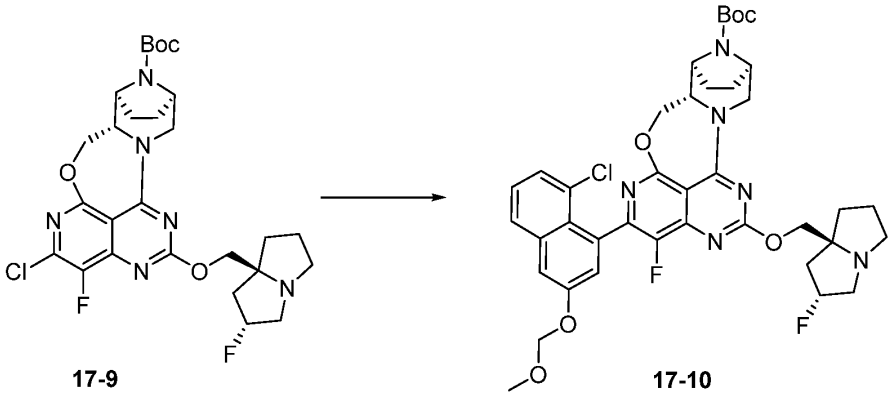
[0449] DIPEA (1.8 mL, 10.3 mmol) was added dropwise to the solution of **Intermediate 17-5** (600 mg, 1.32 mmol) and **Intermediate 17-7** (471 mg, 1.32 mmol) in dichloromethane (8 mL) at 0°C and the reaction mixture was stirred at 0°C for 10 min. The reaction mixture was purified by flash column chromatography on silica gel (0% to 10% methanol in dichloromethane) to give **Intermediate 17-8**. LCMS: 775.0.

Intermediate 17-9: tert-butyl (5aS,6S,9R)-2-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



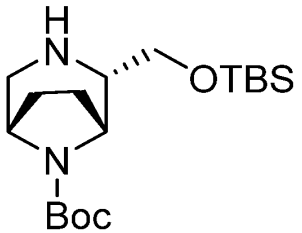
[0450] TBAF (1.0 M in THF, 3.62 mL) was added dropwise to the solution of **Intermediate 17-8** (700 mg, 0.904 mmol) in THF (10 mL) at 0°C. The reaction mixture was warmed to rt and stirred for 12 h. Saturated aqueous solution of NH_4Cl (50 mL) was added to the mixture. It was extracted with EtOAc (2 × 100 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% to 100% EtOAc in hexanes) to give **Intermediate 17-9**. LCMS: 579.0.

Intermediate 17-10: tert-butyl (5aS,6S,9R)-2-(8-chloro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0451] n-BuLi (2.70 M in hexanes, 0.051 mL) was added dropwise to the solution of 1-bromo-8-chloro-3-(methoxymethoxy)naphthalene (41.7 mg, 0.138 mmol) in 2-methyltetrahydrofuran (1.5 mL) at -78°C. The resulting solution was stirred at -78°C for 5 min before the solution of zinc chloride (0.073 mL, 1.9 M in 2-methyltetrahydrofuran) was added dropwise at -78°C. The mixture was warmed to rt and stirred at rt for 10 min. The solution was transferred to a reaction vial containing **Intermediate 17-9** (40 mg, 0.069 mmol) and palladium-tetrakis(triphenylphosphine) (8.0 mg, 0.0069 mmol) at rt under N_2 atmosphere. The reaction mixture was stirred at 90°C for 90 min before it was cooled to rt. Saturated aqueous solution of NH_4Cl (20 mL) was added. The mixture was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with brine (30 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (0% to 10% methanol in dichloromethane) to give **Intermediate 17-10**. LCMS: 765.0.

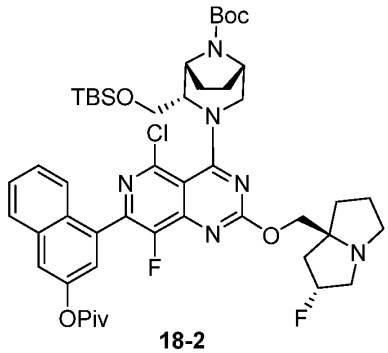
Intermediate 18-1: tert-butyl (1R,2S,5S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



18-1

[0452] **Intermediate 18-1** was synthesized in a manner similar to **Intermediate 17-7** using 8-(tert-butyl) 2-ethyl (1R,2S,5S)-4-oxo-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate instead of 8-(tert-butyl) 2-ethyl (1S,2S,5R)-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate. LCMS: 357.3

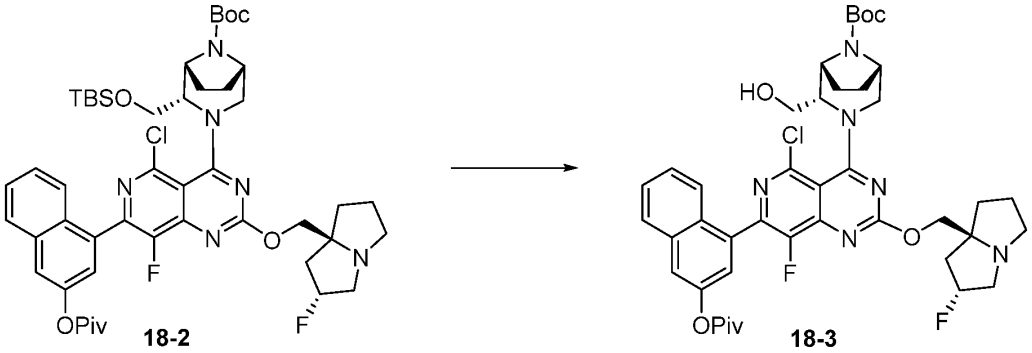
Intermediate 18-2: tert-butyl (1R,2S,5S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3-(5-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(3-(pivaloyloxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



18-2

[0453] **Intermediate 18-2** was synthesized in a manner similar to **Intermediate 20-7** using **Intermediate 18-1** instead of **Intermediate 17-7**. LCMS: 921.3.

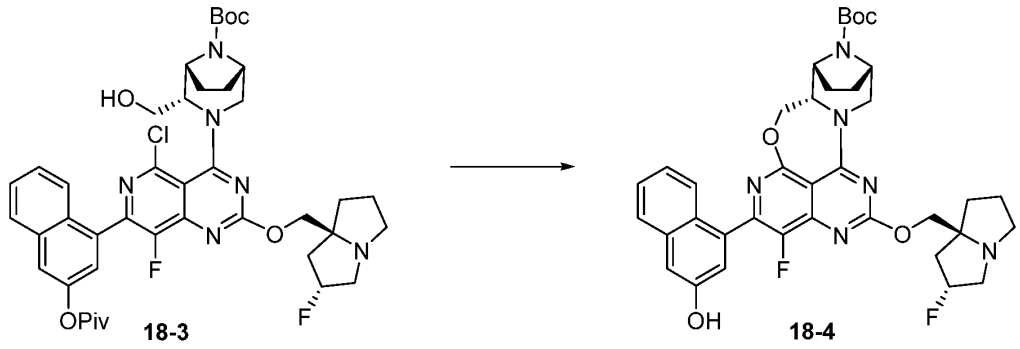
Intermediate 18-3: tert-butyl (1R,2S,5S)-3-(5-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(3-(pivaloyloxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0454] TBAF (1.0 M in THF, 0.40 mL) was added to the solution of **Intermediate 18-2** (50 mg, 0.054 mmol) in THF (1 mL) at 0°C. The mixture was stirred at rt for 2 h. Saturated aqueous solution of NH_4Cl (2 mL) was added. The mixture was extracted with EtOAc (2 × 5 mL). The

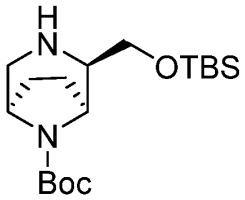
combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC (0.1% trifluoroacetic acid in acetonitrile/water) to give **Intermediate 18-3**. LCMS: 806.9.

Intermediate 18-4: tert-butyl (5aS,6R,9S)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(3-hydroxynaphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0455] Sodium hydride (60%, 7.12 mg, 0.186 mmol) was added to the solution of **Intermediate 18-3** (15.0 mg, 0.0186 mmol) in dry THF (0.5 mL) at rt. The resulting reaction mixture was stirred at 70°C for 15 min before it was cooled to rt. Saturated aqueous solution of NH_4Cl (1 mL) was added to quench the reaction. It was extracted with EtOAc (2 × 2 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give **Intermediate 18-4**. LCMS: 687.0.

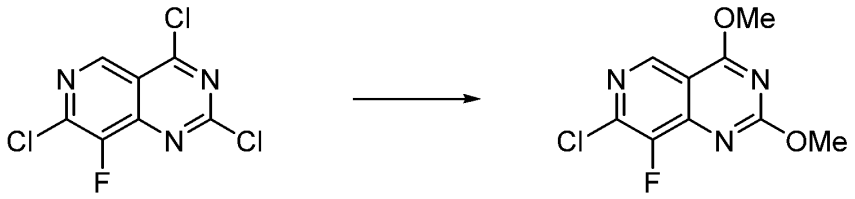
Intermediate 19-1: tert-butyl (1S,2R,5R)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



19-1

[0456] Intermediate 19-1 was synthesized in a manner similar to **Intermediate 18-1** using 8-(tert-butyl) 2-ethyl (1S,2R,5R)-4-oxo-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate instead of 8-(tert-butyl) 2-ethyl (1R,2S,5S)-4-oxo-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate. LCMS: 357.2.

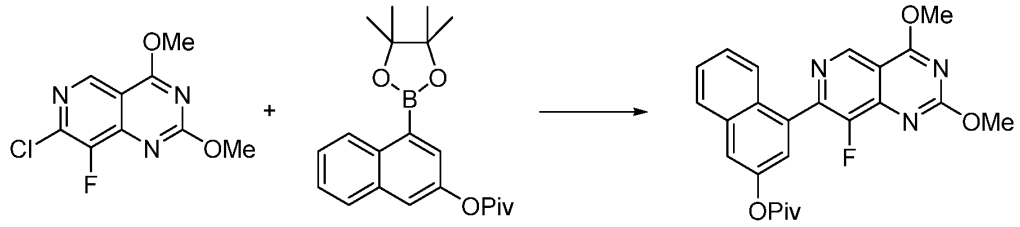
Intermediate 20-1: 7-chloro-8-fluoro-2,4-dimethoxypyrido[4,3-d]pyrimidine



20-1

[0457] The solution of NaOMe (1.50 g, 25% in MeOH) was added dropwise to the solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (700 mg, 2.77 mmol) in 2-methyltetrahydrofuran (30 mL) at 0°C. The reaction mixture was stirred at 0°C for 0.5 h. Saturated aqueous ammonium chloride solution (50 mL) was added. The mixture was extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated to give **Intermediate 20-1**. LCMS: 244.3.

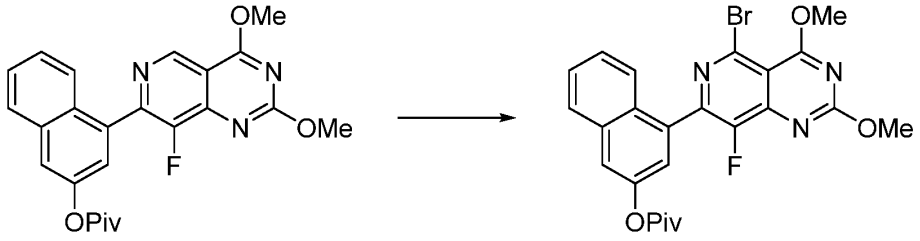
Intermediate 20-2: 4-(8-fluoro-2,4-dimethoxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-yl pivalate



20-1 **20-2**

[0458] The reaction mixture of [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-naphthyl] 2,2-dimethylpropanoate (833 mg, 2.35 mmol), **Intermediate 20-1** (500 mg, 2.05 mmol), potassium carbonate (567 mg, 4.10 mmol) and Palladium-tetrakis(triphenylphosphine) (237 mg, 0.205 mmol) in dioxane (10 mL) and water (2 mL) was stirred at 90°C under N_2 atmosphere for 2 h. After cooling to rt, water (10 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic phase was washed with brine (100 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (0% to 30% EtOAc in hexanes) to give **Intermediate 20-2**. LCMS: 436.4.

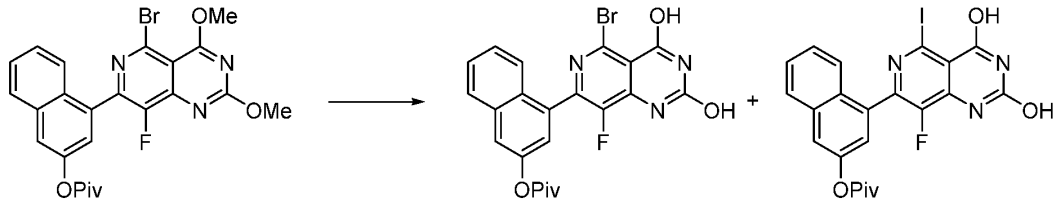
Intermediate 20-3: 4-(5-bromo-8-fluoro-2,4-dimethoxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-yl pivalate



20-2 **20-3**

[0459] Intermediate 20-3 was synthesized in a manner similar to **Intermediate 17-3** using **Intermediate 20-2** instead of **Intermediate 17-2**. LCMS: 514.1, 516.2.

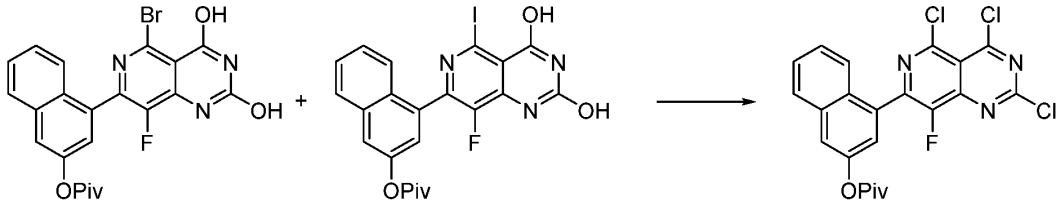
Intermediates 20-4a and 20-4b: 4-(5-bromo-8-fluoro-2,4-dihydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-yl pivalate (Intermediate 20-4a) and 4-(8-fluoro-2,4-dihydroxy-5-iodopyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-yl pivalate (Intermediate 20-4b)



20-3 **20-4a** **20-4b**

[0460] The reaction mixture of **Intermediate 20-3** (80.0 mg, 0.156 mmol) and sodium iodide (117 mg, 0.778 mmol) in acetic acid (2 mL) was stirred at 80°C for 2 h before it was cooled to rt. The volatile components were evaporated *in vacuo*. Saturated aqueous solution of sodium bicarbonate (30 mL) was added. The mixture was extracted with EtOAc (2 × 30 mL) and the combined organic phase was dried with Na_2SO_4. Evaporation of the solvent gave the mixture of **Intermediate 20-4a** and **Intermediate 20-4b** with a ratio of 1:1. LCMS: 486.6 and 488.2 for **Intermediate 20-4a**; 534.4 for **Intermediate 20-4b**.

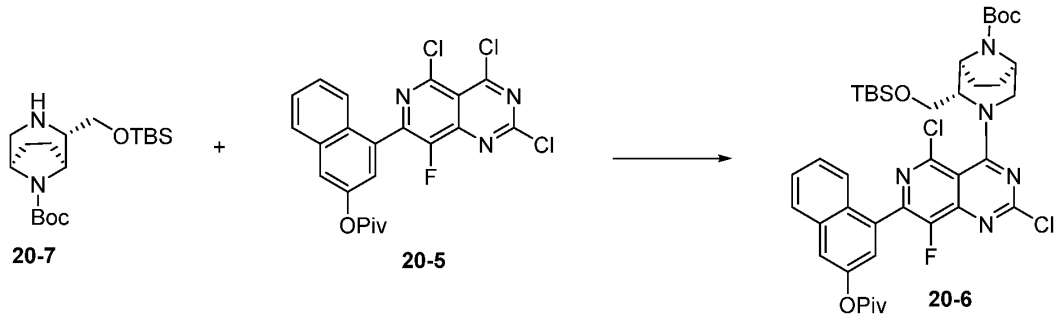
Intermediate 20-5: 4-(2,4,5-trichloro-8-fluoropyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-yl pivalate



20-4a **20-4b** **20-5**

[0461] Intermediate 20-5 was synthesized in a manner similar to **Intermediate 17-5** using **Intermediate 20-4a** and **Intermediate 20-4b** instead of **Intermediate 17-4**. LCMS: 478.0, 480.0.

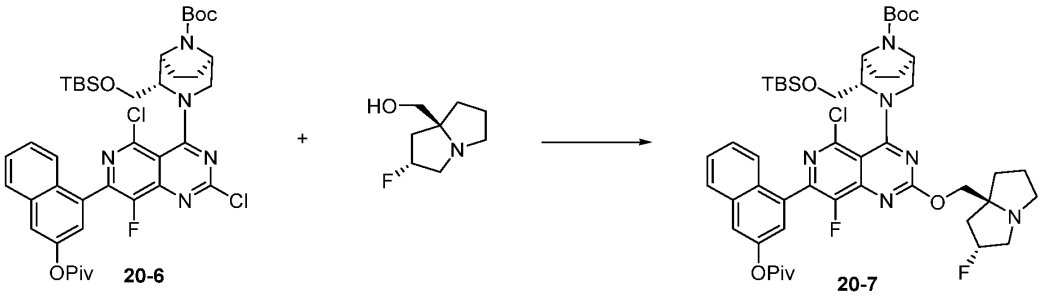
Intermediate 20-6: tert-butyl (1S,2S,5R)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3-(2,5-dichloro-8-fluoro-7-(3-(pivaloyloxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



20-7 **20-5** **20-6**

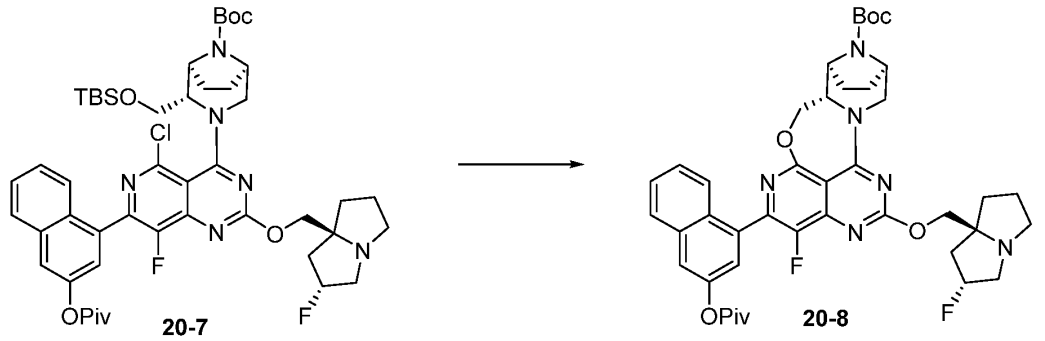
[0462] Intermediate 20-6 was synthesized in a manner similar to **Intermediate 17-8** using **Intermediate 20-5** instead of **Intermediate 17-5**. LCMS: 798.5.

Intermediate 20-7: tert-butyl (1S,2S,5R)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3-(5-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(3-(pivaloyloxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



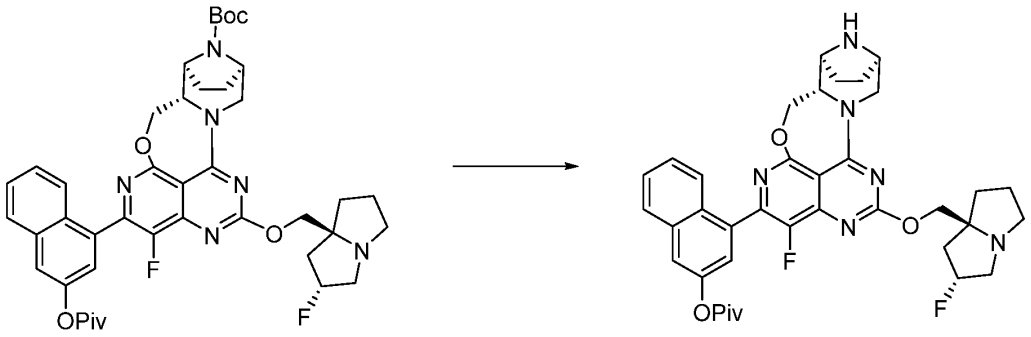
[0463] Intermediate 20-7 was synthesized in a manner similar to **Intermediate 17-2** using **Intermediate 20-6** instead of **Intermediate 17-1**. LCMS: 921.7.

Intermediate 20-8: tert-butyl (5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(3-(pivaloyloxy)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0464] Intermediate 20-8 was synthesized in a manner similar to **Intermediate 17-9** using **Intermediate 20-7** instead of **Intermediate 17-8**. LCMS: 771.1.

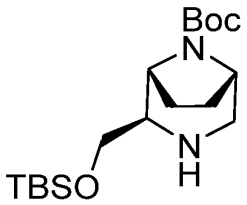
Intermediate 20-9: 4-((5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-yl pivalate



20-8 20-9

[0465] TFA was added drop wise to the solution of **Intermediate 20-8** (25.0 mg, 0.0324 mmol) in dichloromethane at rt. The mixture was stirred at rt for 1 h. The volatile components were evaporated *in vacuo* to give **Intermediate 20-9**. LCMS: 671.1.

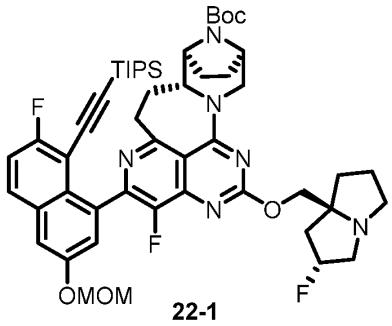
Intermediate 21-1: tert-butyl (1R,2R,5S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



21-1

[0466] Intermediate 21-1 was synthesized in a manner similar to **Intermediate 17-7** using 8-(tert-butyl) 2-ethyl (1R,2R,5S)-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate instead of 8-(tert-butyl) 2-ethyl (1S,2S,5R)-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate. LCMS: 357.3

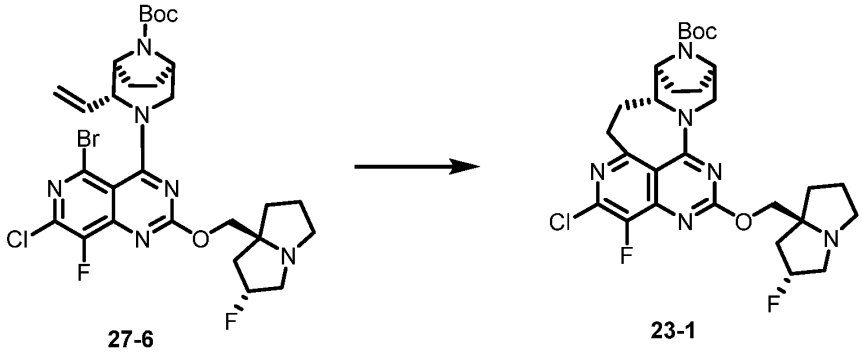
Intermediate 22-1: tert-butyl (5aR,6S,9R)-2-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



22-1

[0467] Intermediate 22-1 was synthesized in a manner similar to **Intermediate 27-7** using ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane instead of 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. LCMS: 927.2.

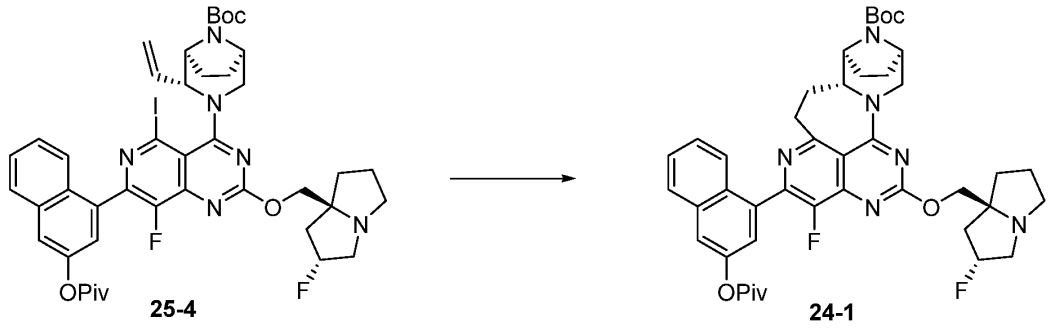
Intermediate 23-1: tert-butyl (5aR,6S,9R)-2-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



27-6 23-1

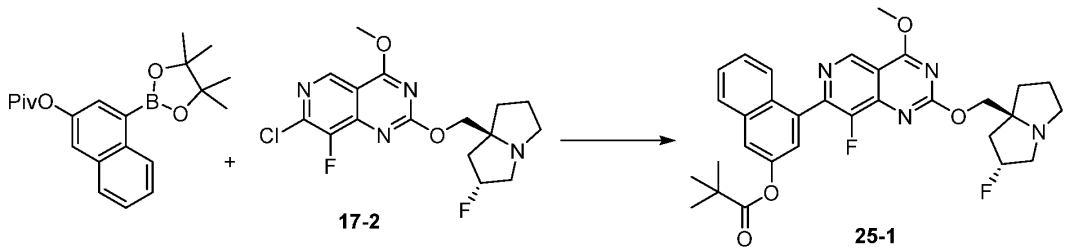
[0468] Intermediate 23-1 was synthesized in a manner similar to **Intermediate 24-1** using **Intermediate 27-6** instead of **Intermediate 25-4**. LCMS: 577.2.

Intermediate 24-1: 4-((5aR,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-yl pivalate



[0469] The solution of 9-borabicyclo[3.3.1]nonane (0.50 M in THF, 0.067 mL) was added to the solution of **Intermediate 25-4** (10.0 mg, 0.0112 mmol) in THF (0.5 mL) at rt. The solution was stirred at 60°C for 90 min before it was cooled to rt. Water (0.25 mL) was added and the mixture was transferred to a reaction vial containing Pd(dppf)Cl_2 and cesium carbonate (10.9 mg, 0.0335 mmol). The resulting mixture was stirred at 90°C for 30 min. It was cooled to rt. Water (2 mL) was added, and the mixture was extracted with EtOAc (2 × 2 mL). The combined organic phase was washed with brine (5 mL), dried with Na_2SO_4, and concentrated. The residue was purified by reverse phase preparative HPLC (0.1% trifluoroacetic acid in acetonitrile/water) to give **Intermediate 24-1**. LCMS: 769.1.

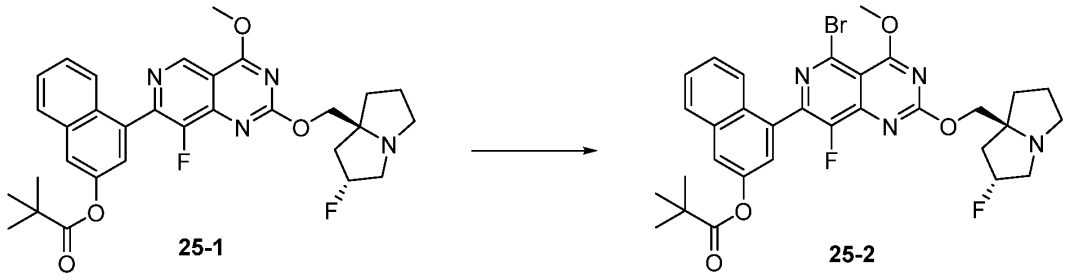
Intermediate 25-1: 4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methoxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-yl pivalate



[0470] The reaction mixture of [4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-naphthyl] 2,2-dimethylpropanoate (1.18 g, 3.33 mmol), **Intermediate 17-2** (1.08 g, 2.90 mmol), $Pd(PPh_3)_4$ (335 mg, 0.29 mmol), and K_2CO_3 (802 mg, 5.80 mmol) in dioxane (5 mL) and water (1 mL) was stirred at 90°C under N_2 atmosphere for 2 h. After cooling to rt, water was added, and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic phase was washed with brine (100 mL)

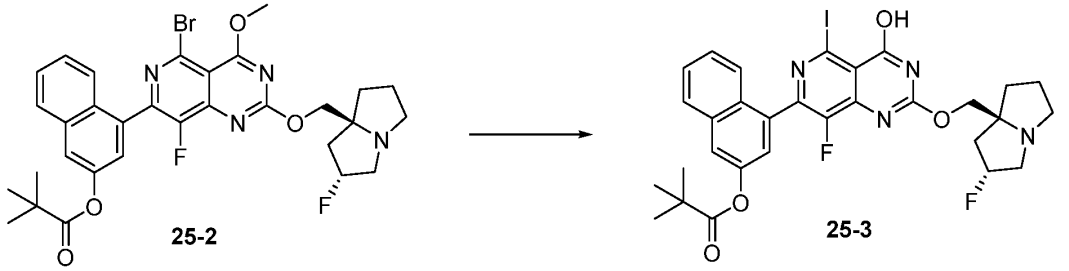
and dried with Na_2SO_4. The residue was purified by flash column chromatography on silica gel (0% to 10% MeOH in dichloromethane) to give **Intermediate 25-1**. LCMS: 563.4.

Intermediate 25-2: 4-(5-bromo-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methoxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-yl pivalate



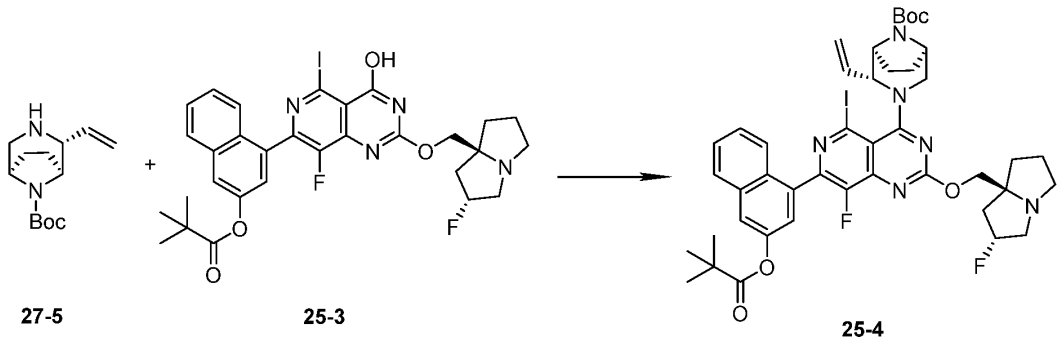
[0471] Intermediate 25-1 was synthesized in a manner similar to **Intermediate 17-3** using **Intermediate 25-1** instead of **Intermediate 17-2**. LCMS: 641.1, 643.0.

Intermediate 25-3: 4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxy-5-iodopyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-yl pivalate



[0472] Intermediate 25-3 was synthesized in a manner similar to **Intermediate 17-4** using **Intermediate 25-2** instead of **Intermediate 17-3**. LCMS: 674.9.

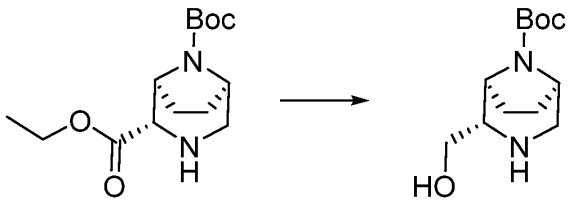
Intermediate 25-4: tert-butyl (1S,2R,5R)-3-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-iodo-7-(3-(pivaloyloxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-2-vinyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



27-5 25-3 25-4

[0473] HATU (41.9 mg, 0.178 mmol) was added to the reaction mixture of **Intermediate 25-3** (40.0 mg, 0.0593 mmol) and **Intermediate 27-5** (21.2 mg, 0.0890 mmol) in MeCN followed by the addition of DIPEA (23.0 mg, 0.178 mmol) at rt. The reaction mixture was stirred at rt for 12 h before it was filtered. The filtrate was purified by reverse phase preparative HPLC (0.1% trifluoroacetic acid in acetonitrile/water) to give **Intermediate 25-4**. LCMS: 895.0.

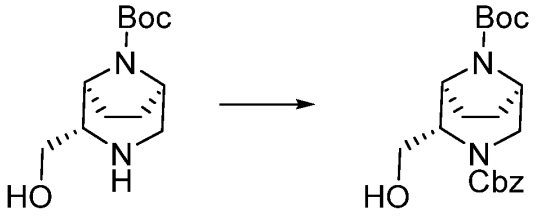
Intermediate 27-1: tert-butyl (1S,2S,5R)-2-(hydroxymethyl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate



27-1

[0474] LAH (1.0 M in tetrahydrofuran, 20.0 mL, 20.0 mmol) was added dropwise to a vigorously stirred solution of 8-(tert-butyl) 2-ethyl (1R,2S,5S)-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate (4.00 g, 14.1 mmol) in tetrahydrofuran (40.0 mL) at 0°C. The reaction mixture was stirred at 0°C for 2 hours before it was quenched with solid sodium sulfate decahydrate. The mixture was filtered and concentrated under reduced pressure to give the crude **Intermediate 27-1**, which was used for the next step without purification. LCMS: 243.0.

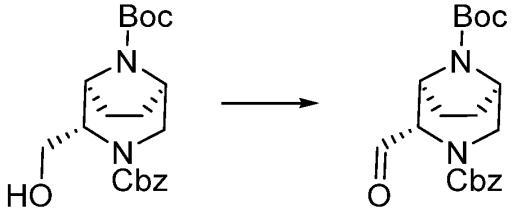
Intermediate 27-2: 3-benzyl 8-(tert-butyl) (1S,2S,5R)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



27-1 **27-2**

[0475] To a vigorously stirred solution of **Intermediate 27-1** (1.50 g, 6.19 mmol) in ethyl acetate (15 mL) and water (15 mL) was added sodium bicarbonate (1.56 g, 18.6 mmol) in one portion, then benzyl chloroformate (1.32 mL, 9.28 mmol) was added to the solution slowly with stirring at 0°C. The resulted solution was stirred at room temperature for 12 hours. The organic layer was separated from the reaction mixture. The aqueous phase was extracted with ethyl acetate (3 x 30 mL). The organic layer was collected and combined, dried over magnesium sulfate, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 50% ethyl acetate in hexanes) to give **Intermediate 27-2**. LCMS: 376.8 $[M+H]^+$, 399.1 $[M+Na]^+$.

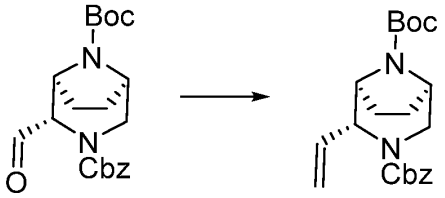
Intermediate 27-3: 3-benzyl 8-(tert-butyl) (1S,2S,5R)-2-formyl-3,8-diazabicyclo [3.2.1]octane-3,8-dicarboxylate



27-2 **27-3**

[0476] To a vigorously stirred solution of **Intermediate 27-2** (2.01 g, 5.30 mmol) in dichloromethane (25 mL) under nitrogen was added Dess Martin periodinane (2.49 g, 5.80 mmol) at room temperature. The mixture was stirred at room temperature for 12 hours before saturated aqueous sodium bicarbonate (50 mL) was added. The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0% to 50% ethyl acetate in hexanes) to give **Intermediate 27-3**. LCMS: 375.0.

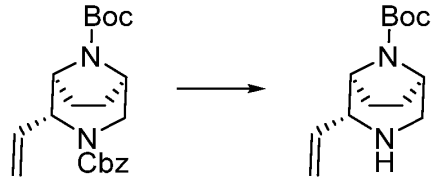
Intermediate 27-4: 3-benzyl 8-(tert-butyl) (1S,2R,5R)-2-vinyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



27-3 **27-4**

[0477] To a vigorously stirred solution of methyltriphenylphosphonium bromide (4.99 g, 14.0 mmol) in tetrahydrofuran (22 mL) at room temperature was added KHMDS solution (1.0 M in tetrahydrofuran, 14.0 mL, 14.0 mmol) dropwise to afford a solution. The mixture was stirred for 1 hour at room temperature and was cooled to -78°C whereupon a solution of **Intermediate 27-3** (1.74 g, 4.65 mmol) in tetrahydrofuran (22 mL) was added dropwise over 20 minutes. The resulting solution was allowed to gradually warm to room temperature and stir for 3 hours. The mixture was quenched with methanol (40 mL) and stirred for 15 min. Saturated aqueous ammonium chloride solution (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0% to 40% ethyl acetate in hexanes) to give **Intermediate 27-4**. LCMS: 395.1 $[M+Na]^+$.

Intermediate 27-5: tert-butyl (1S,2R,5R)-2-vinyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

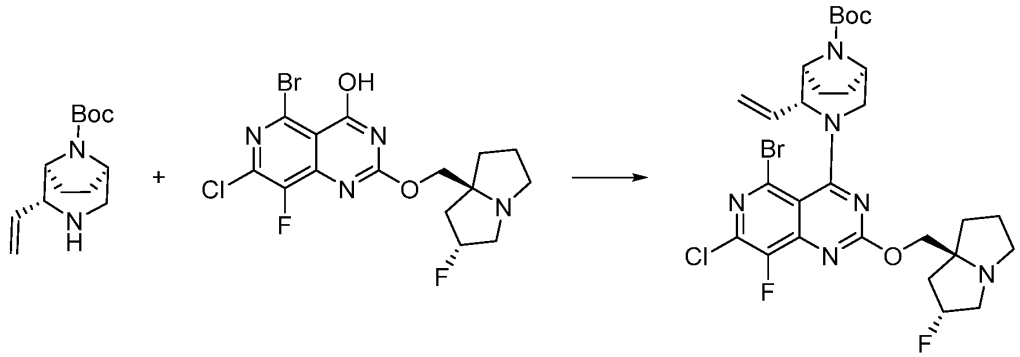


27-4 **27-5**

[0478] To a vigorously stirred solution of palladium(II) acetate (9.5 mg, 0.0426 mmol) in dichloromethane (5.3 mL), triethyl silane (0.27 mL, 1.70 mmol) was added dropwise, followed by the addition of triethylamine (0.12 µL, 0.851 µmol). The resulting mixture was stirred for 15 minutes at room temperature before the solution of **Intermediate 27-4** (317 mg, 0.851 mmol) in dichloromethane (2 mL) was added dropwise. The reaction mixture was stirred for 90 hours at room temperature. The mixture was diluted with saturated aqueous sodium bicarbonate (20 mL).

The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0% to 100% ethyl acetate in hexanes then 0% to 20% methanol in dichloromethane) to give **Intermediate 27-5**. LCMS: 238.9.

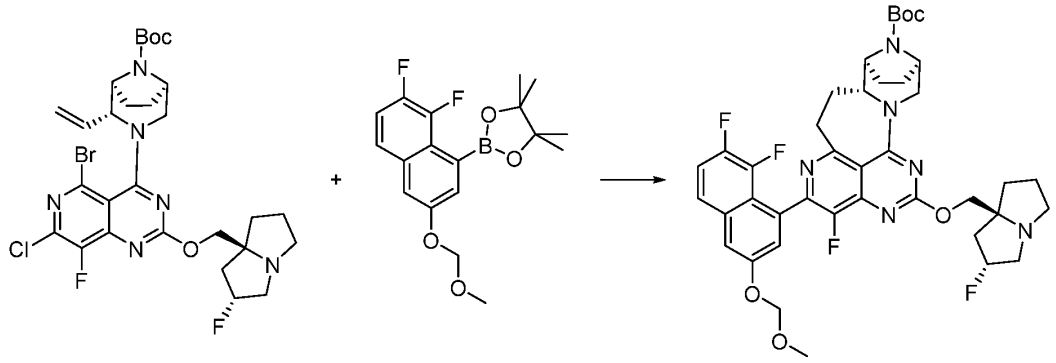
Intermediate 27-6: tert-butyl (1*S*,2*R*,5*R*)-3-(5-bromo-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-vinyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



27-5 **17-4** **27-6**

[0479] To a vigorously stirred solution of **Intermediate 17-4** (371.0 mg, 0.851 mmol) in phosphoryl chloride (4.93 mL), *N,N*-diisopropylethylamine (0.45 mL, 2.55 mmol) was added dropwise at room temperature and the reaction mixture was stirred at 55°C for 5 min before it was cooled to rt. The mixture was concentrated under reduced pressure. To the solution of the residue and **Intermediate 27-5** (203 mg, 0.851 mmol) in dichloromethane (6.4 mL), DIPEA (1.80 mL, 10.3 mmol) was added dropwise at 0°C. The reaction mixture was stirred at 0°C for 10 min before it was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 100% ethyl acetate in hexanes) to give **Intermediate 27-6**. LCMS: 656.9.

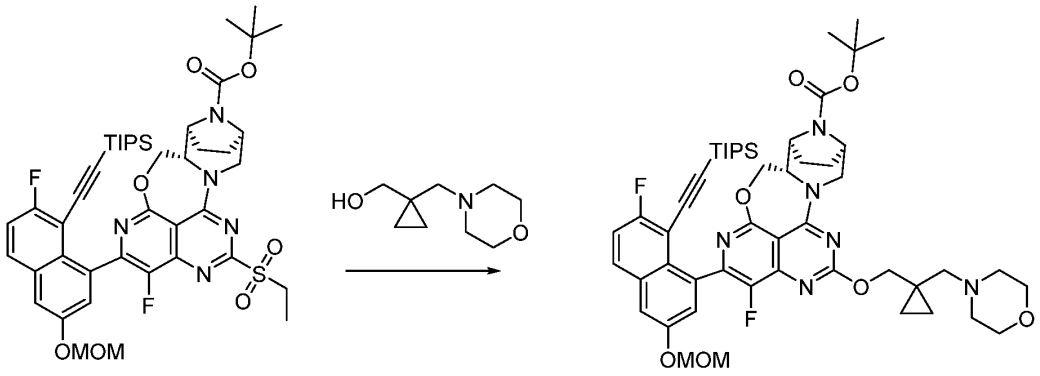
Intermediate 27-7: tert-butyl (5aR,6S,9R)-2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



27-6 27-7

[0480] To a vigorously stirred solution of **Intermediate 27-6** (50.0 mg, 0.0112 mmol) in tetrahydrofuran (3 mL), the solution of 9-borabicyclo[3.3.1]nonane (0.50 M in tetrahydrofuran, 0.45 mL, 0.23 mmol) was added at room temperature. The resulting solution was stirred at 60°C for 90 minutes before it was cooled to room temperature. Degassed water (1.5 mL) was added and the mixture was transferred to a reaction vial charged with chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)] palladium(II) (5.7 mg, 0.00762 mmol), 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (53.4 mg, 0.152 mmol), and sodium carbonate (10.9 mg, 0.0335 mmol). The resulting mixture was stirred at 80°C for 5 hours then cool to room temperature. The solution was filtered and purified with reverse phase preparative HPLC (0.1% trifluoroacetic acid in acetonitrile/water) to give **Intermediate 27-7**. LCMS: 765.0.

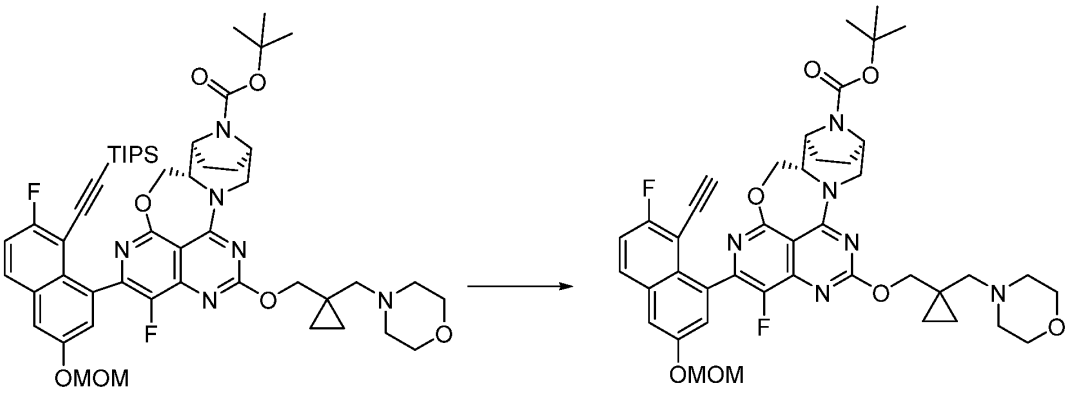
Intermediate 28-1: tert-butyl (5aS,6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



13-9 28-1

[0481] Lithium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 35 μL, 35 μmol) was added over 1 min via syringe to a stirred mixture of **Intermediate 13-9** (20.0 mg, 23.1 μmol), (1-(morpholinomethyl)cyclopropyl)methanol (7.9 mg, 44 μmol), and tetrahydrofuran (0.5 mL) at room temperature. After 10 min ethyl acetate and saturated aqueous sodium bicarbonate solution were added sequentially. The organic layer was washed with water, was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure to give **Intermediate 28-1**. LCMS: 941.2.

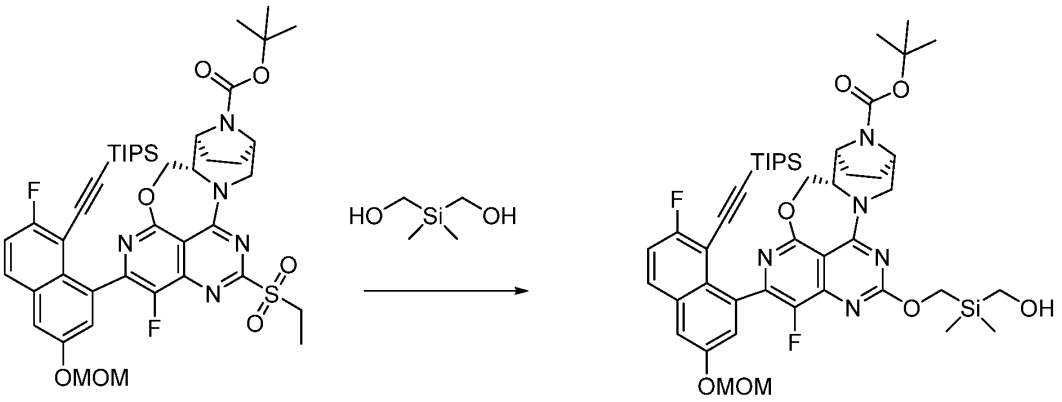
Intermediate 28-2: tert-butyl (5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



28-1 **28-2**

[0482] Cesium fluoride (80.2 mg, 531 μmol) was added to a vigorously stirred solution of **Intermediate 28-1** (20 mg, 21.2 μmol) in *N*,*N*-dimethylformamide (0.5 mL) at room temperature. After 30 min, ethyl acetate and saturated aqueous sodium bicarbonate solution were added sequentially. The organic layer was washed with water, was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure to give **Intermediate 28-2**. LCMS: 784.9.

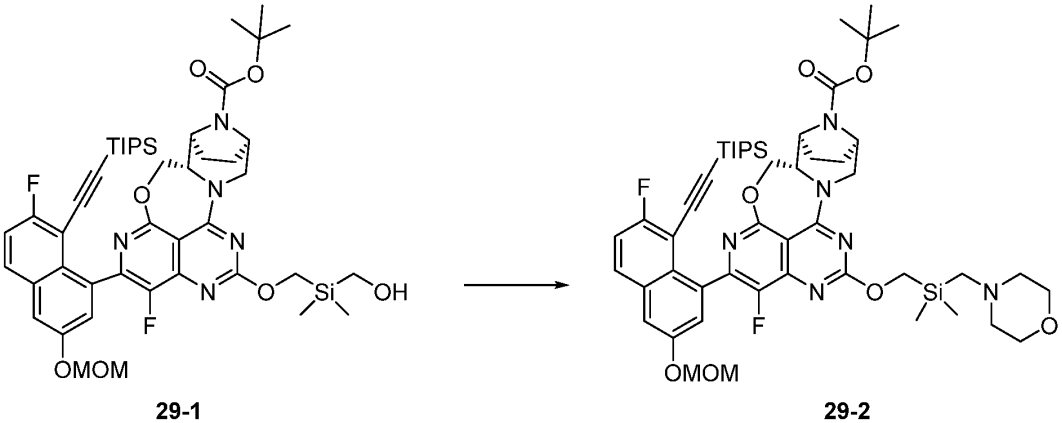
Intermediate 29-1: tert-butyl (5aS,6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((hydroxymethyl)dimethylsilyl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



13-9 29-1

[0483] Lithium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 87 μL, 87 μmol) was added over 1 min via syringe to a stirred mixture of **Intermediate 13-9** (50.0 mg, 58 μmol), (dimethylsilanediyl)dimethanol (13.9 mg), and tetrahydrofuran (1 mL) at room temperature. After 10 min ethyl acetate, and saturated aqueous sodium bicarbonate solution were added sequentially. The organic layer was washed with water, was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure to give **Intermediate 29-1**. LCMS: 890.4.

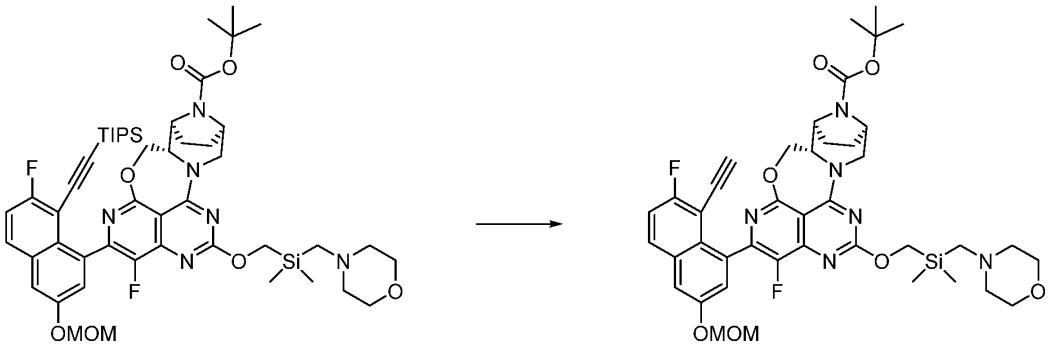
Intermediate 29-2: tert-butyl (5aS,6S,9R)-12-((dimethyl(morpholinomethyl)silyl) methoxy)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl) ethynyl)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



29-1 29-2

[0484] To a solution of **Intermediate 29-1** (50 mg, 0.058 mmol), *N*,*N*-diisopropylethylamine (0.06 ml, 0.35 mmol) in DMF (1 mL) was added methane sulfonyl chloride (0.018 ml, 0.232 mmol) at 0°C, the mixture was stirred at the same temperature for 30 min. the reaction mixture was partitioned between EtOAc and water, the organic phase was washed with brine, dried $MgSO_4$, filtered and concentrated. The residue was dissolved in a mixture of acetonitrile/acetone 1:1 (2 ml) then DIPEA (0.05 ml, 0.28 mmol), morpholine (0.029 ml, 0.34 mmol), and NaI (42 mg, 0.284 mmol) were added. Reaction mixture was stirred at 80°C for 2 h. Ethyl acetate, and saturated aqueous sodium bicarbonate solution were added sequentially. The organic layer was washed with water, was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure to give **Intermediate 29-2**. LCMS: 958.9.

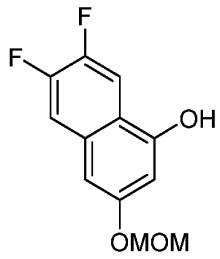
Intermediate 29-3: tert-butyl (5aS,6S,9R)-12-((dimethyl(morpholinomethyl)silyl) methoxy)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



29-2 29-3

[0485] Cesium fluoride (118 mg, 0.78 mmol) was added to a vigorously stirred solution of **Intermediate 29-2** (30 mg, 31.3 µmol) in *N*,*N*-dimethylformamide (1 mL) at room temperature. After 30 min, ethyl acetate and saturated aqueous sodium bicarbonate solution were added sequentially. The organic layer was washed with water, was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure to give **Intermediate 29-3**. LCMS: 802.8.

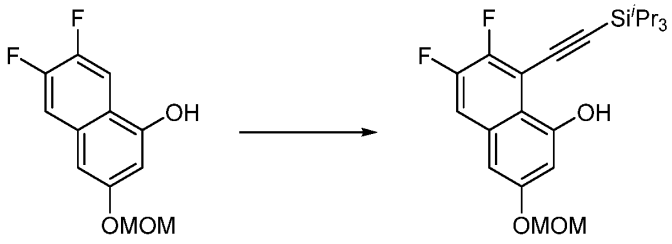
Intermediate 30-1: 6,7-difluoro-3-(methoxymethoxy)naphthalen-1-ol



30-1

[0486] Intermediate 30-1 was synthesized in a manner similar to **Intermediate 5-4** using methyl 2-bromo-4,5-difluorobenzoate instead of **Intermediate 5-2**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.0, 11.2 Hz, 1H), 7.41 (dd, J = 7.6, 11.2 Hz, 1H), 6.93 (s, 1H), 6.59 (s, 1H), 5.48 (s, 1H), 5.25 (s, 2H), 3.52 (s, 3H).

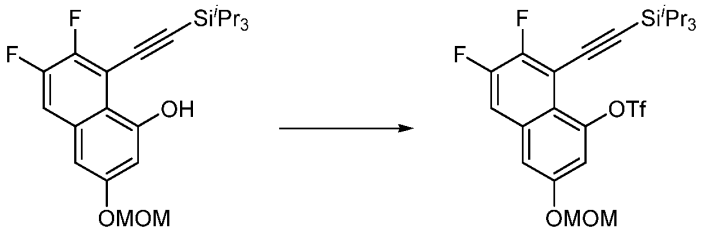
Intermediate 30-2: 6,7-difluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol



30-1 **30-2**

[0487] To a solution of **Intermediate 30-1** (0.870 g, 3.625 mmol) in 1,4-dioxane (6.090 mL) were added bromoethynyltriisopropylsilane (0.993 g, 3.806 mmol), KOAc (0.712 g, 7.250 mmol) and dichlororuthenium-1-isopropyl-4-methyl-benzene dimer (0.222 g, 0.363 mmol). The resulting mixture was stirred at 110°C for 2 h. After completion of the reaction, reaction mass was quenched with water (20 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to get the crude material which was subjected to column chromatographic purification using silica (100-200 mesh) and product was eluted at 2%-3% ethyl acetate in pet ether to yield **Intermediate 30-2**. LCMS: 421.6.

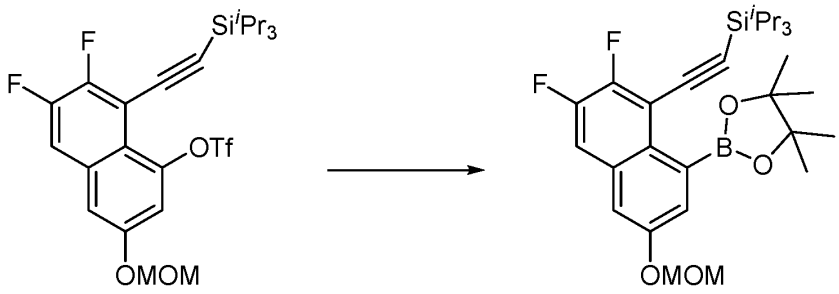
Intermediate 30-3: 6,7-difluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate



30-2 **30-3**

[0488] To a solution of **Intermediate 30-2** (970 mg, 2.306 mmol) in DCM (19.4 mL), were added DIPEA (1.03 mL, 5.766 mmol), Tf_2O (0.7 mL, 4.6 mmol) (0.387 mL, 2.306 mmol) at -40°C and stirred for 1h. After completion of the reaction, reaction mass was quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to get the crude material which was subjected to column chromatographic purification using silica (100-200 mesh) and product was eluted at 5%-7% ethyl acetate in pet ether to yield **Intermediate 30-3**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (dd, J = 8.0, 10.8 Hz, 1H), 7.72 (s, 1H), 7.49 (s, 1H), 5.37 (s, 2H), 3.42 (s, 3H), 1.22 – 1.15 (m, 21H).

Intermediate 30-4: ((2,3-difluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane

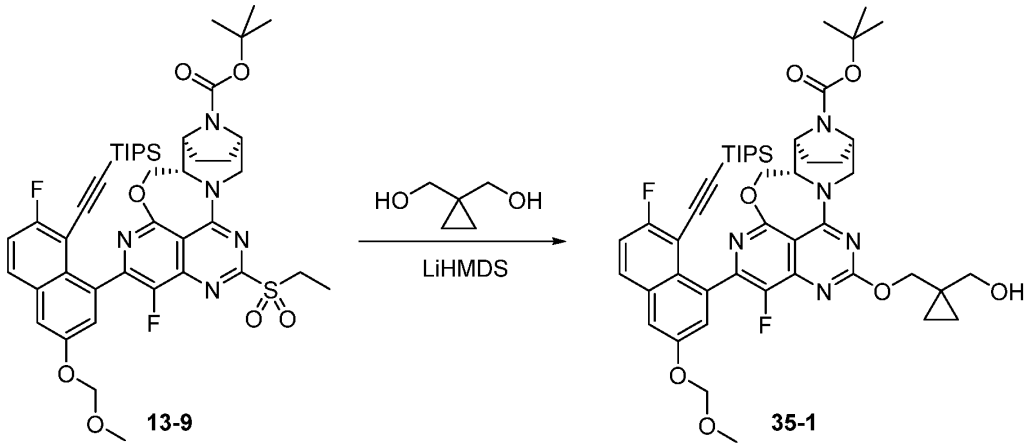


30-3 **30-4**

[0489] To a stirred solution of **Intermediate 30-3** (1.2 g, 2.174 mmol) in 1,4-dioxane (18 mL), were added 4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.1 g, 4.348 mmol) and KOAc (1.06 g, 10.870 mmol). Reaction mixture was degassed with argon gas for 10 min. $PdCl_2$(dppf) (159 mg, 0.217 mmol) was added and again degassed the reaction mixture for 5 min.

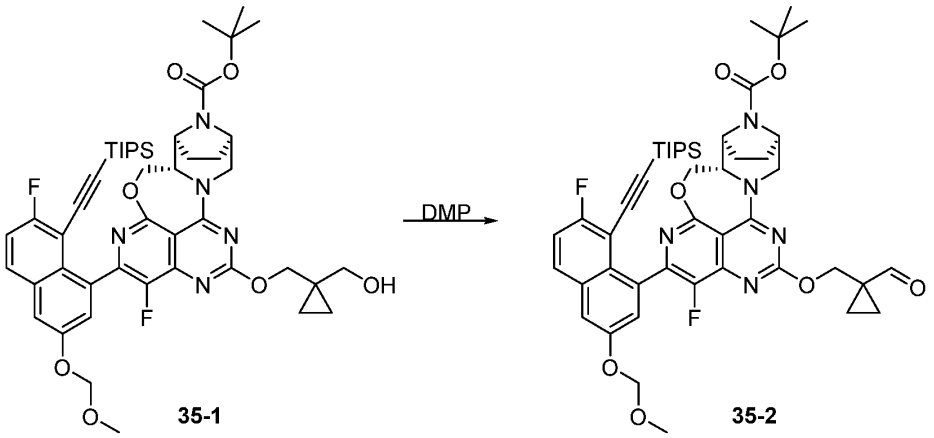
Resulting mixture was heated to 130°C under stirring for 6h. After completion of the reaction, reaction mass was filtered, diluted with water (30 ml) and extracted with ethyl acetate (50 mL), concentrated under reduced pressure to get the crude material. The crude material was purified by column chromatography using silica (100-200 mesh) and product was eluted at 10%-12% ethyl acetate in pet ether to yield **Intermediate 30-4**. LCMS: 531.5.

Intermediate 35-1: tert-butyl (5aS,6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-((1-(hydroxymethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



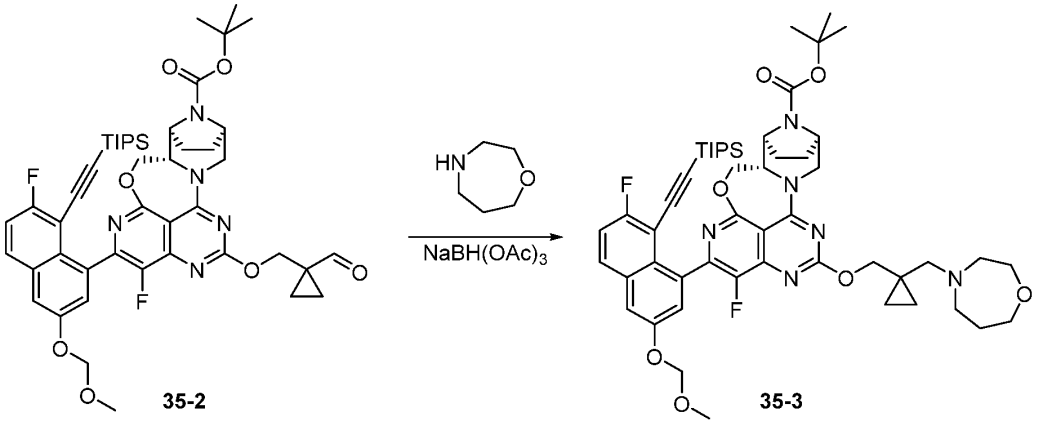
[0490] A mixture of **Intermediate 13-9** (179.1 mg, 0.21 mmol) and [1-(hydroxymethyl)cyclopropyl]methanol (55.1 mg, 0.54 mmol) was co-evaporated with toluene (x 2) and dissolved in THF (2 mL). The solution was stirred at rt as LiHMDS solution (1.0 M in THF, 0.22 mL) was added over 1 min. After 10 min, the reaction mixture was diluted with ether (~15 mL), ethyl acetate (~10 mL), and saturated $NaHCO_3$ (~5 mL) and the layers were separated. The organic layer was washed with water (x 1), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography on silica gel (30 to 100% ethyl acetate in hexanes) to give **Intermediate 35-1**. LCMS: 872.5.

Intermediate 35-2: tert-butyl (5aS,6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-((1-formylcyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



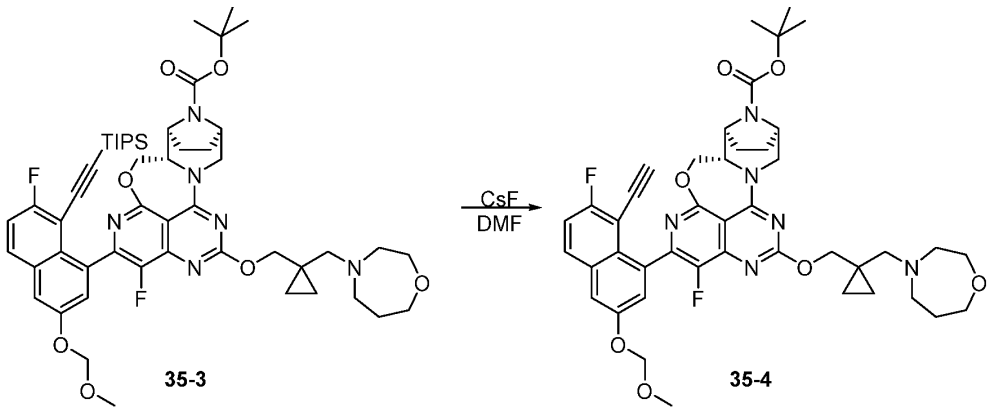
[0491] A suspension of **Intermediate 35-1** (128.1 mg, 147 umol) in CH_2Cl_2 (4 mL) was stirred at rt as Dess-Martin periodinane (178.6 mg, 421 umol) was added. After 20 min, the reaction mixture was diluted with ethyl acetate (~25 mL) and washed with saturated $NaHCO_3$ solution (~10 mL) with water (~15 mL), the separated organic layer was washed with water (~25 mL x 1). After the aq. layer was extracted with ethyl acetate (25 mL x 1), the two organic layers were combined, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography on silica gel (0 to 100% ethyl acetate in hexanes) to give **Intermediate 35-2**. LCMS: 870.5.

Intermediate 35-3: tert-butyl (5aS,6S,9R)-12-((1-((1,4-oxazepan-4-yl)methyl)cyclopropyl)methoxy)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



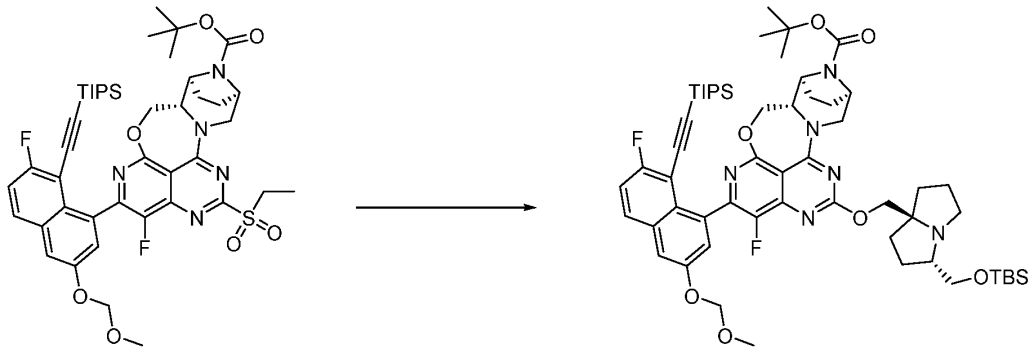
[0492] A mixture of **Intermediate 35-2** (8.91 mg, 10.2 umol), 1,4-oxazepane (34.9 mg, 34.9 umol), and sodium triacetoxyborohydride (10.2 mg, 47.9 umol) in THF (1 mL) was stirred at rt. After 16 h, the reaction mixture was diluted with ethyl acetate (25 mL) and washed with saturated $NaHCO_3$ (~25 mL x 1) and then water (~25 mL x 1). After the combined aqueous layers were extracted with ethyl acetate (~20 mL x 1), the resulting organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to give crude **Intermediate 35-3**. LCMS: 955.6.

Intermediate 35-4: tert-butyl (5aS,6S,9R)-12-((1-((1,4-oxazepan-4-yl)methyl)cyclopropyl)methoxy)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0493] To a mixture of crude **Intermediate 35-3** (10.2 umol) and CsF (40.99 mg, 270 umol) was added DMF (0.5 mL) and the resulting solution was stirred for 1 h at rt. After the reaction mixture was diluted with saturated $NaHCO_3$ solution (~10 mL), water (~5 mL), and ethyl acetate (~15 mL), two layers were separated. The organic layer was washed with water (~15 mL x 2) and the combined aqueous layers were extracted with ethyl acetate (~15 mL x 1). The organic layers were combined, dried ($MgSO_4$), and concentrated to give crude **Intermediate 35-4**. LCMS: 799.4.

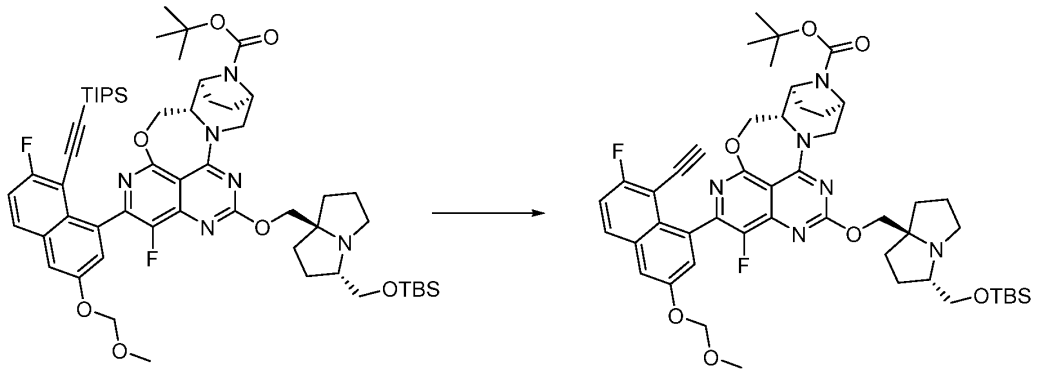
Intermediate 36-1: tert-butyl (5aS,6S,9R)-12-(((3S,7aS)-3-(((tert-butyldimethylsilyl) oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



13-9 **36-1**

[0494] A mixture of **Intermediate 13-9** (300 mg, 330 μmol) and [(3S,8S)-3-[[tert-butyl(dimethyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (141 mg, 495 μmol) was azeotroped from toluene (500 uL) and dissolved in anhydrous N,N-dimethylformamide (6.0 mL) under argon atmosphere. Sodium hydride (60% dispersion in mineral oil, 19 mg, 495 μmol) was added and the mixture was stirred overnight at room temperature. Additional sodium hydride (60% dispersion in mineral oil, 19 mg, 495 μmol) was added and the mixture was stirred for a further 2 h. Brine (6 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give **Intermediate 36-1**. LCMS: 1055.6.

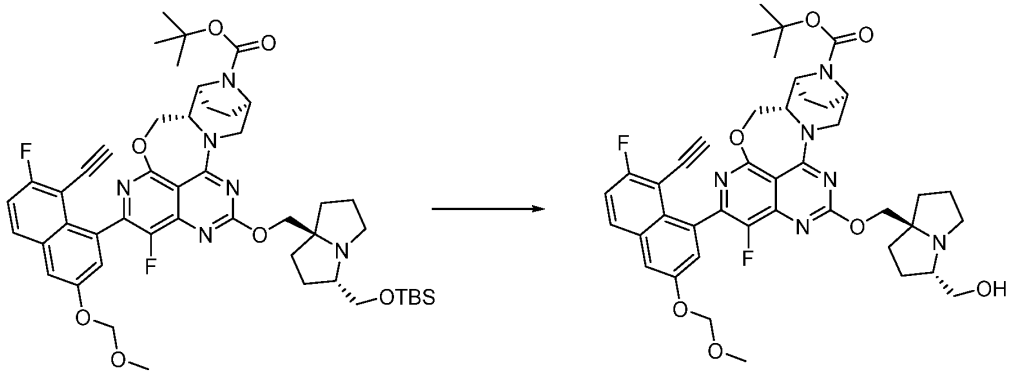
Intermediate 36-2: tert-butyl (5aS,6S,9R)-12-(((3S,7aS)-3-(((tert-butyldimethylsilyl)oxy) methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



36-1 **36-2**

[0495] Intermediate 36-2 was prepared in a manner analogous to **Intermediate 13-11** using **Intermediate 36-1** as the starting material. The product was purified by flash column chromatography on basic alumina (0% to 75% ethyl acetate in hexanes) to give **Intermediate 36-2**. LCMS: 899.5.

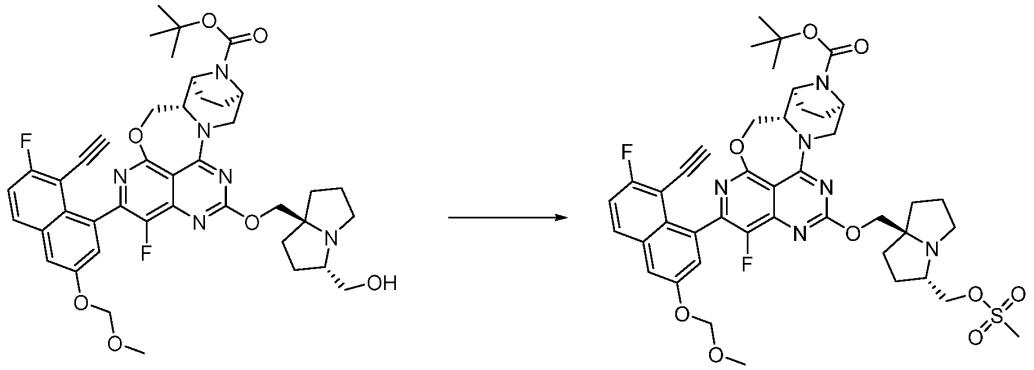
Intermediate 36-3: tert-butyl (5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((3S,7aS)-3-(hydroxymethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



36-2 **36-3**

[0496] Intermediate 36-2 (221 mg, 246 µmol) was dissolved in anhydrous tetrahydrofuran (2 mL) and tetra-n-butyl ammonium fluoride (1 M in tetrahydrofuran, 320 uL, 320 µmol) was added via syringe. The resulting solution was stirred at room temperature overnight. Additional tetra-n-butyl ammonium fluoride (1 M in THF, 64 uL, 64 µmol) was added via syringe and stirring was continued at room temperature for a further 72 hours. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on basic alumina (0% to 100% ethyl acetate in hexanes then 0% to 40% methanol in ethyl acetate) to give **Intermediate 36-3**. LCMS: 785.4.

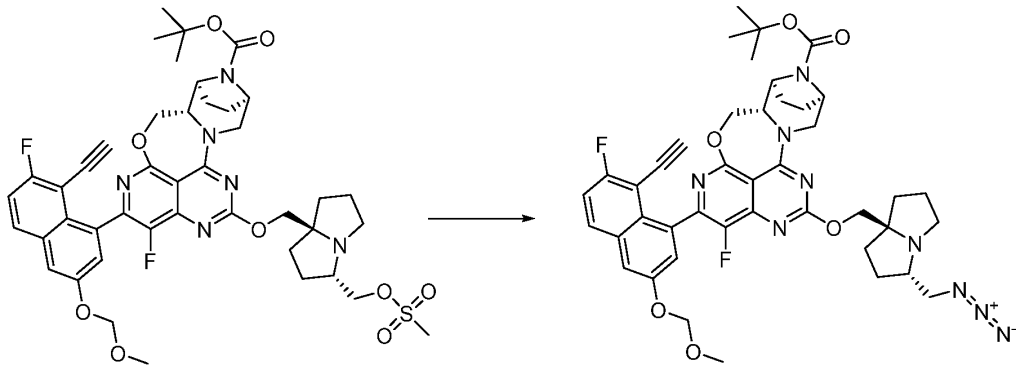
Intermediate 36-4: tert-butyl (5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((3S,7aS)-3-(((methylsulfonyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



36-3 36-4

[0497] Intermediate 36-3 (30 mg, 38 µmol) was dissolve in tetrahydrofuran (1 mL) and cooled to 0°C. Methanesulfonyl chloride (8.9 µL, 115 µmol) was added followed by triethylamine (16 µL, 115 µmol). The mixture was stirred at 0°C for 30 min. Brine (1 mL) and saturated aqueous sodium carbonate (1 mL) were added and the mixture was extracted with ethyl acetate (2 x 1 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography on basic alumina using a gradient of ethyl acetate in hexanes (0% to 100%) followed by a gradient of methanol in ethyl acetate (0-20%) to afford **Intermediate 36-4**. LCMS: 863.4.

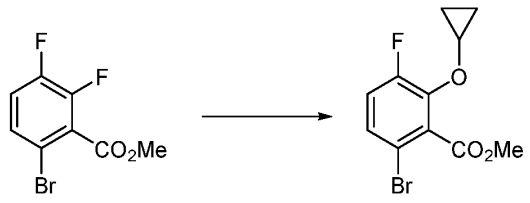
Intermediate 36-5: tert-butyl (5aS,6S,9R)-12-(((3S,7aS)-3-(azidomethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



36-4 **36-5**

[0498] To a solution of **Intermediate 36-4** (28 mg, 32 μmol) in N,N-dimethylformamide (1 mL) was added sodium azide (11 mg, 162 μmol) and the resulting mixture was stirred at 70°C overnight. Brine (1 mL) and saturated aqueous sodium carbonate (1 mL) were added and the mixture was extracted with ethyl acetate (2 x 1 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified via flash column chromatography on basic alumina using a gradient of ethyl acetate in hexanes (0% to 100%) to afford **Intermediate 36-5**. LCMS: 810.4.

Intermediate 42-1: methyl 6-bromo-2-cyclopropoxy-3-fluorobenzoate

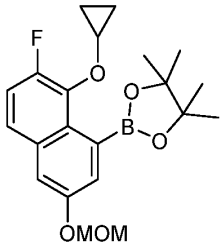


42-1

[0499] To a suspension of NaH (7.55 g, 179.26 mmol) and cyclopropanol (4.54 mL, 71.70 mmol) in THF (360 mL), was added methyl 6-bromo-2,3-difluorobenzoate (18 g, 71.70 mmol) at -40°C. The reaction mixture was allowed to warm up to room temperature and stirred for 4 h. After completion of the reaction, reaction mass was carefully quenched with water (70 mL) and extracted with ethyl acetate (2 x 90 mL). The combined organic layer was washed with brine

(70 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to get the crude adduct. The crude material was subjected to silica gel (100-200 mesh) column chromatography eluting with 8-10% ethyl acetate in petroleum ether to yield **Intermediate 42-1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.20 (m, 1H), 7.06-7.01 (m, 1H), 4.31-4.29 (m, 1H), 3.99 (s, 3H), 0.82 (s, 2H), 0.61-0.57 (m, 2H).

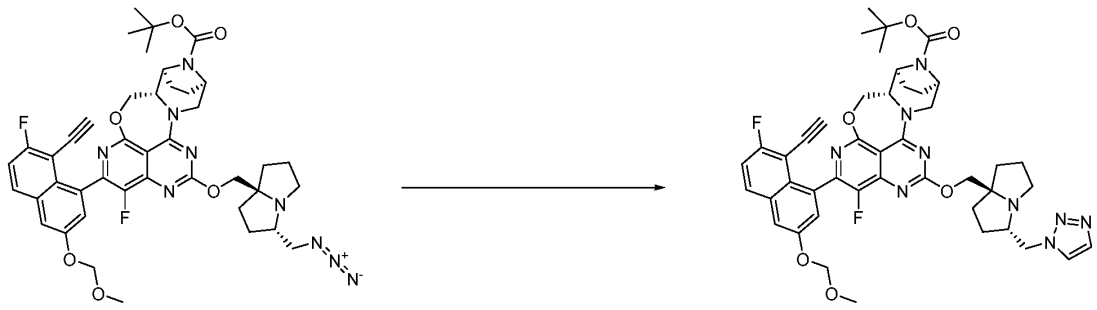
Intermediate 42-2: 2-(8-cyclopropoxy-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



42-2

[0500] Intermediate 42-2 was synthesized in a manner similar to **Intermediate 7-5** using **Intermediate 42-1** instead of **Intermediate 7-1**. LCMS: 389.3.

Intermediate 49-1: tert-butyl (5aS,6S,9R)-12-(((3S,7aS)-3-((1H-1,2,3-triazol-1-yl)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

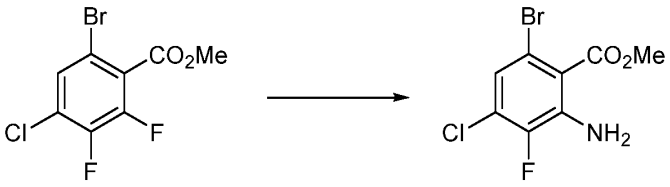


36-5 **49-1**

[0501] A vial was charged with **Intermediate 36-5** (10 mg, 12 μmol), copper (II) sulfate (0.6 mg, 2.5 μmol), potassium carbonate (8.5 mg, 62 μmol) and sodium ascorbate (0.8 mg, 4.9 μmol). Water (250 μL) and methanol (250 μL) were added followed by trimethylsilylacetylene (44 μL, 310 μmol). The resulting mixture was stirred vigorously at room temperature overnight. Brine (1

mL) was added and the mixture was extracted with ethyl acetate (2 x 1 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on basic alumina using a gradient of ethyl acetate in hexanes (0% to 100%) followed by methanol in ethyl acetate (0% to 20%) to give **Intermediate 49-1**. LCMS: 836.4.

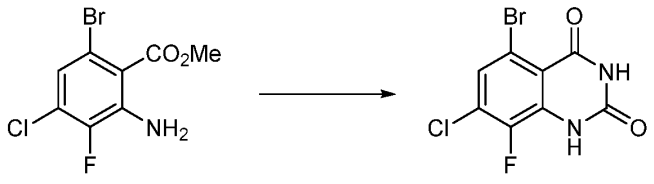
Intermediate 52-1: methyl 2-amino-6-bromo-4-chloro-3-fluorobenzoate



52-1

[0502] Ammonia solution (0.4 M in 1,4-dioxane, 9.57 mL, 4 mmol) was added via syringe to a stirred mixture of methyl 6-bromo-4-chloro-2,3-difluorobenzoate (600 µL, 3.48 mmol), *N*,*N*-diisopropylethylamine (666 µL, 3.83 mmol), and acetonitrile (1.5 mL) at room temperature, and the resulting mixture was heated to 80°C. After 91 min, ammonia solution (0.4 M in 1,4-dioxane, 6.00 mL, 2 mmol) was added via syringe, and the resulting mixture was heated to 105°C. After 5.5 h, the resulting mixture was heated to 115°C. After 64 h, the resulting mixture was cooled to room temperature, and diethyl ether (100 mL) and ethyl acetate (25 mL) were added sequentially. The organic layer was washed with a mixture of water and brine (3:1 v:v, 50 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 12% ethyl acetate in hexanes) to give **Intermediate 52-1**. LCMS: 281.9.

Intermediate 52-2: 5-bromo-7-chloro-8-fluoroquinazoline-2,4(1*H*,3*H*)-dione

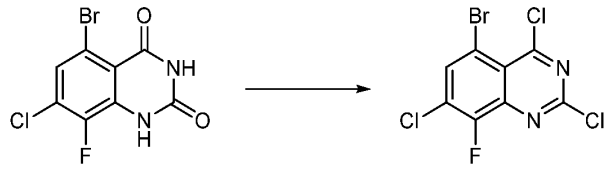


52-1 **52-2**

[0503] 2,2,2-Trichloroacetyl isocyanate (138 µL, 1.16 mmol) was added over 2 min via syringe to a stirred solution of **Intermediate 52-1** (298 mg, 1.05 mmol) in tetrahydrofuran (1.5 mL) at 0°C, and the resulting mixture was warmed to room temperature. After 38 min, the resulting

mixture was concentrated under reduced pressure. Ammonia solution (20% wt in methanol, 5.50 mL, 39 mmol) was added via syringe, and the resulting mixture was stirred vigorously. After 20 min, the resulting mixture was concentrated under reduced pressure to give **Intermediate 52-2**. LCMS: 292.9.

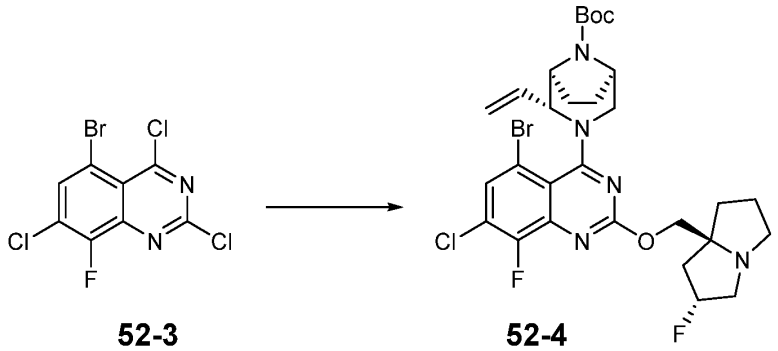
Intermediate 52-3: 5-bromo-2,4,7-trichloro-8-fluoroquinazoline



52-2 **52-3**

[0504] *N*,*N*-Diisopropylethylamine (802 µL, 4.60 mmol) was added via syringe to a mixture of **Intermediate 52-2** (310 mg, 1.06 mmol) and phosphorous(V) oxychloride (10 mL) at 100°C. After 20 min, the resulting mixture was cooled to room temperature and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 80% dichloromethane in hexanes) to give **Intermediate 52-3**. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.09 (d, J = 6.6 Hz, 1H).

Intermediate 52-4: tert-butyl (1*S*,2*R*,5*R*)-3-(5-bromo-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)quinazolin-4-yl)-2-vinyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

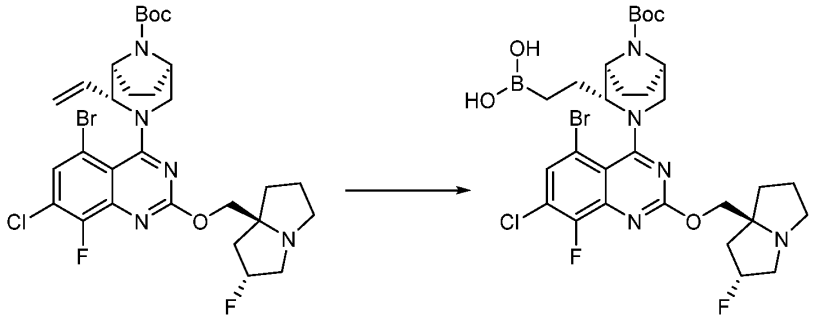


52-3 **52-4**

[0505] Intermediate 27-5 (72.1 mg, 303 µmol) and *N*,*N*-diisopropylethylamine (55.4 µL, 318 µmol) were added sequentially to a vigorously stirred solution of **Intermediate 52-3** (100 mg, 303 µmol) in dichloromethane (1.4 mL) at 0°C. After 30 min, citric acid (0.3 g), diethyl ether (40 mL), and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (2 × 30 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated

under reduced pressure. 2-Methyltetrahydrofuran (0.5 mL) and [(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (50.6 mg, 318 μmol) were added sequentially, and the resulting mixture was vigorously stirred at room temperature. Potassium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 318 μL, 320 μmol) was added over 1 min via syringe, and the resulting mixture was heated to 90°C. After 120 min, the resulting mixture was cooled to room temperature, and saturated aqueous sodium bicarbonate solution (5 mL), diethyl ether (40 mL), and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (20 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrate under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 5% methanol in dichloromethane) to give **Intermediate 52-4**. LCMS: 654.2.

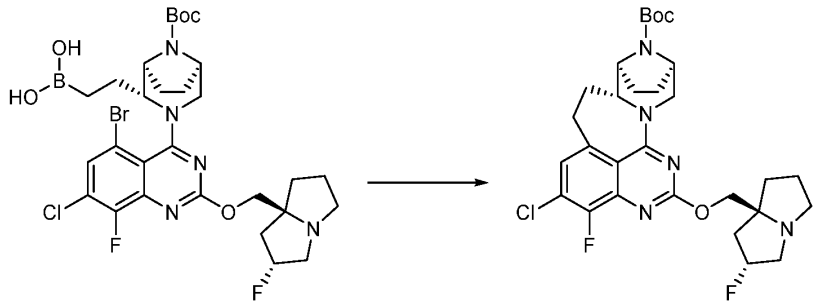
Intermediate 52-5: (2-((1*S*,2*R*,5*R*)-3-(5-bromo-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)quinazolin-4-yl)-8-(tert-butoxycarbonyl)-3,8-diazabicyclo[3.2.1]octan-2-yl)ethyl)boronic acid



52-4 **52-5**

[0506] 9-Borabicyclo[3.3.1]nonane solution (0.50 M in tetrahydrofuran, 759 μL, 380 μmol) was added via syringe to a vigorously stirred solution of **Intermediate 52-4** (82.8 mg, 126 μmol) in tetrahydrofuran (0.3 mL) at room temperature, and the resulting mixture was heated to 60°C. After 80 min, the resulting mixture was cooled to room temperature, and water (0.3 mL) was added via syringe. After 60 min, the resulting mixture was concentrated under reduced pressure, and the residue was purified by reverse phase preparative HPLC (0.1% trifluoroacetic acid in acetonitrile/water) to give **Intermediate 52-5**. LCMS: 700.2.

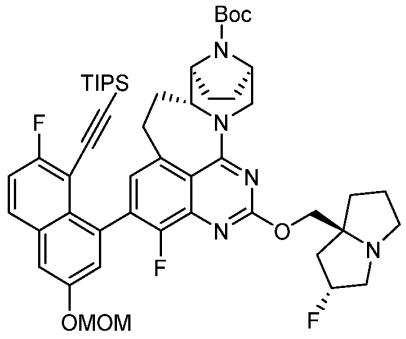
Intermediate 52-6: tert-butyl (1*S*,4*R*,14a*R*)-11-chloro-10-fluoro-8-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate



52-5 52-6

[0507] Aqueous potassium phosphate solution (1.5 M, 126 μL, 190 μmol) was added via syringe to a vigorously stirred mixture of **Intermediate 52-5** (40.7 mg, 58.1 μmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (4.6 mg, 6.3 μmol), and 1,4-dioxane (0.8 mL) at room temperature, and the resulting mixture was heated to 90°C. After 15 min, the resulting mixture was cooled to room temperature, and diethyl ether (40 mL) and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (20 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by reverse phase preparative HPLC (0.1% acetic acid in acetonitrile/water) to give **Intermediate 52-6**. LCMS: 576.2.

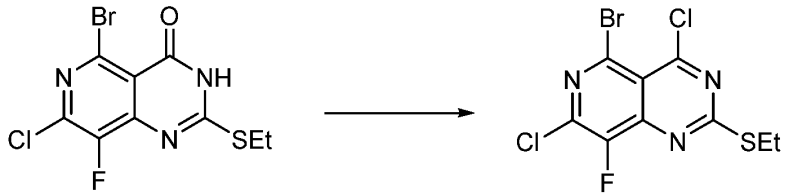
Intermediate 52-7: *tert*-butyl (1*S*,4*R*,14a*R*)-10-fluoro-11-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-8-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate



52-7

[0508] **Intermediate 52-7** was synthesized in a manner similar to **Intermediate 4-1** using **Intermediate 52-6** instead of **Intermediate 17-9** and using ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane instead of ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane. LCMS: 926.5.

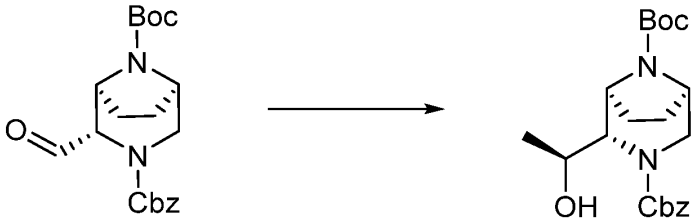
Intermediate 53-1: 5-bromo-4,7-dichloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidine



13-3 **53-1**

[0509] *N*,*N*-Diisopropylethylamine (884 μL, 5.08 mmol) was added via syringe to a mixture of **Intermediate 13-3** (839 mg, 2.48 mmol) and phosphorous(V) oxychloride (10 mL) at room temperature, and the resulting mixture was stirred at rt for 15 min before it was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 13% ethyl acetate in hexanes) to give **Intermediate 53-1**. LCMS: 357.9.

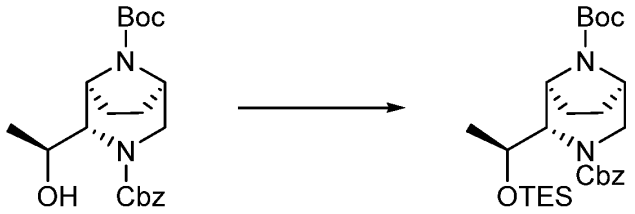
Intermediate 53-2: 3-benzyl 8-(tert-butyl) (1S,2S,5R)-2-((S)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



27-3 **53-2**

[0510] A solution of methyl magnesium bromide in 2-methyltetrahydrofuran (3.4 M, 424 μL, 1.44 mmol) was added via syringe to a mixture of **Intermediate 27-3** (180 mg, 0.481 mmol) in 2-methyltetrahydrofuran (4 mL) at -78°C. The resulting mixture was stirred at -78°C for 15 min before it was quenched with 5 mL of saturated aqueous solution of NH_4Cl. The mixture was extracted with EtOAc (2 × 10 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give **Intermediate 53-2**. LCMS: 391.1.

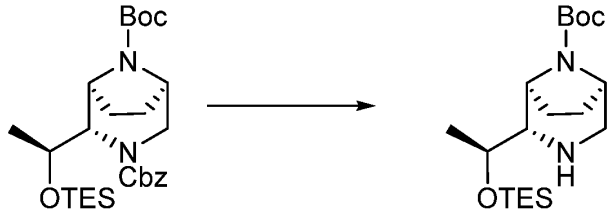
Intermediate 53-3: 3-benzyl 8-(tert-butyl) (1S,2S,5R)-2-((S)-1-((triethylsilyl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



53-2 **53-3**

[0511] Chlorotrimethylsilane (309 mg, 2.05 mmol) was added dropwise to the solution of **53-2** (320 mg, 0.820 mmol), imidazole (167 mg, 2.46 mmol) and DMAP (20 mg, 0.164 mmol) in DCM (4 mL) at 0°C. 10 mL of saturated aqueous solution of Na_2CO_3 was added. The mixture was extracted with EtOAc (2 × 15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (0 to 50% EtOAc in hexanes) to give **Intermediate 53-3**. LCMS: 505.5.

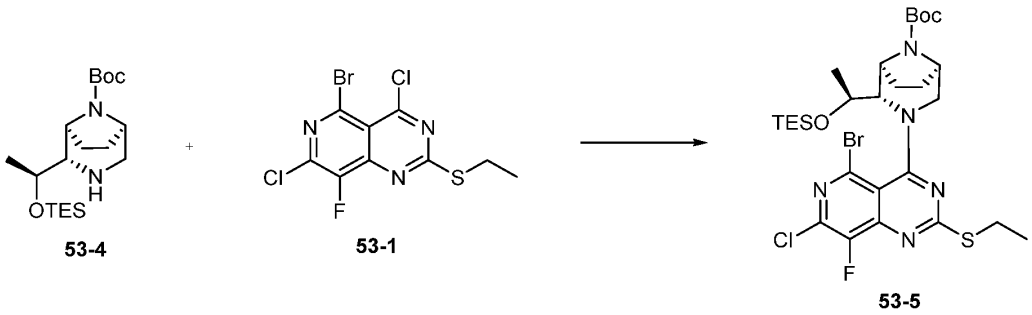
Intermediate 53-4: tert-butyl (1S,2S,5R)-2-((S)-1-((triethylsilyl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



53-3 **53-4**

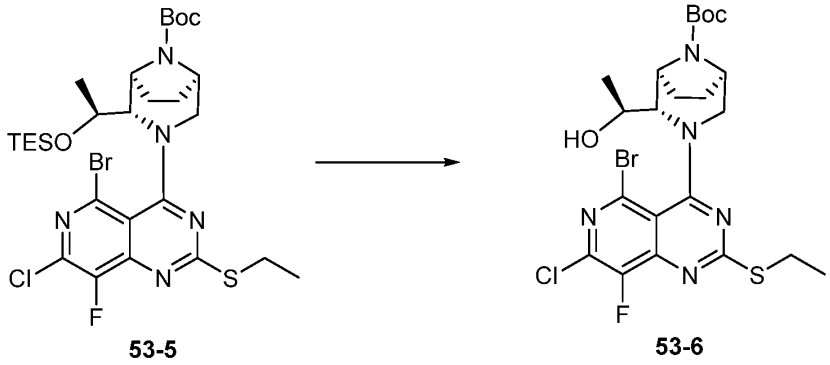
[0512] Intermediate 53-4 was synthesized in a manner similar to **Intermediate 27-5** using **Intermediate 53-3** instead of **Intermediate 27-4**. LCMS: 371.3.

Intermediate 53-5: tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-((S)-1-((triethylsilyl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



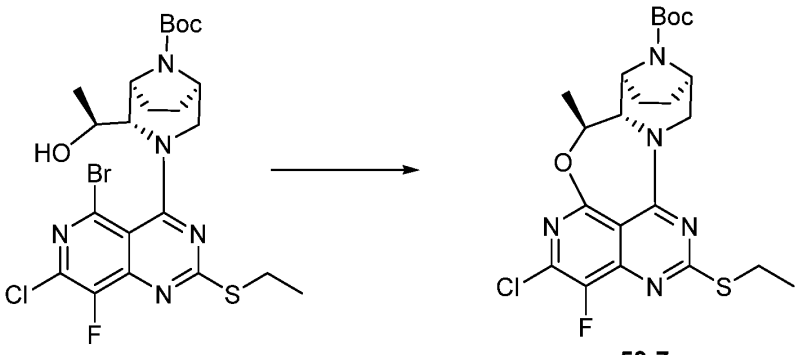
[0513] The solution of **Intermediate 53-4** (34.4 mg, 0.0924 mmol), **Intermediate 53-1** (30 mg, 0.0840 mmol) and DIPEA (35.4 mg, 0.274 mmol) in DCM (1 mL) was stirred at 60°C for 3 before it was cooled to rt. The mixture was purified by flash column chromatography on silica gel (0 to 80% EtOAc in hexanes) to give **Intermediate 53-5**. LCMS: 690.3, 692.2.

Intermediate 53-6: tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-((S)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



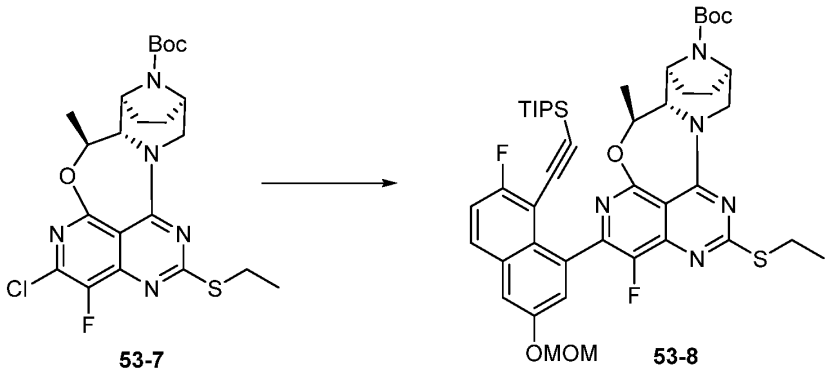
[0514] TBAF (1.0 M in THF, 0.579 mL) was added dropwise to the solution of **Intermediate 53-5** (100 mg, 0.145 mmol) in THF (2 mL) at 0°C. The reaction mixture was warmed to rt and stirred for 1 h. Saturated aqueous solution of NH_4Cl (20 mL) was added to the mixture. It was extracted with EtOAc (2 × 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% to 100% EtOAc in hexanes) to give **Intermediate 53-6**. LCMS: 576.2, 578.0.

Intermediate 53-7: tert-butyl (8S,8aS,9S,12R)-5-chloro-2-(ethylthio)-4-fluoro-8-methyl-8a,9,10,11,12,13-hexahydro-8H-7-oxa-1,3,6,13a,14-pentaaza-9,12-methanonaphtho[1,8-ab]heptalene-14-carboxylate



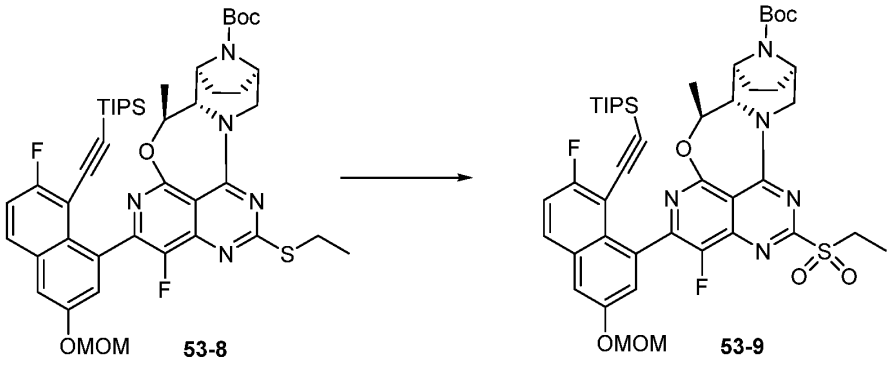
[0515] TBAF (1.0 M in THF, 0.217 mL) was added dropwise to the solution of the solution of **Intermediate 53-7** (50 mg, 0.0867) in THF at rt. The resulting solution was stirred at 75°C for 3 h before it was cooled to rt. Saturated aqueous solution of NH_4Cl (20 mL) was added to the mixture. It was extracted with EtOAc (2 × 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (30% to 100% EtOAc in hexanes) to give **Intermediate 53-7**. LCMS: 496.3.

Intermediate 53-8: tert-butyl (5S,5aS,6S,9R)-12-(ethylthio)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



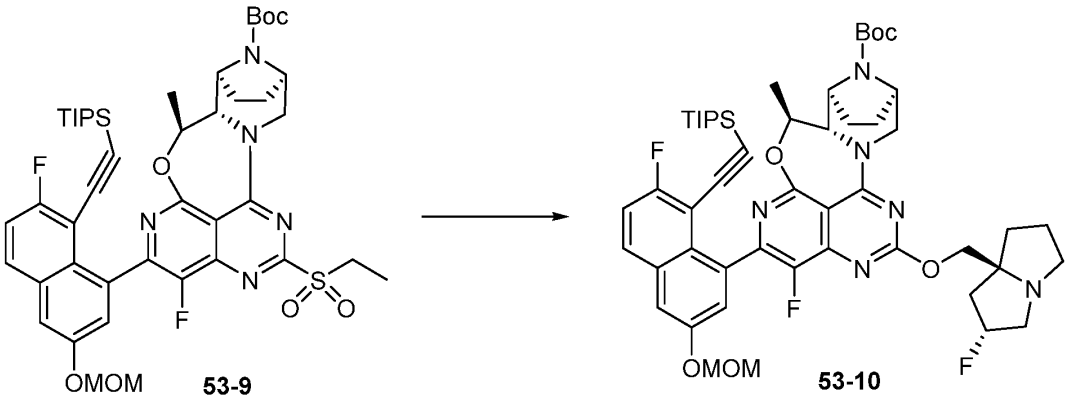
[0516] Intermediate 53-8 was synthesized in a manner similar to **Intermediate 13-8** using **Intermediate 53-7** instead of **Intermediate 13-7**. LCMS: 846.8.

Intermediate 53-9: tert-butyl (5S,5aS,6S,9R)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



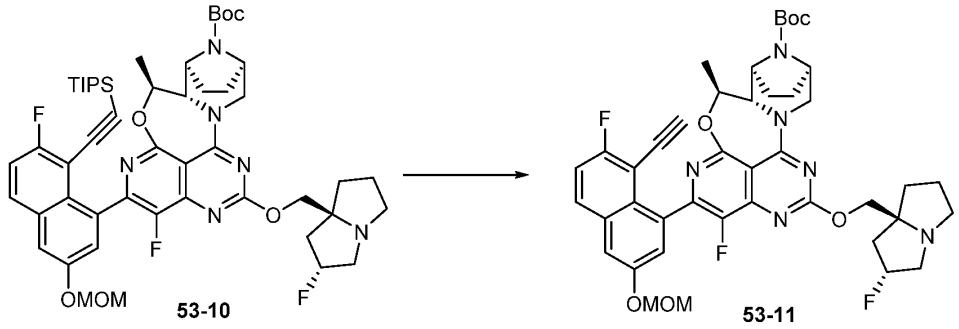
[0517] Intermediate 53-9 was synthesized in a manner similar to **Intermediate 13-9** using **Intermediate 53-8** instead of **Intermediate 13-8**. LCMS: 878.4.

Intermediate 53-10: tert-butyl (5S,5aS,6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



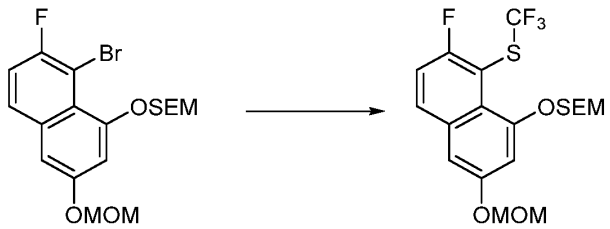
[0518] Intermediate 53-10 was synthesized in a manner similar to **Intermediate 13-10** using **Intermediate 53-9** and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol instead of **Intermediate 13-9** and **Intermediate 13-14**. LCMS: 943.6.

Intermediate 53-11: tert-butyl (5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0519] **Intermediate 53-11** was synthesized in a manner similar to **Intermediate 13-11** using **Intermediate 53-10** instead of **Intermediate 13-10**. LCMS: 787.0.

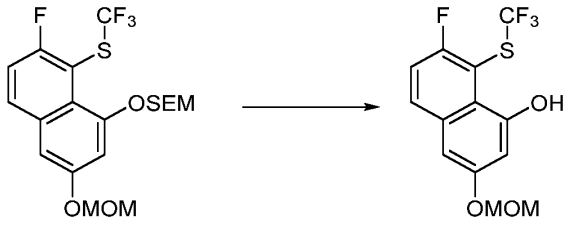
Intermediate 54-1: (2-(((7-fluoro-3-(methoxymethoxy)-8-((trifluoromethyl)thio)naphthalen-1-yl)oxy)methoxy)ethyl)trimethylsilane



[0520] Isopropylmagnesium chloride lithium chloride complex solution (1.3 M in tetrahydrofuran, 297 μL, 390 μmol) was added over 1 min via syringe to a stirred solution of **Intermediate 14-2** (111 mg, 257 μmol) in tetrahydrofuran (0.40 mL) at −40°C. After 50 min, the resulting mixture was cooled to −78°C over 10 min, and 1,2-bis(trifluoromethyl)disulfane (104 μL, 772 μmol) was added over 1 min via syringe. The resulting mixture was allowed to warm to −60°C over 180 min. The resulting mixture was warmed to room temperature. After 30 min, saturated aqueous ammonium chloride solution (5 mL), diethyl ether (40 mL), and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (35 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 8.5% ethyl acetate in hexanes) to give **Intermediate 54-1**. ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.13 (dd, J = 9.1, 5.7

Hz, 1H), 7.51 (dd, J = 9.1, 8.3 Hz, 1H), 7.25 (d, J = 2.4 Hz, 1H), 7.18 (dd, J = 2.4, 0.8 Hz, 1H), 5.49 (s, 2H), 5.34 (s, 2H), 3.98 – 3.87 (m, 2H), 3.50 (s, 3H), 1.08 – 0.99 (m, 2H), 0.03 (s, 9H).

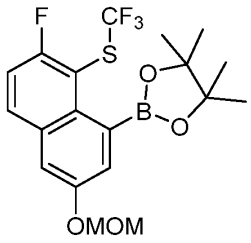
Intermediate 54-2: 7-fluoro-3-(methoxymethoxy)-8-((trifluoromethyl)thio)naphthalen-1-ol



54-1 **54-2**

[0521] Tetrabutylammonium fluoride solution (1.0 M in tetrahydrofuran, 2.56 mL, 2.6 mmol) was added via syringe to a stirred mixture of **Intermediate 54-1** (116 mg, 256 μmol) and 3-methylpentane-2,4-dione (29.8 μL, 256 μmol) at room temperature, and the resulting mixture was heated to 60°C. After 13 min, the resulting mixture was heated to 80°C. After 104 min, the resulting mixture was cooled to room temperature, and diethyl ether (60 mL), citric acid (25 mg), and saturated aqueous ammonium chloride solution (10 mL) were added sequentially. The organic layer was washed with water (2 × 40 mL), was dried over anhydrous magnesium sulfate, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 15% ethyl acetate in hexanes) to give **Intermediate 54-2**. LCMS: 321.0 $[M-H]^-$.

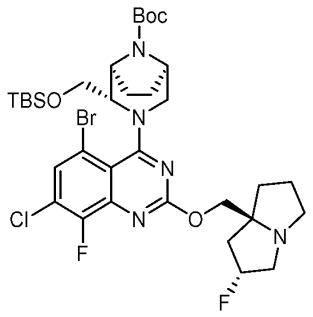
Intermediate 54-3: 2-(7-fluoro-3-(methoxymethoxy)-8-((trifluoromethyl)thio) naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



54-3

[0522] Intermediate 54-3 was synthesized in a manner similar to **Intermediate 7-5** using **Intermediate 54-2** instead of **Intermediate 7-3**. LCMS: 401.1 $[M-CH_3O]^+$.

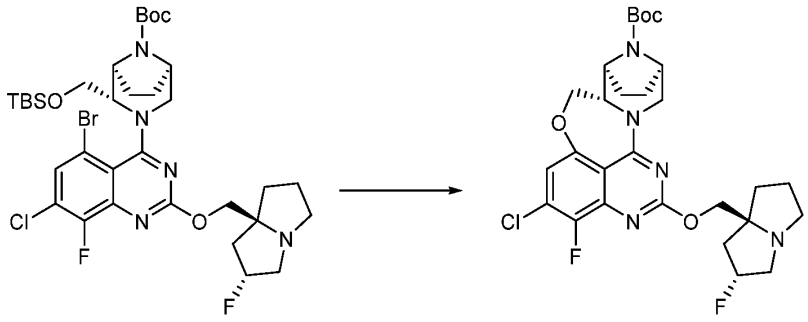
Intermediate 57-1: tert-butyl (1*S*,2*S*,5*R*)-3-(5-bromo-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)quinazolin-4-yl)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



57-1

[0523] Intermediate 57-1 was synthesized in a manner similar to **Intermediate 52-4** using **Intermediate 17-7** instead of **Intermediate 27-5**. LCMS: 772.2.

Intermediate 57-2: tert-butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-13-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazoline-15-carboxylate

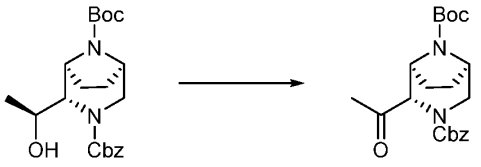


57-1 **57-2**

[0524] Tetrabutylammonium fluoride solution (1.0 M in tetrahydrofuran, 500 µL, 500 µmol) was added via syringe to a stirred solution of **Intermediate 57-1** (48.8 mg, 63.1 µmol) in tetrahydrofuran (0.5 mL) at room temperature. After 3 h, diethyl ether (40 mL), ethyl acetate (20 mL), saturated aqueous ammonium chloride solution (3 mL), and saturated aqueous sodium carbonate solution (10 mL) were added sequentially. The organic layer was washed with water (2 × 40 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. Cesium carbonate (61.7 mg, 189 µmol), *rac*-BINAP-Pd-G3 (3.1 mg, 3.2 µmol), and toluene (1.0 mL) were added sequentially, and the resulting mixture was heated to 90°C. After

25 min, the resulting mixture was heated to 115°C. After 150 min, the resulting mixture was cooled to room temperature and was filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by reverse phase preparative HPLC (0.1% acetic acid in acetonitrile/water) to give **Intermediate 57-2**. LCMS: 578.2.

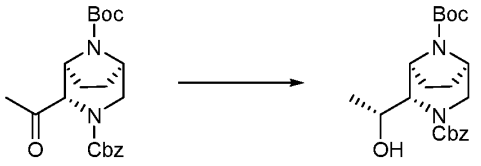
Intermediate 61-1: 3-benzyl 8-(tert-butyl) (1S,2S,5R)-2-acetyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



53-2 61-1

[0525] Intermediate **61-1** was synthesized in a manner similar to **27-3** using intermediate **53-2** instead of intermediate **27-2**. LCMS: 389.1.

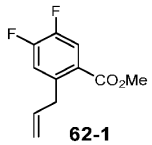
Intermediate 61-2: 3-benzyl 8-(tert-butyl) (1S,2S,5R)-2-((R)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



61-1 61-2

[0526] Sodium borohydride (69.6 mg, 1.84 mmol) was added in small portions to the solution of intermediate **61-1** (650 mg, 1.67 mmol) in THF (3 mL) and MeOH (3 mL) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 30 min before it was quenched with saturated aqueous solution of NH_4Cl (20 mL). The mixture was extracted with EtOAc (3 × 40 mL). The combined organic phase was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (0 to 40% ethyl acetate in hexanes) to give intermediate **61-2**. LCMS: 413.2 $[M+Na]^+$.

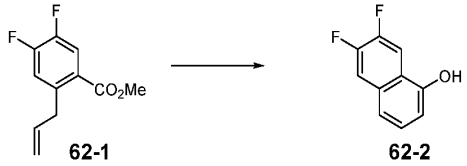
Intermediate 62-1: methyl 2-allyl-4,5-difluorobenzoate



62-1

[0527] Intermediate **62-1** was synthesized in a manner similar to intermediate **7-2** using methyl 2-bromo-4,5-difluorobenzoate instead of intermediate **7-1** and using allyl bromide instead of 3-chloro-2-(methoxymethoxy)prop-1-ene. LCMS: 213.0.

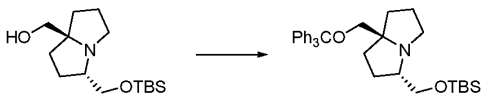
Intermediate 62-2: 6,7-difluoronaphthalen-1-ol



62-1 62-2

[0528] A solution of intermediate **62-2** (200 mg, 943 μmol) in 2-methyltetrahydrofuran (4 mL) was added over 60 min via syringe pump to a vigorously stirred mixture of potassium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 2.36 mL, 2.4 mmol) and 2-methyltetrahydrofuran (16 mL) at 70 °C. After 10 min, the resulting mixture was cooled to room temperature, acetic acid (162 μL, 2.83 mmol) was added via syringe, and the resulting mixture was concentrated under reduced pressure. Methanol (20 mL) and acetic acid (540 μL, 9.43 mmol) were added sequentially. After 20 min, the resulting mixture was concentrated under reduced pressure, and diethyl ether (100 mL), ethyl acetate (25 mL), and saturated aqueous sodium bicarbonate solution (20 mL) were added sequentially. The organic layer was washed with water (60 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 15% ethyl acetate in hexanes) to give intermediate **62-2**. LCMS: 179.0 $[M-H]^-$.

Intermediate 63-1: (3*S*,7a*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-7a-((trityloxy)methyl)hexahydro-1*H*-pyrrolizine



63-1

[0529] Triphenylmethyl chloride (1.17 g, 4.20 mmol) was added to a vigorously stirred mixture of ((3*S*,7a*S*)-3-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (1.00 g, 3.50 mmol), triethylamine (770 μL, 5.25 mmol), 4-(dimethylamino)pyridine (85.6 mg, 701 μmol), and dichloromethane (5.0 mL) at room temperature, and the resulting mixture was heated to 40 °C. After 95 min, the resulting mixture was heated to 65 °C. After 120 min, the resulting mixture was cooled to room temperature, and diethyl ether (100 mL) and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (100 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 5% methanol in dichloromethane) to give intermediate **63-1**. LCMS: 528.3.

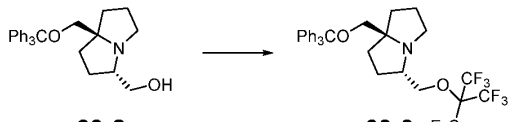
Intermediate 63-2: ((3*S*,7a*S*)-7a-((trityloxy)methyl)hexahydro-1*H*-pyrrolizin-3-yl)methanol



63-1 **63-2**

[0530] Tetrabutylammonium fluoride solution (1.0 M in tetrahydrofuran, 10.5 mL, 11 mmol) was added via syringe to a stirred solution of intermediate **63-1** (1.16 g, 2.20 mmol) in tetrahydrofuran (2.0 mL) at room temperature. After 30 min, the resulting mixture was heated to 50 °C. After 15 min, the resulting mixture was cooled to room temperature, and diethyl ether (100 mL), ethyl acetate (20 mL), saturated aqueous ammonium chloride solution (2.0 mL), and saturated aqueous sodium carbonate solution (10 mL) were added sequentially. The organic layer was washed with water (2 × 100 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 100% methanol in dichloromethane) to give intermediate **63-2**. LCMS: 414.2.

Intermediate 63-3: (3*S*,7a*S*)-3-(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)-7a-((trityloxy)methyl)hexahydro-1*H*-pyrrolizine

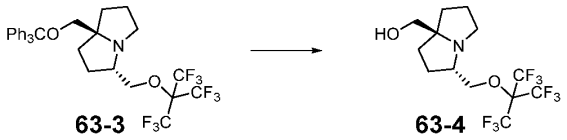


63-2 **63-3**

[0531] Trimethylphosphine solution (1.0 M in tetrahydrofuran, 2.70 mL, 2.7 mmol) was added over 2 min via syringe to a stirred mixture of intermediate **63-2** (447 mg, 1.08 mmol), di-*tert*-butyl (*E*)-diazene-1,2-dicarboxylate (622 mg, 2.70 mmol), 1,1,1,3,3,3-hexafluoro-2-

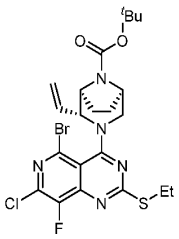
(trifluoromethyl)propan-2-ol (753 μL, 5.40 mmol), and tetrahydrofuran (4.0 mL) at 0 °C, and the resulting mixture was warmed to room temperature. After 7 min, the resulting mixture was heated to 70 °C. After 53 min, the resulting mixture was heated to 90 °C. After 40 min, the resulting mixture was cooled to room temperature and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 5% methanol in dichloromethane) to give intermediate **63-3**. LCMS: 632.2.

Intermediate 63-4: ((3*S*,7a*S*)-3-(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol



[0532] Concentrated hydrochloric acid (346 μL, 4.2 mmol) was added via syringe to a stirred solution of intermediate **63-3** (524 mg, 830 μmol) in methanol (4.0 mL) at room temperature, and the resulting mixture was heated to 60 °C. After 70 min, the resulting mixture was cooled to room temperature. Triethylamine (1.0 mL) was added via syringe, and the resulting mixture was concentrated under reduced pressure. Saturated aqueous sodium carbonate (10 mL) and water were added sequentially. The aqueous layer was extracted with dichloromethane (4 × 35 mL). The combined organic layers were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 100% methanol in dichloromethane) to give intermediate **63-4**. LCMS: 390.1.

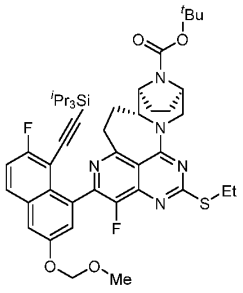
Intermediate 63-5: *tert*-butyl (1*S*,2*R*,5*R*)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-vinyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



63-5

[0533] Intermediate **63-5** was synthesized in a manner similar to intermediate **13-6** using intermediate **27-5** instead of intermediate **13-5**. LCMS: 560.0.

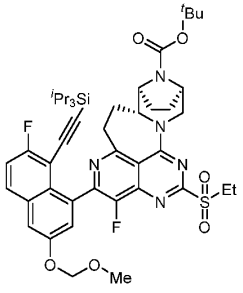
Intermediate 63-6: *tert*-butyl (5a*R*,6*S*,9*R*)-12-(ethylthio)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



63-6

[0534] Intermediate **63-6** was synthesized in a manner similar to intermediate **52-7** using intermediate **63-5** instead of intermediate **52-4**. LCMS: 830.5.

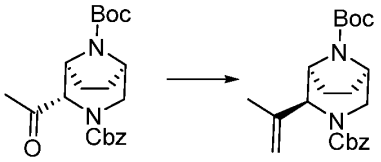
Intermediate 63-7: *tert*-butyl (5a*R*,6*S*,9*R*)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



63-7

[0535] Intermediate **63-7** was synthesized in a manner similar to intermediate **13-9** using intermediate **63-6** instead of intermediate **13-8**. LCMS: 862.4.

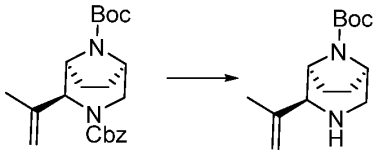
Intermediate 64-1: 3-benzyl 8-(tert-butyl) (1S,2S,5R)-2-(prop-1-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



61-1 64-1

[0536] Intermediate **64-1** was synthesized in a manner similar to **27-4** using intermediate **61-1** instead of intermediate **27-3**. LCMS: 387.0.

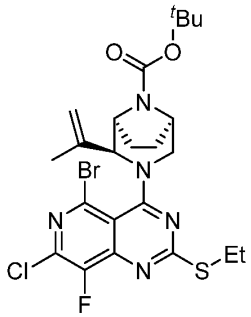
Intermediate 64-2: tert-butyl (1S,2S,5R)-2-(prop-1-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



64-1 64-2

[0537] Intermediate **64-2** was synthesized in a manner similar to **27-5** using intermediate **64-1** instead of intermediate **27-4**. LCMS: 252.9.

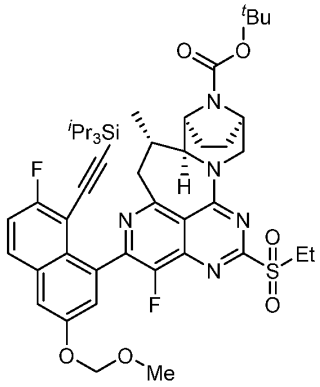
Intermediate 64-3: tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-(prop-1-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



64-3

[0538] Intermediate **64-3** was synthesized in a manner similar to **63-5** using intermediate **64-2** instead of intermediate **13-6**. LCMS: 572.4, 574.0.

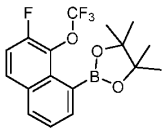
Intermediate 64-4: tert-butyl (5S,5aS,6S,9R)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



64-4

[0539] Intermediate **64-4** was synthesized in a manner similar to **63-7** using intermediate **64-3** instead of intermediate **63-5**. LCMS: 876.4.

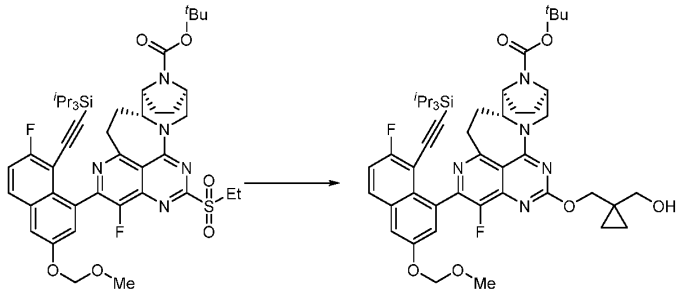
Intermediate 65-1: 2-(7-fluoro-8-(trifluoromethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



65-1

[0540] Intermediate **65-1** was synthesized in a manner similar to intermediate **7-5** using allyl bromide instead of 3-chloro-2-(methoxymethoxy)prop-1-ene. LCMS: 357.1.

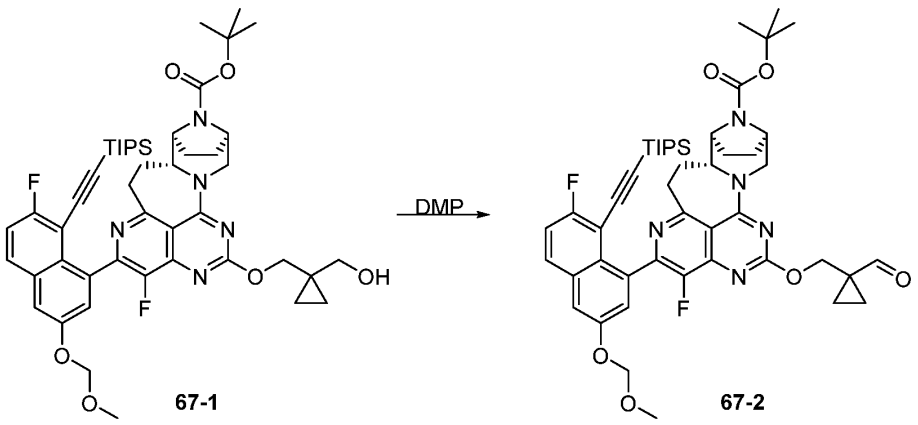
Intermediate 67-1: tert-butyl (5aR,6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-((1-(hydroxymethyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



63-7 67-1

[0541] Intermediate **67-1** was synthesized in a manner similar to intermediate **35-1** using intermediate **63-7** instead of intermediate **13-9**. LCMS: 870.5.

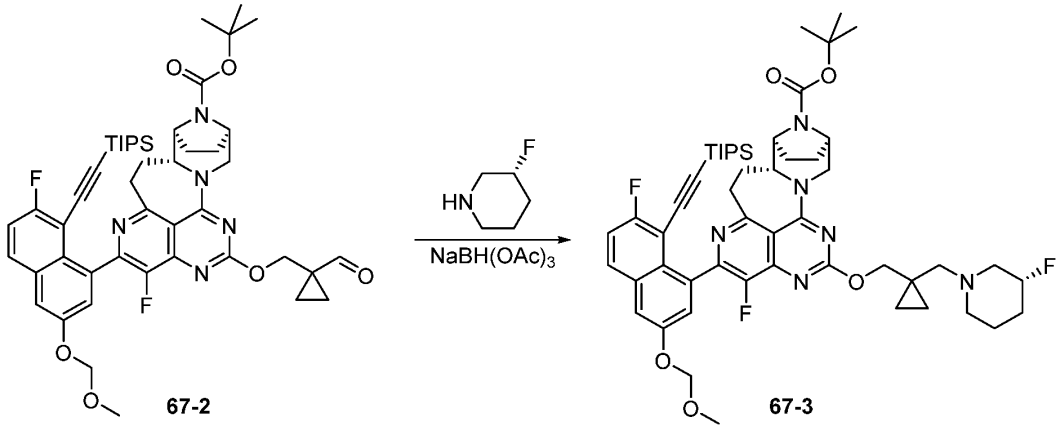
Intermediate 67-2: tert-butyl (5aR,6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-((1-formylcyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



67-1 67-2

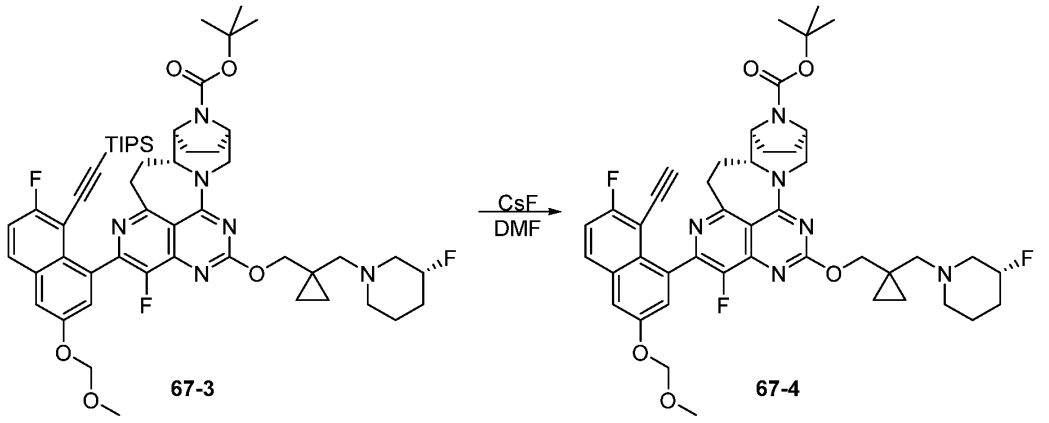
[0542] Intermediate **67-2** was synthesized in a manner similar to intermediate **35-2** using intermediate **67-1** instead of intermediate **35-1**. LCMS: 868.5.

Intermediate 67-3: tert-butyl (5aR,6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-((1-(((R)-3-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



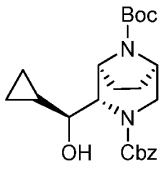
[0543] Intermediate **67-3** was synthesized in a manner similar to intermediate **35-3** using intermediate **67-2** instead of intermediate **35-2** and using (*R*)-3-fluoropiperidine instead of 1,4-oxazepane. LCMS: 955.6.

Intermediate 67-4: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-((1-(((R)-3-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0544] Intermediate **67-4** was synthesized in a manner similar to intermediate **35-4** using intermediate **67-3** instead of intermediate **35-3**. LCMS: 799.4.

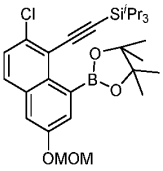
Intermediate 71-1: 3-benzyl 8-(*tert*-butyl) (1*S*,2*S*,5*R*)-2-((*S*)-cyclopropyl(hydroxy)methyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



71-1

[0545] Intermediate **71-1** was synthesized in a manner similar to intermediate **53-2** using cyclopropyl magnesium bromide instead of methyl magnesium bromide. LCMS: 439.2 $[M+Na]^+$.

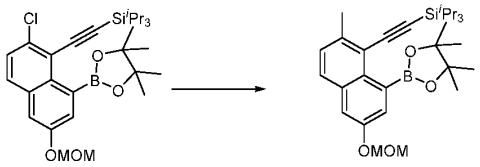
Intermediate 73-1: ((2-chloro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane



73-1

[0546] Example 73-1 was synthesized in a manner similar to intermediate **30-4** using methyl 2-bromo-5-chlorobenzoate instead of methyl 2-bromo-4,5-difluorobenzoate. LCMS: 529.3.

Intermediate 73-2: triisopropyl((6-(methoxymethoxy)-2-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane

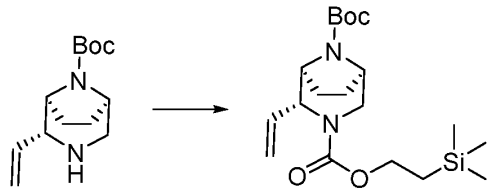


73-1 73-2

[0547] Tetramethyltin (65.5 µL, 473 µmol) was added via syringe to a vigorously stirred mixture of intermediate **73-1** (50.0 mg, 94.5 µmol), [(di(1-adamantyl)-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate (6.9 mg, 9.5 µmol), cesium carbonate (7.7 mg, 24 µmol), and *N*,*N*-dimethylformamide (0.7 mL) at room temperature, and the resulting mixture was heated to 90 °C. After 90 min, the resulting mixture was cooled to room temperature, and diethyl

ether (40 ml), ethyl acetate (20 mL), and saturated aqueous ammonium chloride solution (1 mL) were added sequentially. The organic layer was washed with water (2 × 40 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 7% ethyl acetate in hexanes) to give intermediate **73-2**. LCMS: 509.1.

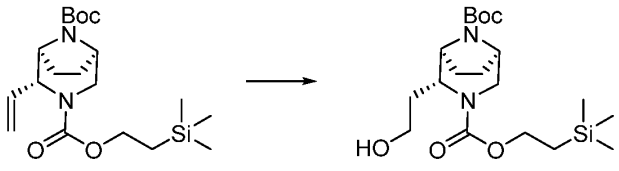
Intermediate 75-1 8-(*tert*-butyl) 3-(2-(trimethylsilyl)ethyl) (1*S*,2*R*,5*R*)-2-vinyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



27-5 **75-1**

[0548] To a vigorously stirred solution of **Intermediate 27-5** (1.00 g, 4.20 mmol) and (2,5-dioxopyrrolidin-1-yl) 2-trimethylsilylethyl carbonate (1.14 g, 4.41 mmol) in dichloromethane (13.9 mL) was added 4-methylmorpholine (0.46 mL, 4.20 mmol) slowly with stirring at room temperature. The resulted solution was stirred at room temperature for 72 hours. The mixture was washed with water (15 mL) and extracted with ethyl acetate (3 x 30 mL). The organic layer was collected and combined, dried over magnesium sulfate, concentrated under reduced pressure to give a liquid. The liquid was purified by silica gel column chromatography (0 to 50% ethyl acetate in hexanes) to give **Intermediate 75-1**. LCMS: 405.1 $[M+Na]^+$.

Intermediate 75-2 8-(*tert*-butyl) 3-(2-(trimethylsilyl)ethyl) (1*S*,2*R*,5*R*)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate

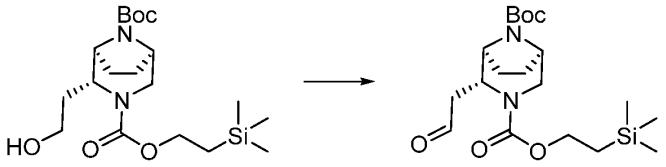


75-1 **75-2**

[0549] To a vigorously stirred solution of **Intermediate 75-1** (50.0 mg, 0.13 mmol) in tetrahydrofuran (1.5 mL) was added the solution of 9-borabicyclo[3.3.1]nonane (0.50 M in tetrahydrofuran, 0.4 mL, 0.20 mmol) dropwise at 0°C. The resulted solution was stirred at 50°C

for 45 minutes. Then hydrogen peroxide (50%wt in water, 0.2 mL, 0.13 mmol) and sodium hydroxide (20 mg, 0.33 mmol) were added at room temperature and the resulting mixture was stirred at room temperature for 30 minutes then quenched with saturated sodium thiosulfate solution (1.5 mL) at 0°C. The mixture was extracted with dichloromethane (3 x 10 mL). The organic layer was collected and combined, dried over magnesium sulfate, concentrated under reduced pressure to give a liquid. The liquid was purified by silica gel column chromatography (0 to 100% ethyl acetate in hexanes) to give **Intermediate 75-2**. LCMS: 400.7 $[M+H]^+$, 423.1 [M+Na]+.

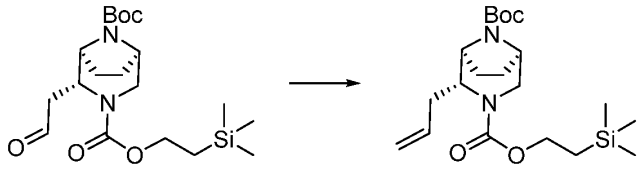
Intermediate 75-3 8-(*tert*-butyl) 3-(2-(trimethylsilyl)ethyl) (1*S*,2*R*,5*R*)-2-(2-oxoethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



75-2 **75-3**

[0550] To a vigorously stirred solution of **Intermediate 75-2** (0.55 g, 1.37 mmol) in dichloromethane (5 mL) under nitrogen was added Dess Martin periodinane (0.64 g, 1.51 mmol) at room temperature. The mixture was stirred at room temperature for 12 hours before saturated aqueous sodium bicarbonate (10 mL) was added. The mixture was extracted with ethyl acetate (3 × 10 mL) and the combined organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0% to 50% ethyl acetate in hexanes) to give **Intermediate 75-3**. LCMS: 421.1 $[M+Na]^+$.

Intermediate 75-4 8-(*tert*-butyl) 3-(2-(trimethylsilyl)ethyl) (1*S*,2*R*,5*R*)-2-allyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate

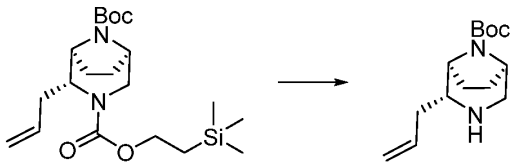


75-3 **75-4**

[0551] To a vigorously stirred solution of methyltriphenylphosphonium bromide (1.29 g, 3.62 mmol) in tetrahydrofuran (5.8 mL) at room temperature was added KHMDS solution (1.0 M in

tetrahydrofuran, 3.30 mL, 3.30 mmol) dropwise to afford a solution. The mixture was stirred for 1 hour at room temperature and was cooled to -78°C whereupon a solution of **Intermediate 75-3** (0.44 g, 1.10 mmol) in tetrahydrofuran (5.8 mL) was added dropwise over 20 minutes. The resulting solution was allowed to gradually warm to room temperature and stir for 3 hours. The mixture was quenched with methanol (10 mL) and stirred for 15 min. Saturated aqueous ammonium chloride solution (12 mL) was added and the mixture was extracted with ethyl acetate (3 × 12 mL). The combined organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0% to 40% ethyl acetate in hexanes) to give **Intermediate 75-4**. LCMS: 419.2 $[M+Na]^+$.

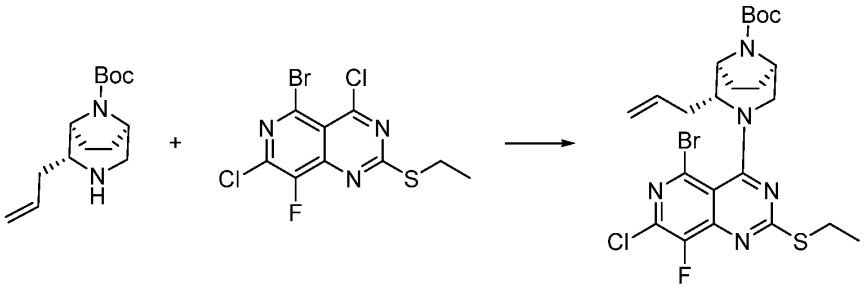
Intermediate 75-5 *tert*-butyl (1*S*,2*R*,5*R*)-2-allyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



75-4 **75-5**

[0552] Cesium fluoride (95.8 mg, 0.63 mmol) was added to a vigorously stirred solution of **Intermediate 75-4** (50.0 mg, 0.13 mmol) in *N*,*N*-dimethylformamide (0.8 mL) at room temperature. The resulting mixture was stirred at 90°C for 30 minutes. After cooled to room temperature, the mixture was filtered, washed by dichloromethane (5 mL), and the filtrate was concentrated under reduced pressure to give crude product of **Intermediate 75-5**, which was used for the next step without purification. LCMS: 253.0.

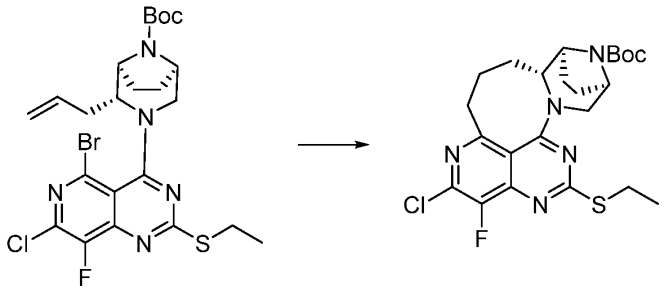
Intermediate 75-6 tert-butyl (1S,2R,5R)-2-allyl-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



75-5 **53-1** **75-6**

[0553] A mixture of **Intermediate 75-5** (230 mg, 0.911 mmol), **Intermediate 53-1** (342 mg, 0.957 mmol) and DIPEA (384 mg, 2.97 mmol) in DCM (1.3 mL) was stirred at room temperature for 24 minutes. The mixture was purified by flash column chromatography on silica gel (0 to 80% EtOAc in hexanes) to give **Intermediate 75-6**. LCMS: 574.0.

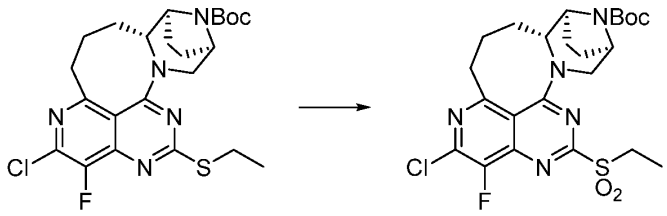
Intermediate 75-7 *tert*-butyl (6a*R*,7*S*,10*R*)-2-chloro-13-(ethylthio)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate



75-6 **75-7**

[0554] To a vigorously stirred solution of **Intermediate 75-6** (30.0 mg, 0.052 mmol) in anhydrous 1,4-dioxane (0.5 mL), the solution of 9-borabicyclo[3.3.1]nonane (0.50 M in tetrahydrofuran, 0.12 mL, 0.06 mmol) was added at room temperature. The resulting solution was stirred at 50 °C for 1 hour before it was cooled to room temperature. The solution was transferred to a reaction vial containing $Pd(dppf)Cl_2$ (3.70 mg, 0.0052 mmol), potassium phosphate (36.6 mg, 0.16 mmol) and degassed water (0.1 mL) at rt under nitrogen atmosphere. The reaction mixture was stirred at 90°C for 10 minutes before it was cooled to room temperature. The mixture was washed with water (2 mL) and extracted with ethyl acetate (3 x 5 mL). The organic layer was collected and combined, dried over magnesium sulfate, concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0 to 50% ethyl acetate in hexanes) to give **Intermediate 75-7**. LCMS: 494.1.

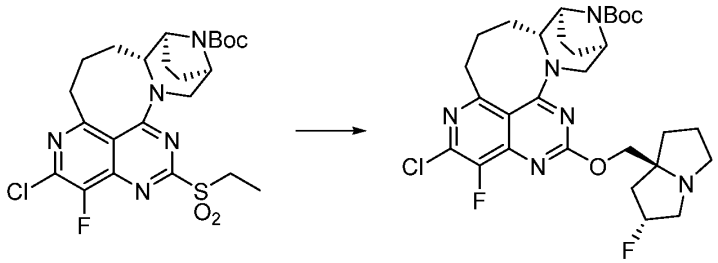
Intermediate 75-8 ***tert*-butyl (6a*R*,7*S*,10*R*)-2-chloro-13-(ethylsulfonyl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate**



75-7 **75-8**

[0555] Intermediate 75-8 was synthesized in a manner similar to **Intermediate 13-9** using **Intermediate 75-7** instead of **Intermediate 13-8**. LCMS: 526.1.

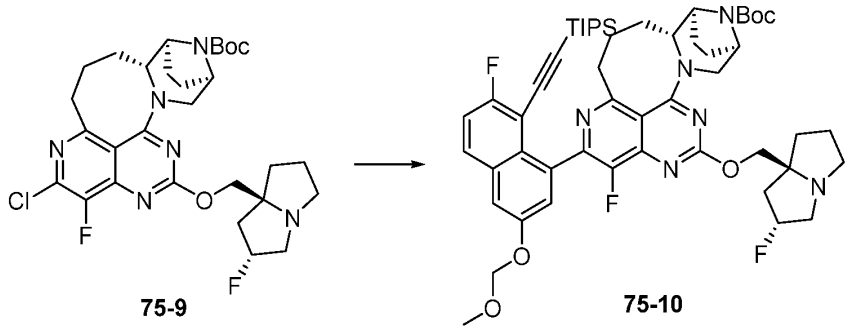
Intermediate 75-9 ***tert*-butyl (6a*R*,7*S*,10*R*)-2-chloro-1-fluoro-13-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate**



75-8 **75-9**

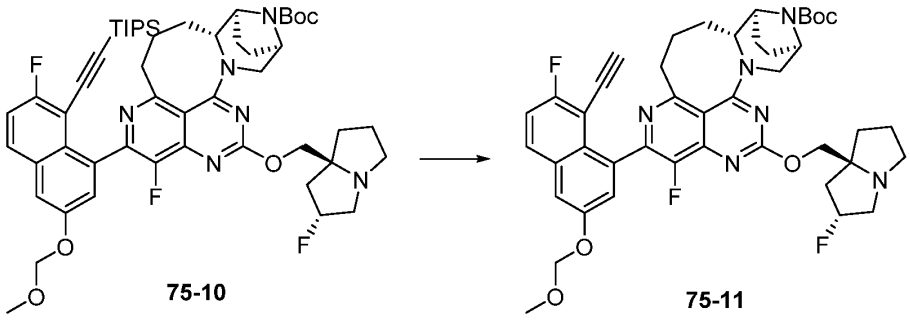
[0556] Intermediate 75-9 was synthesized in a manner similar to **Intermediate 53-10** using **Intermediate 75-8** instead of **Intermediate 53-9**. LCMS: 591.2.

Intermediate 75-10 ***tert*-butyl (6a*R*,7*S*,10*R*)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate**



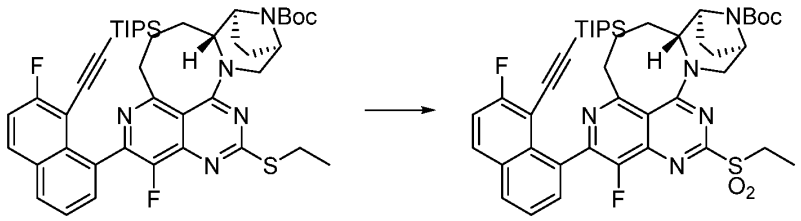
[0557] Intermediate 75-10 was synthesized in a manner similar to **Intermediate 2-1** using **Intermediate 75-9** instead of **Intermediate 17-9**. LCMS: 941.3.

Intermediate 75-11 ***tert*-butyl (6a*R*,7*S*,10*R*)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-13-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate**



[0558] Intermediate 75-11 was synthesized in a manner similar to Intermediate 13-11 using Intermediate 75-10 instead of Intermediate 13-10. LCMS: 784.9.

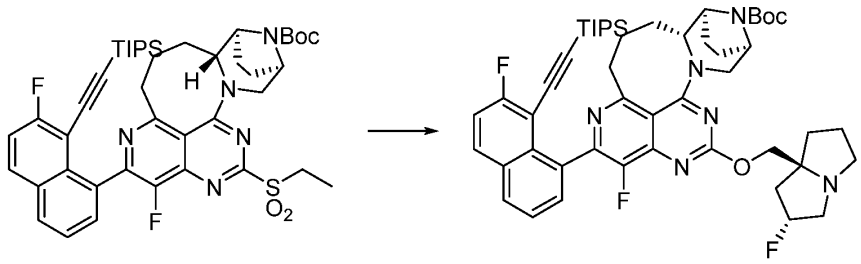
Intermediate 76-0 *tert*-butyl (6a*R*,7*S*,10*R*)-13-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate



115-1 76-0

[0559] 3-Chloroperoxybenzoic acid (77% wt, 4590 mg, 20.5 mmol) was added in two equal portions over 5 min to a vigorously stirred solution of **Intermediate 115-1** (7.30 g, 9.31 mmol) in dichloromethane (131 mL) at 0°C. After 125 min, the resulting mixture was warmed to room temperature. The residue was purified by flash column chromatography on silica gel (0% to 75% ethyl acetate in hexanes) to give **Intermediate 76-0**. LCMS: 816.4.

Intermediate 76-1 *tert*-butyl (6a*R*,7*S*,10*R*)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate

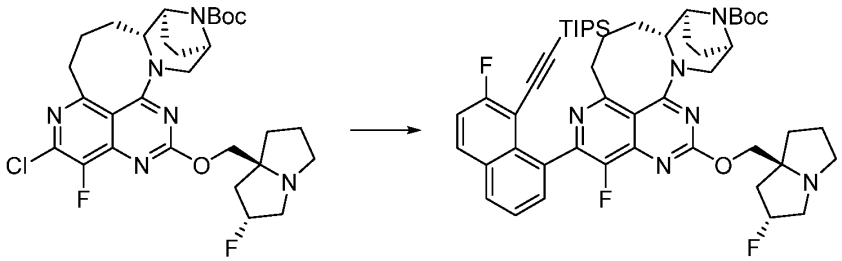


76-0 76-1

[0560] Lithium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 1.84 mL, 1.84 mmol) was added over 1 min via syringe to a stirred mixture of **Intermediate 76-0** (1000 mg, 1.23 mmol), [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (725.4 mg, 4.56 mmol), and 2-methyltetrahydrofuran (25.8 mL) 0°C. After 2 hours, ethyl acetate (20 mL), and water (5 mL) were added sequentially at 0°C. The aqueous layer was washed with ethyl acetate (3 × 20 mL).

The organic layers were combined and dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure to give **Intermediate 76-1**. LCMS: 881.1.

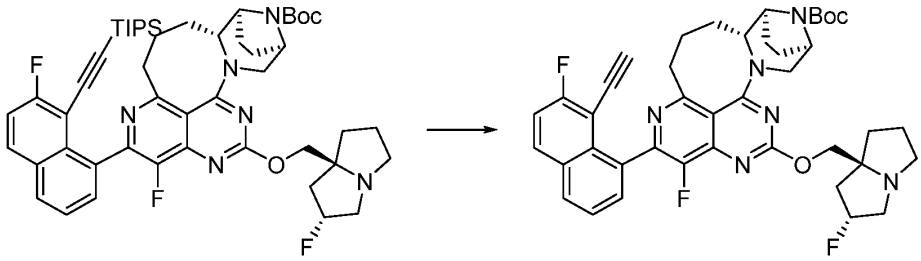
Intermediate 76-1 *tert*-butyl (6a*R*,7*S*,10*R*)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate



75-9 **76-1**

[0561] Intermediate 76-1 was synthesized in a manner similar to **Intermediate 4-1** using **Intermediate 75-9** instead of **Intermediate 17-9**. LCMS: 881.1.

Intermediate 76-2 *tert*-butyl (6a*R*,7*S*,10*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate

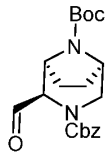


76-1 **76-2**

[0562] Cesium fluoride (37.8 mg, 0.249 mmol) was added to a vigorously stirred solution of **Intermediate 76-1** (21.9 mg, 24.9 μmol) in *N*,*N*-dimethylformamide (0.6 mL) at room temperature. After 1 hour, diethyl ether (4 mL), ethyl acetate (2 mL), and saturated aqueous sodium bicarbonate solution (1 mL) were added sequentially. The organic layer was washed with water (2 × 4 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated

under reduced pressure. The residue was purified by silica gel column chromatography (0 to 60% ethyl acetate in hexanes) to give **Intermediate 76-2**. LCMS: 724.9.

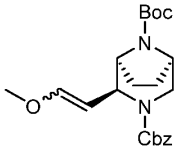
Intermediate 77-1: 3-benzyl 8-(tert-butyl) (1S,2R,5R)-2-formyl-3,8-diazabicyclo [3.2.1]octane-3,8-dicarboxylate



77-1

[0563] Intermediate **77-1** was synthesized in a manner similar to intermediate **27-3** using 8-(tert-butyl) 2-ethyl (1S,2R,5R)-4-oxo-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate instead of 8-(tert-butyl) 2-ethyl (1S,2S,5R)-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate. LCMS: 375.2

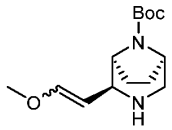
Intermediate 77-2: 3-benzyl 8-(tert-butyl) (1S,2S,5R)-2-(2-methoxyvinyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate:



77-2

[0564] Methoxymethyl(triphenyl)phosphonium bromide (1.03 g, 2.67 mmol) was dissolved in10 ml of THF and cooled to -78 °C. To it was added KHMDS solution (1 M in THF, 2.67 ml, 2.67 mmol). The reaction mixture was stirred vigorously 15 minutes then warmed to 0 °C and stirred vigorously for 30 minutes. To it was dropwise added a solution of O3-benzyl O8-tert-butyl (1S,2R,5R)-2-formyl-3,8-diazabicyclo [3.2.1] octane-3,8-dicarboxylate (500 mg, 1.34 mmol) in 10 ml of THF. After stirring vigorously for 8 minutes, the mixture was warmed to room temperature, and stirred for overnight. The mixture was diluted with ethyl ether and quenched the reaction with water. The organic layer was separated and the aqueous phase extracted with EtOAc. The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography over silica gel gave intermediate **77-2**. LCMS: 403.3.

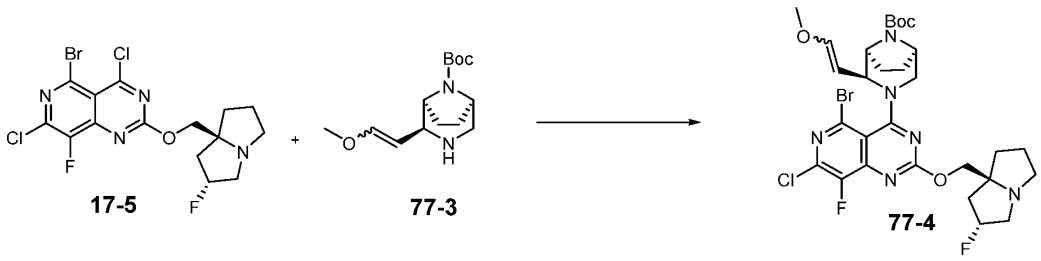
Intermediate 77-3: tert-butyl (1S,2S,5R)-2-(2-methoxyvinyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



77-3

[0565] Intermediate **77-3** was synthesized in a manner similar to intermediate **27-5** using intermediate **77-2** instead of intermediate **27-4**. LCMS: 269.2

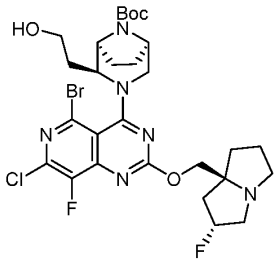
Intermediate 77-4: tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-(2-methoxyvinyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



17-5 **77-3** **77-4**

[0566] Intermediate **77-4** was synthesized in a manner similar to intermediate **17-8** using intermediate **77-3** instead of intermediate **17-7**. LCMS: 687.2

Intermediate 77-5: tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

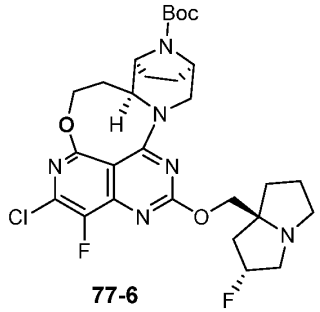


77-5

[0567] Intermediate 77-4 (22 mg, 0.032 mmol) was dissolved in 1 ml of DCM and to it was added 0.1 ml of HCl solution (4 N, in 1,4-dioxane). It was concentrated to dryness after 5 minutes; then

dissolved in 1.5 ml of THF and to it was added sodium borohydride (12.1 mg, 0.32 mmol), stirred at room temperature for 1hour. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate and water, dried (MgSO4), filtered and concentrated. The residue was purified by RP-HPLC. LCMS: 674.2

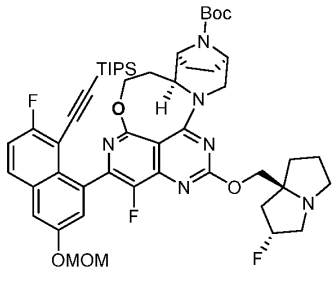
Intermediate 77-6: tert-butyl (6aS,7S,10R)-2-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



77-6

[0568] Intermediate **77-6** was synthesized in a manner similar to intermediate **18-4** using intermediate **77-5** instead of intermediate **18-3**. LCMS: 593.3

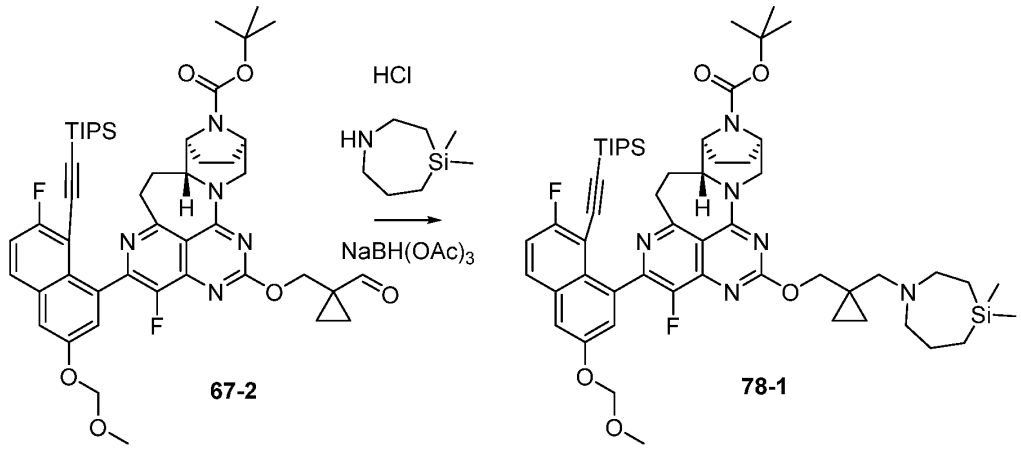
Intermediate 77-7: tert-butyl (6aS,7S,10R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



77-7

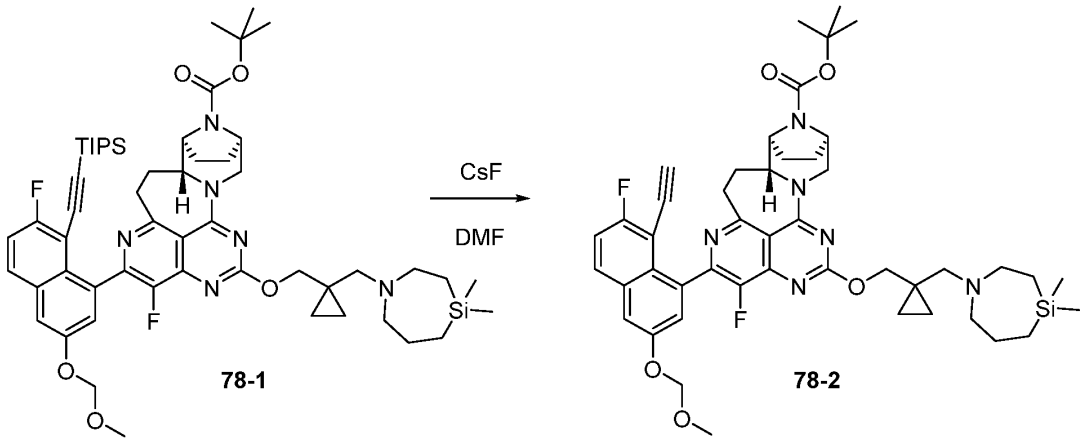
[0569] Intermediate **77-7** was synthesized in a manner similar to intermediate **2-1** using intermediate **77-6** instead of intermediate **17-9**. LCMS: 943.6

Intermediate 78-1: tert-butyl (5aR,6S,9R)-12-((1-((4,4-dimethyl-1,4-azasilepan-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



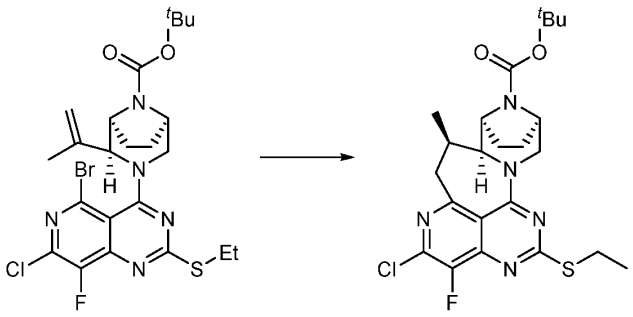
[0570] Intermediate 78-1 was synthesized in a manner similar to intermediate **67-3** using 4,4-dimethyl-1,4-azasilepane hydrochloride instead of (R)-3-fluoropiperidine. LCMS: 995.6.

Intermediate 78-2: tert-butyl (5aR,6S,9R)-12-((1-((4,4-dimethyl-1,4-azasilepan-1-yl)methyl)cyclopropyl)methoxy)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0571] Intermediate **78-2** was synthesized in a manner similar to intermediate **35-4.** LCMS: 839.5.

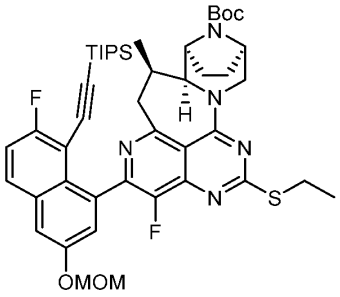
Intermediate 79-1: tert-butyl (5R,5aS,6S,9R)-2-chloro-12-(ethylthio)-1-fluoro-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



64-3 79-1

[0572] To a solution of $[Ir(cod)Cl]_2$ (25.6 mg, 34.9 μmol) and 1,2-bis(diphenylphosphino)ethane(27.8 mg, 69.8 μmol) in THF (2 mL) was added pinacolborane (223 mg, 1.75 mmol) and intermediate **64-3** (200 mg, 349 μmol). The reaction mixture was stirred under N_2 atmosphere at 70℃ overnight before it was quenched with MeOH (0.2 mL). After evaporation of the volatile components, the residue was purified with flash chromatography on silica gel (0 to 30% ethyl acetate in hexanes) to give the boronate intermediate. $Pd(dppf)Cl_2$ (12 mg, 0.17 mmol) and potassium phosphate tribasic monohydrate (120 mg, 0.514 mmol) were added to a vial containing the boronate intermediate. The reaction vial was flushed with N_2. Dioxane (2 mL) and water (0.5) were added, and the resulting mixture was stirred at 90℃ under N_2 for 20 min before it was cooled to rt. Water (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified with flash chromatography on silica gel (0 to 50% ethyl acetate in hexanes) to give the intermediate **79-1**. LCMS: 494.0 $[M+H]^+$.

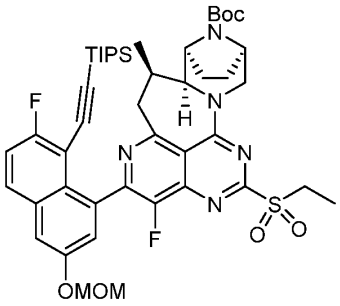
Intermediate 79-2: tert-butyl (5R,5aS,6S,9R)-12-(ethylthio)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



79-2

[0573] Intermediate 79-2 was synthesized in a manner similar to **Intermediate 75-10** using **Intermediate 79-1** instead of **Intermediate 75-9**. LCMS: 844.4 $[M+H]^+$.

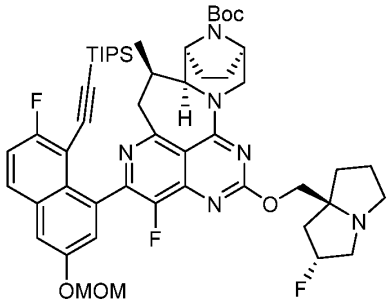
Intermediate 79-3: tert-butyl (5R,5aS,6S,9R)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



79-3

[0574] Intermediate 79-3 was synthesized in a manner similar to **Intermediate 75-8** using **Intermediate 79-2** instead of **Intermediate 75-7**. LCMS: 876.3 $[M+H]^+$.

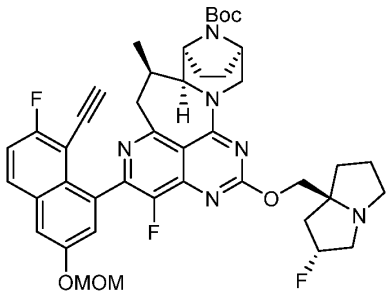
Intermediate 79-4: tert-butyl (5R,5aS,6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



79-4

[0575] Intermediate 79-4 was synthesized in a manner similar to **Intermediate 75-9** using **Intermediate 79-3** instead of **Intermediate 75-8**. LCMS: 941.0 $[M+H]^+$.

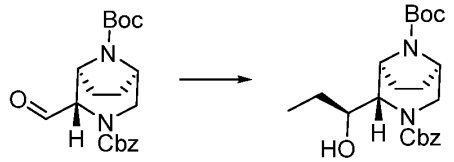
Intermediate 79-5: tert-butyl (5R,5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



79-5

[0576] Intermediate 79-5 was synthesized in a manner similar to **Intermediate 75-11** using **Intermediate 79-4** instead of **Intermediate 75-11**. LCMS: 784.9 $[M+H]^+$

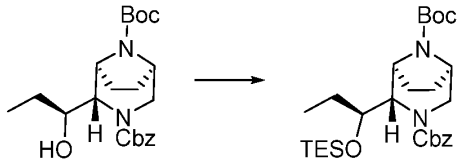
Intermediate 80-1 3-benzyl 8-(*tert*-butyl) (1*S*,2*S*,5*R*)-2-((*S*)-1-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



27-3 80-1

[0577] Intermediate 80-1 was synthesized in a manner similar to **Intermediate 53-2** using ethyl magnesium bromide instead of methyl magnesium bromide. LCMS: 427.2 $[M+Na]^+$.

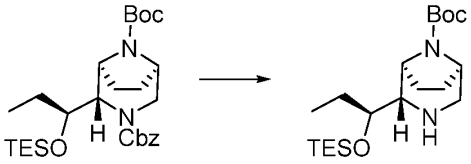
Intermediate 80-2 3-benzyl 8-(*tert*-butyl) (1*S*,2*S*,5*R*)-2-((*S*)-1-((triethylsilyl)oxy)propyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



80-1 80-2

[0578] Intermediate 80-2 was synthesized in a manner similar to **Intermediate 53-3** using **Intermediate 80-1** instead of **Intermediate 53-2**. LCMS: 520.6 $[M+H]^+$, 541.9 $[M+Na]^+$.

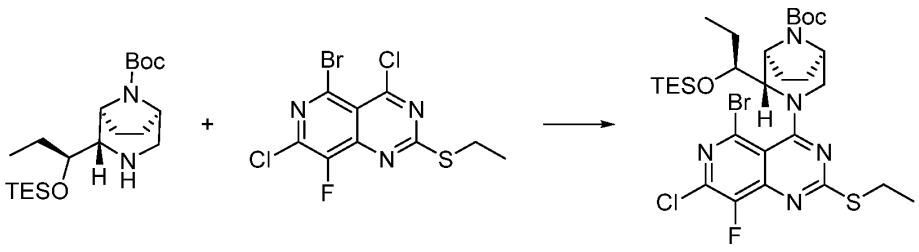
Intermediate 80-3 *tert*-butyl (1*S*,2*S*,5*R*)-2-((*S*)-1-((triethylsilyl)oxy)propyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



80-2 80-3

[0579] Intermediate 80-3 was synthesized in a manner similar to **Intermediate 53-4** using **Intermediate 80-2** instead of **Intermediate 53-3**. LCMS: 385.3.

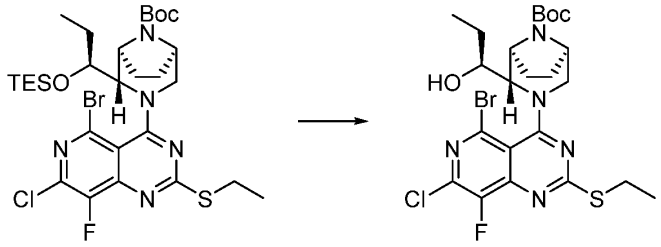
Intermediate 80-4 *tert*-butyl (1*S*,2*S*,5*R*)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-2-((*S*)-1-((triethylsilyl)oxy)propyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



80-3 53-1 80-4

[0580] Intermediate 80-4 was synthesized in a manner similar to **Intermediate 53-5** using **Intermediate 80-3** instead of **Intermediate 53-4**. LCMS: 706.4.

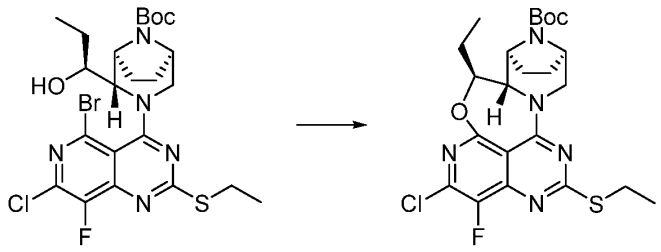
Intermediate 80-5 tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-((S)-1-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



80-4 80-5

[0581] Intermediate 80-5 was synthesized in a manner similar to **Intermediate 53-6** using **Intermediate 80-4** instead of **Intermediate 53-5**. LCMS: 592.0.

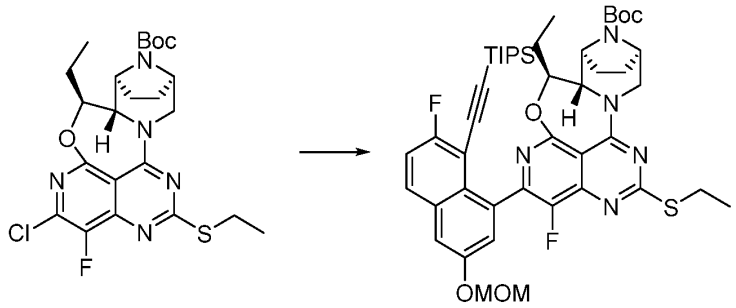
Intermediate 80-6 *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-5-ethyl-12-(ethylthio)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



80-5 80-6

[0582] Intermediate 80-6 was synthesized in a manner similar to **Intermediate 53-7** using **Intermediate 80-5** instead of **Intermediate 53-6**. LCMS: 510.6.

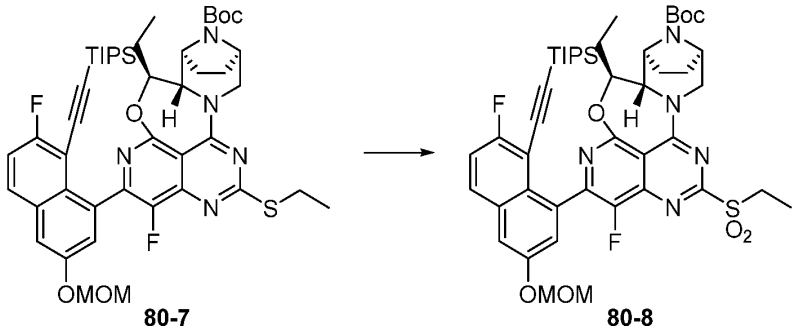
Intermediate 80-7 *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-ethyl-12-(ethylthio)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



80-6 80-7

[0583] Intermediate 80-7 was synthesized in a manner similar to **Intermediate 13-8** using **Intermediate 80-6** instead of **Intermediate 13-7**. LCMS: 861.0.

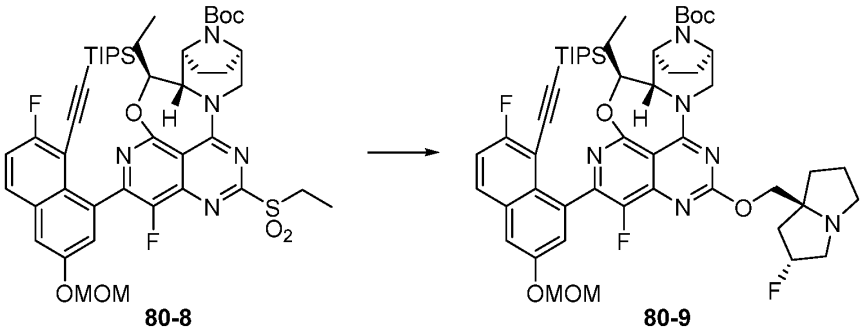
Intermediate 80-8 ***tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-ethyl-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



80-7 **80-8**

[0584] Intermediate 80-8 was synthesized in a manner similar to **Intermediate 13-9** using **Intermediate 80-7** instead of **Intermediate 13-8**. LCMS: 892.8.

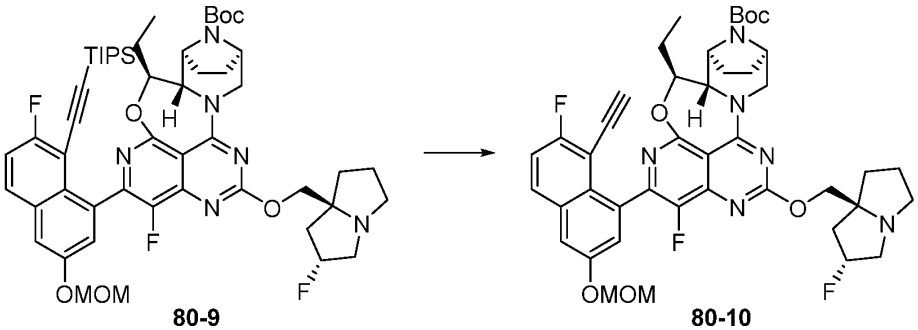
Intermediate 80-9 ***tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-ethyl-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



80-8 **80-9**

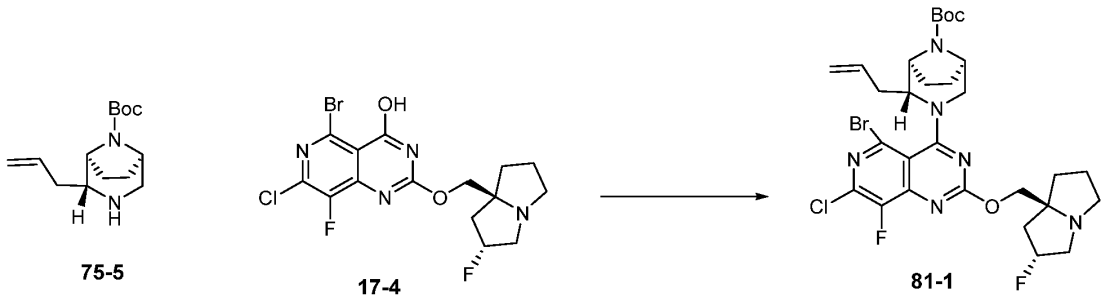
[0585] Intermediate 80-9 was synthesized in a manner similar to **Intermediate 13-10** using **Intermediate 80-8** instead of **Intermediate 13-9**. LCMS: 957.7.

Intermediate 80-10 ***tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-ethyl-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



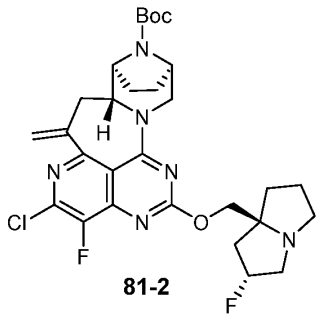
[0586] Intermediate 80-10 was synthesized in a manner similar to **Intermediate 13-11** using **Intermediate 80-9** instead of **Intermediate 13-10**. LCMS: 801.1.

Intermediate 81-1: tert-butyl (1S,2R,5R)-2-allyl-3-(5-bromo-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate:



[0587] Intermediate **81-1** was synthesized in a manner similar to intermediate **27-6** using intermediate **75-5** instead of intermediate **27-5**. LCMS: 671.2

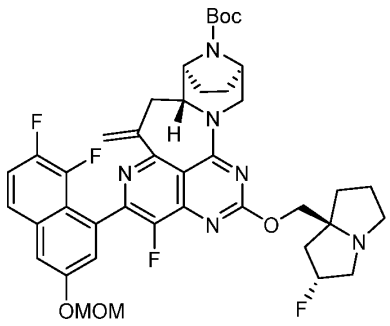
Intermediate 81-2: tert-butyl (5aR,6S,9R)-2-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methylene-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate:



81-2

[0588] The reaction mixture of **81-1** (20 mg, 0.0299 mmol), $Pd(dppf)Cl_2$ (4.37 mg, 0.006 mmol), and cesium carbonate (29.2mg, 0.089 mmol) in THF (2 mL) and water (0.5 mL) was stirred under N_2 atmosphere at 90 °C for 30 minutes before it was cooled to room temperature. Water was added, and the mixture was extracted with EtOAc. The combined organic phase was washed with brine, dried over with Na_2SO_4, filtered and concentrated. The residue was purified by reverse phase preparative HPLC (0.1% trifluoroacetic acid in acetonitrile/water) to give intermediate **81-2**. LCMS: 589.3

Intermediate 81-3: tert-butyl (5aR,6S,9R)-2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methylene-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate:

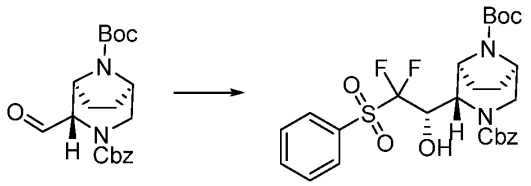


81-3

[0589] Intermediate **81-3** was synthesized in a manner similar to **Intermediate 13-8** using intermediate **81-2** instead of intermediate **13-7** and using 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane instead of ((2-

fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane. LCMS: 777.4

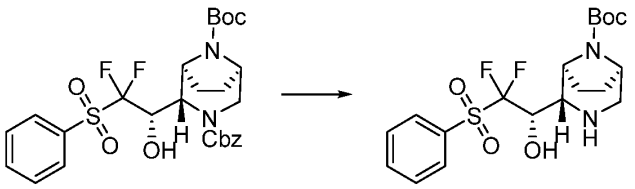
Intermediate 82-1 3-benzyl 8-(*tert*-butyl) (1*S*,2*S*,5*R*)-2-((*S*)-2,2-difluoro-1-hydroxy-2-(phenylsulfonyl)ethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



27-3 82-1

[0590] Lithium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 0.2 mL, 0.2 mmol) was added dropwise to a vigorously stirred solution of **Intermediate 27-3** (37.4 mg, 0.1 mmol) and difluoromethylsulfonylbenzene (19.2 mg, 0.1 mmol) in tetrahydrofuran (0.6 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 1 hour before it was quenched with saturated aqueous ammonium chloride solution (2 mL) at -78 °C. The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0% to 70% ethyl acetate in hexanes) to give **Intermediate 82-1**. LCMS: 589.1 $[M+Na]^+$.

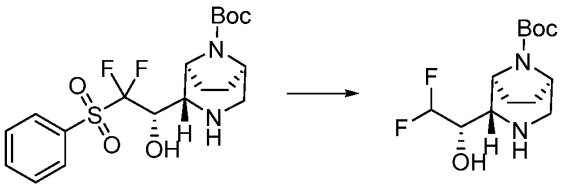
Intermediate 82-2 *tert*-butyl (1*S*,2*S*,5*R*)-2-((*S*)-2,2-difluoro-1-hydroxy-2-(phenylsulfonyl)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



82-1 82-2

[0591] Intermediate 82-2 was synthesized in a manner similar to **Intermediate 53-4** using **Intermediate 82-1** instead of **Intermediate 53-3**. LCMS: 432.9.

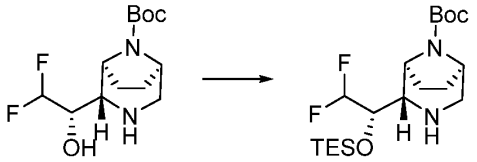
Intermediate 82-3 *tert*-butyl (1*S*,2*S*,5*R*)-2-((*S*)-2,2-difluoro-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



82-2 82-3

[0592] Sodium hydrogen phosphate (37.3 mg, 0.26 mmol) and sodium mercury amalgam (57.7 mg, 0.26 mmol) were added to a vigorously stirred solution of **Intermediate 82-2** (18.6 mg, 0.043 mmol) in methanol (1.0 mL) at -41 °C. The reaction mixture was warmed up to room temperature and stirred at room temperature overnight before it was filtered through celite. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0% to 10% methanol in dichloromethane) to give **Intermediate 82-3**. LCMS: 292.9.

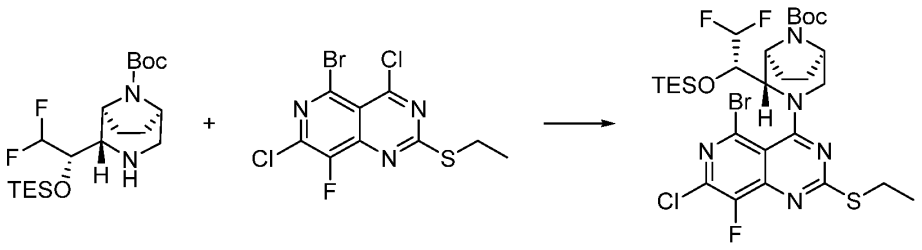
Intermediate 82-4 *tert*-butyl (1*S*,2*S*,5*R*)-2-((*S*)-2,2-difluoro-1-((triethylsilyl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



82-3 82-4

[0593] Intermediate 82-4 was synthesized in a manner similar to **Intermediate 53-3** using **Intermediate 82-3** instead of **Intermediate 53-2**. LCMS: 407.2.

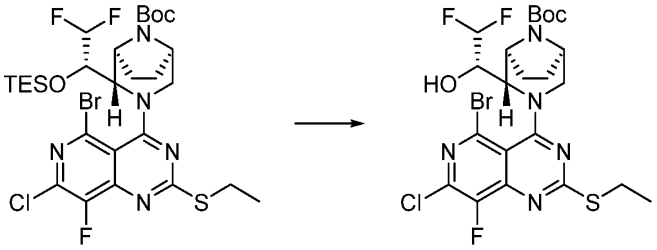
Intermediate 82-5 ***tert*-butyl (1*S*,2*S*,5*R*)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-2-((*S*)-2,2-difluoro-1-((triethylsilyl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**



82-4 53-1 82-5

[0594] Intermediate 82-5 was synthesized in a manner similar to **Intermediate 53-5** using **Intermediate 82-4** instead of **Intermediate 53-4**. LCMS: 728.0.

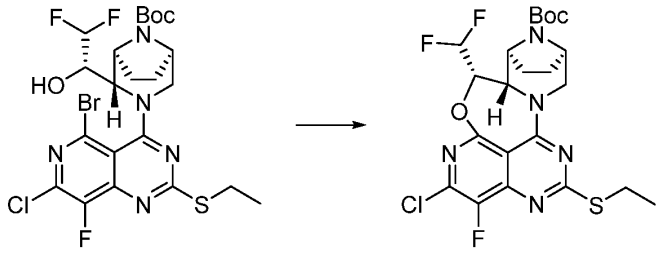
Intermediate 82-6 ***tert*-butyl (1*S*,2*S*,5*R*)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-2-((*S*)-2,2-difluoro-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**



82-5 82-6

[0595] Intermediate 82-6 was synthesized in a manner similar to **Intermediate 53-6** using **Intermediate 82-5** instead of **Intermediate 53-5**. LCMS: 613.8.

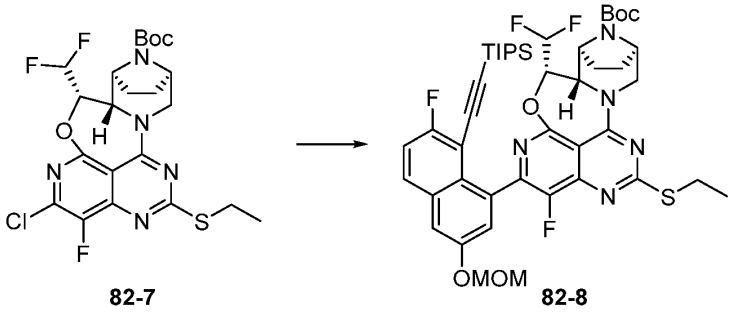
Intermediate 82-7 ***tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-5-(difluoromethyl)-12-(ethylthio)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



82-6 82-7

[0596] Intermediate 82-7 was synthesized in a manner similar to **Intermediate 53-7** using **Intermediate 82-6** instead of **Intermediate 53-6**. LCMS: 532.4.

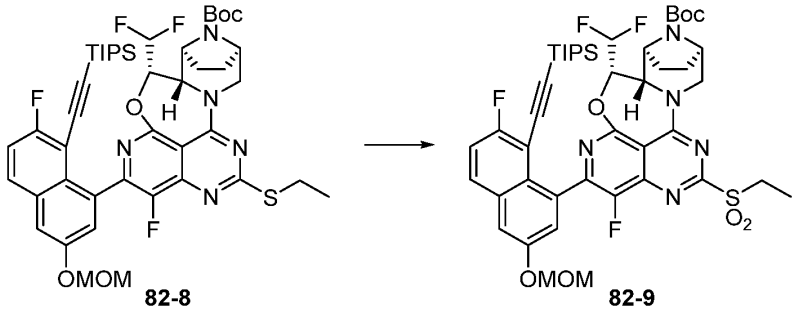
Intermediate 82-8 ***tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-(difluoromethyl)-12-(ethylthio)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



82-7 82-8

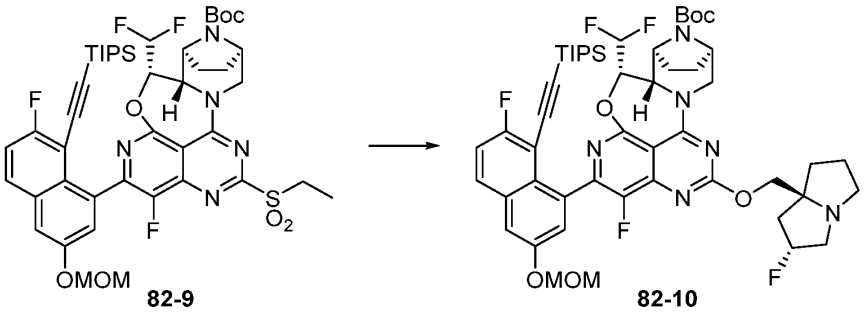
[0597] Intermediate 82-8 was synthesized in a manner similar to **Intermediate 53-8** using **Intermediate 82-7** instead of **Intermediate 53-7**. LCMS: 886.2.

Intermediate 82-9 ***tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-(difluoromethyl)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



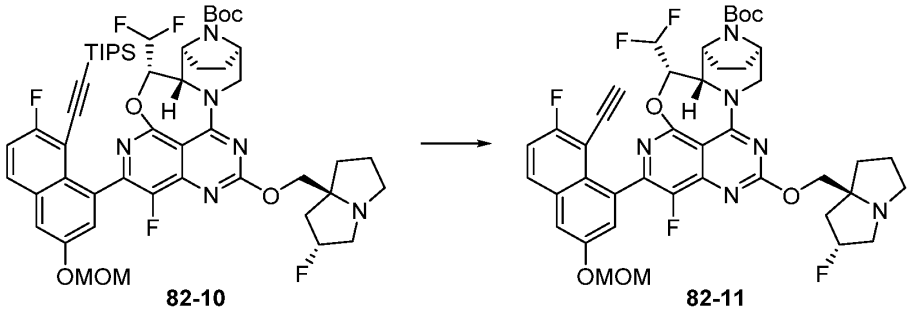
[0598] Intermediate 82-9 was synthesized in a manner similar to **Intermediate 53-9** using **Intermediate 82-8** instead of **Intermediate 53-8**. LCMS: 914.3.

Intermediate 82-10 ***tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-(difluoromethyl)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



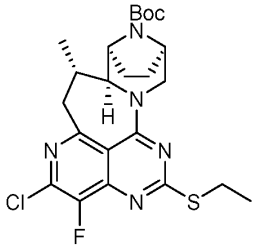
[0599] Intermediate 82-10 was synthesized in a manner similar to **Intermediate 53-10** using **Intermediate 82-9** instead of **Intermediate 53-9**. LCMS: 979.6.

Intermediate 82-11 *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-(difluoromethyl)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



[0600] Intermediate 82-11 was synthesized in a manner similar to Intermediate 53-11 using Intermediate 82-10 instead of Intermediate 53-10. LCMS: 823.0.

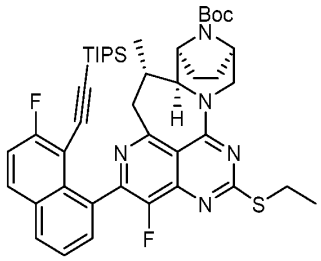
Intermediate 84-1: tert-butyl (5S,5aS,6S,9R)-2-chloro-12-(ethylthio)-1-fluoro-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



84-1

[0601] Intermediate 84-1 was synthesized in a manner similar to **Intermediate 75-7** using **Intermediate 64-3** instead of **Intermediate 75-6**. LCMS: 494.6 $[M+H]^+$

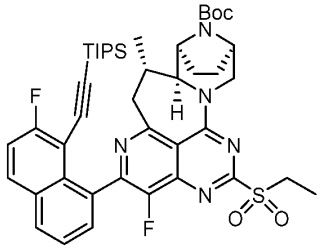
Intermediate 84-2: tert-butyl (5S,5aS,6S,9R)-12-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



84-2

[0602] Intermediate 84-2 was synthesized in a manner similar to **Intermediate 76-1** using **Intermediate 84-1** instead of **Intermediate 75-9**. LCMS: 784.9 $[M+H]^+$

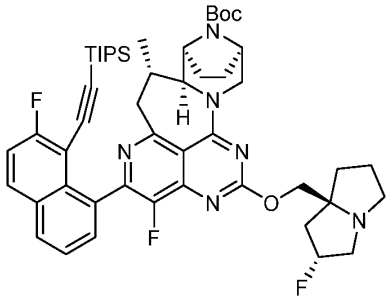
Intermediate 84-3: tert-butyl (5S,5aS,6S,9R)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



84-3

[0603] Intermediate 84-3 was synthesized in a manner similar to **Intermediate 75-8** using **Intermediate 84-2** instead of **Intermediate 75-7**. LCMS: 816.6 $[M+H]^+$

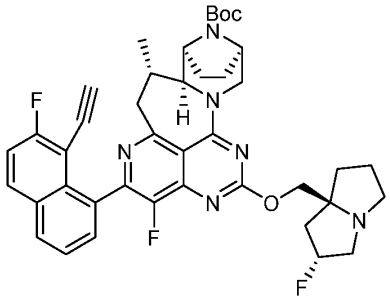
Intermediate 84-4: tert-butyl (5S,5aS,6S,9R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



84-4

[0604] Intermediate 84-4 was synthesized in a manner similar to **Intermediate 75-9** using **Intermediate 84-3** instead of **Intermediate 75-8**. LCMS: 881.6 $[M+H]^+$

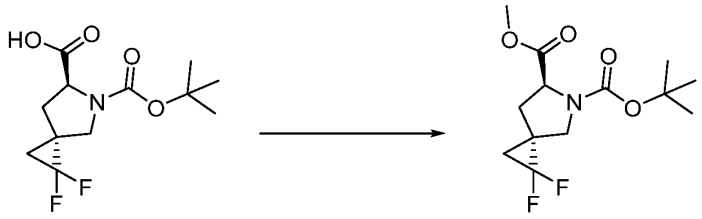
Intermediate 84-5: tert-butyl (5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



84-5

[0605] Intermediate 84-5 was synthesized in a manner similar to **Intermediate 75-11** using **Intermediate 84-4** instead of **Intermediate 75-10**. LCMS: 725.0 $[M+H]^+$

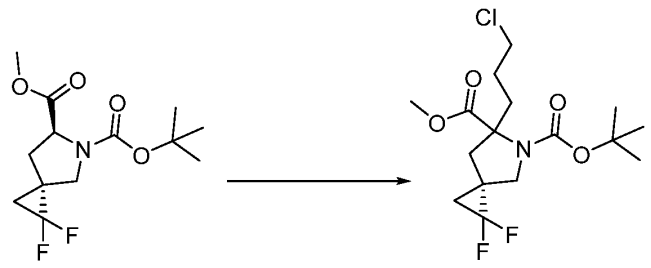
Intermediate 85-1: 5-(tert-butyl) 6-methyl (3S,6S)-1,1-difluoro-5-azaspiro[2.4]heptane-5,6-dicarboxylate



85-1

[0606] To an oven dried flask was added (3S,6S)-5-tert-butoxycarbonyl-2,2-difluoro-5-azaspiro[2.4]heptane-6-carboxylic acid (2.5 g, 9 mmol) and anhydrous methanol (20mL) under Ar. (Trimethylsilyl)diazomethane (2M in diethyl ether, 6.7mL, 14 mmol) was added dropwise. Additional (trimethylsilyl)diazomethane was added until a persistent yellow color was achieved. The reaction was quenched with 2N hydrochloric acid. The mixture was concentrated in vacuo to remove methanol then ethyl acetate was added. The mixture was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting material was purified by flash column chromatography on silica gel using a gradient of ethyl acetate in hexanes (0 to 60%) to afford Intermediate **85-1**. LCMS[M+Na]$^+$: 314.2.

Intermediate 85-2: 5-(tert-butyl) 6-methyl (3S)-6-(3-chloropropyl)-1,1-difluoro-5-azaspiro[2.4]heptane-5,6-dicarboxylate

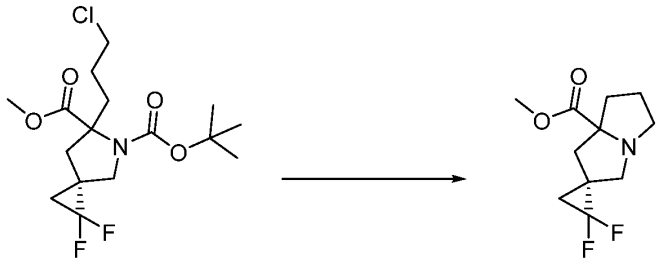


85-1 **85-2**

[0607] Intermediate **85-1** (2.3 g, 7.8 mmol) was left on high vac overnight. The flask was purged/filled with argon several times and then anhydrous tetrahydrofuran (50 mL) was added. The solution was cooled to -78C and LiHMDS (1M in tetrahydrofuran, 9.4 mL, 9.4 mmol) was added dropwise. The resulting mixture was stirred at -78C for 1h then anhydrous hexamethylphosphoramide (8.2 mL, 47 mmol) was added dropwise followed by 1-chloro-3-iodo-propane (1.3 mL, 13 mmol). The resulting solution was allowed to warm to room temperature in

the bath and stirred overnight. The solution was diluted with diethyl ether and washed with saturated aqueous ammonium chloride, 0.1M hydrochloric acid, water and brine. The solution was then dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using a gradient of ethyl acetate in hexanes (0 to 50%) to afford Intermediate **85-2**.

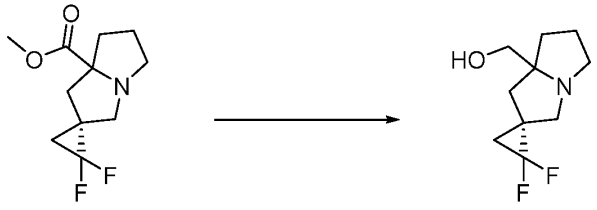
Intermediate 85-3: methyl (1S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizine]-7a'(5'H)-carboxylate



85-2 **85-3**

[0608] Intermediate **85-2** (2.9 g, 7.8 mmol) was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (5 mL) was added. The solution was stirred at room temperature for 30 min. Toluene (2 mL) was added and the solution was concentrated in vacuo and left on high vacuum for 30 min. The residue was taken up into N,N-dimethylformamide (10 mL). Potassium iodide (130 mg, 780 μmol) and potassium carbonate (5.4 g, 39 mmol) were added. The mixture was stirred vigorously overnight at 50C. The mixture was diluted with water and extracted 3 times with ethyl acetate. The aqueous layer was saturated with sodium chloride and extracted 3 times with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by basic alumina column chromatography using a gradient of ethyl acetate in hexanes (0 to 50%) to afford Intermediate **85-3**. LCMS: 232.2.

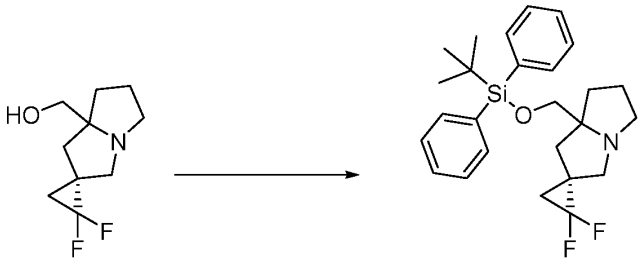
Intermediate 85-4: ((1S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol



85-3 **85-4**

[0609] Intermediate **85-3** (971 mg, 4.2 mmol) was azeotroped from toluene and dissolved in tetrahydrofuran (3 mL). An oven dried vial was charged with 1M lithium aluminum hydride in tetrahydrofuran (6.3 mL, 6.3 mmol) under Ar. The solution was diluted to 0.5M with tetrahydrofuran and cooled to 0C. The ester solution was added dropwise and the resulting solution was stirred at 0C for 10 min. The solution was diluted with diethyl ether and 240 uL of water was added slowly at 0C. 240 uL of 3N sodium hydroxide was added followed by 720 uL of water. The resulting mixture was stirred vigorously at room temperature for 15 minutes. Magnesium sulfate was added and vigorous stirring was continued for an additional 15 minutes. The mixture was filtered, rinsing thoroughly with ethyl acetate. The filtrate was concentrated in vacuo to give Intermediate **85-4**. LCMS: 204.2.

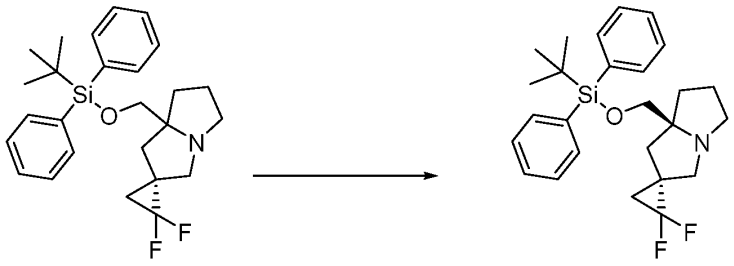
Intermediate 85-5: (1S)-7a'-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-difluorotetrahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizine]



85-4 **85-5**

[0610] Intermediate **85-4** (767 mg, 3.8 mmol) was azeotroped from toluene. Imidazole (771 mg, 11 mmol) was added and the mixture was dissolved in N,N-dimethylformamide (7 mL) and cooled to 0C. tert-butylchlorodiphenylsilane (1.5 mL, 5.7 mmoL) was added and the resulting solution was stirred over night at room temperature. Water was added and the mixture was extracted twice with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel using a gradient of methanol in dichloromethane (0 to 10%) to give Intermediate **85-5**. LCMS: 442.3.

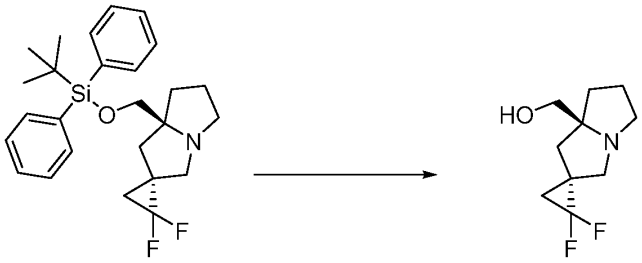
Intermediate 85-6: (1S,7a'S)-7a'-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-difluorotetrahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizine]



85-5 **85-6**

[0611] Intermediate **85-6** was purified by chiral SFC to give Intermediate **85-6** as the minor diastereomer (first eluting peak).

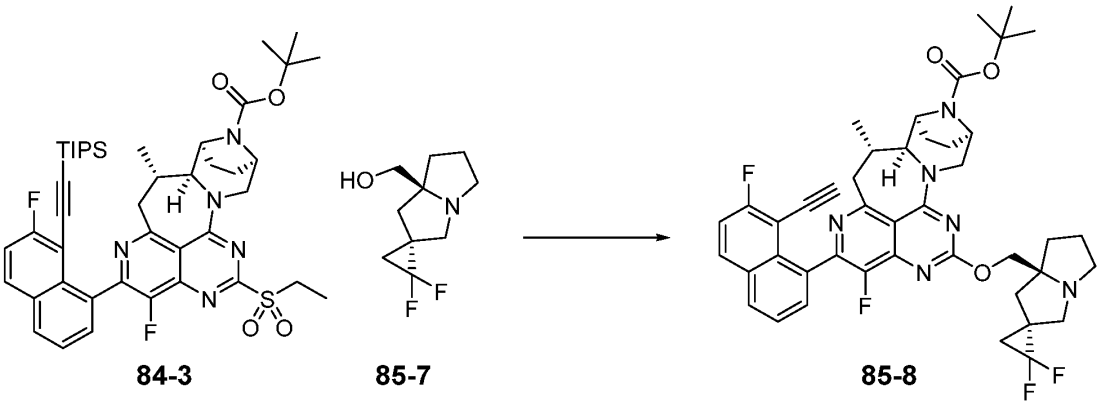
Intermediate 85-7: ((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol



85-6 **85-7**

[0612] Intermediate **85-6** (30 mg, 68 μmol) was dissolved in tetrahydrofuran (0.5 mL) and tetra-n-butylammonium fluoride (1M in tetrahydrofuran, 0.1 mL, 100 μmol) was added. The resulting solution was stirred for 24h at room temperature. The reaction mixture was concentrated in vacuo and dissolved in 1 mL of toluene. 1/3 of the solution was used in the next step without purification.

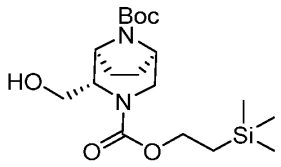
Intermediate 85-8: tert-butyl (5S,5aS,6S,9R)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



84-3 85-7 85-8

[0613] A solution of Intermediate **85-7** (5 mg, 25 μmol) in toluene was added to a vial charged with Intermediate **84-3** (20mg, 25 μmol). The solution was concentrated in vacuo and dissolved in tetrahydrofuran (0.5 mL). LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) was added and the resulting solution was stirred at room temperature for 1h. The solution was diluted with ethyl acetate and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on basic alumina using a gradient of ethyl acetate in hexanes (0 to 100%) to give Intermediate **85-8**. LCMS: 769.4.

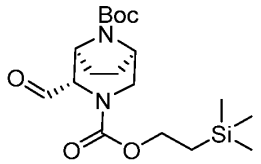
Intermediate 86-1: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate:



86-1

[0614] Intermediate 86-1 was synthesized in a manner similar to **Intermediate 75-1** using **Intermediate 27-1** instead of **Intermediate 27-5**. LCMS: 409.1 $[M+Na]^+$

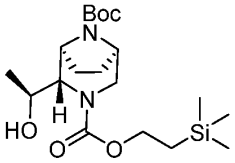
Intermediate 86-2: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-formyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



86-2

[0615] Intermediate 86-2 was synthesized in a manner similar to **Intermediate 27-3** using **Intermediate 86-1** instead of **Intermediate 27-2**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.46 (d, *J* = 3.8 Hz, 1H), 4.41 – 4.20 (m, 4H), 3.83 (s, 1H), 3.60 (d, *J* = 12.2 Hz, 1H), 3.24 (d, *J* = 12.3 Hz, 1H), 2.14 – 2.02 (m, 1H), 1.84 (ddt, *J* = 25.8, 14.9, 7.0 Hz, 3H), 1.49 (s, 9H), 1.11 – 0.97 (m, 2H), 0.06 (s, 9H).

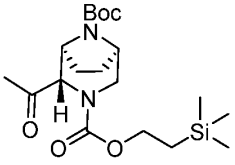
Intermediate 86-3: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-((S)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



86-3

[0616] Intermediate 86-3 was synthesized in a manner similar to **Intermediate 53-2** using **Intermediate 86-2** instead of **Intermediate 27-3**. LCMS: 401.2 $[M+H]^+$

Intermediate 86-4: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-acetyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate

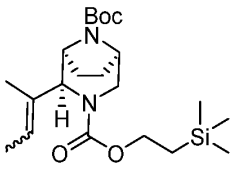


86-4

[0617] Intermediate 86-4 was synthesized in a manner similar to **Intermediate 61-1** using **Intermediate 86-3** instead of **Intermediate 53-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 4.40 (s,

1H), 4.31 (s, 2H), 4.25 – 4.14 (m, 2H), 3.50 (d, *J* = 3.3 Hz, 1H), 3.41 (s, 2H), 2.24 (s, 3H), 2.03 (s, 1H), 1.95 (s, 2H), 1.82 – 1.68 (m, 1H), 1.01 (t, *J* = 8.3 Hz, 2H), 0.06 (s, 9H).

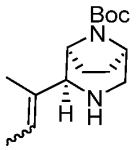
Intermediate 86-5: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-(but-2-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



86-5

[0618] Intermediate 86-5 was synthesized in a manner similar to **Intermediate 64-1** using **Intermediate 86-4** and ethyltriphenylphosphonium bromide instead of **Intermediate 61-1** and methyltriphenylphosphonium bromide LCMS: 433.1 $[M + Na]^+$

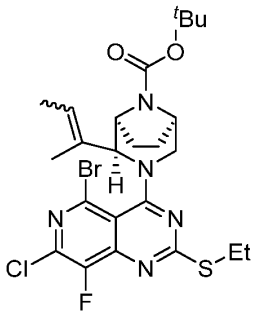
Intermediate 86-6: tert-butyl (1S,2S,5R)-2-(but-2-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



86-6

[0619] Intermediate 86-6 was synthesized in a manner similar to **Intermediate 75-5** using **Intermediate 86-5** instead of **Intermediate 75-4** and LCMS: 267.0 $[M + H]^+$

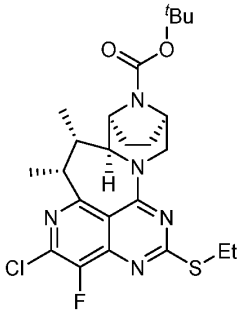
Intermediate 86-7: tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-(but-2-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



86-7

[0620] Intermediate 86-7 was synthesized in a manner similar to **Intermediate 64-3** using **Intermediate 86-6** instead of **Intermediate 64-2**. LCMS: 586.7, 588.1 $[M + H]^+$

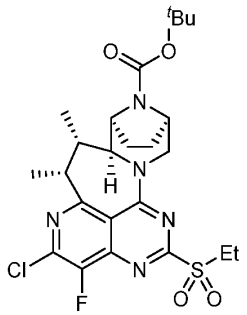
Intermediate 86-8: tert-butyl (4R,5S,5aS,6S,9R)-2-chloro-12-(ethylthio)-1-fluoro-4,5-dimethyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



86-8

[0621] Intermediate 86-8 was synthesized in a manner similar to **Intermediate 84-1** using **Intermediate 86-7** instead of **Intermediate 64-3**. LCMS: 508.5 $[M + H]^+$

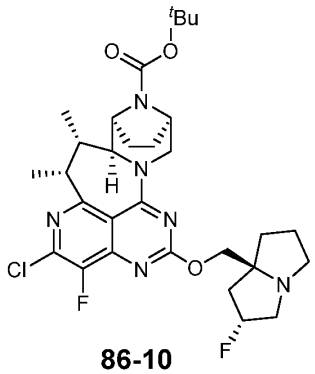
Intermediate 86-9: tert-butyl (4R,5S,5aS,6S,9R)-2-chloro-12-(ethylsulfonyl)-1-fluoro-4,5-dimethyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



86-9

[0622] Intermediate 86-9 was synthesized in a manner similar to **Intermediate 75-8** using **Intermediate 86-8** instead of **Intermediate 75-7**. LCMS: 540.3 $[M + H]^+$

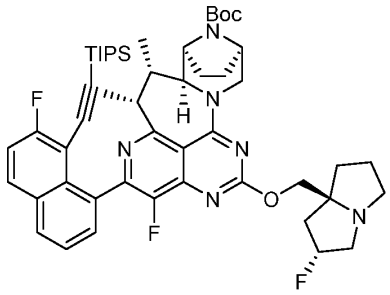
Intermediate 86-10: tert-butyl (4R,5S,5aS,6S,9R)-2-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5-dimethyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



86-10

[0623] Intermediate 86-10 was synthesized in a manner similar to **Intermediate 75-9** using **Intermediate 86-9** instead of **Intermediate 75-8**. LCMS: 605.3 $[M + H]^+$

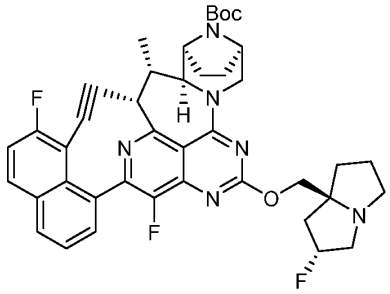
Intermediate 86-11: tert-butyl (4R,5S,5aS,6S,9R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5-dimethyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



86-11

[0624] Intermediate 86-11 was synthesized in a manner similar to **Intermediate 76-1** using **Intermediate 86-10** instead of **Intermediate 75-9**. LCMS: 895.1 $[M + H]^+$

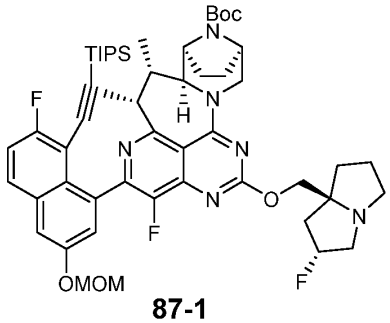
Intermediate 86-12: tert-butyl (4R,5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5-dimethyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



86-12

[0625] Intermediate 86-12 was synthesized in a manner similar to **Intermediate 76-2** using **Intermediate 86-11** instead of **Intermediate 76-1**. LCMS: 739.0 $[M + H]^+$

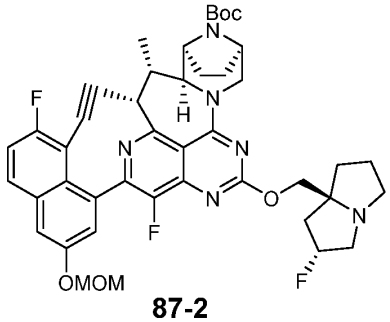
Intermediate 87-1: tert-butyl (4R,5S,5aS,6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5-dimethyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



87-1

[0626] Intermediate 87-1 was synthesized in a manner similar to **Intermediate 75-10** using **Intermediate 86-10** instead of **Intermediate 75-9**. LCMS: 955.4 $[M + H]^+$

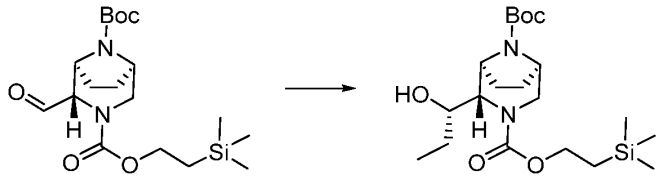
Intermediate 87-2: tert-butyl (4R,5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5-dimethyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



87-2

[0627] Intermediate 87-2 was synthesized in a manner similar to **Intermediate 75-11** using **Intermediate 87-1** instead of **Intermediate 75-10**. LCMS: 799.1 $[M + H]^+$

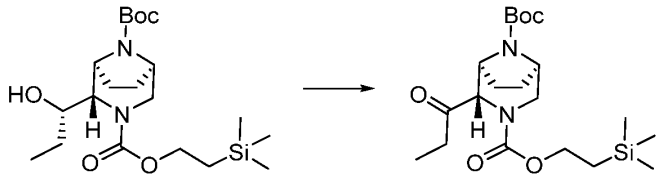
Intermediate 90-1 8-(*tert*-butyl) 3-(2-(trimethylsilyl)ethyl) (1*S*,2*S*,5*R*)-2-((*S*)-1-hydroxypropyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



86-2 **90-1**

[0628] Intermediate 90-1 was synthesized in a manner similar to **Intermediate 53-2** using ethyl magnesium bromide instead of methyl magnesium bromide and using **Intermediate 86-2** instead of **Intermediate 27-3**. LCMS: 437.1 $[M+Na]^+$.

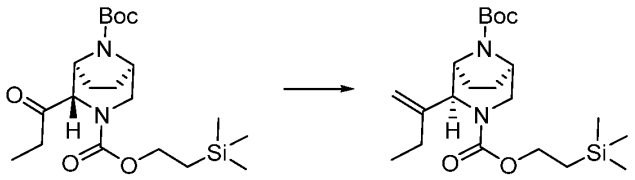
Intermediate 90-2 8-(*tert*-butyl) 3-(2-(trimethylsilyl)ethyl) (1*S*,2*S*,5*R*)-2-propionyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



90-1 **90-2**

[0629] Intermediate 90-2 was synthesized in a manner similar to **Intermediate 27-3** using **Intermediate 90-1** instead of **Intermediate 27-2**. LCMS: 412.7.

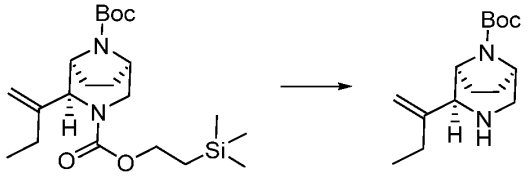
Intermediate 90-3 8-(*tert*-butyl) 3-(2-(trimethylsilyl)ethyl) (1*S*,2*S*,5*R*)-2-(but-1-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



90-2 **90-3**

[0630] Intermediate 90-3 was synthesized in a manner similar to **Intermediate 27-4** using **Intermediate 90-2** instead of **Intermediate 27-3**. LCMS: 410.8.

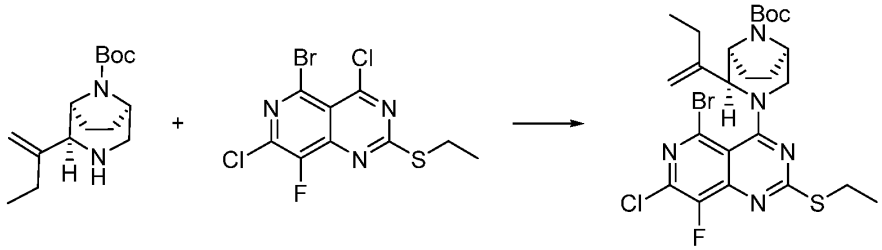
Intermediate 90-4 ***tert*-butyl (1*S*,2*S*,5*R*)-2-(but-1-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**



90-3 **90-4**

[0631] Intermediate 90-4 was synthesized in a manner similar to **Intermediate 75-5** using **Intermediate 90-3** instead of **Intermediate 75-4**. LCMS: 267.0.

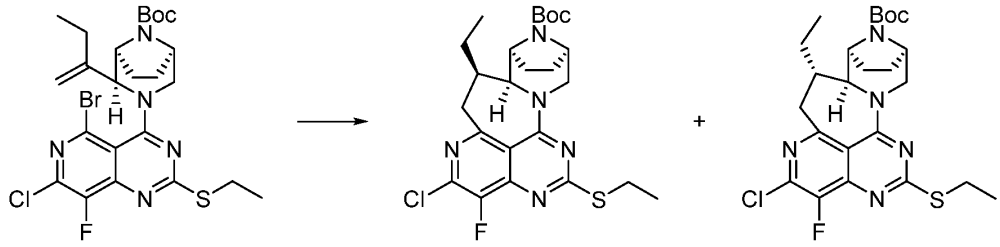
Intermediate 90-5 ***tert*-butyl (1*S*,2*S*,5*R*)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-2-(but-1-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**



90-4 **53-1** **90-5**

[0632] Intermediate 90-5 was synthesized in a manner similar to **Intermediate 53-5** using **Intermediate 90-4** instead of **Intermediate 53-4**. LCMS: 588.2.

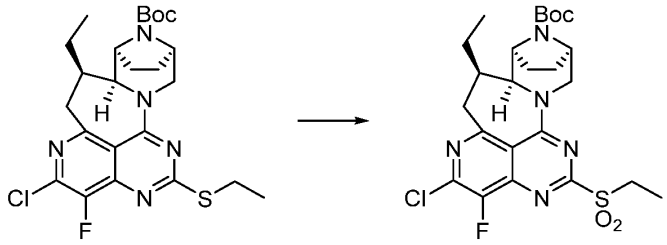
Intermediate 90-6 *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-chloro-5-ethyl-12-(ethylthio)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate and Intermediate 91-1 *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-5-ethyl-12-(ethylthio)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



90-5 **90-6** **91-1**

[0633] Intermediate 90-6 and Intermediate 91-1 were synthesized in a manner similar to Intermediate 75-7 using Intermediate 90-5 instead of Intermediate 75-6. LCMS: 508.8.

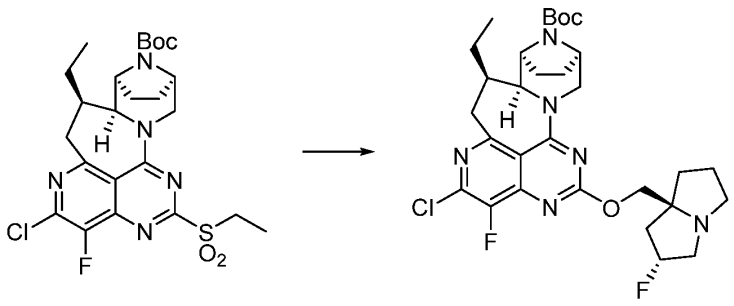
Intermediate 90-7 *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-chloro-5-ethyl-12-(ethylsulfonyl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



90-6 **90-7**

[0634] Intermediate 90-7 was synthesized in a manner similar to **Intermediate 13-9** using **Intermediate 90-6** instead of **Intermediate 13-8**. LCMS: 540.2.

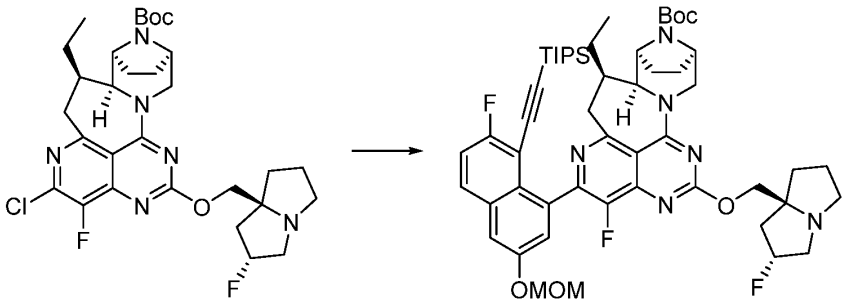
Intermediate 90-8 *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-chloro-5-ethyl-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



90-7 90-8

[0635] Intermediate 90-8 was synthesized in a manner similar to **Intermediate 53-10** using **Intermediate 90-7** instead of **Intermediate 53-9**. LCMS: 605.1.

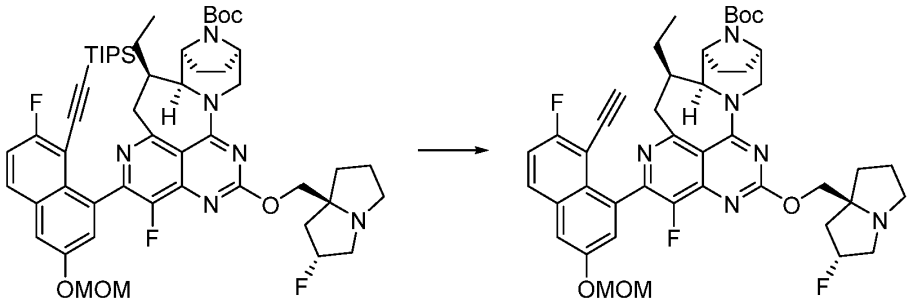
Intermediate 90-9 *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-5-ethyl-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



90-8 90-9

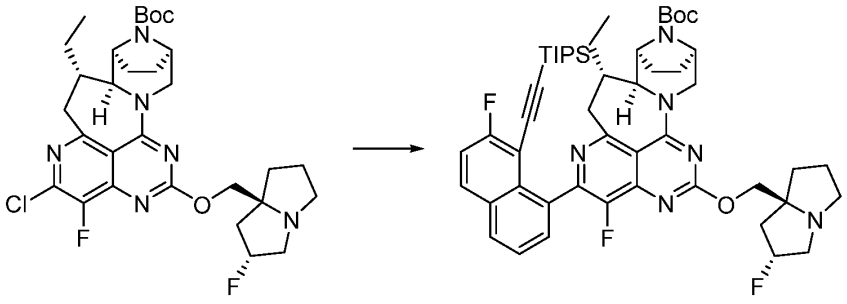
[0636] Intermediate 90-9 was synthesized in a manner similar to **Intermediate 2-1** using **Intermediate 90-8** instead of **Intermediate 17-9**. LCMS: 955.4.

Intermediate 90-10 ***tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-5-ethyl-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



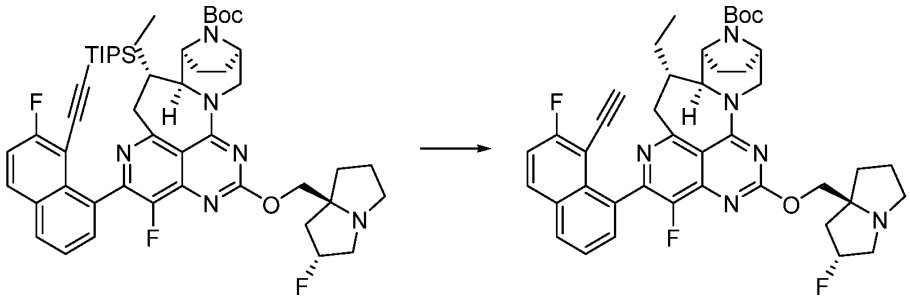
[0637] Intermediate 90-10 was synthesized in a manner similar to **Intermediate 13-11** using **Intermediate 90-9** instead of **Intermediate 13-10**. LCMS: 798.8.

Intermediate 91-2 ***tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-ethyl-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



[0638] Intermediate 91-2 was synthesized in a manner similar to **Intermediate 4-1** using **Intermediate 91-1** instead of **Intermediate 17-9**. LCMS: 895.6.

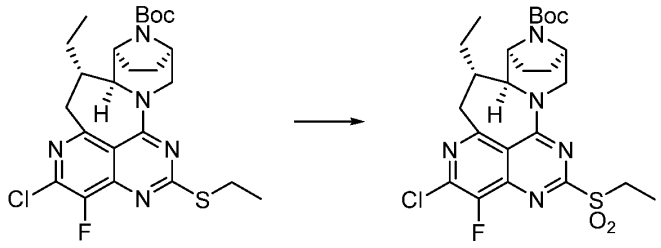
Intermediate 91-3 ***tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-ethyl-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



91-2 **91-3**

[0639] Intermediate 91-3 was synthesized in a manner similar to **Intermediate 13-11** using **Intermediate 91-2** instead of **Intermediate 13-10**. LCMS: 739.0.

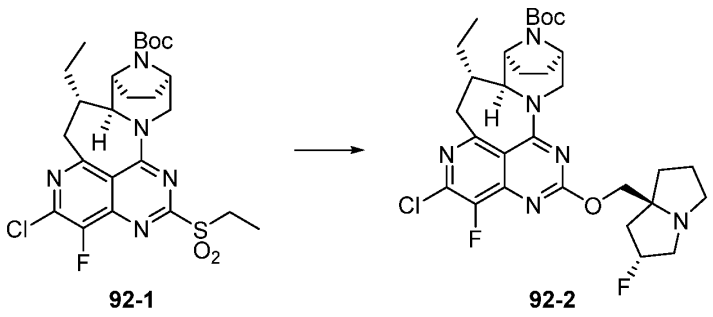
Intermediate 92-1 ***tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-5-ethyl-12-(ethylsulfonyl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



91-1 **92-1**

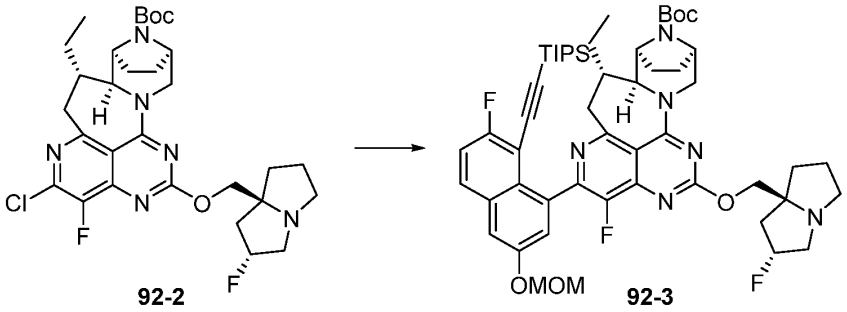
[0640] Intermediate 92-1 was synthesized in a manner similar to **Intermediate 13-9** using **Intermediate 91-1** instead of **Intermediate 13-8**. LCMS: 540.2.

Intermediate 92-2 ***tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-5-ethyl-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



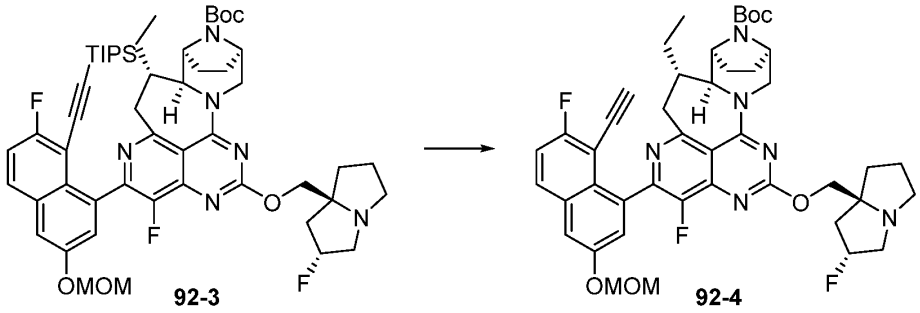
[0641] Intermediate 92-2 was synthesized in a manner similar to **Intermediate 53-10** using **Intermediate 92-1** instead of **Intermediate 53-9**. LCMS: 605.2.

Intermediate 92-3 ***tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-ethyl-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



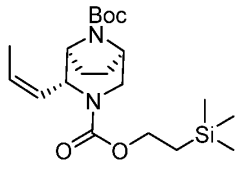
[0642] Intermediate 92-3 was synthesized in a manner similar to **Intermediate 2-1** using **Intermediate 92-2** instead of **Intermediate 17-9**. LCMS: 955.6.

Intermediate 92-4 ***tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-ethyl-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



[0643] Intermediate 92-4 was synthesized in a manner similar to **Intermediate 13-11** using **Intermediate 92-3** instead of **Intermediate 13-10**. LCMS: 798.9.

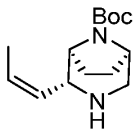
Intermediate 93-1: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2R,5R)-2-((Z)-prop-1-en-1-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



93-1

[0644] Intermediate 93-1 was synthesized in a manner similar to **Intermediate 27-4** using ethyltriphenylphosphonium bromide instead of methyltriphenylphosphonium bromide. LCMS: 419.2 $[M + Na]^+$

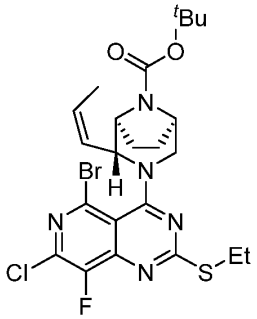
Intermediate 93-2: tert-butyl (1S,2R,5R)-2-((Z)-prop-1-en-1-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



93-2

[0645] Intermediate 93-2 was synthesized in a manner similar to **Intermediate 75-5** using **Intermediate 93-1** instead of **Intermediate 75-4**. LCMS: 253.0 $[M + H]^+$

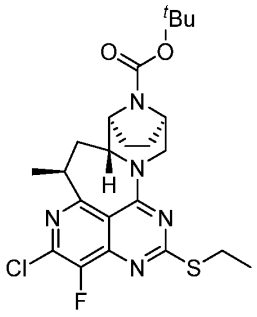
Intermediate 93-3: tert-butyl (1S,2R,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-((Z)-prop-1-en-1-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



93-3

[0646] Intermediate 93-3 was synthesized in a manner similar to **Intermediate 63-5** using **Intermediate 93-2** instead of **Intermediate 27-5**. LCMS: 572.6, 574.1 $[M + H]^+$

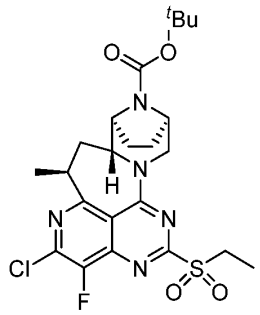
Intermediate 93-4: tert-butyl (4S,5aS,6S,9R)-2-chloro-12-(ethylthio)-1-fluoro-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



93-4

[0647] Intermediate 93-4 was synthesized in a manner similar to **Intermediate 75-7** using **Intermediate 93-3** instead of **Intermediate 75-6**. *S*-methyl isomer is the slower eluted fraction in the silica gel chromatography purification. LCMS: 494.5 $[M + H]^+$

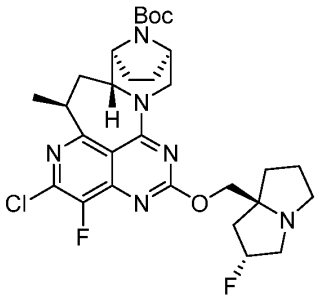
Intermediate 93-5: tert-butyl (4S,5aS,6S,9R)-2-chloro-12-(ethylsulfonyl)-1-fluoro-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



93-5

[0648] Intermediate 93-5 was synthesized in a manner similar to **Intermediate 86-9** using **Intermediate 93-4** instead of **Intermediate 86-8**. LCMS: 526.2 $[M + H]^+$

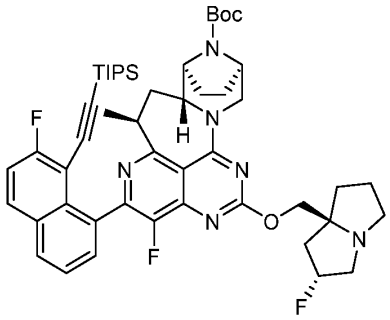
Intermediate 93-6: tert-butyl (4S,5aS,6S,9R)-2-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



93-6

[0649] Intermediate 93-6 was synthesized in a manner similar to **Intermediate 75-9** using **Intermediate 93-5** instead of **Intermediate 75-8**. LCMS: 591.2 $[M + H]^+$

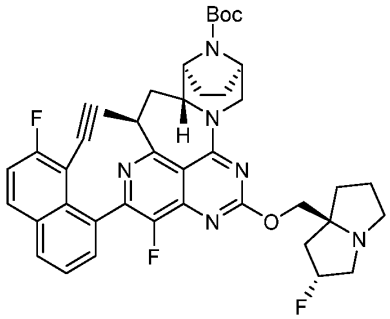
Intermediate 93-7: tert-butyl (4S,5aS,6S,9R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



93-7

[0650] Intermediate 93-7 was synthesized in a manner similar to **Intermediate 76-1** using **Intermediate 93-6** instead of **Intermediate 75-9**. LCMS: 881.3 $[M + H]^+$

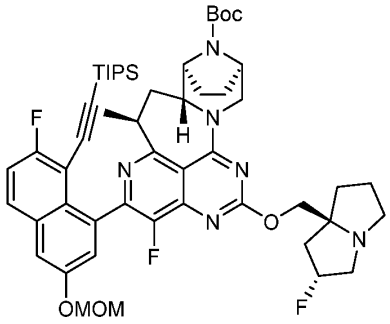
Intermediate 93-8: tert-butyl (4S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



93-8

[0651] Intermediate 93-8 was synthesized in a manner similar to **Intermediate 76-2** using **Intermediate 93-7** instead of **Intermediate 76-1**. LCMS: 725.1 $[M + H]^+$

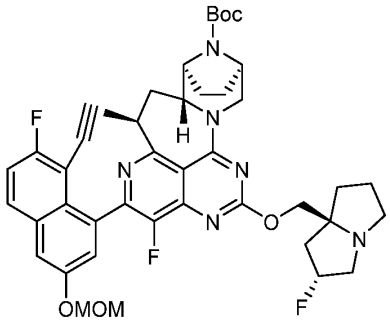
Intermediate 94-1: tert-butyl (4S,5aS,6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



94-1

[0652] Intermediate 94-1 was synthesized in a manner similar to **Intermediate 75-10** using **Intermediate 93-6** instead of **Intermediate 75-9**. LCMS: 941.2 $[M + H]^+$

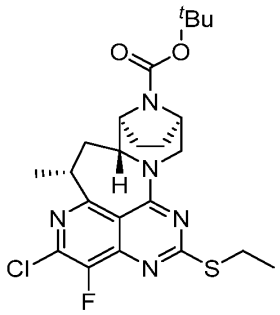
Intermediate 94-2: tert-butyl (4S,5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



94-2

[0653] Intermediate 94-2 was synthesized in a manner similar to **Intermediate 75-11** using **Intermediate 94-1** instead of **Intermediate 75-10**. LCMS: 785.0 $[M + H]^+$

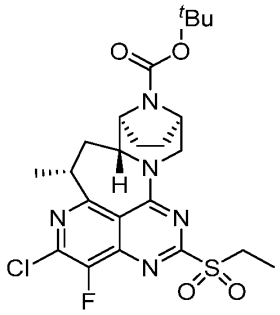
Intermediate 95-1: tert-butyl (4R,5aS,6S,9R)-2-chloro-12-(ethylthio)-1-fluoro-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



95-1

[0654] Intermediate 95-1 was synthesized in a manner similar to **Intermediate 75-7** using **Intermediate 93-3** instead of **Intermediate 75-6**. *R*-methyl isomer was the faster eluted fraction in the silica gel chromatography purification. LCMS: 494.6 $[M + H]^+$

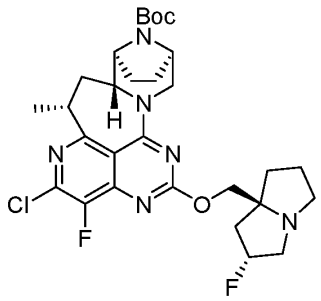
Intermediate 95-2: tert-butyl (4R,5aS,6S,9R)-2-chloro-12-(ethylsulfonyl)-1-fluoro-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



95-2

[0655] Intermediate 95-2 was synthesized in a manner similar to **Intermediate 86-9** using **Intermediate 95-1** instead of **Intermediate 86-8**. LCMS: 526.2 $[M + H]^+$

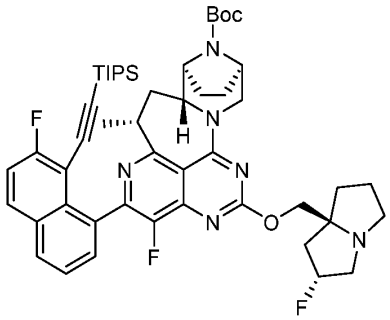
Intermediate 95-3: tert-butyl (4R,5aS,6S,9R)-2-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



95-3

[0656] Intermediate 95-3 was synthesized in a manner similar to **Intermediate 75-9** using **Intermediate 95-2** instead of **Intermediate 75-8**. LCMS: 591.2 $[M + H]^+$

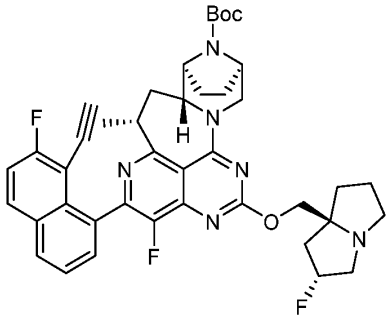
Intermediate 95-4: tert-butyl (4R,5aS,6S,9R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



95-4

[0657] Intermediate 95-4 was synthesized in a manner similar to **Intermediate 76-1** using **Intermediate 95-3** instead of **Intermediate 75-9**. LCMS: 881.3 $[M + H]^+$

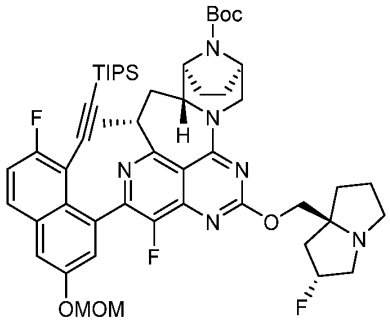
Intermediate 95-5: tert-butyl (4R,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



95-5

[0658] Intermediate 95-5 was synthesized in a manner similar to **Intermediate 76-2** using **Intermediate 95-4** instead of **Intermediate 76-1**. LCMS: 725.0 $[M + H]^+$

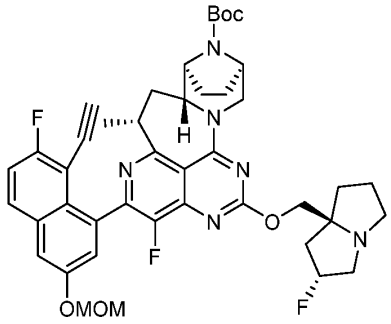
Intermediate 96-1: tert-butyl (4R,5aS,6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



96-1

[0659] Intermediate 96-1 was synthesized in a manner similar to **Intermediate 75-10** using **Intermediate 95-3** instead of **Intermediate 75-9**. LCMS: 941.6 $[M + H]^+$

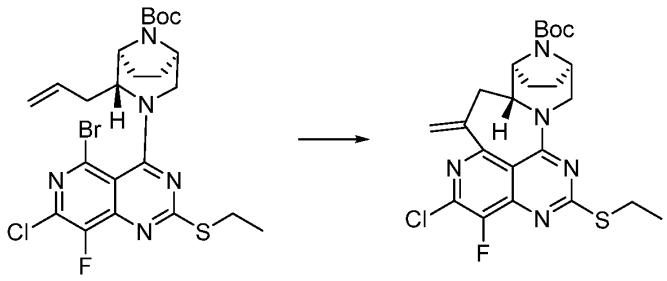
Intermediate 96-2: tert-butyl (4R,5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



96-2

[0660] **Intermediate 96-2** was synthesized in a manner similar to **Intermediate 75-11** using **Intermediate 96-1** instead of **Intermediate 75-10**. LCMS: 785.0 $[M + H]^+$

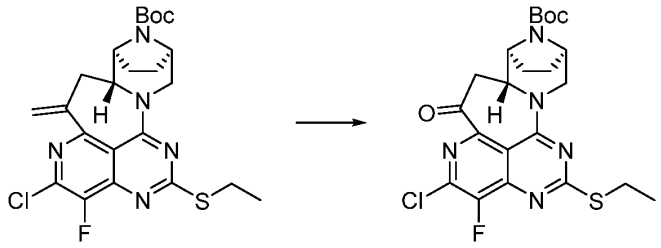
Intermediate 97-1 *tert*-butyl (5a*R*,6*S*,9*R*)-2-chloro-12-(ethylthio)-1-fluoro-4-methylene-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



75-6 97-1

[0661] The solution of **Intermediate 75-6** (30.0 mg, 0.052 mmol), $Pd(dppf)Cl_2$ (7.66 mg, 0.0105 mmol), cesium carbonate (51.2 mg, 0.16 mmol) in anhydrous 1,4-dioxane (1.0 mL) and degassed water (0.2 mL) was vigorously stirred at 90 °C for 15 minutes before it was cooled to room temperature. The mixture was washed with water (2 mL) and extracted with ethyl acetate (3 x 5 mL). The organic layer was collected and combined, dried over magnesium sulfate, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0 to 50% ethyl acetate in hexanes) to give **Intermediate 97-1**. LCMS: 492.1.

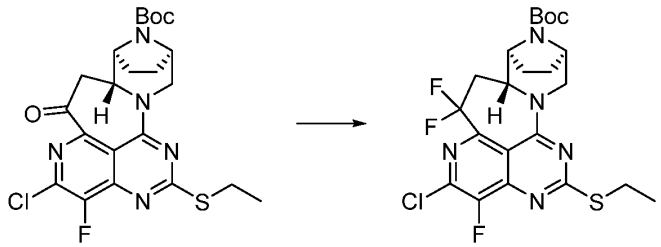
Intermediate 97-2 *tert*-butyl (5a*R*,6*S*,9*R*)-2-chloro-12-(ethylthio)-1-fluoro-4-oxo-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



97-1 97-2

[0662] A vigorously stirred solution of **Intermediate 97-1** (10.1 mg, 0.021 mmol) in anhydrous dichloromethane (0.5 mL), was bubbled with ozone at -78 ˚C for until the color of solution was changed to light yellow. The solution was then bubbled with nitrogen for 1 minute and dimethyl sulfide (1.8 µL, 0.025 mmol) was added at -78 ˚C. The mixture was stirred at -78 ˚C before being warmed to room temperature. The mixture was purified by silica gel column chromatography (0 to 50% ethyl acetate in hexanes) to give **Intermediate 97-2**. LCMS: 494.0.

Intermediate 97-3 *tert*-butyl (5a*R*,6*S*,9*R*)-2-chloro-12-(ethylthio)-1,4,4-trifluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

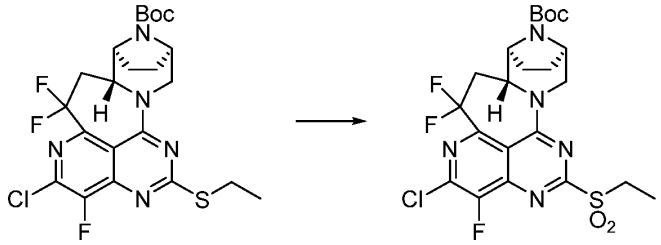


97-2 97-3

[0663] To a vigorously stirred solution of **Intermediate 97-2** (5.8 mg, 0.012 mmol) in anhydrous dichloromethane (1.0 mL), was added diethylaminosulfur trifluoride at 0 ˚C. The mixture was warmed to 30 ˚C and stirred at 30 ˚C for 24 hours before it was transferred into saturated sodium bicarbonate solution (2 mL). The resulting mixture was extracted with dichloromethane (3 x 5 mL). The organic layer was collected and combined, dried over magnesium sulfate, and

concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0 to 20% ethyl acetate in hexanes) to give **Intermediate 97-3**. LCMS: 516.1.

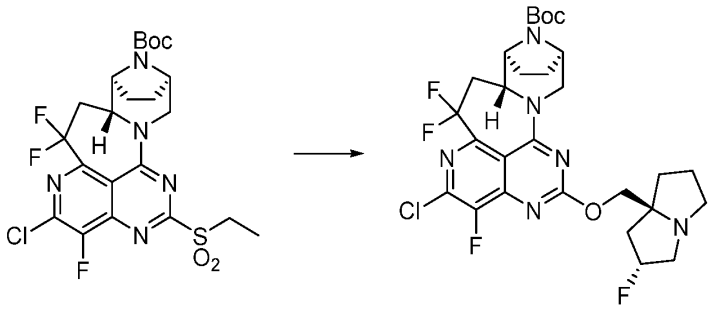
Intermediate 97-4 ***tert*-butyl (5a*R*,6*S*,9*R*)-2-chloro-12-(ethylsulfonyl)-1,4,4-trifluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



97-3 97-4

[0664] Intermediate 97-4 was synthesized in a manner similar to **Intermediate 13-9** using **Intermediate 97-3** instead of **Intermediate 13-8**. LCMS: 548.0.

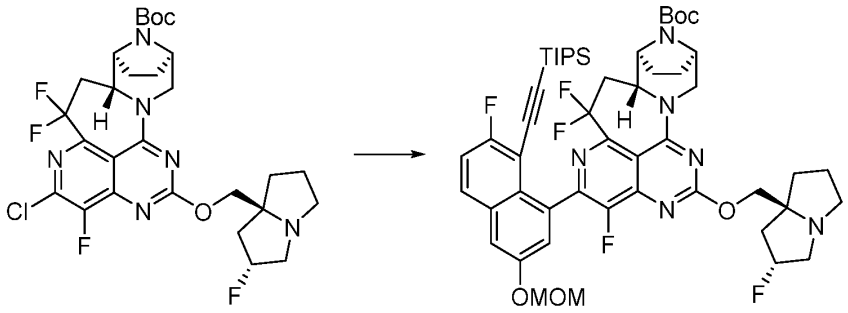
Intermediate 97-5 ***tert*-butyl (5a*R*,6*S*,9*R*)-2-chloro-1,4,4-trifluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



97-4 97-5

[0665] Intermediate 97-5 was synthesized in a manner similar to **Intermediate 53-10** using **Intermediate 97-4** instead of **Intermediate 53-9**. LCMS: 613.1.

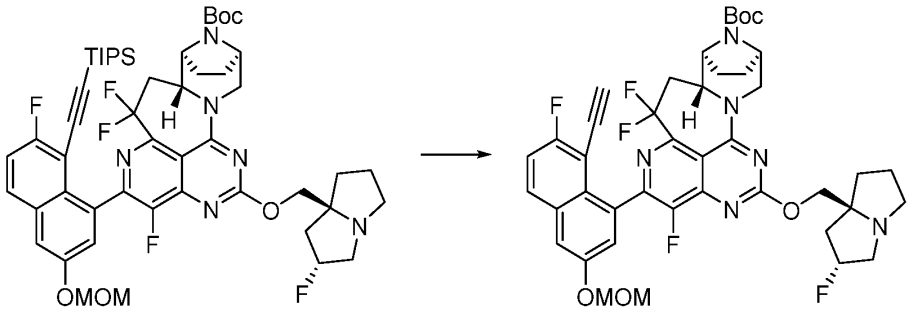
Intermediate 97-6 ***tert*-butyl (5a*R*,6*S*,9*R*)-1,4,4-trifluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



97-5 **97-6**

[0666] Intermediate 97-6 was synthesized in a manner similar to **Intermediate 2-1** using **Intermediate 97-5** instead of **Intermediate 17-9**. LCMS: 963.3.

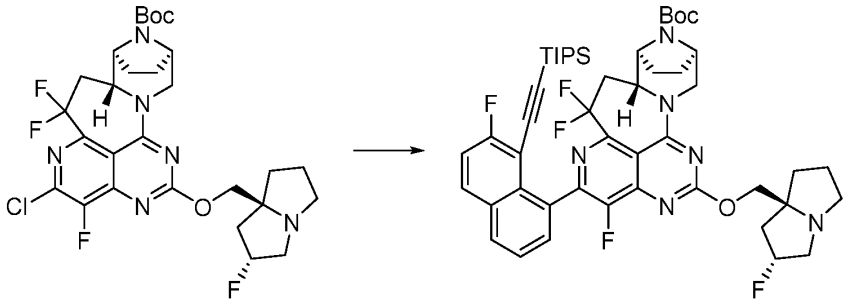
Intermediate 97-7 ***tert*-butyl (5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1,4,4-trifluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



97-6 **97-7**

[0667] Intermediate 97-7 was synthesized in a manner similar to **Intermediate 13-11** using **Intermediate 97-6** instead of **Intermediate 13-10**. LCMS: 807.0.

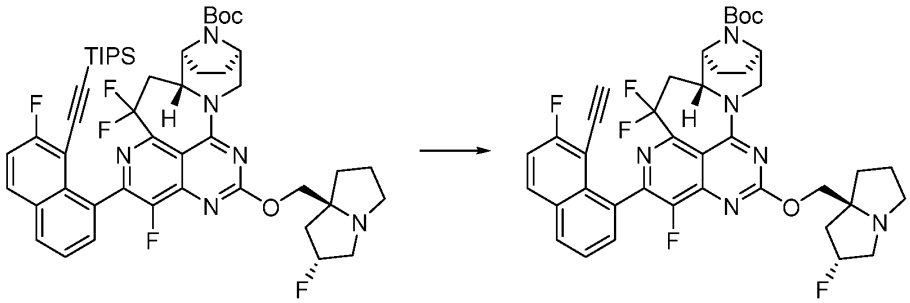
Intermediate 98-1 *tert*-butyl (5a*R*,6*S*,9*R*)-1,4,4-trifluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



97-5 98-1

[0668] Intermediate 98-1 was synthesized in a manner similar to **Intermediate 4-1** using **Intermediate 97-5** instead of **Intermediate 17-9**. LCMS: 903.1.

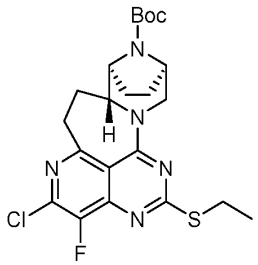
Intermediate 98-2 *tert*-butyl (5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1,4,4-trifluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



98-1 98-2

[0669] Intermediate 98-2 was synthesized in a manner similar to **Intermediate 13-11** using **Intermediate 98-1** instead of **Intermediate 13-10**. LCMS: 747.0.

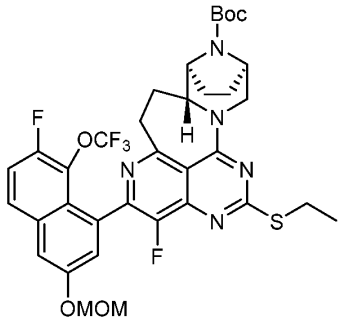
Intermediate 99-1: tert-butyl (5aR,6S,9R)-2-chloro-12-(ethylthio)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



99-1

[0670] Intermediate 99-1 was synthesized in a manner similar to **Intermediate 75-7** using **Intermediate 63-5** instead of **Intermediate 75-6**. LCMS: 480.5 $[M + H]^+$

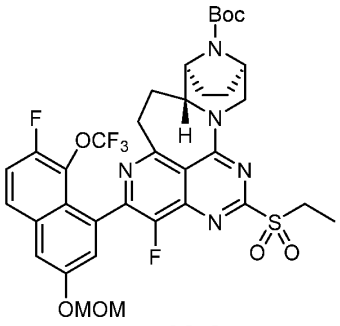
Intermediate 99-2: tert-butyl (5aR,6S,9R)-12-(ethylthio)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-(trifluoromethoxy)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



99-2

[0671] Intermediate 99-2 was synthesized in a manner similar to **Intermediate 79-2** using **Intermediate 99-1** and **Intermediate 7-5** instead of **Intermediate 79-1** and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane. LCMS: 734.4 $[M + H]^+$

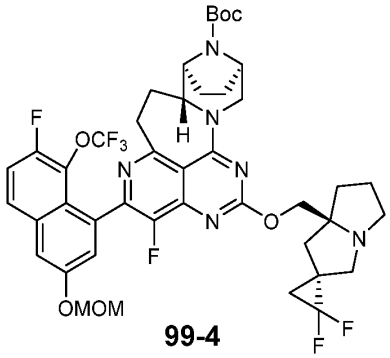
Intermediate 99-3: tert-butyl (5aR,6S,9R)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-(trifluoromethoxy)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



99-3

[0672] Intermediate 99-3 was synthesized in a manner similar to **Intermediate 79-3** using **Intermediate 99-2** instead of **Intermediate 79-2.** LCMS: 766.1 $[M + H]^+$

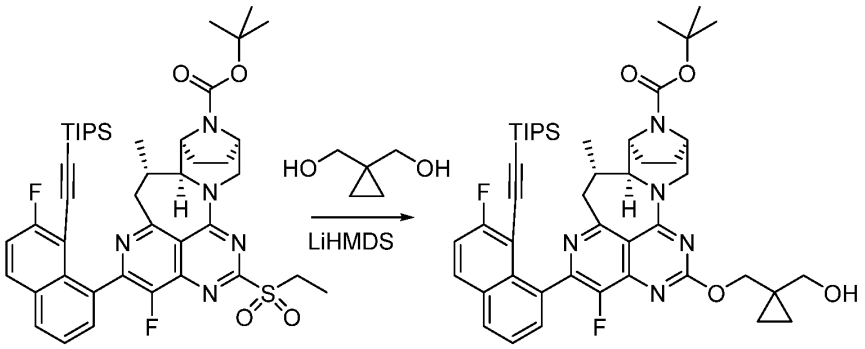
Intermediate 99-4: tert-butyl (5aR,6S,9R)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-(trifluoromethoxy)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



99-4

[0673] Intermediate 99-4 was synthesized in a manner similar to **Intermediate 79-4** using **Intermediate 99-3** and ((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol instead of **Intermediate 79-3** and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol**.** LCMS: 875.0 $[M + H]^+$

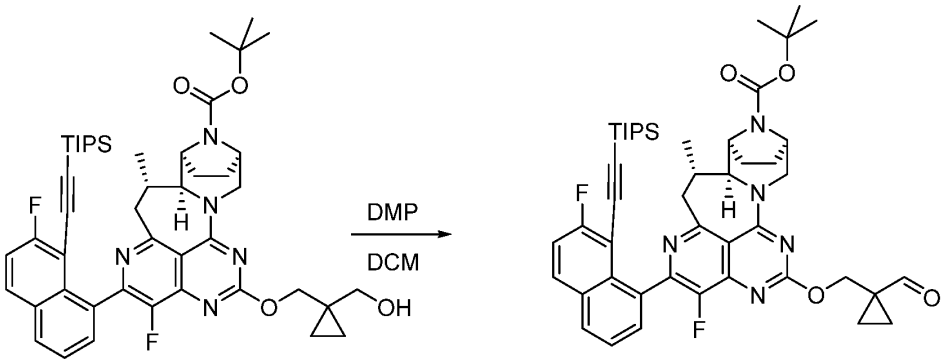
Intermediate 100-1: tert-butyl (5S,5aS,6S,9R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



84-3 100-1

[0674] Intermediate **100-1** was synthesized in a manner similar to intermediate **35-1** using intermediate **84-3** instead of intermediate **13-9.** LCMS: 824.5.

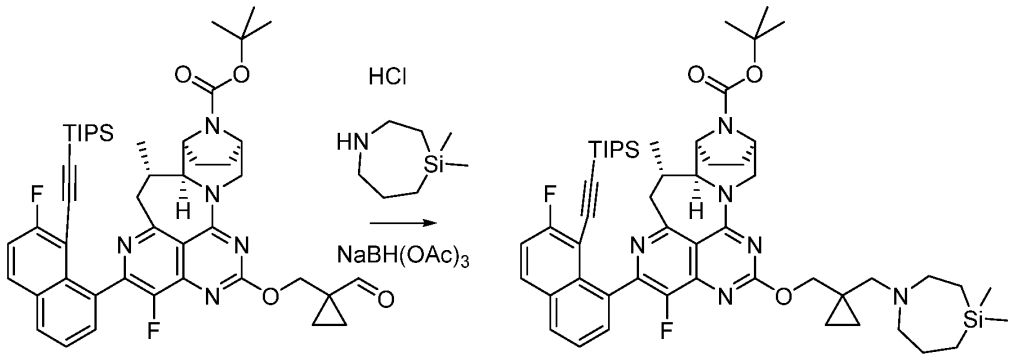
Intermediate 100-2: tert-butyl (5S,5aS,6S,9R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-((1-formylcyclopropyl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



100-1 100-2

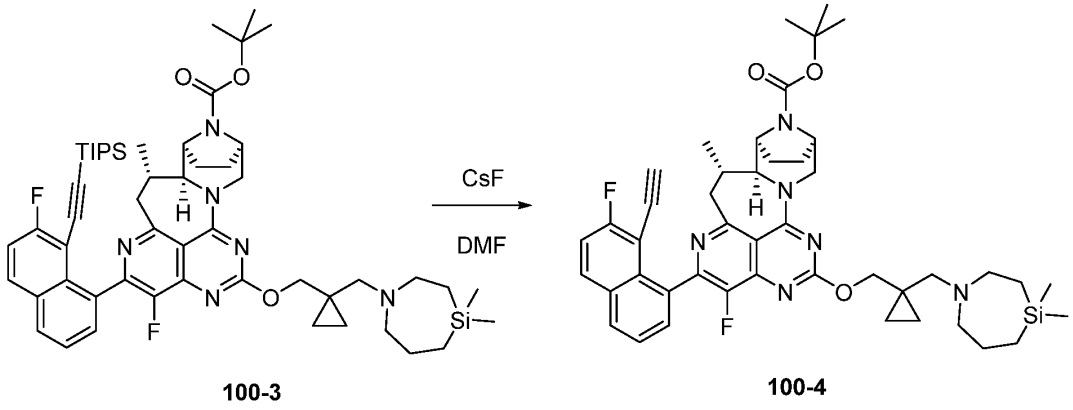
[0675] Intermediate **100-2** was synthesized in a manner similar to intermediate **35-2** using intermediate **100-1** instead of intermediate **35-1.** LCMS: 822.4.

Intermediate 100-3: tert-butyl (5S,5aS,6S,9R)-12-((1-((4,4-dimethyl-1,4-azasilepan-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



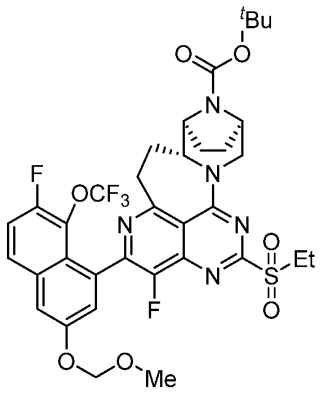
[0676] Intermediate **100-3** was synthesized in a manner similar to intermediate **35-3** using intermediate **100-2** instead of intermediate **35-2.** LCMS: 949.6.

Intermediate 100-4: tert-butyl (5S,5aS,6S,9R)-12-((1-((4,4-dimethyl-1,4-azasilepan-1-yl)methyl)cyclopropyl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0677] Intermediate **100-4** was synthesized in a manner similar to intermediate **35-4** using intermediate **100-3** instead of intermediate **35-3.** LCMS: 793.8.

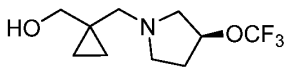
Intermediate 102-1: tert-butyl (5aR,6S,9R)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-(trifluoromethoxy)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



102-1

[0678] Intermediate **102-1** was synthesized in a manner similar to intermediate **63-7** using intermediate **7-5** instead of ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane. LCMS: 766.2.

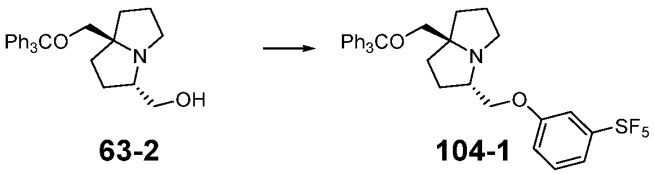
Intermediate 103-1: (1-((4-(trifluoromethoxy)piperidin-1-yl)methyl)cyclopropyl)methanol



103-1

[0679] Intermediate **103-1** was synthesized in a manner similar to intermediate **106-2** using (S)-3-(trifluoromethoxy)pyrrolidine instead of 4-(trifluoromethoxy)piperidine. LCMS: 240.300.

Intermediate 104-1: (3*S*,7a*S*)-3-((3-(pentafluoro-λ^6-sulfaneyl)phenoxy)methyl)-7a-((trityloxy)methyl)hexahydro-1*H*-pyrrolizine

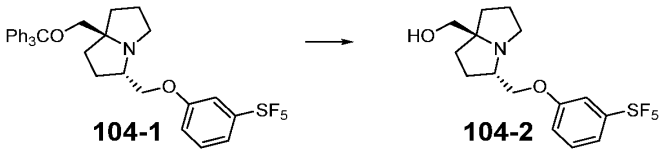


63-2 104-1

[0680] To a solution of intermediate **63-2** (300 mg, 725.43 umol, 1 *eq*) and (3-bromophenyl)-pentafluoro-λ^6-sulfane (308.01 mg, 1.09 mmol, 1.5 *eq*) in PhMe (5 mL) was added RockPhos Pd

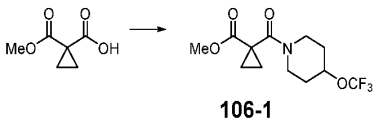
G_3 (60.82 mg, 72.54 umol, 0.1 *eq*) and Cs_2CO_3 (472.72 mg, 1.45 mmol, 2 *eq*). The reaction mixture was evacuated and refilled with N_2 3 times. The resulting mixture was stirred at 110°C for 2 hrs under N_2. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC(column: Phenomenex C18 75*30mm*3um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN];B%: 75%-98%,8min) to give intermediate **104-1**. LCMS: 616.2.

Intermediate 104-2: ((3*S*,7a*S*)-3-((3-(pentafluoro- λ⁶-sulfaneyl)phenoxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol



[0681] A mixture of intermediate **104-1** (270 mg, 438.53 umol, 1 eq) in HCl/MeOH (0.2 mL) and MeOH (0.8 mL) was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC(column: Phenomenex Luna 80*30mm*3um;mobile phase: [water(HCl)-ACN];B%: 20%-40%,8min) to give intermediate **104-2**. LCMS: 374.1.

Intermediate 106-1: methyl 1-(4-(trifluoromethoxy)piperidine-1-carbonyl)cyclopropane-1-carboxylate

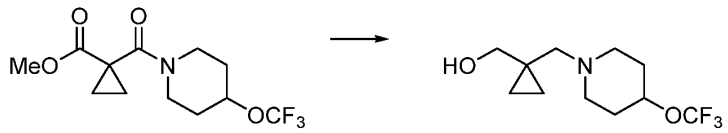


106-1

[0682] *N*,*N*-Diisopropylethylamine (430 μL, 2.50 mmol) was added via syringe to a stirred mixture of 1-(methoxycarbonyl)cyclopropane-1-carboxylic acid (120 mg, 830 μmol), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (467 mg, 1.20 mmol), and *N*,*N*-dimethylformamide (1.6 mL) at room temperature. After 30 min, the resulting mixture was added via syringe to 4-(trifluoromethoxy)piperidine hydrochloride (216 mg, 1.10 mmol). After 238 min, saturated aqueous sodium bicarbonate solution was added, and the aqueous layer was extracted with diethyl ether (4 × 5 mL). The combined organic layers were washed with brine (2 × 10 mL), were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column

chromatography on silica gel (0 to 100% ethyl acetate in hexanes) to give intermediate **106-1**. LCMS: 296.0.

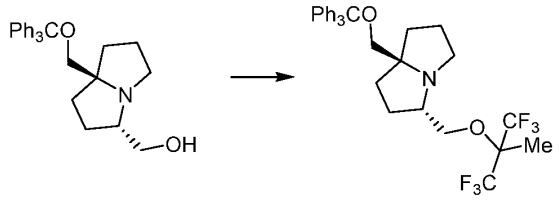
Intermediate 106-2: (1-((4-(trifluoromethoxy)piperidin-1-yl)methyl)cyclopropyl)methanol



106-1 **106-2**

[0683] Lithium aluminum hydride solution (2.0 M in tetrahydrofuran, 700 μL, 1.4 mmol) was added dropwise via syringe to a stirred solution of intermediate **106-1** (204 mg, 690 μmol) in tetrahydrofuran (3.0 mL) at 0 °C. After 34 min, water (50 μL), aqueous sodium hydroxide solution (6.0 M, 50 μL), and water (150 μL) were added sequentially, and the resulting mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on basic alumina (0 to 100% ethyl acetate in hexanes) to give intermediate **106-2**. LCMS: 254.1.

Intermediate 109-1: (3S,7aS)-3-(((1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)oxy)methyl)-7a-((trityloxy)methyl)hexahydro-1H-pyrrolizine

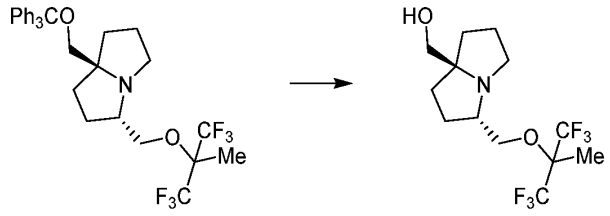


63-2 **109-1**

[0684] A mixture of intermediate **63-2** (100 mg, 241.81 umol, 1.00 *eq*) and 1,1,1,3,3,3-hexafluoro-2-methyl-propan-2-ol (176.10 mg, 967.23 umol, 4.00 *eq*) in PhMe (1 mL) was degassed and purged with N_2 3 times, and then 2-(tributyl-λ^5-phosphanylidene)acetonitrile (233.45 mg, 967.23 umol, 4.00 *eq*) was added at 0°C. The mixture was stirred at 80°C for 12 hrs under N_2 atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex C18 80*40mm*3um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN];B%: 40%-70%,8min) to give intermediate **109-1**. ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.40 (br.d, 6H, J = 7.6 Hz), 7.26-7.19 (m, 6H), 7.18-7.12 (m, 3H), 3.85 (br.s, 1H), 3.78-3.62 (m, 1H), 3.10 (br.d, 1H, J = 1.6 Hz), 2.88

(br.d, 1H, *J* = 8.4 Hz), 2.81-2.65 (m, 2H), 2.63-2.50 (m, 1H), 2.05-1.98 (m, 1H), 1.72-1.62 (m, 4H), 1.61-1.55 (m, 3H), 0.86-0.71 (m, 3H).

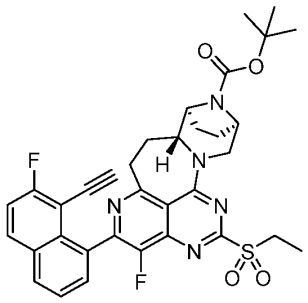
Intermediate 109-2: ((3*S*,7a*S*)-3-(((1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol



109-1 **109-2**

[0685] To a solution of intermediate **109-1** (80 mg, 138.50 umol, 1 *eq*) in MeOH (2 mL) was added HCl/MeOH (4 M) (0.5 mL). The mixture was stirred at 25 °C for 1 hr. The reaction solution was blow-dried with N_2. The residue was diluted with H_2O (5 mL) and washed with EtOAc (5 mL * 3). The aqueous phase was filtered and was freeze-dried to give intermediate **109-2** as its HCl salt. LCMS: 336.1.

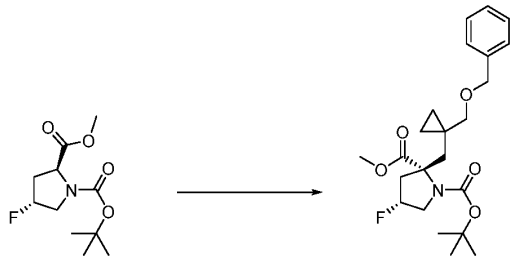
Intermediate 113-1: tert-butyl (5aR,6S,9R)-12-(ethylsulfonyl)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



113-1

[0686] Intermediate **113-1** was prepared in a manner analogous to Intermediate **122-2** using (8-ethynyl-7-fluoronaphthalen-1-yl) pinacol boronate.

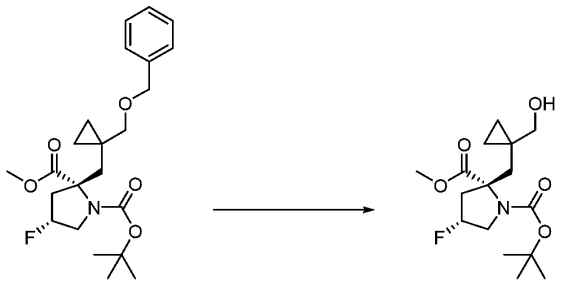
Intermediate 113-2: 1-(tert-butyl) 2-methyl (2R,4R)-2-((1-((benzyloxy)methyl)cyclopropyl)methyl)-4-fluoropyrrolidine-1,2-dicarboxylate



113-2

[0687] O1-tert-butyl O2-methyl (2S,4R)-4-fluoropyrrolidine-1,2-dicarboxylate (4.1 g, 17 mmol) was dissolved in tetrahydrofuran in an oven dried flask under argon. The solution was cooled to -78C and LiHMDS (1M in tetrahydrofuran, 20 mL, 20 mmol) was added dropwise. The resulting solution was stirred at -78C for 1h. Hexamethylphosphoramide (29 mL, 165 mmol) was added dropwise followed by [1-(bromomethyl)cyclopropyl]methoxymethylbenzene (5.4 g, 21 mmol). The resulting solution was allowed to warm to room temperature and stirred for 3 days. The solution was diluted with diethyl ether and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel using a gradient of ethyl acetate in hexanes (0 to 40%) to provide Intermediate **113-2**. LCMS $[M+Na]^+$: 444.2.

Intermediate 113-3: 1-(tert-butyl) 2-methyl (2R,4R)-4-fluoro-2-((1-(hydroxymethyl)cyclopropyl)methyl)pyrrolidine-1,2-dicarboxylate

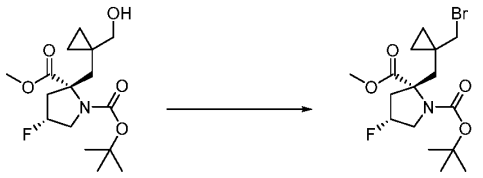


113-2 113-3

[0688] Intermediate **113-2** (4.5 g, 11 mmol) was dissolved in ethanol (40 mL) and 10% palladium on carbon (1.1 g, 1.1 mmol) was added. The flask was purged and filled with hydrogen 3 times and the mixture was stirred at room temperature under hydrogen overnight. The reaction mixture was filtered through celite, rinsing with ethyl acetate, and concentrated in vacuo. The resulting

residue was purified by flash column chromatography on silica gel using a gradient of ethyl acetate in hexanes (0 to 80%) to provide Intermediate **113-3**. LCMS $[M+Na]^+$: 354.2.

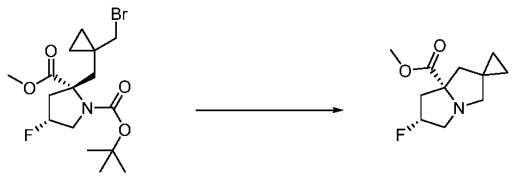
Intermediate 113-4: 1-(tert-butyl) 2-methyl (2R,4R)-2-((1-(bromomethyl)cyclopropyl)methyl)-4-fluoropyrrolidine-1,2-dicarboxylate



113-3 **113-4**

[0689] Intermediate **113-3** (2.9 g, 8.9 mmol), triphenylphosphine (3.4 g, 13 mmol) and carbon tetrabromide (4.4 g, 13 mmol) were dissolved in dichloromethane (30 mL) and the resulting solution was stirred overnight at room temperature. The solution was diluted with hexanes and purified by flash column chromatography on silica gel using a gradient of ethyl acetate in hexanes (0 to 80%) to provide Intermediate **113-4**. LCMS $[M+Na]^+$: 416.1.

Intermediate 113-5: methyl (6'R,7a'R)-6'-fluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizine]-7a'(5'H)-carboxylate

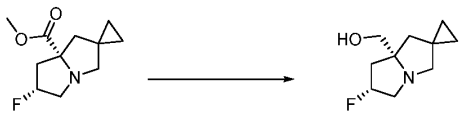


113-4 **113-5**

[0690] Intermediate **113-4** (3.5 g, 8.9 mmol) was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (5 mL) was added. The solution was stirred at room temperature for 30 min. Toluene (2 mL) was added and the solution was concentrated in vacuo and left on high vacuum for 30 min. The residue was taken up into N,N-dimethylformamide (10 mL). Potassium iodide (150 mg, 890 mmol) and potassium carbonate (3.6 g, 27 mmol) were added. The mixture was stirred vigorously overnight at 50C. The mixture was poured into a mixture of saturated aqueous sodium carbonate and brine and extracted with ethyl acetate. Before each extraction, the aqueous layer was saturated with sodium chloride. The aqueous layer was extracted twice more with ethyl acetate and 3 times with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by basic alumina

column chromatography using a gradient of ethyl acetate in hexanes (0 to 100%) to afford Intermediate **113-5**. LCMS: 214.1.

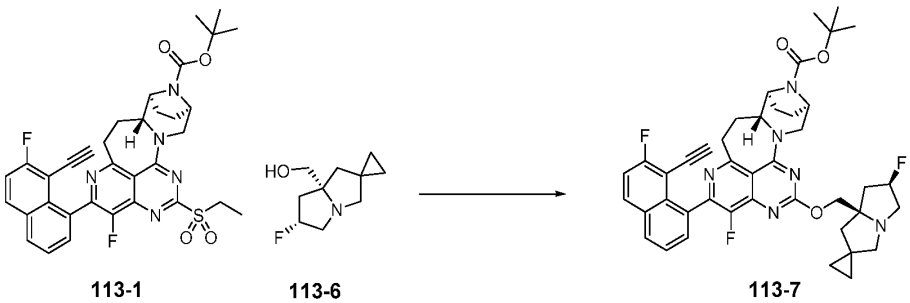
Intermediate 113-6: ((6'R,7a'R)-6'-fluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol



113-5 **113-6**

[0691] Intermediate **113-5** (98 mg, 460 μmol) was dissolved in tetrahydrofuran (1 mL). An oven dried vial was charged with 1M lithium aluminum hydride in tetrahydrofuran (6.3 mL, 6.3 mmol) under Ar. The solution was diluted to 0.5M with tetrahydrofuran and cooled to 0C. The ester solution was added dropwise and the resulting solution was stirred at 0C for 30 min. The solution was diluted with diethyl ether and 26 uL of water was added slowly at 0C. 26 uL of 3N sodium hydroxide was added followed by 75 uL of water. The resulting mixture was stirred vigorously at room temperature for 15 minutes. Magnesium sulfate was added and vigorous stirring was continued for an additional 15 minutes. The mixture was filtered, rinsing thoroughly with ethyl acetate. The filtrate was concentrated in vacuo to give Intermediate **113-6**. LCMS: 186.2.

Intermediate 113-7: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((6'R,7a'R)-6'-fluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

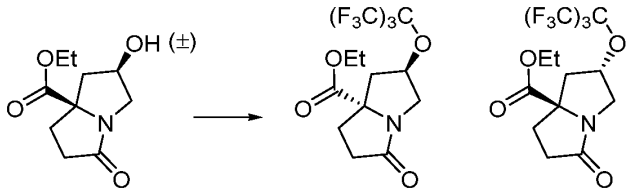


113-1 **113-6** **113-7**

[0692] Intermediate **113-1** (5mg, 7.7 μmol) and Intermediate **113-6** (2.9 mg, 16 μmol) were azeotroped together from toluene and dissolved in 2-methyltetrahydrofuran (0.5 mL). LiHMDS (1M in tetrahydrofuran, 16 uL, 16 μmol) was added and the resulting solution was stirred at room

temperature for 5 minutes. The solution was diluted with ethyl acetate and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to give crude Intermediate **113-7** which was used directly in the next step without purification. LCMS: 737.4.

Intermediate 114-0: ethyl (2*R*,7a*S*)-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate

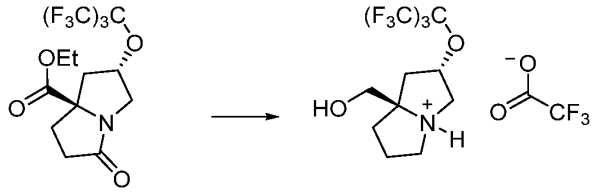


129-0 **114-0**

[0693] To a solution of ethyl (2*R*,7a*R*)-ethyl 2-hydroxy-5-oxohexahydro-1*H*-pyrrolizine-7a-carboxylate (500.00 mg, 2.34 mmol, 1.00 *eq*) and 1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-ol (553.48 mg, 2.34 mmol, 1.00 *eq*) in PhMe (2.00 mL) was added CMBP (1.70 g, 7.03 mmol, 3.00 *eq*) at 0°C under N_2. The mixture was stirred at 80°C for 12 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by *prep*-HPLC(column: Phenomenex Luna 80*30mm*3um;mobile phase: [water(HCl)-ACN];B%: 35%-60%,8min) to give a mixture of intermediate **129-0** and **114-0**. The enantiomers were separated by chiral SFC (column: DAICEL CHIRALPAK IC(250mm*30mm,10um);mobile phase: [0.1%NH3H2O IPA];B%: 12%-12%,7min). The peak with shorter Rt (Rt = 0.385) was designated as intermediate **129-0**, the absolute stereochemistry of which was assigned arbitrarily. Intermediate **129-0**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 4.15 (q, *J* = 7.2 Hz, 2H), 3.91 (d, *J* = 13.2 Hz, 1H), 3.33-3.31 (m, 1H), 2.80-2.59 (m, 3H), 2.39-2.35 (m, 1H), 2.10-1.98 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H).

[0694] The peak with longer Rt (Rt =0.597) was designated as intermediate **114-0**, the absolute stereochemistry of which was assigned arbitrarily. Intermediate **114-0**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 4.15 (q, *J* = 7.2 Hz, 2H), 3.91 (d, *J* = 13.6 Hz, 1H), 3.33-3.31 (m, 1H), 2.80-2.59 (m, 3H), 2.39-2.35 (m, 1H), 2.11-1.98 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H).

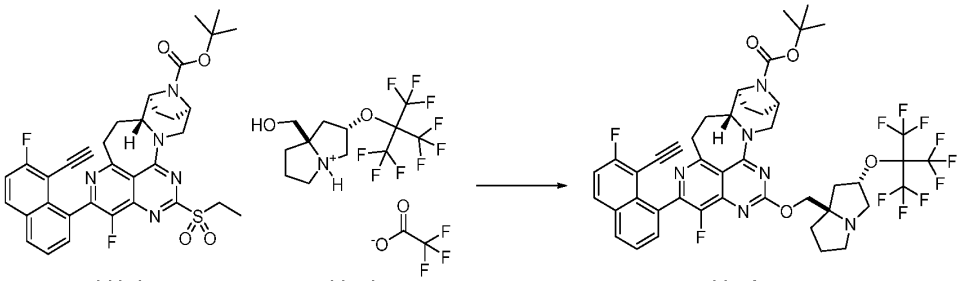
Intermediate 114-1: ((2*S*,7a*R*)-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol trifluoracetic acid salt



114-0 114-1

[0695] To a solution of intermediate **114-0** (60.00 mg, 139.13 umol, 1 eq) in THF (2 mL) was added $NaBH_4$ (42.11 mg, 1.11 mmol, 8 eq) and BF_3•Et_2O (315.94 mg, 2.23 mmol, 274.73 uL, 16 eq) at 0°C under N_2. The mixture was stirred at 60°C for 1 hr under N_2. The reaction mixture was quenched by addition saturated aqueous NH_4Cl solution (2 mL) at 0°C, and then extracted with EtOAc (2 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC(column: Phenomenex Luna C18 100*30mm*5um;mobile phase: [water(TFA)-ACN];B%: 10%-40%,10min) to give intermediate **114-1**, the absolute stereochemistry of which was assigned arbitrarily. LCMS: 376.0.

Intermediate 114-2: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*trans*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

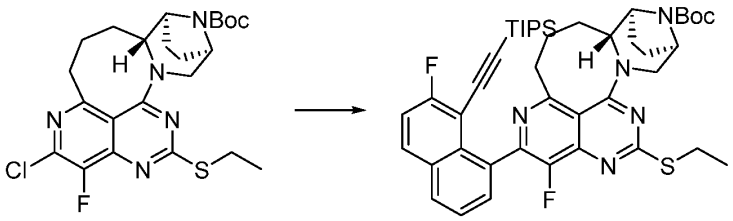


113-1 114-1 114-2

[0696] Intermediate **113-1** (5 mg, 7.7 μmol) and Intermediate **114-1** (7 mg, 14 μmol) were azeotroped together from toluene and dissolved in 2-methyltetrahydrofuran (0.5 mL). LiHMDS (1M in tetrahydrofuran, 31 uL, 31 μmol) was added and the resulting solution was stirred at room temperature for 5 minutes. The solution was diluted with ethyl acetate and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over sodium sulfate,

filtered and concentrated in vacuo to give crude Intermediate **114-2** as a single unknown *trans* pyrrolizidine isomer, which was used directly in the next step without purification. LCMS: 927.4.

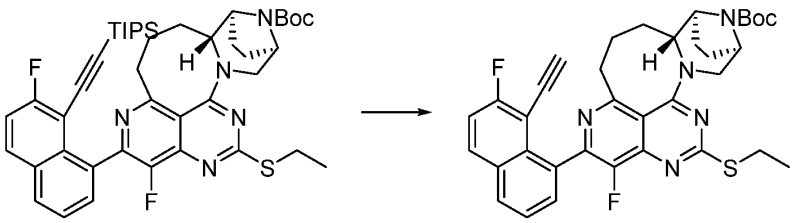
Intermediate 115-1 ***tert*-butyl (6a*R*,7*S*,10*R*)-13-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate**



75-7 **115-1**

[0697] A vigorously stirred mixture of **Intermediate 75-7** (181 mg, 0.367 mmol), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (prepared according to WO 2021/041671) (249 mg, 0.550 mmol), [(di(1-adamantyl)-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate (13.2 mg, 36.7 μmol), potassium phosphate (253 mg, 1.10 mmol), tetrahydrofuran (5.4 mL), and degassed water (1.1 mL) was heated to 70°C. After 80 min, the resulting mixture was cooled to room temperature, and diethyl ether (40 mL) and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (30 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 50% ethyl acetate in hexanes) to give **Intermediate 115-1**. LCMS: 784.4.

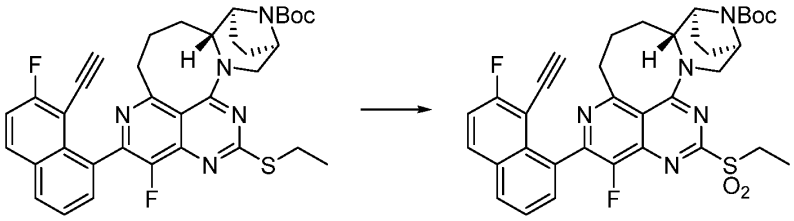
Intermediate 115-2 ***tert*-butyl (6a*R*,7*S*,10*R*)-13-(ethylthio)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate**



115-1 **115-2**

[0698] Cesium fluoride (415 mg, 2.73 mmol) was added to a vigorously stirred solution of **Intermediate 115-1** (214 mg, 0.273 mmol) in *N*,*N*-dimethylformamide (6.2 mL) at room temperature. After 40 min, diethyl ether (40 mL), ethyl acetate (20 mL), and saturated aqueous sodium bicarbonate solution (10 mL) were added sequentially. The organic layer was washed with water (2 × 40 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 60% ethyl acetate in hexanes) to give **Intermediate 115-2**. LCMS: 628.2.

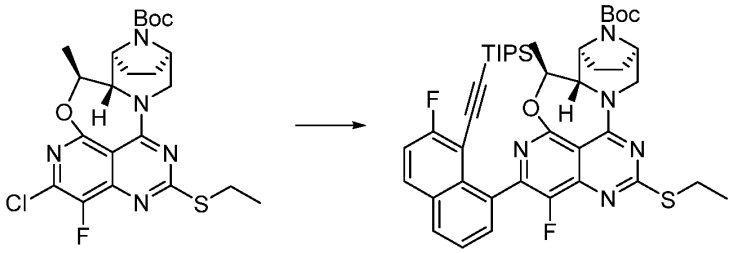
Intermediate 115-3 *tert*-butyl (6a*R*,7*S*,10*R*)-13-(ethylsulfonyl)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate



115-2 115-3

[0699] 3-Chloroperoxybenzoic acid (77% wt, 123 mg, 0.55 mmol) was added in two equal portions over 5 min to a vigorously stirred solution of **Intermediate 115-2** (157 mg, 0.25 mmol) in dichloromethane (3.5 mL) at 0°C. After 90 min, the resulting mixture was warmed to room temperature. The residue was purified by flash column chromatography on silica gel (0% to 75% ethyl acetate in hexanes) to give **Intermediate 115-3**. LCMS: 660.3.

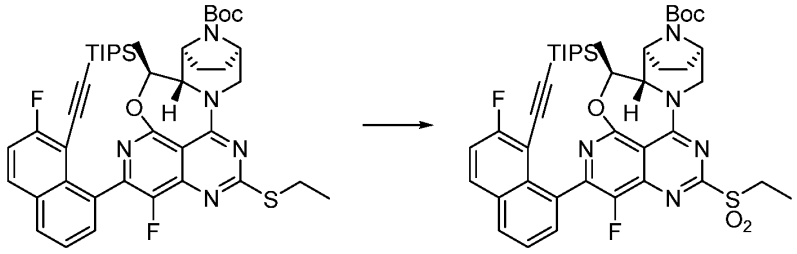
Intermediate 116-1 *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



53-7 116-1

[0700] Intermediate 116-1 was synthesized in a manner similar to **Intermediate 4-1** using **Intermediate 53-7** instead of **Intermediate 17-9**. LCMS: 786.3.

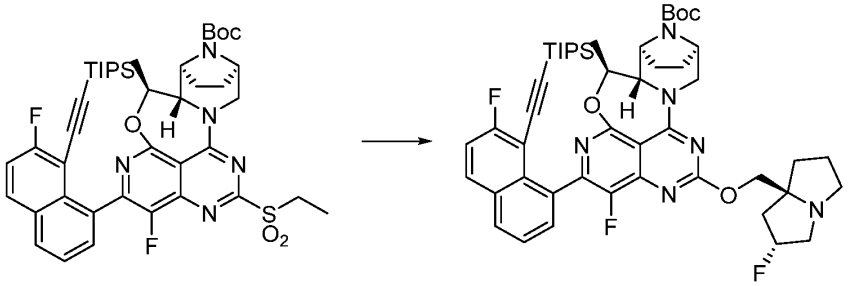
Intermediate 116-2 *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



116-1 116-2

[0701] Intermediate 116-2 was synthesized in a manner similar to **Intermediate 13-9** using **Intermediate 116-1** instead of **Intermediate 13-8**. LCMS: 818.2.

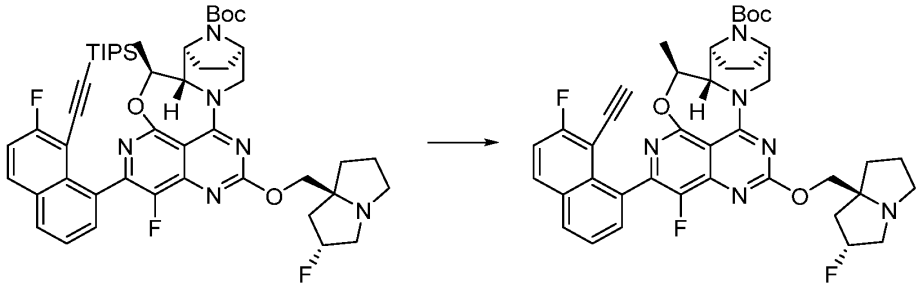
Intermediate 116-3 *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



116-2 116-3

[0702] Intermediate 116-3 was synthesized in a manner similar to **Intermediate 13-10** using **Intermediate 116-2** instead of **Intermediate 13-9**. LCMS: 883.0.

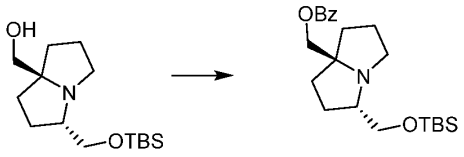
Intermediate 116-4 *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



116-3 116-4

[0703] Intermediate 116-4 was synthesized in a manner similar to Intermediate 13-11 using Intermediate 116-3 instead of Intermediate 13-10. LCMS: 727.0.

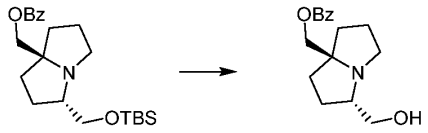
Intermediate 119-1: ((3*S*,7a*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methyl benzoate



119-1

[0704] To a solution of ((3S,7aS)-3-(((tert-butyldimethylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol (830 mg, 2.91 mmol, 1 *eq*) in DCM (5 mL) was added triethylamine (588.36 mg, 5.81 mmol, 809.29 μL, 2 *eq*) and benzoyl chloride (612.99 mg, 4.36 mmol, 506.60 μL, 1.5 eq) at 0 °C. The mixture was stirred at 25 °C for 0.5 hr. The unreacted benzoyl chloride was quenched by addition H_2O (30 mL) at 0°C, and the resulting mixture was extracted with DCM (30mL * 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (PE: EtOAc = 1: 0 to 0: 1) to give intermediate **119-1**. LCMS: 390.2.

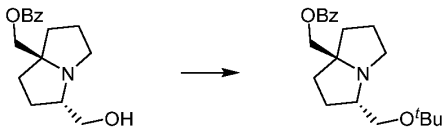
Intermediate 119-2: ((3*S*,7a*S*)-3-(hydroxymethyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methyl benzoate



119-1 **119-2**

[0705] A mixture of intermediate **119-1** (1.26 g, 3.23 mmol, 1 eq) and CsF (9.83 g, 64.68 mmol, 2.38 mL, 20 eq) in DMF (20 mL) was stirred at 50 °C for 12 hr. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Welch Xtimate C18 250*70mm#10um;mobile phase: [water(NH_4HCO_3)-ACN];B%: 15%-45%,20min) to give intermediate **119-2**. LCMS: 276.2.

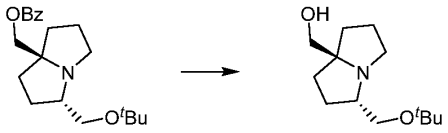
Intermediate 119-3: ((3*S*,7a*S*)-3-(*tert*-butoxymethyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methyl benzoate



119-2 **119-3**

[0706] To a solution of 2,4,6-tritert-butoxy-1,3,5-triazine (162.01 mg, 544.78 umol, 3 eq) and $Sc(OTf)_3$ (178.75 mg, 363.18 umol, 2 eq) in DCM (5 mL) was added [(3S,8S)-3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methyl benzoate (50 mg, 181.59 umol, 1 eq) in a glovebox. The mixture was stirred at 25 °C for 12 hrs. The combined reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN];B%: 30%-70%,8min) to give intermediate **119-3**. LCMS: 332.2.

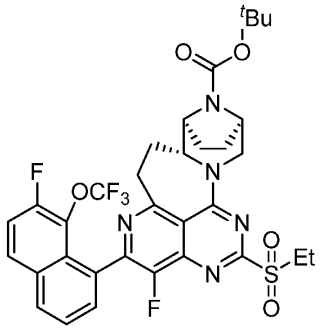
Intermediate 119-4: ((3*S*,7a*S*)-3-(*tert*-butoxymethyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol



119-3 119-4

[0707] To a solution of intermediate **119-3** (83 mg, 250.42 umol, 1 eq) in MeOH (2 mL) was added K_2CO_3 (69.22 mg, 500.83 umol, 2 eq). The mixture was stirred at 25 °C for 12 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(NH_4HCO_3)-ACN];B%: 10%-40%,10min) to give intermediate **119-4**. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 3.57 (m, 1 H) 3.39 - 3.45 (m, 1 H) 3.25 - 3.35 (m, 2 H) 3.10 - 3.18 (m, 1 H) 2.85 - 2.90 (m, 1 H) 2.63 - 2.72 (m, 1 H) 1.91 - 2.07 (m, 1 H) 1.45 - 1.82 (m, 8 H) 1.20 (s, 9 H).

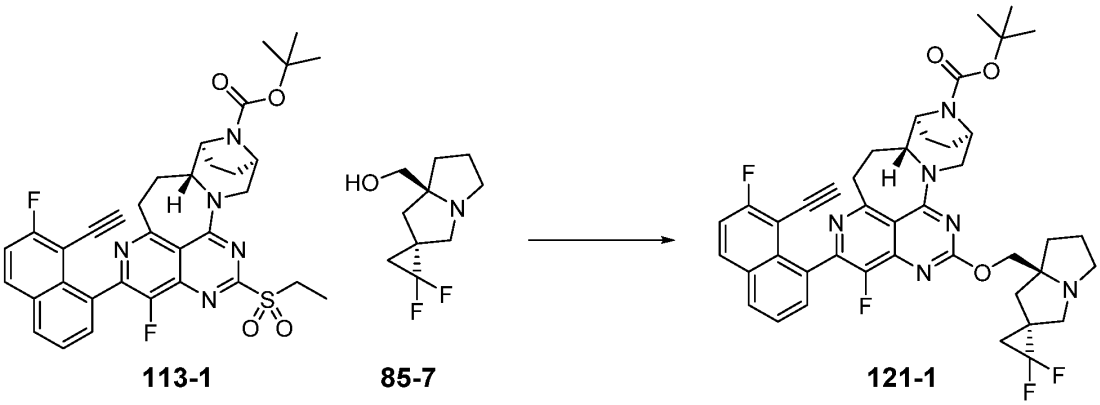
Intermediate 120-1: tert-butyl (5aR,6S,9R)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-(trifluoromethoxy)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



120-1

[0708] Intermediate **120-1** was synthesized in a manner similar to intermediate **102-1** using intermediate **65-1** instead of intermediate **7-5.** LCMS: 706.2.

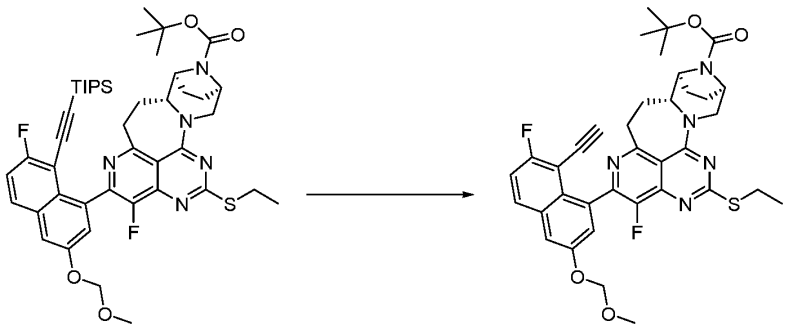
Intermediate 121-1: tert-butyl (5aR,6S,9R)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



113-1 85-7 121-1

[0709] Intermediate **121-1** was prepared in a manner analogous to Intermediate **85-8** using Intermediate **113-1** as the starting material. LCMS: 755.3.

Intermediate 122-1: tert-butyl (5aR,6S,9R)-12-(ethylthio)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

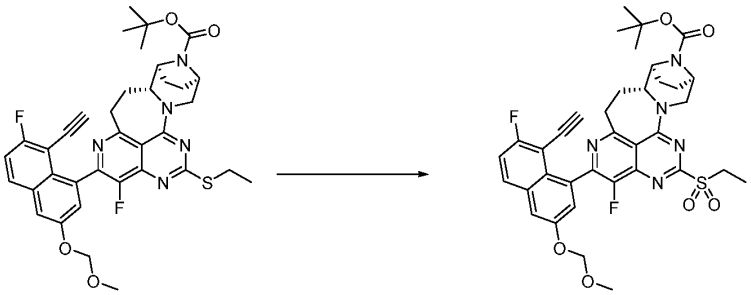


63-6 122-1

[0710] A vial was charged with Intermediate **63-6** (850mg, 1 mmol) and cesium fluoride (3.7 g, 25 mmol). N,N-dimethylformamide (17 mL) was added and the resulting mixture was stirred vigorously at room temperature for 30 min. The mixture was diluted with diethyl ether and ethyl acetate, and washed with saturated aqueous sodium bicarbonate, water, and brine. The solution was dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified

by flash column chromatography on silica gel using a gradient of ethyl acetate in hexanes (0-100%) to give Intermediate **122-1**. LCMS 674.3.

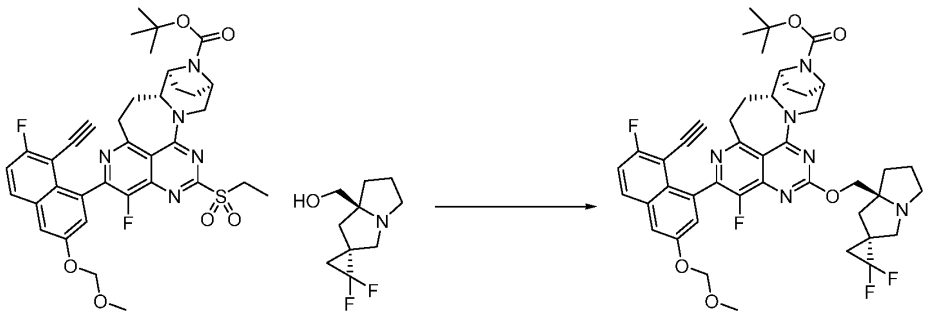
Intermediate 122-2: tert-butyl (5aR,6S,9R)-12-(ethylsulfonyl)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



122-1 **122-2**

[0711] Intermediate **122-2** was prepared in a manner analogous to Intermediate **13-9** using Intermediate **122-1** as the starting material. LCMS: 706.2.

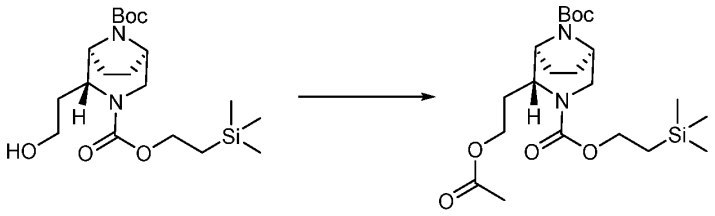
Intermediate 122-3: tert-butyl (5aR,6S,9R)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



122-2 **85-7** **122-3**

[0712] Intermediate **122-3** was prepared in a manner analogous to Intermediate **85-8** using Intermediate **122-2** as the starting material. LCMS: 815.4.

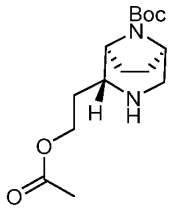
Intermediate 123-1: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2R,5R)-2-(2-acetoxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



75-2 **123-1**

[0713] Intermediate **75-2** (950 mg, 2.37 mmol) was dissolved in pyridine (20 ml) and cooled to 0 °C. To it was added acetic anhydride (1.12 ml, 11.9 mmol) and 4-Dimethylaminopyridine (57.9 mg, 0.474 mmol). The reaction mixture was stirred at 0 °C for 10 minutes. Upon completion, it was concentrated to dryness under reduced pressure and purified by silica gel chromatography eluting with ethyl acetate in hexane to afford the title compound. LCMS: 465.3

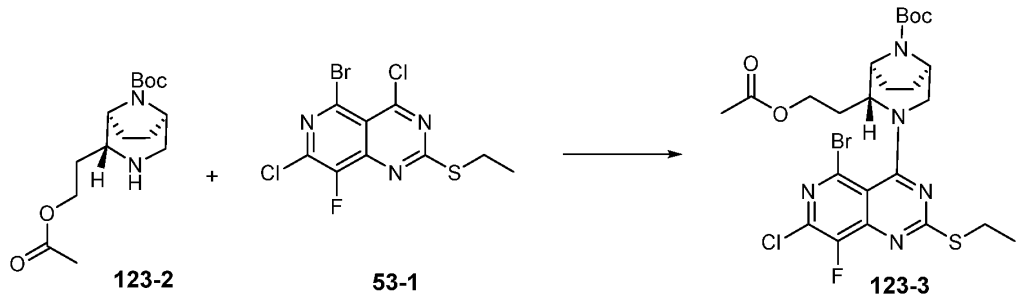
Intermediate 123-2: tert-butyl (1S,2R,5R)-2-(2-acetoxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



123-2

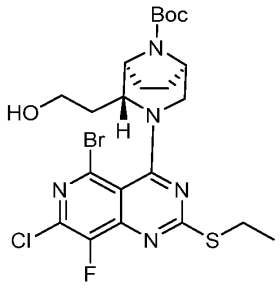
[0714] Intermediate **123-2** was synthesized in a manner similar to intermediate **75-5** using intermediate **123-1** instead of intermediate **75-4**. LCMS: 299.2

Intermediate 123-3: tert-butyl (1S,2R,5R)-2-(2-acetoxyethyl)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0715] Intermediate **123-3** was synthesized in a manner similar to Intermediate **53-5** using Intermediate **123-2** instead of Intermediate **53-4**. LCMS: 619.3.

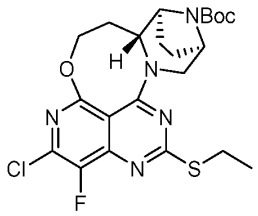
Intermediate 123-4: tert-butyl (1S,2R,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-(2-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



123-4

[0716] Intermediate **123-3** (270 mg, 0.436 mmol) was dissolved in THF (6 ml) /MeOH (4 ml) /water (2 ml) and to it was added lithium hydroxide monohydrate (91.5 mg, 2.18 mmol). The reaction mixture was stirred at room temperature for 10 minutes. Upon completion, it was partitioned between ethyl acetate and brine. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated to dryness to afford the title compound. LCMS: 576.2.

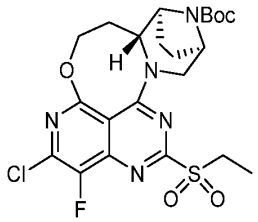
Intermediate 123-5: tert-butyl (6aR,7S,10R)-2-chloro-13-(ethylthio)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



123-5

[0717] Intermediate **123-4** (180 mg, 0.312 mmol), CuI (11.9 mg, 0.0124 mmol) and t-BuONa (60 mg, 0.624 mmol) were charged into a microwave tube and DMF (2 mL) was added. The system was evacuated and backfilled with argon three times. The reaction mixture was kept stirring at 100 °C for overnight. The cooled solution was diluted with ethyl acetate and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography to afford the title compound. LCMS: 496.2.

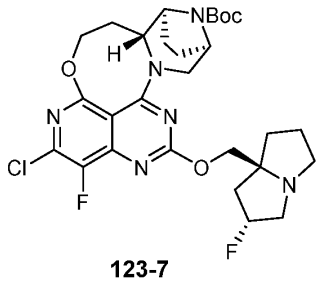
Intermediate 123-6: tert-butyl (6aR,7S,10R)-2-chloro-13-(ethylsulfonyl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



123-6

[0718] Intermediate **123-6** was synthesized in a manner similar to Intermediate **13-9** using Intermediate **123-5** instead of Intermediate **13-8**. LCMS: 528.2.

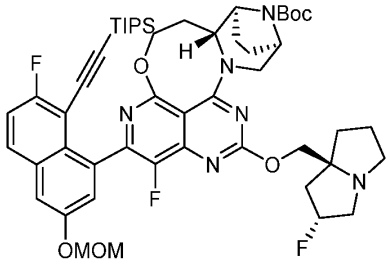
Intermediate 123-7: tert-butyl (6aR,7S,10R)-2-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



123-7

[0719] Intermediate **123-7** was synthesized in a manner similar to Intermediate **53-10** using Intermediate **123-6** instead of Intermediate **53-9**. LCMS: 593.3.

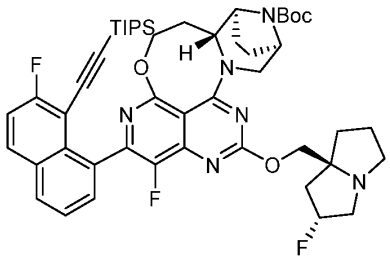
Intermediate 123-8: tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



123-8

[0720] Intermediate **123-8** was synthesized in a manner similar to Intermediate **2-1** using Intermediate **123-7** instead of Intermediate **17-9**. LCMS: 943.5.

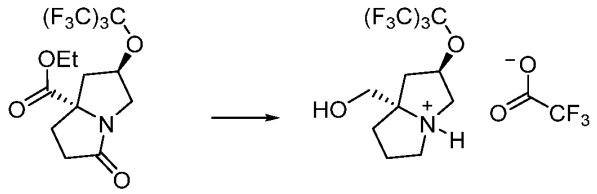
Intermediate 124-1: tert-butyl (6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



124-1

[0721] Intermediate **124-1** was synthesized in a manner similar to Intermediate **4-1** using Intermediate **123-7** instead of Intermediate **17-9**. LCMS: 883.5.

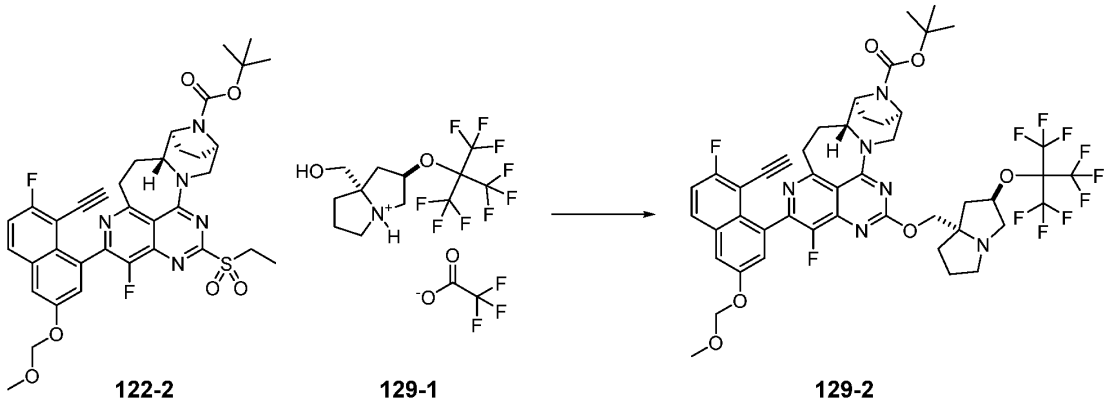
Intermediate 129-1: ((2*R*,7a*S*)-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol trifluoroacetic acid salt



129-0 **129-1**

[0722] Intermediate **129-1**, the absolute stereochemistry of which was assigned arbitrarily, was synthesized in a manner similar to intermediate **114-1** using intermediate **129-0** instead of intermediate **114-0**. ^{1}H-NMR (400 MHz,$CDCl_3$)δ ppm 12.98-12.47 (m, 1H), 5.19 (s, 1H), 4.01-3.92 (m, 2H), 3.88-3.80 (m, 1H), 3.72-3.54 (m, 1H), 3.40 (d, J = 13.6 Hz, 1H), 3.35-3.23 (m, 1H), 2.86 dd, J = 5.6, 14.8 Hz, 1H), 2.22 (s, 2H), 2.19-2.07 (m, 3H).

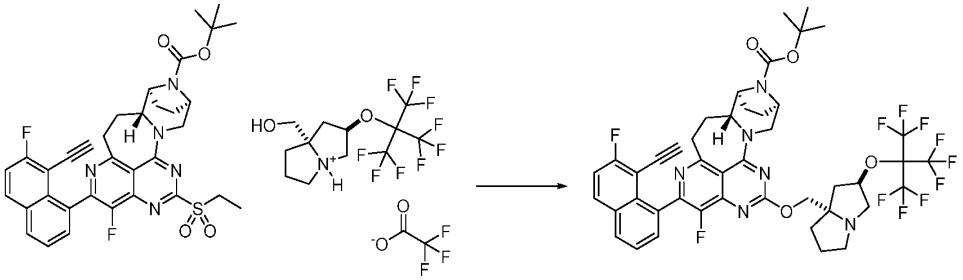
Intermediate 129-2: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-((*trans*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



122-2 129-1 129-2

[0723] Intermediate **122-2** (5 mg, 7.7 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **129-1** (5.7 mg, 12 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature for 5 minutes. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **129-2** as a single unknown *trans* pyrrolizidine isomer, which was used directly in the next step without purification. LCMS: 987.4.

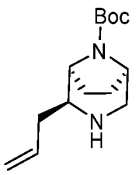
Intermediate 130-1: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*trans*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



113-1 129-1 130-1

[0724] Intermediate **113-1** (5 mg, 7.7 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **129-1** (5.7 mg, 12 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature for 5 minutes. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **130-1** as a single unknown *trans* pyrrolizidine isomer, which was used directly in the next step without purification. LCMS: 927.4.

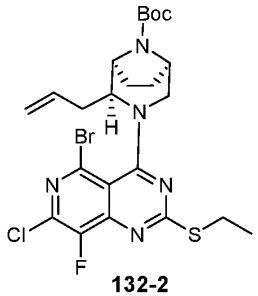
Intermediate 132-1: tert-butyl (1S,2S,5R)-2-allyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate:



132-1

[0725] Intermediate **132-1** was synthesized in a manner similar to Intermediate **75-5** using intermediate **170-1** instead of intermediate **27-5**. LCMS: 253.2.

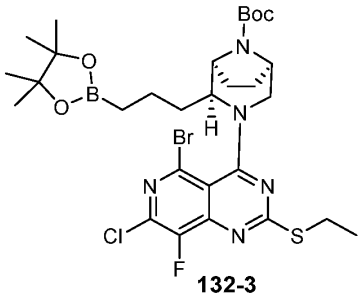
Intermediate 132-2: tert-butyl (1S,2S,5R)-2-allyl-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



132-2

[0726] Intermediate **132-2** was synthesized in a manner similar to Intermediate **53-5** using Intermediate **132-1** instead of Intermediate **53-4**. LCMS: 572.1.

Intermediate 132-3: tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

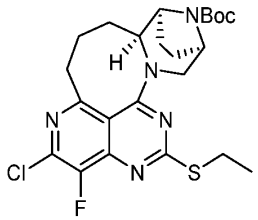


132-3

[0727] Intermediate **132-2** (57 mg, 0.1 mmol) was dissolved in dichloromethane (1 mL) and the stirred solution was evacuated and refilled with argon (3x). To this solution 1,2-bis(diphenylphosphino)ethane (12.2 mg, 0.03 mmol) was added, followed by bis(1,5-cyclooctadiene)diiridium(I) dichloride (10.3 mg, 0.015 mmol), after which the resulting mixture was again evacuated and refilled with nitrogen (3x). After stirring for 30 minutes at room temperature, the reaction mixture was cooled to 0 °C and a solution of pinacolborane (0.0229 ml, 0.015 mmol) in dichloromethane (0.5 mL) was added dropwise over 15 min. After the addition, the ice bath was removed, and the reaction was stirred for additional 90 minutes at room temperature. Upon completion, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude mixture

was purified by column chromatography (silica gel, 0 → 20% EtOAc in hexanes) to afford the title compound. LCMS: 702.2

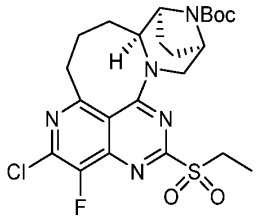
Intermediate 132-4: tert-butyl (6aS,7S,10R)-2-chloro-13-(ethylthio)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



132-4

[0728] Intermediate **132-3** (30 mg, 0.043 mmol) was dissolved in 1 mL dioxane and 0.5 mL water. Sodium carbonate (18.5 mg, 0.175 mmol) was added, and the mixture was degassed and backfilled with argon (3x). $Pd(dppf)Cl_2$ (4.6 mg, 0.006 mmol) was added, and the mixture was heated at 90 ˚C for 1 hour. The mixture was cooled to room temperature, diluted with EtOAc and washed with sat. aq. ammonium chloride solution. Combined organic fractions were washed with brine, dried and concentrated. The crude product was purified by column chromatography (silica gel, 0 → 20% EtOAc in hexanes) to afford the title compound. LCMS: 494.2

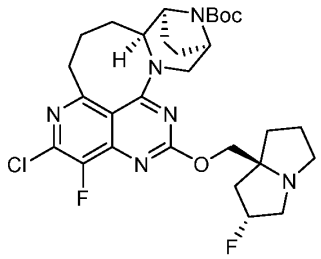
Intermediate 132-5: tert-butyl (6aS,7S,10R)-2-chloro-13-(ethylsulfonyl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



132-5

[0729] Intermediate **132-5** was synthesized in a manner similar to Intermediate **13-9** using Intermediate **132-4** instead of Intermediate **13-8**. LCMS: 526.2.

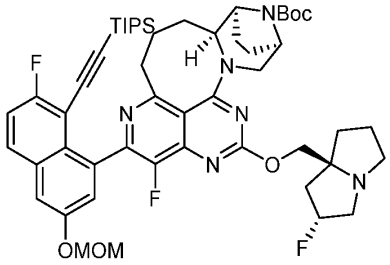
Intermediate 132-6: tert-butyl (6aS,7S,10R)-2-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



132-6

[0730] Intermediate **132-6** was synthesized in a manner similar to Intermediate **53-10** using Intermediate **132-5** instead of Intermediate **53-9**. LCMS: 591.3.

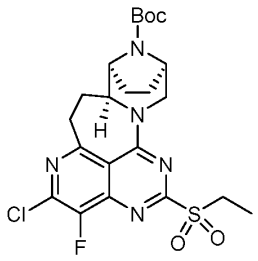
Intermediate 132-7: tert-butyl (6aS,7S,10R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



132-7

[0731] Intermediate **132-7** was synthesized in a manner similar to Intermediate **2-1** using Intermediate **132-6** instead of Intermediate **17-9**. LCMS: 942.6.

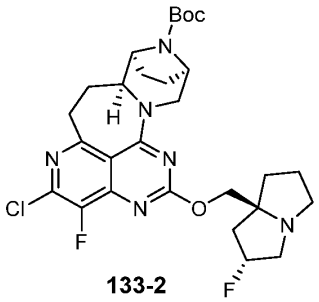
Intermediate 133-1: tert-butyl (5aS,6S,9R)-2-chloro-12-(ethylsulfonyl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



133-1

[0732] Intermediate **133-1** was synthesized in a manner similar to Intermediate **13-9** using Intermediate **170-4** instead of Intermediate **13-8**. LCMS: 512.2.

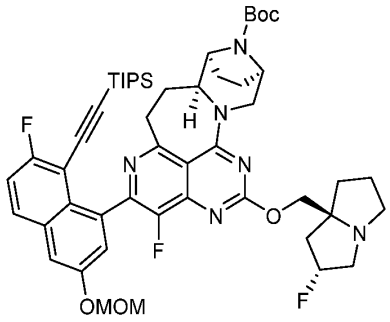
Intermediate 133-2: tert-butyl (5aS,6S,9R)-2-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



133-2

[0733] Intermediate **133-2** was synthesized in a manner similar to Intermediate **53-10** using Intermediate **133-1** instead of Intermediate **53-9**. LCMS: 578.3.

Intermediate 133-3: tert-butyl (5aS,6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

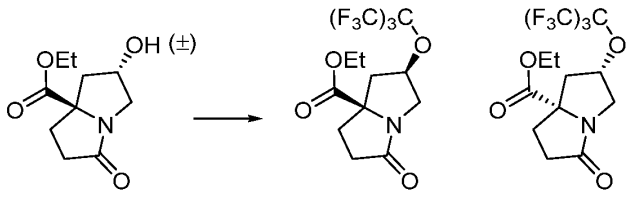


133-3

[0734] Intermediate **133-3** was synthesized in a manner similar to Intermediate **2-1** using Intermediate **133-2** instead of Intermediate **17-9**. LCMS: 927.6.

Intermediate 144-0: (2R,7aR)-ethyl 2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-5-oxohexahydro-1H-pyrrolizine-7a-carboxylate

Intermediate 134-0: (2S,7aS)-ethyl 2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)-5-oxohexahydro-1H-pyrrolizine-7a-carboxylate



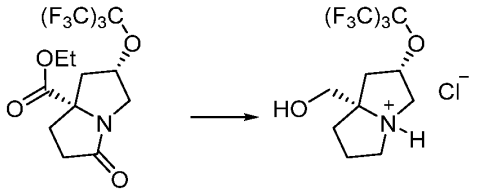
144-0 134-0

[0735] To a solution of *rac*-ethyl (2S,7aR)-2-hydroxy-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (200.00 mg, 937.96 μmol, 1.00 *eq*) and 1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-ol (221.39 mg, 937.96 μmol, 1.00 *eq*) in PhMe (2.00 mL) was added 2-(tributyl-λ^5-phosphanylidene)acetonitrile (679.13 mg, 2.81 mmol, 3.00 *eq*) at 0°C under N_2. The mixture was stirred at 80°C for 12 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by *prep*-HPLC(column: Phenomenex luna C18 80*40mm*3 um; mobile phase: [water(HCl)-ACN];B%: 45%-75%,7min) to give a mixture of intermediate **144-0** and **134-0**. The mixture of enantiomers was separated by SFC (column: DAICEL

CHIRALPAK IC(250mm*30mm,10um);mobile phase: [0.1%NH_3H_2O IPA];B%: 10%-10%,7min). The peak with shorter Rt (Rt=0.995) was designated as intermediate **144-0**, the absolute stereochemistry of which was assigned arbitrarily. Intermediate **144-0**: ^{1}H-NMR (400 MHz,CDCl3) δ ppm = 14.50 - 14.48 (m, 1H), 4.97 - 4.90 (m, 1H), 4.17 - 4.10 (m, 2H), 4.10 - 4.04 (m, 1H), 3.22 (d, J = 13.6 Hz, 1H), 2.81 - 2.66 (m, 2H), 2.51 - 2.30 (m, 2H), 2.12 - 1.98 (m, 1H), 1.91 (dd, J = 6.4, 14.4 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H).

[0736] The peak with longer Rt (Rt=1.283) was designated as intermediate **134-0**, the absolute stereochemistry of which was assigned arbitrarily. Intermediate **134-0**: ^{1}H-NMR (400 MHz,$CDCl_3$) δ ppm = 5.25 - 5.12 (m, 1H), 4.14 - 4.07 (m, 2H), 4.06 - 3.99 (m, 1H), 3.06 - 2.96 (m, 1H), 2.67 - 2.57 (m, 1H), 2.56 - 2.51 (m, 1H), 2.34 - 2.18 (m, 4H), 1.23 - 1.17 (m, 3H).

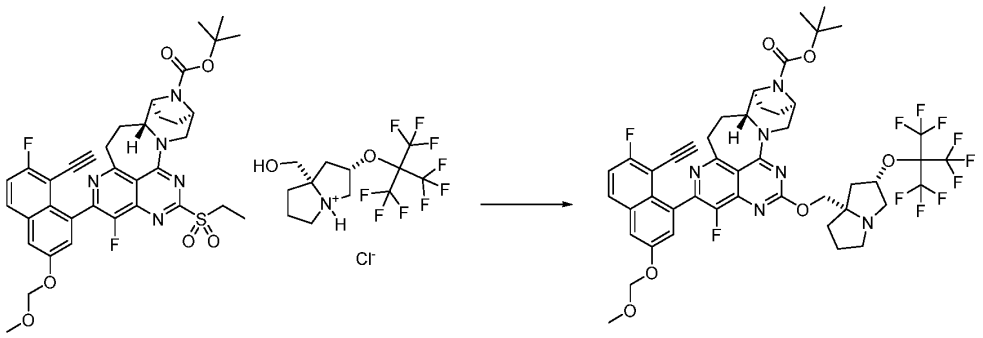
Intermediate 134-1: ((2*S*,7a*S*)-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol hydrogen chloride salt



134-0 **134-1**

[0737] To a mixture of intermediate **134-0** (60.00 mg, 139.13 umol, 1.00 *eq*) in THF (2.00 mL) was added BF_3•Et_2O (315.95 mg, 2.23 mmol, 274.74 uL, 16.00 *eq*) at 0°C under N_2, the reaction mixture was stirred at 0°C for 5 mins, then $NaBH_4$ (42.11 mg, 1.11 mmol, 8.00 *eq*) was added, the reaction mixture was stirred at 60°C for 1 hr under N_2. To the reaction mixture was added sat.aq. NH_4Cl (10.00 mL) slowly and stirred at 0°C for 0.5 hr under N_2, and then extracted with EtOAc (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC(column: Phenomenex Luna C18 100*30mm*5um;mobile phase: [water(TFA)-ACN];B%: 10%-40%,10min) to give crude intermediate **134-1**, which was repurified by chiral SFC to give intermediate **134-1**, the absolute stereochemistry of which was assigned arbitrarily. ^{1}H-NMR (400 MHz,CDCl3)δppm = 5.10 - 5.03 (m, 1H), 4.14 (d, J = 12.8 Hz, 1H), 4.05 (br d, J = 13.2 Hz, 1H), 3.73 - 3.59 (m, 2H), 3.24 - 3.11 (m, 2H), 2.66 - 2.56 (m, 1H), 2.69 - 2.54 (m, 1H), 2.44 - 2.34 (m, 1H), 2.33 - 2.20 (m, 2H), 2.12 - 1.99 (m, 1H), 1.92 - 1.81 (m, 1H).

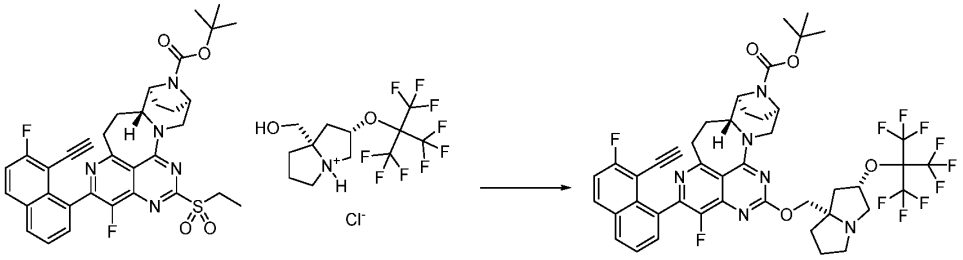
Intermediate 134-2: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-((*cis*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



122-2 134-1 134-2

[0738] Intermediate **122-2** (5 mg, 7.7 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **134-1** (4.8 mg, 12 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature for 5 minutes. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **134-2** as a single unknown *cis* pyrrolizidine isomer, which was used directly in the next step without purification. LCMS: 987.4.

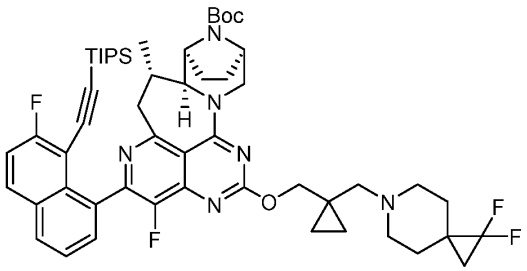
Intermediate 135-1: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*cis*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



113-1 134-1 135-1

[0739] Intermediate **113-1** (5 mg, 7.7 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **134-1** (4.8 mg, 12 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature for 5 minutes. Additional LiHMDS was added dropwise until full conversion was observed by LCMS. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **135-1** as a single unknown *cis* pyrrolizidine isomer, which was used directly in the next step without purification. LCMS: 927.4.

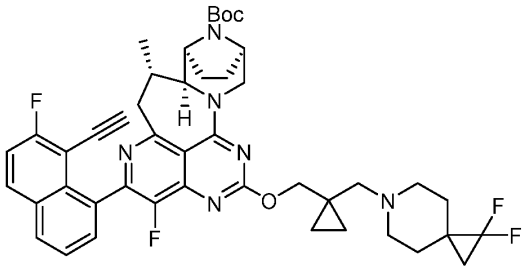
Intermediate 136-1: tert-butyl (5S,5aS,6S,9R)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



136-1

[0740] Intermediate 136-1 was synthesized in a manner similar to **Intermediate 84-4** using (1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methanol instead of ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol. LCMS: 953.3 $[M + H]^+$

Intermediate 136-2: tert-butyl (5S,5aS,6S,9R)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

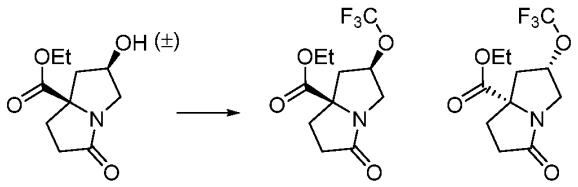


136-2

[0741] Intermediate 136-2 was synthesized in a manner similar to **Intermediate 84-5** using **Intermediate 136-1** instead of **Intermediate 84-4.** LCMS: 797.1 $[M + H]^+$

Intermediate 137-0: (2*R*,7a*R*)-ethyl 5-oxo-2-(trifluoromethoxy)hexahydro-1*H*-pyrrolizine-7a-carboxylate

Intermediate 139-0: (2*S*,7a*S*)-ethyl 5-oxo-2-(trifluoromethoxy)hexahydro-1*H*-pyrrolizine-7a-carboxylate

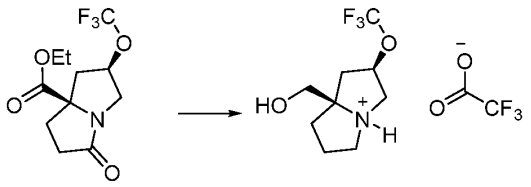


137-0 139-0

[0742] To a solution of *rac*-ethyl (2*R*,7a*R*)-2-hydroxy-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (50.00 mg, 234.49 umol, 1 eq) in EtOAc (2 mL) was added AgOTf (180.75 mg, 703.47 umol, 3 eq), $TMSCF_3$ (100.03 mg, 703.47 umol, 3 eq), KF (54.49 mg, 937.96 umol, 21.97 uL, 4 eq), 2-fluoropyridine (68.30 mg, 703.47 umol, 60.44 uL, 3 eq) and Selectfluor (83.07 mg, 234.49 umol, 1 eq). The mixture was stirred at 25 °C for 12 hr. The residue was separated by chiral SFC (column: (s,s) WHELK-O1 (100×4.6mm I.D., 3.5um);mobile phase: A: CO2,

B:IPA(0.1%IPAm, v/v): 10%-50%, 3.4mL/min). The peak with shorter Rt (Rt = 1.210) was designated as intermediate **137-0**, the absolute stereochemistry of which was assigned arbitrarily. Intermediate **137-0**: LCMS: 282.1. The peak with longer Rt (Rt = 1.454) was designated as intermediate **139-0**, the absolute stereochemistry of which was assigned arbitrarily. Intermediate **139-0**: LCMS: 282.1.

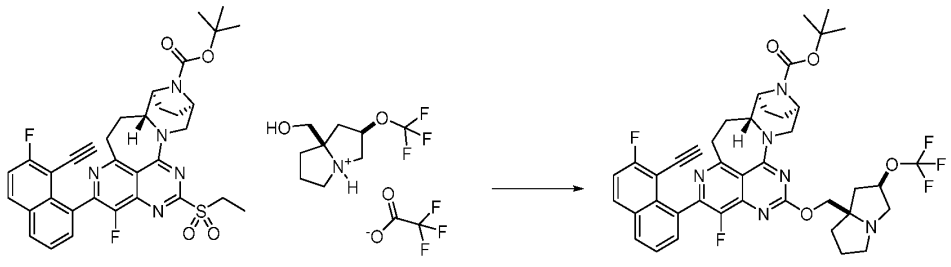
Intermediate 137-1: ((2*R*,7a*R*)-2-(trifluoromethoxy)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol trifluoracetic acid salt



137-0 **137-1**

[0743] To a mixture of intermediate **137-0**(60 mg, 213.35 umol, 1 *eq*) in THF (3 mL) was added BF_3•Et_2O (484.49 mg, 3.41 mmol, 421.30 uL, 16 *eq*) at 0°C under N_2. The reaction mixture was stirred at 0°C for 5 mins, then $NaBH_4$ (64.57 mg, 1.71 mmol, 8 *eq*) was added, the reaction mixture was stirred at 60°C for 1 hr under N_2. To the reaction mixture was added sat.aq. NH_4Cl (10 mL) slowly and the reaction mixture was stirred at 0°C for 0.5 hr under N_2, and then extracted with EtOAc (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC(column: Phenomenex Luna C18 100*30mm*5um;mobile phase: [water(TFA)-ACN];B%: 1%-20%,10min) to give intermediate **137-1**, the absolute stereochemistry of which was assigned arbitrarily. LCMS: 226.1.

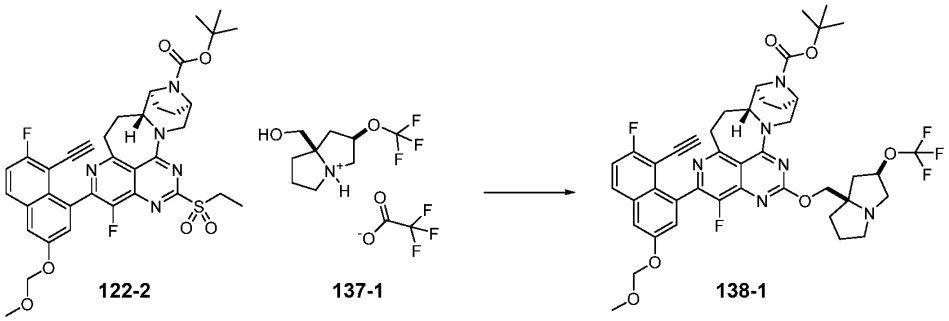
Intermediate 137-2: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*cis*-2-(trifluoromethoxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



113-1 **137-1** **137-2**

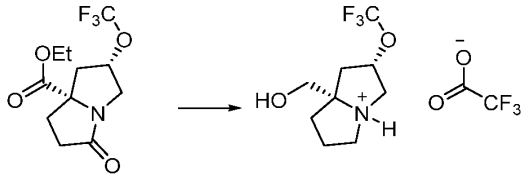
[0744] Intermediate **113-1** (5 mg, 7.7 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **137-1** (4 mg, 12 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature for 5 minutes. Additional LiHMDS was added dropwise until full conversion was observed by LCMS. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **137-2** as a single unknown *cis* pyrrolizidine isomer, which was used directly in the next step without purification. LCMS: 777.4.

Intermediate 138-1: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-((*cis*-2-(trifluoromethoxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0745] Intermediate **122-2** (5 mg, 7.7 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **137-1** (4 mg, 12 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature for 5 minutes. Additional LiHMDS was added dropwise until full conversion was observed by LCMS. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **138-1** as a single unknown *cis* pyrrolizidine isomer, which was used directly in the next step without purification. LCMS: 837.4.

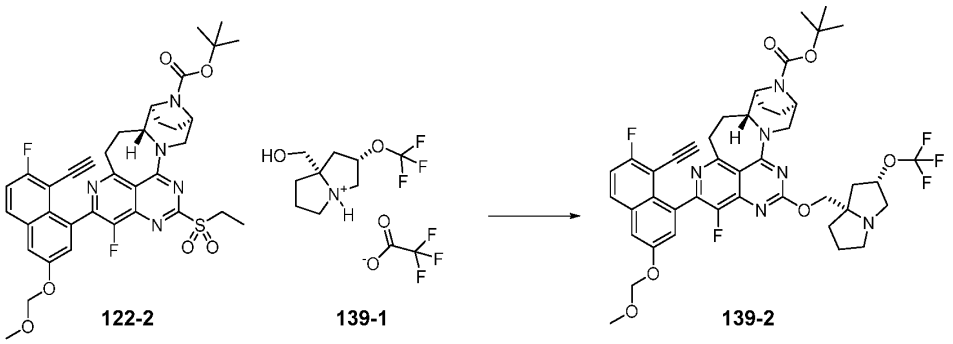
Intermediate 139-1: ((2*S*,7a*S*)-2-(trifluoromethoxy)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol trifluoracetic acid salt



139-0 139-1

[0746] To a mixture of intermediate **139-0** (25 mg, 88.9 umol, 1 *eq*) and THF (2 mL) was added BF_3•Et_2O (201.9 mg, 1.4 mmol, 175.5 uL, 16 *eq*) at 0°C under N_2, the reaction mixture was stirred at 0°C for 5 mins, then $NaBH_4$ (26.9 mg, 711.2 umol, 8 *eq*) was added, the reaction mixture was stirred at 60°C for 1 hr under N_2. To the reaction mixture was added sat. aq. NH4Cl (10 mL) slowly and stirred at 0°C for 0.5 hr under N_2, and then extracted with EtOAc (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [water(TFA)-ACN];B%: 1%-20%,10min) to give intermediate **139-1**, the absolute stereochemistry of which was assigned arbitrarily. LCMS: 226.1.

Intermediate 139-2: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-((*cis*-2-(trifluoromethoxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

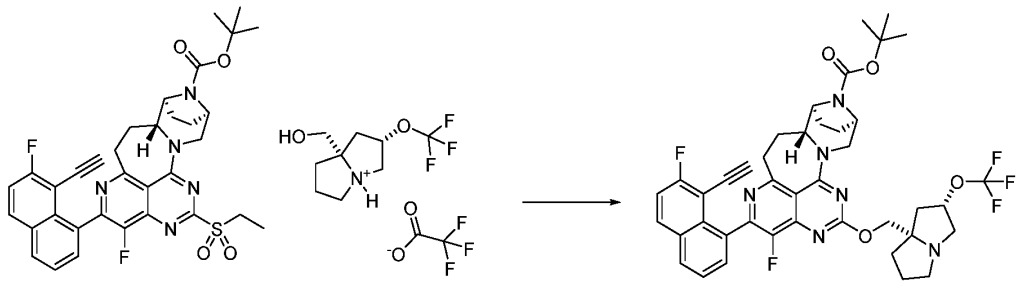


122-2 139-1 139-2

[0747] Intermediate **122-2** (6 mg, 8 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **139-1** (4 mg, 12 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature

for 5 minutes. Additional LiHMDS was added dropwise until conversion was observed by LCMS. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **139-2** as a single unknown *cis* pyrrolizidine isomer, which was used directly in the next step without purification. LCMS: 837.4.

Intermediate 140-1: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*cis*-2-(trifluoromethoxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

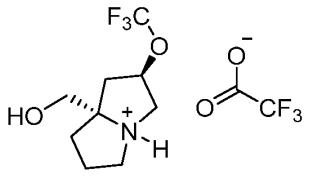


113-1 139-1 140-1

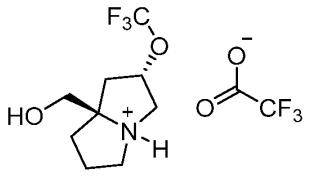
[0748] Intermediate **113-1** (6 mg, 9 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **139-1** (4 mg, 13 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature for 5 minutes. Additional 1M LiHMDS was added drop by drop until complete conversion was observed by LCMS. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **140-1** as a single unknown *cis* pyrrolizidine isomer, which was used directly in the next step without purification. LCMS: 777.4.

Intermediate 141-0: ((2*R*,7a*S*)-2-(trifluoromethoxy)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol trifluoroacetic acid salt

Intermediate 141-1: ((2*S*,7a*R*)-2-(trifluoromethoxy)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol trifluoroacetic acid salt



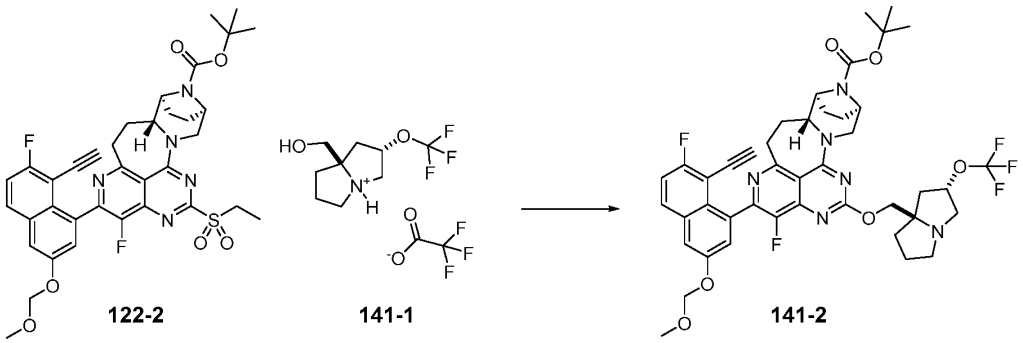
141-0



141-1

[0749] Intermediate **141-0**, the absolute stereochemistry of which was assigned arbitrarily, and intermediate **141-1**, the absolute stereochemistry of which was assigned arbitrarily, were synthesized in a manner similar to intermediate **137-1** and **139-1**, respectively, using *rac*-(2*S*,7a*R*)-ethyl 2-hydroxy-5-oxohexahydro-1*H*-pyrrolizine-7a-carboxylate instead of *rac*-ethyl (2*R*,7a*R*)-2-hydroxy-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate. Intermediate **141-0**: LCMS: 226.1. Intermediate **141-1**: LCMS: 226.1.

Intermediate 141-2: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-((*trans*-2-(trifluoromethoxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

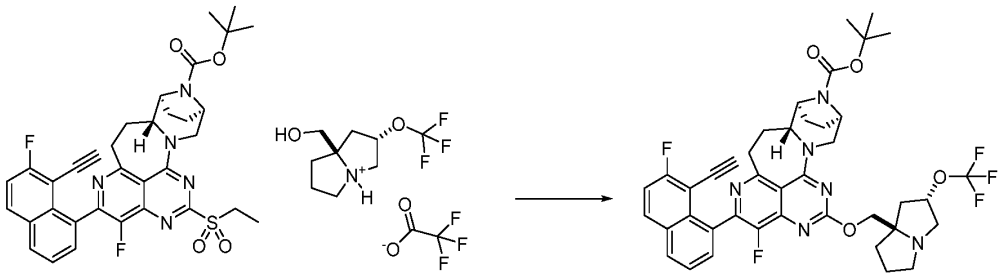


122-2 **141-1** **141-2**

[0750] Intermediate **122-2** (5 mg, 7.4 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **141-1** (4 mg, 12 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature

for 5 minutes. Additional 1M LiHMDS was added until complete conversion was observed by LCMS. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **141-2** as a single unknown *trans* pyrrolizidine isomer, which was used directly in the next step without purification. LCMS: 837.4.

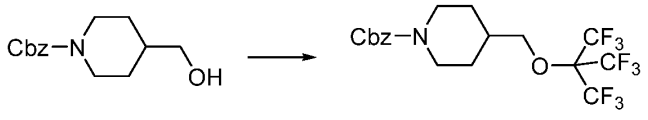
Intermediate 142-1: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*trans*-2-(trifluoromethoxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



113-1 141-1 142-1

[0751] Intermediate **113-1** (5 mg, 8 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **141-1** (4 mg, 12 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature for 5 minutes. Additional 1M LiHMDS was added until conversion was observed by LCMS. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **142-1** as a single unknown *trans* pyrrolizidine isomer, which was used directly in the next step without purification. LCMS: 777.4.

Intermediate 143-1: benzyl 4-(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)piperidine-1-carboxylate



143-1

[0752] A solution of benzyl 4-(hydroxymethyl)piperidine-1-carboxylate (500.1 mg, 2.0 mmol) and di-tert-butyl azodicarboxylate (2311.9 mg, 10.0 mmol) in tetrahydrofuran (9.mL) was stirred at 0 °C as 1 M trimethylphosphine in tetrahydrofuran (10 mL, 10 mmol) followed by nonafluoro-tert-BuOH (2.8 mL, 20.1 mmol) were added. After addition, the reaction mixture was stirred at 0 °C for 30 min and then at 70 °C overnight. The reaction mixture was diluted with ethyl acetate and the resulting solution was washed with sat'd NH_4Cl (x 2), sat'd $NaHCO_3$ (x 2), and brine (x 1). After the resulting organic solution was dried ($MgSO_4$), and concentrated, the residue was purified by silica gel column chromatography eluting 0-45% ethyl acetate in hexane to give intermediate 143-1. LCMS: 468.2.

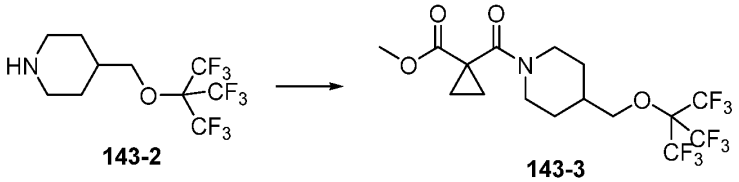
Intermediate 143-2: 4-(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)piperidine



143-1 143-2

[0753] A mixture of benzyl intermediate 143-1 (264.1 mg, 0.565 mmol) and 10% palladium on carbon (28.1 mg) in ethanol (10 mL) was stirred under H_2 atmosphere. After 1 h, the reaction mixture was filtered and the filtrate was concentrated to give intermediate 143-2. LCMS: 334.1.

Intermediate 143-3: methyl 1-(4-(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)piperidine-1-carbonyl)cyclopropane-1-carboxylate

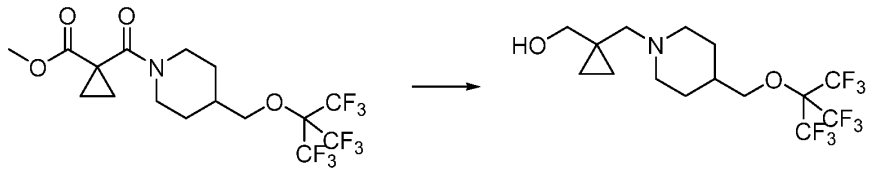


143-2 143-3

[0754] A mixture of intermediate 143-2 (0.57 mmol), 1-methoxycarbonylcyclopropanecarboxylic acid (88.3 mg, 0.613 mmol), and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (331.1 mg, 0.87 mmol) in dimethylformamide (1.5 mL) was stirred at rt as diisopropylethylamine (0.34 mL, 2.0 mmol) was added. The resulting mixture was stirred at rt. After 3 d, the reaction mixture was diluted with ethyl acetate (25 mL) and washed with saturated $NaHCO_3$ (~25 mL x 1) and then water (~25 mL x 1). After the aqueous fractions were extracted with ethyl acetate (~20 mL x 1), the resulting organic fractions were combined, dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel

column chromatography eluting 0-100% ethyl acetate in hexane to give intermediate 143-3. LCMS: 460.2.

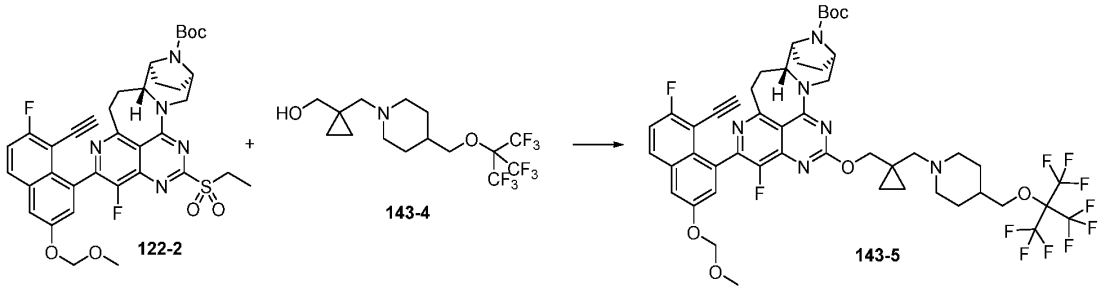
Intermediate 143-4: (1-((4-(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)piperidin-1-yl)methyl)cyclopropyl)methanol



143-3 143-4

[0755] A solution of methyl intermediate **143-3** (198.9 mg, 0.44 mmol) was stirred at 0 °C as 2 M lithium aluminum hydride (0.44 mL, 0.88 mmol) was added. The resulting mixture was stirred at rt for 3 h. The reaction mixture was stirred at 0 °C as sodium sulfate decahydrate (~2.3 g). After the mixture was stirred for 10 min, it was diluted with ethyl acetate (~20 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography eluting 0-100% ethyl acetate in hexane to give intermediate **143-4**. LCMS: 418.2.

Intermediate 143-5: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-((1-((4-(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

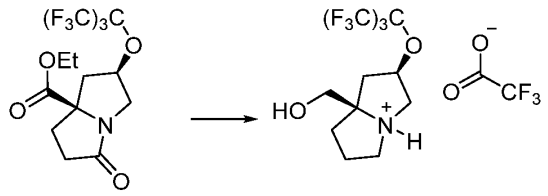


122-2 143-4 143-5

[0756] A mixture of intermediate **122-2** (41.4 mg, 58.7 umol) and intermediate **143-4** (34.8 mg, 83.5 umol) was co-evaporated with toluene (x 2) and dissolved in 2-methyltetrahydrofuran (0.7 mL). The solution was stirred at 0 °C as 1 M lithium bis(trimethylsilyl)amide was added dropwise. After 15 min, the reaction mixture was diluted with Sat'd $NaHCO_3$ and the product was extracted with ethyl acetate (x 2). After the extracts were washed with water (x 1), the organic

fractions were combined, dried ($MgSO_4$), and concentrated to give intermediate **143-5**. LCMS: 1029.4.

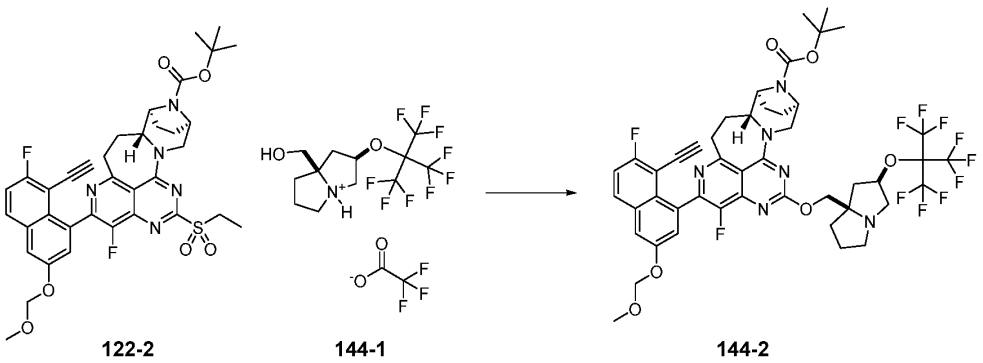
Intermediate 144-1: ((2*R*,7a*R*)-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol trifluoroacetic acid salt



144-0 144-1

[0757] To a solution of intermediate **144-0** (100 mg, 231.88 umol, 1 eq) in THF (4 mL) was added BF_3•Et_2O (526.57 mg, 3.71 mmol, 457.89 uL, 16 eq) and $NaBH_4$ (70.18 mg, 1.86 mmol, 8 eq) at 0°C. The mixture was stirred at 60°C for 2 hrs. The reaction mixture was quenched by addition saturated aqueous NH_4Cl solution (3 mL) at 0°C, and then extracted with EtOAc (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um;mobile phase: [water(TFA)-ACN];B%: 10%-40%,10min) to give intermediate **144-1**, the absolute stereochemistry of which was assigned arbitrarily. LCMS: 376.1.

Intermediate 144-2: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-((*cis*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

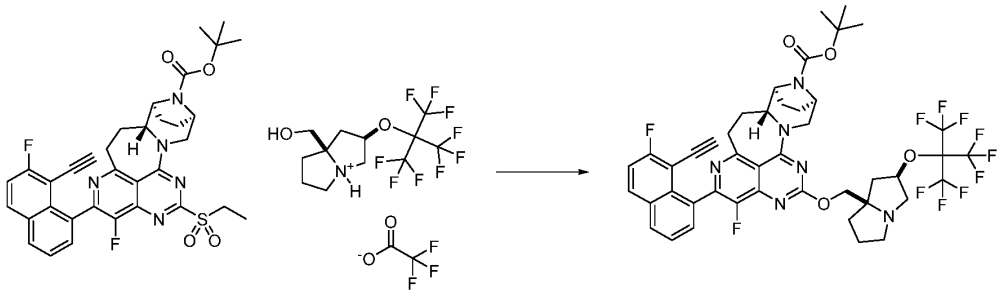


122-2 144-1 144-2

[0758] Intermediate **122-2** (5 mg, 7 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **144-1** (5.5 mg, 12 μmol) was left on high vacuum

overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 26 uL, 26 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature for 5 minutes. Additional LiHMDS was added dropwise until full conversion was observed by LCMS. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **144-2** as a single unknown *cis* pyrrolizidine isomer, which was used directly in the next step without purification. LCMS: 987.4.

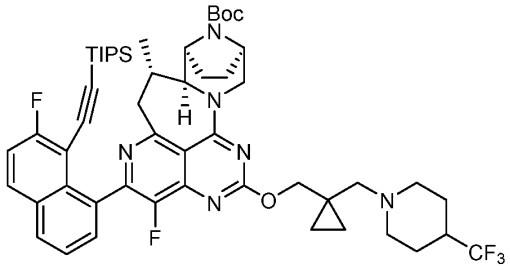
Intermediate 145-1: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*cis*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



113-1 144-1 145-1

[0759] Intermediate **113-1** (5 mg, 8 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **144-1** (6 mg, 12 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 26 uL, 26 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature for 5 minutes. Additional LiHMDS was added dropwise until conversion was observed by LCMS. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **145-1** as a single unknown *cis* pyrrolizidine isomer, which was used directly in the next step without purification. LCMS: 927.4.

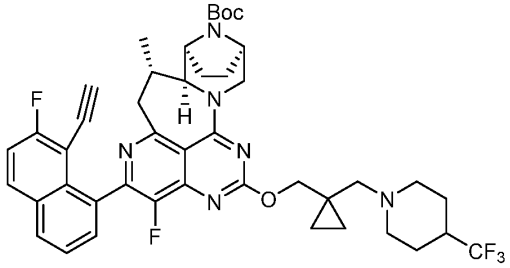
Intermediate 146-1: tert-butyl (5S,5aS,6S,9R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-12-((1-((4-(trifluoromethyl)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



146-1

[0760] Intermediate 146-1 was synthesized in a manner similar to **Intermediate 84-4** using (1-((4-(trifluoromethyl)piperidin-1-yl)methyl)cyclopropyl)methanol instead of ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol. LCMS: 959.2 $[M + H]^+$

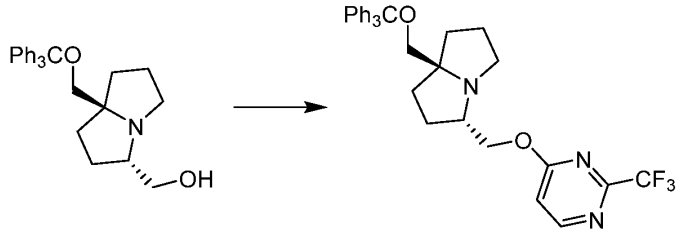
Intermediate 146-2: tert-butyl (5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-12-((1-((4-(trifluoromethyl)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



146-2

[0761] Intermediate 146-2 was synthesized in a manner similar to **Intermediate 84-5** using **Intermediate 146-1** instead of **Intermediate 84-4.** LCMS: 803.1 $[M + H]^+$

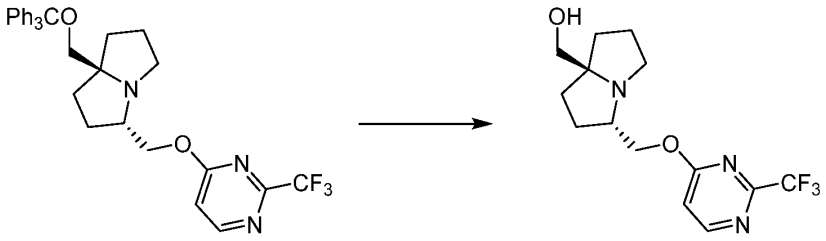
Intermediate 148-1: (3S,7aS)-3-(((2-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)-7a-((trityloxy)methyl)hexahydro-1H-pyrrolizine



63-2 148-1

[0762] To a mixture of intermediate **63-2** (50 mg, 120.90 umol, 1 eq) in THF (2 mL) was added t-BuOK (1 M, 181.35 uL, 1.5 eq) at 0°C, and the resulting mixture was stirred at 0°C for 30 mins, then 4-chloro-2-(trifluoromethyl)pyrimidine (26.48 mg, 145.08 umol, 1.2 eq) was added, then the reaction mixture was stirred at 25°C for 30 mins. The reaction mixture was quenched with H_2O (10 ml) and was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN];B%: 70%-95%,8min) to give intermediate **148-1**. LCMS: 318.1 $[M–C_{19}H_{13}]^+$.

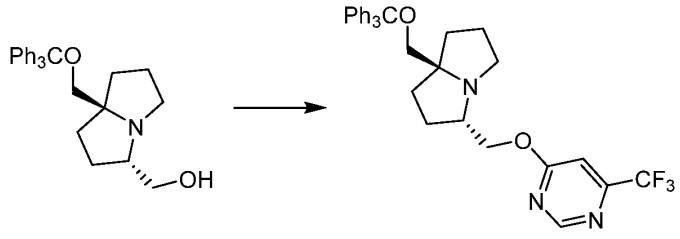
Intermediate 148-2: ((3*S*,7a*S*)-3-(((2-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol



148-1 148-2

[0763] To a solution of intermediate **148-1** (130 mg, 232.30 umol, 1 eq) in EtOAc (1 mL) was added HCl/EtOAc (0.25 mL). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure. The residue was diluted with H_2O (5 mL) and was washed with EtOAc (4 mL * 3). The combined aqueous phases were lyophilized to give intermediate **148-2** as its HCl salt. LCMS: 318.1.

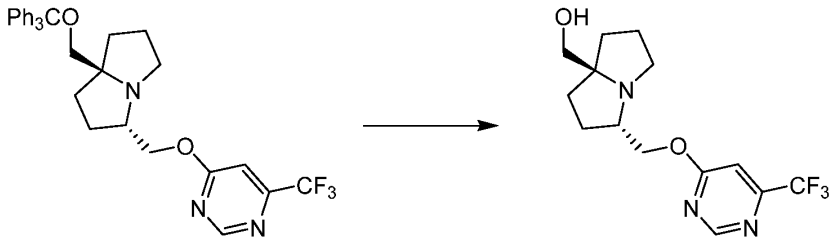
Intermediate 149-0: (3S,7aS)-3-(((6-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)-7a-((trityloxy)methyl)hexahydro-1H-pyrrolizine



63-2 149-0

To a solution of intermediate **63-2** (50 mg, 120.90 μmol) in THF (1 mL) was added t-BuOK (1 M, 181.36 μL) at 0°C for 30 mins, then 4-chloro-6-(trifluoromethyl)pyrimidine (26.48 mg, 145.09 μmol) was added. The mixture was stirred at 25°C for 30 mins. The reaction mixture was quenched by addition saturated aqueous NH_4Cl (5 mL) at 0°C, and then extracted with EtOAc (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC(column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN];B%: 50%-95%,8min) to give intermediate **149-0**. LCMS: 560.2.

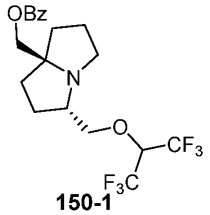
Intermediate 149-1: ((3*S*,7a*S*)-3-(((6-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol



149-0 149-1

[0764] A mixture of intermediate **149-0** (120 mg, 214.43 μmol) in EtOAc (2 mL) and HCl/EtOAc (0.5 mL) was stirred at 25 °C for 1 hr. The reaction solution is blow-dried with N_2. The residue was purified by *prep*-HPLC(column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(NH4HCO3)-ACN];B%: 10%-40%,8min) to give intermediate **149-1**. LCMS: 318.0.

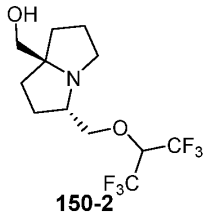
Intermediate 150-1: ((3*S*,7a*S*)-3-(((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methyl benzoate



150-1

[0765] Intermediate **150-1** was synthesized in a manner similar to intermediate **109-1** using intermediate **119-2** instead of intermediate **63-2** and using 1,1,1,3,3,3-hexafluoropropan-2-ol instead of 1,1,1,3,3,3-hexafluoro-2-methyl-propan-2-ol. ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 8.08 (d, J = 7.3 Hz, 2H), 7.65-7.56 (m, 1H), 7.53-7.43 (m, 2H), 4.26-4.22 (m, 1H), 4.21-4.14 (m, 2H), 4.10-4.04 (m, 1H), 3.50-3.41 (m, 1H), 2.99 (br d, J = 1.3 Hz, 1H), 2.83-2.72 (m, 1H), 2.22-2.09 (m, 1H), 2.03-1.86 (m, 4H), 1.86-1.79 (m, 2H), 1.64-1.56 (m, 2H).

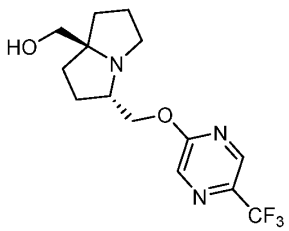
Intermediate 150-2: ((3*S*,7a*S*)-3-(((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol



150-2

[0766] Intermediate **150-2** was synthesized in a manner similar to intermediate **119-4** using intermediate **150-1** instead of intermediate **119-3**. LCMS: 322.0.

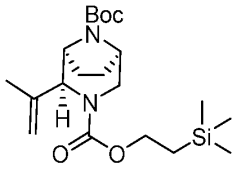
Intermediate 155-1: ((3S,7aS)-3-(((5-(trifluoromethyl)pyrazin-2-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



155-1

[0767] Intermediate **155-1** was synthesized in a manner similar to intermediate **148-2** using 2-chloro-5-(trifluoromethyl)pyrazine instead of 4-chloro-2-(trifluoromethyl)pyrimidine. LCMS: 318.0.

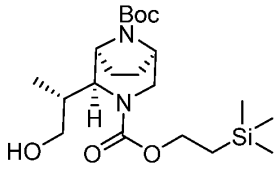
Intermediate 156-1: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-(prop-1-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



156-1

[0768] Intermediate 156-1 was synthesized in a manner similar to **64-1** using intermediate **86-4** instead of intermediate **61-1**. LCMS: 419.1 $[M + Na]^+$.

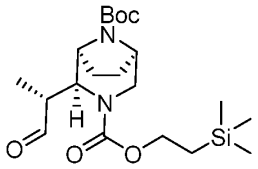
Intermediate 156-2: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-((R)-1-hydroxypropan-2-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



156-2

[0769] Intermediate **156-2** was synthesized in a manner similar to **75-2** using intermediate **156-1** instead of intermediate **75-1**. This isomer is the faster eluted fraction. LCMS: 415.3 $[M + H]^+$.

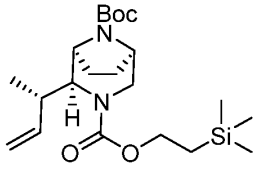
Intermediate 156-3: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-((R)-1-oxopropan-2-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



156-3

[0770] Intermediate **156-3** was synthesized in a manner similar to **75-3** using intermediate **156-2** instead of intermediate **75-2**. LCMS: 413.3 $[M + H]^+$.

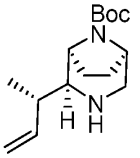
Intermediate 156-4: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-((S)-but-3-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



156-4

[0771] Intermediate **156-4** was synthesized in a manner similar to **75-4** using intermediate **156-3** instead of intermediate **75-3**. LCMS: 411.0 $[M + H]^+$.

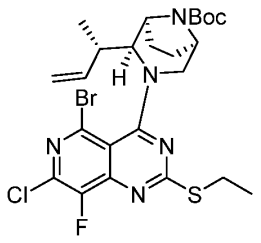
Intermediate 156-5: tert-butyl (1S,2S,5R)-2-((S)-but-3-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



156-5

[0772] Intermediate **156-5** was synthesized in a manner similar to **75-5** using intermediate **156-4** instead of intermediate **75-4**. LCMS: 267.1 $[M + H]^+$.

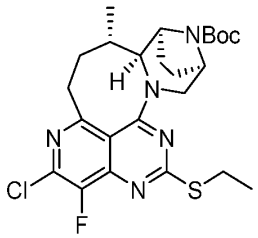
Intermediate 156-6: tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-((S)-but-3-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



156-6

[0773] Intermediate **156-6** was synthesized in a manner similar to **75-6** using intermediate **156-5** instead of intermediate **75-5**. LCMS: 586.8, 588.2 $[M + H]^+$.

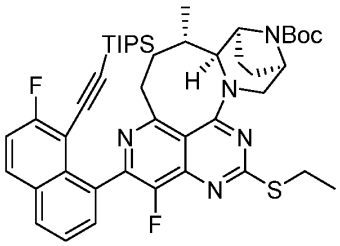
Intermediate 156-7: tert-butyl (6S,6aS,7S,10R)-2-chloro-13-(ethylthio)-1-fluoro-6-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



156-7

[0774] Intermediate **156-7** was synthesized in a manner similar to **75-7** using intermediate **156-6** instead of intermediate **75-6**. LCMS: 508.7 $[M + H]^+$.

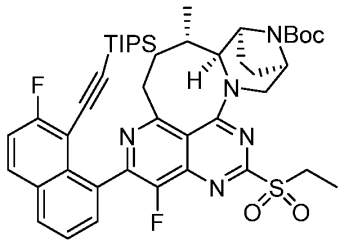
Intermediate 156-8: tert-butyl (6S,6aS,7S,10R)-13-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



156-8

[0775] Intermediate **156-8** was synthesized in a manner similar to **76-1** using intermediate **156-7** instead of intermediate **75-9**. LCMS: 798.5 $[M + H]^+$.

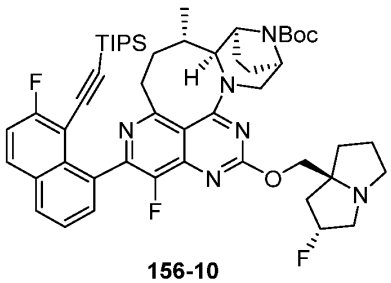
Intermediate 156-9: tert-butyl (6S,6aS,7S,10R)-13-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



156-9

[0776] Intermediate **156-9** was synthesized in a manner similar to **75-8** using intermediate **156-8** instead of intermediate **75-7**. LCMS: 830.5 $[M + H]^+$.

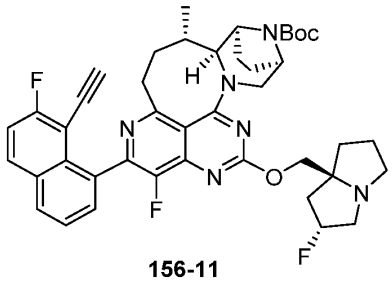
Intermediate 156-10: tert-butyl (6S,6aS,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



156-10

[0777] Intermediate **156-10** was synthesized in a manner similar to **75-9** using intermediate **156-9** instead of intermediate **75-8**. LCMS: 895.1 $[M + H]^+$.

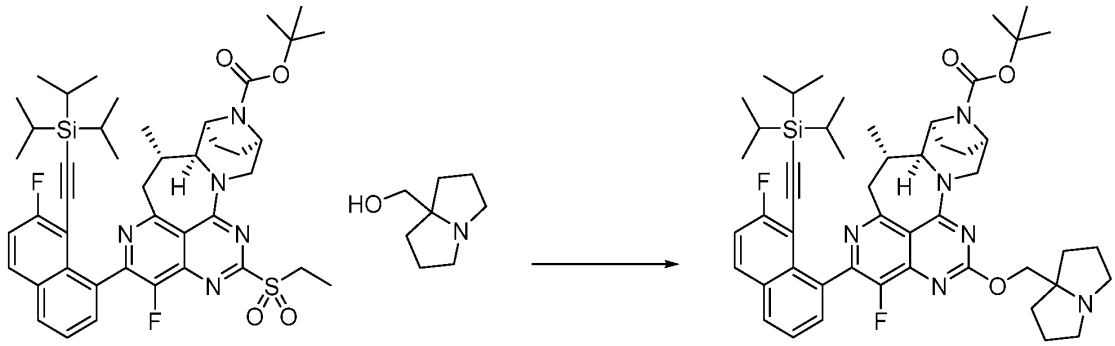
Intermediate 156-11: tert-butyl (6S,6aS,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



156-11

[0778] Intermediate **156-11** was synthesized in a manner similar to **76-2** using intermediate **156-10** instead of intermediate **76-1**. LCMS: 739.0 $[M + H]^+$.

Intermediate 157-1: tert-butyl (5S,5aS,6S,9R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-12-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

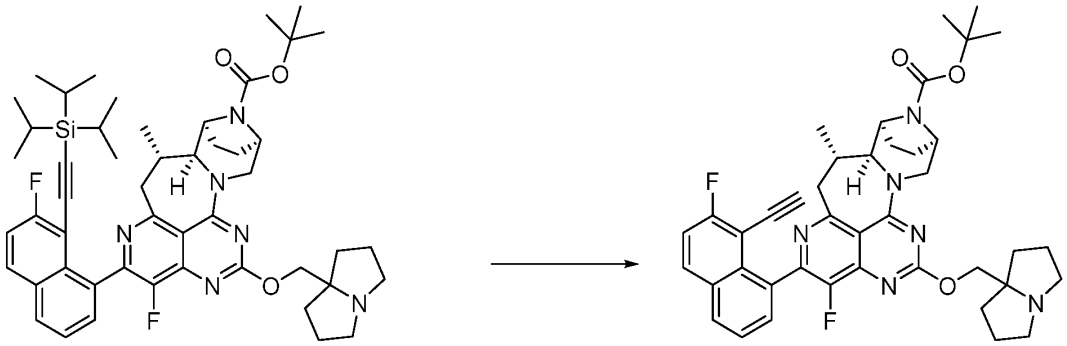


84-3 157-1

[0779] Intermediate **84-3** (5 mg, 6 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). 1,2,3,5,6,7-Hexahydropyrrolizin-8-ylmethanol (1.7mg, 12 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 11 uL, 11 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature for 5 minutes. Additional LiHMDS was added until complete conversion was observed by LCMS. The solution was diluted with ethyl acetate and diethyl ether and washed with

a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **157-1,** which was used directly in the next step without purification. LCMS: 863.5.

Intermediate 157-2: tert-butyl (5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-12-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



157-1 **157-2**

[0780] A vial was charged with Intermediate **157-1** (5.3 mg, 6 μmol) and cesium fluoride (22 mg, 150 μmol). N,N-dimethylformamide (0.5 mL) was added and the resulting mixture was stirred vigorously for 30 minutes. Acetic acid (0.37 uL, 6 μmol) and diethyl ether were added and the mixture was filtered and concentrated in vacuo to give crude Intermediate **157-2**, which was used without purification in the next step. LCMS 707.4

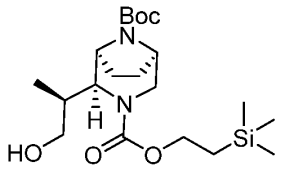
Intermediate 158-1: (1'H,3'H,5'H-dispiro[cyclopropane-1,2'-pyrrolizine-6',1''-cyclopropan]-7a'(7'H)-yl)methanol



158-1

[0781] Intermediate **158-1** was prepared in a manner analogous to Intermediate **113-6** using O5-tert-butyl O6-methyl (6S)-5-azaspiro[2.4]heptane-5,6-dicarboxylate as the starting material. LCMS: 194.2.

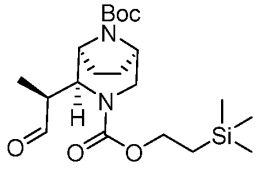
Intermediate 159-1: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-((S)-1-hydroxypropan-2-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



159-1

[0782] Intermediate **159-1** was synthesized in a manner similar to **75-2** using intermediate **156-1** instead of intermediate **75-1**. This isomer is the slower eluted fraction. LCMS: 415.3 $[M + H]^+$.

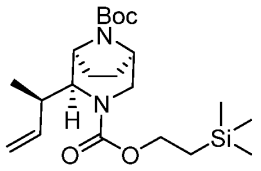
Intermediate 159-2: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-((S)-1-oxopropan-2-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



159-2

[0783] Intermediate **159-2** was synthesized in a manner similar to **75-3** using intermediate **159-1** instead of intermediate **75-2**. LCMS: 413.3 $[M + H]^+$.

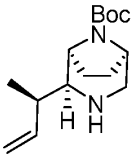
Intermediate 159-3: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-((R)-but-3-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



159-3

[0784] Intermediate **159-3** was synthesized in a manner similar to **75-4** using intermediate **159-2** instead of intermediate **75-3**. LCMS: 411.0 $[M + H]^+$.

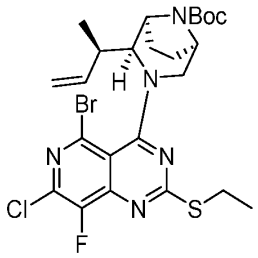
Intermediate 159-4: tert-butyl (1S,2S,5R)-2-((R)-but-3-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



159-4

[0785] Intermediate **159-4** was synthesized in a manner similar to **75-5** using intermediate **159-3** instead of intermediate **75-4**. LCMS: 267.1 $[M + H]^+$.

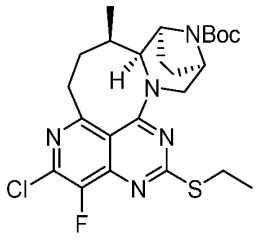
Intermediate 159-5: tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-((R)-but-3-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



159-5

[0786] Intermediate **159-5** was synthesized in a manner similar to **75-6** using intermediate **159-4** instead of intermediate **75-5**. LCMS: 586.7, 588.2 $[M + H]^+$.

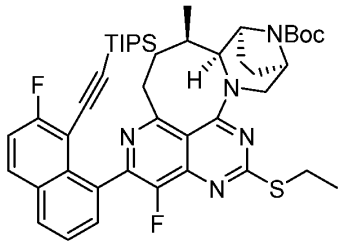
Intermediate 159-6: tert-butyl (6R,6aS,7S,10R)-2-chloro-13-(ethylthio)-1-fluoro-6-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



159-6

[0787] Intermediate **159-6** was synthesized in a manner similar to **75-7** using intermediate **159-5** instead of intermediate **75-6**. LCMS: 508.7 $[M + H]^+$.

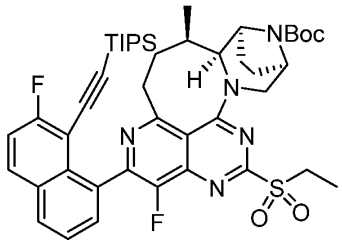
Intermediate 159-7: tert-butyl (6R,6aS,7S,10R)-13-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



159-7

[0788] Intermediate **159-7** was synthesized in a manner similar to **76-1** using intermediate **159-6** instead of intermediate **75-9**. LCMS: 798.5 $[M + H]^+$.

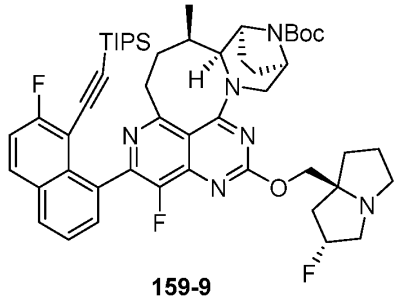
Intermediate 159-8: tert-butyl (6R,6aS,7S,10R)-13-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-6-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



159-8

[0789] Intermediate **159-8** was synthesized in a manner similar to **75-8** using intermediate **159-7** instead of intermediate **75-7**. LCMS: 830.5 $[M + H]^+$.

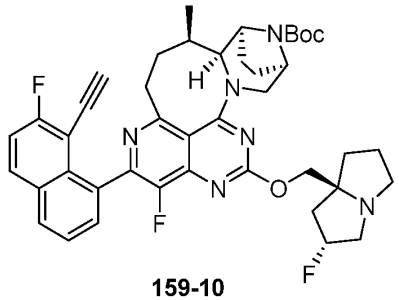
Intermediate 159-9: tert-butyl (6R,6aS,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



159-9

[0790] Intermediate **159-9** was synthesized in a manner similar to **75-9** using intermediate **159-8** instead of intermediate **75-8**. LCMS: 895.1 $[M + H]^+$.

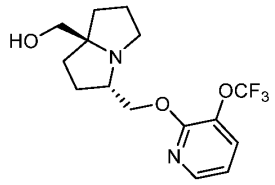
Intermediate 159-10: tert-butyl (6R,6aS,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



159-10

[0791] Intermediate **159-10** was synthesized in a manner similar to **76-2** using intermediate **159-9** instead of intermediate **76-1**. LCMS: 739.0 $[M + H]^+$.

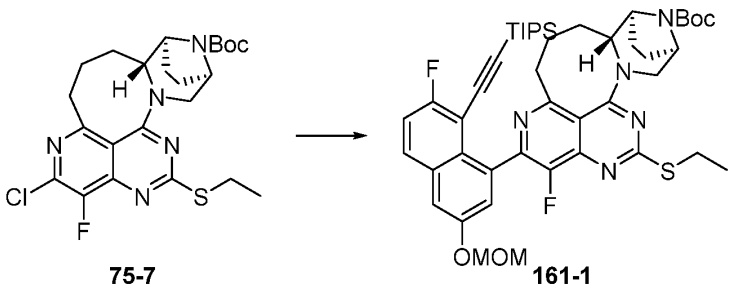
Intermediate 160-1: ((3S,7aS)-3-(((3-(trifluoromethoxy)pyridin-2-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



160-1

[0792] Intermediate **160-1** was synthesized in a manner similar to intermediate **148-2** using 2-chloro-3-(trifluoromethoxy)pyridine instead of 4-chloro-2-(trifluoromethyl)pyrimidine. LCMS: 333.1.

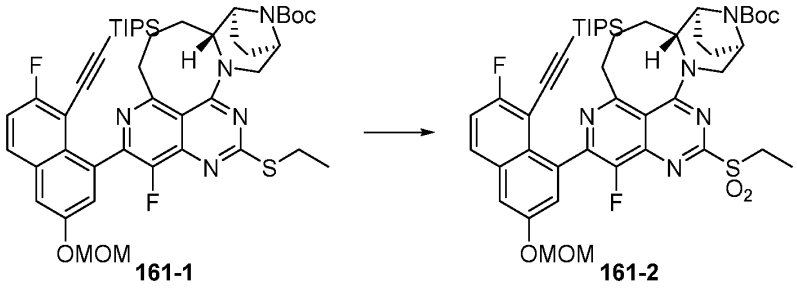
Intermediate 161-1 *tert*-butyl (6a*R*,7*S*,10*R*)-13-(ethylthio)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate



75-7 161-1

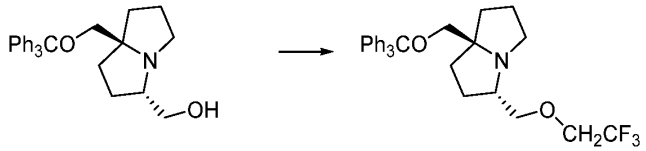
[0793] Intermediate 161-1 was synthesized in a manner similar to **Intermediate 13-8** using **Intermediate 75-7** instead of **Intermediate 13-7**. LCMS: 844.6.

Intermediate 161-2 *tert*-butyl (6a*R*,7*S*,10*R*)-13-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate



[0794] **Intermediate 161-2** was synthesized in a manner similar to **Intermediate 13-9** using **Intermediate 161-1** instead of **Intermediate 13-8**. LCMS: 876.3.

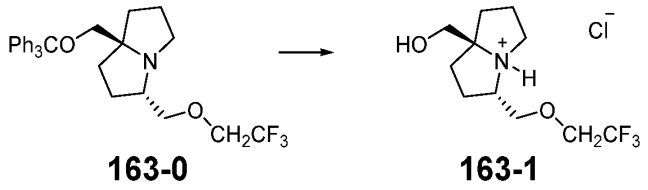
Intermediate 163-0: (3*S*,7a*S*)-3-((2,2,2-trifluoroethoxy)methyl)-7a-((trityloxy)methyl)hexahydro-1*H*-pyrrolizine



63-2 **163-0**

[0795] To a solution of 2,2,2-trifluoroethanol (36.29 mg, 362.71 umol, 26.10 uL, 3 eq) and intermediate **63-2** (50 mg, 120.90 umol, 1 eq) in PhMe (2 mL) was added 2-(tributyl-λ^5-phosphanylidene)acetonitrile (87.54 mg, 362.71 umol, 3 eq). The mixture was stirred at 80°C for 12 hr under N_2. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC(column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(NH_4HCO_3)-ACN];B%: 50%-85%,8min) to ginve intermediate **163-0**. LCMS: 632.2.

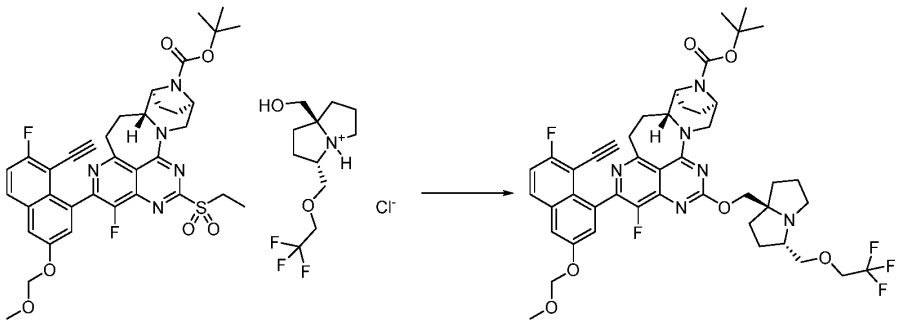
Intermediate 163-1: ((3*S*,7a*S*)-3-((2,2,2-trifluoroethoxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol hydrogen chloride salt



163-0 **163-1**

[0796] To a solution of intermediate **163-0** (170 mg, 343.04 umol, 1 eq) in EtOAc (2 mL) was added HCl/EtOAc (0.5 mL).The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC(column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [water(HCl)-ACN]; B%: 1%-20%,10min) to give intermediate **163-1**. LCMS: 254.1.

Intermediate 163-2: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((3S,7aS)-3-((2,2,2-trifluoroethoxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

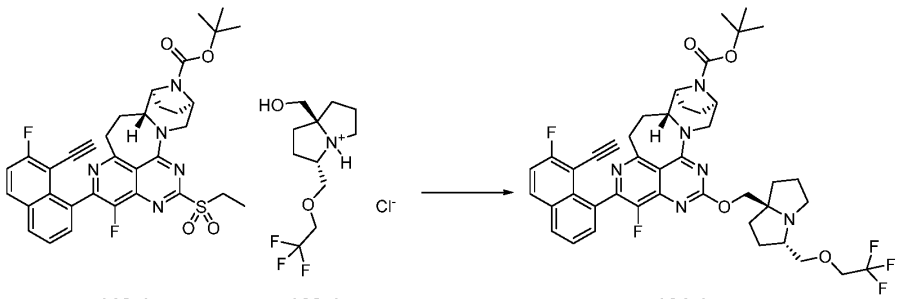


122-2 **163-1** **163-2**

[0797] Intermediate **122-2** (5 mg, 7 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **163-1** (3.4 mg, 12 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 26 uL, 26 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature for 5 minutes. Additional LiHMDS was added dropwise until conversion was observed by LCMS. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium

sulfate, filtered and concentrated in vacuo to give crude Intermediate **163-2**, which was used directly in the next step without purification. LCMS: 865.4.

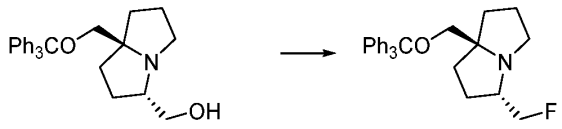
Intermediate 164-1: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((3S,7aS)-3-((2,2,2-trifluoroethoxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



113-1 163-1 164-1

[0798] Intermediate **113-1** (6 mg, 9 μmol) was azeotroped from toluene then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). Intermediate **163-1** (3.7 mg, 13 μmol) was left on high vacuum overnight then dissolved in 2-methyl-tetrahydrofuran (0.5 mL). To the alcohol was added LiHMDS (1M in tetrahydrofuran, 26 uL, 26 μmol) and the resulting solution was added to the sulfone solution under argon atmosphere. The resulting solution was stirred at room temperature for 5 minutes. Additional LiHMDS was added dropwise until full conversion was observed by LCMS. The solution was diluted with ethyl acetate and diethyl ether and washed with a mixture of saturated aqueous sodium carbonate and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **164-1**, which was used directly in the next step without purification. LCMS: 805.4.

Intermediate 165-0: (3*S*,7a*S*)-3-(fluoromethyl)-7a-((trityloxy)methyl)hexahydro-1*H*-pyrrolizine

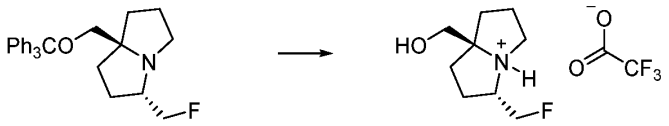


63-2 165-0

[0799] To a solution of intermediate **63-2** (100 mg, 241.81 umol, 1 eq) in DCM (5 mL) were added sequentially triethylamine (48.94 mg, 483.62 umol, 67.31 uL, 2 eq) and methanesulfonyl

chloride (41.55 mg, 362.71 umol, 28.07 uL, 1.5 eq) at 0°C. The mixture was stirred at 25°C for 1 hr. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (10 ml) and extracted with DCM (10 ml*3), the combined organic phase was washed with brine (10 ml), and then dried over Na_2SO_4, filtered and concentrated. To one third of the residue at room temperature was added tetrabutylammonium fluoride solution (1.0 M in tetrahydrofuran, 10.0 mL, 10 mmol), and the resulting mixture was stirred vigorously and was heated to 70 °C. After 12 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with $NaHCO_3$ （10 mL） and extracted with EtOAc 30 mL(10mL *3). The combined organic layers were washed with brine 20 mL (10 mL *2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(NH_4HCO_3)-ACN];B%: 35%-75%,8min) to give intermediate **165-0**. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.32 - 7.27 (m, 6H), 7.13 - 7.08 (m, 6H), 7.06 - 7.01 (m, 3H), 4.48 - 4.33 (m, 2H), 3.14 - 2.99 (m, 1H), 2.83 (d, 1H, J = 8.4 Hz), 2.68 (d, 2H, J = 8.4 H), 2.51 (dt, 1H, J = 6.0, 9.2 Hz), 1.98 - 1.89 (m, 1H), 1.66 - 1.44 (m, 6H), 1.34 - 1.20 (m, 1H).

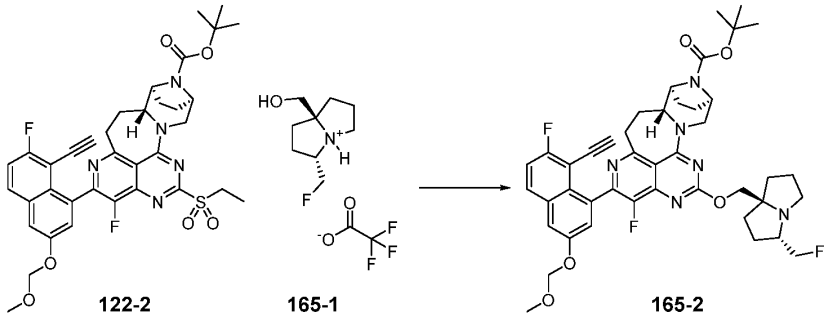
Intermediate 165-1: ((3*S*,7a*S*)-3-(fluoromethyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol trifluoroacetic acid salt



165-0 **165-1**

[0800] Intermediate **165-0** (140 mg, 336.91 umol, 1 eq) was dissolved in EtOAc (1.6 mL) and HCl/EtOAc (0.4 mL). The mixture was stirred at 25°C for 1 hr. The residue was purified by *prep*-HPLC (column: Phenomenex Luna C18 100*30mm*5um;mobile phase: [water(TFA)-ACN];B%: 1%-10%,10min) to give intermediate **165-1**. LCMS: 174.1.

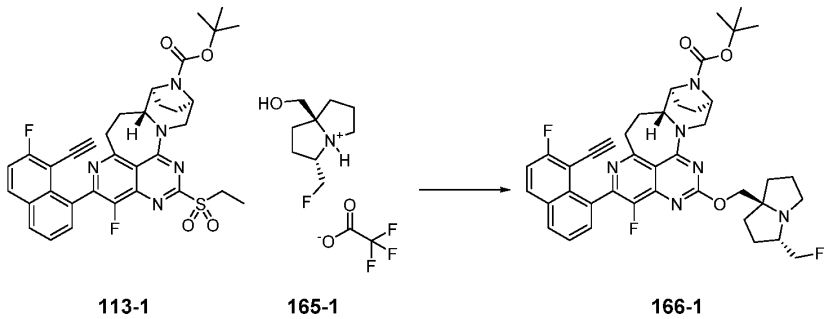
Intermediate 165-2: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((3S,7aS)-3-(fluoromethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



122-2 165-1 165-2

[0801] Intermediate **122-2** (5.5 mg, 8 μmol) and Intermediate **165-1** (3.4 mg, 12 μmol) were azeotroped together from toluene with N,N-diisopropylethylamine (20 uL) and dissolved in 2-methyl-tetrahydrofuran (0.5 mL) under argon. LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) was added and the resulting solution was stirred at room temperature for 5 minutes. The solution was diluted with diethyl ether and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **165-2**, which was used directly in the next step without purification. LCMS: 785.4.

Intermediate 166-1: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((3S,7aS)-3-(fluoromethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

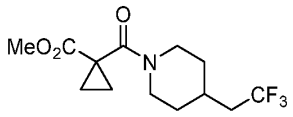


113-1 165-1 166-1

[0802] Intermediate **113-1** (5.5 mg, 8 μmol) and Intermediate **165-1** (3.7 mg, 13 μmol) were azeotroped together from toluene with N,N-diisopropylethylamine (20 uL) and dissolved in 2-methyl-tetrahydrofuran (0.5 mL) under argon. LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol)

was added and the resulting solution was stirred at room temperature for 5 minutes. The solution was diluted with diethyl ether and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **166-1**, which was used directly in the next step without purification. LCMS: 725.4.

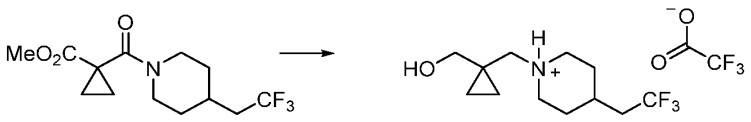
Intermediate 167-0: methyl 1-(4-(2,2,2-trifluoroethyl)piperidine-1-carbonyl)cyclopropane-1-carboxylate



167-0

[0803] To a solution of 4-(2,2,2-trifluoroethyl)piperidine hydrochloride (100 mg, 491.1 umol, 1 eq) in DMF (1 mL) was added DIEA (190.4 mg, 1.5 mmol, 256.6 uL, 3 eq), 1-(methoxycarbonyl)cyclopropanecarboxylic acid (70.8 mg, 491.1 umol, 1 eq) and HATU (280.1 mg, 736.6 umol, 1.5 eq). The mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(FA)-ACN];B%: 10%-45%,8min) to give intermediate **167-0**. LCMS: 294.1.

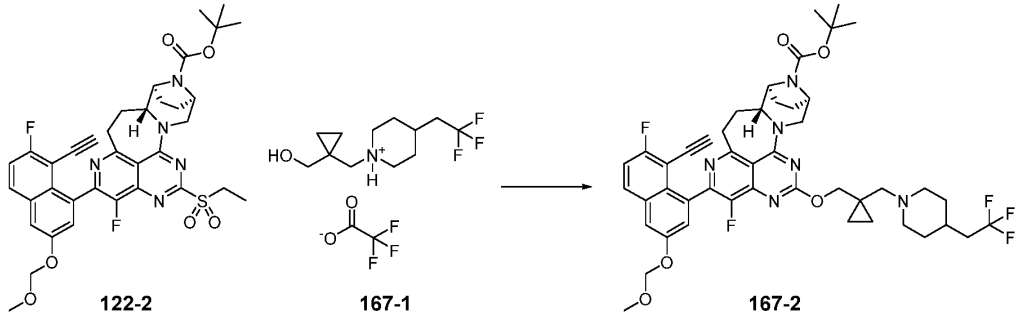
Intermediate 167-1: (1-((4-(2,2,2-trifluoroethyl)piperidin-1-yl)methyl)cyclopropyl)methanol trifluoroacetic acid salt



167-0 **167-1**

[0804] To a mixture of methyl intermediate **167-0** (60 mg, 204.6 umol, 1 eq) in THF (2 mL) was added BF_3•Et_2O (464.6 mg, 3.3 mmol, 404.0 uL, 16 eq) at 0°C under N_2, the reaction mixture was stirred at 0°C for 5 mins. Then $NaBH_4$ (61.9 mg, 1.6 mmol, 8 eq) was added, and the reaction mixture was stirred at 60°C for 1 hr under N_2. To the reaction mixture was added sat.aq. NH_4Cl (10 mL) slowly and the reaction mixture was stirred at 0°C for 0.5 hr under N_2, and then extracted with EtOAc (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [water(TFA)-ACN];B%: 1%-30%,10min) to give intermediate **167-1**. LCMS: 252.1.

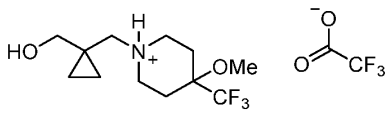
Intermediate 167-2: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-((1-((4-(2,2,2-trifluoroethyl)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



122-2 167-1 167-2

[0805] Intermediate **122-2** (5.5 mg, 8 μmol) and Intermediate **167-1** (4.3 mg, 12 μmol) were azeotroped together from toluene with N,N-diisopropylethylamine (20 uL) and dissolved in 2-methyl-tetrahydrofuran (0.5 mL) under argon. LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) was added and the resulting solution was stirred at room temperature for 5 minutes. The solution was diluted with diethyl ether and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **167-2**, which was used directly in the next step without purification. LCMS: 863.4.

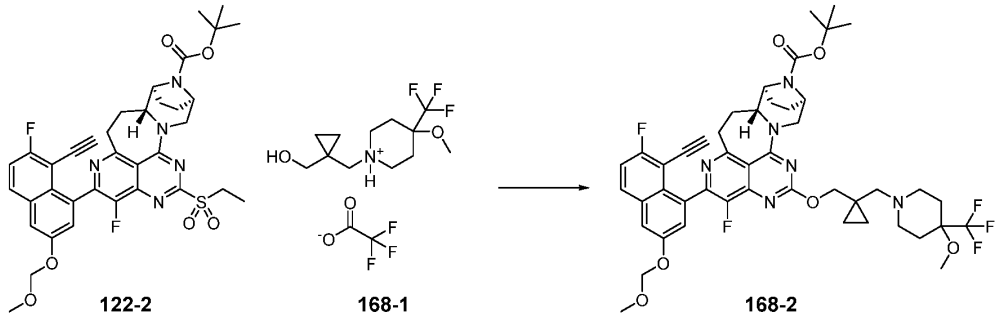
Intermediate 168-1: (1-((4-methoxy-4-(trifluoromethyl)piperidin-1-yl)methyl)cyclopropyl)methanol trifluoroacetic acid salt



168-1

[0806] Intermediate **168-1** was synthesized in a manner similar to intermediate **167-1** using 4-methoxy-4-(trifluoromethyl)piperidine instead of 4-(2,2,2-trifluoroethyl)piperidine hydrochloride. ^{1}H-NMR (400 MHz,$CDCl_3$) δ ppm = 3.99 - 3.88 (m, 2H), 3.60 (s, 2H), 3.43 (s, 3H), 3.04 (s, 2H), 2.81 (t, J = 12.4 Hz, 2H), 2.39 (t, J = 13.6 Hz, 2H), 2.13 (d, J = 14.8 Hz, 2H), 0.83 - 0.75 (m, 2H), 0.60 - 0.52 (m, 2H).

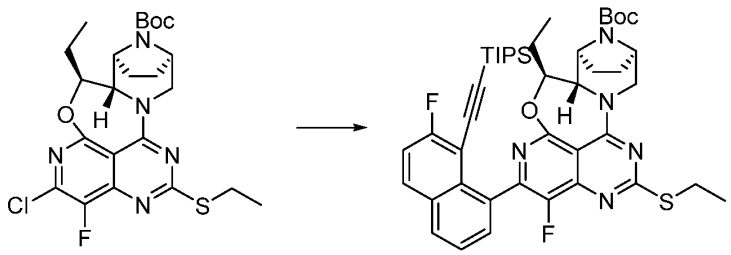
Intermediate 168-2: tert-butyl (5aR,6S,9R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-((1-((4-methoxy-4-(trifluoromethyl)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



122-2 168-1 168-2

[0807] Intermediate **122-2** (5.5 mg, 8 μmol) and Intermediate **168-1** (4.5 mg, 12 μmol) were azeotroped together from toluene with N,N-diisopropylethylamine (20 uL) and dissolved in 2-methyl-tetrahydrofuran (0.5 mL) under argon. LiHMDS (1M in tetrahydrofuran, 27 uL, 27 μmol) was added and the resulting solution was stirred at room temperature for 5 minutes. The solution was diluted with diethyl ether and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to give crude Intermediate **168-2**, which was used directly in the next step without purification. LCMS: 879.4.

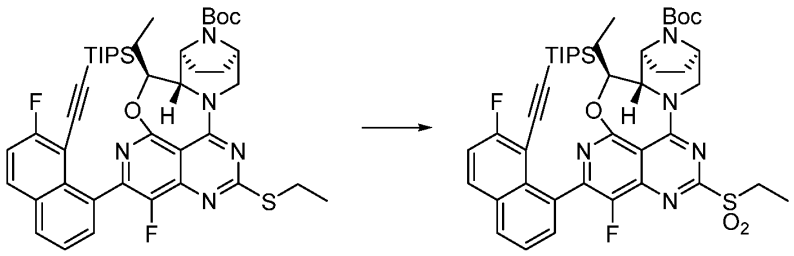
Intermediate 169-1 *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-ethyl-12-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



80-6 169-1

[0808] Intermediate 169-1 was synthesized in a manner similar to **Intermediate 4-1** using **Intermediate 80-6** instead of **Intermediate 17-9**. LCMS: 800.7.

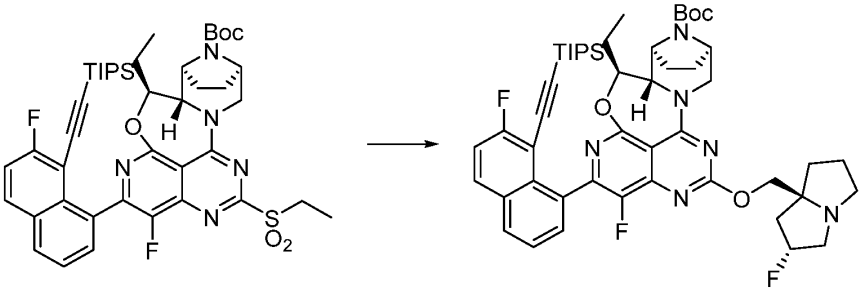
Intermediate 169-2 tert-butyl (5S,5aS,6S,9R)-5-ethyl-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



169-1 169-2

[0809] Intermediate 169-2 was synthesized in a manner similar to **Intermediate 13-9** using **Intermediate 169-1** instead of **Intermediate 13-8**. LCMS: 832.6.

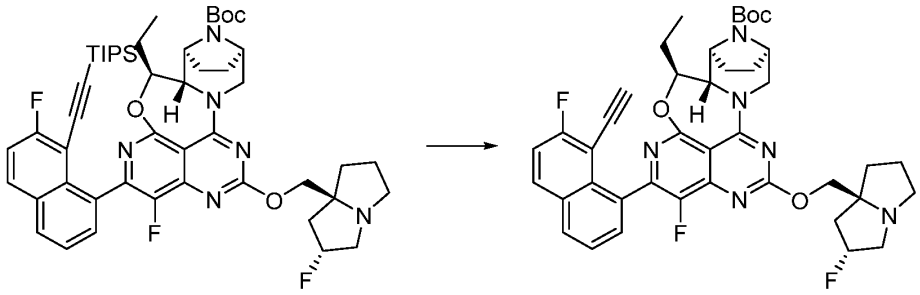
Intermediate 169-3 tert-butyl (5S,5aS,6S,9R)-5-ethyl-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



169-2 169-3

[0810] Intermediate 169-3 was synthesized in a manner similar to **Intermediate 13-10** using **Intermediate 169-2** instead of **Intermediate 13-9**. LCMS: 897.3.

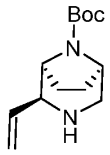
Intermediate 169-4 *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-5-ethyl-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



169-3 169-4

[0811] Intermediate 169-4 was synthesized in a manner similar to Intermediate 13-11 using Intermediate 169-3 instead of Intermediate 13-10. LCMS: 741.1.

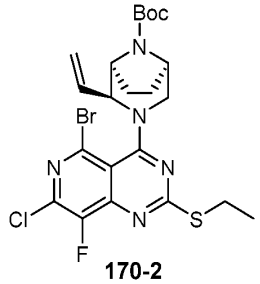
Intermediate 170-1: tert-butyl (1S,2S,5R)-2-vinyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



170-1

[0812] Intermediate **170-1** was synthesized in a manner similar to Intermediate **27-5** using 8-(tert-butyl) 2-ethyl (1R,2R,5S)-4-oxo-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate instead of 8-(tert-butyl) 2-ethyl (1R,2S,5S)-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate. LCMS: 239.2

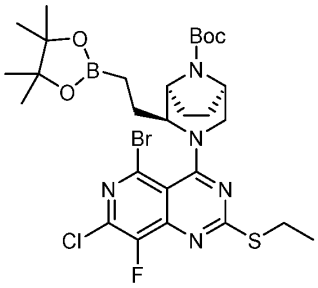
Intermediate 170-2: tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-vinyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



170-2

[0813] Intermediate **170-2** was synthesized in a manner similar to Intermediate **53-5** using Intermediate **170-1** instead of Intermediate **53-4**. LCMS: 558.1

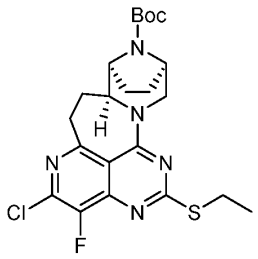
Intermediate 170-3: tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



170-3

[0814] Intermediate **170-3** was synthesized in a manner similar to Intermediate **132-3** using Intermediate **170-2** instead of Intermediate **132-2**. LCMS: 686.3

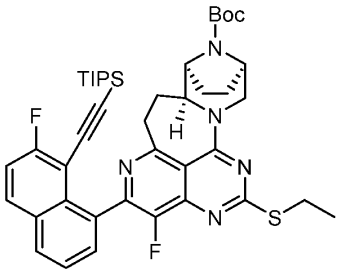
Intermediate 170-4: tert-butyl (5aS,6S,9R)-2-chloro-12-(ethylthio)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



170-4

[0815] Intermediate **170-4** was synthesized in a manner similar to Intermediate **132-4** using Intermediate **170-3** instead of Intermediate **132-3**. LCMS: 480.2

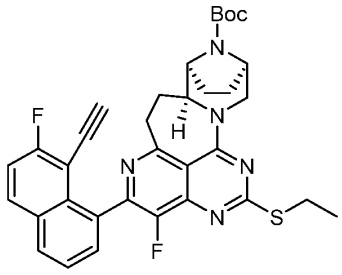
Intermediate 170-5: tert-butyl (5aS,6S,9R)-12-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



170-5

[0816] Intermediate **170-5** was synthesized in a manner similar to Intermediate **4-1** using Intermediate **170-4** instead of Intermediate **17-9**. LCMS: 771.4.

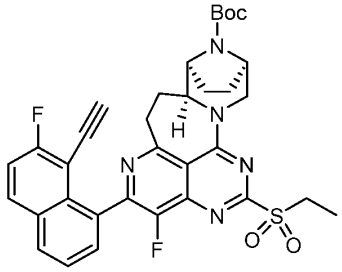
Intermediate 170-6: tert-butyl (5aS,6S,9R)-12-(ethylthio)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



170-6

[0817] Intermediate **170-6** was synthesized in a manner similar to Intermediate **28-2** using Intermediate **170-5** instead of Intermediate **28-1**. LCMS: 615.3

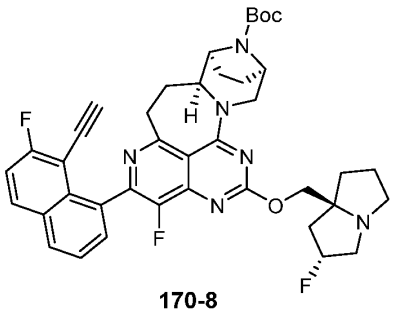
Intermediate 170-7: tert-butyl (5aS,6S,9R)-12-(ethylsulfonyl)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



170-7

[0818] Intermediate **170-7** was synthesized in a manner similar to Intermediate **13-9** using Intermediate **170-6** instead of Intermediate **13-8**. LCMS: 646.3.

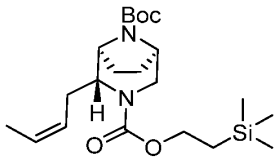
Intermediate 170-8: tert-butyl (5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



170-8

[0819] Intermediate **170-8** was synthesized in a manner similar to Intermediate **53-10** using Intermediate **170-7** instead of Intermediate **53-9**. LCMS: 711.4

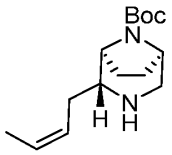
Intermediate 171-1: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2R,5R)-2-((Z)-but-2-en-1-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



171-1

[0820] To a vigorously stirred solution of (ethyl)triphenylphosphonium bromide bromide (0.782 g, 2.11 mmol) in tetrahydrofuran (10 mL) at room temperature was added KHMDS solution (1.0 M in tetrahydrofuran, 1.8 mL, 2.6 mmol) dropwise to afford a solution. The mixture was stirred for 1 hour at room temperature and was cooled to -78°C whereupon a solution of **Intermediate 75-3** (280 mg, 0.703 mmol) in tetrahydrofuran (5 mL) was added dropwise over 20 minutes. The resulting solution was allowed to gradually warm to room temperature and stir for 3 hours. The mixture was quenched with methanol (10 mL) and stirred for 15 min. Saturated aqueous ammonium chloride solution (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0% to 40% ethyl acetate in hexanes) to give **Intermediate 171-1** LCMS: 433.6 $[M + Na]^+$.

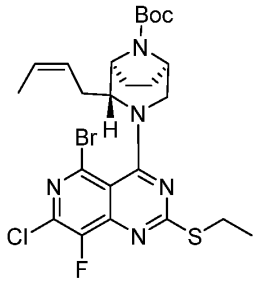
Intermediate 171-2: tert-butyl (1S,2R,5R)-2-((Z)-but-2-en-1-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



171-2

[0821] Cesium fluoride (481 mg, 3.17 mmol) was added to a vigorously stirred solution of **Intermediate 171-1** (260 mg, 0.63 mmol) in *N,N*-dimethylformamide (2.0 mL) at room temperature. The resulting mixture was stirred at 90°C for 30 minutes. After cooled to room temperature, the mixture was diluted with EtOAc (30 mL), filtered, and the filtrate was concentrated under reduced pressure to give crude product of **Intermediate 171-2**, which was used for the next step without purification. LCMS: 267.1 $[M + H]^+$.

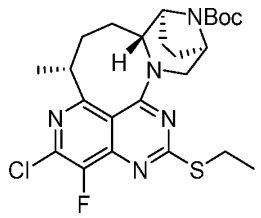
Intermediate 171-3: tert-butyl (1S,2R,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-((Z)-but-2-en-1-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



171-3

[0822] A mixture of **Intermediate 171-2** (160 mg, 0.601 mmol), **Intermediate 53-1** (200 mg, 0.560 mmol) and DIPEA (217 mg, 1.68 mmol) in DCM (5 mL) was stirred at rt for 3 h. The mixture was purified by flash column chromatography on silica gel (0 to 80% EtOAc in hexanes) to give **Intermediate 171-3**. LCMS: 586.6, 588.2 $[M + H]^+$.

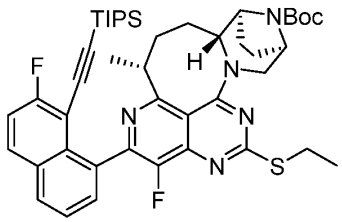
Intermediate 171-4: tert-butyl (4R,6aR,7S,10R)-2-chloro-13-(ethylthio)-1-fluoro-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



171-4

[0823] To a vigorously stirred solution of **Intermediate 171-3** (2.30 g, 3.92 mmol) in anhydrous 2-methyl THF (8 mL), the solution of 9-borabicyclo[3.3.1]nonane (0.50 M in tetrahydrofuran, 11.8 mL, 5.88 mmol) was added at room temperature. The resulting solution was stirred at 70 °C for 0.5 hour before it was cooled to room temperature. The solution was transferred to a reaction vial containing $Pd(dppf)Cl_2$ (247 mg, 0.35 mmol), potassium phosphate (2.23 g, 10.5 mmol) and degassed water (1.5 mL) at rt under nitrogen atmosphere. The reaction mixture was stirred at 90°C for 10 minutes before it was cooled to room temperature. The mixture was washed with water (20 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was collected and combined, dried over magnesium sulfate, concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0 to 50% ethyl acetate in hexanes) to give an inseparable mixture of **171-4**, **174-1**, and **182-1** as the faster eluted fraction, and **175-2** as the slower eluted fraction. LCMS: 508.4 $[M + H]^+$.

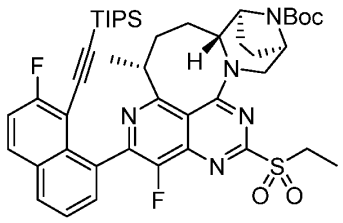
Intermediate 171-5: tert-butyl (4R,6aR,7S,10R)-13-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



171-5

[0824] A vigorously stirred mixture of **171-4**, **174-1**, and **182-1** (1.35 g, 2.66 mmol), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (prepared according to WO 2021/041671) (2.40 g, 5.31 mol), [(di(1-adamantyl)-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate (387 mg, 0.53 mmol), potassium phosphate (1.69 g, 7.97 mmol) in tetrahydrofuran (10 mL) and water (5 mL) was heated to 70°C. After 80 min, the resulting mixture was cooled to room temperature, and ethyl acetate (200 mL) were added sequentially. The organic layer was washed with brine (100 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 50% ethyl acetate in hexanes) to give an inseparable mixture of **171-5** and **174-2** as the slower eluted fraction, and **182-2** as the faster eluted fraction. LCMS: 798.6 $[M + H]^+$.

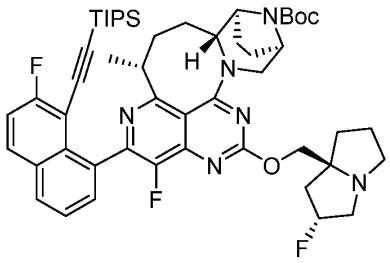
Intermediate 171-6: tert-butyl (4R,6aR,7S,10R)-13-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



171-6

[0825] 3-Chloroperoxybenzoic acid (77% wt, 535 mg, 2.39 mmol) was added in small portions over 5 min to a vigorously stirred solution of mixture of **Intermediate 171-5** and **174-2** (760 mg, 0.95 mmol) in dichloromethane (15.0 mL) at 0°C. After 25 min, the resulting mixture was warmed to room temperature. After 60 min, the solution was filtered and the filtrated concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0% to 75% ethyl acetate in hexanes) to give Intermediate **171-6** as faster eluted fraction, and **174-3** as the slower eluted fraction. LCMS: 830.4 $[M + H]^+$.

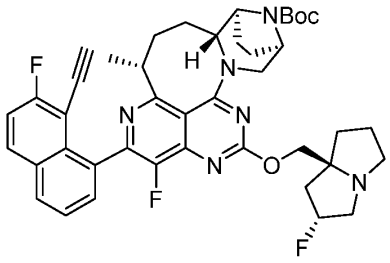
Intermediate 171-7: tert-butyl (4R,6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



171-7

[0826] Lithium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 452 μL, 452 μmol) was added over 1 min via syringe to a stirred mixture of **Intermediate 171-6** (250 mg, 301 μmol), (2*R*,7a*S*)-2-Fluorotetrahydro-1*H*-pyrrolizine-7a(5*H*)-methano (125 mg, 785 μmol), and tetrahydrofuran (2.5 mL) at 0 °C. After 30 min, ethyl acetate (20 mL), and saturated aqueous sodium chloride solution (20 mL) were added sequentially. The organic layer was washed with water (30 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure to give the crude product of **Intermediate 171-7**. LCMS: 895.2 $[M + H]^+$.

Intermediate 171-8: tert-butyl (4R,6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate

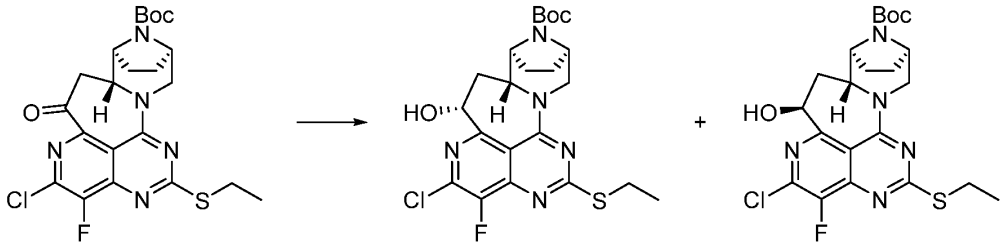


171-8

[0827] Cesium fluoride (687 mg, 4.52 mmol) was added to a vigorously stirred solution of **Intermediate 171-7** (270 mg, 0.302 mmol) in *N*,*N*-dimethylformamide (5 mL) at room temperature. After 30 min, ethyl acetate (100 mL) was added. The mixture was filtered, and the

filtrated was concentrated under reduced pressure to give the crude product of **Intermediate 171-8**. LCMS: 739.1 $[M + H]^+$.

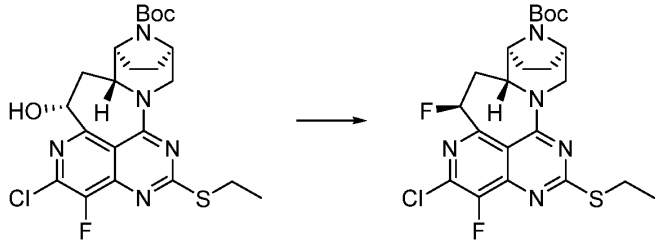
Intermediate 172-1 ***tert*-butyl (4*R*,5a*R*,6*S*,9*R*)-2-chloro-12-(ethylthio)-1-fluoro-4-hydroxy-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate and Intermediate 173-1** ***tert*-butyl (4*S*,5a*R*,6*R*,9*S*)-2-chloro-12-(ethylthio)-1-fluoro-4-hydroxy-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



97-2 **172-1** **173-1**

[0828] Sodium borohydride (118.5 mg, 4.9 mmol) was added to a vigorously stirred solution of **Intermediate 97-2** (35.2 mg, 0.071 mmol) in methanol (0.45 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 25 minutes before it was quenched with water (1 mL) at 0 °C. The mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0% to 80% ethyl acetate in hexanes) to give **Intermediate 172-1** and **Intermediate 173-1**. LCMS: 496.6.

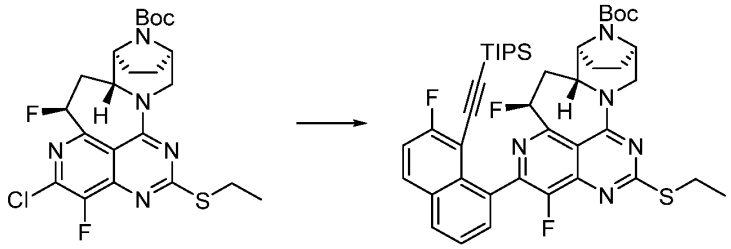
Intermediate 172-2 ***tert*-butyl (4*S*,5a*R*,6*S*,9*R*)-2-chloro-12-(ethylthio)-1,4-difluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



172-1 **172-2**

[0829] To a vigorously stirred solution of **Intermediate 172-1** (61.0 mg, 0.12 mmol) in anhydrous dichloromethane (0.57 mL), was added diethylaminosulfur trifluoride at -78 ˚C. The mixture was stirred at -78 ˚C for 1 hour before it was quenched with water (1 mL) and saturated aqueous sodium bicarbonate solution (1 mL) at -78 ˚C. The resulting mixture was extracted with dichloromethane (3 x 5 mL). The organic layer was collected and combined, dried over magnesium sulfate, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0 to 50% ethyl acetate in hexanes) to give **Intermediate 172-2**. LCMS: 498.6.

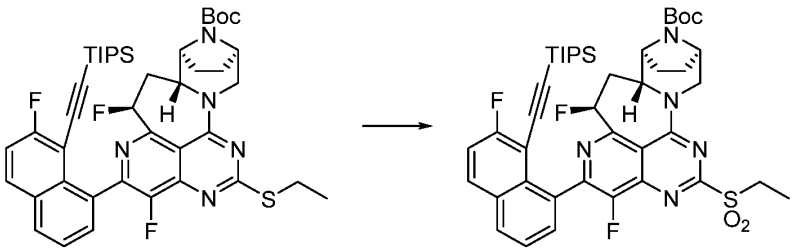
Intermediate 172-3 *tert*-butyl (4*S*,5a*R*,6*S*,9*R*)-12-(ethylthio)-1,4-difluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



172-2 172-3

[0830] Intermediate 172-3 was synthesized in a manner similar to **Intermediate 13-8** using **Intermediate 172-2** instead of **Intermediate 13-7**. LCMS: 788.6.

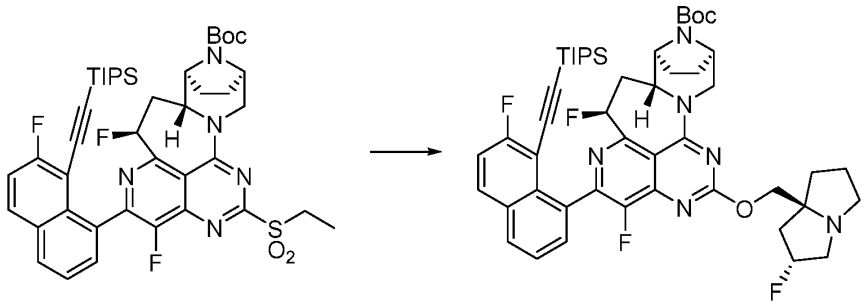
Intermediate 172-4 tert-butyl (4S,5aR,6S,9R)-12-(ethylsulfonyl)-1,4-difluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



172-3 172-4

[0831] Intermediate 172-4 was synthesized in a manner similar to **Intermediate 13-9** using **Intermediate 172-3** instead of **Intermediate 13-8**. LCMS: 820.4.

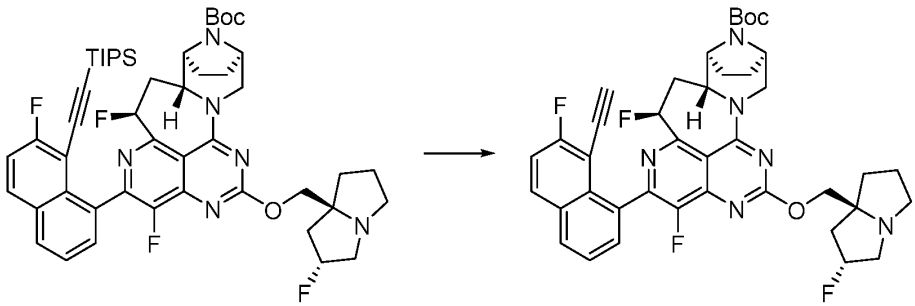
Intermediate 172-5 tert-butyl (4S,5aR,6S,9R)-1,4-difluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



172-4 172-5

[0832] Intermediate 172-5 was synthesized in a manner similar to **Intermediate 13-10** using **Intermediate 172-4** instead of **Intermediate 13-9**. LCMS: 885.2.

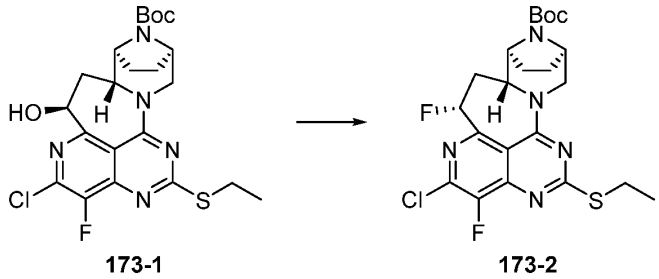
Intermediate 172-6 *tert*-butyl (4*S*,5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1,4-difluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



172-5 172-6

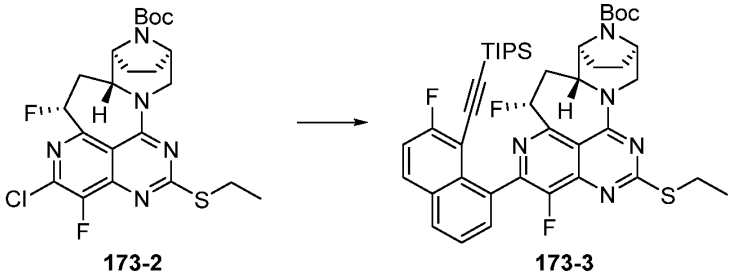
[0833] Intermediate 172-6 was synthesized in a manner similar to Intermediate 13-11 using Intermediate 172-5 instead of Intermediate 13-10. LCMS: 729.0.

Intermediate 173-2 ***tert*-butyl (4*R*,5a*R*,6*S*,9*R*)-2-chloro-12-(ethylthio)-1,4-difluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



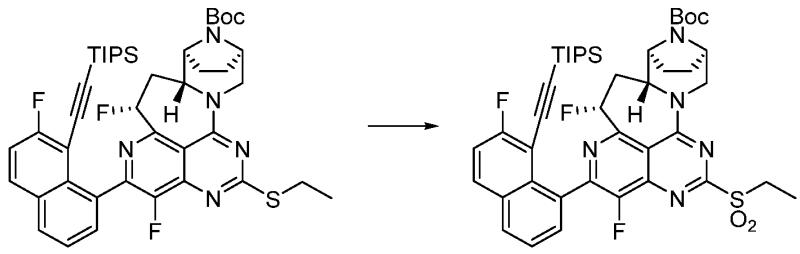
[0834] Intermediate 173-2 was synthesized in a manner similar to Intermediate 172-2 using Intermediate 173-1 instead of Intermediate 172-1. LCMS: 498.2.

Intermediate 173-3 ***tert*-butyl (4*R*,5a*R*,6*S*,9*R*)-12-(ethylthio)-1,4-difluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



[0835] Intermediate 173-3 was synthesized in a manner similar to **Intermediate 13-8** using **Intermediate 173-2** instead of **Intermediate 13-7**. LCMS: 788.5.

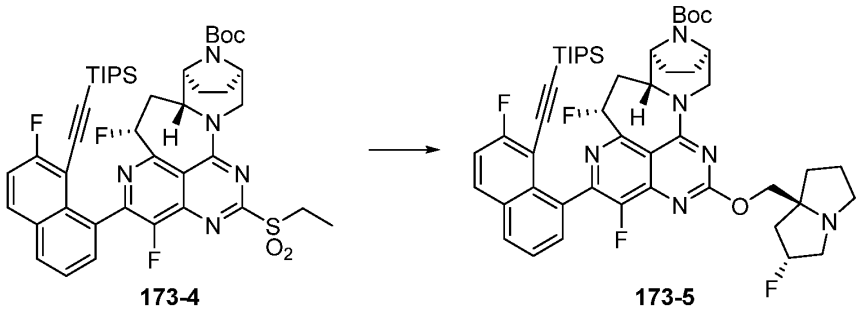
Intermediate 173-4 tert-butyl (4R,5aR,6S,9R)-12-(ethylsulfonyl)-1,4-difluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



173-3 173-4

[0836] Intermediate 173-4 was synthesized in a manner similar to **Intermediate 13-9** using **Intermediate 173-3** instead of **Intermediate 13-8**. LCMS: 820.2.

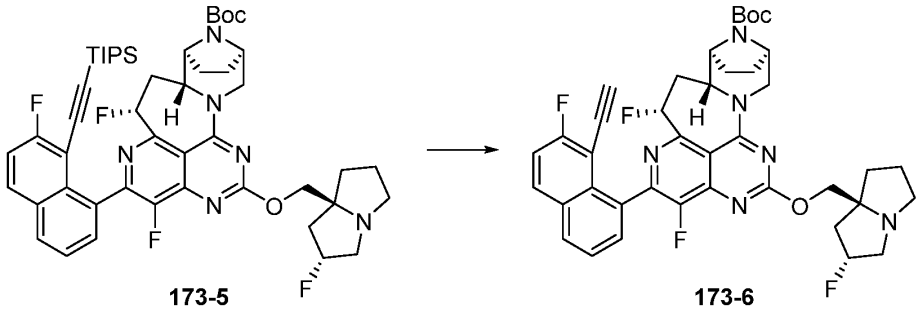
Intermediate 173-5 tert-butyl (4R,5aR,6S,9R)-1,4-difluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



173-4 173-5

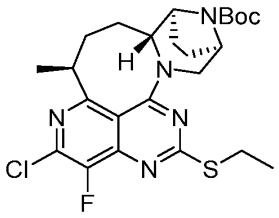
[0837] Intermediate 173-5 was synthesized in a manner similar to **Intermediate 13-10** using **Intermediate 173-4** instead of **Intermediate 13-9**. LCMS: 885.2.

Intermediate 173-6 *tert*-butyl (4*R*,5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1,4-difluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



[0838] Intermediate 173-6 was synthesized in a manner similar to Intermediate 13-11 using Intermediate 173-5 instead of Intermediate 13-10. LCMS: 728.9.

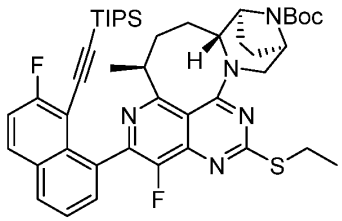
Intermediate 174-1: tert-butyl (4S,6aR,7S,10R)-2-chloro-13-(ethylthio)-1-fluoro-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



174-1

[0839] Intermediate **174-1** was synthesized in a manner similar to **75-7** using intermediate **171-3** instead of intermediate **75-6**. LCMS: 508.3 $[M + H]^+$.

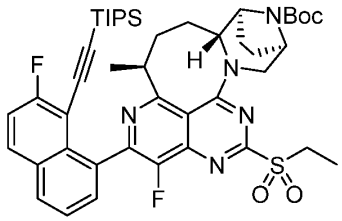
Intermediate 174-2: tert-butyl (4S,6aR,7S,10R)-13-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



174-2

[0840] Intermediate **174-2** was synthesized in a manner similar to **76-1** using intermediate **174-1** instead of intermediate **75-9**. LCMS: 798.6 $[M + H]^+$.

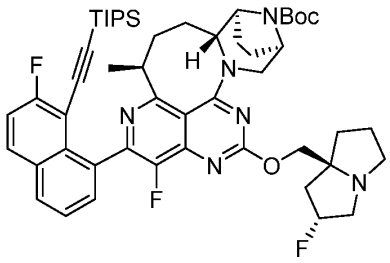
Intermediate 174-3: tert-butyl (4S,6aR,7S,10R)-13-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



174-3

[0841] Intermediate **174-3** was synthesized in a manner similar to **75-8** using intermediate **174-2** instead of intermediate **75-7**. LCMS: 830.4 $[M + H]^+$.

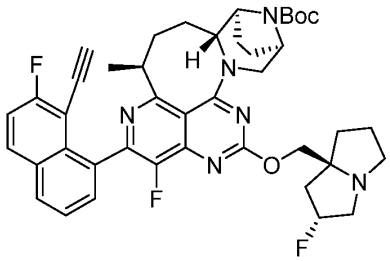
Intermediate 174-4: tert-butyl (4S,6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



174-4

[0842] Intermediate **174-4** was synthesized in a manner similar to **75-9** using intermediate **174-3** instead of intermediate **75-8**. LCMS: 895.2 $[M + H]^+$.

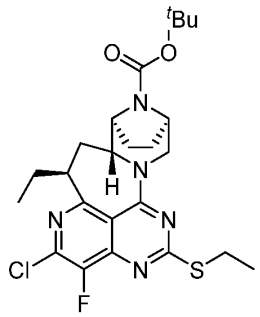
Intermediate 174-5: tert-butyl (4S,6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



174-5

[0843] Intermediate **174-5** was synthesized in a manner similar to **76-2** using intermediate **174-4** instead of intermediate **76-1**. LCMS: 739.1 $[M + H]^+$.

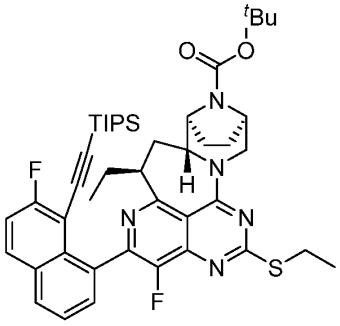
Intermediate 175-1: tert-butyl (4S,5aR,6S,9R)-2-chloro-4-ethyl-12-(ethylthio)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



175-1

[0844] Intermediate **175-1** was synthesized in a manner similar to **75-7** using intermediate **171-3** instead of intermediate **75-6**. LCMS: 508.3 $[M + H]^+$.

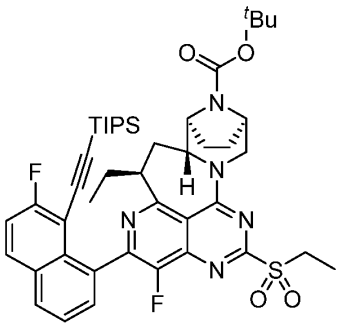
Intermediate 175-2: tert-butyl (4S,5aR,6S,9R)-4-ethyl-12-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



175-2

[0845] Intermediate **175-2** was synthesized in a manner similar to **76-1** using intermediate **175-1** instead of intermediate **75-9**. LCMS: 798.6 $[M + H]^+$.

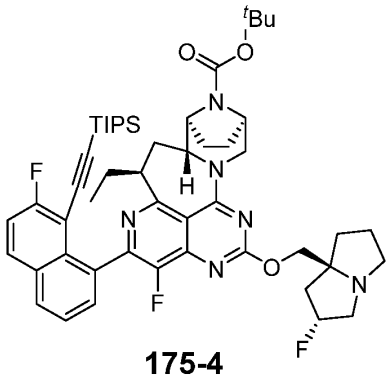
Intermediate 175-3: tert-butyl (4S,5aR,6S,9R)-4-ethyl-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



175-3

[0846] Intermediate **175-3** was synthesized in a manner similar to **75-8** using intermediate **175-2** instead of intermediate **75-7**. LCMS: 830.4 $[M + H]^+$.

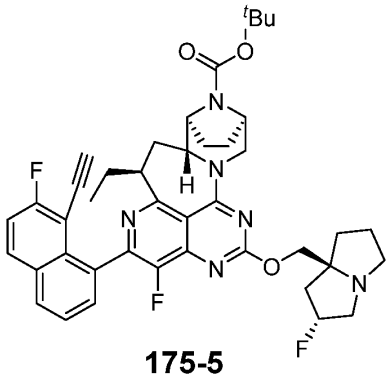
Intermediate 175-4: tert-butyl (4S,5aR,6S,9R)-4-ethyl-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



175-4

[0847] Intermediate **175-4** was synthesized in a manner similar to **75-9** using intermediate **175-3** instead of intermediate **75-8**. LCMS: 895.2 $[M + H]^+$.

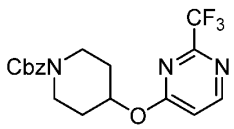
Intermediate 175-5: tert-butyl (4S,5aR,6S,9R)-4-ethyl-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



175-5

[0848] Intermediate **175-5** was synthesized in a manner similar to **76-2** using intermediate **175-4** instead of intermediate **76-1**. LCMS: 739.1 $[M + H]^+$.

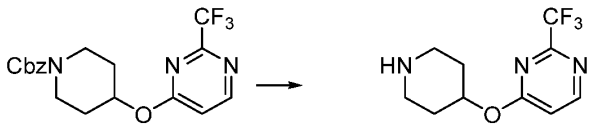
Intermediate 180-1: benzyl 4-((2-(trifluoromethyl)pyrimidin-4-yl)oxy)piperidine-1-carboxylate



180-1

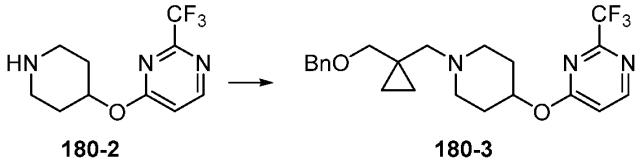
[0849] At 0 °C, sodium hydride (60 % in mineral oil, 73 mg, 1.79 mmol) was add to benzyl 4-hydroxypiperidine-1-carboxylate (211 mg, 0.897 mmol) in 2 mL DMF. 4-Bromo-2-(trifluoromethyl)pyrimidine 1 (204 mg, 0.897 mmol) was added after 10 minutes. The reaction was stirred at 0 °C for 30 minutes. The reaction was quenched by adding saturated bicarbonate solution, and the product was extracted with EtOAc. The organic layer was concentrated down and purified by silica column (eluting with EtOAc/hexane, 0-100%) to give intermediate **180-1**. LCMS: 382.2.

Intermediate 180-2: 4-(piperidin-4-yloxy)-2-(trifluoromethyl)pyrimidine



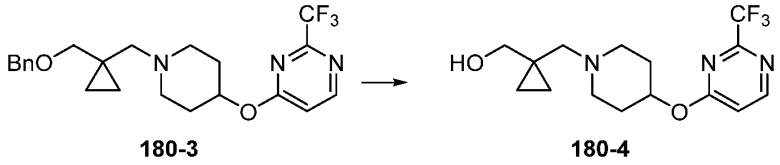
[0850] A stirred mixture of intermediate **180-1** (81 mg, 0.21 mmol), EtOAc (10 mL), EtOH (10 mL), and palladium (10% wt on activated carbon, 30 mg) was placed under an atmosphere of hydrogen gas (balloon) at room temperature. After 1 h, the resulting mixture was filtered, and the filtrate was concentrated under reduced pressure to give intermediate **180-2**. LCMS: 248.2.

Intermediate 180-3: 4-((1-((1-((benzyloxy)methyl)cyclopropyl)methyl)piperidin-4-yl)oxy)-2-(trifluoromethyl)pyrimidine



[0851] In a round bottom flask, 1-((benzyloxy)methyl)cyclopropane-1-carbaldehyde (40 mg, 0.21 mmol) and intermediate **180-2** (52 mg, 0.21 mmol) were dissolved in 1.5 mL THF. The reaction was stirred at room temperature for 30 minutes, and sodium triacetoxyborohydride (89 mg, 0.42 mmol) was added followed by a drop of acetic acid. The reaction was stirred at room temperature overnight. A saturated bicarbonate solution was added to the reaction, and the product was extracted with ethyl acetate. The organic layer was concentrated down and purified by silica column (eluting with EtOAc/hexane, 0-100%) to give intermediate **180-3**. LCMS: 422.2.

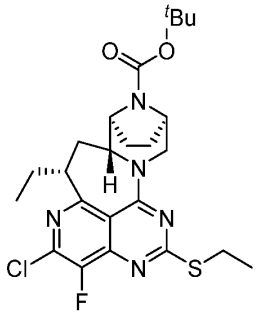
Intermediate 180-4: (1-((4-((2-(trifluoromethyl)pyrimidin-4-yl)oxy)piperidin-1-yl)methyl)cyclopropyl)methanol



[0852] A stirred mixture of intermediate **180-3** (65 mg, 0.154 mmol), EtOAc (5 mL), EtOH (5 mL), palladium (10% wt on activated carbon, 20 mg) at room temperature was placed under an

atmosphere of hydrogen gas (balloon). After 1 h, the resulting mixture was filtered, and the filtrate was concentrated under reduced pressure to give intermediate **180-4**. LCMS: 332.2.

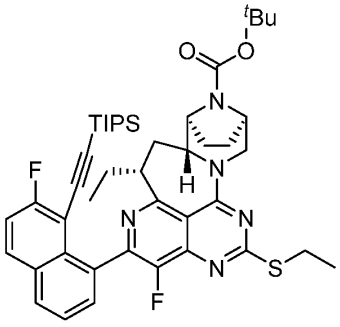
Intermediate 182-1: tert-butyl (4R,5aR,6S,9R)-2-chloro-4-ethyl-12-(ethylthio)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



182-1

[0853] Intermediate **182-1** was synthesized in a manner similar to **75-7** using intermediate **171-3** instead of intermediate **75-6**. LCMS: 508.3 $[M + H]^+$.

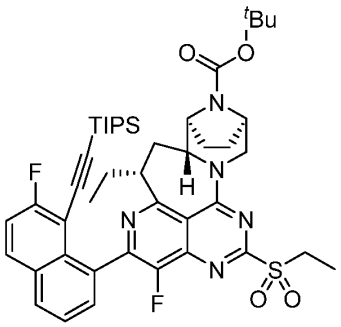
Intermediate 182-2: tert-butyl (4R,5aR,6S,9R)-4-ethyl-12-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



182-2

[0854] Intermediate **182-2** was synthesized in a manner similar to **76-1** using intermediate **182-1** instead of intermediate **75-9**. LCMS: 798.6 $[M + H]^+$.

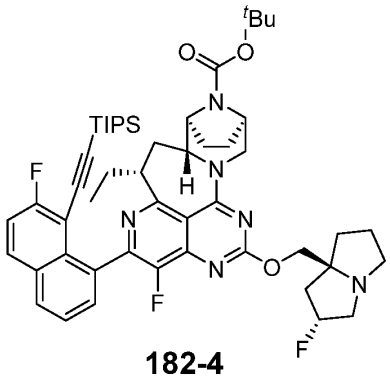
Intermediate 182-3: tert-butyl (4R,5aR,6S,9R)-4-ethyl-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



182-3

[0855] Intermediate **182-3** was synthesized in a manner similar to **75-8** using intermediate **182-2** instead of intermediate **75-7**. LCMS: 830.4 $[M + H]^+$.

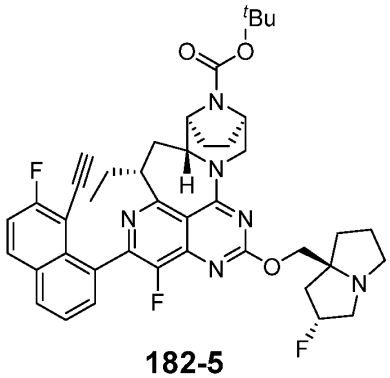
Intermediate 182-4: tert-butyl (4R,5aR,6S,9R)-4-ethyl-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



182-4

[0856] Intermediate **182-4** was synthesized in a manner similar to **75-9** using intermediate **182-3** instead of intermediate **75-8**. LCMS: 895.2 $[M + H]^+$.

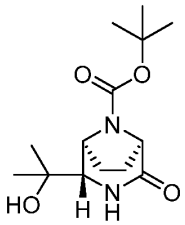
Intermediate 182-5: tert-butyl (4R,5aR,6S,9R)-4-ethyl-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



182-5

[0857] Intermediate **182-5** was synthesized in a manner similar to **76-2** using intermediate **182-4** instead of intermediate **76-1**. LCMS: 739.1 $[M + H]^+$.

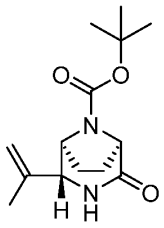
Intermediate 183-1: tert-butyl (1S,2S,5R)-2-(2-hydroxypropan-2-yl)-4-oxo-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



183-1

[0858] 8-(tert-butyl) 2-ethyl (1S,2S,5R)-4-oxo-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate (5 g, 16.8 mmol) was dissolved in dry THF (50 mL) under an atmosphere of nitrogen. After Cooling to 0 °C, a solution of methyl magnesium bromide in THF (15.7 mL, 3.2 M solution in 2-MeTHF, 50.3 mmol) was added dropwise via syringe. The solution was allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was slowly quenched with adding saturated ammonium chloride solution and water. The reaction mixture was extracted with EtOAc (3X), and the organic layers were combined and washed with saturated sodium chloride solution, and dried over magnesium sulfate. The solvents were removed by rotary evaporation. The residue was purified by SGC eluting with MeOH/DCM to afford **intermediate 183-1**. MS(m/z) 284.9 $[M+H]^+$

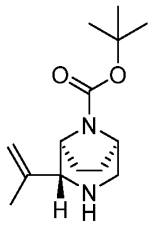
Intermediate 183-2: tert-butyl (1R,4R,5S)-2-oxo-4-(prop-1-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



183-2

[0859] A mixture of tert-butyl (1R,2S,5S)-2-(2-hydroxypropan-2-yl)-4-oxo-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (3500 mg, 12.3 mmol) and Martin Sulfurane (16.5 g, 24.6 mmol) in toluene (50 mL) was stirred at rt for 2 hours. The reaction mixture was evaporated and purified by SGC eluting with EtOAc/hex to afford **intermediate 183-2**. MS(m/z) 288.9 $[M+Na]^+$

Intermediate 183-3: tert-butyl (1S,2R,5R)-2-(prop-1-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

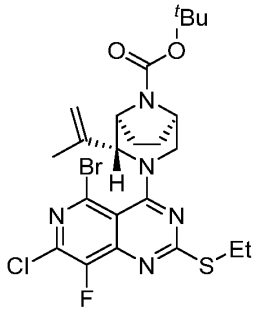


183-3

[0860] A flame-dried round-bottomed flask was charged with $AlCl_3$ (1577 mg, 11.8 mmol) and dry THF (25 mL) under a nitrogen atmosphere. The mixture was cooled to 0°C, and $LiAlH_4$ (5.9 ml, 11.8 mmol, 2 M solution in THF) was added. After the mixture was stirred for 30 min at 0 °C, a solution of tert-butyl (1S,4R,5R)-2-oxo-4-(prop-1-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.1 g, 7.88 mmol) in dry THF (25 mL) was added via syringe. The reaction mixture was stirred for 45 min at 0 °C, quenched by the addition of saturated aqueous NH_4Cl, and extracted three times with ethyl acetate; the combined organic phases were washed with brine and dried with $MgSO_4$. The solution was filtered and concentrated under reduced pressure. The residue was purified by alumina basic column eluting with EtOAc/hex to afford **intermediate 183-3**. HNMR (400 MHz, CD_3OD) δ 4.98 (dd, J = 2.8, 1.4 Hz, 2H), 4.12 (dd, J = 30.2, 6.5 Hz, 2H), 3.38 – 3.24

(m, 1H), 2.94 (d, J = 12.2 Hz, 1H), 2.75 (dd, J = 12.5, 2.1 Hz, 1H), 1.96 – 1.62 (m, 7H), 1.51 (s, 9H). MS(m/z) 252.9 $[M+H]^+$.

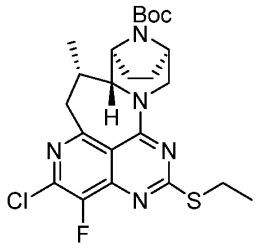
Intermediate 183-4: tert-butyl (1S,2R,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-(prop-1-en-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



183-4

[0861] Intermediate **183-4** was synthesized in a manner similar to **64-3** using intermediate **183-3** instead of intermediate **64-2**. LCMS: 573.0, 574.3 $[M + H]^+$.

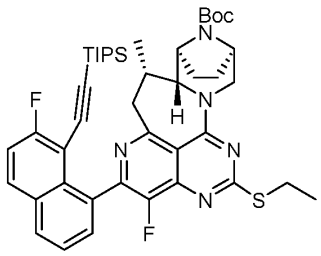
Intermediate 183-5: tert-butyl (5S,5aR,6S,9R)-2-chloro-12-(ethylthio)-1-fluoro-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



183-5

[0862] Intermediate 183-5 was synthesized in a manner similar to **Intermediate 75-7** using **Intermediate 183-4** instead of **Intermediate 75-6**. Slower eluted fraction on silica gel column chromatography. LCMS: 494.5 $[M+H]^+$

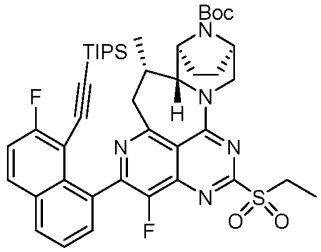
Intermediate 183-6: tert-butyl (5S,5aR,6S,9R)-12-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



183-6

[0863] Intermediate 183-6 was synthesized in a manner similar to **Intermediate 76-1** using **Intermediate 183-5** instead of **Intermediate 75-9**. LCMS: 784.8 $[M+H]^+$

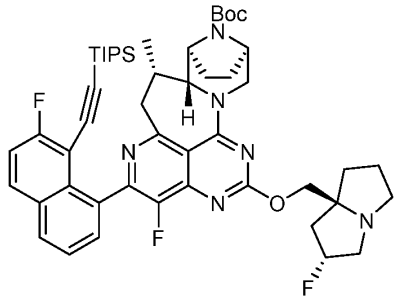
Intermediate 183-7: tert-butyl (5S,5aR,6S,9R)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



183-7

[0864] Intermediate 183-7 was synthesized in a manner similar to **Intermediate 75-8** using **Intermediate 183-6** instead of **Intermediate 75-7**. LCMS: 816.8 $[M+H]^+$

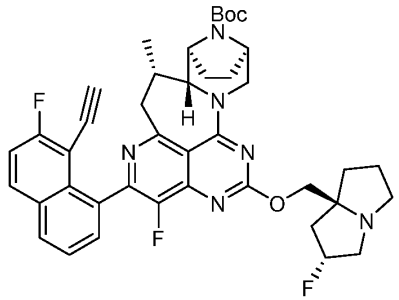
Intermediate 183-8: tert-butyl (5S,5aR,6S,9R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



183-8

[0865] Intermediate 183-8 was synthesized in a manner similar to **Intermediate 75-9** using **Intermediate 183-7** instead of **Intermediate 75-8**. LCMS: 881.1 $[M+H]^+$

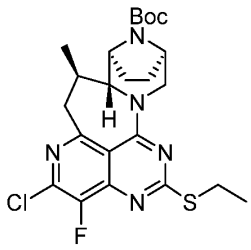
Intermediate 183-9: tert-butyl (5S,5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



183-9

[0866] Intermediate 183-9 was synthesized in a manner similar to **Intermediate 75-11** using **Intermediate 183-8** instead of **Intermediate 75-10**. LCMS: 725.1 $[M+H]^+$

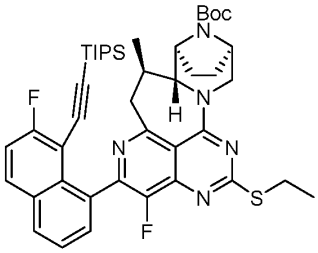
Intermediate 184-1: tert-butyl (5R,5aR,6S,9R)-2-chloro-12-(ethylthio)-1-fluoro-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



184-1

[0867] Intermediate 184-1 was synthesized in a manner similar to **Intermediate 75-7** using **Intermediate 183-4** instead of **Intermediate 75-6**. Faster eluted fraction on silica gel column chromatography. LCMS: 494.3 $[M+H]^+$

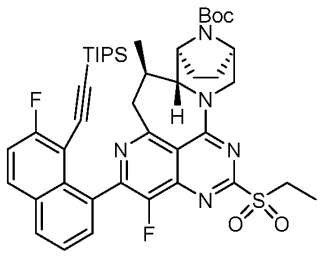
Intermediate 184-2: tert-butyl (5R,5aR,6S,9R)-12-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



184-2

[0868] Intermediate 184-2 was synthesized in a manner similar to **Intermediate 76-1** using **Intermediate 184-1** instead of **Intermediate 75-9**. LCMS: 784.5 $[M+H]^+$

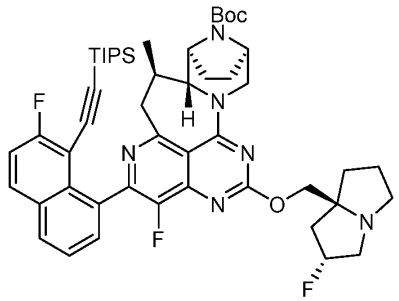
Intermediate 184-3: tert-butyl (5R,5aR,6S,9R)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



184-3

[0869] Intermediate 184-3 was synthesized in a manner similar to **Intermediate 75-8** using **Intermediate 184-2** instead of **Intermediate 75-7**. LCMS: 816.4 $[M+H]^+$

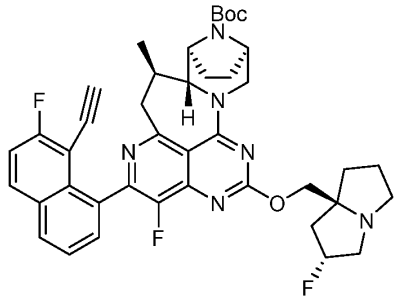
Intermediate 184-4: tert-butyl (5R,5aR,6S,9R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



184-4

[0870] Intermediate 184-4 was synthesized in a manner similar to **Intermediate 75-9** using **Intermediate 184-3** instead of **Intermediate 75-8**. LCMS: 881.1 $[M+H]^+$

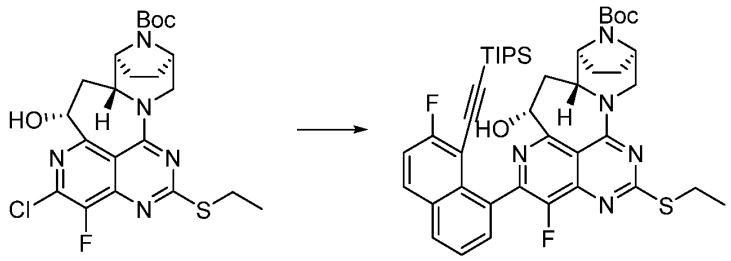
Intermediate 184-5: tert-butyl (5R,5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



184-5

[0871] Intermediate 184-5 was synthesized in a manner similar to **Intermediate 75-11** using **Intermediate 184-4** instead of **Intermediate 75-10**. LCMS: 725.1 $[M+H]^+$

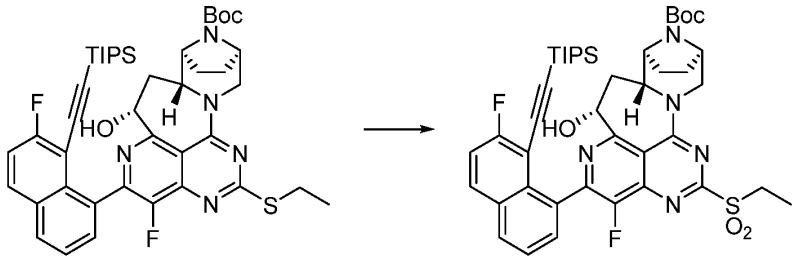
Intermediate 186-1 *tert*-butyl (4*R*,5a*R*,6*S*,9*R*)-12-(ethylthio)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4-hydroxy-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



172-1 186-1

[0872] Intermediate 186-1 was synthesized in a manner similar to **Intermediate 13-8** using **Intermediate 172-1** instead of **Intermediate 13-7**. LCMS: 786.7.

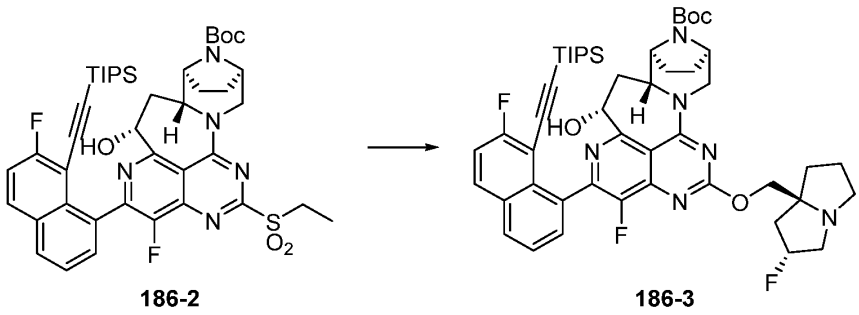
Intermediate 186-2 tert-butyl (4R,5aR,6S,9R)-12-(ethylsulfonyl)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4-hydroxy-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



186-1 186-2

[0873] Intermediate 186-2 was synthesized in a manner similar to **Intermediate 13-9** using **Intermediate 186-1** instead of **Intermediate 13-8**. LCMS: 818.3.

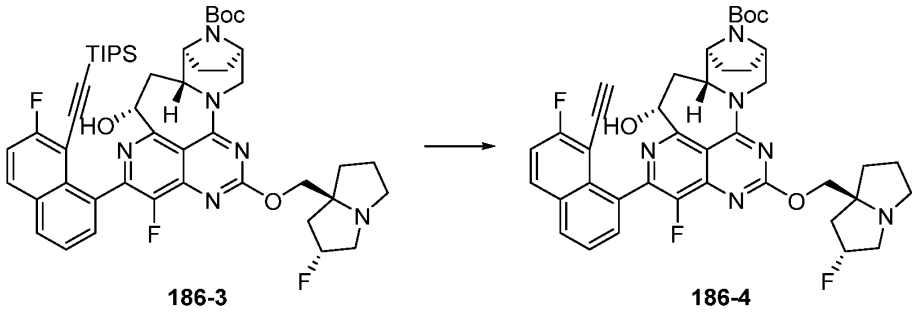
Intermediate 186-3 tert-butyl (4R,5aR,6S,9R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxy-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



186-2 186-3

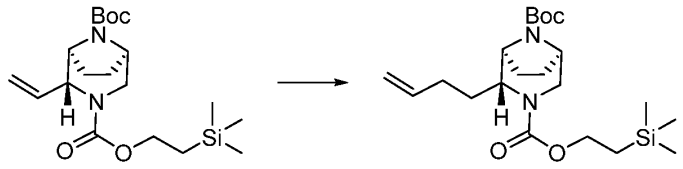
[0874] Intermediate 186-3 was synthesized in a manner similar to **Intermediate 13-10** using **Intermediate 186-2** instead of **Intermediate 13-9**. LCMS: 883.1.

Intermediate 186-4 ***tert*-butyl (4*R*,5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxy-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate**



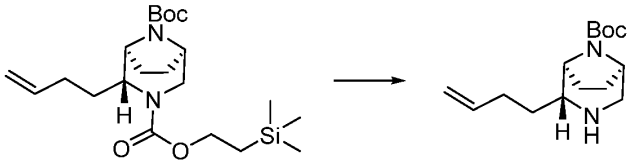
[0875] Intermediate 186-4 was synthesized in a manner similar to Intermediate 13-11 using Intermediate 186-3 instead of Intermediate 13-10. LCMS: 727.1.

Intermediate 188-1 8-(*tert*-butyl) 3-(2-(trimethylsilyl)ethyl) (1*S*,2*R*,5*R*)-2-(but-3-en-1-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



[0876] To a vigorously stirred solution of **Intermediate 75-1** (70.0 mg, 0.18 mmol) in anhydrous 2-methyltetrahydrofuran (2.1 mL), a solution of 9-borabicyclo[3.3.1]nonane (0.50 M in tetrahydrofuran, 0.55 mL, 0.28 mmol) was added at room temperature. The resulting solution was stirred at 50 °C for 100 minutes before it was cooled to room temperature. The solution was transferred to a reaction vial containing $Pd(dppf)Cl_2$ (13.0 mg, 0.018 mmol), potassium phosphate (213.5 mg, 0.92 mmol), bromoethylene (1.0 M in tetrahydrofuran, 0.80 mL, 0.80 mmol) and degassed water (0.29 mL) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 70°C for 12 minutes before it was cooled to room temperature. The mixture was washed with water (2 mL) and extracted with ethyl acetate (3 x 5 mL). The organic layer was collected and combined, dried over magnesium sulfate, concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0 to 50% ethyl acetate in hexanes) to give **Intermediate 188-1**. LCMS: 433.2 $[M+Na]^+$.

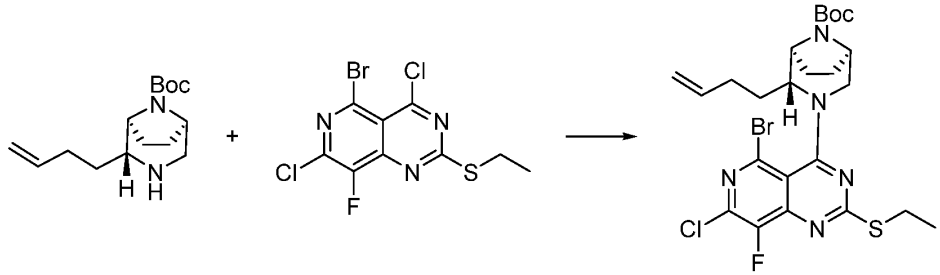
Intermediate 188-2 *tert*-butyl (1*S*,2*R*,5*R*)-2-(but-3-en-1-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



188-1 188-2

[0877] Intermediate 188-2 was synthesized in a manner similar to **Intermediate 75-5** using **Intermediate 188-1** instead of **Intermediate 75-4**. LCMS: 267.0.

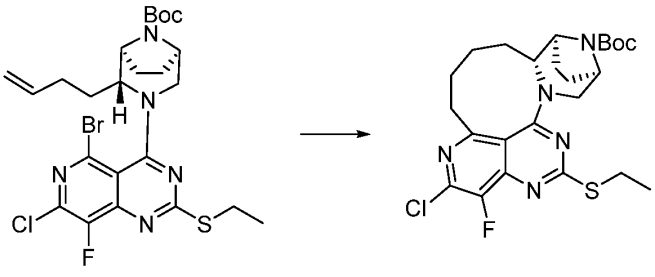
Intermediate 188-3 *tert*-butyl (1*S*,2*R*,5*R*)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-(but-3-en-1-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



188-2 53-1 188-3

[0878] Intermediate 188-3 was synthesized in a manner similar to **Intermediate 53-5** using **Intermediate 188-2** instead of **Intermediate 53-4**. LCMS: 588.1.

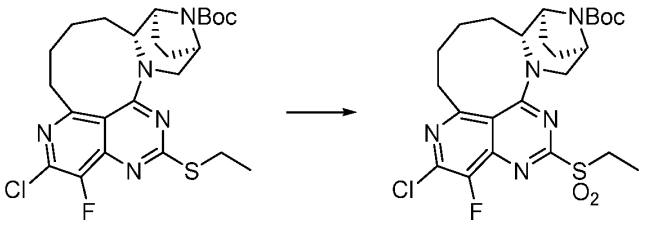
Intermediate 188-4 tert-butyl (7aR,8S,11R)-2-chloro-14-(ethylthio)-1-fluoro-4,5,6,7,7a,8,9,10,11,12-decahydro-3,12a,13,15,16-pentaaza-8,11-methanocyclohepta[4,5]cyclonona[1,2,3-de]naphthalene-16-carboxylate



188-3 188-4

[0879] Intermediate 188-4 was synthesized in a manner similar to Intermediate 75-7 using Intermediate 188-3 instead of Intermediate 75-6. LCMS: 508.3.

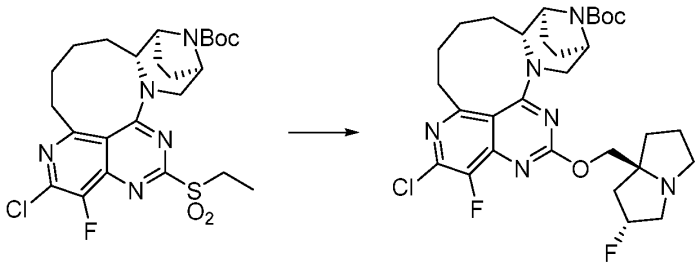
Intermediate 188-5 ***tert*-butyl (7a*R*,8*S*,11*R*)-2-chloro-14-(ethylsulfonyl)-1-fluoro-4,5,6,7,7a,8,9,10,11,12-decahydro-3,12a,13,15,16-pentaaza-8,11-methanocyclohepta[4,5]cyclonona[1,2,3-*de*]naphthalene-16-carboxylate**



188-4 188-5

[0880] Intermediate 188-5 was synthesized in a manner similar to **Intermediate 13-9** using **Intermediate 188-4** instead of **Intermediate 13-8**. LCMS: 539.9.

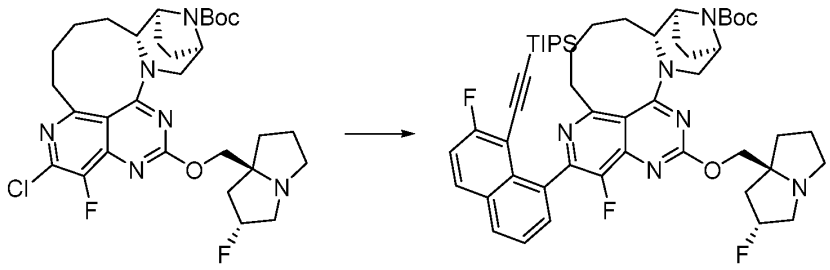
Intermediate 188-6 ***tert*-butyl (7a*R*,8*S*,11*R*)-2-chloro-1-fluoro-14-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,6,7,7a,8,9,10,11,12-decahydro-3,12a,13,15,16-pentaaza-8,11-methanocyclohepta[4,5]cyclonona[1,2,3-*de*]naphthalene-16-carboxylate**



188-5 188-6

[0881] Intermediate 188-6 was synthesized in a manner similar to **Intermediate 53-10** using **Intermediate 188-5** instead of **Intermediate 53-9**. LCMS: 605.0.

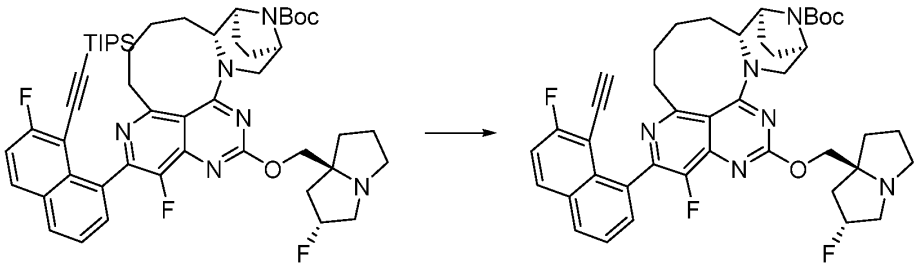
Intermediate 188-7 ***tert*-butyl (7a*R*,8*S*,11*R*)-2-chloro-1-fluoro-14-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,6,7,7a,8,9,10,11,12-decahydro-3,12a,13,15,16-pentaaza-8,11-methanocyclohepta[4,5]cyclonona[1,2,3-*de*]naphthalene-16-carboxylate**



188-6 188-7

[0882] Intermediate 188-7 was synthesized in a manner similar to **Intermediate 2-1** using **Intermediate 188-6** instead of **Intermediate 17-9**. LCMS: 895.1.

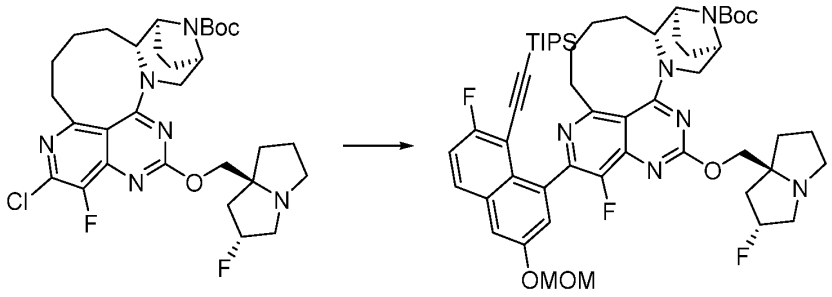
Intermediate 188-8 tert-butyl (7aR,8S,11R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-14-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,6,7,7a,8,9,10,11,12-decahydro-3,12a,13,15,16-pentaaza-8,11-methanocyclohepta[4,5]cyclonona[1,2,3-de]naphthalene-16-carboxylate



188-7 188-8

[0883] Intermediate 188-8 was synthesized in a manner similar to **Intermediate 13-11** using **Intermediate 188-7** instead of **Intermediate 13-10**. LCMS: 739.1.

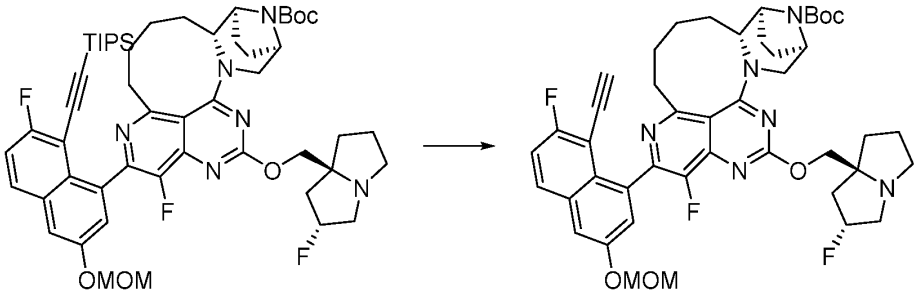
Intermediate 189-1 ***tert*-butyl (7a*R*,8*S*,11*R*)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-14-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,6,7,7a,8,9,10,11,12-decahydro-3,12a,13,15,16-pentaaza-8,11-methanocyclohepta[4,5]cyclonona[1,2,3-*de*]naphthalene-16-carboxylate**



188-6 189-1

[0884] Intermediate 189-1 was synthesized in a manner similar to **Intermediate 2-1** using **Intermediate 188-6** instead of **Intermediate 17-9**. LCMS: 955.3.

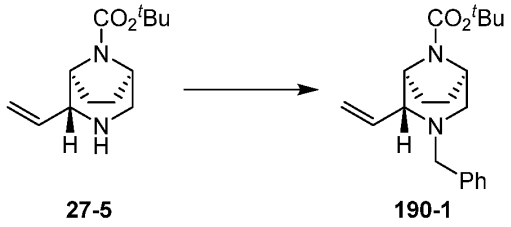
Intermediate 189-2 tert-butyl (7aR,8S,11R)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-14-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,6,7,7a,8,9,10,11,12-decahydro-3,12a,13,15,16-pentaaza-8,11-methanocyclohepta[4,5]cyclonona[1,2,3-de]naphthalene-16-carboxylate



189-1 189-2

[0885] Intermediate 189-2 was synthesized in a manner similar to **Intermediate 13-11** using **Intermediate 189-1** instead of **Intermediate 13-10**. LCMS: 799.0.

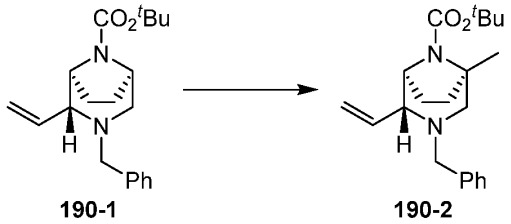
Intermediate 190-1: tert-butyl (1S,2R,5R)-3-benzyl-2-vinyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



27-5 190-1

[0886] Benzyl bromide (633 μL, 5.32 mmol) was added to a stirred mixture of intermediate **27-5** (1.15 g, 4.84 mmol), *N*,*N*-diisopropylethylamine (1.22 mL, 7.01 mmol), and acetonitrile at room temperature, and the resulting mixture was heated to 80 °C. After 40 min, the resulting mixture was heated to 90 °C. After 17 h, the resulting mixture was cooled to room temperature and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 12% ethyl acetate in hexanes) to give intermediate **190-1**. LCMS: 329.2.

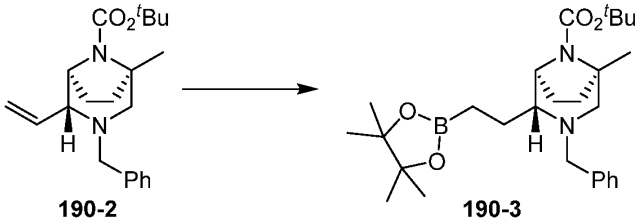
Intermediate 190-2: tert-butyl (1R,4R,5S)-3-benzyl-1-methyl-4-vinyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



190-1 190-2

[0887] Secondary butyllithium solution (1.31 M in cyclohexane, 2.81 mL, 3.67 mmol) was added over 2 min via syringe to a vigorously stirred mixture of intermediate **190-1** (402 mg, 1.22 mmol), *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (551 μL, 3.67 mmol), and diethyl ether (4.5 mL) at −40 °C. After 1 min, the resulting mixture was warmed to 0 °C. After 35 min, the resulting mixture was cooled to −78 °C over 5 min, and iodomethane (267 μL, 4.29 mmol) was added via syringe. After 5 min, the resulting mixture was warmed to 0 °C. After 90 min, triethylamine (3.0 mL) and saturated aqueous sodium bicarbonate solution (4.0 mL) were added sequentially, and the resulting mixture was warmed to room temperature. Diethyl ether (40 mL) and ethyl acetate (20 mL) were added sequentially, and the organic layer was washed with a mixture of water and brine (3:1 v:v, 10 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 5.5% ethyl acetate in hexanes) to give intermediate **190-2**. LCMS: 343.2.

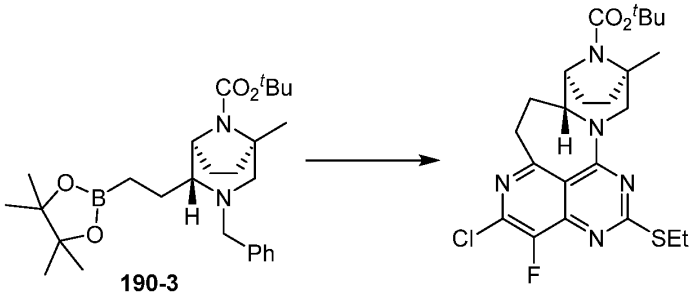
Intermediate 190-3: tert-butyl (1R,4R,5S)-3-benzyl-1-methyl-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



190-2 190-3

[0888] Bis(1,5-cyclooctadiene)diiridium(I) dichloride (58.8 mg, 87.6 μmol) was added to a vigorously stirred mixture of intermediate **190-2** (200 mg, 584 μmol), ethylenebis(diphenylphosphine) (69.8 mg, 175 μmol), and dichloromethane (0.2 mL) at room temperature. After 8 min, the resulting mixture was cooled to 0 °C over 3 min. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (169 μmol, 1.17 mmol) was added via syringe over 10 min, and the resulting mixture was warmed to room temperature. After 5 h, the resulting mixture was purified by flash column chromatography on silica gel (0 to 40% ethyl acetate in hexanes) to give intermediate **190-3**. LCMS: 471.3.

Intermediate 190-4: tert-butyl (5aR,6S,9R)-2-chloro-12-(ethylthio)-1-fluoro-9-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

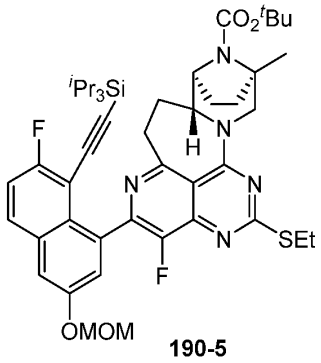


190-3 190-4

[0889] A vigorously agitated mixture of intermediate **190-3** (223 mg, 474 μmol), palladium(II) hydroxide (20% wt on activated carbon, 49.9 mg, 71 μmol), and tetrahydrofuran (3.0 mL) at room temperature in a glass shaker was placed under an atmosphere of hydrogen gas (50 psi). After 16.5 h, the resulting mixture was filtered through celite. The filtrate was concentrated under reduced pressure. Dichloromethane (1.0 mL) and *N*,*N*-diisopropylethylamine (248 μL, 1.42 mmol) were added sequentially, and the resulting mixture was stirred at room temperature. Intermediate **53-1**

(180 mg, 474 μmol) was added. After 40 min, saturated aqueous ammonium chloride solution (10 mL), aqueous hydrogen chloride solution (2.0 M, 1.0 mL), diethyl ether (40 mL), and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (15 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (34.7 mg, 47.4 μmol) and 1,4-dioxane (4.5 mL) were added sequentially, and the resulting mixture was vigorously stirred and was sparged with nitrogen gas. After 15 min, sparging was ceased, and saturated aqueous sodium carbonate solution (2.0 M, 949 μL, 1.9 mmol) was added via syringe. The resulting mixture was heated to 90 °C. After 50 min, the resulting mixture was heated to 110 °C. After 70 min, the resulting mixture was cooled to room temperature, and diethyl ether (40 mL) and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (20 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 to 24% ethyl acetate in hexanes) to give intermediate **190-4**. LCMS: 494.2.

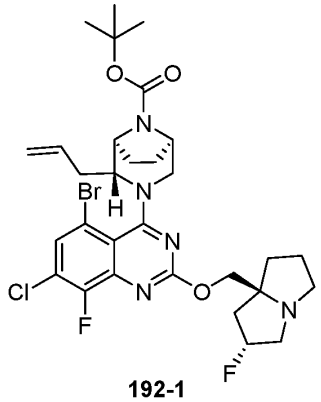
Intermediate 190-5: tert-butyl (5aR,6S,9R)-12-(ethylthio)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-9-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



190-5

[0890] Intermediate **190-5** was synthesized in a manner similar to intermediate **52-7** using intermediate **190-4** instead of intermediate **52-6**. LCMS: 844.1.

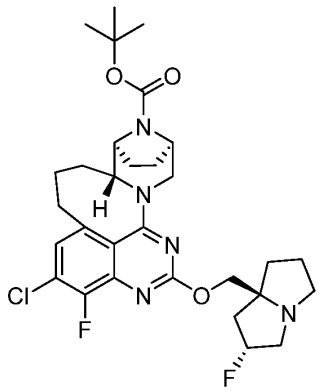
Intermediate 192-1: tert-butyl (1S,2R,5R)-2-allyl-3-(5-bromo-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



192-1

[0891] Intermediate **192-1** was synthesized in a manner similar to intermediate **52-4** using intermediate **75-5** instead of intermediate **27-5**. LCMS: 668.2.

Intermediate 192-2: tert-butyl (1S,4R,15aR)-11-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,4,5,13,14,15,15a-octahydro-1H-1,4-epiminoazepino[1',2':1,8]azocino[2,3,4-de]quinazoline-16-carboxylate

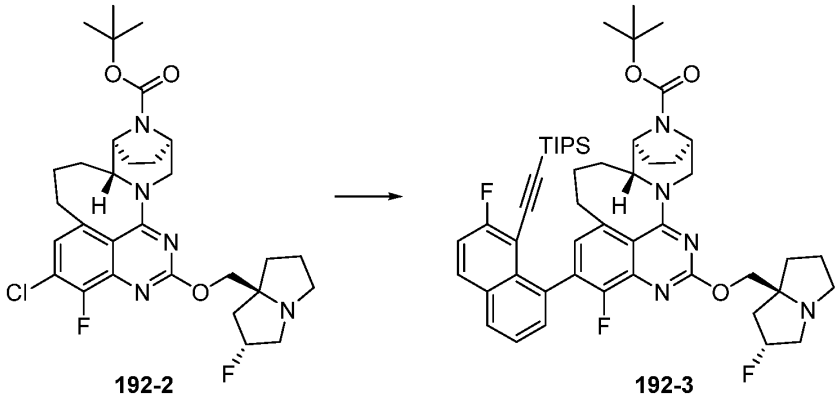


192-2

[0892] A solution of intermediate **192-1** (109.9 mg, 164 umol; azeotroped with toluene 3 x) in tetrahydrofuran (0.4 mL) was stirred at rt as 0.5 M 9-borabicyclo[3.3.1]nonane in tetrahydrofuran (0.99 mL) was added. The resulting solution was heated at 60 °C heating block for 90 min and then cooled to rt. To the reaction mixture was added water (0.4 mL) and stirred at rt for 1 h. To the resulting solution was added 1.5 M aqueous tripotassium phosphate (1.10 mL, 1.64 umol) and the mixture was purged with Ar gas for 15 min. To this degassed vial were

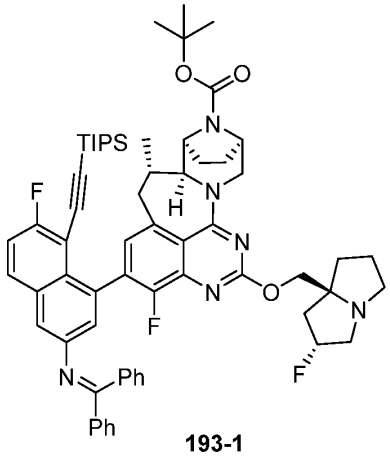
added ferrouscyclopenta-1,3-dien-1-yl(diphenyl)phosphane dichloropalladium (12.74 mg, 17.4 umol), and dioxane (2.1 mL). The resulting mixture was purged with Ar gas for 15 min again. The resulting solution was heated at 90 °C heating block for 1 h and then cooled to rt. The reaction mixture was diluted with saturated sodium bicarbonate (~5 mL), and the product was extracted with ethyl acetate (~10 mL x 3). The extracts were combined, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography eluting 40-100% ethyl acetate in hexane followed by 0-20% MeOH in ethyl acetate to give intermediate **192-2**. LCMS: 590.3.

Intermediate 192-3: tert-butyl (1S,4R,15aR)-10-fluoro-11-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,4,5,13,14,15,15a-octahydro-1H-1,4-epiminoazepino[1',2':1,8]azocino[2,3,4-de]quinazoline-16-carboxylate



[0893] A mixture of intermediate **192-2** (9.01 mg, 15.3 umol), 2-[2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl-triisopropyl-silane (9.52 mg, 21.0umol), and cataCXium A Pd G3 (2.23 mg, 3.06 umol) in 1,4-dioxane (0.4 mL) and 1.5 M aqueous tripotassium phosphate (0.11 mL) was purged with Ar gas for 15 min and then reacted at 120 oC for 30 min in uW reactor. The reaction mixture was diluted with saturated sodium bicarbonate (~25 mL) and the product was extracted with ethyl acetate (~20 mL x 2). The combined extracts were dried ($MgSO_4$), and concentrated to give intermediate **192-3**. LCMS: 880.2.

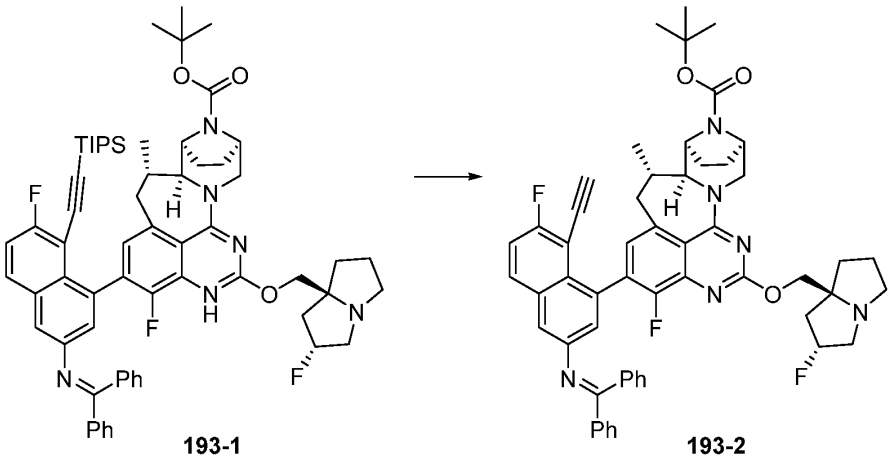
Intermediate 193-1: tert-butyl (1S,4R,14S,14aS)-11-(3-((diphenylmethylene)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-14-methyl-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate



193-1

[0894] Intermediate **193-1** was synthesized in a manner similar to intermediate **192-3** using intermediate **64-2** instead of intermediate **75-5** and using *N*-(6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)-1,1-diphenylmethanimine (WO2022170999) instead of 2-[2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl-triisopropyl-silane. LCMS: 1059.3.

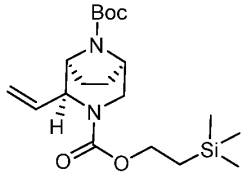
Intermediate 193-2: tert-butyl (1S,4R,14S,14aS)-11-(3-((diphenylmethylene)amino)-8-ethynyl-7-fluoronaphthalen-1-yl)-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-14-methyl-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate



193-1 193-2

[0895] To a mixture of intermediate **193-1** (16.17 mg, 15.3 umol) and CsF (35.24 mg, 232 umol) was added DMF (0.6 mL) and the resulting solution was stirred for 1 h at rt. After the reaction mixture was diluted with saturated sodium bicarbonate solution (~10 mL), water (~15 mL), the product was extracted with ethyl acetate (~20 mL x 2). The organic extracts were washed with water (~25 mL x 1), combined, dried ($MgSO_4$), and concentrated. The resulting residue was purified by silica gel column chromatography eluting 0-20% MeOH in dichloromethane to give intermediate **193-2**. LCMS: 903.5.

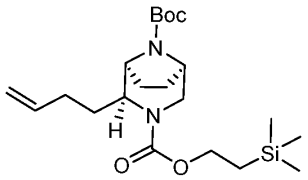
Intermediate 194-1: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-vinyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



194-1

[0896] Intermediate **194-1** was synthesized in a manner similar to intermediate **75-1** using 8-(*tert*-butyl) 2-ethyl (1*S*,2*R*,5*R*)-4-oxo-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate (WO2022188729) instead of 8-(*tert*-butyl) 2-ethyl (1*S*,2*S*,5*R*)-4-oxo-3,8-diazabicyclo[3.2.1]octane-2,8-dicarboxylate. LCMS: 405.3 $[M+Na]^+$.

Intermediate 194-2: 8-(tert-butyl) 3-(2-(trimethylsilyl)ethyl) (1S,2S,5R)-2-(but-3-en-1-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate

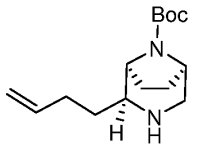


5299-i-3

[0897] To a vial charged with intermediate **194-1** (224 mg, 0.523 mmol) and 2-Me-THF (3 ml), 9-BBN (1.96 ml, 0.98 mmol, 0.5 M in THF) was added under N_2 atmosphere. The reaction mixture was stirred at 50 °C. Upon full consumption of the starting material (about 100 minutes), the mixture was cooled to room temperature. To another vial, $Pd(dppf)Cl_2$ (37 mg, 0.052 mmol) and K_3PO_4 (610 mg, 2.62 mmol) were added, evacuate and refill with N_2 three times, to it was added degassed water (1.5 ml), the crude hydroboration solution and vinyl bromide solution (2.3 ml, 2.3

mmol, 1 M in THF). The resulting mixture was stirred at 70 °C for 20 minutes and cooled to room temperature. It was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate, filtered, and concentrated to dryness. The residue was purified by silica gel chromatography eluting with ethyl acetate / hexane to afford intermediate **194-2**. LCMS: 433.2 (M+Na).

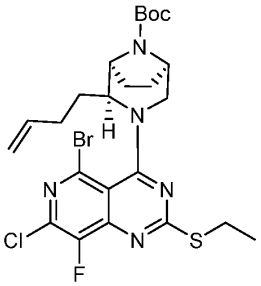
Intermediate 194-3: tert-butyl (1S,2S,5R)-2-(but-3-en-1-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



194-3

[0898] To the vial charged with compound intermediate **194-2** (130 mg, 0.32 mmol) and cesium fluoride (240 mg, 1.58 mmol). To it was added DMF (1.3 ml). The mixture was stirred at 70 °C for 4 hours. Upon the completion of this reaction, the mixture was filtered thru a celite pad the filtrate was concentrated to give intermediate **194-3**. LCMS: 267.2

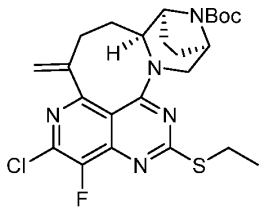
Intermediate 194-4: tert-butyl (1S,2S,5R)-3-(5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-(but-3-en-1-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



194-4

[0899] To a vial charged with intermediate **194-3** (100 mg, 0.375 mmol) and **Intermediate 53-1** (134 mg, 0.375 mmol), dichloromethane (1 ml) was added under N_2 protection and cooled to 0 °C. To it was added N, N-diisopropylethylamine (0.196 ml, 1.13 mmol). The resulting mixture was stirred under 0 °C for 12 min before loaded onto ISCO flash column directly and eluting with ethyl acetate / hexane to afford intermediate **194-4**. LCMS: 588.2.

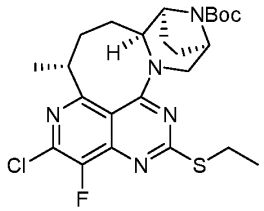
Intermediate 194-5: tert-butyl (6aS,7S,10R)-2-chloro-13-(ethylthio)-1-fluoro-4-methylene-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



194-5

[0900] Intermediate **194-4** (100 mg, 0.17 mmol) was dissolved in acetonitrile (3 mL) and purged with argon. To it was added triethylamine (0.071 ml, 0.511 mmol) and tetrakis(triphenylphosphine)palladium(0) (19.7 mg, 0.017 mmol). The reaction mixture was stirred at 100 °C for 1-hour. Upon completion, it cooled to room temperature and concentrated to dryness. The residue was Purify by silica gel chromatography eluting with ethyl acetate and hexane to afford intermediate **194-5**. LCMS: 506.2.

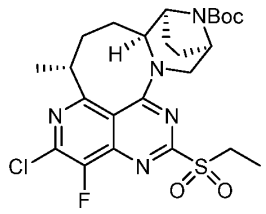
Intermediate 194-6: tert-butyl (4R,6aS,7S,10R)-2-chloro-13-(ethylthio)-1-fluoro-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



194-6

[0901] Intermediate **194-5** (91 mg, 0.18 mmol) was dissolved in 5 ml of ethyl acetate and was sparged under an argon atmosphere. platinum(iv) oxide (20.4 mg, 0.0899 mmol) was added, and the mixture was sparged under a hydrogen atmosphere (1 atm, balloon). The mixture was stirred vigorously for 4 hours. after sparged with argon, it was filtered through a pad of Celite®. The Celite® was washed with ethyl acetate. The filtrate was concentrated to dryness and purified by RP-HPLC to afford intermediate **194-6** (methylated carbon stereocenter stereochemistry assigned arbitrarily). LCMS: 508.2.

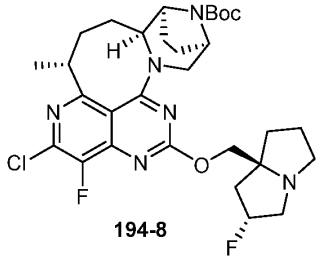
Intermediate 194-7: tert-butyl (4R,6aS,7S,10R)-2-chloro-13-(ethylsulfonyl)-1-fluoro-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



194-7

[0902] Intermediate 194-7 was synthesized in a manner similar to **intermediate 13-9** using intermediate **194-6** instead of intermediate **13-8**. LCMS: 540.2.

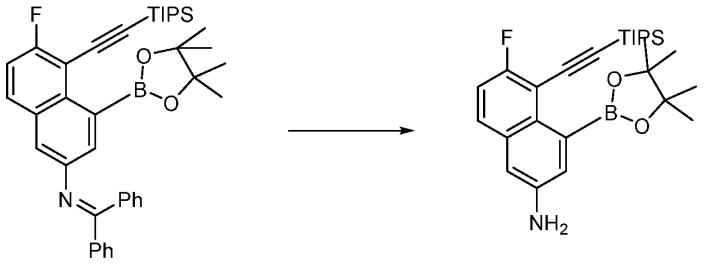
Intermediate 194-8: tert-butyl (4R,6aS,7S,10R)-2-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



194-8

[0903] Azeotrope compound **194-7** (41 mg, 0.0759 mmol) and [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (24.2 mg, 0.152 mmol) with 1 mL toluene 2 times, then dissolve in THF (1 ml). Lithium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 114 μL, 0.114 mmol) was added under 0 °C. The reactions were stirred at 0 °C for 15 min. Upon completion, the mixture was diluted with ethyl acetate and quenched with H_2O under 0 °C and extract with ethyl acetate. Organic layer was dried over sodium sulfate and conc in vacuo. The residue was purified with reverse phase prep HPLC to afford intermediate **194-8**. LCMS: 605.2

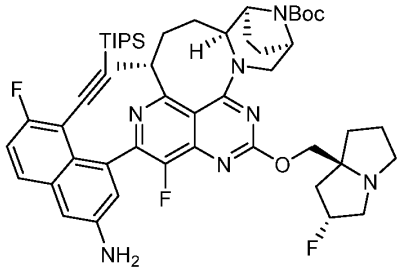
Intermediate 194-9: 6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-amine



194-9

[0904] *N*-(6-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)-1,1-diphenylmethanimine (150 mg, 0.24 mmol) was dissolved in 1 mL ethyl acetate. A solution of HCl in 1,4-dixoane (4.0M, 0.59 ml, 24 mmol) was added followed by water (0.0085 ml, 0.47 mmol) to facilitate hydrolysis. After 1-hour, desired product precipitated out from the solution. Hexane was added and the resulting mixture was filtered to give intermediate **194-9**. LCMS: 468.3.

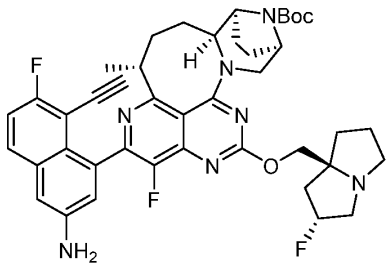
Intermediate 194-10: tert-butyl (4R,6aS,7S,10R)-2-(3-amino-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



194-10

[0905] Intermediate **194-10** was synthesized in a manner similar to intermediate **4-1** using intermediate **194-8** and intermediate **194-9** instead of intermediate **17-9** and ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (WO2021041671) . LCMS: 910.6.

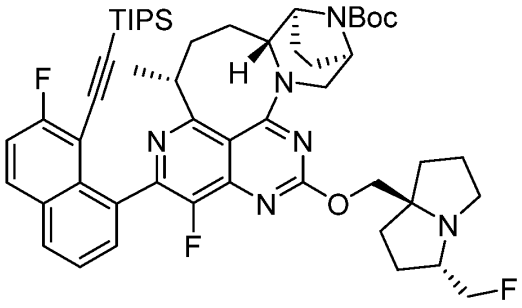
Intermediate 194-11: tert-butyl (4R,6aS,7S,10R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



194-11

[0906] Cesium fluoride (92 mg, 606 μmol) was added to a vigorously stirred solution of intermediate **194-10** (23 mg, 25.3 μmol) in *N*,*N*-dimethylformamide (0.6 mL) at room temperature. After 30 min, diethyl ether (40 mL) and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (2 × 40 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduce pressure to afford intermediate **194-11**. LCMS: 754.4.

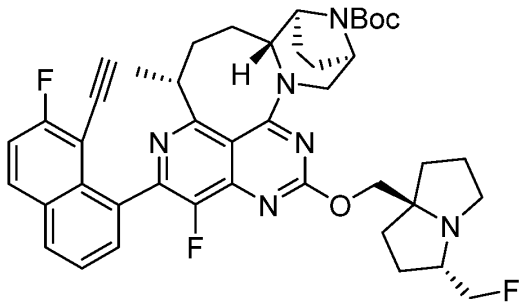
Intermediate 195-1: tert-butyl (4R,6aR,7S,10R)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-13-(((3S,7aS)-3-(fluoromethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



195-1

[0907] Intermediate **195-1** was synthesized in a manner similar to **171-7** using intermediate **165-1** instead of intermediate ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol. LCMS: 909.3.

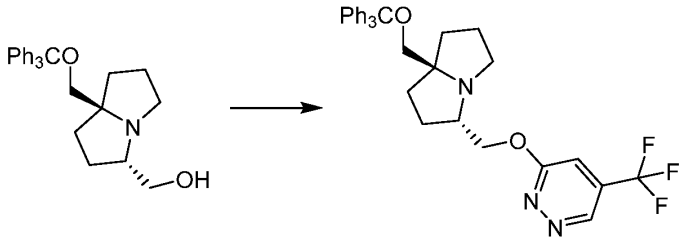
Intermediate 195-2: tert-butyl (4R,6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((3S,7aS)-3-(fluoromethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



195-2

[0908] Intermediate **195-2** was synthesized in a manner similar to **171-8** using intermediate **195-1** instead of intermediate **171-7**. LCMS: 753.1.

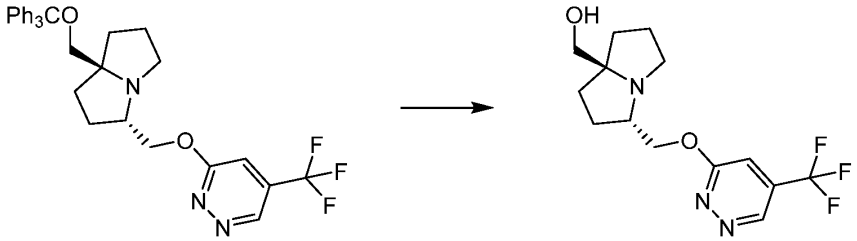
Intermediate 198-0: (3S,7aS)-3-(((5-(trifluoromethyl)pyridazin-3-yl)oxy)methyl)-7a-((trityloxy)methyl)hexahydro-1H-pyrrolizine



63-2 **198-0**

[0909] To a mixture of intermediate **63-2** (300 mg, 725 μmol) in THF (1.5 mL) was added t-BuOK solution (1.0 M in tetrahydrofuran, 1.09 mL, 1.1 mmol), and the resulting mixture was degassed and purged with N_2 3 times at 0°C for 0.5 hr. 3-Chloro-5-(trifluoromethyl)pyridazine (158.9 mg, 870.5 μmol) was added, the reaction mixture was stirred at 25°C for 1 hr under N_2 atmosphere. The unreacted alkoxides were quenched by addition saturated aqueous H_2O (4 mL) at 0°C, and the aqueous layer was extracted with EtOAc (4 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by purified by flash silica gel chromatography (12 g Silica Flash Column, Eluent of 0~20% Dichloromethane / Methanol gradient @80 mL/min) to give intermediate **198-0**. LCMS: 560.2.

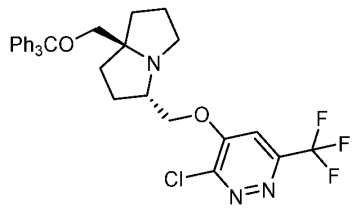
Intermediate 198-1: ((3S,7aS)-3-(((5-(trifluoromethyl)pyridazin-3-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



198-0 198-1

[0910] To a solution of intermediate **198-0** (300 mg, 536 μmol) in EtOAc (0.5 mL) was added HCl/EtOAc (0.5 mL). The mixture was stirred at 25°C for 0.5 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC(column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(NH_4HCO_3)-ACN];gradient:5%-30% B over 8 min) to give intermediate **198-1**. LCMS: 318.1.

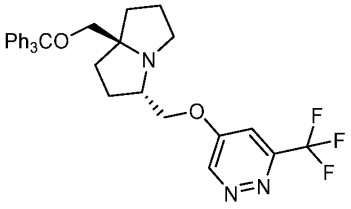
Intermediate 199-1: (3S,7aS)-3-(((3-chloro-6-(trifluoromethyl)pyridazin-4-yl)oxy)methyl)-7a-((trityloxy)methyl)hexahydro-1H-pyrrolizine



199-1

[0911] To a solution of intermediate **63-2** (50.00 mg, 120.90 μmol) in THF (2.00 mL) was added t-BuOK (1 M, 181.36 μL) at 0°C under N_2. The mixture was stirred at 0°C for 0.5 hr, then 4-bromo-3-chloro-6-(trifluoromethyl)pyridazine (47.41 mg, 181.36 μmol) was added to the mixture, and the mixture was stirred at 25°C for 0.5 hr. The reaction mixture was quenched by addition saturated aqueous NH_4Cl solution (20.00 mL) at 0°C, and then extracted with EtOAc (20.00 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC(column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [H_2O(0.05% NH_3H_2O+10mM NH_4HCO_3)-ACN];gradient:60%-90% B over 8.0 min) to give intermediate **199-1**. LCMS: 594.3.

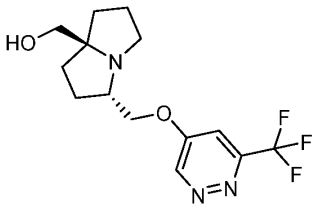
Intermediate 199-2: (3S,7aS)-3-(((6-(trifluoromethyl)pyridazin-4-yl)oxy)methyl)-7a-((trityloxy)methyl)hexahydro-1H-pyrrolizine



199-2

[0912] To a solution of intermediate **199-1** (150.00 mg, 252.50 μmol) in MeOH (1.00 mL) was added Pd/C (150.00 mg, 10% purity) under Ar. Then triethylamine (127.75 mg, 1.26 mmol, 175.72 μL) was added to the mixture at 0°C. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15psi) at 25°C for 1 hr. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give intermediate **199-2**. LCMS 560.3.

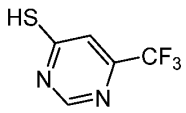
Intermediate 199-3: ((3S,7aS)-3-(((6-(trifluoromethyl)pyridazin-4-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



199-3

[0913] To a solution of intermediate **199-2** (150.00 mg, 268.04 μmol) in EtOAc (1.00 mL) was added HCl/EtOAc (1.00 mL, 4M). The mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC(column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [H_2O(10mM NH_4HCO_3)-ACN];gradient:5%-45% B over 8.0 min) to give intermediate **199-3**. LCMS: 318.1.

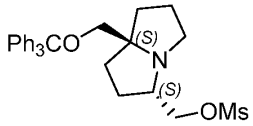
Intermediate 201-1: 6-(trifluoromethyl)pyrimidine-4-thiol



201-1

[0914] To a solution of 4-chloro-6-(trifluoromethyl)pyrimidine (1 g, 5.48 mmol) in MeOH (10 mL) was added NaSH (921.42 mg, 16.44 mmol). The mixture was stirred at 25°C for 12 hrs. The reaction mixture was concentrated under reduced pressure. The residue was diluted with H_2O (15 mL) and extracted with EtOAc (20 mL *3). The combined organic layers were washed with brine (10 mL *2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether) to afford intermediate **201-1**. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 14.66 (br s, 1H), 8.63 - 8.25 (m, 1H), 7.54 (s, 1H).

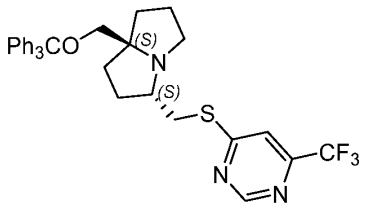
Intermediate 201-2: ((3S,7aS)-7a-((trityloxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl methanesulfonate



201-2

[0915] To a solution of intermediate **63-2** (300.00 mg, 725.43 μmol) in DCM (3.00 mL) was added TEA (293.62 mg, 2.90 mmol, 403.88 μL) and methanesulfonyl chloride (249.30 mg, 2.18 mmol, 168.44 μL) at 0°C. The mixture was stirred at 25°C for 1 hr. The reaction mixture was quenched with $NaHCO_3$ (10%, 10 ml), and then extracted with DCM (10.00 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give intermediate **201-2**. LCMS: 492.3.

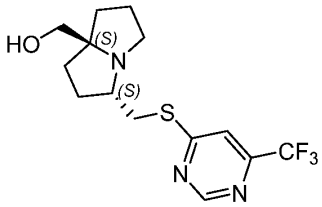
Intermediate 201-3: (3S,8S)-3-[[6-(trifluoromethyl)pyrimidin-4-yl]sulfanylmethyl]-8-(trityloxymethyl)-1,2,3,5,6,7-hexahydropyrrolizine



201-3

[0916] To a solution of intermediate **201-2** (300 mg, 610.20 μmol) in DMF (5 mL) was added TEA (185.24 mg, 1.83 mmol, 254.80 μL) and 6-(trifluoromethyl)pyrimidine-4-thiol (219.86 mg, 1.22 mmol). The mixture was stirred at 70°C for 12 hrs. The reaction mixture was concentrated under reduced pressure. The residue was diluted with H_2O (15 mL) and extracted with EtOAc (20 mL *3). The combined organic layers were washed with brine (10 mL *2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE:EtOAc = 3:1) to afford intermediate **201-3**. LCMS: 576.4.

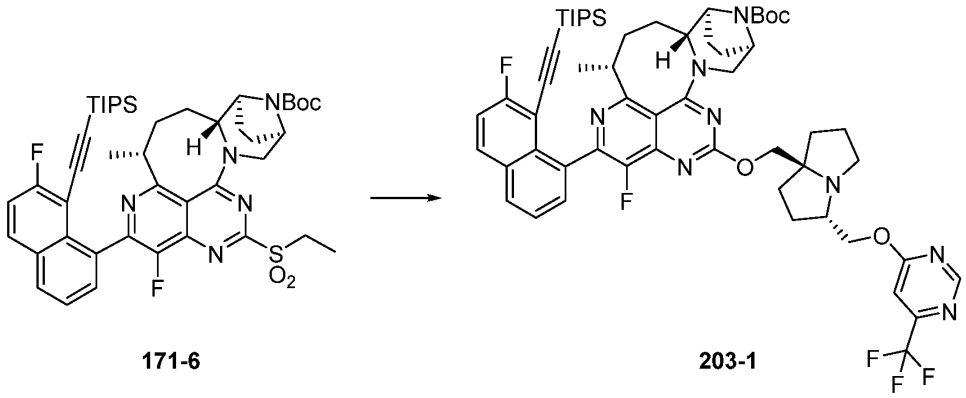
Intermediate 201-4: (3S,8S)-3-[[6-(trifluoromethyl)pyrimidin-4-yl]sulfanylmethyl]-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol



201-4

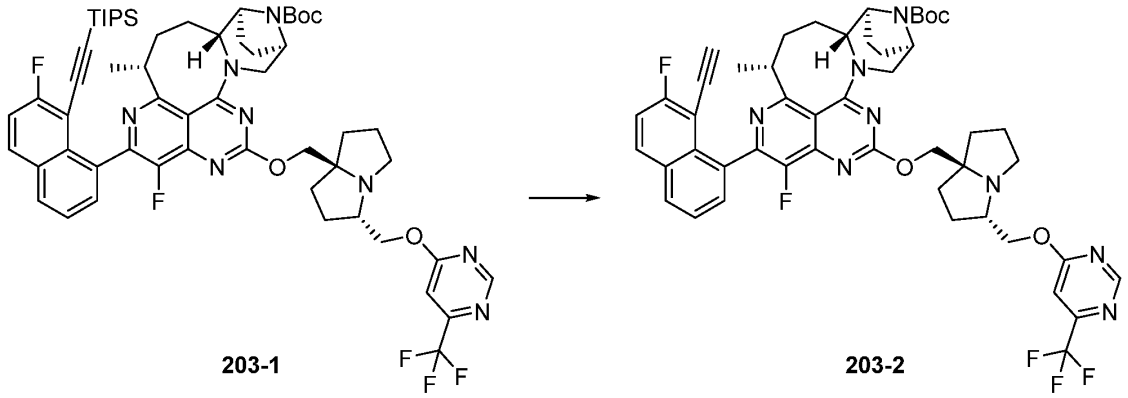
[0917] To a solution of intermediate **201-3** (240 mg, 416.89 μmol) in EtOAc (1 mL) was added HCl/EtOAc (1 mL). The mixture was stirred at 25°C for 0.2 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [water(NH_4HCO_3)-ACN];B%: 20%-50%,8min) to afford intermediate **201-4**. LCMS: 334.1.

Intermediate 203-1: *tert*-butyl (4*R*,6a*R*,7*S*,10*R*)-1-fluoro-2-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-4-methyl-13-(((3*S*,7a*S*)-3-(((6-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate



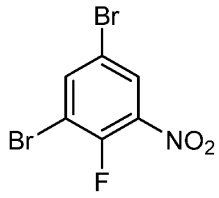
[0918] Lithium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 27.7 μL, 27.7 μmol) was added over 1 min via syringe to a stirred mixture of **Intermediate 171-6** (11.5 mg, 13.9 μmol), **((3*S*,7a*S*)-3-(((6-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol** (11.5 mg, 36.1 μmol), and 2-methyltetrahydrofuran (0.24 mL) at 0°C. After 1 hour, ethyl acetate (2 mL), and water (0.5 mL) were added sequentially at 0°C. The aqueous layer was washed with ethyl acetate (3 × 2 mL). The organic layers were combined and dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure to give **Intermediate 203-1**. LCMS: 1053.3.

Intermediate 203-2: *tert*-butyl (4*R*,6a*R*,7*S*,10*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-4-methyl-13-(((3*S*,7a*S*)-3-(((6-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene-15-carboxylate



[0919] Cesium fluoride (31.6 mg, 0.208 mmol) was added to a vigorously stirred solution of **Intermediate 203-1** (14.6 mg, 13.9 μmol) in *N*,*N*-dimethylformamide (0.2 mL) at room temperature. After 1 hour, diethyl ether (4 mL), ethyl acetate (2 mL), and saturated aqueous sodium bicarbonate solution (1 mL) were added sequentially. The organic layer was washed with water (2 × 4 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure to give **Intermediate 203-2**. LCMS: 897.2.

Intermediate 204-1: 1,5-dibromo-2-fluoro-3-nitrobenzene

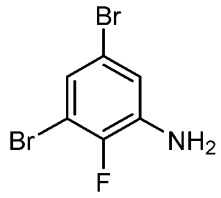


204-1

[0920] To a solution of 1-bromo-2-fluoro-3-nitro-benzene (70 g, 318.19 mmol) in H_2SO_4 (20 mL) was added NBS (56.63 g, 318.19 mmol). The mixture was stirred at 50°C for 3 hrs. The reaction mixture was quenched with ice water (1000 mL) and extracted with EtOAc (700 ml*3). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by purified by flash silica gel chromatography (100 g Silica Flash Column, Eluent of 0~10% Ethyl acetate / Petroleum ether gradient @80 mL/min) to

give intermediate **204-1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 2.4, 5.9 Hz, 1H), 7.93 (dd, J = 3.0, 5.5 Hz, 1H).

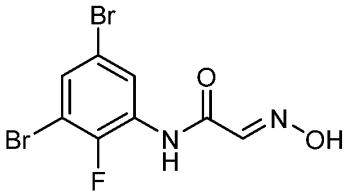
Intermediate 204-2: 3,5-dibromo-2-fluoroaniline



204-2

[0921] To a solution of intermediate **204-1** (70 g, 234.20 mmol) and Fe (39.24 g, 702.60 mmol) in H_2O (30 mL) was added HCl (120 mL) at 25°C. The mixture was stirred at 100°C for 1 hr. The reaction mixture was filtered, the filter cake was extracted with EtOAc (200 mL), and the combined filtrates were concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (100 g Silica Flash Column, Eluent of 0~20% Ethyl acetate / Petroleum ether gradient @80 mL/min) to give intermediate **204-2**. LCMS: 269.9.

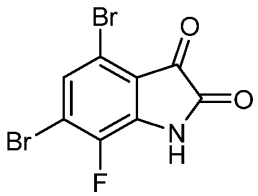
Intermediate 204-3: (*E*)-*N*-(3,5-dibromo-2-fluorophenyl)-2-(hydroxyimino)acetamide



204-3

[0922] To a solution of 2,2,2-trichloroethane-1,1-diol (55.36 g, 334.69 mmol, 43.59 mL), Na_2SO_4 (253.54 g, 1.78 mol, 181.10 mL) and $NH_2OH.HCl$ (54.27 g, 780.93 mmol) in H_2O (300 mL) was added intermediate **204-2** (60 g, 223.12 mmol) in EtOH (45 mL) and HCl (6 mL) and H_2O (150 mL) at 50°C. The mixture was stirred at 70°C for 12 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give intermediate **204-3**. LCMS: 340.8.

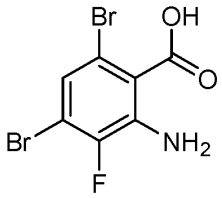
Intermediate 204-4: 4,6-dibromo-7-fluoroindoline-2,3-dione



204-4

[0923] To a solution of H_2SO_4 (50 mL) in 50 °C was added intermediate **204-3** (60 g, 176.50 mmol) in portions, then the mixture was stirred at 70 °C for 1 hr. The reaction mixture was cooled to room temperature and slowly added to ice water (200 ml), and the resulting mixture was filtered. The filter cake was concentrated under reduced pressure to give intermediate **204-4**. LCMS: 323.9.

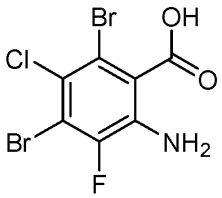
Intermediate 204-5: 2-amino-4,6-dibromo-3-fluorobenzoic acid



204-5

[0924] To a solution of intermediate **204-4** (20 g, 61.94 mmol) in NaOH (2 M, 309.68 mL) was added H_2O_2 (35.11 g, 309.68 mmol, 29.76 mL, 30% purity) at 0°C. The mixture was stirred at 25°C for 16 hrs. The reaction mixture was adjusted to pH=2 with 1M HCl (200 ml), then the reaction mixture was filtered, and the filter cake concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex luna c18 250mm*100mm*10um;mobile phase: [water(FA)-ACN];B%: 25%-55%,min) to give intermediate **204-5**. LCMS: 313.8.

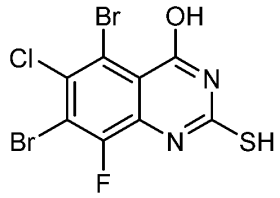
Intermediate 204-6: 2-amino-4,6-dibromo-5-chloro-3-fluorobenzoic acid



204-6

[0925] To a solution of intermediate **204-5** (11 g, 35.15 mmol) in H_2SO_4 (50 mL) was added NCS (9.39 g, 70.31 mmol) at 25°C. The mixture was stirred at 80°C for 12 hrs. The reaction mixture was added to ice H_2O (50 ml), then the reaction mixture was filtered, and the filter cake concentrated under reduced pressure to give intermediate **204-6**. LCMS: 347.8.

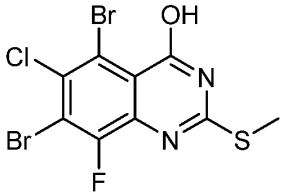
Intermediate 204-7: 5,7-dibromo-6-chloro-8-fluoro-2-sulfanyl-quinazolin-4-ol



204-7

[0926] To the solution of intermediate **204-6** (8.00 g, 23.03 mmol) in DCM (40.00 mL) was added $SOCl_2$ (16.44 g, 138.18 mmol, 10.04 mL) and DMF (168.34 mg, 2.30 mmol, 177.20 µL), the reaction mixture stirred at 60°C for 5 hrs. The reaction mixture was concentrated under reduced pressure to give a residue, then in acetone (40.00 mL) was added NH_4SCN (2.63 g, 34.55 mmol, 2.63 mL), the reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was filtered, the filter cake was washed with H_2O (100.00 ml) and 10% NaOH (30 ml) then the solid was triturated with MeOH (50.00 ml) and ACN (50.00 ml) to give intermediate **204-7**.

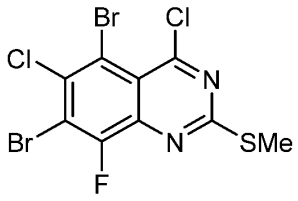
Intermediate 204-8: 5,7-dibromo-6-chloro-8-fluoro-2-(methylthio)quinazolin-4-ol



204-8

[0927] To a mixture of intermediate **204-7** (1.00 g, 2.57 mmol) in MeOH (20.00 mL) and H_2O (10.00 mL) was added NaOH (205.94 mg, 5.15 mmol) and MeI (730.81 mg, 5.15 mmol, 320.53 µL) at 25°C, the reaction mixture was stirred at 25°C for 30 mins. H_2O (20.00 ml) was added to the reaction mixture, and the reaction mixture was adjusted to pH = 6 with 1 N HCl (10.00 ml) then the reaction mixture was filtered, and the filter cake was triturated with MeOH (50.00 ml) and ACN (50.00 ml) at 25°C. The resulting filter cake was concentrated under reduced pressure to give intermediate **204-8**. LCMS: 402.8.

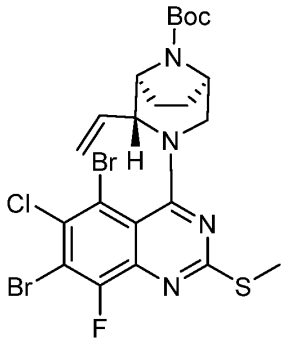
Intermediate 204-9: 5,7-dibromo-4,6-dichloro-8-fluoro-2-(methylthio)quinazoline



204-9

[0928] Intermediate **204-9** was synthesized in a manner similar to **53-1** using intermediate intermediate **204-8** instead of intermediate **13-3**. LCMS: 421.0.

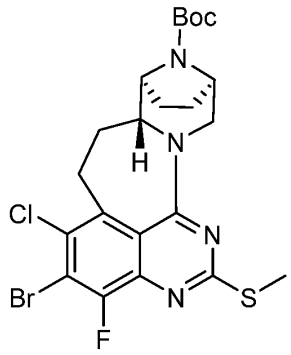
Intermediate 204-10: tert-butyl (1S,2R,5R)-3-(5,7-dibromo-6-chloro-8-fluoro-2-(methylthio)quinazolin-4-yl)-2-vinyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



204-10

[0929] Intermediate **204-10** was synthesized in a manner similar to **63-5** using intermediate **204-9-1** instead of intermediate **53-1**. LCMS: 623.4.

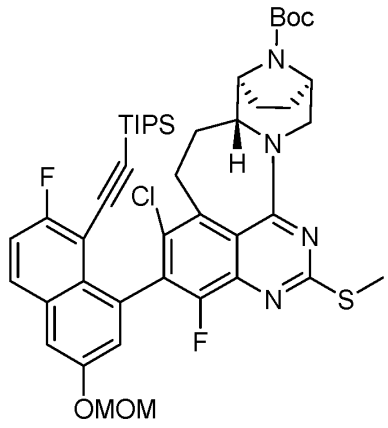
Intermediate 204-11: tert-butyl (1S,4R,14aR)-11-bromo-12-chloro-10-fluoro-8-(methylthio)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate



204-11

[0930] The solution of 9-BBN (4.04 mL, 0.5 M) was added to the solution of intermediate **204-10** (950 mg, 1.53 mmol) in 2-MeTHF (5 mL) at rt under N_2 atmosphere. The reaction mixture was stirred at 50℃ for 1 h before it was cooled to rt. The mixture was transferred via a syringe to a vial containing K_3PO_4 (871 mg, 4.11 mmol), Pd(dtbpf)Cl_2 (136 mg, 0.2 mmol) and degassed water (1 mL) under N_2 atmosphere. The reaction mixture was stirred at 90℃ for 20 min before it was cooled to rt. EtOAc (150 mL) was added and the mixture was washed with brine (150 mL). The organic phase was separated and dried over Na_2SO_4 and filtered. After concentrated in vacuo, the residue was purified with ISCO (silica gel, EtOAc-hexanes 0-80%) to give intermediate **204-11**. LCMS: 543.7.

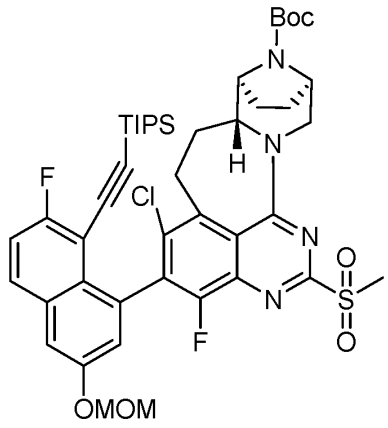
Intermediate 204-12: tert-butyl (1S,4R,14aR)-12-chloro-10-fluoro-11-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-8-(methylthio)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate



204-12

[0931] The reaction mixture of intermediate **204-11** (30 mg, 0.055 mmol), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (prepared according to WO 2021/041671) (56.5 mg, 0.11 mmol, cataCXium® A Pd G3 (8.0 mg, 0.011 mmol) and Cs_2CO_3 (53.9 mg, 0.165 mmol) in toluene (2 mL) and degassed water (0.5 mL) was stirred at 100℃ under N_2 for 90 min before it was cooled to rt. EtOAc (20 mL) was added. The organic phase was separated, washed with brine (15 mL), dried over Na_2SO_4, concentrated in vacuo and purified with column chromatography (silica, EtOAc-hexanes 0-60%) to give intermediate **204-12**. LCMS: 849.8.

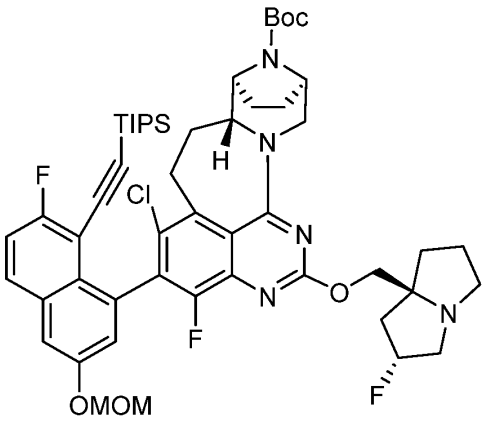
Intermediate 204-13: tert-butyl (1S,4R,14aR)-12-chloro-10-fluoro-11-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-8-(methylsulfonyl)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate



204-13

[0932] Intermediate **204-13** was synthesized in a manner similar to **63-7** using intermediate **204-12** instead of intermediate **63-6**. LCMS: 881.9.

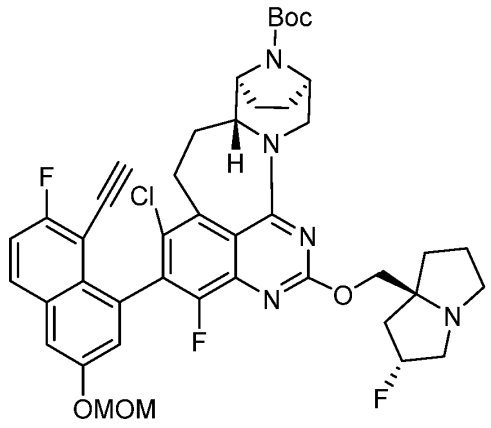
Intermediate 204-14: tert-butyl (1S,4R,14aR)-12-chloro-10-fluoro-11-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate



204-14

[0933] Intermediate **204-14** was synthesized in a manner similar to **79-4** using intermediate **204-13** instead of intermediate **79-3**. LCMS: 960.8.

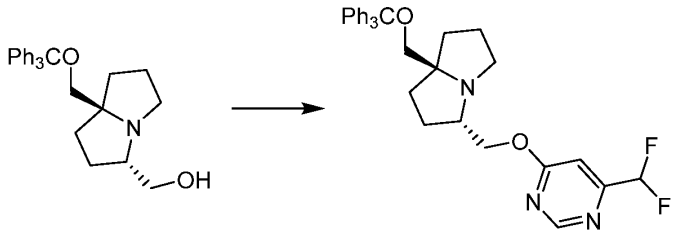
Intermediate 204-15: tert-butyl (1S,4R,14aR)-12-chloro-11-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline-15-carboxylate



204-15

[0934] Intermediate **204-15** was synthesized in a manner similar to **79-5** using intermediate **204-14** instead of intermediate **79-4**. LCMS: 960.8.

Intermediate 205-1: (3S,7aS)-3-(((6-(difluoromethyl)pyrimidin-4-yl)oxy)methyl)-7a-((trityloxy)methyl)hexahydro-1H-pyrrolizine

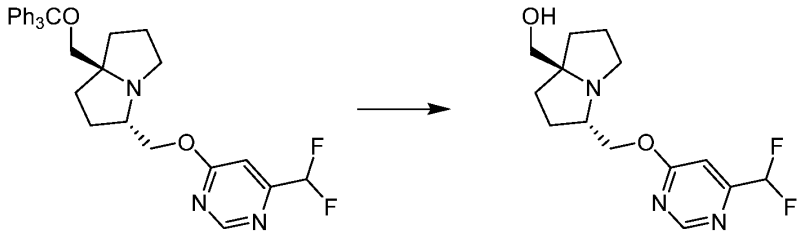


63-2 **205-1**

[0935] To a solution of intermediate **63-2** (200.0 mg, 483.6 μmol) in THF (5.00 mL) was added t-BuOK solution (1.0 M in tetrahydrofuran, 483.6 μL, 480 μmol) at 0°C under N_2, and the resulting mixture was stirred at 0°C for 0.5 hr, then 4-chloro-6-(difluoromethyl)pyrimidine (238.7 mg, 1.45 mmol) was added to the mixture. The mixture was stirred at 25°Cfor 2 hrs under N_2. The alkoxides were quenched by addition of saturated aqueous NH_4Cl solution (15.00 mL) at 0°C, and the aqueous layer was extracted with EtOAc (30 mL * 3). The combined organic layers were dried

over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (Plate PE:EtOAc =3:1) to give intermediate **205-1**. LCMS: 542.4.

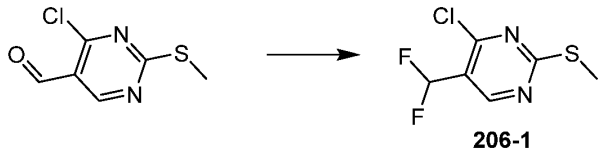
Intermediate 205-2: ((3S,7aS)-3-(((6-(difluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



205-1 **205-2**

[0936] To a solution of intermediate **205-1** (150.0 mg, 276.9 μmol) in EtOAc (2.00 mL) was added HCl/EtOAc (1.00 mL). The mixture was stirred at 25°C for 0.5 hr. The reaction mixture was concentrated under N_2 to give a residue and then adjusted with 1 M $NH_3.H_2O$ to pH 6-7. The residue was purified by *prep*-HPLC(column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [H2O(10mM NH4HCO3)-ACN];gradient:5%-50% B over 8.0 min) to give intermediate **205-2**. LCMS: 300.2.

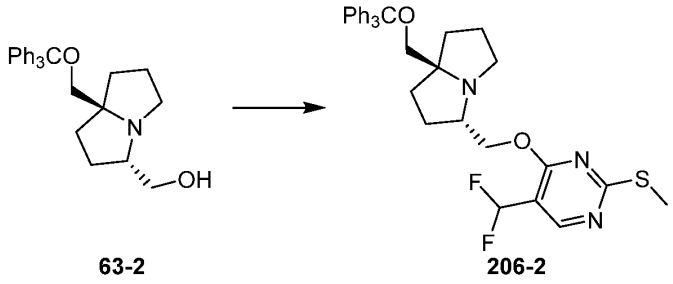
Intermediate 206-1: 4-chloro-5-(difluoromethyl)-2-(methylthio)pyrimidine



206-1

[0937] To a solution of 4-chloro-2-methylsulfanyl-pyrimidine-5-carbaldehyde (1.00 g, 5.30 mmol) in DCE (15 mL) was added DAST (2.56 g, 15.90 mmol, 2.10 mL). The mixture was stirred at 25°C for 1 hr. The acids were quenched with sat. aq. $NaHCO_3$ (20 ml), and the aqueous layer was extracted with DCM (20 ml*3). The combined organic layers were washed with brine (30 mL *2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE:EtOAc = 10:1) to give intermediate **206-1**. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.67 (s, 1H), 6.86 (t, J = 54.2 Hz, 1H), 2.61 (s, 3H).

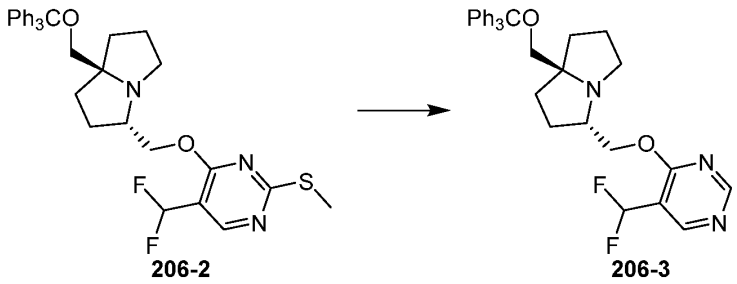
Intermediate 206-2: (3S,7aS)-3-(((5-(difluoromethyl)-2-(methylthio)pyrimidin-4-yl)oxy)methyl)-7a-((trityloxy)methyl)hexahydro-1H-pyrrolizine



63-2 206-2

[0938] To a solution of intermediate **63-2** (500 mg, 1.21 mmol) in THF (5 mL) was added t-BuOK solution (1.0 M in tetrahydrofuran, 1.81 mL, 1.8 mmol) at 0°C. After 30 min, intermediate **206-1** (305.6 mg, 1.45 mmol) was added. The mixture was stirred at 25°C for 1 hr under N_2. The alkoxides were quenched by addition of saturated aqueous NH_4Cl solution (10 mL) at 0°C, and the aqueous layer was extracted with EtOAc (20 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE:EtOAc = 3:1) to give intermediate **206-2**. LCMS: 588.3.

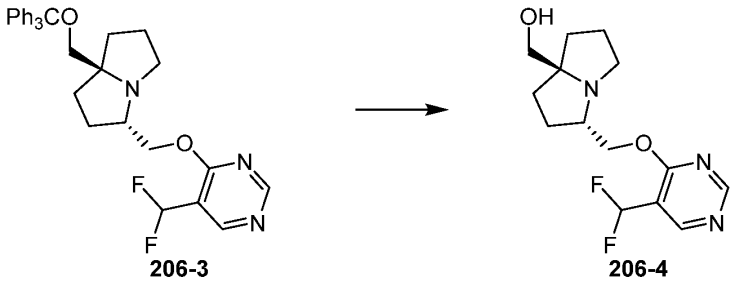
Intermediate 206-3: (3S,7aS)-3-(((5-(difluoromethyl)pyrimidin-4-yl)oxy)methyl)-7a-((trityloxy)methyl)hexahydro-1H-pyrrolizine



206-2 206-3

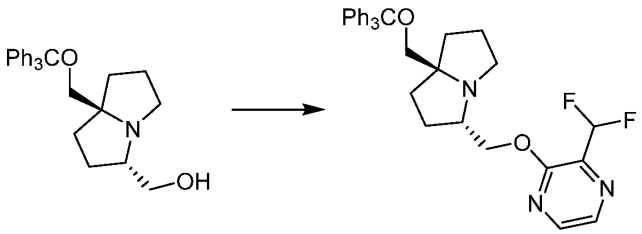
[0939] To a solution of intermediate **206-2** (70.0 mg, 119 μmol) in THF (2 mL) was added Pd/C (70.0 mg, 65.8 μmol, 10% purity) and Et_3SiH (277 mg, 2.38 mmol, 380 μL) at 0°C. The mixture was stirred at 25°C for 1 hr under H_2 (15 Psi). The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give intermediate **206-3**. LCMS: 542.3.

Intermediate 206-4: ((3S,7aS)-3-(((5-(difluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



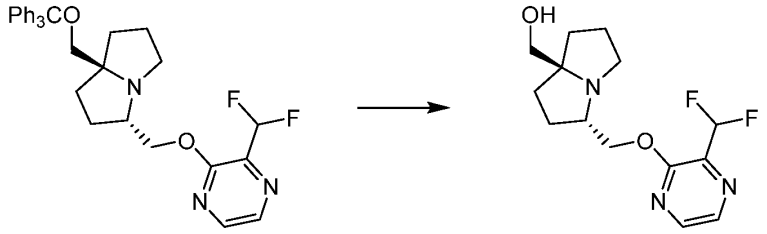
[0940] To a solution of intermediate **206-3** (50.0 mg, 92.3 μmol) in EtOAc (1 mL) was added HCl/EtOAc (1 mL). The mixture was stirred at 25°C for 0.2 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [H_2O(10mM NH_4HCO_3)-ACN];gradient:5%-35% B over 8.0 min) to give intermediate **206-4**. LCMS: 300.1.

Intermediate 207-1: (3S,7aS)-3-(((3-(difluoromethyl)pyrazin-2-yl)oxy)methyl)-7a-((trityloxy)methyl)hexahydro-1H-pyrrolizine



[0941] To a solution of intermediate **63-2** (950 mg, 2.30 mmol) in THF (4 mL) was added NaH (183.8 mg, 4.6 mmol, 60% purity) at 0°C for 0.5 hr. To the mixture was added 2-chloro-3-(difluoromethyl)pyrazine (491.4 mg, 2.99 mmol), and the resulting mixture was stirred at 40°C for 12 hrs. The unreacted bases was quenched by addition saturated aqueous NH_4Cl solution (5 mL) at 0°C, and the aqueous layer was extracted with EtOAc (5 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (4 g Silica Flash Column, Eluent of 0~20% Ethyl acetate / Petroleum ether gradient @40 mL/min) to give intermediate **207-1**. LCMS: 542.3.

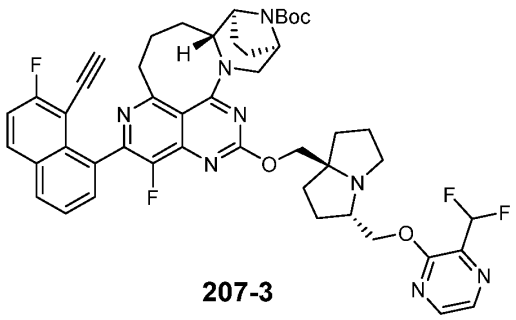
Intermediate 207-2: ((3S,7aS)-3-(((3-(difluoromethyl)pyrazin-2-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



207-1 207-2

[0942] To a solution of intermediate **207-1** (250 mg, 462 μmol) in EtOAc (1 mL) was added HCl/EtOAc (1 mL). The mixture was stirred at 20°C for 0.5 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC(column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [H_2O(10mM NH_4HCO_3)-ACN];gradient:1%-25% B over 8.0 min) to give intermediate **207-2**. LCMS: 300.1.

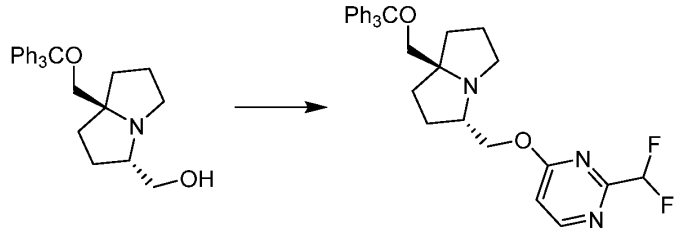
Intermediate 207-3: tert-butyl (6aR,7S,10R)-13-(((3S,7aS)-3-(((3-(difluoromethyl)pyrazin-2-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene-15-carboxylate



207-3

[0943] Lithium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 54.6 μL, 54.6 μmol) was added to a stirred reaction mixture of intermediate **115-3** (20.0 mg, 30.3 μmol), intermediate **207-2** (13.6 mg, 45.5 μmol), and tetrahydrofuran (1 mL) at 0 °C. Upon completion (about 5 min), added brine and extracted with ethyl acetate. The organic layer was washed with aqueous sodium carbonate and water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by RP-HPLC (15 % to 90 % 0.1% TFA in MeCN/0.1% TFA in H_2O). Fractions containing the product were pooled and lyophilized to yield intermediate **207-3**. LCMS:865.5.

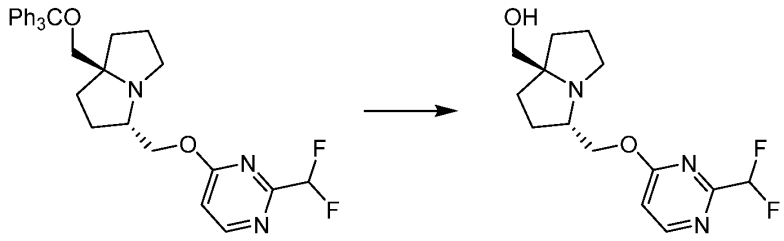
Intermediate 208-1: (3S,7aS)-3-(((2-(difluoromethyl)pyrimidin-4-yl)oxy)methyl)-7a-((trityloxy)methyl)hexahydro-1H-pyrrolizine



63-2 208-1

[0944] To a solution intermediate **63-2** (140.0 mg, 338.5 μmol) in THF (2 mL) was added t-BuOK (1.0 M in tetrahydrofuran, 507.80 μL, 510 μmol) at 0°C under N_2, and the mixture was stirred at 0°C for 0.5 hr, then 4-chloro-2-(difluoromethyl)pyrimidine (83.6 mg, 508 μmol) was added to the mixture. The mixture was stirred at 25°C for 1 hr under N_2. The alkoxides were quenched by addition of saturated aqueous NH_4Cl (10 mL) at 0°C, and then extracted with EtOAc (15 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC (PE:EtOAc =0:1) to give intermediate **208-1**. LCMS: 542.4.

Intermediate 208-2: ((3S,7aS)-3-(((2-(difluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol

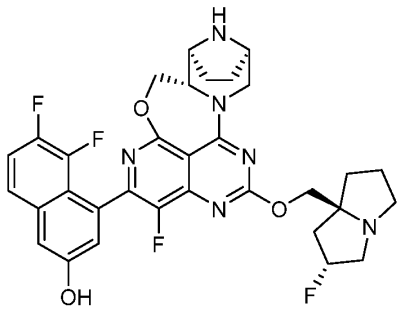


208-1 208-2

[0945] To a solution of intermediate **208-1** (300.0 mg, 553.9 μmol) in EtOAc (1.50 mL) was added HCl/EtOAc (1.50 mL). The mixture was stirred at 25°C for 0.5 hr. The reaction mixture was concentrated under N_2 to give a residue and then adjusted with 1 M $NH_3.H_2O$ to pH = 6-7. The residue was purified by *prep*-HPLC(column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [H2O(10mM NH4HCO3)-ACN];gradient:10%-50% B over 8.0 min) to give intermediate **208-2**. LCMS: 300.1.

III. Compounds

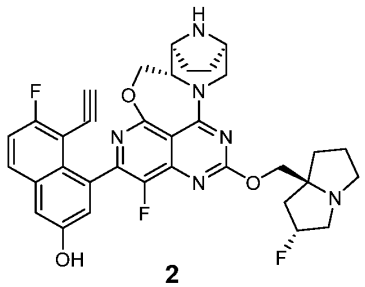
Example 1, Compound 1: 5,6-difluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol



1

[0946] Aqueous sodium carbonate solution (2.0 M, 86.4 μL, 170 μmol) was added via syringe to a vigorously stirred mixture of **Intermediate 17-9** (20.0 mg, 34.5 μmol), 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (WO2021041671) (12.1 mg, 34.5 μmol), [(di(1-adamantyl)-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate (2.5 mg, 3.5 μmol), and 1,4-dioxane (1.0 mL) at room temperature, and the resulting mixture was heated to 90°C. After 15 min, the resulting mixture was cooled to room temperature, and ethyl acetate (50 mL) was added. The organic layer was washed with a mixture of water and brine (3:1 v:v, 30 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. Dichloromethane (3.0 mL) and trifluoroacetic acid (1.5 mL) were added sequentially, and the resulting mixture was heated to 50°C. After 15 min, the resulting mixture was cooled to room temperature and was concentrated under reduced pressure. The residue was purified by reverse phase preparative HPLC (0.1% acetic acid in acetonitrile/water) to give **Compound 1**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.61 (s, 1H), 7.47 – 7.35 (m, 1H), 7.33 (s, 1H), 7.29 – 7.15 (m, 1H), 5.36 (d, J = 53.4 Hz, 1H), 5.08 (d, J = 13.7 Hz, 1H), 4.63 (d, J = 13.2 Hz, 1H), 4.49 (td, J = 13.1, 12.7, 7.5 Hz, 1H), 4.38 (d, J = 11.5 Hz, 1H), 4.31 (d, J = 10.9 Hz, 1H), 4.23 – 4.12 (m, 1H), 3.76 (d, J = 5.9 Hz, 1H), 3.68 (d, J = 5.8 Hz, 1H), 3.48 – 2.96 (m, 5H), 2.49 – 1.73 (m, 10H), 1.96 (s, 6H). LCMS: 623.2.

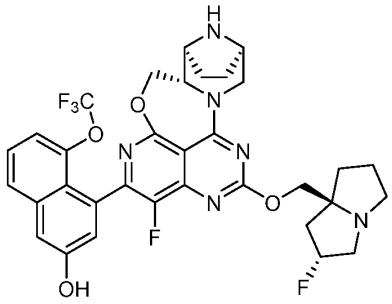
Example 2, Compound 2: 5-ethynyl-6-fluoro-4-((5a*S*,6S,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol



2

[0947] Cesium fluoride (100 mg, 658 μmol) was added to a vigorously stirred solution of **Intermediate 2-1** (28.5 mg, 30.7 μmol) in *N*,*N*-dimethylformamide (0.6 mL) at room temperature. After 30 min, diethyl ether (40 mL) and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (2 × 40 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduce pressure. Acetonitrile (0.3 mL) was added via syringe, and the resulting mixture was cooled to 0°C. Hydrogen chloride solution (4.0 M in 1,4-dioxane, 184 μL, 740 μmol) was added via syringe. After 75 min, the resulting mixture was purified by reverse phase preparative HPLC (0.1% acetic acid in acetonitrile/water) to give **Compound 2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.91 – 7.81 (m, 1H), 7.38 – 7.29 (m, 2H), 7.27 – 7.15 (m, 1H), 5.36 (d, J = 53.6 Hz, 1H), 5.18 – 5.04 (m, 1H), 4.68 – 4.58 (m, 1H), 4.48 (ddd, J = 12.9, 7.5, 4.5 Hz, 1H), 4.37 (t, J = 10.2 Hz, 1H), 4.33 – 4.27 (m, 1H), 4.17 (d, J = 7.3 Hz, 1H), 3.81 – 3.74 (m, 1H), 3.69 (d, J = 5.8 Hz, 1H), 3.62 – 3.00 (m, 6H), 2.47 – 1.73 (m, 10H), 1.96 (s, 6H). LCMS: 629.2.

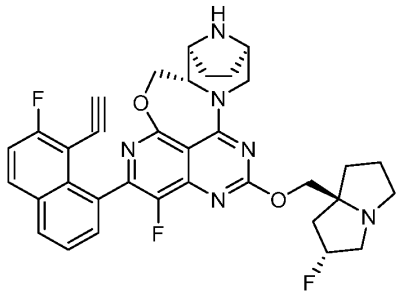
Example 3, Compound 3: 4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-(trifluoromethoxy)naphthalen-2-ol



3

[0948] Compound 3 was synthesized in a manner similar to **Compound 1** using **Intermediate 3-1** instead of 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.78 (d, J = 8.8 Hz, 1H), 7.47 (td, J = 8.0, 4.8 Hz, 1H), 7.37 (d, J = 2.4 Hz, 1H), 7.26 – 7.14 (m, 2H), 5.38 (d, J = 53.4 Hz, 1H), 5.18 – 4.97 (m, 1H), 4.73 – 4.56 (m, 1H), 4.52 – 4.28 (m, 3H), 4.22 – 4.10 (m, 1H), 3.80 – 3.66 (m, 2H), 3.55 – 3.04 (m, 5H), 2.52 – 1.68 (m, 10H), 1.96 (s, 6H). LCMS: 671.2.

Example 4, Compound 4: (5a*S*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene

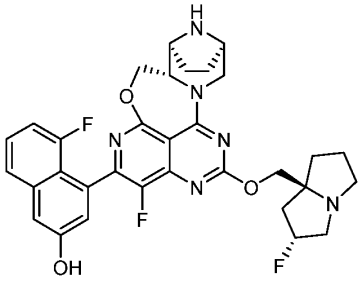


4

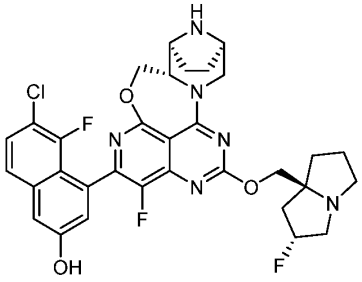
[0949] Compound 4 was synthesized in a manner similar to **Compound 2** using **Intermediate 4-1** instead of **Intermediate 2-1**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.13 (d, J = 8.3 Hz, 2H), 7.72 – 7.57 (m, 2H), 7.46 (td, J = 9.0, 4.9 Hz, 1H), 5.43 (d, J = 53.2 Hz, 1H), 5.10 (d, J = 13.7 Hz, 1H), 4.65 (dd, J = 13.1, 6.3 Hz, 1H), 4.55 – 4.44 (m, 2H), 4.40 (dd, J = 11.4, 3.7 Hz, 1H), 4.19 (d,

J = 7.1 Hz, 1H), 3.81 (d, J = 5.9 Hz, 1H), 3.79 – 3.71 (m, 1H), 3.68 – 2.97 (m, 6H), 2.56 – 1.77 (m, 10H), 1.96 (s, 6H). LCMS: 613.2.

Examples 5 and 6: Compound 5 (5-fluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol) and Compound 6 (6-chloro-5-fluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol)



5



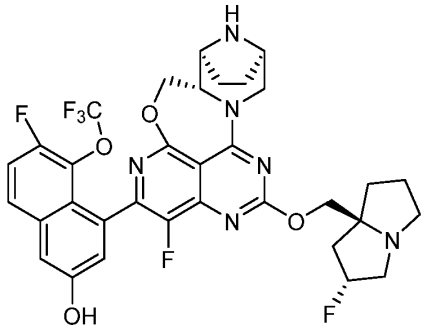
6

[0950] Compound 5 and **Compound 6** were synthesized in a manner similar to **Compound 1** using **Intermediate 5-6** instead of 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

[0951] Compound 5: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.62 – 7.56 (m, 1H), 7.46 – 7.35 (m, 1H), 7.32 (s, 1H), 7.21 – 7.08 (m, 1H), 7.01 – 6.87 (m, 1H), 5.33 (d, J = 54.0 Hz, 1H), 5.08 (d, J = 9.8 Hz, 1H), 4.62 (d, J = 13.1 Hz, 1H), 4.56 – 4.41 (m, 1H), 4.32 (d, J = 10.9 Hz, 1H), 4.26 (d, J = 10.6 Hz, 1H), 4.23 – 4.11 (m, 1H), 3.74 (s, 1H), 3.66 (s, 1H), 3.56 – 2.98 (m, 5H), 2.43 – 1.73 (m, 10H), 1.96 (s, 6H). LCMS: 605.3.

[0952] Compound 6: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.63 – 7.56 (m, 1H), 7.51 – 7.41 (m, 1H), 7.32 (s, 1H), 7.28 – 7.13 (m, 1H), 5.34 (d, J = 53.9 Hz, 1H), 5.08 (d, J = 13.6 Hz, 1H), 4.61 (t, J = 12.9 Hz, 1H), 4.49 (td, J = 13.6, 7.4 Hz, 1H), 4.34 (d, J = 10.6 Hz, 1H), 4.28 (d, J = 10.6 Hz, 1H), 4.17 (t, J = 9.5 Hz, 1H), 3.83 – 3.70 (m, 1H), 3.67 (d, J = 5.8 Hz, 1H), 3.49 – 2.98 (m, 5H), 2.45 – 1.73 (m, 10H), 1.96 (s, 6H). LCMS: 639.2.

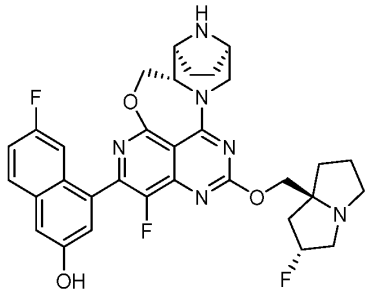
Example 7, Compound 7: 6-fluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-(trifluoromethoxy)naphthalen-2-ol



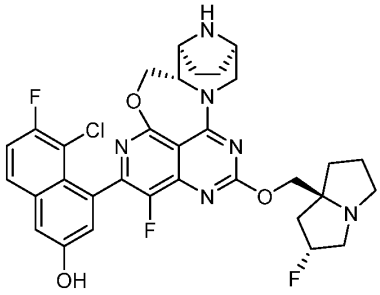
7

[0953] Compound 7 was synthesized in a manner similar to **Compound 1** using **Intermediate 7-5** instead of 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.91 – 7.83 (m, 1H), 7.47 (td, J = 9.5, 4.4 Hz, 1H), 7.41 – 7.25 (m, 2H), 5.37 (d, J = 53.5 Hz, 1H), 5.08 (dd, J = 25.1, 13.6 Hz, 1H), 4.64 (dd, J = 18.5, 12.9 Hz, 1H), 4.52 – 4.40 (m, 1H), 4.38 (d, J = 10.1 Hz, 1H), 4.31 (d, J = 10.8 Hz, 1H), 4.17 (dd, J = 19.1, 7.1 Hz, 1H), 3.76 (s, 1H), 3.68 (d, J = 6.8 Hz, 1H), 3.54 – 3.00 (m, 5H), 2.55 – 1.71 (m, 10H), 1.96 (s, 6H). LCMS: 689.2.

Examples 8 and 9: Compound 8 (6-fluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol) and Compound 9 (5-chloro-6-fluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol)



8



9

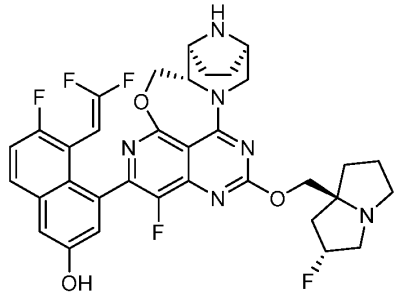
[0954] Aqeuous potassium phosphate solution (1.5 M, 288 μL, 430 μmol) was added via syringe to a vigorously stirred mixture of **Intermediate 17-9** (50.0 mg, 86.4 μmol), **Intermediate 8-1** (31.7 mg, 86.4 μmol), [(di(1-adamantyl)-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate (3.1 mg, 43 μmol), and tetrahydrofuran (1.0 mL) at room temperature, and the resulting mixture was heated to 70°C. After 35 min, the resulting mixture was heated to 90°C. after 4 h, the resulting mixture was cooled to room temperature, and ethyl acetate (50 mL) was added. The organic layer was washed with a mixture of water and brine (3:1 v:v, 30 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. Dichloromethane (3.0 mL) and trifluoroacetic acid (1.5 mL) were added sequentially, and the resulting mixture was heated to 50°C. After 15 min, the resulting mixture was cooled to room temperature and was concentrated under reduced pressure. The residue was

purified by reverse phase preparative HPLC (0.1% acetic acid in acetonitrile/water) to give **Compound 8** and **Compound 9**.

[0955] Compound 8: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 – 7.76 (m, 1H), 7.35 – 7.22 (m, 4H), 5.35 (d, J = 53.8 Hz, 1H), 5.09 (d, J = 13.4 Hz, 1H), 4.64 (d, J = 13.3 Hz, 1H), 4.51 (dd, J = 13.1, 7.5 Hz, 1H), 4.36 (d, J = 10.6 Hz, 1H), 4.29 (d, J = 10.5 Hz, 1H), 4.18 (d, J = 7.4 Hz, 1H), 3.76 (s, 1H), 3.66 (d, J = 5.0 Hz, 1H), 3.53 – 2.99 (m, 5H), 2.44 – 1.74 (m, 10H), 1.96 (s, 6H). LCMS: 605.2.

[0956] Compound 9: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.86 – 7.77 (m, 1H), 7.45 – 7.38 (m, 1H), 7.38 – 7.35 (m, 1H), 7.28 – 7.14 (m, 1H), 5.37 (d, J = 53.6 Hz, 1H), 5.09 (t, J = 14.1 Hz, 1H), 4.67 – 4.55 (m, 1H), 4.55 – 4.43 (m, 1H), 4.38 (dd, J = 10.9, 3.3 Hz, 1H), 4.31 (d, J = 10.8 Hz, 1H), 4.18 (dd, J = 17.5, 7.3 Hz, 1H), 3.79 – 3.71 (m, 1H), 3.71 – 3.63 (m, 1H), 3.54 – 3.03 (m, 5H), 2.48 – 1.76 (m, 10H), 1.96 (s, 6H). LCMS: 639.2.

Example 10, Compound 10: 5-(2,2-difluorovinyl)-6-fluoro-4-((5a*S*,6*S*,9R)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol

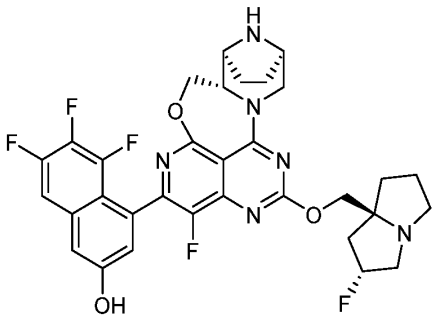


10

[0957] Potassium carbonate (56.6 mg, 407 μmol) was added to a vigorously stirred mixture of **Compound 9** (13.0 mg, 20.3 μmol), 2-(2,2-difluorovinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (19.3 mg, 102 μmol), [(di(1-adamantyl)-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate (3.0 mg, 41 μmol), and 1,4-dioxane (0.5 mL) at room temperature, and the resulting mixture was heated to 90°C. After 36 min, the resulting mixture was heated to 100°C. After 180 min, the resulting mixture was cooled to room temperature and was purified by reverse phase preparative HPLC (0.1% acetic acid in acetonitrile/water) to give **Compound 10**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.91 – 7.25 (m, 4H), 7.25 – 7.12 (m, 1H),

5.33 (d, J = 53.9 Hz, 1H), 5.14 – 4.98 (m, 1H), 4.69 – 4.58 (m, 1H), 4.55 – 4.39 (m, 1H), 4.32 (d, J = 10.3 Hz, 1H), 4.25 (d, J = 11.0 Hz, 1H), 4.22 – 4.08 (m, 1H), 3.75 (s, 1H), 3.67 (s, 1H), 3.62 – 2.97 (m, 5H), 2.50 – 1.65 (m, 10H), 1.96 (s, 6H). LCMS: 667.2.

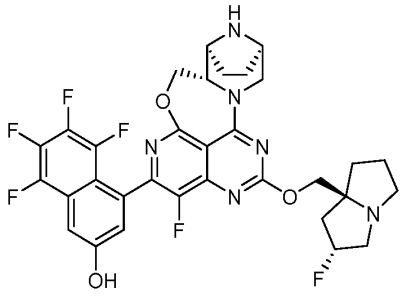
Example 11, Compound 11: 5,6,7-trifluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol



11

[0958] Compound 11 was synthesized in a manner similar to **Compound 1** using **Intermediate 11-1** instead of 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.57 – 7.46 (m, 1H), 7.29 (s, 1H), 7.26 – 7.14 (m, 1H), 5.36 (d, J = 53.8 Hz, 1H), 5.08 (d, J = 13.6 Hz, 1H), 4.63 (d, J = 13.4 Hz, 1H), 4.49 (td, J = 13.0, 7.3 Hz, 1H), 4.36 (d, J = 10.8 Hz, 1H), 4.29 (d, J = 10.7 Hz, 1H), 4.23 – 4.09 (m, 1H), 3.76 (s, 1H), 3.68 (d, J = 5.8 Hz, 1H), 3.52 – 3.03 (m, 5H), 2.47 – 1.73 (m, 10H), 1.96 (s, 6H). LCMS: 641.2.

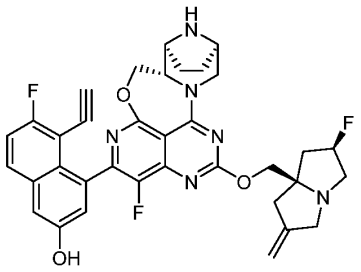
Example 12, Compound 12: 5,6,7,8-tetrafluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol



12

[0959] **Compound 12** was synthesized in a manner similar to **Compound 1** using **Intermediate 12-2** instead of 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.45 (s, 1H), 7.34 – 7.20 (m, 1H), 5.35 (d, J = 53.9 Hz, 1H), 5.08 (d, J = 13.5 Hz, 1H), 4.63 (d, J = 13.5 Hz, 1H), 4.56 – 4.44 (m, 1H), 4.35 (d, J = 10.7 Hz, 1H), 4.28 (d, J = 10.6 Hz, 1H), 4.18 (d, J = 8.4 Hz, 1H), 3.76 (s, 1H), 3.67 (d, J = 5.6 Hz, 1H), 3.52 – 3.01 (m, 5H), 2.45 – 1.74 (m, 10H), 1.96 (s, 6H). LCMS: 659.2.

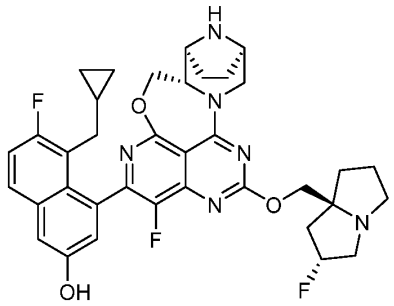
Example 13, Compound 13: 5-ethynyl-6-fluoro-4-((5a*S*,6*S*,9R)-1-fluoro-12-(((2*R*,7a*R*)-2-fluoro-6-methylenetetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol



13

[0960] Hydrogen chloride solution (4.0 M in 1,4-dioxane, 500 μL, 2.0 mmol) was added via syringe to a vigorously stirred solution of **Intermediate 13-11** (18.2 mg, 23.1 μmol) in acetonitrile (0.3 mL) at 0°C. After 49 min, the resulting mixture was purified by reverse phase preparative HPLC (0.1% acetic acid in acetonitrile/water) to give **Compound 13**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.91 – 7.78 (m, 1H), 7.38 – 7.27 (m, 2H), 7.26 – 7.14 (m, 1H), 5.35 (d, J = 53.2 Hz, 1H), 5.14 – 5.07 (m, 1H), 5.03 (d, J = 3.4 Hz, 2H), 4.62 (dd, J = 13.2, 8.0 Hz, 1H), 4.59 – 4.44 (m, 1H), 4.44 – 4.36 (m, 1H), 4.30 (d, J = 10.4 Hz, 1H), 4.17 (d, J = 7.2 Hz, 1H), 3.78 (d, J = 13.9 Hz, 2H), 3.74 – 3.66 (m, 1H), 3.55 – 3.11 (m, 4H), 3.04 – 2.81 (m, 2H), 2.51 (q, J = 12.0, 10.6 Hz, 2H), 2.15 (dd, J = 40.8, 14.3 Hz, 1H), 2.07 – 1.74 (m, 4H), 1.96 (s, 6H). LCMS: 641.2.

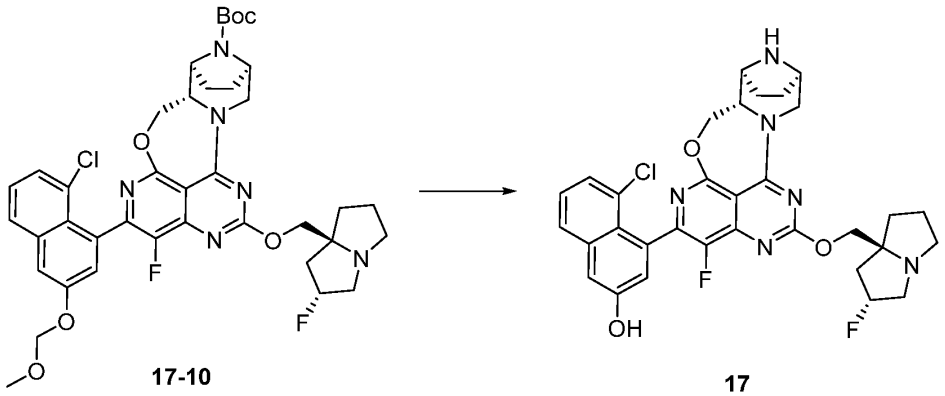
Example 14, Compound 14: 5-(cyclopropylmethyl)-6-fluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol



14

[0961] Compound 14 was synthesized in a manner similar to **Compound 1** using **Intermediate 14-5** instead of 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.69 (ddd, J = 8.9, 5.8, 2.7 Hz, 1H), 7.35 – 7.20 (m, 2H), 7.16 – 7.05 (m, 1H), 5.35 (d, J = 53.2 Hz, 1H), 5.19 – 5.00 (m, 1H), 4.72 – 4.58 (m, 1H), 4.54 – 4.41 (m, 1H), 4.36 (dd, J = 10.7, 2.4 Hz, 1H), 4.30 (dd, J = 10.6, 2.0 Hz, 1H), 4.16 (dd, J = 23.5, 7.0 Hz, 1H), 3.77 (s, 1H), 3.67 (d, J = 7.3 Hz, 1H), 3.57 – 3.14 (m, 4H), 3.14 – 3.01 (m, 1H), 2.53 – 1.66 (m, 11H), 1.96 (s, 6H), 0.99 – 0.55 (m, 2H), 0.27 – -0.26 (m, 4H). LCMS: 659.3.

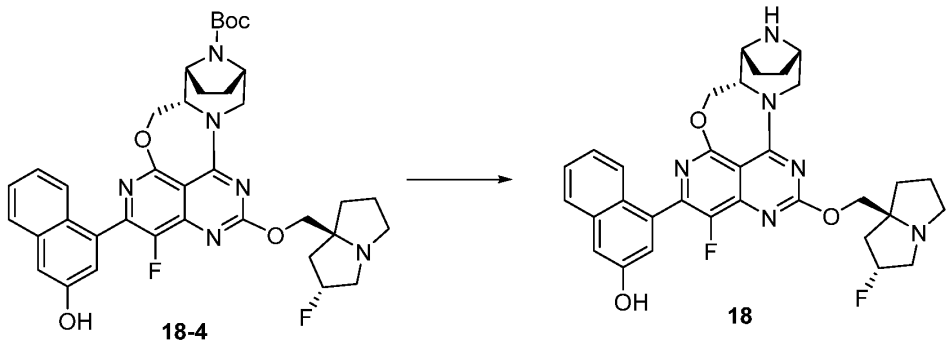
Example 17, Compound 17: 5-chloro-4-((5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



17-10 17

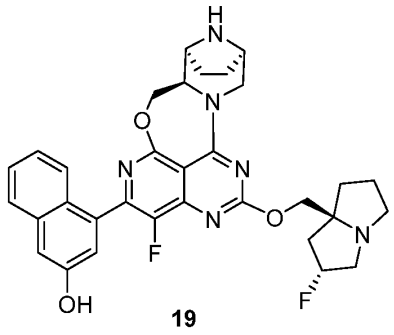
[0962] TFA (1.0 mL) was added dropwise to the solution of **Intermediate 17-10** (100 mg, 0.13 mmol) in dichloromethane (2 mL) at rt and the resulting solution was stirred at rt for 1.5 h before it was concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC (0.1% trifluoroacetic acid in acetonitrile/water) to give **Example 17**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.79 – 7.72 (m, 1H), 7.41 – 7.30 (m, 3H), 7.20 – 7.10 (m, 1H), 5.67 – 5.49 (m, 1H), 5.45 – 5.28 (m, 1H), 4.79 – 4.60 (m, 4H), 4.53 – 4.29 (m, 3H), 4.11 – 3.83 (m, 3H), 3.57 – 3.43 (m, 2H), 2.79 – 2.05 (m, 10H). LCMS: 621.0.

Example 18, Compound 18: 4-((5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



[0963] Compound 18 was synthesized in a manner similar to **Compound 17** using **Intermediate 18-4** instead of **Intermediate 17-10**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.78 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.34 – 7.20 (m, 3H), 5.73 – 5.47 (m, 1H), 4.96 – 4.65 (m, 8H), 4.61 – 4.33 (m, 3H), 4.10 – 3.82 (m, 4H), 3.56 – 3.43 (m, 1H), 2.82 – 2.01 (m, 7H). LCMS: 587.0.

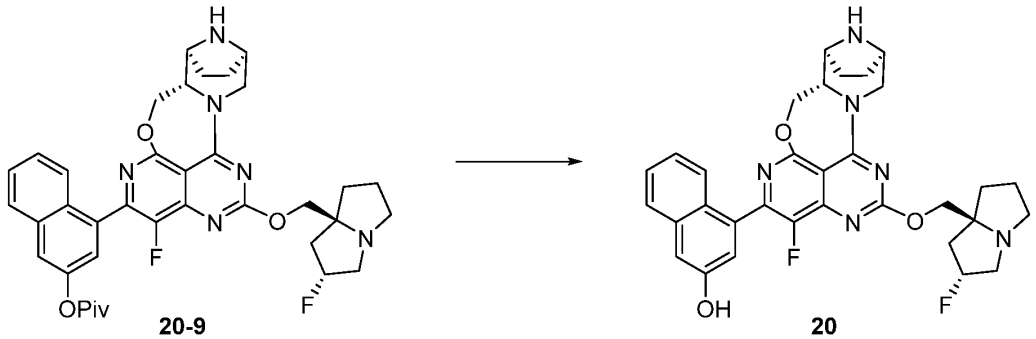
Example 19, Compound 19: 4-((5aR,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



19

[0964] **Compound 19** was synthesized in a manner similar to **Compound 18** using **Intermediate 19-1** instead of **Intermediate 18-1**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.78 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.45 (dd, J = 7.5 Hz, 1H), 7.33 – 7.20 (m, 3H), 5.60 (d, J = 51.8 Hz, 1H), 4.96 – 4.66 (m, 8H), 4.59 – 4.33 (m, 3H), 4.14 – 3.83 (m, 4H), 3.60 – 3.43 (m, 1H), 2.83 – 2.03 (m, 7H). LCMS: 587.0.

Example 20, Compound 20: 4-((5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol

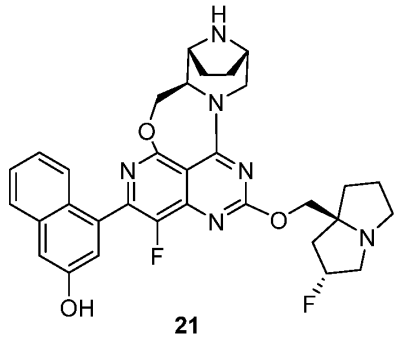


20-9 20

[0965] The crude product of **Intermediate 20-9** (21.8 mg, 0.0325 mmol) was dissolved in dioxane (1 mL) and water (0.3 mL). Lithium hydroxide monohydrate (13.6 mg, 0.325 mmol) was added in one portion to the mixture. It was stirred at rt for 2 h. The mixture was filtered, and the filtrate was purified by reverse phase preparative HPLC (0.1% trifluoroacetic acid in acetonitrile/water) to give **Compound 20**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.78 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.46 (dd, J = 8.3, 6.8 Hz, 1H), 7.33 – 7.21 (m, 3H), 5.71 – 5.52 (m, 1H), 5.39 (dd, J

= 14.7, 2.6 Hz, 1H), 4.97 – 4.66 (m, 7H), 4.51 – 4.33 (m, 3H), 4.14 – 3.80 (m, 3H), 3.64 – 3.43 (m, 2H), 2.83 – 2.03 (m, 7H). LCMS: 587.0.

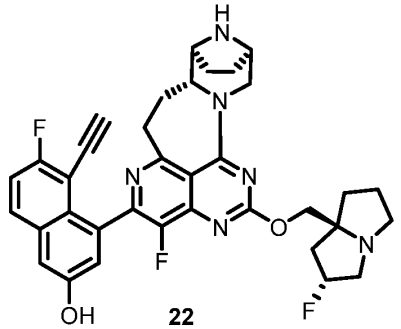
Example 21, Compound 21: 4-((5aR,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



21

[0966] Compound 21 was synthesized in a manner similar to **Compound 20** using **Intermediate 21-1** instead of **Intermediate 17-7**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.78 (d, J = 8.3 Hz, 1H), 7.61 – 7.55 (m, 1H), 7.49 – 7.42 (m, 1H), 7.33 – 7.20 (m, 3H), 5.60 (d, J = 51.7 Hz, 1H), 5.38 (dd, J = 14.7, 2.6 Hz, 1H), 4.92 – 4.65 (m, 7H), 4.53 – 4.31 (m, 3H), 4.12 – 3.84 (m, 3H), 3.60 – 3.45 (m, 2H), 2.83 – 2.07 (m, 7H). LCMS: 587.0.

Example 22, Compound 22: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol

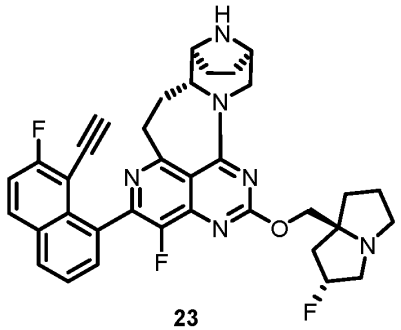


22

[0967] Compound 22 was synthesized in a manner similar to **Compound 2** using **Intermediate 22-1** instead of **Intermediate 2-1**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 – 7.86 (m, 1H), 7.42 – 7.31 (m, 2H), 7.26 – 7.10 (m, 1H), 5.81 – 5.69 (m, 1H), 5.68 – 5.51 (m, 1H), 4.96 – 4.66 (m,

5H), 4.38 (d, *J* = 19.3 Hz, 2H), 4.21 – 3.84 (m, 4H), 3.60 – 3.22 (m, 4H), 2.78 – 1.98 (m, 9H). LCMS: 627.0.

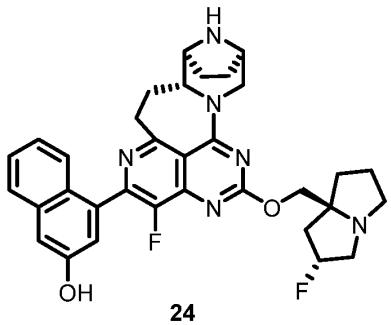
Example 23, Compound 23: (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



23

[0968] Compound 23 was synthesized in a manner similar to **Compound 4** using **Intermediate 23-1** instead of **Intermediate 17-9**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.16 (d, *J* = 7.9 Hz, 2H), 7.75 – 7.59 (m, 2H), 7.54 – 7.41 (m, 1H), 5.74 (t, *J* = 12.9 Hz, 1H), 5.59 (d, *J* = 51.7 Hz, 1H), 4.98 – 4.64 (m, 5H), 4.44 – 4.31 (m, 2H), 4.20 – 3.84 (m, 4H), 3.64 – 3.38 (m, 4H), 2.82 – 1.98 (m, 9H). LCMS: 611.2.

Example 24, Compound 24: 4-((5aR,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol

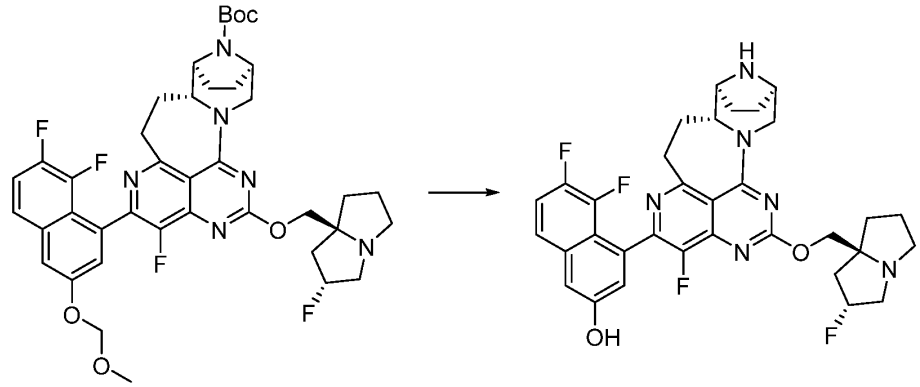


24

[0969] Compound 24 was synthesized in a manner similar to **Compound 20** using **Intermediate 24-1** instead of **Intermediate 20-8**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.79 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.29 – 7.20 (m, 2H),

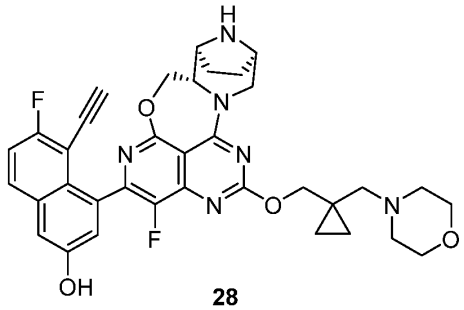
5.76 (dd, *J* = 14.6, 3.0 Hz, 1H), 5.61 (d, *J* = 52.0 Hz, 1H), 4.97 – 4.65 (m, 5H), 4.43 – 4.31 (m, 2H), 4.19 – 3.86 (m, 4H), 3.60 – 3.39 (m, 4H), 2.83 – 1.99 (m, 9H). LCMS: 585.1.

Example 27, Compound 27: 5,6-difluoro-4-((5aR,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



[0970] **Compound 27** was synthesized in a manner similar to **Compound 17** using **Intermediate 27-7** instead of **Intermediate 17-10**. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.62 (s, 1H), 7.49 – 7.29 (m, 2H), 7.23 (d, J = 10.0 Hz, 1H), 5.66 (dd, 2H), 4.72 (d, J = 12.7 Hz, 2H), 4.50 – 3.75 (m, 6H), 3.55 – 3.38 (m, 3H), 2.83 – 1.88 (m, 13H). LCMS: 620.9.

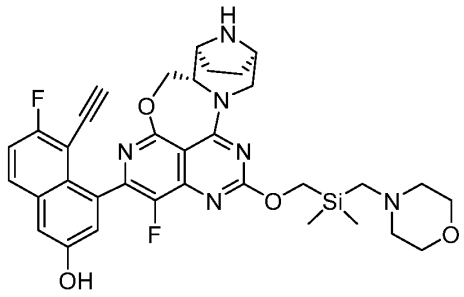
Example 28, Compound 28: 5-ethynyl-6-fluoro-4-((5aS,6S,9R)-1-fluoro-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



[0971] Hydrogen chloride solution (4.0 M in 1,4-dioxane, 500 µL, 2.0 mmol) was added via syringe to a vigorously stirred solution of **Intermediate 28-2** (15 mg, 19 µmol) in acetonitrile (0.3 mL) at 0°C. After 49 min, the resulting mixture was purified by reverse phase preparative HPLC (0.1% TFA in acetonitrile/water) to give **Example 28**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96

– 7.82 (m, 1H), 7.48 (d, J = 15.6 Hz, 1H), 7.43 – 7.29 (m, 4H), 5.44 – 5.24 (m, 1H), 4.80 – 4.58 (m, 2H), 4.59 – 4.27 (m, 6H), 4.08 (d, J = 11.2 Hz, 2H), 4.03 – 3.73 (m, 4H), 3.64 (d, J = 14.8 Hz, 3H), 3.51 (t, J = 6.8 Hz, 2H), 3.42 (q, J = 6.7 Hz, 2H), 1.96 – 1.82 (m, 2H), 0.97 (ddt, J = 26.1, 21.6, 8.8 Hz, 4H). LCMS: 640.9.

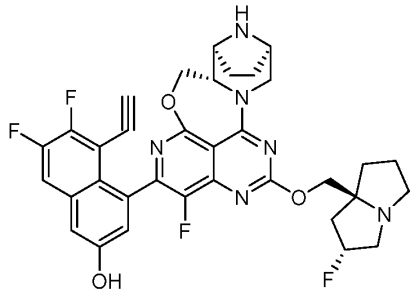
Example 29, Compound 29: 4-((5aS,6S,9R)-12-((dimethyl(morpholinomethyl)silyl) methoxy)-1-fluoro-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



29

[0972] Hydrogen chloride solution (4.0 M in 1,4-dioxane, 500 µL, 2.0 mmol) was added via syringe to a vigorously stirred solution of **Intermediate 29-3** (15 mg, 19 µmol) in acetonitrile (0.3 mL) at 0°C. After 49 min, the resulting mixture was purified by reverse phase preparative HPLC (0.1% acetic acid in acetonitrile/water) to give **Compound 29.** LCMS: 658.7. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.86 (ddt, J = 9.1, 5.6, 3.2 Hz, 1H), 7.35 (dt, J = 5.7, 3.1 Hz, 1H), 7.32 – 7.13 (m, 1H), 5.20 – 5.05 (m, 1H), 4.75 – 4.57 (m, 1H), 4.47 (ddd, J = 13.1, 7.5, 5.2 Hz, 1H), 4.29 (qd, J = 14.2, 2.2 Hz, 2H), 4.16 (d, J = 7.2 Hz, 1H), 4.01 (tt, J = 4.5, 2.0 Hz, 1H), 3.90 – 3.73 (m, 3H), 3.65 – 3.44 (m, 2H), 3.09 – 2.92 (m, 1H), 2.62 – 2.40 (m, 4H), 2.21 (s, 2H), 1.25 – 0.83 (m, 2H), 0.22 (d, J = 34.3 Hz, 6H).

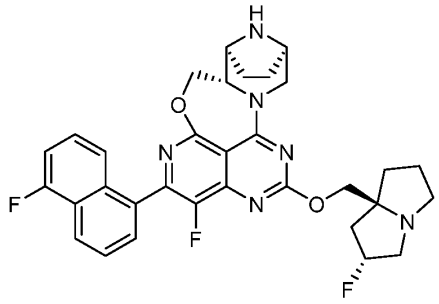
Example 30, Compound 30: 5-ethynyl-6,7-difluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol



30

[0973] Compound 30 was synthesized in a manner similar to **Compound 2** using **Intermediate 30-4** instead of **Intermediate 2-1**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (ddd, J = 11.4, 8.1, 3.7 Hz, 1H), 7.30 (d, J = 2.6 Hz, 1H), 7.23 – 7.11 (m, 1H), 5.33 (d, J = 54.0 Hz, 1H), 5.13 – 5.02 (m, 1H), 4.62 (dd, J = 12.7, 6.6 Hz, 1H), 4.47 (dt, J = 13.0, 6.4 Hz, 1H), 4.39 – 4.28 (m, 1H), 4.28 – 4.19 (m, 1H), 4.15 (d, J = 7.3 Hz, 1H), 3.80 – 3.70 (m, 1H), 3.71 – 3.11 (m, 6H), 3.10 – 3.01 (m, 1H), 2.45 – 1.69 (m, 10H), 1.96 (s, 6H). LCMS: 647.2.

Example 31, Compound 31: (5a*S*,6*S*,9*R*)-1-fluoro-2-(5-fluoronaphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene

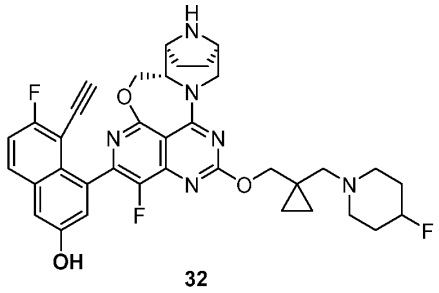


31

[0974] *n*-Butyllithium solution (2.70 M in heptane, 39.7 µL, 107 µmol) was added over 1 min via syringe to a vigorously stirred solution of 1-bromo-5-fluoronaphthalene (24.1 mg, 107 µmol) in 2-methyltetrahydrofuran (0.4 mL) at −78°C. After 10 min, zinc chloride solution (1.9 M in 2-methyltetrahydrofuran, 56.4 µL, 110 µmol) was added via syringe, and the resulting mixture was

warmed to room temperature. After 14 min, **Intermediate 17-9** (10.0 mg, 17.3 μmol), tetrakis(triphenylphosphine)palladium(0) (5.0 mg, 4.3 μmol), and triethylamine (16.8 μL, 121 μmol) were added sequentially, and the resulting mixture was heated to 100°C. After 40 min, the resulting mixture was cooled to room temperature, and diethyl ether (40 mL), ethyl acetate (20 mL), and a mixture of citric acid (50 mg) and saturated aqueous sodium carbonate solution (5 mL) were added sequentially. The organic layer was washed with water (40 mL), was dried over magnesium sulfate, was filtered, and was concentrated under reduced pressure. Dichloromethane (3.0 mL) and trifluoroacetic acid (1.5 mL) were added sequentially, and the resulting mixture was heated to 50°C. After 15 min, the resulting mixture was cooled to room temperature and was concentrated under reduced pressure. The residue was purified by reverse phase preparative HPLC (0.1% acetic acid in acetonitrile/water) to give **Compound 31**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.28 (dd, J = 7.2, 2.6 Hz, 1H), 7.78 – 7.65 (m, 2H), 7.57 (d, J = 8.5 Hz, 1H), 7.47 (td, J = 8.5, 8.0, 5.7 Hz, 1H), 7.33 – 7.23 (m, 1H), 5.37 (d, J = 53.0 Hz, 1H), 5.14 – 5.04 (m, 1H), 4.64 (d, J = 13.2 Hz, 1H), 4.51 (dd, J = 13.3, 7.5 Hz, 1H), 4.39 (d, J = 10.7 Hz, 1H), 4.31 (d, J = 10.8 Hz, 1H), 4.18 (d, J = 7.4 Hz, 1H), 3.77 (d, J = 5.9 Hz, 1H), 3.69 (d, J = 5.8 Hz, 1H), 3.52 – 3.17 (m, 4H), 3.16 – 3.06 (m, 1H), 2.63 – 1.66 (m, 10H), 1.96 (s, 6H). LCMS: 589.2.

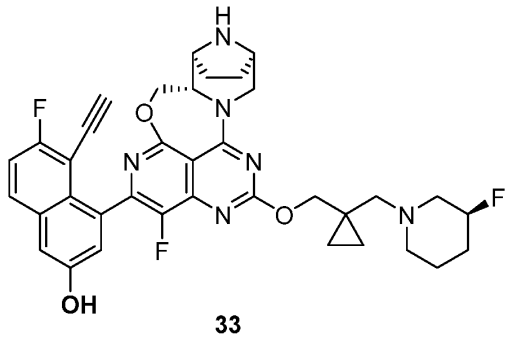
Example 32, Compound 32: 5-ethynyl-6-fluoro-4-((5aS,6S,9R)-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



32

[0975] Compound 32 was synthesized in a manner similar to **Compound 35** using 4-fluoropiperidine hydrochloride instead of 1,4-oxazepane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.86 (ddd, J = 9.1, 5.7, 3.3 Hz, 1H), 7.36 (s, 1H), 7.35 – 7.20 (m, 2H), 5.30 – 5.24 (m, 1H), 4.81 – 4.56 (m, 3H), 4.55 – 4.37 (m, 3H), 4.33 (m, 2H), 3.79 (m, 1H), 3.68 – 3.34 (m, 4H), 3.24 (s, 3H), 2.42 – 1.95 (m, 8H), 0.98 (d, J = 7.4 Hz, 2H), 0.87 (s, 2H). LCMS: 657.3.

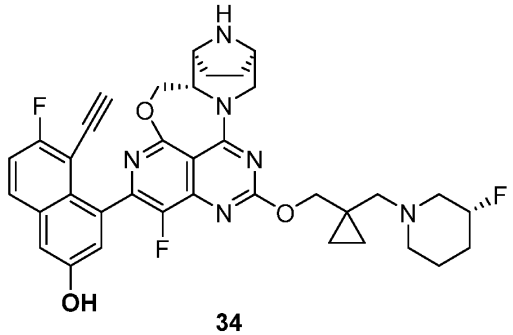
Example 33, Compound 33: 5-ethynyl-6-fluoro-4-((5aS,6S,9R)-1-fluoro-12-((1-(((S)-3-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



33

[0976] Compound 33 was synthesized in a manner similar to **Compound 35** using (3*S*)-3-fluoropiperidine hydrochloride instead of 1,4-oxazepane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (ddd, *J* = 9.2, 5.7, 3.8 Hz, 1H), 7.34 – 7.34 (m, 1H), 7.32 – 7.30 (m, 1H), 7.24 – 7.20 (m, 1H), 5.35 (t, *J* = 16.4 Hz, 1H), 5.19 – 5.07 (m, 1H), 4.79 – 4.68 (m, 1H), 4.68 – 4.50 (m, 2H), 4.50 – 4.12 (m, 5H), 3.82 – 3.35 (m, 5H), 3.14 (m, 2H), 2.38 – 1.95 (m, 6H), 1.90 (m, 2H), 1.17 – 0.66 (m, 4H). LCMS: 657.3.

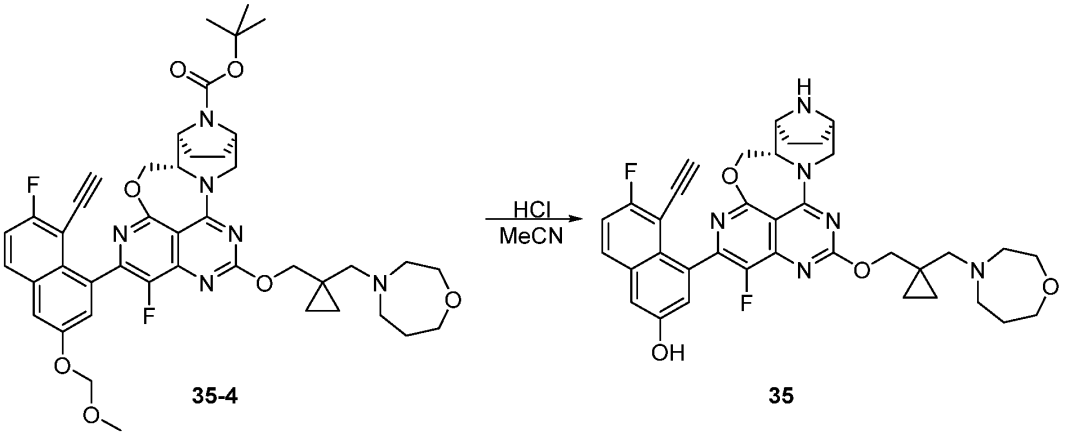
Example 34, Compound 34: 5-ethynyl-6-fluoro-4-((5aS,6S,9R)-1-fluoro-12-((1-(((R)-3-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



34

[0977] Compound 34 was synthesized in a manner similar to **Compound 35** using (3*R*)-3-fluoropiperidine hydrochloride instead of 1,4-oxazepane. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.85 (ddd, J = 9.3, 5.7, 2.0 Hz, 1H), 7.35 – 7.34 (m, 1H), 7.32 – 7.29 (m, 1H), 7.27 – 7.20 (m, 1H), 5.37 (t, J = 15.1 Hz, 1H), 5.18 – 5.06 (m, 1H), 4.80 – 4.04 (m, 8H), 3.79 – 3.33 (m, 5H), 3.24 – 2.92 (m, 2H), 2.46 – 2.03 (m, 6H), 1.93 – 1.57 (m, 2H), 1.20 – 0.67 (m, 4H). LCMS: 657.4.

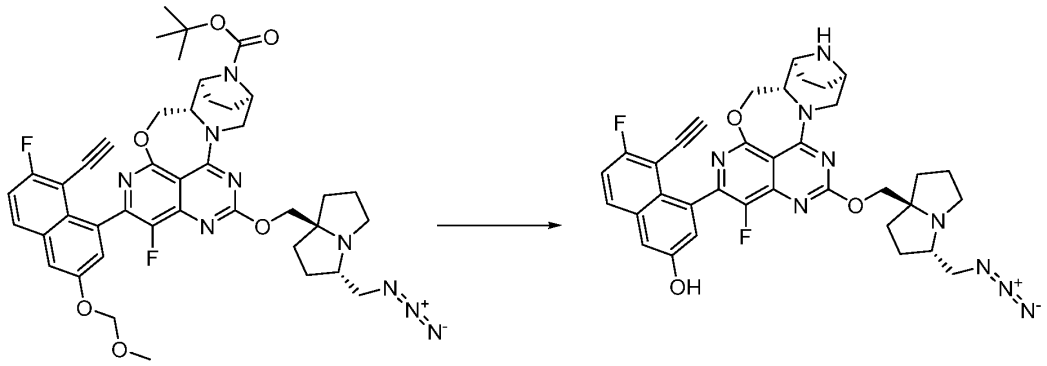
Example 35, Compound 35: 4-((5aS,6S,9R)-12-((1-((1,4-oxazepan-4-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



35-4 35

[0978] To a solution of crude **Intermediate 35-4** (10.2 umol) in MeCN (0.3 mL) was stirred at 0°C as 4 M HCl in dioxane (0.5 mL) was added. The resulting solution was stirred for 1 h at 0°C. After the reaction mixture was concentrated by rotorvap without heating, the residue was dissolved in MeOH (0.5 mL), filtered, and purified by preparative HPLC (Gemini 5 um NX-C18 110 A LC Column 250 x 21.2 mm AX) eluting 10-40% acetonitrile (0.1% TFA) in water (0.1% TFA) over 20 min and the collected product containing fractions were freeze-dried to give **Compound 35**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.86 (ddd, J = 9.0, 5.8, 2.2 Hz, 1H), 7.35 – 7.34 (m, 1 H), 7.32 – 7.31 (m, 1H), 7.27 – 7.21 (m, 1H), 5.32 – 5.24 (m, 1H), 4.79 – 4.57 (m, 2H), 4.58 – 4.37 (m, 3H), 4.32 (m, 2H), 3.88 (m, 6H), 3.60 – 3.48 (m, 2H), 3.42 (d, J = 16.7 Hz, 4H), 2.45 – 2.03 (m, 6H), 0.94 (d, J = 42.9 Hz, 4H). LCMS: 655.3.

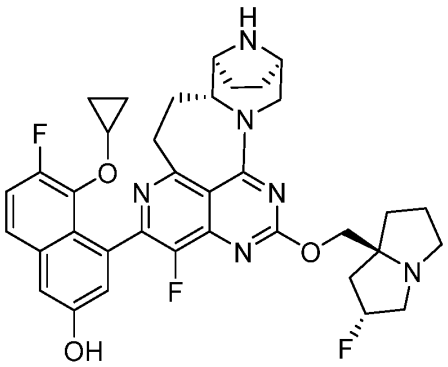
Example 36, Compound 36: 4-((5aS,6S,9R)-12-(((3S,7aS)-3-(azidomethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1-fluoro-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



36-5 **36**

[0979] Intermediate 36-5 was dissolved in acetonitrile (500 uL) and cooled to 0°C. Hydrogen chloride solution (4.0 M in 1,4-dioxane, 500 µL, 2.0 mmol) was added via syringe with vigorous stirring. Stirring was continued for 50 minutes at 0°C. The solution was then concentrated *in vacuo* and purified by reverse phase preparative HPLC (0.1% TFA acid in acetonitrile/water) to give **Compound 36.** ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (ddd, J = 9.2, 5.7, 1.5 Hz, 1H), 7.37 (d, J = 2.6 Hz, 1H), 7.34 (dd, J = 9.0, 3.2 Hz, 1H), 7.27 (d, J = 2.6 Hz, 1H), 7.22 (d, J = 2.6 Hz, 1H), 5.37 (td, J = 14.1, 2.7 Hz, 1H), 4.81 – 4.60 (m, 3.5H), 4.50 (dd, J = 16.1, 5.9 Hz, 1H), 4.39 – 4.34 (m, 2H), 4.26 – 4.20 (m, 1H), 4.19 – 4.06 (m, 1H), 3.96 (dt, J = 13.9, 4.3 Hz, 1H), 3.77 – 3.65 (m, 2H), 3.62 – 3.49 (m, 2H), 3.41 – 3.35 (m, 1H), 2.48 – 2.00 (m, 12H). LCMS: 666.3.

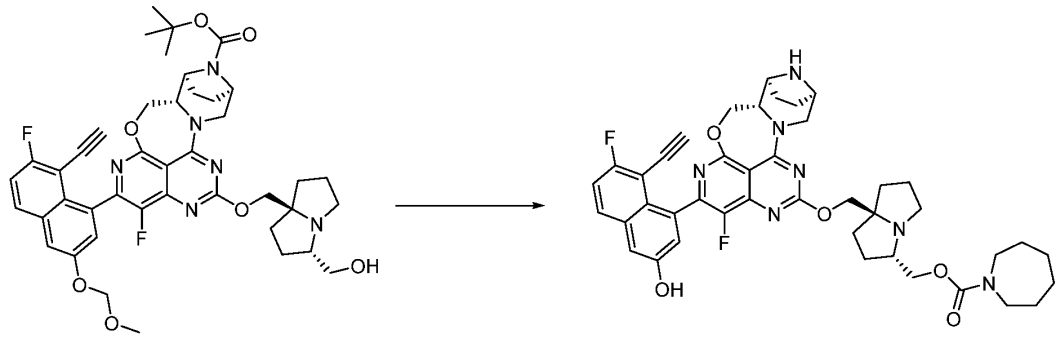
Example 37, Compound 37: 5-cyclopropoxy-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



37

[0980] Compound 37 was synthesized in a manner similar to **Compound 40** using 2-(8-cyclopropoxy-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane instead of 2-(7-chloro-8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and using 0.1% trifluoroacetic acid in acetonitrile/water instead of 0.1% acetic acid in acetonitrile/water. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.53 (ddd, J = 8.7, 4.9, 3.1 Hz, 1H), 7.39 – 7.26 (m, 2H), 7.07 (dd, J = 12.7, 2.5 Hz, 1H), 5.80 – 5.45 (m, 2H), 4.75 – 4.63 (m, 2H), 4.41 (dt, J = 12.3, 5.9 Hz, 1H), 4.33 (s, 1H), 4.21 – 3.75 (m, 6H), 3.60 – 3.35 (m, 4H), 2.92 – 1.66 (m, 12H), 0.47 – -0.38 (m, 3H). LCMS: 659.0

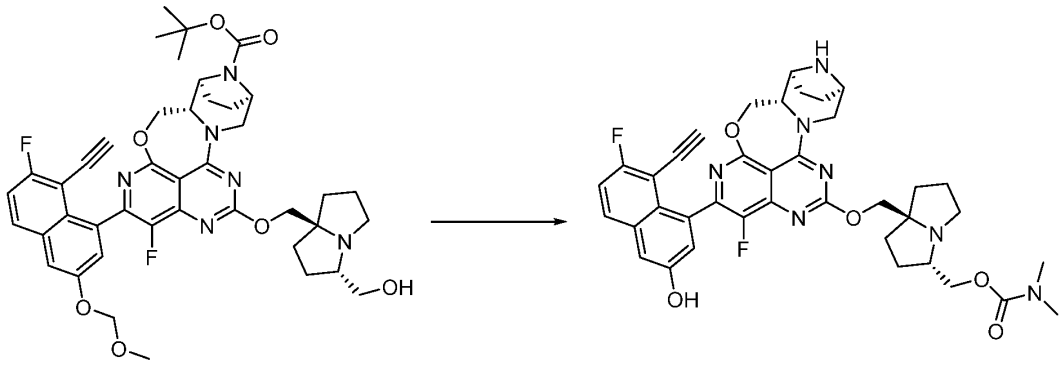
Example 38, Compound 38: ((3S,7aS)-7a-((((5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-12-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl azepane-1-carboxylate



36-3 38

Intermediate 36-3 (10 mg, 13 μmol) and 4-nitrophenyl chloroformate (3.9 mg, 19 μmol) were dissolved in anhydrous tetrahydrofuran (500 uL) under argon atmosphere. The solution was cooled to 0°C and N,N-diisopropylethylamine (6.7 uL, 38 μmol) was added via syringe. The mixture was stirred at 0°C for 30 min then azepane (4.3 uL, 38 μmol) was added. The resulting mixture was stirred at room temperature for 30 minutes and then concentrated *in vacuo*. The residue was taken up into acetonitrile (500 uL) and cooled to 0°C. Hydrogen chloride solution (4.0 M in 1,4-dioxane, 500 μL, 2.0 mmol) was added via syringe with vigorous stirring. Stirring was continued for 50 minutes at 0°C. The solution was then concentrated *in vacuo* and purified by reverse phase preparative HPLC (0.1% TFA acid in acetonitrile/water) to give **Compound 38.** ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.89 (dd, J = 9.1, 5.7 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.23 (dd, J = 21.8, 2.5 Hz, 1H), 5.44 – 5.32 (m, 1H), 4.80 – 4.73 (m, 2H), 4.71 – 4.63 (m, 2H), 4.56 – 4.45 (m, 2H), 4.44 – 4.25 (m, 4H), 3.65 – 3.36 (m, 8H), 2.52 – 2.04 (m, 12H), 1.69 (s, 4H), 1.57 (dt, J = 6.3, 3.0 Hz, 4H). LCMS: 766.4.

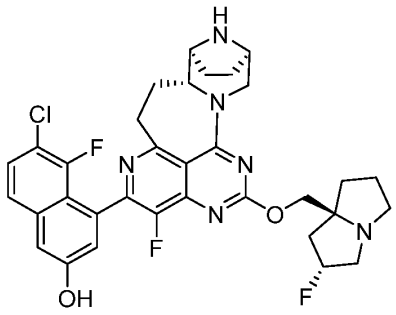
Example 39, Compound 39: ((3S,7aS)-7a-((((5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-12-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate



36-3 39

[0981] Compound 39 was prepared in a manner analogous to **Compound 38** except that dimethylamine (2M in tetrahydrofuran) was used in place of azepane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 – 7.84 (m, 1H), 7.37 (dd, J = 2.6, 1.4 Hz, 1H), 7.34 (dd, J = 9.0, 3.9 Hz, 1H), 7.23 (dd, J = 21.6, 2.6 Hz, 1H), 5.43 – 5.32 (m, 1H), 4.81 – 4.72 (m, 2H), 4.71 – 4.64 (m, 2H), 4.56 – 4.44 (m, 2H), 4.42 – 4.24 (m, 4H), 3.66 – 3.53 (m, 2H), 3.52 – 3.40 (m, 2H), 3.01 – 2.87 (m, 6H), 2.53 – 2.06 (m, 12H). LCMS: 712.3.

Example 40, Compound 40: 6-chloro-5-fluoro-4-((5aR,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol

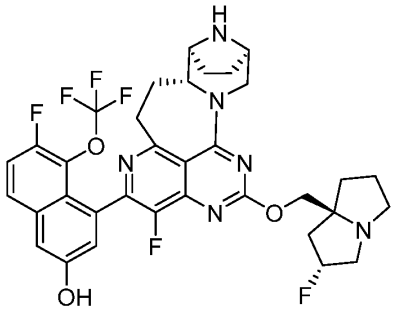


40

[0982] Compound 40 was synthesized in a manner similar to **Compound 6** using **Intermediate 23-1** instead of **Intermediate 17-9** and using 0.1% trifluoroacetic acid in acetonitrile/water instead

of 0.1% acetic acid in acetonitrile/water. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.61 (d, J = 8.9 Hz, 1H), 7.45 (td, J = 8.8, 8.1, 4.1 Hz, 1H), 7.33 (t, J = 2.3 Hz, 1H), 7.21 (dd, J = 12.6, 2.4 Hz, 1H), 5.77 – 5.46 (m, 2H), 4.75 – 4.64 (m, 2H), 4.44 – 4.27 (m, 2H), 4.16 – 3.83 (m, 4H), 3.58 – 3.37 (m, 3H), 2.83 – 1.95 (m, 13H). LCMS: 636.9.

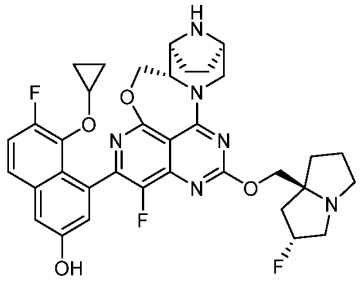
Example 41, Compound 41: 6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-(trifluoromethoxy)naphthalen-2-ol



41

[0983] Compound 41 was synthesized in a manner similar to **Compound 7** using **Intermediate 23-1** instead of **Intermediate 17-9** and using 0.1% trifluoroacetic acid in acetonitrile/water instead of 0.1% acetic acid in acetonitrile/water. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.89 (ddd, J = 9.3, 5.1, 2.4 Hz, 1H), 7.48 (td, J = 9.7, 2.6 Hz, 1H), 7.40 (d, J = 2.5 Hz, 1H), 7.33 (dd, J = 8.7, 2.4 Hz, 1H), 5.80 – 5.50 (m, 2H), 4.71 (d, J = 2.2 Hz, 2H), 4.41 (td, J = 12.1, 4.7 Hz, 1H), 4.34 (s, 1H), 4.20 – 3.84 (m, 4H), 3.59 – 3.35 (m, 3H), 2.84 – 1.98 (m, 12H), 1.93 – 1.75 (m, 1H). LCMS: 687.0.

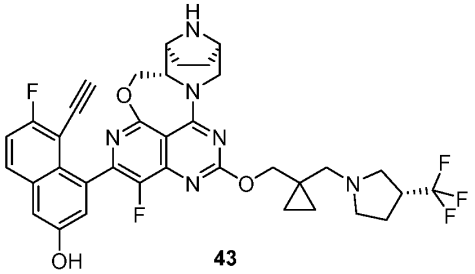
Example 42, Compound 42: 5-cyclopropoxy-6-fluoro-4-((5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



42

[0984] Compound 42 was synthesized in a manner similar to **Compound 1** using **Intermediate 42-2** instead of 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.53 (dd, J = 9.1, 4.9 Hz, 1H), 7.34 (ddd, J = 11.4, 9.1, 2.4 Hz, 1H), 7.28 (dd, J = 2.5, 1.2 Hz, 1H), 7.12 – 7.04 (m, 1H), 5.58 (d, J = 51.8 Hz, 1H), 5.33 (dd, J = 50.1, 14.6 Hz, 1H), 4.81 – 4.64 (m, 4H), 4.55 – 4.30 (m, 3H), 4.10 – 3.79 (m, 4H), 3.62 – 3.41 (m, 2H), 2.79 – 2.54 (m, 2H), 2.49 – 2.02 (m, 8H), 0.35 – 0.01 (m, 3H), -0.06 (s, 1H). LCMS: 661.3.

Example 43, Compound 43: 5-ethynyl-6-fluoro-4-((5aS,6S,9R)-1-fluoro-12-((1-(((R)-3-(trifluoromethyl)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol

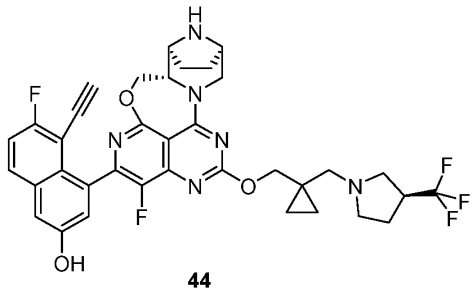


43

[0985] Compound 43 was synthesized in a manner similar to **Compound 35** using (3*R*)-3-(trifluoromethyl)pyrrolidine hydrochloride instead of 1,4-oxazepane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.86 (dd, *J* = 9.1, 5.7 Hz, 1H), 7.35 – 7.34 (m, 1H), 7.32 – 7.31 (m, 1H), 7.26 – 7.22 (m, 1H), 5.36 – 5.21 (m, 1H), 4.86 (s, 1H), 4.79 – 4.68 (m, 1H), 4.64 (m, 1H), 4.46 (m, 3H),

4.33 (m, 2H), 4.01 (m, 2H), 3.63 – 3.35 (m, 6H), 2.41 (s, 1H), 2.33 – 1.99 (m, 5H), 1.04 – 0.81 (m, 4H). LCMS: 693.3.

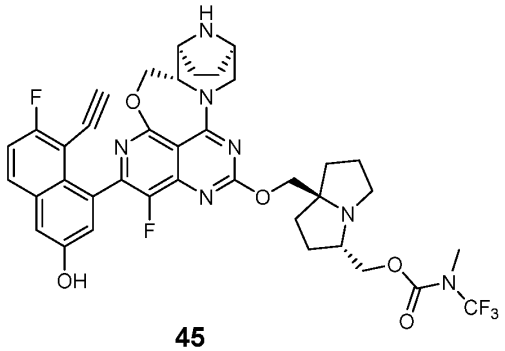
Example 44, Compound 44: 5-ethynyl-6-fluoro-4-((5aS,6S,9R)-1-fluoro-12-((1-(((S)-3-(trifluoromethyl)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



44

[0986] Compound 44 was synthesized in a manner similar to **Compound 35** using (3*S*)-3-(trifluoromethyl)pyrrolidine hydrochloride instead of 1,4-oxazepane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.86 (ddd, J = 8.8, 5.7, 2.6 Hz, 1H), 7.35 – 7.34 (m, 1H), 7.32 – 7.31 (m, 1H), 7.24 – 7.19 (m, 1H), 5.30 (t, J = 14.0 Hz, 1H), 4.86 (s, 1H), 4.78 – 4.68 (m, 1H), 4.63 (m, 1H), 4.59 – 4.36 (m, 3H), 4.32 (m, 2H), 3.95 (s, 2H), 3.62 – 3.36 (m, 6H), 2.41 (s, 1H), 2.34 – 2.01 (m, 5H), 0.94 (m, 4H). LCMS: 693.3.

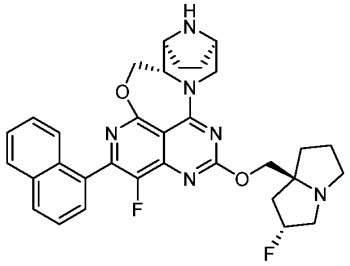
Example 45, Compound 45: ((3*S*,7a*S*)-7a-((((5a*S*,6*S*,9*R*)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-12-yl)oxy)methyl)hexahydro-1*H*-pyrrolizin-3-yl)methyl methyl(trifluoromethyl)carbamate



45

[0987] Methyl isothiocyanate (46.8 μL, 684 μmol) and acetonitrile (3.42 mL) were added simultaneously to a mixture of triphosgene (81.2 mg, 274 μmol) and silver(I) fluoride (434 mg, 3.42 mmol) at 0°C, and the resulting mixture was vigorously stirred and was heated to 50°C. After 20 h, the resulting mixture was cooled to room temperature and was filtered. A portion of the filtrate (319 μL) was added via syringe to a stirred mixture of **Intermediate 36-3** (10.0 mg, 12.7 μmol), *N*,*N*-diisopropylethylamine (22.2 μL, 127 μmol), 4-(dimethylamino)pyridine (3.1 mg, 26 μmol), and dichloromethane (0.8 mL) at room temperature. After 70 min, diethyl ether (40 mL) and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (30 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. Acetonitrile (0.3 mL) was added via syringe, and the resulting mixture was vigorously stirred and was cooled to 0°C. Hydrogen chloride solution (4.0 M in 1,4-dioxane, 500 μL, 2.0 mmol) was added via syringe. After 90 min, the resulting mixture was purified by reverse phase preparative HPLC (0.1% acetic acid in acetonitrile/water) to give **Compound 45**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.86 (ddd, J = 8.9, 5.7, 2.7 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.28 – 7.15 (m, 1H), 5.16 – 5.04 (m, 1H), 4.64 (dd, J = 12.5, 6.9 Hz, 1H), 4.60 – 4.34 (m, 5H), 4.17 (d, J = 6.7 Hz, 1H), 3.88 (s, 1H), 3.78 (s, 1H), 3.70 (d, J = 5.8 Hz, 1H), 3.60 – 3.01 (m, 7H), 2.42 – 1.68 (m, 12H), 1.96 (s, 6H). LCMS: 766.3.

Example 46, Compound 46: (5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-2-(naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene

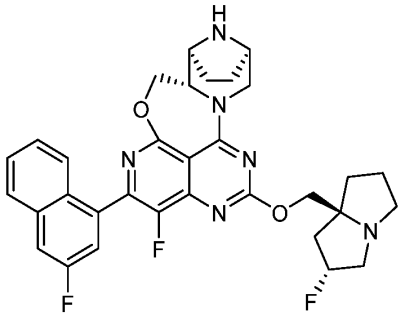


46

[0988] Compound 46 was synthesized in a manner similar to **Compound 1** using naphthalen-1-ylboronic acid instead of 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and using 0.1% trifluoroacetic acid in acetonitrile/water instead of 0.1% acetic acid in acetonitrile/water. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.12 – 8.05 (m, 1H), 8.05 – 7.99 (m, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.61 – 7.55 (m, 1H), 7.51 (ddd, J = 8.3, 6.8, 1.4 Hz, 1H), 5.72 – 5.49 (m, 1H), 5.40 (dd, J = 14.7, 2.7 Hz, 1H), 4.82 – 4.74 (m,

2H), 4.74 – 4.66 (m, 2H), 4.47 (d, J = 6.2 Hz, 1H), 4.37 (d, J = 6.0 Hz, 2H), 4.13 – 3.87 (m, 3H), 3.67 – 3.03 (m, 3H), 2.87 – 1.86 (m, 10H). LCMS: 571.3.

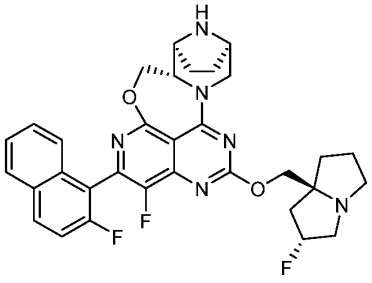
Example 47, Compound 47: (5a*S*,6*S*,9*R*)-1-fluoro-2-(3-fluoronaphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



47

[0989] Compound 47 was synthesized in a manner similar to **Compound 1** using 2-(3-fluoronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (US20200331911) instead of 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and using 0.1% trifluoroacetic acid in acetonitrile/water instead of 0.1% acetic acid in acetonitrile/water. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.00 (dd, J = 8.3, 1.0 Hz, 1H), 7.80 – 7.70 (m, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.55 – 7.44 (m, 2H), 5.73 – 5.49 (m, 1H), 5.39 (dd, J = 14.8, 2.7 Hz, 1H), 4.82 – 4.75 (m, 2H), 4.75 – 4.66 (m, 2H), 4.48 (d, J = 6.1 Hz, 1H), 4.37 (d, J = 5.8 Hz, 2H), 4.13 – 3.86 (m, 3H), 3.66 – 3.09 (m, 3H), 2.81 – 1.94 (m, 10H). LCMS: 589.2.

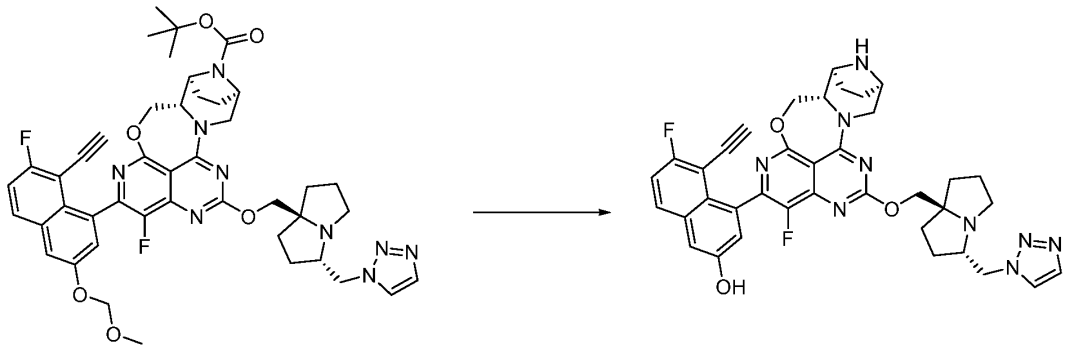
Example 48, Compound 48: (5a*S*,6*S*,9*R*)-1-fluoro-2-(2-fluoronaphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



48

[0990] Compound 48 was synthesized in a manner similar to **Compound 1** using (2-fluoronaphthalen-1-yl)boronic acid instead of 2-(7,8-difluoro-3-(methoxymethoxy) naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and using 0.1% trifluoroacetic acid in acetonitrile/water instead of 0.1% acetic acid in acetonitrile/water. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.15 (dd, J = 9.1, 5.6 Hz, 1H), 8.03 (d, J = 7.4 Hz, 1H), 7.71 – 7.43 (m, 4H), 5.61 (d, J = 51.5 Hz, 1H), 5.47 – 5.33 (m, 1H), 4.93 – 4.66 (m, 4H), 4.53 – 4.43 (m, 1H), 4.43 – 4.32 (m, 2H), 4.14 – 3.86 (m, 3H), 3.65 – 3.18 (m, 3H), 2.81 – 1.96 (m, 10H). LCMS: 589.2.

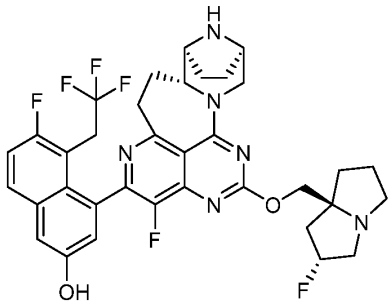
Example 49, Compound 49: 4-((5aS,6S,9R)-12-(((3S,7aS)-3-((1H-1,2,3-triazol-1-yl)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1-fluoro-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



49-1 49

[0991] Compound 49 was prepared in a manner analogous to **Compound 13** using **Intermediate 49-1** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.13 (dd, J = 7.2, 1.1 Hz, 1H), 7.88 (ddd, J = 9.1, 5.7, 2.0 Hz, 1H), 7.79 (dd, J = 3.9, 1.1 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.28 (d, J = 2.6 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 5.35 (td, J = 15.0, 2.7 Hz, 1H), 4.97 (ddd, J = 10.3, 8.2, 5.3 Hz, 2H), 4.79 – 4.53 (m, 5H), 4.49 (dd, J = 14.8, 5.7 Hz, 1H), 4.41 – 4.31 (m, 2H), 3.76 (dd, J = 11.7, 5.0 Hz, 1H), 3.60 – 3.49 (m, 3H), 3.42 (d, J = 1.0 Hz, 1H), 2.49 – 2.04 (m, 12H). LCMS: 692.3.

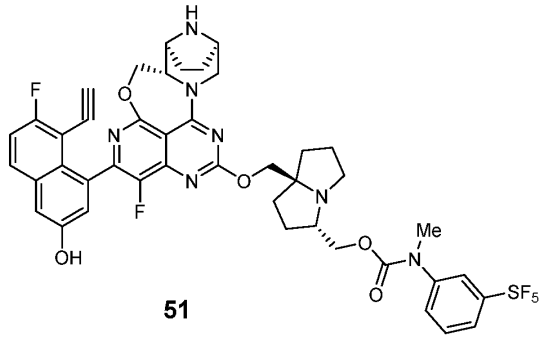
Example 50, Compound 50: 6-fluoro-4-((5a*R*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-(2,2,2-trifluoroethyl)naphthalen-2-ol



50

[0992] Compound 50 was synthesized in a manner similar to **Compound 14** using 2,2,2-trifluoroethyl trifluoromethanesulfonate instead of (iodomethyl)cyclopropane and using **Intermediate 23-1** instead of **Intermediate 17-9**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 – 7.86 (m, 1H), 7.42 – 7.32 (m, 2H), 7.23 – 7.14 (m, 1H), 5.55 (t, J = 13.4 Hz, 1H), 5.34 (d, J = 53.9 Hz, 1H), 4.33 (d, J = 10.4 Hz, 1H), 4.26 (d, J = 10.6 Hz, 1H), 4.11 (d, J = 8.3 Hz, 1H), 3.76 – 3.12 (m, 7H), 3.12 – 2.97 (m, 2H), 2.67 – 1.49 (m, 14H), 1.96 (s, 6H). LCMS: 685.3.

Example 51, Compound 51: ((3*S*,7a*S*)-7a-((((5a*S*,6*S*,9*R*)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-12-yl)oxy)methyl)hexahydro-1*H*-pyrrolizin-3-yl)methyl methyl(3-(pentafluoro-λ^6-sulfaneyl)phenyl)carbamate

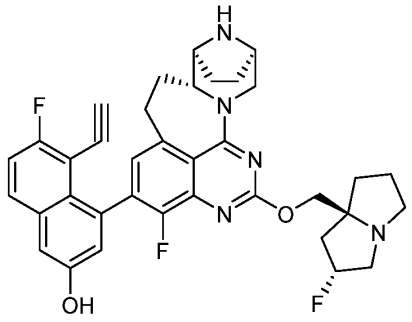


51

[0993] Triphosgene (7.0 mg, 24 μmol) was added to a stirred mixture of *N*-methyl-3-(pentafluoro-λ^6-sulfaneyl)aniline (prepared according to, for instance, CN111454186) (22.4 mg, 96.1 μmol), pyridine (7.7 μL, 96 μmol), and dichloromethane (0.8 mL) at 0°C, and the resulting mixture was

warmed to room temperature. After 117 min, **Intermediate 36-3** (10.0 mg, 12.7 μmol), 4-(dimethylamino)pyridine (3.1 mg, 26 μmol), and *N*,*N*-diisopropylethylamine (22.2 μL, 127 μmol) were added sequentially. After 127 min, the resulting mixture was heated to 70°C. After 108 min, the resulting mixture was heated to 120°C in a microwave reactor. After 30 min, the resulting mixture was cooled to room temperature. After 17 min, the resulting mixture was heated to 120°C in a microwave reactor. After 135 min, the resulting mixture was cooled to room temperature. After 13 h, diethyl ether (40 mL) and ethyl acetate (20 mL) were added sequentially. The organic layer was washed with water (30 mL), was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. Acetonitrile (0.3 mL) was added via syringe, and the resulting mixture was vigorously stirred and was cooled to 0°C. Hydrogen chloride solution (4.0 M in 1,4-dioxane, 500 μL, 2.0 mmol) was added via syringe. After 90 min, the resulting mixture was purified by reverse phase preparative HPLC (0.1% acetic acid in acetonitrile/water) to give **Compound 51**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 – 7.80 (m, 2H), 7.73 (s, 1H), 7.63 – 7.54 (m, 2H), 7.39 – 7.27 (m, 2H), 7.27 – 7.14 (m, 1H), 5.07 (dd, J = 14.5, 6.1 Hz, 1H), 4.69 – 4.58 (m, 1H), 4.53 – 4.27 (m, 3H), 4.16 (d, J = 7.3 Hz, 1H), 3.98 – 2.70 (m, 10H), 2.46 – 1.49 (m, 12H), 1.96 (s, 6H). LCMS: 900.3.

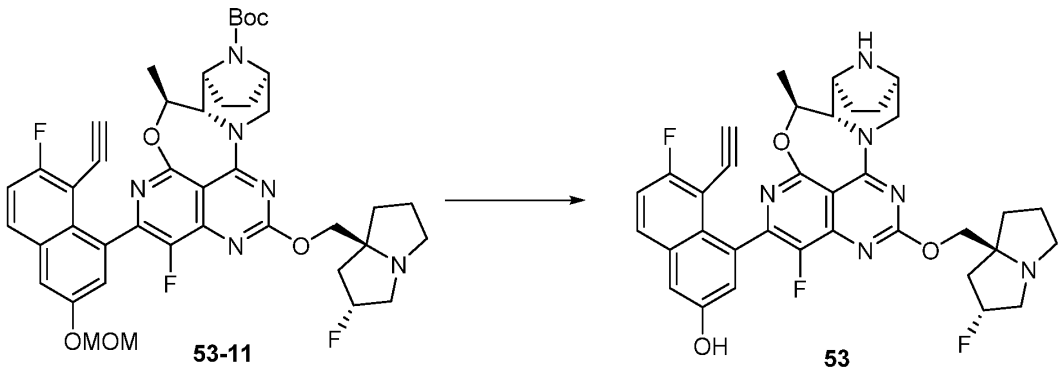
Example 52, Compound 52: 5-ethynyl-6-fluoro-4-((1*S*,4*R*,14a*R*)-10-fluoro-8-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)naphthalen-2-ol



52

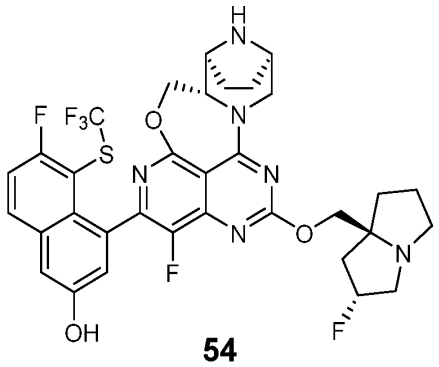
[0994] Compound 52 was synthesized in a manner similar to **Compound 2** using **Intermediate 52-7** instead of **Intermediate 2-1**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.84 (ddd, J = 8.8, 5.8, 2.5 Hz, 1H), 7.33 (dd, J = 9.0, 3.6 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.09 (dd, J = 14.0, 2.6 Hz, 1H), 7.04 (t, J = 7.3 Hz, 1H), 5.56 – 5.23 (m, 2H), 4.45 – 4.26 (m, 2H), 4.15 – 4.05 (m, 1H), 3.78 (s, 1H), 3.61 – 3.08 (m, 7H), 2.51 – 1.64 (m, 14H), 1.96 (s, 6H). LCMS: 626.3.

Example 53, Compound 53: 5-ethynyl-6-fluoro-4-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



[0995] Compound 53 was synthesized in a manner similar to **Compound 13** using **Intermediate 53-11** instead of **Intermediates 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.92 – 7.85 (m, 1H), 7.40 – 7.31 (m, 2H), 7.28 – 7.13 (m, 1H), 5.70 – 5.49 (m, 2H), 4.80 – 4.66 (m, 3H), 4.42 (dd, J = 8.6, 3.6 Hz, 1H), 4.37 (s, 1H), 4.28 (dd, J = 6.4 Hz, 1H), 4.13 – 3.85 (m, 3H), 3.57 – 3.44 (m, 2H), 2.82 – 2.04 (m, 7H), 1.72 – 1.57 (m, 3H). LCMS: 642.9.

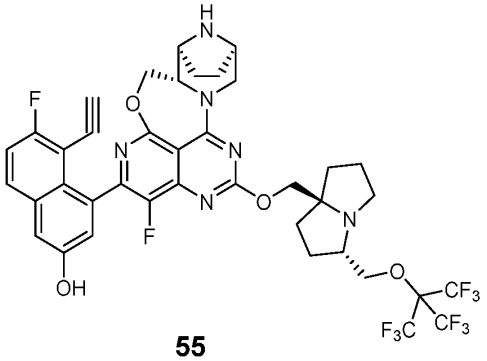
Example 54, Compound 54: 6-fluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-((trifluoromethyl)thio)naphthalen-2-ol



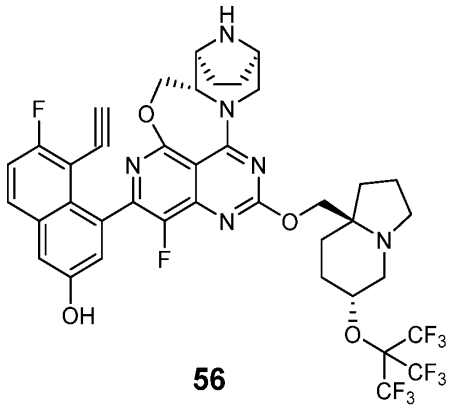
[0996] Compound 54 was synthesized in a manner similar to **Compound 1** using **Intermediate 54-3** instead of 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.09 (dd, J = 9.1, 5.7 Hz, 1H), 7.53 – 7.43 (m, 1H), 7.43 – 7.38 (m, 1H), 7.38 – 7.26 (m, 1H), 5.33 (d, J = 54.0 Hz, 1H), 5.07 (dd, J = 26.6, 13.5

Hz, 1H), 4.60 (t, J = 13.6 Hz, 1H), 4.54 – 4.38 (m, 1H), 4.32 (d, J = 10.5 Hz, 1H), 4.26 (d, J = 10.4 Hz, 1H), 4.22 – 4.05 (m, 1H), 3.81 – 3.10 (m, 7H), 3.10 – 2.94 (m, 1H), 2.46 – 1.58 (m, 10H), 1.96 (s, 6H). LCMS: 705.2.

Examples 55 and 56: Compound 55 (5-ethynyl-6-fluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((3*S*,7a*S*)-3-(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol) and Compound 56 (5-ethynyl-6-fluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*R*,8a*S*)-6-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)hexahydroindolizin-8a(1*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol)



55



56

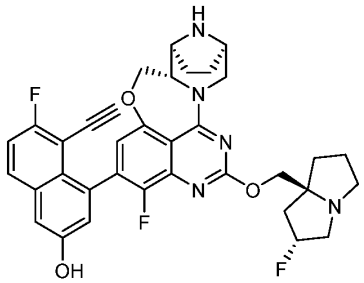
[0997] Trimethylphosphine solution (1.0 M in tetrahydrofuran, 63.7 µL, 64 µmol) was added via syringe to a stirred mixture of **Intermediate 36-3** (10.0 mg, 12.7 µmol), di-*tert*-butyl (*E*)-diazene-1,2-dicarboxylate (14.8 mg, 63.7 µmol), 1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl) propan-2-ol (14.2 µL, 102 µmol), and 2-methyltetrahydrofuran (0.8 mL) at 0°C, and the resulting mixture was warmed to room temperature. After 60 min, the resulting mixture was heated to 90°C. After 75

min, the resulting mixture was cooled to room temperature and was concentrated under reduced pressure. Acetonitrile (0.3 mL) was added via syringe, and the resulting mixture was vigorously stirred and was cooled to 0°C. Hydrogen chloride solution (4.0 M in 1,4-dioxane, 500 μL, 2.0 mmol) was added via syringe. After 90 min, the resulting mixture was purified by reverse phase preparative HPLC (0.1% acetic acid in acetonitrile/water) to give **Compound 55** and **Compound 56**.

[0998] Compound 55: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (ddd, J = 9.0, 5.7, 3.2 Hz, 1H), 7.39 – 7.28 (m, 2H), 7.27 – 7.12 (m, 1H), 5.09 (dd, J = 13.4, 8.7 Hz, 1H), 4.70 – 4.56 (m, 1H), 4.54 – 4.21 (m, 5H), 4.16 (d, J = 7.2 Hz, 1H), 3.76 (s, 1H), 3.71 – 2.75 (m, 6H), 2.32 – 1.28 (m, 12H), 1.96 (s, 6H). LCMS: 859.2.

[0999] Compound 56: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (ddd, J = 9.1, 5.7, 3.4 Hz, 1H), 7.38 – 7.27 (m, 2H), 7.27 – 7.13 (m, 1H), 5.15 – 5.00 (m, 1H), 4.69 – 4.57 (m, 1H), 4.57 – 4.41 (m, 3H), 4.38 – 4.23 (m, 1H), 4.15 (d, J = 7.1 Hz, 1H), 3.77 (s, 1H), 3.68 (d, J = 5.9 Hz, 1H), 3.63 – 3.17 (m, 4H), 3.14 – 3.03 (m, 2H), 2.25 – 1.15 (m, 12H), 1.96 (s, 6H). LCMS: 859.2.

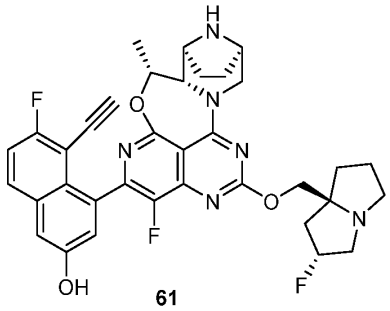
Example 57, Compound 57: 5-ethynyl-6-fluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-13-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-2-yl)naphthalen-2-ol



57

[1000] Compound 57 was synthesized in a manner similar to **Compound 52** using **Intermediate 57-2** instead of **Intermediate 52-6**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.83 (t, J = 7.6 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.11 – 7.05 (m, 1H), 6.82 – 6.76 (m, 1H), 5.34 (d, J = 53.9 Hz, 1H), 5.13 (t, J = 14.4 Hz, 1H), 4.51 (d, J = 13.1 Hz, 1H), 4.42 – 4.20 (m, 3H), 4.17 – 4.07 (m, 1H), 3.80 – 2.73 (m, 8H), 2.46 – 1.31 (m, 10H), 1.96 (s, 6H). LCMS: 628.2.

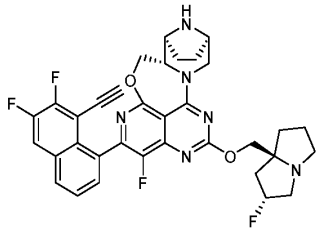
Example 61, Compound 61: 5-ethynyl-6-fluoro-4-((5R,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



61

[1001] Compound **61** was synthesized in a manner similar to **53** using intermediate **61-2** instead of intermediate **53-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 – 7.84 (m, 1H), 7.41 – 7.14 (m, 3H), 5.60 (d, J = 51.8 Hz, 1H), 5.11 – 4.98 (m, 1H), 4.85 – 4.80 (m, 2H), 4.78 – 4.62 (m, 3H), 4.34 – 4.19 (m, 2H), 4.09 – 3.86 (m, 3H), 3.71 – 3.45 (m, 2H), 2.82 – 1.87 (m, 12H), 1.70 - 1.60 (m, 3H). LCMS: 643.1.

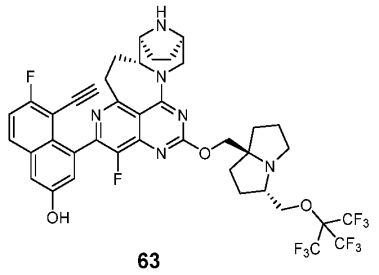
Example 62, Compound 62: (5a*S*,6*S*,9*R*)-2-(8-ethynyl-6,7-difluoronaphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



62

[1002] Compound 62 was synthesized in a manner similar to **Compound 30** using intermediate **62-2** instead of intermediate **30-1**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.11 – 8.04 (m, 1H), 7.97 (ddd, J = 10.9, 8.2, 3.3 Hz, 1H), 7.74 – 7.56 (m, 2H), 5.34 (d, J = 53.8 Hz, 1H), 5.08 (dd, J = 12.9, 6.8 Hz, 1H), 4.70 – 4.58 (m, 1H), 4.55 – 4.42 (m, 1H), 4.40 – 4.30 (m, 1H), 4.30 – 4.22 (m, 1H), 4.16 (d, J = 7.2 Hz, 1H), 3.89 – 3.12 (m, 7H), 3.12 – 3.00 (m, 1H), 2.45 – 1.70 (m, 10H), 1.96 (s, 6H). LCMS: 631.2.

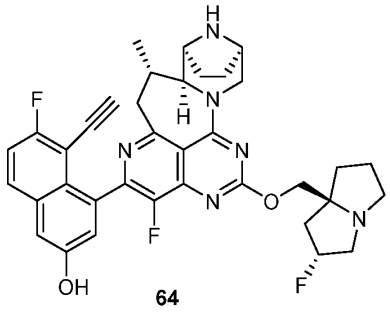
Example 63, Compound 63: 5-ethynyl-6-fluoro-4-((5a*R*,6*S*,9*R*)-1-fluoro-12-(((3*S*,7a*S*)-3-(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol



63

[1003] Compound 63 was synthesized in a manner similar to **Compound 13** using intermediate **63-7** instead of intermediate **13-9** and using intermediate **63-4** instead of intermediate **13-14**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (ddd, J = 9.1, 5.7, 3.3 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.26 – 7.16 (m, 1H), 5.66 – 5.45 (m, 1H), 4.56 – 4.41 (m, 2H), 4.41 – 4.31 (m, 2H), 4.16 (dt, J = 12.0, 6.0 Hz, 1H), 3.90 – 2.92 (m, 7H), 2.50 – 1.69 (m, 16H), 1.97 (s, 6H). LCMS: 857.3.

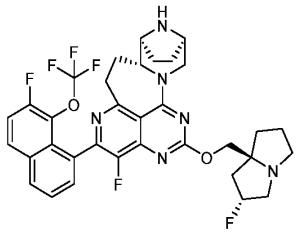
Example 64, Compound 64: 5-ethynyl-6-fluoro-4-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



64

[1004] Compound **64** was synthesized in a manner similar to Compound **63** using intermediate **64-4** instead of intermediate **63-7** and using ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol instead of intermediate **63-4**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.96 – 7.85 (m, 1H), 7.46 – 7.13 (m, 3H), 5.61 (d, *J* = 51.5 Hz, 1H), 5.19 (d, *J* = 14.7 Hz, 1H), 4.81 – 4.64 (m, 2H), 4.46 – 3.40 (m, 8H), 3.28 – 2.10 (m, 11H), 1.38 – 1.19 (m, 3H). LCMS: 640.9.

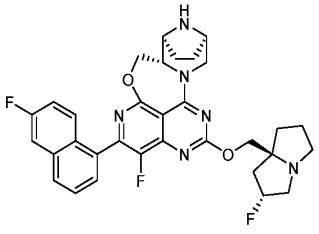
Example 65, Compound 65: (5a*R*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-8-(trifluoromethoxy)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



65

[1005] Compound **65** was synthesized in a manner similar to Compound **23** using intermediate **65-1** instead of ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.02 (d, J = 8.2 Hz, 1H), 7.86 – 7.76 (m, 1H), 7.72 – 7.63 (m, 2H), 7.61 (d, J = 6.9 Hz, 1H), 7.33 (td, J = 8.8, 2.7 Hz, 1H), 5.35 (d, J = 53.7 Hz, 1H), 5.09 (dd, J = 13.5, 2.3 Hz, 1H), 4.64 (dd, J = 13.3, 2.1 Hz, 1H), 4.50 (dd, J = 13.3, 7.5 Hz, 1H), 4.37 (d, J = 10.6 Hz, 1H), 4.29 (d, J = 10.6 Hz, 1H), 4.17 (d, J = 7.3 Hz, 1H), 3.76 (d, J = 6.0 Hz, 1H), 3.68 (d, J = 5.8 Hz, 1H), 3.64 – 2.97 (m, 5H), 2.48 – 1.70 (m, 10H), 1.96 (s, 6H). LCMS: 530.2.

Example 66, Compound 66: (5a*S*,6*S*,9*R*)-1-fluoro-2-(6-fluoronaphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene

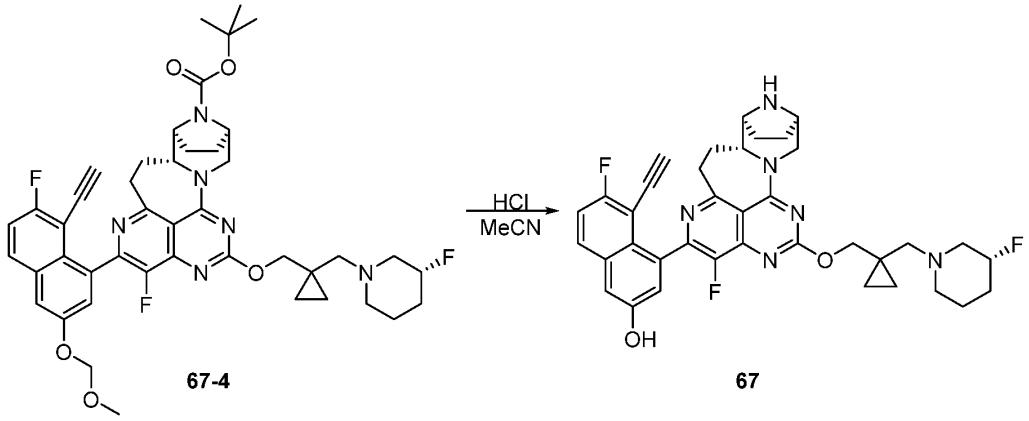


66

[1006] Compound **66** was synthesized in a manner similar to Compound **1** using 2-(6-fluoronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane instead of 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (400

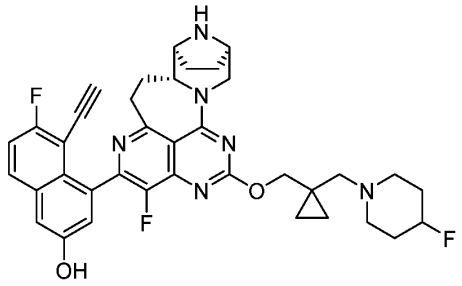
MHz, Methanol-d_4) δ 8.02 (d, J = 8.2 Hz, 1H), 7.86 – 7.76 (m, 1H), 7.72 – 7.63 (m, 2H), 7.61 (d, J = 6.9 Hz, 1H), 7.33 (td, J = 8.8, 2.7 Hz, 1H), 5.35 (d, J = 53.7 Hz, 1H), 5.09 (dd, J = 13.5, 2.3 Hz, 1H), 4.64 (dd, J = 13.3, 2.1 Hz, 1H), 4.50 (dd, J = 13.3, 7.5 Hz, 1H), 4.37 (d, J = 10.6 Hz, 1H), 4.29 (d, J = 10.6 Hz, 1H), 4.17 (d, J = 7.3 Hz, 1H), 3.76 (d, J = 6.0 Hz, 1H), 3.68 (d, J = 5.8 Hz, 1H), 3.64 – 2.97 (m, 5H), 2.48 – 1.70 (m, 10H), 1.96 (s, 6H). LCMS: 589.2.

Example 67, Compound 67: 7-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((1-(((3R)-3-fluorocyclohexyl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



[1007] Compound **67** was synthesized in a manner similar to Compound **35** using intermediate **67-4** instead of intermediate **35-4**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.87 (ddd, J = 9.2, 5.7, 1.6 Hz, 1H), 7.36 (dd, J = 2.6, 1.2 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.19 (dd, J = 16.6, 2.5 Hz, 1H), 5.70 (t, J = 16.8 Hz, 1H), 5.16 (d, J = 44.9 Hz, 1H), 4.62 (dd, J = 34.3, 11.9 Hz, 1H), 4.43 – 4.18 (m, 4H), 4.11 (s, 1H), 3.82 – 3.55 (m, 2H), 3.51 (d, J = 1.0 Hz, 1H), 3.50 – 3.31 (m, 4H), 3.17 – 2.92 (m, 2H), 2.46 (q, J = 11.3, 7.9 Hz, 2H), 2.35 – 1.62 (m, 8H), 1.17 – 0.65 (m, 4H). LCMS: 655.4.

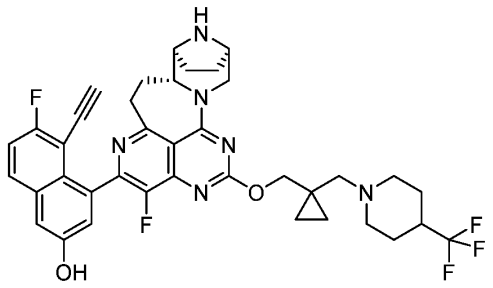
Example 68, Compound 68: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



68

[1008] Compound **68** was synthesized in a manner similar to Compound **67** using 4-fluoropiperidine instead of (*R*)-3-fluoropiperidine. ^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.87 (ddd, J = 9.0, 5.7, 2.9 Hz, 1H), 7.36 (dd, J = 2.7, 1.1 Hz, 1H), 7.32 (dt, J = 9.0, 4.5 Hz, 1H), 7.20 (dd, J = 15.9, 2.6 Hz, 1H), 5.64 (t, J = 15.5 Hz, 1H), 4.97 (d, J = 47.4 Hz, 1H), 4.64 – 4.40 (m, 2H), 4.36 (d, J = 10.5 Hz, 1H), 4.31 (s, 1H), 4.12 (s, 1H), 3.81 (q, J = 21.2, 15.6 Hz, 2H), 3.51 (td, J = 8.4, 3.4 Hz, 2H), 3.44 – 3.02 (m, 6H), 2.56 – 2.35 (m, 2H), 2.35 – 1.94 (m, 8H), 1.08 – 0.76 (m, 4H). LCMS: 655.4.

Example 69, Compound 69: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((1-((4-(trifluoromethyl)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol

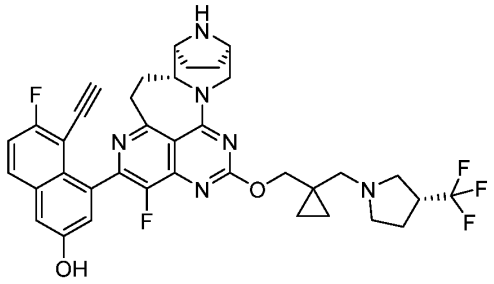


69

[1009] Compound **69** was synthesized in a manner similar to Compound **67** using 4-(trifluoromethyl)piperidine instead of (*R*)-3-fluoropiperidine. ^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.87 (ddd, J = 9.0, 5.7, 2.9 Hz, 1H), 7.36 (t, J = 2.2 Hz, 1H), 7.33 (td, J = 9.0, 4.2 Hz, 1H), 7.21 (dd, J = 16.4, 2.5 Hz, 1H), 5.64 (td, J = 16.0, 14.5, 3.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 0.5H), 4.49 (s, 1H),4.38 (d, J = 11.8 Hz, 0.5H), 4.37 (d, J = 12.0 Hz, 1H), 4.28 (s, 1H), 4.12 (s, 1H), 3.99 (d,

J = 12.8 Hz, 2H), 3.66 – 3.48 (m, 2H), 3.47 – 3.31 (m, 4H), 3.03 (s, 2H), 2.59 (s, 1H), 2.45 (t, J = 12.1 Hz, 2H), 2.17 (t, J = 14.7 Hz, 2H), 2.11 – 1.85 (m, 6H), 0.99 (s, 2H), 0.88 (s, 2H). LCMS: 705.4.

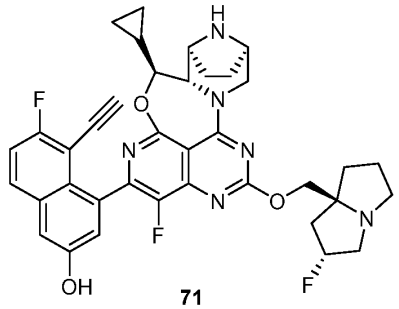
Example 70, Compound 70: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((1-(((R)-3-(trifluoromethyl)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



70

[1010] Compound **70** was synthesized in a manner similar to Compound **67** using (*R*)-3-(trifluoromethyl)pyrrolidine instead of (*R*)-3-fluoropiperidine. ^{1}H NMR (400 MHz, Methanol-d$_4$) δ 7.87 (ddd, J = 9.2, 5.7, 2.2 Hz, 1H), 7.37 (t, J = 2.4 Hz, 1H), 7.33 (dt, J = 9.0, 4.5 Hz, 1H), 7.21 (dd, J = 15.4, 2.5 Hz, 1H), 5.66 (ddd, J = 17.8, 14.6, 3.0 Hz, 1H), 4.55 (d, J = 11.9 Hz, 0.5H), 4.48 (s, 1H), 4.43 – 4.33 (m, 1.5H), 4.30 (s, 1H), 4.12 (s, 1H), 3.57 – 3.32 (m, 12H), 2.56 – 2.32 (m, 3H), 2.26 (s, 1H), 2.16 – 1.94 (m, 4H), 1.08 – 0.80 (m, 4H). LCMS: 691.4.

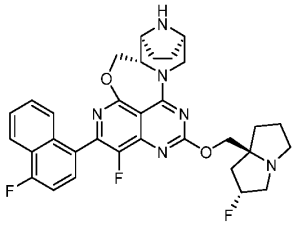
Example 71, Compound 71: 4-((5*S*,5a*S*,6*S*,9*R*)-5-cyclopropyl-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



71

[1011] Compound **71** was synthesized in a manner similar to Compound **53** using intermediate **71-1** instead of intermediates **53-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (dt, J = 9.2, 5.4 Hz, 1H), 7.40 – 7.28 (m, 2H), 7.19 (dd, J = 43.7, 2.5 Hz, 1H), 5.68 – 5.47 (m, 2H), 4.85 – 4.59 (m, 5H), 4.37 (s, 1H), 4.09 – 3.83 (m, 4H), 3.69 (d, J = 1.0 Hz, 1H), 3.59 – 3.42 (m, 2H), 3.35 (dd, J = 4.7, 1.3 Hz, 1H), 2.75 – 2.54 (m, 2H), 2.51 – 2.03 (m, 4H), 1.31 (d, J = 9.9 Hz, 2H), 0.85 (dtt, J = 13.3, 8.6, 4.7 Hz, 2H), 0.60 (ddt, J = 26.0, 8.9, 4.2 Hz, 2H). LCMS: 668.9.

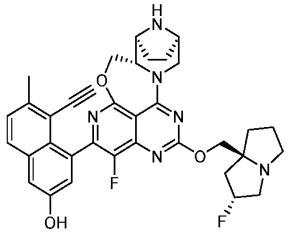
Example 72, Compound 72: (5a*S*,6*S*,9*R*)-1-fluoro-2-(4-fluoronaphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



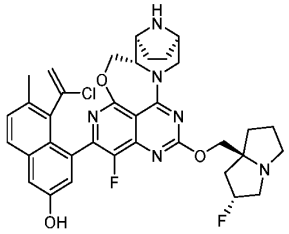
72

[1012] Compound **72** was synthesized in a manner similar to Compound **1** using 2 (4-fluoronaphthalen-1-yl)boronic acid instead of 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.21 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.69 – 7.56 (m, 3H), 7.40 – 7.32 (m, 1H), 5.35 (d, J = 53.5 Hz, 1H), 5.09 (dd, J = 13.6, 2.3 Hz, 1H), 4.64 (dd, J = 13.4, 2.1 Hz, 1H), 4.50 (dd, J = 13.3, 7.5 Hz, 1H), 4.36 (d, J = 10.6 Hz, 1H), 4.29 (d, J = 10.6 Hz, 1H), 4.17 (d, J = 7.4 Hz, 1H), 3.76 (d, J = 5.8 Hz, 1H), 3.68 (d, J = 5.9 Hz, 1H), 3.62 – 3.13 (m, 4H), 3.13 – 3.02 (m, 1H), 2.47 – 1.74 (m, 10H), 1.96 (s, 6H). LCMS: 589.2.

Examples 73 and 74: 5-ethynyl-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-6-methylnaphthalen-2-ol (Compound 73) and 5-(1-chlorovinyl)-4-((5a*S*,6*R*,9*S*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-6-methylnaphthalen-2-ol (Compound 74)



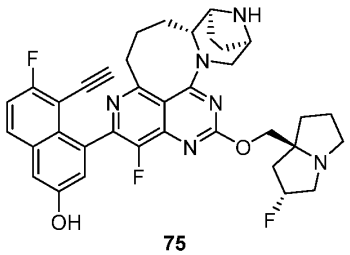
73



74

[1013] Compound **73** and Compound **74** were synthesized in a manner similar to Compound **4** using intermediate **73-2** instead of ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane. Compound **73**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.74 – 7.67 (m, 1H), 7.42 – 7.34 (m, 1H), 7.29 – 7.24 (m, 1H), 7.20 – 7.04 (m, 1H), 5.33 (d, J = 54.0 Hz, 1H), 5.12 – 5.03 (m, 1H), 4.68 – 4.55 (m, 1H), 4.52 – 4.39 (m, 1H), 4.35 – 4.20 (m, 2H), 4.19 – 4.10 (m, 1H), 3.75 (s, 1H), 3.70 – 3.62 (m, 1H), 3.61 – 3.12 (m, 5H), 3.10 – 3.00 (m, 1H), 2.56 – 1.67 (m, 13H), 1.96 (s, 6H). LCMS: 625.1. Compound **74**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.75 – 7.70 (m, 1H), 7.39 – 7.33 (m, 1H), 7.29 – 7.26 (m, 1H), 7.15 – 7.01 (m, 1H), 5.33 (d, J = 54.3 Hz, 1H), 5.25 – 4.77 (m, 3H), 4.65 – 4.56 (m, 1H), 4.53 – 4.38 (m, 1H), 4.36 – 4.29 (m, 1H), 4.28 – 4.21 (m, 1H), 4.18 – 4.09 (m, 1H), 3.80 – 2.95 (m, 7H), 2.48 – 1.65 (m, 13H), 1.96 (s, 6H). LCMS: 661.2.

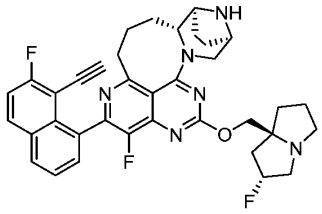
Example 75, Compound 75: 5-ethynyl-6-fluoro-4-((6a*R*,7*S*,10*R*)-1-fluoro-13-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalen-2-yl)naphthalen-2-ol



75

[1014] Compound **75** was synthesized in a manner similar to Compound **13** using **Intermediate 75-11** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 (ddd, J = 8.9, 5.7, 3.1 Hz, 1H), 7.54 – 7.24 (m, 3H), 5.61 (d, J = 52.2 Hz, 1H), 5.50 – 5.37 (m, 1H), 4.94 – 4.88 (m, 1H), 4.84 – 4.81 (m, 1H), 4.80 – 4.67 (m, 1H), 4.49 – 4.20 (m, 2H), 4.12 (d, J = 6.2 Hz, 1H), 4.09 – 3.63 (m, 4H), 3.60 – 3.38 (m, 2H), 3.17 – 1.69 (m, 15H). LCMS: 641.0.

Example 76, Compound 76: (6a*R*,7*S*,10*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene

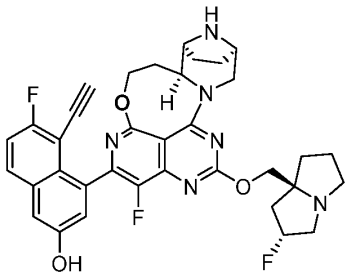


76

[1015] Hydrogen chloride solution (4.0 M in 1,4-dioxane, 91.7 μL, 0.367 mmol) was added via syringe to a vigorously stirred solution of **Intermediate 76-2** (18.0 mg, 24.9 μmol) in acetonitrile (0.3 mL) at room temperature. After 75 min, the resulting mixture was purified by reverse phase preparative HPLC (0.1% trifluoroacetic acid in acetonitrile/water) to give Compound **76**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.23 – 8.01 (m, 2H), 7.67 (q, J = 10.0, 8.5 Hz, 2H), 7.47 (td, J = 9.0, 3.3 Hz, 1H), 5.59 (d, J = 51.9 Hz, 1H), 5.40 (d, J = 13.6 Hz, 1H), 4.95 – 4.88 (m, 2H), 4.83 – 4.68

(m, 3H), 4.40 – 4.26 (m, 1H), 4.17 (d, *J* = 9.4 Hz, 1H), 4.11 – 3.99 (m, 1H), 3.98 – 3.82 (m, 2H), 3.67 (d, *J* = 14.6 Hz, 1H), 3.63 – 3.35 (m, 1H), 3.16 – 1.62 (m, 15H). LCMS: 625.0.

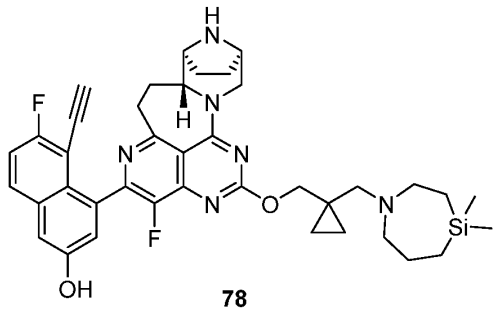
Example 77, Compound 77: 5-ethynyl-6-fluoro-4-((6aS,7S,10R)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol



77

[1016] Compound **77** was synthesized in a manner similar to Compound **2** using intermediate **77-7** instead of **Intermediate 2-1:**. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.88 (dd, J = 9.3, 5.6 Hz, 1H), 7.45 – 7.07 (m, 3H), 5.77 – 5.50 (m, 2H), 4.96 – 4.90 (m, 1H), 4.79 – 4.63 (m, 2H), 4.43 – 4.13 (m, 3H), 4.10 – 3.81 (m, 3H), 3.70 – 3.36 (m, 3H), 2.84 – 2.27 (m, 8H), 2.30 – 1.73 (m, 5H). LCMS: 643.3.

Example 78, Compound 78: 4-((5aR,6S,9R)-12-((1-((4,4-dimethyl-1,4-azasilepan-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol

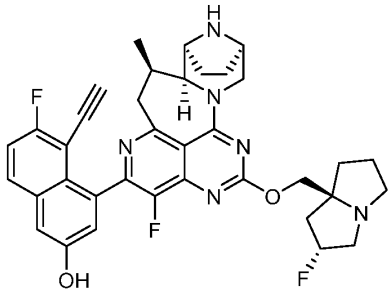


78

[1017] Acetonitrile (2 mL) was added via syringe to intermediate **78-2**, and the resulting mixture was cooled to 0°C. Hydrogen chloride solution (4.0 M in 1,4-dioxane, 184 µL, 740 µmol) was added via syringe. After 75 min, the resulting mixture was purified by reverse phase preparative

HPLC (0.1% acetic acid in acetonitrile/water) to give **Compound 78**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.97 – 7.79 (m, 1H), 7.46 – 7.30 (m, 2H), 7.29 – 7.11 (m, 1H), 5.81 – 5.60 (m, 1H), 4.81 – 4.59 (m, 1H), 4.45 – 4.10 (m, 4H), 3.96 – 2.95 (m, 8H), 2.60 – 2.36 (m, 2H), 2.19 – 1.85 (m, 7H), 1.23 – 0.79 (m, 9H), 0.20 – 0.09 (m, 3H), 0.08 – -0.08 (m, 3H). LCMS: 695.1.

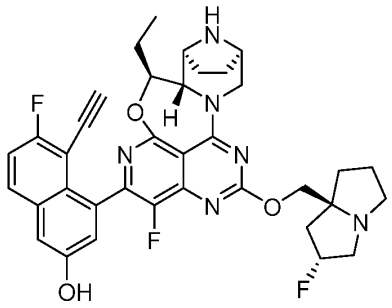
Example 79, Compound 79: 5-ethynyl-6-fluoro-4-((5R,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



79

[1018] Compound **79** was synthesized in a manner similar to Compound **76** using **Intermediate 79-4** instead of **Intermediate 76-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.97 – 7.85 (m, 1H), 7.46 – 7.09 (m, 3H), 5.74 – 5.45 (m, 2H), 4.81 – 4.66 (m, 1H), 4.33 (d, J = 26.7 Hz, 3H), 4.07 – 3.74 (m, 5H), 3.55 – 3.41 (m, J = 1.6 Hz, 1H), 3.25 – 2.14 (m, 10H), 2.04 (s, J = 8.8 Hz, 3H). LCMS: 640.9 $[M+H]^+$

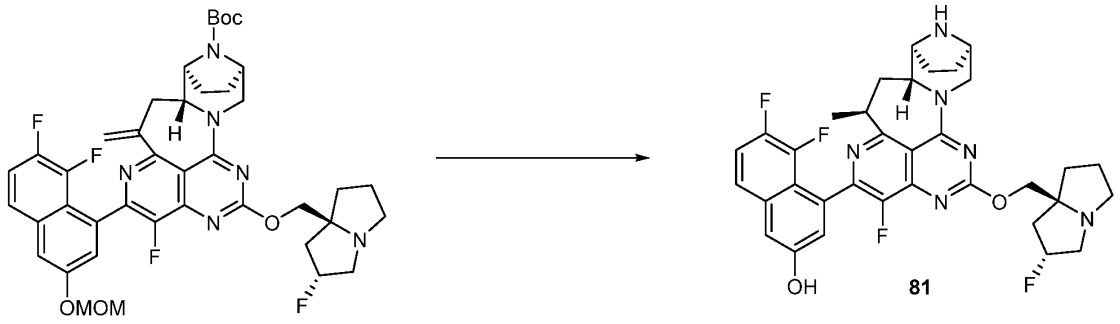
Example 80, Compound 80: 4-((5*S*,5a*S*,6*S*,9*R*)-5-ethyl-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



80

[1019] Compound **80** was synthesized in a manner similar to Compound **13** using **Intermediate 80-10** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.86 (ddd, J = 8.9, 5.7, 2.8 Hz, 1H), 7.41 – 7.28 (m, 2H), 7.19 (dd, J = 38.4, 2.5 Hz, 1H), 5.72 – 5.47 (m, 2H), 4.71 (d, J = 3.5 Hz, 2H), 4.62 – 4.43 (m, 2H), 4.40 – 4.23 (m, 2H), 4.14 – 3.80 (m, 3H), 3.73 – 3.34 (m, 3H), 2.98 – 1.72 (m, 13H), 1.18 (td, J = 7.2, 3.2 Hz, 3H). LCMS: 657.0.

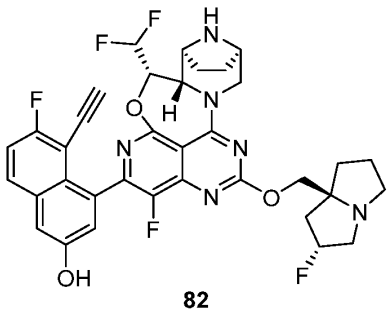
Example 81, Compound 81: 5,6-difluoro-4-((4S,5aR,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



81-3 81

[1020] Intermediate 81-3 (2.5 mg, 0.003 mmol) in 1 ml of ethanol and 3 ml of ethyl acetate was sparged under an argon atmosphere. Palladium on carbon (10 wt %) (0.5 mg) was added and the mixture was sparged under a hydrogen atmosphere (1 atm, balloon). The mixture was stirred vigorously for one hour and then sparged under an argon atmosphere. It was filtered through a pad of Celite®. The Celite® was washed with absolute ethanol and the filtrate was concentrated to dryness. Dichloromethane (0.5 mL) and trifluoroacetic acid (0.5 mL) were added sequentially, and the resulting mixture was stirred at room temperature for 30 minutes, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase preparative HPLC (0.1% trifluoroacetic acid in acetonitrile/water) to give Compound **81** (methylated stereo-center was arbitrary assigned): **:** ^{1}H NMR (400 MHz, Methanol-d4) δ 7.67 – 7.62 (m, 1H), 7.43 (q, J = 8.9 Hz, 1H), 7.36 (t, J = 2.2 Hz, 1H), 7.26 (d, J = 10.2 Hz, 1H), 5.76 (d, J = 13.4 Hz, 1H), 5.60 (d, J = 51.7 Hz, 1H), 4.77 – 4.70 (m, 2H), 4.49 (t, J = 8.7 Hz, 1H), 4.36 (s, 1H), 4.12 (s, 1H), 3.93 (d, J = 15.4 Hz, 3H), 3.72 (s, 2H), 3.61 – 3.46 (m, 1H), 2.82 – 2.56 (m, 2H), 2.49 – 2.32 (m, 6H), 2.14 (d, J = 43.0 Hz, 4H), 1.47 (d, J = 7.3 Hz, 3H). LCMS: 635.3.

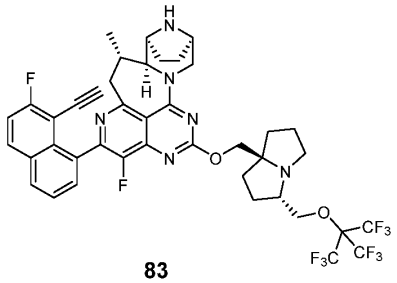
Example 82, Compound 82: 4-((5*S*,5a*S*,6*S*,9R)-5-(difluoromethyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



82

[1021] Compound **82** was synthesized in a manner similar to Compound **13** using **Intermediate 82-11** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (ddd, J = 8.8, 5.8, 2.4 Hz, 1H), 7.41 – 7.31 (m, 2H), 7.22 (dd, J = 58.4, 2.6 Hz, 1H), 6.68 – 6.28 (m, 1H), 5.58 (d, J = 51.6 Hz, 1H), 5.26 (d, J = 11.3 Hz, 1H), 5.06 (d, J = 14.2 Hz, 1H), 4.89 (d, J = 5.6 Hz, 1H), 4.78 – 4.67 (m, 2H), 4.62 (t, J = 6.2 Hz, 1H), 4.57 (s, 1H), 4.31 (d, J = 6.2 Hz, 1H), 4.07 – 3.82 (m, 3H), 3.70 (dd, J = 14.5, 5.9 Hz, 1H), 3.57 – 3.44 (m, 1H), 2.85 – 1.85 (m, 11H). LCMS: 678.9.

Example 83, Compound 83: (5*S*,5a*S*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((3*S*,7a*S*)-3-(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene

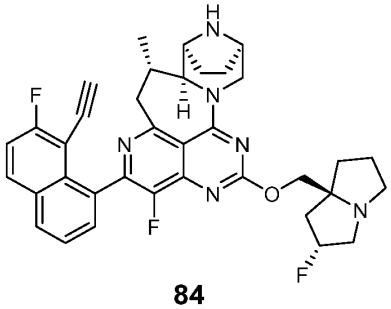


83

[1022] Compound **83** was synthesized in a manner similar to Compound **63** using intermediate **84-3** instead of intermediate **63-7** and using ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane instead of ((2-fluoro-6-(methoxymethoxy)-8-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.19 – 8.08 (m, 2H), 7.73 – 7.57 (m, 2H), 7.50 – 7.42 (m, 1H), 5.00 – 4.91 (m, 1H), 4.49 – 4.38 (m, 1H), 4.37 – 4.23 (m, 1H), 3.80 – 3.62 (m, 3H), 3.57 (d, J = 12.8 Hz, 1H), 3.45 – 2.67 (m, 6H), 2.32 – 1.27 (m, 15H), 1.96 (s, 6H), 1.27 – 1.12 (m, 3H). LCMS: 855.3.

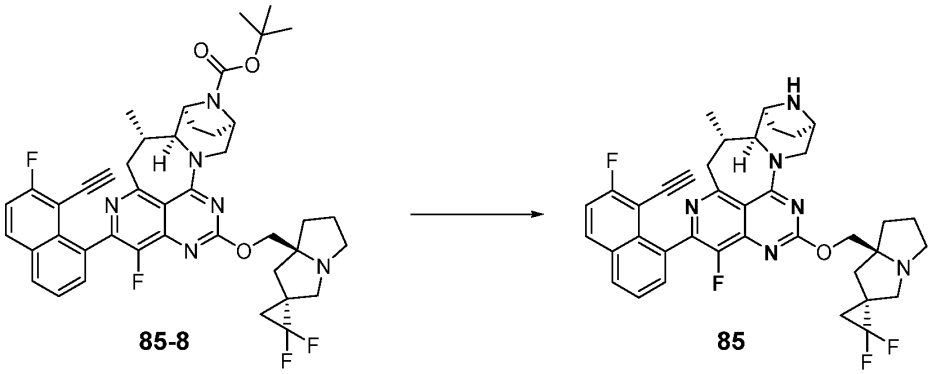
Example 84, Compound 84: (5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



84

[1023] Compound **84** was synthesized in a manner similar to Compound **76** using **Intermediate 84-5** instead of **Intermediate 76-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.21 – 8.12 (m, 2H), 7.74 – 7.58 (m, 2H), 7.48 (dd, J = 9.0 Hz, 1H), 5.61 (dd, J = 51.8, 3.8 Hz, 1H), 5.20 (dd, J = 14.8, 2.2 Hz, 1H), 4.83 – 4.64 (m, 2H), 4.36 (dd, J = 20.5, 15.2 Hz, 2H), 4.13 – 3.83 (m, 4H), 3.55 – 3.40 (m, 2H), 3.29 – 1.92 (m, 14H), 1.36 – 1.18 (m, 3H). LCMS: 625.0 $[M+H]^+$

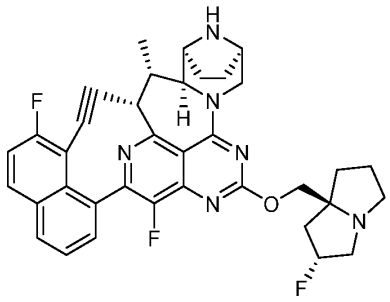
Example 85, Compound 85: (5S,5aS,6S,9R)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



85-8 **85**

[1024] Compound **85** was prepared in a manner analogous to Compound **36** using Intermediate **85-8** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 (ddd, J = 9.1, 5.8, 3.3 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.22 (dd, J = 15.7, 2.7 Hz, 1H), 5.74 (td, J = 13.6, 3.0 Hz, 1H), 4.78 (qd, J = 12.4, 3.2 Hz, 2H), 4.40 (dd, J = 12.1, 4.6 Hz, 1H), 4.35 (s, 1H), 4.20 – 4.10 (m, 1H), 4.04 (dt, J = 12.5, 4.9 Hz, 1H), 3.86 (dt, J = 11.3, 5.6 Hz, 1H), 3.60 – 3.36 (m, 3H), 3.24 (dt, J = 12.9, 7.3 Hz, 1H), 2.66 (dd, J = 14.0, 6.1 Hz, 1H), 2.57 – 2.37 (m, 2H), 2.35 – 1.98 (m, 4H), 1.85 – 1.76 (m, 2H). LCMS: 669.4.

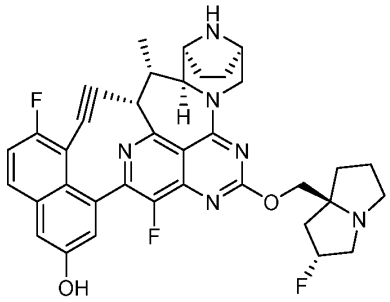
Example 86, Compound 86: (4R,5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5-dimethyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



86

[1025] Compound **86** was synthesized in a manner similar to Compound **76** using **Intermediate 86-12** instead of Intermediate **76-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.15 (ddd, *J* = 8.5, 5.1, 2.8 Hz, 2H), 7.74 – 7.52 (m, 2H), 7.47 (td, *J* = 8.9, 1.8 Hz, 1H), 5.60 (d, *J* = 51.7 Hz, 1H), 5.20 (d, *J* = 14.4 Hz, 1H), 4.82 – 4.63 (m, 2H), 4.38 (d, *J* = 17.8 Hz, 2H), 4.10 – 3.82 (m, 4H), 3.60 – 3.44 (m, 1H), 3.18 – 3.07 (m, 1H), 3.01 – 1.91 (m, 10H), 1.42 – 1.30 (m, 3H), 1.12 – 0.99 (m, 3H). LCMS: 639.0 $[M + H]^+$

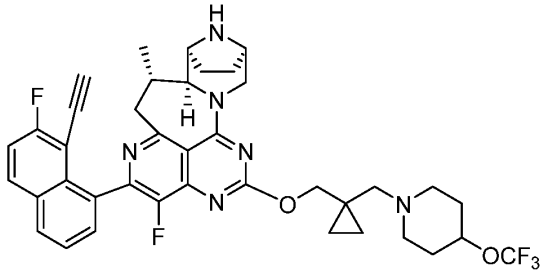
Example 87, Compound 87: 5-ethynyl-6-fluoro-4-((4R,5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5-dimethyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



87

[1026] Compound **87** was synthesized in a manner similar to Compound **75** using **Intermediate 87-2** instead of **Intermediate 75-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.97 – 7.89 (m, 1H), 7.44 – 7.25 (m, 3H), 5.63 (d, J = 51.6 Hz, 1H), 5.20 (dd, J = 115.2, 13.0 Hz, 2H), 4.46 (s, 2H), 4.15 – 3.43 (m, 5H), 3.28 – 2.15 (m, 14H), 1.44 – 1.37 (m, 3H), 1.11 (dd, J = 8.5, 5.9 Hz, 3H). LCMS: 639.0 $[M + H]^+$.

Example 88, Compound 88: (5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-12-((1-((4-(trifluoromethoxy)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene

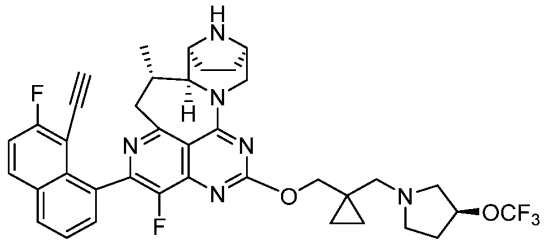


88

[1027] Compound **88** was synthesized in a manner similar to Compound **67** using intermediate **84-3** instead of intermediate **63-7** and using 4-(trifluoromethoxy)piperidine hydrochloride instead of (*R*)-3-fluoropiperidine. 1H NMR (400 MHz, Methanol-d4) δ 8.16 (ddd, J = 9.1, 6.5, 3.1 Hz, 2H), 7.75 – 7.66 (m, 2H), 7.48 (t, J = 8.9 Hz, 1H), 5.14 (dd, J = 14.6, 2.3 Hz, 1H), 4.84 (m, 1H), 4.61 (dd, J = 44.2, 13.1 Hz, 1H), 4.51 – 4.23 (m, 2H), 3.83 (dd, J = 46.1, 10.2 Hz, 4H), 3.57 – 3.38 (m, 3H), 3.26 (d, J = 12.7

Hz, 2H), 3.11 (dt, J = 12.4, 6.4 Hz, 2H), 2.87 (dd, J = 25.6, 13.6 Hz, 1H), 2.50 – 1.90 (m, 9H), 1.27 (dd, J = 13.2, 6.5 Hz, 3H), 0.96 (d, J = 38.5 Hz, 4H). LCMS: 719.4.

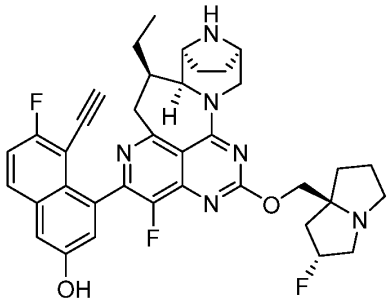
Example 89, Compound 89: (5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-12-((1-(((S)-3-(trifluoromethoxy)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



89

[1028] Compound **89** was synthesized in a manner similar to Compound **67** using intermediate **84-3** instead of intermediate **63-7** and using (*S*)-3-(trifluoromethoxy)pyrrolidine hydrochloride instead of (*R*)-3-fluoropiperidine. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.11 (m, 2H), 7.75 – 7.65 (m, 2H), 7.48 (t, J = 8.9 Hz, 1H), 5.31 – 5.08 (m, 2H), 4.62 – 4.19 (m, 5H), 3.88 (d, J = 14.3 Hz, 2H), 3.78 – 3.53 (m, 3H), 3.42 (dd, J = 24.9, 11.4 Hz, 4H), 3.10 (dt, J = 13.0, 6.7 Hz, 1H), 2.86 (dd, J = 22.4, 13.5 Hz, 1H), 2.41 (m, 1H), 2.31 – 1.92 (m, 5H), 1.26 (dd, J = 14.7, 6.5 Hz, 3H), 0.96 (d, J = 32.6 Hz, 4H). LCMS: 705.3.

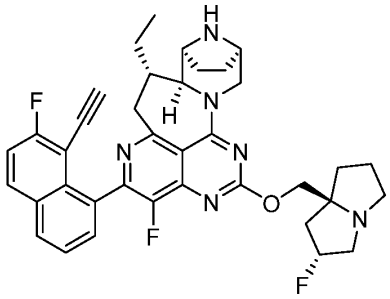
Example 90, Compound 90: 4-((5R,5aS,6S,9R)-5-ethyl-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



90

[1029] Compound **90** was synthesized in a manner similar to Compound **13** using **Intermediate 90-10** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (ddd, J = 8.9, 5.7, 3.1 Hz, 1H), 7.44 – 7.30 (m, 2H), 7.21 (dd, J = 53.6, 2.5 Hz, 1H), 5.59 (d, J = 51.7 Hz, 1H), 5.45 (d, J = 14.4 Hz, 1H), 4.95 – 4.87 (m, 3H), 4.83 – 4.63 (m, 2H), 4.42 – 4.17 (m, 1H), 4.11 – 3.58 (m, 5H), 3.55 – 3.41 (m, 1H), 2.90 – 1.40 (m, 13H), 1.14 (t, J = 7.1 Hz, 3H), 1.03 – 0.72 (m, 1H). LCMS: 655.0.

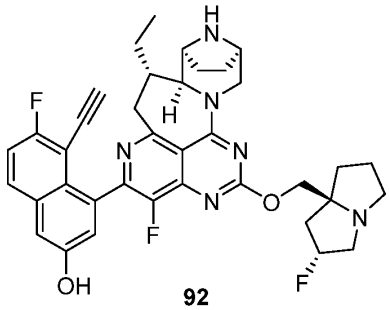
Example 91, Compound 91: (5*S*,5a*S*,6*S*,9*R*)-5-ethyl-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



91

[1030] Compound **91** was synthesized in a manner similar to Compound **13** using **Intermediate 91-3** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.26 – 8.05 (m, 2H), 7.73 – 7.53 (m, 2H), 7.46 (t, J = 8.9 Hz, 1H), 5.58 (d, J = 51.8 Hz, 1H), 5.17 (d, J = 14.4 Hz, 1H), 4.96 – 4.87 (m, 2H), 4.84 – 4.79 (m, 1H), 4.77 (dd, J = 12.7, 6.6 Hz, 1H), 4.65 (d, J = 12.4 Hz, 1H), 4.38 (s, 2H), 4.12 – 3.79 (m, 4H), 3.79 – 3.63 (m, 1H), 3.59 – 3.39 (m, 1H), 3.19 – 3.04 (m, 1H), 2.93 – 1.24 (m, 12H), 1.21 – 1.08 (m, 3H). LCMS: 638.9.

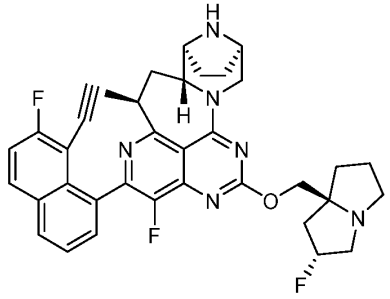
Example 92, Compound 92: 4-((5*S*,5a*S*,6*S*,9*R*)-5-ethyl-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



92

[1031] Compound **92** was synthesized in a manner similar to Compound **13** using **Intermediate 92-4** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (dd, J = 9.1, 5.7 Hz, 1H), 7.42 – 7.28 (m, 2H), 7.18 (dd, J = 39.3, 2.6 Hz, 1H), 5.58 (d, J = 51.9 Hz, 1H), 5.17 (d, J = 14.5 Hz, 1H), 4.96 – 4.87 (m, 2H), 4.83 – 4.71 (m, 1H), 4.66 (d, J = 12.3 Hz, 1H), 4.38 (s, 2H), 4.09 – 3.76 (m, 5H), 3.71 – 3.38 (m, 2H), 3.12 (dd, J = 21.8, 13.5 Hz, 1H), 2.91 – 1.24 (m, 14H), 1.13 (q, J = 7.2 Hz, 3H). LCMS: 654.8.

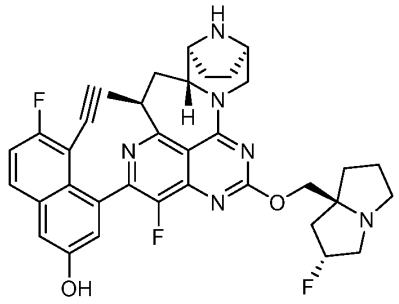
Example 93, Compound 93: (4S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



93

[1032] Compound **93** was synthesized in a manner similar to Compound **76** using **Intermediate 93-8** instead of **Intermediate 76-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.16 (dd, J = 8.8, 6.3 Hz, 2H), 7.74 – 7.63 (m, 2H), 7.53 – 7.44 (m, 1H), 5.83 – 5.75 (m, 1H), 5.59 (d, J = 51.9 Hz, 1H), 4.79 – 4.65 (m, 2H), 4.49 (dd, J = 11.6, 6.0 Hz, 1H), 4.37 (s, 1H), 4.17 – 3.44 (m, 9H), 2.79 – 2.03 (m, 10H), 1.56 – 1.39 (m, 3H). LCMS: 625.0 $[M + H]^+$

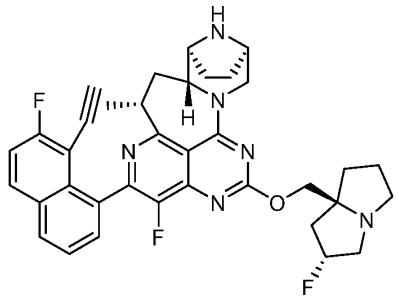
Example 94, Compound 94: 5-ethynyl-6-fluoro-4-((4S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



94

[1033] Compound **94** was synthesized in a manner similar to Compound **75** using **Intermediate 94-2** instead of **Intermediate 75-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 – 7.86 (m, 1H), 7.41 – 7.32 (m, 2H), 7.27 – 7.19 (m, 1H), 5.79 (dd, J = 14.7, 3.0 Hz, 1H), 5.59 (d, J = 51.7 Hz, 1H), 4.80 – 4.66 (m, 2H), 4.54 – 4.43 (m, 1H), 4.37 (s, 1H), 4.17 – 3.43 (m, 9H), 2.78 – 1.98 (m, 15H), 1.52 – 1.40 (m, 3H). LCMS: 641.0 $[M + H]^+$

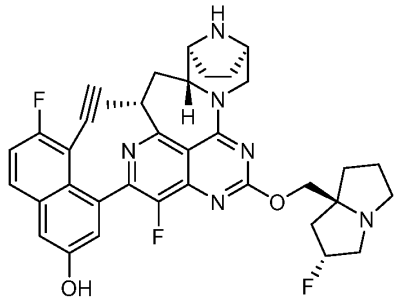
Example 95, Compound 95: (4R,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



95

[1034] Compound **95** was synthesized in a manner similar to Compound **76** using **Intermediate 95-5** instead of **Intermediate 76-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.14 (dd, J = 8.5, 5.8 Hz, 2H), 7.67 (t, J = 6.4 Hz, 1H), 7.46 (td, J = 8.9, 3.2 Hz, 1H), 5.84 – 5.74 (m, 1H), 5.59 (d, J = 52.2 Hz, 1H), 4.79 – 4.63 (m, 2H), 4.48 (dd, J = 12.8, 4.7 Hz, 1H), 4.35 (s, 1H), 4.18 – 3.84 (m, 5H), 3.58 – 3.45 (m, 3H), 2.80 – 1.87 (m, 12H), 1.51 (t, J = 6.8 Hz, 3H). LCMS: 625.0 $[M + H]^+$

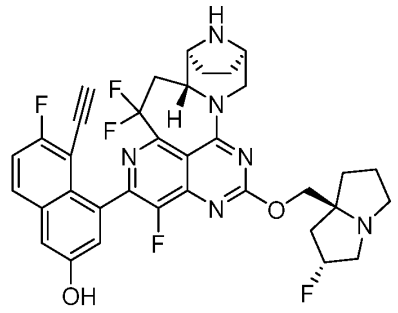
Example 96, Compound 96: 5-ethynyl-6-fluoro-4-((4R,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



96

[1035] Compound **96** was synthesized in a manner similar to Compound **75** using **Intermediate 96-2** instead of **Intermediate 75-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.92 – 7.86 (m, 1H), 7.40 – 7.29 (m, 2H), 7.26 – 7.19 (m, 1H), 5.82 – 5.73 (m, 1H), 5.59 (d, J = 51.7 Hz, 1H), 4.78 – 4.65 (m, 1H), 4.48 (d, J = 9.5 Hz, 1H), 4.34 (s, 1H), 4.19 – 3.83 (m, 5H), 3.58 – 3.43 (m, 2H), 2.79 – 1.86 (m, 15H), 1.52 (t, J = 7.1 Hz, 3H). LCMS: 641.0 $[M + H]^+$

Example 97, Compound 97: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1,4,4-trifluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol

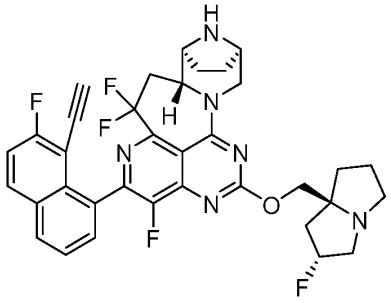


97

[1036] Compound **97** was synthesized in a manner similar to Compound **13** using **Intermediate 97-7** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.95 – 7.81 (m, 0H), 7.45 – 7.32 (m, 2H), 7.24 (dd, J = 33.6, 2.6 Hz, 1H), 5.58 (dd, J = 32.8, 17.5 Hz, 2H), 4.75 (d, J = 2.3 Hz, 2H), 4.64 – 4.51 (m, 1H), 4.41 (s, 1H), 4.28 (d, J = 6.2 Hz, 1H), 4.11 – 3.81 (m, 4H),

3.69 – 3.37 (m, 3H), 3.16 – 2.83 (m, 3H), 2.70 – 2.54 (m, 2H), 2.53 – 2.42 (m, 1H), 2.36 (dt, *J* = 12.1, 6.9 Hz, 3H), 2.22 (d, *J* = 14.8 Hz, 5H). LCMS: 662.8.

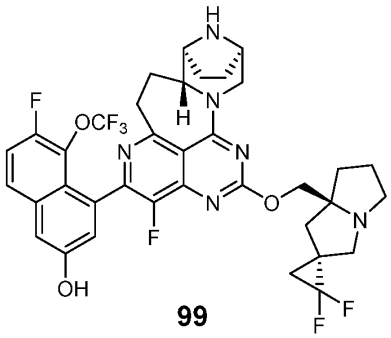
Example 98, Compound 98: (5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1,4,4-trifluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



98

[1037] Compound **98** was synthesized in a manner similar to Compound **13** using **Intermediate 98-2** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.06 (m, 2H), 7.79 – 7.57 (m, 2H), 7.47 (td, *J* = 8.9, 3.4 Hz, 1H), 5.71 – 5.45 (m, 2H), 4.81 – 4.63 (m, 2H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.41 (s, 1H), 4.27 (s, 1H), 4.11 – 3.83 (m, 3H), 3.63 – 3.44 (m, 2H), 3.19 – 2.02 (m, 14H). LCMS: 646.8.

Example 99, Compound 99: 4-((5aR,6S,9R)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalen-2-yl)-6-fluoro-5-(trifluoromethoxy)naphthalen-2-ol

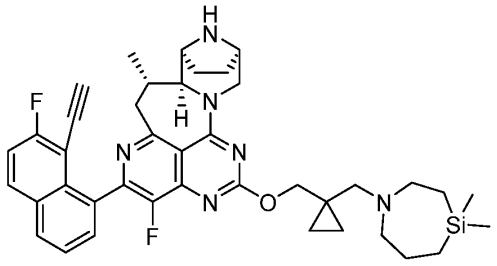


99

[1038] Compound **99** was synthesized in a manner similar to Compound **75** using **Intermediate 99-4** instead of **Intermediate 75-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.97 (dd, *J* = 9.5, 4.9

Hz, 1H), 7.63 – 7.21 (m, 3H), 5.85 (d, *J* = 14.0 Hz, 1H), 4.66 (s, 1H), 4.44 (s, 1H), 4.25 (s, 1H), 4.10 – 4.00 (m, 1H), 3.97 – 3.86 (m, 1H), 3.79 – 3.45 (m, 4H), 3.28 – 3.15 (m, 2H), 2.80 – 2.47 (m, 2H), 2.40 – 2.07 (m, 2H), 1.93 – 1.79 (m, 2H). LCMS: 731.0 $[M + H]^+$.

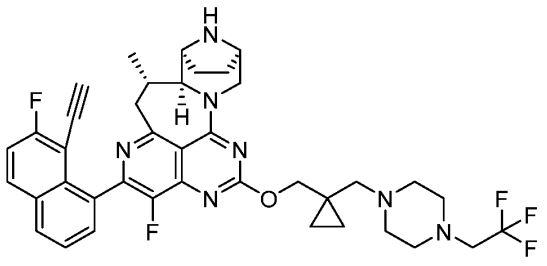
Example 100, Compound 100: (5S,5aS,6S,9R)-12-((1-((4,4-dimethyl-1,4-azasilepan-1-yl)methyl)cyclopropyl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



100

[1039] Compound **100** was synthesized in a manner similar to Compound **78.** ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.26 – 8.11 (m, 2H), 7.77 – 7.56 (m, 2H), 7.55 – 7.44 (m, 1H), 5.14 (dd, *J* = 14.4, 2.2 Hz, 1H), 4.76 – 4.27 (m, 4H), 3.93 – 2.72 (m, 9H), 2.32 – 1.83 (m, 7H), 1.52 – 0.78 (m, 13H), 0.22 – -0.03 (m, 6H). LCMS: 693.1.

Example 101, Compound 101: (5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-12-((1-((4-(2,2,2-trifluoroethyl)piperazin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene

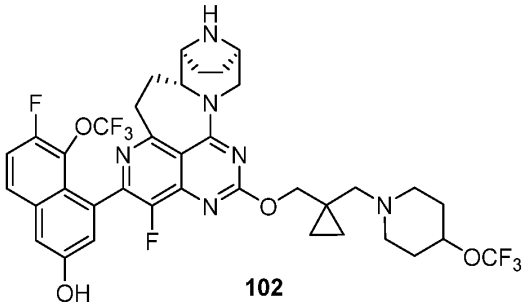


101

[1040] Compound **101** was synthesized in a manner similar to Compound **100** using 1-(2,2,2-trifluoroethyl)piperazine instead of 4,4-dimethyl-1,4-azasilepane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.22 – 8.12 (m, 2H), 7.76 – 7.55 (m, 2H), 7.56 – 7.39 (m, 1H), 5.13 (d, *J* = 14.5 Hz, 1H),

4.71 – 4.24 (m, 4H), 3.96 – 3.72 (m, 3H), 3.58 – 2.66 (m, 12H), 2.35 – 1.90 (m, 6H), 1.42 – 0.78 (m, 8H). LCMS: 718.2.

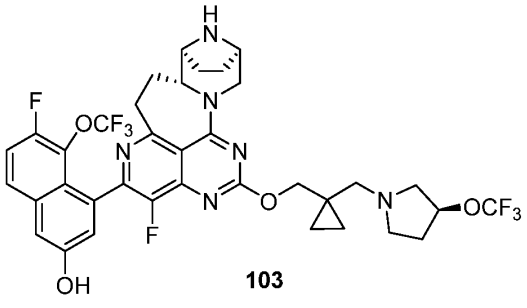
Example 102, Compound 102: 6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((1-((4-(trifluoromethoxy)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-(trifluoromethoxy)naphthalen-2-ol



102

[1041] Compound **102** was synthesized in a manner similar to Compound **106** using intermediate **102-1** instead of intermediate **106-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (ddd, J = 9.3, 5.1, 2.3 Hz, 1H), 7.47 (td, J = 9.6, 2.1 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.31 (dd, J = 6.9, 2.5 Hz, 1H), 5.67 (dd, J = 29.8, 14.7 Hz, 1H), 4.68 – 4.26 (m, 5H), 4.16 – 4.08 (m, 1H), 4.08 – 3.68 (m, 3H), 3.57 – 3.33 (m, 5H), 3.16 (s, 1H), 2.58 – 1.99 (m, 9H), 1.94 – 1.74 (m, 1H), 1.01 (s, 2H), 0.89 (s, 2H). LCMS: 781.3.

Example 103, Compound 103: 6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((1-(((S)-3-(trifluoromethoxy)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-(trifluoromethoxy)naphthalen-2-ol

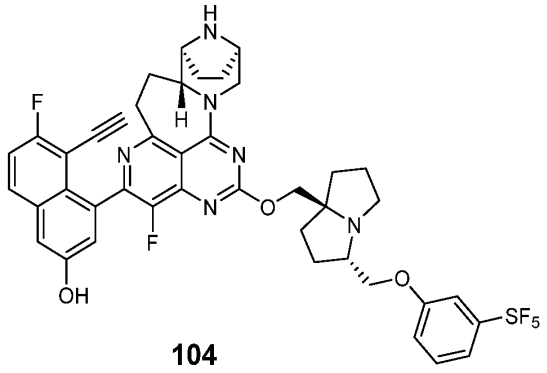


103

[1042] Compound **103** was synthesized in a manner similar to Compound **102** using intermediate **103-1** instead of intermediate **102-1**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (ddd, J = 8.7, 5.1,

3.1 Hz, 1H), 7.47 (td, *J* = 9.6, 2.5 Hz, 1H), 7.40 (dd, *J* = 2.6, 1.4 Hz, 1H), 7.31 (dd, *J* = 5.9, 2.5 Hz, 1H), 5.69 (ddd, *J* = 25.1, 14.7, 3.1 Hz, 1H), 5.25 (s, 1H), 4.57 – 4.24 (m, 4H), 4.23 – 4.04 (m, 1H), 3.65 – 3.32 (m, 7H), 2.73 – 2.24 (m, 3H), 2.17 – 1.75 (m, 4H), 1.05 – 0.83 (m, 4H). LCMS: 767.3.

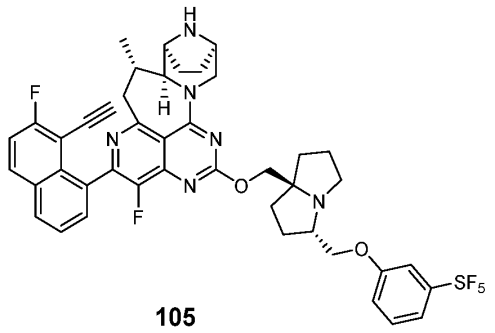
Example 104, Compound 104: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-(((3S,7aS)-3-((3-(pentafluoro- λ6-sulfaneyl)phenoxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



104

[1043] Compound **104** was synthesized in a manner similar to Compound **122** using intermediate **104-2** instead of ((1*S*,7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.89 (td, *J* = 9.0, 5.7 Hz, 1H), 7.51 – 7.41 (m, 3H), 7.41 – 7.28 (m, 2H), 7.27 – 7.11 (m, 2H), 5.83 – 5.65 (m, 1H), 4.86 – 4.64 (m, 2H), 4.59 – 4.29 (m, 3H), 4.16 (s, 1H), 3.69 – 3.06 (m, 6H), 2.61 – 0.36 (m, 16H). LCMS: 840.8.

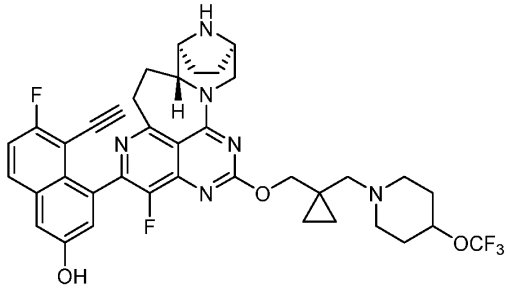
Example 105, Compound 105: (5*S*,5a*S*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-12-(((3*S*,7a*S*)-3-((3-(pentafluoro- λ^6-sulfaneyl)phenoxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



105

[1044] Compound **105** was synthesized in a manner similar to Compound **83** using intermediate **104-2** instead of intermediate **63-4** and using 0.1% trifluoroacetic acid in acetonitrile/water instead of 0.1% acetic acid in acetonitrile/water. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.22 – 8.10 (m, 2H), 7.76 – 7.18 (m, 7H), 5.21 (d, J = 14.7 Hz, 1H), 4.88 (s, 6H), 3.96 – 3.84 (m, 1H), 3.66 – 1.87 (m, 20H), 1.42 – 1.16 (m, 3H). LCMS: 838.9.

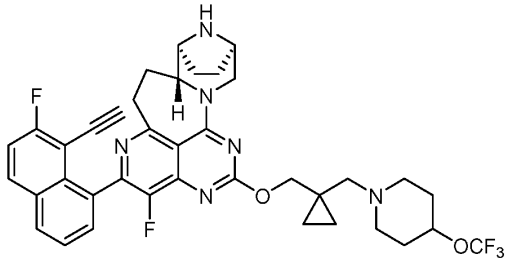
Example 106, Compound 106: 5-ethynyl-6-fluoro-4-((5a*R*,6*S*,9*R*)-1-fluoro-12-((1-((4-(trifluoromethoxy)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol



106

[1045] Compound **106** was synthesized in a manner similar to Compound **122** using intermediate **106-2** instead of ((1*S*,7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 (ddd, *J* = 9.0, 5.7, 3.0 Hz, 1H), 7.43 – 7.30 (m, 2H), 7.22 (dd, *J* = 16.0, 2.6 Hz, 1H), 5.80 – 5.55 (m, 1H), 5.06 – 4.24 (m, 5H), 4.15 (s, 1H), 4.08 – 3.72 (m, 2H), 3.64 – 3.04 (m, 6H), 2.59 – 1.91 (m, 12H), 1.10 – 0.83 (m, 4H). LCMS: 721.0.

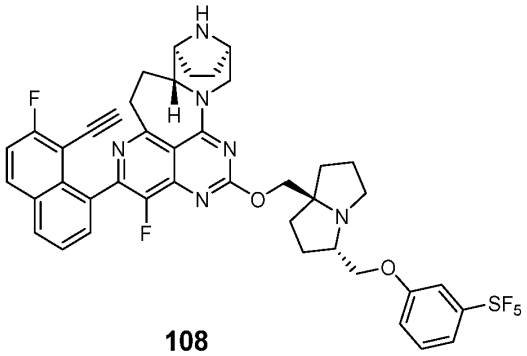
Example 107, Compound 107: (5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((1-((4-(trifluoromethoxy)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



107

[1046] Compound **107** was synthesized in a manner similar to Compound **113** using intermediate **106-2** instead of ((6'*R*,7a'*R*)-6'-fluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.10 (m, 2H), 7.74 – 7.60 (m, 2H), 7.54 – 7.41 (m, 1H), 5.78 – 5.57 (m, 1H), 4.94 – 4.27 (m, 5H), 4.15 (s, 1H), 4.08 – 3.71 (m, 2H), 3.64 – 3.06 (m, 6H), 2.60 – 1.26 (m, 12H), 1.11 – 0.81 (m, 4H). LCMS: 705.0.

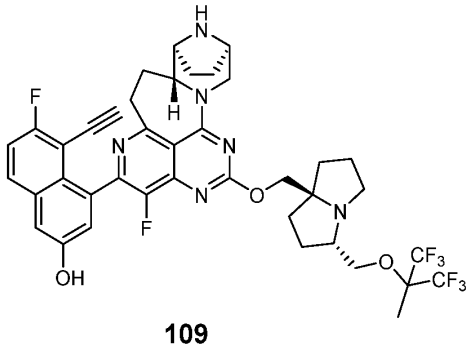
Example 108, Compound 108: (5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((3*S*,7a*S*)-3-((3-(pentafluoro-λ^6-sulfaneyl)phenoxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



108

[1047] Compound **108** was synthesized in a manner similar to Compound **113** using intermediate **104-2** instead of ((6'*R*,7a'*R*)-6'-fluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.07 (m, 2H), 7.75 – 7.57 (m, 2H), 7.57 – 7.33 (m, 4H), 7.27 – 7.10 (m, 1H), 5.83 – 5.65 (m, 1H), 4.99 – 4.65 (m, 2H), 4.58 – 4.30 (m, 3H), 4.16 (s, 1H), 3.67 – 3.10 (m, 6H), 2.64 – 1.89 (m, 16H). LCMS: 824.9.

Example 109, Compound 109: 4-((5a*R*,6*S*,9*R*)-12-(((3*S*,7a*S*)-3-(*tert*-butoxymethyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol

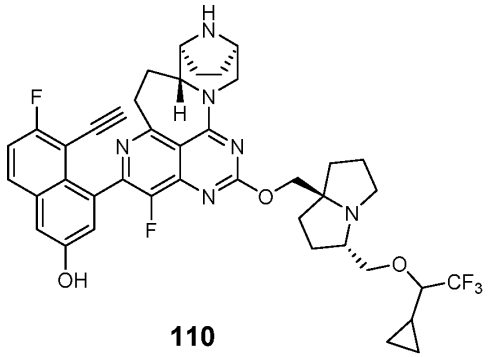


109

[1048] Compound **109** was synthesized in a manner similar to Compound **122** using intermediate **109-2** instead of ((1*S*,7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-

7a'(5'*H*)-yl)methanol. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 – 7.85 (m, 1H), 7.43 – 7.31 (m, 2H), 7.29 – 7.19 (m, 1H), 5.73 (ddd, *J* = 14.5, 11.3, 3.0 Hz, 1H), 4.81 – 4.62 (m, 2H), 4.48 – 4.19 (m, 3H), 4.19 – 4.06 (m, 2H), 3.65 – 3.18 (m, 5H), 2.59 – 1.94 (m, 16H), 1.83 – 1.68 (m, 3H). LCMS: 802.9.

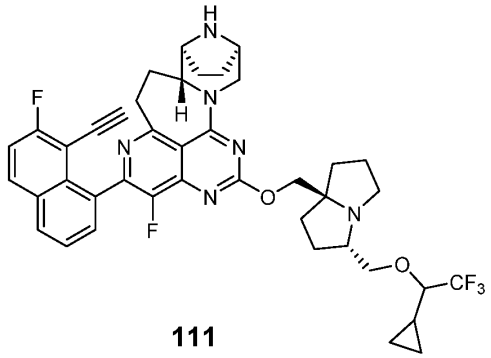
Example 110, Compound 110: 4-((5a*R*,6*S*,9*R*)-12-(((3*S*,7a*S*)-3-((1-cyclopropyl-2,2,2-trifluoroethoxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



110

[1049] Compound **110** was synthesized in a manner similar to Compound **109** using 1-cyclopropyl-2,2,2-trifluoro-ethanol instead of 1,1,1,3,3,3-hexafluoro-2-methyl-propan-2-ol. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 – 7.85 (m, 1H), 7.45 – 7.31 (m, 2H), 7.26 – 7.16 (m, 1H), 5.74 (dd, *J* = 14.2, 10.0 Hz, 1H), 4.82 – 4.59 (m, 2H), 4.46 – 3.89 (m, 6H), 3.71 – 3.05 (m, 5H), 2.65 – 1.83 (m, 16H), 1.08 – 0.34 (m, 5H). LCMS: 760.9.

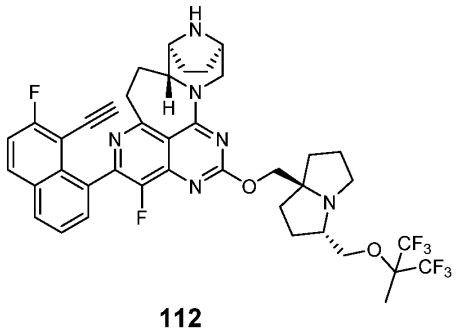
Example 111, Compound 111: (5a*R*,6*S*,9*R*)-12-(((3*S*,7a*S*)-3-((1-cyclopropyl-2,2,2-trifluoroethoxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



111

[1050] Compound **111** was synthesized in a manner similar to Compound **110** using intermediate **113-1** instead of intermediate **122-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.22 – 8.08 (m, 2H), 7.75 – 7.61 (m, 2H), 7.55 – 7.42 (m, 1H), 5.81 – 5.67 (m, 1H), 4.79 – 4.59 (m, 2H), 4.47 – 3.90 (m, 6H), 3.72 – 3.13 (m, 5H), 2.65 – 1.88 (m, 16iH), 1.08 – 0.32 (m, 5H). LCMS: 744.9.

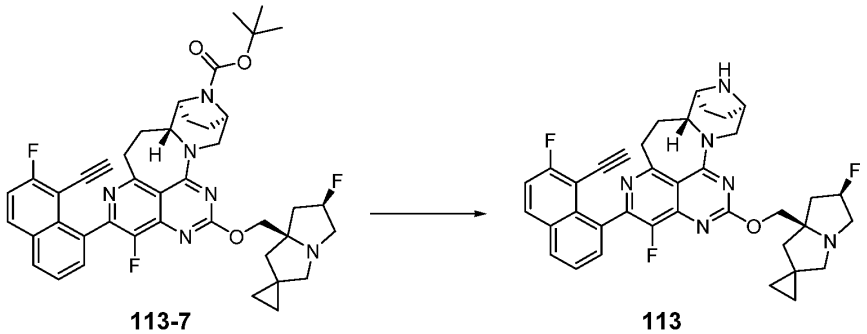
Example 112, Compound 112: (5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((3*S*,7a*S*)-3-(((1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



112

[1051] Compound **112** was synthesized in a manner similar to Compound **109** using intermediate **113-1** instead of intermediate **122-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.23 – 8.03 (m, 2H), 7.74 – 7.60 (m, 2H), 7.54 – 7.44 (m, 1H), 5.80 – 5.65 (m, 1H), 4.77 – 4.63 (m, 2H), 4.48 – 4.06 (m, 5H), 3.67 – 3.24 (m, 5H), 2.62 – 1.93 (m, 16H), 1.82 – 1.66 (m, 3H). LCMS: 786.9.

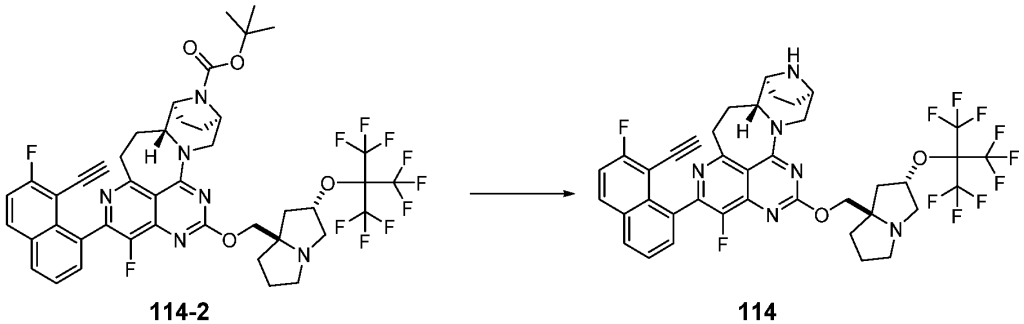
Example 113, Compound 113: (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((6'R,7a'R)-6'-fluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



113-7 113

[1052] Compound **113** was prepared in a manner analogous to Compound **36** using Intermediate **113-7** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.15 (ddd, J = 8.5, 5.7, 2.6 Hz, 2H), 7.74 – 7.62 (m, 2H), 7.48 (td, J = 9.0, 5.5 Hz, 1H), 5.73 (ddd, J = 14.6, 11.3, 3.0 Hz, 1H), 5.60 (d, J = 51.3 Hz, 1H), 4.93 – 4.70 (m, 2H), 4.41 (dd, J = 12.3, 4.6 Hz, 2H), 4.36 (s, 1H), 4.16 (s, 1H), 4.09 (d, J = 13.8 Hz, 1H), 4.01 (dd, J = 11.7, 2.1 Hz, 1H), 3.80 – 3.35 (m, 5H), 3.20 – 3.14 (m, 1H), 2.89 – 2.37 (m, 4H), 2.08 (dd, J = 15.2, 7.0 Hz, 4H), 1.90 (d, J = 13.4 Hz, 1H), 0.95 (t, J = 7.6 Hz, 2H), 0.77 (dd, J = 8.8, 5.8 Hz, 2H). LCMS: 637.3.

Example 114, Compound 114: (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*trans*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene

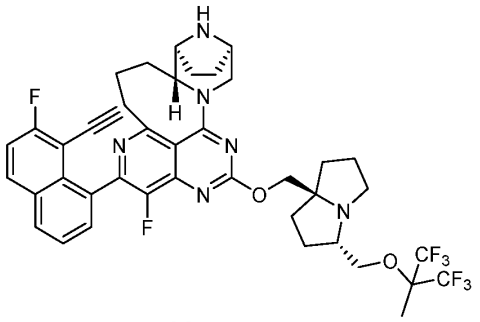


114-2 114

[1053] Compound **114** was prepared in a manner analogous to Compound **36** using Intermediate **114-2** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.15 (ddd, J = 8.9, 5.8, 2.5 Hz, 2H), 7.73 – 7.61 (m, 2H), 7.48 (td, J = 8.9, 5.0 Hz, 1H), 5.79 – 5.64 (m, 1H), 5.45 (s, 1H), 4.72 (s,

2H), 4.40 (d, J = 10.6 Hz, 1H), 4.34 (s, 1H), 4.21 – 4.12 (m, 2H), 3.97 – 3.88 (m, 1H), 3.78 (d, J = 13.9 Hz, 1H), 3.59 – 3.35 (m, 5H), 2.90 (dt, J = 15.1, 5.0 Hz, 1H), 2.57 – 1.98 (m, 12H). LCMS: 827.3.

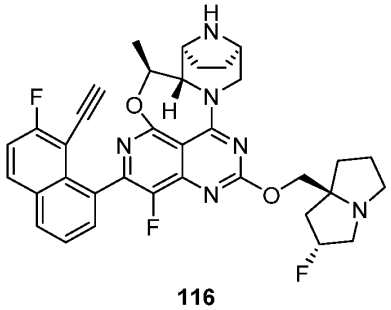
Example 115, Compound 115: (6a*R*,7*S*,10*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((3*S*,7a*S*)-3-(((1,1,1,3,3,3-hexafluoro-2-methylpropan-2-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene



115

[1054] Compound **115** was synthesized in a manner similar to Compound **109** using intermediate **115-3** instead of intermediate **122-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.23 – 8.10 (m, 2H), 7.75 – 7.61 (m, 2H), 7.54 – 7.43 (m, 1H), 5.47 – 5.36 (m, 1H), 4.80 – 4.65 (m, 2H), 4.42 – 3.94 (m, 5H), 3.78 – 2.87 (m, 7H), 2.52 – 1.15 (m, 19H). LCMS: 800.9.

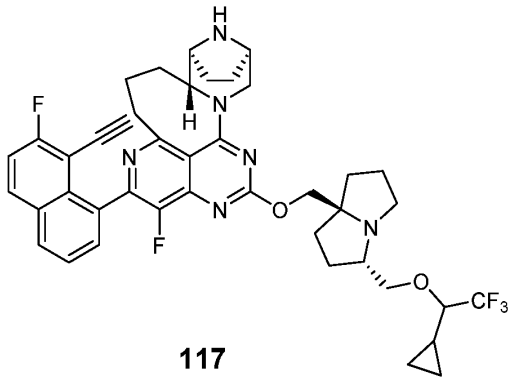
Example 116, Compound 116: (5*S*,5a*S*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



116

[1055] Compound **116** was synthesized in a manner similar to Compound **13** using **Intermediate 116-3** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.19 – 8.06 (m, 2H), 7.73 – 7.55 (m, 2H), 7.46 (q, J = 9.0 Hz, 1H), 5.69 – 5.47 (m, 2H), 4.79 – 4.62 (m, 3H), 4.44 – 4.38 (m, 1H), 4.36 (s, 1H), 4.27 (t, J = 6.4 Hz, 1H), 4.09 – 3.84 (m, 3H), 3.76 – 3.38 (m, 3H), 2.80 – 2.54 (m, 2H), 2.52 – 2.41 (m, 1H), 2.36 (dt, J = 12.1, 6.1 Hz, 3H), 2.25 – 2.02 (m, 2H), 1.63 (dd, J = 6.4, 5.4 Hz, 3H). LCMS: 627.0.

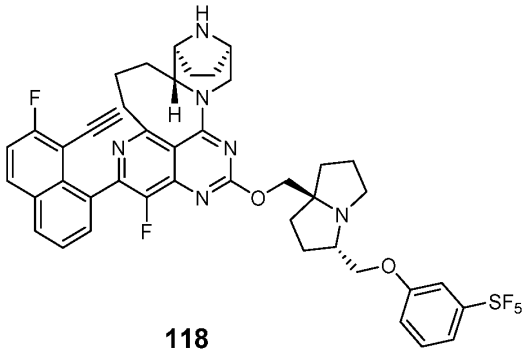
Example 117, Compound 117: (6a*R*,7*S*,10*R*)-13-(((3*S*,7a*S*)-3-((1-cyclopropyl-2,2,2-trifluoroethoxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene



117

[1056] Compound **117** was synthesized in a manner similar to Compound **115** using 1-cyclopropyl-2,2,2-trifluoro-ethanol instead of 1,1,1,3,3,3-hexafluoro-2-methyl-propan-2-ol. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.21 – 8.10 (m, 2H), 7.73 – 7.60 (m, 2H), 7.52 – 7.45 (m, 1H), 5.49 – 5.35 (m, 1H), 4.83 – 4.62 (m, 2H), 4.52 – 3.78 (m, 6H), 3.77 – 2.89 (m, 7H), 2.53 – 1.63 (m, 16H), 1.14 – 0.87 (m, 1H), 0.76 – 0.36 (m, 4H). LCMS: 758.9.

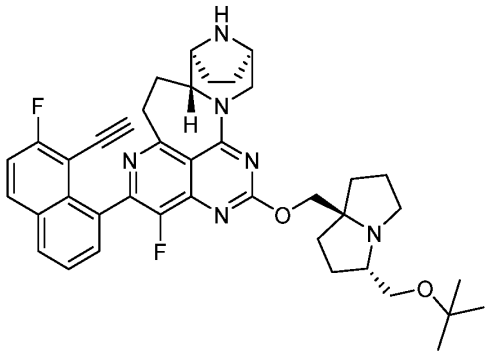
Example 118, Compound 118: (6a*R*,7*S*,10*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((3*S*,7a*S*)-3-((3-(pentafluoro-λ^6-sulfaneyl)phenoxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene



118

[1057] Compound **118** was synthesized in a manner similar to Compound **115** using intermediate **104-2** instead of intermediate **109-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.23 – 8.07 (m, 2H), 7.74 – 7.60 (m, 2H), 7.56 – 7.15 (m, 5H), 5.57 – 5.31 (m, 1H), 4.98 – 4.02 (m, 7H), 3.80 – 3.22 (m, 5H), 3.14 – 2.85 (m, 2H), 2.64 – 1.61 (m, 16H). LCMS: 838.9.

Example 119, Compound 119: (5a*R*,6*S*,9*R*)-12-(((3*S*,7a*S*)-3-(*tert*-butoxymethyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene

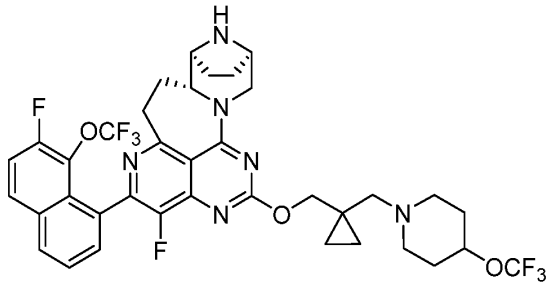


119

[1058] Compound **119** was synthesized in a manner similar to Compound **115** using intermediate **119-4** instead of intermediate **109-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.21 – 8.11 (m, 2H), 7.74 – 7.61 (m, 2H), 7.52 – 7.44 (m, 1H), 5.83 – 5.67 (m, 1H), 4.80 – 4.58 (m, 2H), 4.45 – 4.32

(m, 2H), 4.24 – 3.99 (m, 2H), 3.83 – 3.72 (m, 6H), 3.71 – 3.22 (m, 71H), 2.60 – 1.92 (m, 16H), 1.26 – 1.10 (m, 9H). LCMS: 679.0.

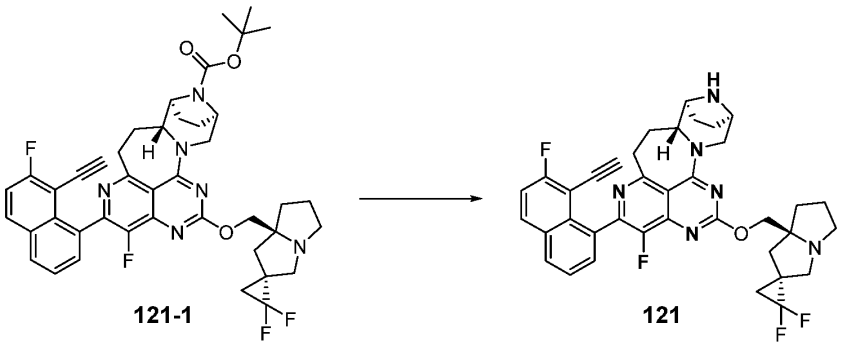
Example 120, Compound 120: (5aR,6S,9R)-1-fluoro-2-(7-fluoro-8-(trifluoromethoxy)naphthalen-1-yl)-12-((1-((4-(trifluoromethoxy)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



120

[1059] Compound **120** was synthesized in a manner similar to Compound **102** using intermediate **120-1** instead of intermediate **102-1**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.25 – 8.12 (m, 2H), 7.81 – 7.72 (m, 2H), 7.68 – 7.57 (m, 1H), 5.69 (dd, J = 26.8, 14.7 Hz, 1H), 4.70 – 4.29 (m, 4H), 4.16 (d, J = 6.4 Hz, 1H), 4.04 – 3.76 (m, 2H), 3.60 – 3.34 (m, 6H), 3.18 (s, 1H), 2.61 – 1.99 (m, 8H), 1.97 – 1.78 (m, 1H), 1.03 (s, 2H), 0.91 (s, 2H). LCMS: 765.4.

Example 121, Compound 121: (5aR,6S,9R)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene

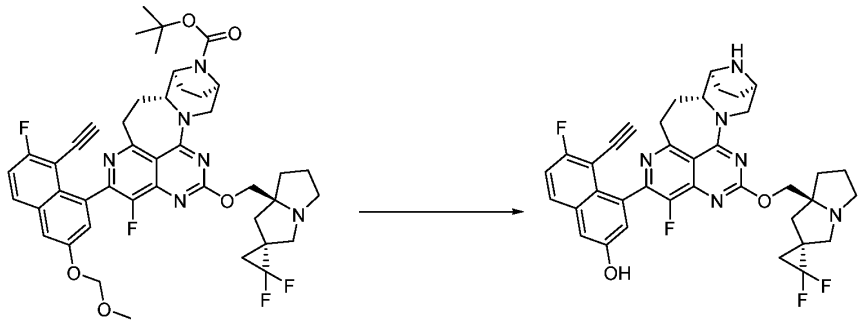


121-1 121

[1060] Compound **121** was prepared in a manner analogous to Compound **36** using Intermediate **121-1** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.19 – 8.11 (m, 2H), 7.73 –

7.62 (m, 2H), 7.48 (td, J = 9.0, 4.8 Hz, 1H), 5.74 (ddd, J = 14.5, 11.5, 3.1 Hz, 1H), 4.83 – 4.72 (m, 2H), 4.41 (dd, J = 12.3, 4.6 Hz, 1H), 4.36 (s, 1H), 4.16 (s, 1H), 4.05 (ddd, J = 12.5, 5.8, 3.5 Hz, 1H), 3.95 – 3.82 (m, 1H), 3.77 – 3.36 (m, 6H), 3.23 (dt, J = 12.2, 7.0 Hz, 1H), 2.67 (dd, J = 13.9, 6.1 Hz, 1H), 2.57 – 2.37 (m, 3H), 2.35 – 2.00 (m, 7H), 1.85 – 1.76 (m, 2H). LCMS: 655.3.

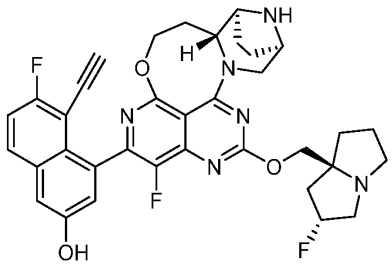
Example 122, Compound 122: 4-((5aR,6S,9R)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



122-3 122

[1061] Compound **122** was prepared in a manner analogous to Compound **36** using Intermediate **122-3** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 (ddd, J = 9.1, 5.8, 3.3 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.22 (dd, J = 15.7, 2.7 Hz, 1H), 5.74 (td, J = 13.6, 3.0 Hz, 1H), 4.78 (qd, J = 12.4, 3.2 Hz, 2H), 4.40 (dd, J = 12.1, 4.6 Hz, 1H), 4.35 (s, 1H), 4.20 – 4.10 (m, 1H), 4.04 (dt, J = 12.5, 4.9 Hz, 1H), 3.86 (dt, J = 11.3, 5.6 Hz, 1H), 3.60 – 3.36 (m, 4H), 3.24 (dt, J = 12.9, 7.3 Hz, 1H), 2.66 (dd, J = 14.0, 6.1 Hz, 1H), 2.57 – 2.37 (m, 3H), 2.35 – 1.98 (m, 9H), 1.85 – 1.76 (m, 2H). LCMS: 671.3.

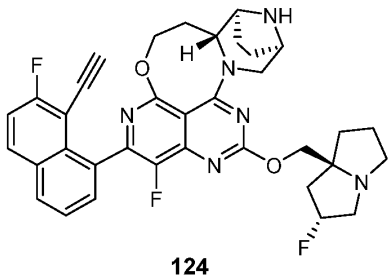
Example 123, Compound 123: 5-ethynyl-6-fluoro-4-((6aR,7S,10R)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol:



123

[1062] Compound **123** was synthesized in a manner similar to Compound **2** using intermediate **123-8** instead of **Intermediate 2-1:** ^{1}H NMR (400 MHz, Methanol-d4) δ 7.90 (ddd, J = 9.2, 5.8, 1.7 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.24 (dd, J = 8.3, 2.6 Hz, 1H), 5.61 (d, J = 51.7 Hz, 1H), 4.75 (dd, J = 6.7, 2.8 Hz, 2H), 4.37 (d, J = 28.5 Hz, 5H), 4.11 – 3.73 (m, 5H), 3.61 – 3.44 (m, 2H), 2.89 – 2.56 (m, 3H), 2.54 – 2.31 (m, 4H), 2.11 (d, J = 48.5 Hz, 5H).. LCMS: 643.3.

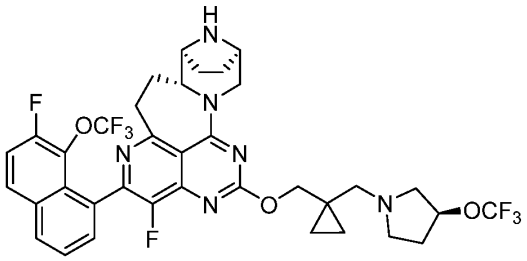
Example 124, Compound 124: (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4-oxa-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



124

[1063] Compound **124** was synthesized in a manner similar to Compound **2** using intermediate **124-1** instead of intermediate **2-1:** ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.15 (dt, J = 5.7, 4.0 Hz, 2H), 7.81 – 7.57 (m, 2H), 7.48 (td, J = 9.0, 2.9 Hz, 1H), 5.61 (d, J = 51.5 Hz, 1H), 4.75 (dd, J = 6.4, 3.7 Hz, 2H), 4.31 (q, J = 31.0, 29.9 Hz, 5H), 4.14 – 3.65 (m, 5H), 3.66 – 3.40 (m, 2H), 2.86 – 2.53 (m, 3H), 2.54 – 2.30 (m, 5H), 2.29 – 1.93 (m, 4H). LCMS: 627.3.

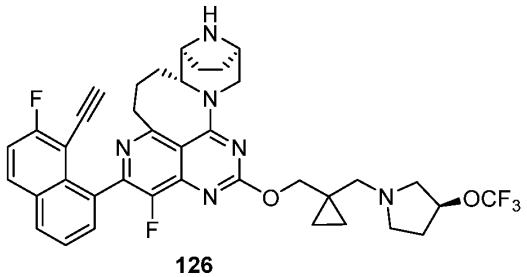
Example 125, Compound 125: (5aR,6S,9R)-1-fluoro-2-(7-fluoro-8-(trifluoromethoxy)naphthalen-1-yl)-12-((1-(((S)-3-(trifluoromethoxy)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



125

[1064] Compound **125** was synthesized in a manner similar to Compound **103** using intermediate **120-1** instead of intermediate **102-1**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.24 – 8.11 (m, 2H), 7.79 – 7.68 (m, 2H), 7.61 (td, J = 9.6, 2.7 Hz, 1H), 5.70 (ddd, J = 22.5, 14.6, 3.0 Hz, 1H), 5.25 (s, 1H), 4.57 – 4.23 (m, 4H), 4.23 – 4.04 (m, 1H), 3.64 – 3.32 (m, 7H), 2.70 – 2.29 (m, 3H), 2.06 (qd, J = 14.9, 13.4, 8.1 Hz, 3H), 1.95 – 1.74 (m, 1H), 1.07 – 0.78 (m, 4H). LCMS: 751.3.

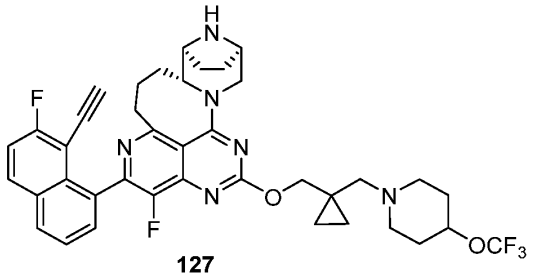
Example 126, Compound 126: (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-((1-(((S)-3-(trifluoromethoxy)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



126

[1065] Compound **126** was synthesized in a manner similar to Compound **115** using intermediate **103-1** instead of intermediate **109-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.19 – 8.10 (m, 2H), 7.74 – 7.59 (m, 2H), 7.51 – 7.43 (m, 1H), 5.46 – 5.33 (m, 1H), 5.23 (s, 1H), 4.68 – 3.88 (m, 6H), 3.84 – 3.32 (m, 7H), 3.10 – 2.88 (m, 2H), 2.86 – 2.18 (m, 3H), 2.13 – 1.66 (m, 6H), 1.03 – 0.87 (m, 4H). LCMS: 705.3.

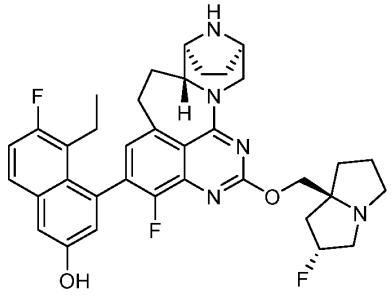
Example 127, Compound 127: (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-((1-((4-(trifluoromethoxy)piperidin-1-yl)methyl)cyclopropyl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



127

[1066] Compound **127** was synthesized in a manner similar to Compound **115** using intermediate **106-2** instead of intermediate **109-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.18 – 8.10 (m, 2H), 7.71 – 7.60 (m, 2H), 7.46 (td, J = 9.0, 3.0 Hz, 1H), 5.42 – 5.32 (m, 1H), 4.68 – 4.42 (m, 2H), 4.29 (s, 1H), 4.16 – 4.03 (m, 2H), 4.01 – 3.56 (m, 5H), 3.51 – 3.36 (m, 3H), 3.21 – 2.90 (m, 3H), 2.43 – 1.65 (m, 11H), 1.01 (s, 2H), 0.90 (s, 2H). LCMS: 719.4.

Example 128, Compound 128: 5-ethyl-6-fluoro-4-((1*S*,4*R*,14a*R*)-10-fluoro-8-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-*de*]quinazolin-11-yl)naphthalen-2-ol

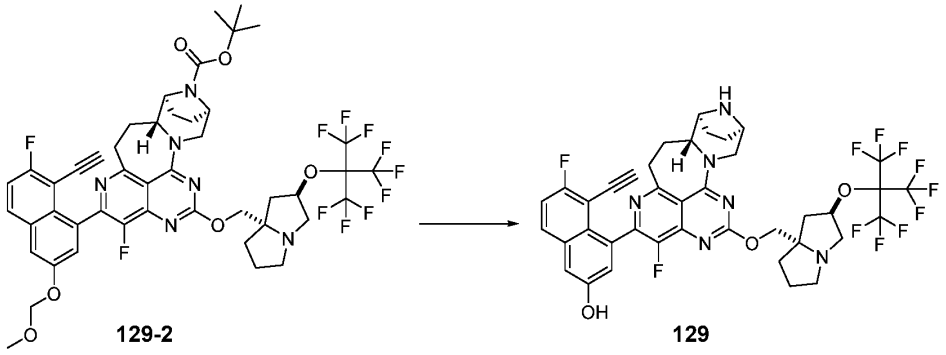


128

[1067] A vigorously stirred mixture of Compound **52** (3.0 mg, 4.8 μmol), palladium(II) hydroxide (20% wt on activated carbon, 8.1 mg, 12 μmol), and ethanol (1.5 mL) was placed under an atmosphere of hydrogen gas (balloon) at room temperature. After 25 min, the resulting mixture

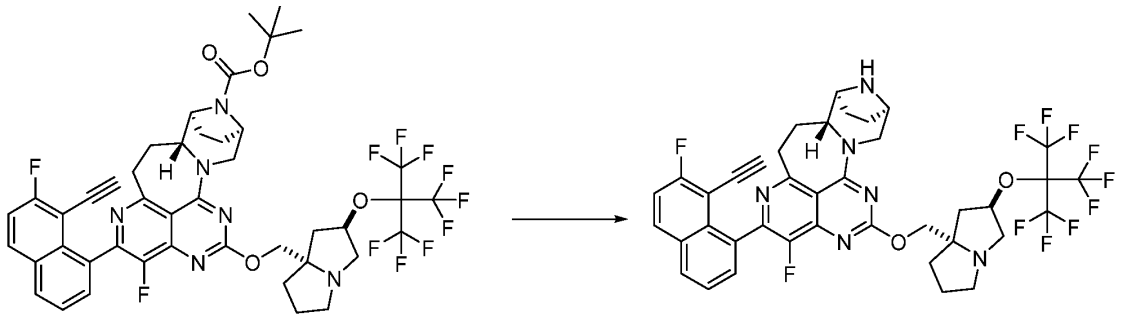
was filtered through celite, and the filtrate was purified by reverse phase preparative HPLC (0.1% acetic acid in acetonitrile/water) to give Compound **128**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.72 – 7.62 (m, 1H), 7.30 – 7.19 (m, 2H), 7.12 (d, J = 7.1 Hz, 1H), 7.01 – 6.91 (m, 1H), 5.60 – 5.32 (m, 2H), 4.52 – 4.33 (m, 2H), 4.19 (d, J = 11.9 Hz, 1H), 3.94 (s, 1H), 3.76 – 3.09 (m, 6H), 2.59 – 1.48 (m, 16H), 1.96 (s, 6H), 0.81 (dt, J = 25.4, 7.3 Hz, 3H). LCMS: 630.3.

Example 129, Compound 129: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((*trans*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



[1068] Compound **129** was prepared in a manner analogous to Compound **36** using Intermediate **129-2** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.89 (ddd, J = 9.1, 5.7, 3.3 Hz, 1H), 7.38 (d, J = 2.5 Hz, 1H), 7.35 (dt, J = 9.0, 4.5 Hz, 1H), 7.22 (dd, J = 15.7, 2.6 Hz, 1H), 5.72 (td, J = 13.8, 3.0 Hz, 1H), 5.45 (s, 1H), 4.72 (s, 2H), 4.40 (dd, J = 12.3, 4.6 Hz, 1H), 4.33 (s, 1H), 4.19 (d, J = 4.9 Hz, 1H), 4.16 (d, J = 4.8 Hz, 1H), 3.93 (dt, J = 11.7, 6.0 Hz, 1H), 3.75 (d, J = 13.7 Hz, 1H), 3.57 – 3.28 (m, 5H), 2.91 (dd, J = 15.1, 5.7 Hz, 1H), 2.56 – 1.99 (m, 11H). LCMS: 843.3.

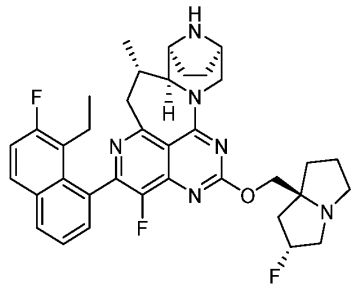
Example 130, Compound 130: (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*trans*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



130-1 130

[1069] Compound **130** was prepared in a manner analogous to Compound **36** using Intermediate **130-1** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.15 (ddd, J = 8.8, 6.5, 2.6 Hz, 2H), 7.74 – 7.60 (m, 2H), 7.48 (td, J = 9.0, 4.7 Hz, 1H), 5.72 (ddd, J = 14.6, 11.5, 3.1 Hz, 1H), 5.45 (s, 1H), 4.72 (s, 2H), 4.41 (dd, J = 12.4, 4.7 Hz, 1H), 4.34 (s, 1H), 4.19 (d, J = 5.0 Hz, 1H), 4.15 (d, J = 4.7 Hz, 1H), 3.93 (dt, J = 11.7, 6.0 Hz, 1H), 3.75 (d, J = 13.8 Hz, 1H), 3.61 – 3.36 (m, 5H), 2.91 (dd, J = 15.0, 5.8 Hz, 1H), 2.58 – 2.00 (m, 11H). LCMS: 827.3.

Example 131, Compound 131: (5*S*,5a*S*,6*S*,9*R*)-2-(8-ethyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene

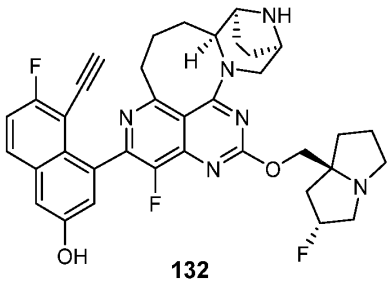


131

[1070] Compound **131** was synthesized in a manner similar to Compound **128** using Compound **84** instead of Compound **52**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.10 – 8.04 (m, 1H), 7.99 – 7.91 (m, 1H), 7.62 – 7.32 (m, 3H), 5.36 (d, *J* = 52.9 Hz, 1H), 5.01 – 4.75 (m, 1H), 4.41 (d, *J* = 10.7 Hz,

1H), 4.26 (d, *J* = 10.8 Hz, 1H), 3.81 – 3.02 (m, 9H), 3.01 – 1.52 (m, 15H), 1.96 (s, 6H), 1.21 – 1.12 (m, 3H), 0.91 – 0.79 (m, 3H). LCMS: 629.0.

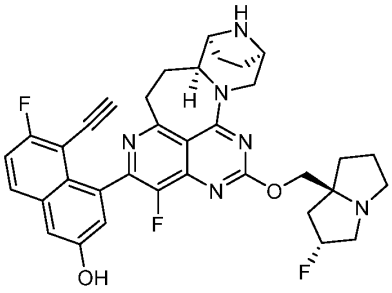
Example 132, Compound 132: 5-ethynyl-6-fluoro-4-((6aS,7S,10R)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol



132

[1071] Compound **132** was synthesized in a manner similar to Compound **2** using intermediate **132-7** instead of **Intermediate 2-1:** ^{1}H NMR (400 MHz, Methanol-d4) δ 7.90 (dt, J = 10.0, 5.4 Hz, 1H), 7.39 (t, J = 2.7 Hz, 1H), 7.37 – 7.10 (m, 2H), 5.61 (d, J = 51.6 Hz, 1H), 5.27 (d, J = 14.8 Hz, 1H), 4.75 (s, 2H), 4.29 (s, 1H), 4.08 (d, J = 15.1 Hz, 1H), 3.97 (s, 3H), 3.91 – 3.65 (m, 2H), 3.53 (d, J = 10.7 Hz, 1H), 3.11 (dt, J = 21.4, 13.0 Hz, 2H), 2.89 – 2.56 (m, 2H), 2.51 – 2.17 (m, 9H), 2.18 – 2.00 (m, 4H). LCMS: 641.3.

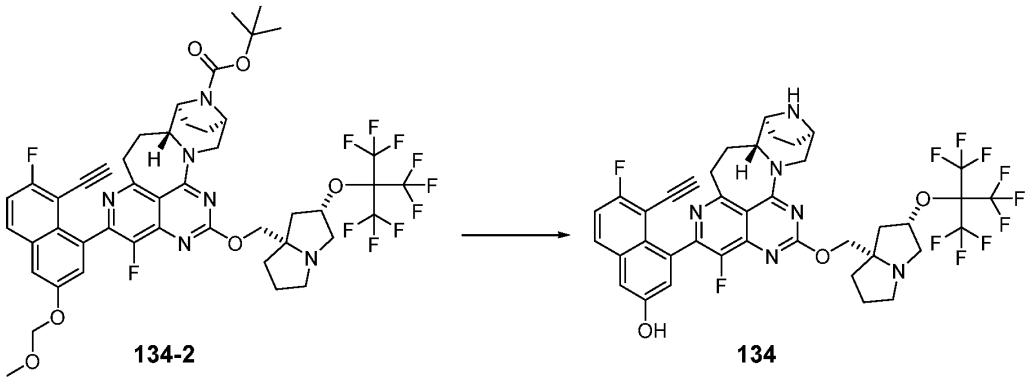
Example 133, Compound 133: 5-ethynyl-6-fluoro-4-((5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



133

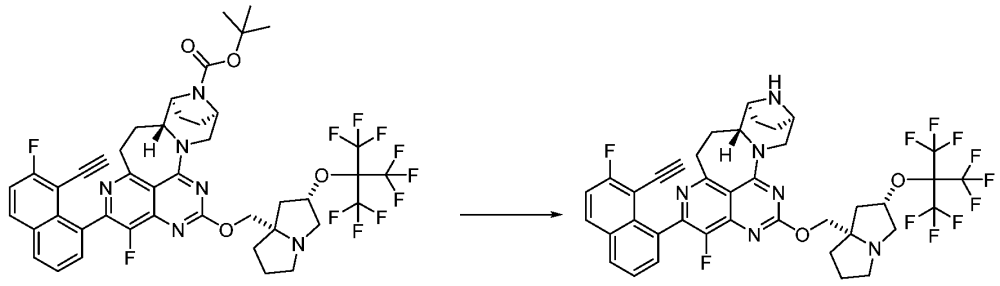
[1072] Compound **133** was synthesized in a manner similar to Compound **2** using intermediate **133-3** instead of **Intermediate 2-1:** ^{1}H NMR (400 MHz, Methanol-d4) δ 7.90 (ddd, J = 8.7, 5.7, 2.5 Hz, 1H), 7.42 – 7.31 (m, 2H), 7.22 (dd, J = 48.0, 2.5 Hz, 1H), 5.60 (d, J = 51.4 Hz, 1H), 5.21 (d, J = 14.8 Hz, 1H), 4.77 (dd, J = 12.4, 4.0 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.40 (s, 1H), 4.31 – 4.19 (m, 1H), 4.17 – 4.00 (m, 1H), 4.00 – 3.84 (m, 4H), 3.80 – 3.64 (m, 1H), 3.63 (d, J = 1.0 Hz, 0H), 3.55 – 3.40 (m, 1H), 3.25 – 3.11 (m, 1H), 2.97 – 2.62 (m, 2H), 2.51 – 2.29 (m, 5H), 2.30 – 2.02 (m, 5H). LCMS: 628.3

Example 134, Compound 134: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((*cis*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



[1073] Compound **134** was prepared in a manner analogous to Compound **36** using Intermediate **134-2** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 (dt, J = 9.1, 5.4 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.22 (dd, J = 17.1, 2.6 Hz, 1H), 5.70 (ddd, J = 14.3, 10.9, 3.1 Hz, 1H), 5.37 (s, 1H), 4.85 – 4.78 (m, 2H), 4.45 – 4.36 (m, 1H), 4.33 (s, 1H), 4.16 (s, 1H), 3.99 (d, J = 13.6 Hz, 1H), 3.73 – 3.61 (m, 2H), 3.59 – 3.26 (m, 5H), 2.75 – 2.58 (m, 2H), 2.56 – 2.38 (m, 3H), 2.30 (d, J = 8.3 Hz, 2H), 2.23 – 1.99 (m, 6H). LCMS: 843.3.

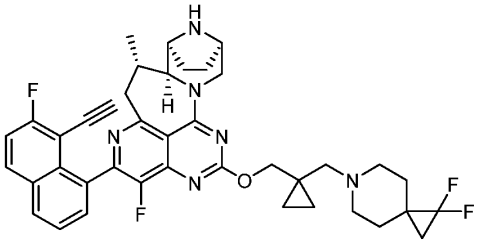
Example 135, Compound 135: (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*cis*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



135-1 135

[1074] Compound **135** was prepared in a manner analogous to Compound **36** using Intermediate **135-1** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.19 – 8.12 (m, 2H), 7.73 – 7.61 (m, 2H), 7.48 (td, J = 8.9, 6.0 Hz, 1H), 5.76 – 5.65 (m, 1H), 5.37 (s, 1H), 4.86 – 4.77 (m, 2H), 4.41 (d, J = 12.1 Hz, 1H), 4.33 (s, 1H), 4.17 (s, 1H), 3.99 (d, J = 13.6 Hz, 1H), 3.75 – 3.35 (m, 7H), 2.78 – 2.58 (m, J = 6.2, 5.3 Hz, 2H), 2.58 – 2.37 (m, 3H), 2.30 (d, J = 7.6 Hz, 2H), 2.23 – 1.99 (m, 5H). LCMS: 827.3.

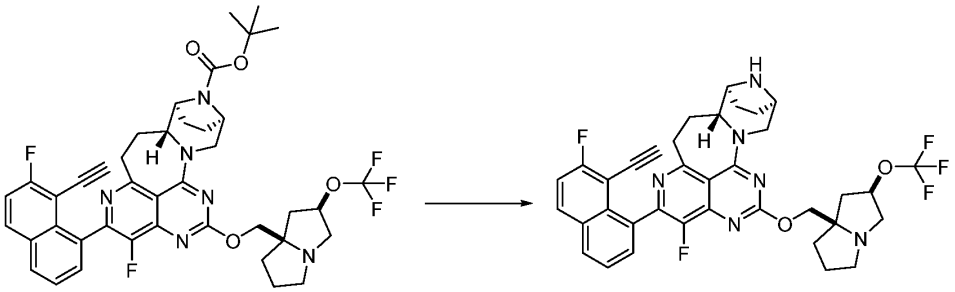
Example 136, Compound 136: (5S,5aS,6S,9R)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



136

[1075] Compound **136** was synthesized in a manner similar to Compound **84** using **Intermediate 136-2** instead of **Intermediate 84-5**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.21 – 8.12 (m, 2H), 7.75 – 7.57 (m, 2H), 7.48 (dd, *J* = 8.9 Hz, 1H), 5.14 (d, *J* = 14.6 Hz, 1H), 4.69 – 4.27 (m, 3H), 4.03 – 3.37 (m, 5H), 3.21 – 1.33 (m, 10H), 1.30 – 1.20 (m, 3H). LCMS: 697.1 $[M+H]^+$

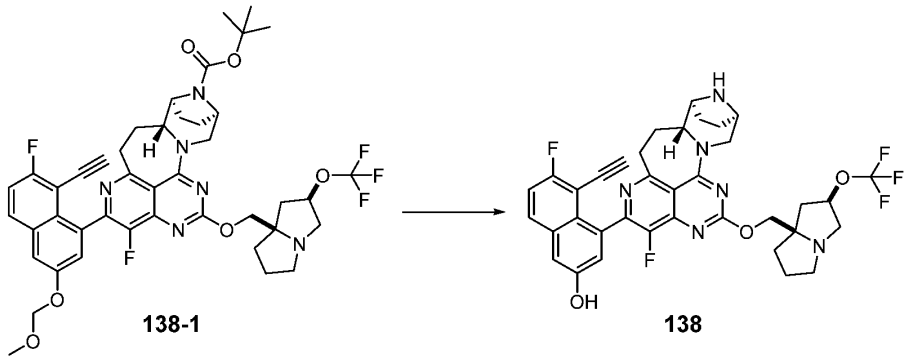
Example 137, Compound 137: (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*cis*-2-(trifluoromethoxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



137-2 137

[1076] Compound **137** was prepared in a manner analogous to Compound **36** using Intermediate **137-2** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.11 (m, 2H), 7.74 – 7.62 (m, 2H), 7.48 (td, J = 9.0, 5.1 Hz, 1H), 5.78 – 5.69 (m, 1H), 5.36 (s, 1H), 4.83 – 4.76 (m, 3H), 4.41 (dd, J = 12.4, 4.7 Hz, 1H), 4.34 (s, 1H), 4.16 (s, 1H), 4.07 – 3.98 (m, 1H), 3.78 – 3.36 (m, 6H), 2.76 (d, J = 15.4 Hz, 1H), 2.61 (dd, J = 15.8, 5.1 Hz, 1H), 2.55 – 2.37 (m, 2H), 2.35 – 2.25 (m, 1H), 2.24 – 2.15 (m, 1H), 2.14 – 1.97 (m, 6H). LCMS: 677.3.

Example 138, Compound 138: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((*cis*-2-(trifluoromethoxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol

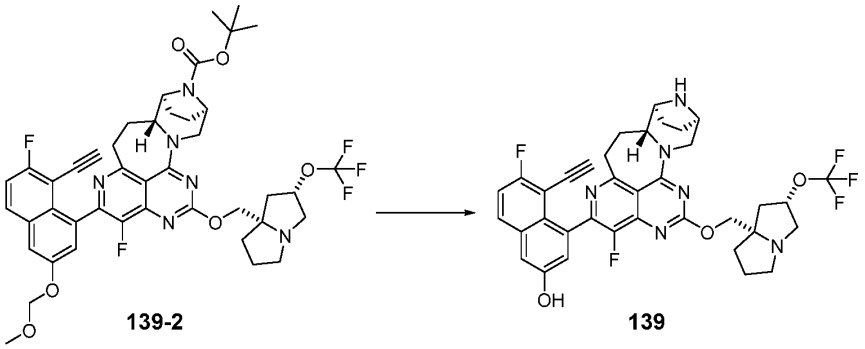


138-1 138

[1077] Compound **138** was prepared in a manner analogous to Compound **36** using Intermediate **138-1** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 (dt, J = 9.5, 5.0 Hz, 1H), 7.39 (d, J = 2.5 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.23 (dd, J = 14.7, 2.6 Hz, 1H), 5.79 – 5.67 (m, 1H), 5.36 (s, 1H), 4.84 – 4.74 (m, 2H), 4.41 (dd, J = 12.4, 4.6 Hz, 1H), 4.34 (s, 1H), 4.16 (s, 1H), 4.03

(t, J = 12.3 Hz, 1H), 3.78 – 3.35 (m, 7H), 2.76 (d, J = 15.6 Hz, 1H), 2.61 (dd, J = 15.5, 4.8 Hz, 1H), 2.54 – 2.00 (m, 10H). LCMS: 693.3.

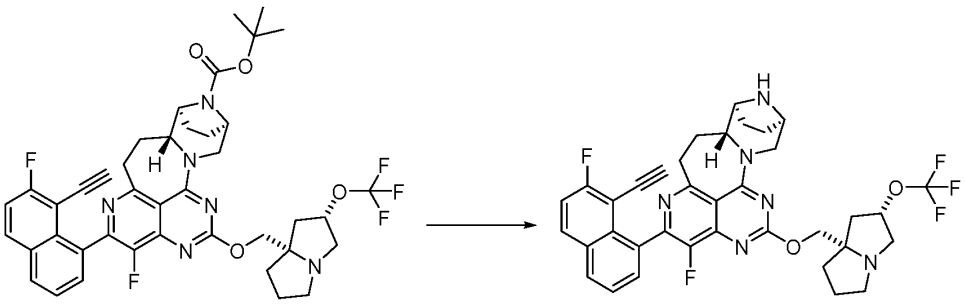
Example 139, Compound 139: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((*cis*-2-(trifluoromethoxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



139-2 139

[1078] Compound **139** was prepared in a manner analogous to Compound **36** using Intermediate **139-2** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 (ddd, J = 8.7, 5.7, 2.3 Hz, 1H), 7.39 (d, J = 2.5 Hz, 1H), 7.35 (dt, J = 9.0, 4.5 Hz, 1H), 7.23 (dd, J = 14.6, 2.6 Hz, 1H), 5.71 (td, J = 14.6, 3.1 Hz, 1H), 5.35 (s, 1H), 4.91 – 4.85 (m, 1H), 4.74 (dd, J = 12.4, 2.6 Hz, 1H), 4.41 (dd, J = 12.1, 4.5 Hz, 1H), 4.34 (s, 1H), 4.16 (s, 1H), 4.00 (t, J = 14.0 Hz, 1H), 3.78 – 3.69 (m, 1H), 3.64 (dd, J = 13.5, 3.9 Hz, 1H), 3.59 – 3.22 (m, 5H), 2.78 (d, J = 15.4 Hz, 1H), 2.61 (d, J = 15.1 Hz, 1H), 2.56 – 2.00 (m, 10H). LCMS: 693.3.

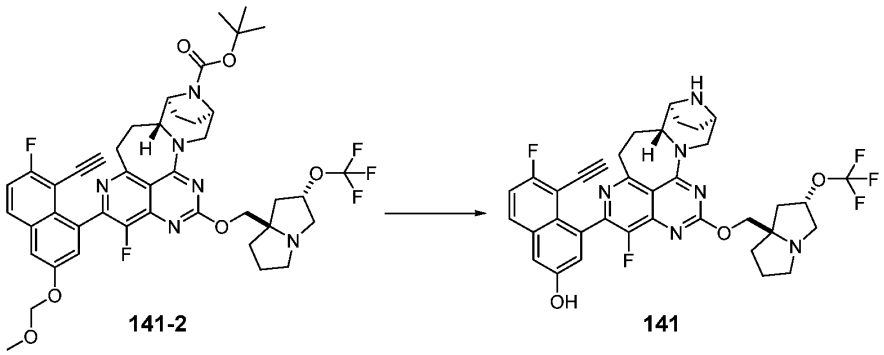
Example 140, Compound 140: (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*cis*-2-(trifluoromethoxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



140-1 140

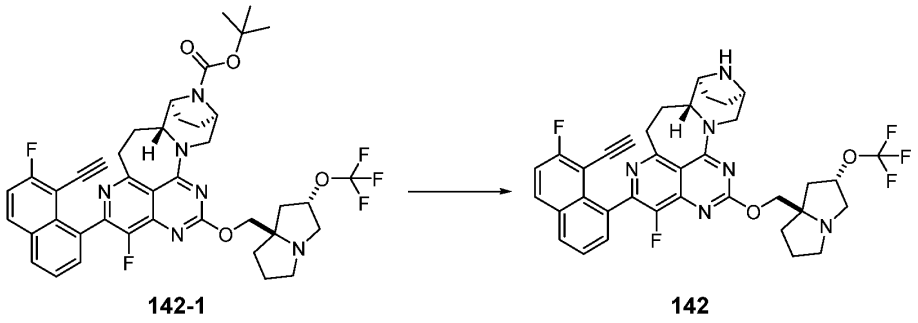
[1079] Compound **140** was prepared in a manner analogous to Compound **36** using Intermediate **140-1** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.10 (m, 2H), 7.75 – 7.62 (m, 2H), 7.48 (td, J = 9.0, 4.4 Hz, 1H), 5.80 – 5.65 (m, 1H), 5.35 (s, 1H), 4.86 – 4.84 (m, 1H), 4.75 (d, J = 12.3 Hz, 1H), 4.41 (dd, J = 12.4, 4.6 Hz, 1H), 4.34 (s, 1H), 4.16 (s, 1H), 4.00 (t, J = 13.1 Hz, 1H), 3.80 – 3.36 (m, 7H), 2.78 (d, J = 15.5 Hz, 1H), 2.66 – 2.37 (m, 4H), 2.35 – 2.26 (m, 3H), 2.25 – 1.98 (m, 4H). LCMS: 667.3.

Example 141, Compound 141: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((*trans*-2-(trifluoromethoxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



[1080] Compound **141** was prepared in a manner analogous to Compound **36** using Intermediate **141-2** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 (ddd, J = 9.0, 5.7, 3.1 Hz, 1H), 7.38 (d, J = 2.5 Hz, 1H), 7.35 (dt, J = 9.0, 4.6 Hz, 1H), 7.22 (dd, J = 15.2, 2.6 Hz, 1H), 5.78 – 5.67 (m, 1H), 5.43 (s, 1H), 4.78 – 4.67 (m, 2H), 4.40 (d, J = 12.5 Hz, 1H), 4.35 (s, 1H), 4.16 (dt, J = 9.5, 4.8 Hz, 2H), 3.97 – 3.78 (m, 2H), 3.33 (dt, J = 3.3, 1.6 Hz, 5H), 2.86 (dd, J = 15.1, 6.0 Hz, 1H), 2.59 (d, J = 15.1 Hz, 1H), 2.54 – 1.95 (m, 10H). LCMS: 693.3.

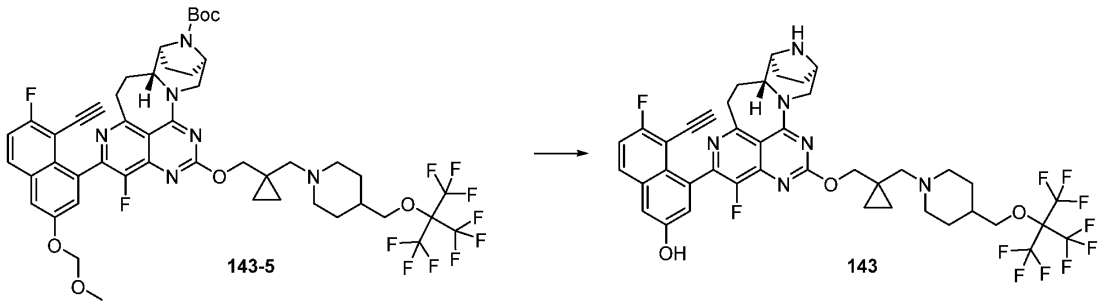
Example 142, Compound 142: (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*trans*-2-(trifluoromethoxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



142-1 142

[1081] Compound **142** was prepared in a manner analogous to Compound **36** using Intermediate **142-1** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.19 – 8.11 (m, 2H), 7.74 – 7.61 (m, 2H), 7.48 (td, J = 9.0, 4.9 Hz, 1H), 5.79 – 5.67 (m, 1H), 5.42 (s, 1H), 4.78 – 4.66 (m, 2H), 4.40 (dd, J = 12.5, 4.6 Hz, 1H), 4.35 (s, 1H), 4.19 – 4.11 (m, 2H), 3.89 (s, 1H), 3.83 (d, J = 14.2 Hz, 1H), 3.62 – 3.34 (m, 5H), 2.86 (dd, J = 15.2, 5.9 Hz, 1H), 2.59 (d, J = 15.1 Hz, 1H), 2.54 – 1.98 (m, 10H). LCMS: 677.3.

Example 143, Compound 143: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((1-((4-(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol

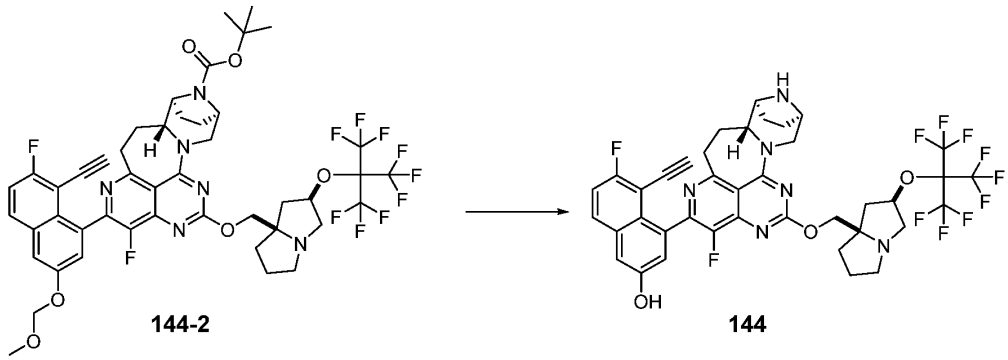


143-5 143

[1082] A solution of intermediate **143-5** (58.7 umol) in acetonitrile (0.5 mL) was stirred at 0 °C as 4 N HCl in dioxane (0.5 mL) was added. The resulting solution was stirred 0 °C. After 1 h, additional 4 N HCl in dioxane (0.5 mL) was added and stirred at 0 °C. After additional 30 min, the reaction mixture was concentrated by rotovap, the residue was dissolved in methanol (0.8 mL), filtered, and purified by preparative HPLC (Gemini 5 um NX-C18 110 A LC Column 250 x 21.2 mm AX) eluting 20-60% acetonitrile (0.1% TFA) in water (0.1% TFA) over 20 min and the

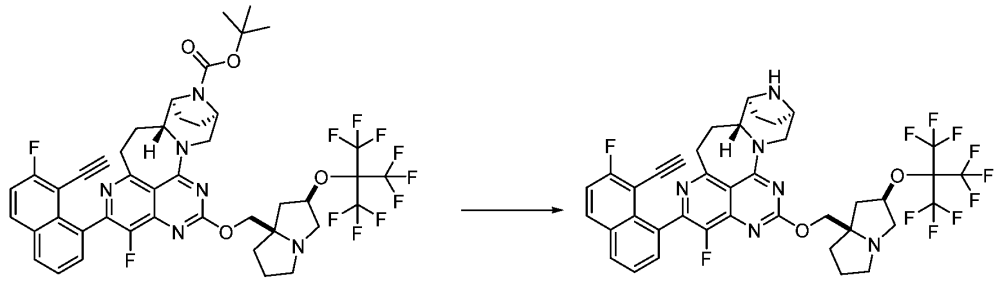
combined fractions were freeze-dried to give Compound **143**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.87 (ddd, J = 9.0, 5.8, 2.8 Hz, 1H), 7.36 (dd, J = 2.7, 1.5 Hz, 1H), 7.32 (dt, J = 8.9, 4.4 Hz, 1H), 7.19 (dd, J = 17.1, 2.6 Hz, 1H), 5.66 (td, J = 14.6, 3.0 Hz, 1H), 4.61 – 4.49 (m, 1H), 4.49 – 4.22 (m, 3H), 4.08 (d, J = 31.8 Hz, 2H), 3.94 (d, J = 10.3 Hz, 3H), 3.86 (d, J = 12.5 Hz, 1H), 3.53 – 3.50 (m, 1H), 3.48 (s, 1H), 3.44 – 3.39 (m, 1H), 3.35 (t, J = 7.0 Hz, 1H), 3.26 – 3.14 (m, 1H), 2.99 (d, J = 16.9 Hz, 2H), 2.58 – 2.31 (m, 2H), 2.06 (d, J = 24.2 Hz, 7H), 1.72 (d, J = 14.7 Hz, 2H), 0.98 (s, 2H), 0.88 (t, J = 8.8 Hz, 2H). LCMS: 885.36.

Example 144, Compound 144: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((*cis*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



[1083] Compound **144** was prepared in a manner analogous to Compound **36** using Intermediate **144-2** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 – 7.84 (m, 1H), 7.42 – 7.30 (m, 2H), 7.27 – 7.18 (m, 1H), 5.77 – 5.62 (m, 1H), 5.33 (d, J = 28.5 Hz, 1H), 4.85 – 4.77 (m, 3H), 4.41 (dd, J = 12.4, 4.6 Hz, 1H), 4.34 (s, 1H), 4.15 (d, J = 11.9 Hz, 1H), 4.00 (d, J = 13.6 Hz, 1H), 3.70 – 3.34 (m, 6H), 2.72 – 2.58 (m, 1H), 2.55 – 2.37 (m, 3H), 2.28 (dd, J = 9.0, 4.5 Hz, 1H), 2.21 – 1.98 (m, 5H), 1.93 – 1.71 (m, 1H). LCMS: 843.3.

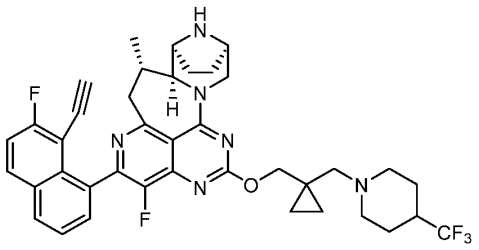
Example 145, Compound 145: (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((*cis*-2-((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



145-1 145

[1084] Compound **145** was prepared in a manner analogous to Compound **36** using Intermediate **145-1** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.11 (m, 2H), 7.75 – 7.62 (m, 2H), 7.48 (td, J = 8.9, 4.1 Hz, 1H), 5.73 (ddd, J = 14.6, 6.7, 3.0 Hz, 1H), 5.36 (s, 1H), 4.85 – 4.79 (m, 2H), 4.42 (dd, J = 12.5, 4.4 Hz, 1H), 4.34 (s, 1H), 4.17 (s, 1H), 3.99 (d, J = 13.6 Hz, 1H), 3.76 – 3.35 (m, 7H), 2.72 – 2.59 (m, 2H), 2.55 – 2.35 (m, 3H), 2.28 (dd, J = 8.7, 4.5 Hz, 2H), 2.22 – 2.00 (m, 5H). LCMS: 827.3.

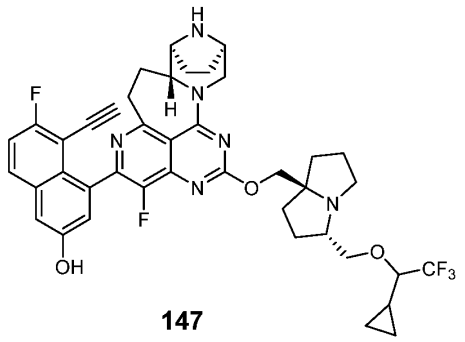
Example 146, Compound 146: (5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-12-((1-((4-(trifluoromethyl)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



146

[1085] Compound **146** was synthesized in a manner similar to Compound **84** using **Intermediate 146-2** instead of **Intermediate 84-5**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.23 – 8.10 (m, 2H), 7.74 – 7.56 (m, 2H), 7.48 (dd, *J* = 8.9 Hz, 1H), 5.12 (d, *J* = 14.5 Hz, 1H), 4.71 – 4.25 (m, 4H), 4.09 – 3.82 (m, 3H), 3.52 – 3.36 (m, 2H), 3.27 – 1.74 (m, 13H), 1.35 – 1.21 (m, 3H). LCMS: 703.1 $[M+H]^+$.

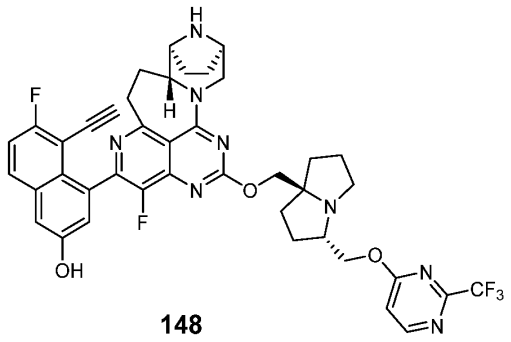
Example 147, Compound 147: 4-((5a*R*,6*S*,9*R*)-12-(((3*S*,7a*S*)-3-((1-cyclopropyl-2,2,2-trifluoroethoxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



147

[1086] Compound **147** was synthesized in a manner similar to Compound **110**. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 7.97 – 7.87 (m, 1H), 7.43 (t, J = 2.6 Hz, 1H), 7.37 (td, J = 9.0, 5.5 Hz, 1H), 7.29 – 7.18 (m, 1H), 5.67 – 5.50 (m, 1H), 4.75 – 4.52 (m, 3H), 4.30 (s, 1H), 4.15 – 3.81 (m, 3H), 3.75 – 3.00 (m, 6H), 2.56 – 1.38 (m, 16H), 0.96 – 0.13 (m, 5H). LCMS: 761.3.

Example 148, Compound 148: 5-ethynyl-6-fluoro-4-((5a*R*,6*S*,9*R*)-1-fluoro-12-(((3*S*,7a*S*)-3-(((2-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol

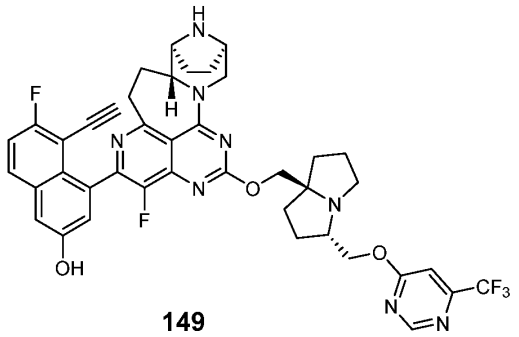


148

[1087] Compound **148** was synthesized in a manner similar to Compound **122** using intermediate **148-2** instead of ((1*S*,7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.40 – 8.27 (m, 1H), 7.96 – 7.89 (m, 1H), 7.50 – 7.42 (m, 1H), 7.40 – 7.27 (m, 2H), 6.61 – 6.52 (m, 1H), 5.68 – 5.49 (m, 1H), 4.83 –

4.50 (m, 5H), 4.36 – 4.17 (m, 2H), 4.11 – 4.01 (m, 1H), 3.71 – 3.19 (m, 4H), 2.95 – 1.51 (m, 16H). LCMS: 785.3.

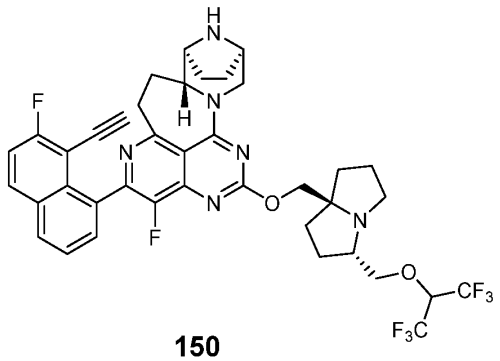
Example 149, Compound 149: 5-ethynyl-6-fluoro-4-((5a*R*,6*S*,9*R*)-1-fluoro-12-(((3*S*,7a*S*)-3-(((6-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol



149

[1088] Compound **149** was synthesized in a manner similar to Compound **122** using intermediate **149-1** instead of ((1*S*,7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.92 – 8.82 (m, 1H), 7.97 – 7.82 (m, 1H), 7.47 – 7.39 (m, 1H), 7.38 – 7.25 (m, 2H), 7.16 – 7.08 (m, 1H), 5.68 – 5.49 (m, 1H), 4.94 – 4.80 (m, 1H), 4.75 – 4.56 (m, 3H), 4.55 – 4.48 (m, 1H), 4.33 – 4.20 (m, 2H), 4.07 – 4.03 (m, 1H), 3.72 – 3.56 (m, 2H), 3.37 – 3.23 (m, 2H), 2.83 – 1.69 (m, 16H). LCMS: 785.3.

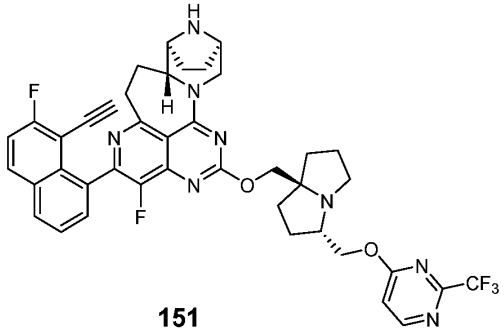
Example 150, Compound 150: (5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((3*S*,7a*S*)-3-(((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



150

[1089] Compound **150** was synthesized in a manner similar to Compound **113** using intermediate **150-2** instead of ((6'*R*,7a'*R*)-6'-fluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.15 (t, J = 8.2 Hz, 2H), 7.74 – 7.62 (m, 2H), 7.52 – 7.43 (m, 1H), 5.70 – 5.50 (m, 1H), 4.83 – 4.48 (m, 4H), 4.38 – 3.93 (m, 5H), 3.76 – 3.46 (m, 2H), 3.39 – 3.19 (m, 2H), 2.58 – 1.23 (m, 16H). LCMS: 773.3.

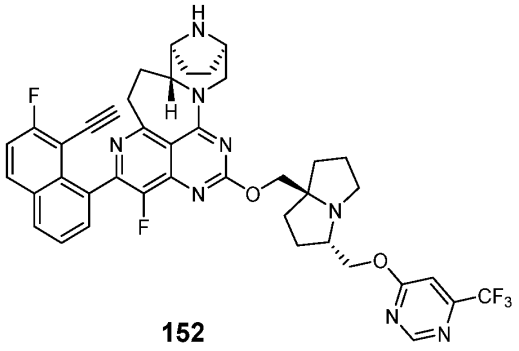
Example 151, Compound 151: (5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((3*S*,7a*S*)-3-(((2-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



151

[1090] Compound **151** was synthesized in a manner similar to Compound **113** using intermediate **148-2** instead of ((6'*R*,7a'*R*)-6'-fluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.42 – 8.32 (m, 1H), 8.22 – 8.10 (m, 2H), 7.81 – 7.62 (m, 2H), 7.56 – 7.35 (m, 1H), 6.70 – 6.56 (m, 1H), 5.66 – 5.49 (m, 1H), 4.88 – 4.75 (m, 1H), 4.74 – 4.52 (m, 4H), 4.33 – 4.19 (m, 2H), 4.11 – 4.03 (m, 1H), 3.73 – 3.50 (m, 2H), 3.42 – 3.22 (m, 2H), 2.63 – 1.77 (m, 16H). LCMS: 769.3.

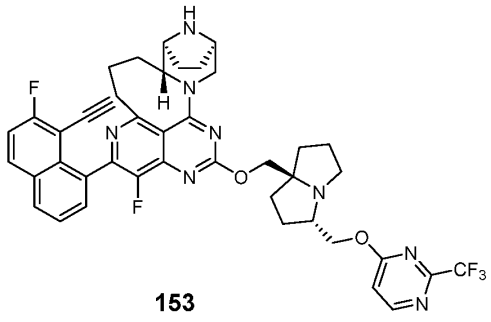
Example 152, Compound 152: (5a*R*, 6*S*, 9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((3*S*,7a*S*)-3-(((6-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



152

[1091] Compound **152** was synthesized in a manner similar to Compound **113** using intermediate **149-1** instead of ((6'*R*,7a'*R*)-6'-fluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.92 – 8.84 (m, 1H), 8.20 – 8.06 (m, 2H), 7.75 – 7.60 (m, 2H), 7.50 – 7.39 (m, 1H), 7.18 – 7.13 (m, 1H), 5.67 – 5.49 (m, 1H), 4.95 – 4.78 (m, 1H), 4.75 – 4.57 (m, 3H), 4.58 – 4.47 (m, 1H), 4.35 – 4.21 (m, 2H), 4.10 – 4.01 (m, 1H), 3.74 – 3.54 (m, 2H), 3.40 – 3.20 (m, 2H), 2.98 – 1.51 (m, 16H). LCMS: 769.3.

Example 153, Compound 153: (6a*R*,7*S*,10*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((3*S*,7a*S*)-3-(((2-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene

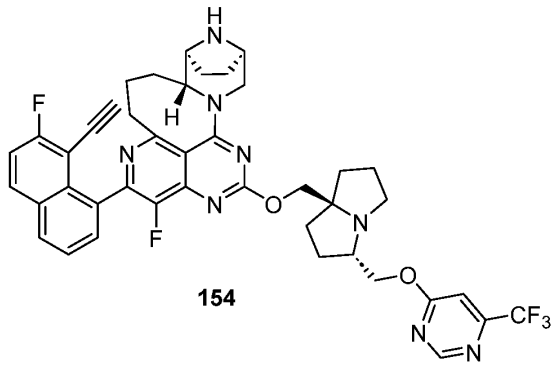


153

[1092] Compound **153** was synthesized in a manner similar to Compound **115** using intermediate **148-2** instead of intermediate **109-2**. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.49 – 8.42 (m, 1H),

8.21 – 8.10 (m, 2H), 7.76 – 7.62 (m, 2H), 7.54 – 7.41 (m, 1H), 6.82 – 6.77 (m, 1H), 5.32 – 5.22 (m, 1H), 4.94 – 4.73 (m, 2H), 4.71 – 4.54 (m, 2H), 4.47 – 3.96 (m, 4H), 3.88 – 3.75 (m, 1H), 3.72 – 3.53 (m, 1H), 3.46 – 3.22 (m, 2H), 3.00 – 2.79 (m, 2H), 2.76 – 1.45 (m, 16H). LCMS: 783.3.

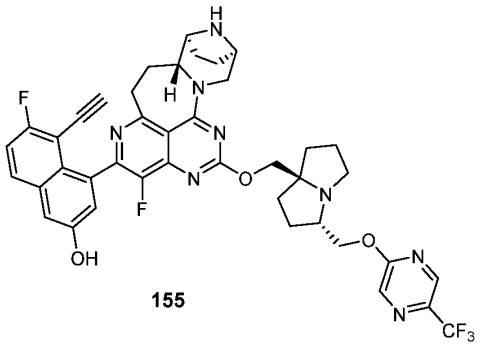
Example 154, Compound 154: (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((3S,7aS)-3-(((6-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



154

[1093] Lithium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 20.0 μL, 20 μmol) was added via syringe to a stirred mixture of intermediate **115-3** (3.6 mg, 5.5 μmol), intermediate **149-1** (4.0 mg, 13 μmol), and tetrahydrofuran (0.1 mL) at room temperature. After 82 min, saturated aqueous sodium bicarbonate solution (1.0 mL) and water (1.0 mL) were added sequentially. The aqueous layer was extracted with diethyl ether (6 × 5.0 mL). The combined organic layers were dried over anhydrous magnesium sulfate, were filtered, and were concentrated under reduced pressure. Acetonitrile (0.2 mL) and hydrogen chloride solution (4.0 M in 1,4-dioxane, 200 μL, 800 μmol) were added sequentially, and the resulting mixture was vigorously stirred at room temperature. After 13 h, the resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase preparative HPLC (0.1% trifluoroacetic acid in acetonitrile/water) to give **Example 154**. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.92 – 8.84 (m, 1H), 8.20 – 8.06 (m, 2H), 7.75 – 7.60 (m, 2H), 7.50 – 7.39 (m, 1H), 7.18 – 7.13 (m, 1H), 5.67 – 5.49 (m, 1H), 4.95 – 4.78 (m, 1H), 4.75 – 4.57 (m, 3H), 4.58 – 4.47 (m, 1H), 4.35 – 4.21 (m, 2H), 4.10 – 4.01 (m, 1H), 3.74 – 3.54 (m, 2H), 3.40 – 3.20 (m, 2H), 2.98 – 1.51 (m, 16H). LCMS: 783.3.

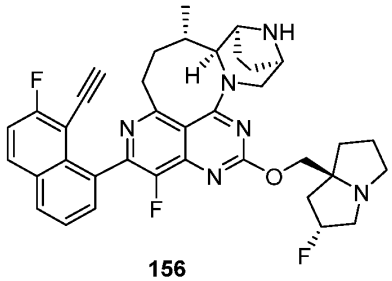
Example 155, Compound 155: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-(((3S,7aS)-3-(((5-(trifluoromethyl)pyrazin-2-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



155

[1094] Compound **155** was synthesized in a manner similar to Compound **122** using intermediate **155-1** instead of ((1*S*,7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol.^{1}H NMR (400 MHz, Methanol-d4) δ 8.59 (d, J = 12.1 Hz, 1H), 8.22 (dd, J = 34.7, 1.2 Hz, 1H), 7.88 (ddd, J = 11.3, 9.2, 5.7 Hz, 1H), 7.41 – 7.28 (m, 2H), 7.23 (dd, J = 24.9, 2.5 Hz, 1H), 5.80 – 5.67 (m, 1H), 4.92 (t, J = 2.9 Hz, 1H), 5.02-4.86(m, 2H), 4.87 – 4.63 (m, 3H), 4.50 (s, 2H), 4.44 – 4.31 (m, 3H), 4.16 (s, 1H), 3.68 – 3.60 (m, 1H), 3.60 – 3.46 (m, 2H), 3.51 – 3.42 (m, 1H), 3.44 – 3.34 (m, 1H), 2.49 (td, J = 13.0, 7.7 Hz, 2H), 2.46 – 2.34 (m, 1H), 2.34 – 2.21 (m, 2H), 2.22 – 2.10 (m, 3H), 2.18 – 1.91 (m, 4H). LCMS: 785.4.

Example 156, Compound 156: (6S,6aS,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene

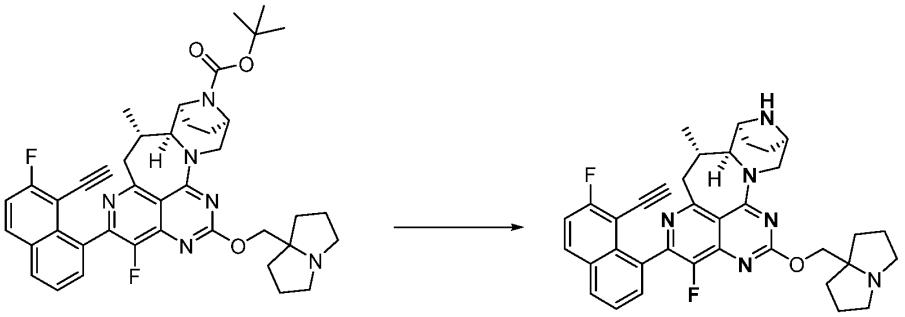


156

[1095] Compound **156** was synthesized in a manner similar to Compound **76** using **Intermediate 156-11** instead of **Intermediate 76-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.24 – 8.11 (m, 2H),

7.82 – 7.61 (m, 2H), 7.53 – 7.45 (m, 1H), 5.61 (d, *J* = 51.6 Hz, 1H), 5.32 (d, *J* = 15.4 Hz, 1H), 4.80 – 4.68 (m, 2H), 4.52 – 3.42 (m, 10H), 3.26 – 2.01 (m, 13H), 1.26 – 1.19 (m, 3H). LCMS: 639.0 $[M+H]^+$.

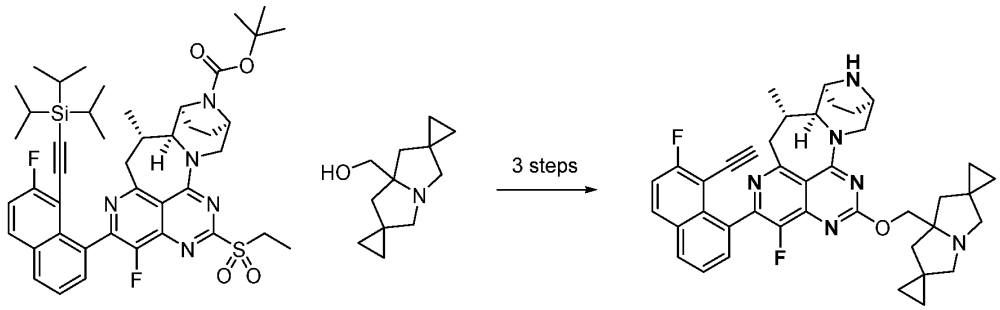
Example 157, Compound 157: (5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-12-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



157-2 157

[1096] Compound **157** was prepared in a manner analogous to Compound **36** using Intermediate **157-2** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.12 (m, 2H), 7.74 – 7.66 (m, 2H), 7.48 (t, J = 8.9 Hz, 1H), 5.20 (d, J = 14.5 Hz, 1H), 4.78 – 4.63 (m, 2H), 4.36 (dd, J = 18.0, 12.8 Hz, 2H), 3.89 (d, J = 14.7 Hz, 1H), 3.80 – 3.62 (m, 4H), 3.52 – 3.39 (m, 1H), 3.27 (d, J = 12.7 Hz, 1H), 3.09 (dt, J = 13.1, 6.7 Hz, 1H), 2.87 (dd, J = 24.1, 13.5 Hz, 1H), 2.43 – 2.03 (m, 12H), 1.27 (dd, J = 15.6, 6.5 Hz, 3H). LCMS: 607.3.

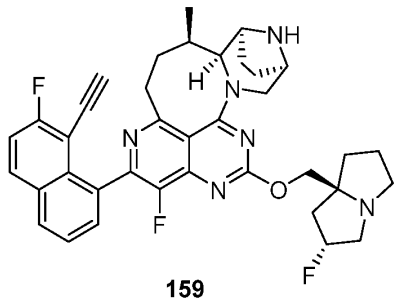
Example 158, Compound 158: (5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-12-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



84-3 158-1 158

[1097] Compound **158** was prepared in a manner analogous to Compound **157** using Intermediates **84-3** and **158-1** as the starting materials. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.11 (m, 2H), 7.72 – 7.66 (m, 2H), 7.48 (t, J = 8.9 Hz, 1H), 5.20 (d, J = 14.4 Hz, 1H), 4.85 – 4.77 (m, 2H), 4.36 (dd, J = 20.2, 15.0 Hz, 2H), 3.90 (d, J = 14.7 Hz, 1H), 3.77 (d, J = 1.0 Hz, 1H), 3.68 (dd, J = 20.2, 11.5 Hz, 2H), 3.56 – 3.34 (m, 3H), 3.28 (d, J = 12.7 Hz, 1H), 3.16 – 3.05 (m, 1H), 2.88 (dd, J = 24.1, 13.5 Hz, 1H), 2.49 – 2.32 (m, 2H), 2.30 – 1.93 (m, 6H), 1.27 (dd, J = 14.8, 6.6 Hz, 3H), 0.94 (dd, J = 7.6, 5.2 Hz, 4H), 0.81 (dd, J = 14.6, 7.6 Hz, 4H). LCMS: 659.3.

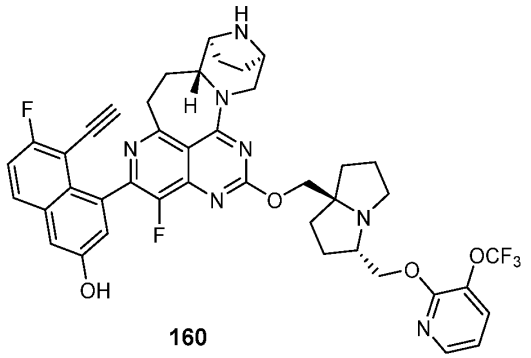
Example 159, Compound 159: (6R,6aS,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



159

[1098] Compound **159** was synthesized in a manner similar to Compound **76** using **Intermediate 159-10** instead of **Intermediate 76-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.12 (m, 2H), 7.80 – 7.54 (m, 2H), 7.52 – 7.45 (m, 1H), 5.69 – 5.52 (m, 2H), 4.79 – 4.69 (m, 2H), 4.32 – 3.45 (m, 9H), 3.07 – 1.88 (m, 12H), 1.65 – 1.49 (m, 3H). LCMS: 639.1 $[M + H]^+$.

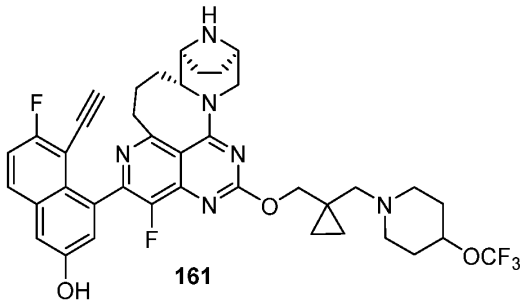
Example 160, Compound 160: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-(((3S,7aS)-3-(((3-(trifluoromethoxy)pyridin-2-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



160

[1099] Compound **160** was synthesized in a manner similar to Compound **122** using intermediate **160-1** instead of ((1*S*,7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.14 (ddd, J = 14.7, 5.0, 1.6 Hz, 1H), 7.89 (dt, J = 9.1, 6.3 Hz, 1H), 7.75 – 7.67 (m, 1H), 7.41 – 7.27 (m, 2H), 7.21 (dd, J = 18.1, 2.6 Hz, 1H), 7.11 (ddd, J = 7.9, 4.9, 4.1 Hz, 1H), 5.81 – 5.64 (m, 1H), 4.82 (d, J = 4.8 Hz, 1H), 4.82 – 4.75 (m, 1H), 4.68 (dd, J = 12.3, 4.9 Hz, 1H), 4.58 – 4.29 (m, 2H), 4.15 (s, 1H), 3.63 (s, 1H), 3.56 (s, 1H), 3.52 (d, J = 1.0 Hz, 1H), 3.33 (d, J = 1.6 Hz, 8H), 2.58 – 2.35 (m, 4H), 2.39 – 2.15 (m, 2H), 2.20 – 1.82 (m, 5H). LCMS: 800.4.

Example 161, Compound 161: 5-ethynyl-6-fluoro-4-((6aR,7S,10R)-1-fluoro-13-((1-((4-(trifluoromethoxy)piperidin-1-yl)methyl)cyclopropyl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol

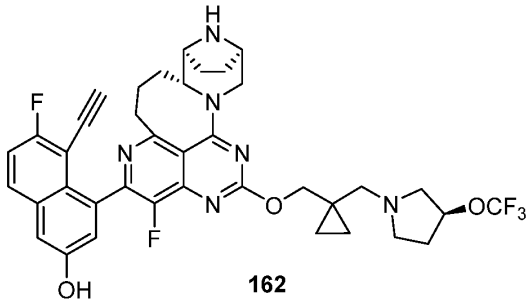


161

[1100] Compound **161** was synthesized in a manner similar to Compound **157** using intermediate **106-2** instead of 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol and using intermediate **161-2**

instead of intermediate **84-3**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 – 7.86 (m, 1H), 7.41 – 7.33 (m, 2H), 7.28 – 7.19 (m, 1H), 5.46 – 5.33 (m, 1H), 4.81 – 4.20 (m, 4H), 4.18 – 3.74 (m, 4H), 3.70 – 3.58 (m, 1H), 3.57 – 3.37 (m, 3H), 3.24 – 3.11 (m, 1H), 3.08 – 2.71 (m, 2H), 2.47 – 2.17 (m, 4H), 2.16 – 1.62 (m, 8H), 1.53 – 1.11 (m, 1H), 1.02 (s, 2H), 0.92 (s, 2H). LCMS: 735.4.

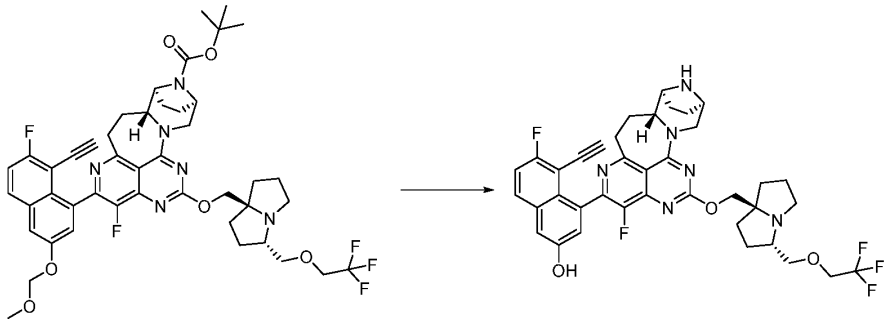
Example 162, Compound 162: 5-ethynyl-6-fluoro-4-((6aR,7S,10R)-1-fluoro-13-((1-((4-(trifluoromethoxy)piperidin-1-yl)methyl)cyclopropyl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)naphthalen-2-ol



162

[1101] Compound **162** was synthesized in a manner similar to Compound **161** using Intermediate **103-1** instead of intermediate **106-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 – 7.87 (m, 1H), 7.42 – 7.33 (m, 2H), 7.27 – 7.19 (m, 1H), 5.45 – 5.34 (m, 1H), 5.25 (s, 1H), 4.61 – 4.42 (m, 2H), 4.32 – 4.23 (m, 1H), 4.19 – 3.74 (m, 4H), 3.72 – 3.37 (m, 5H), 3.27 (s, 1H), 3.07 – 2.91 (m, 2H), 2.74 – 2.22 (m, 3H), 2.15 – 1.67 (m, 7H), 0.97 (m, 4H). LCMS: 721.4.

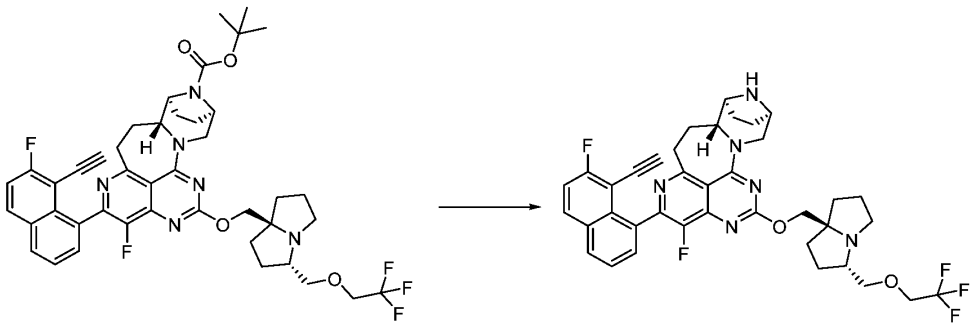
Example 163, Compound 163: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-(((3S,7aS)-3-((2,2,2-trifluoroethoxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



163-2 **163**

[1102] Compound **163** was prepared in a manner analogous to Compound **36** using Intermediate **163-2** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 – 7.85 (m, 1H), 7.40 – 7.32 (m, 2H), 7.22 (dd, J = 14.9, 2.6 Hz, 1H), 5.81 – 5.67 (m, 1H), 4.80 – 4.60 (m, 2H), 4.42 – 3.91 (m, 7H), 3.33 (p, J = 1.7 Hz, 8H), 2.42 (d, J = 8.4 Hz, 5H), 2.31 – 1.97 (m, 8H).. LCMS: 721.2.

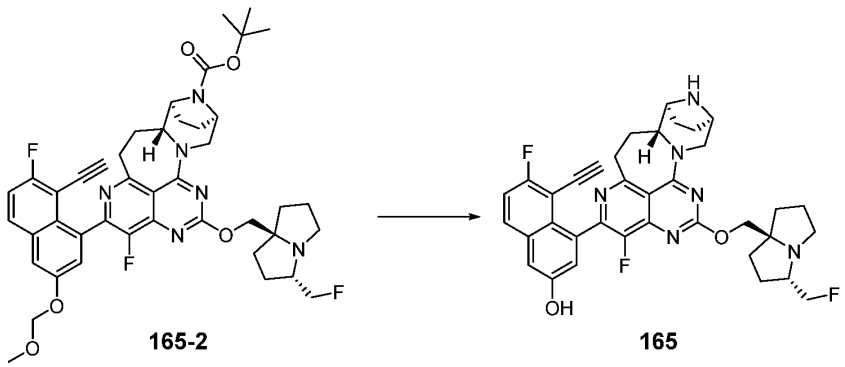
Example 164, Compound 164: (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((3S,7aS)-3-((2,2,2-trifluoroethoxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



164-1 164

[1103] Compound **164** was prepared in a manner analogous to Compound **36** using Intermediate **164-1** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.19 – 8.11 (m, 2H), 7.74 – 7.61 (m, 2H), 7.48 (td, J = 9.0, 4.8 Hz, 1H), 5.74 (td, J = 14.4, 3.0 Hz, 1H), 4.77 – 4.60 (m, 2H), 4.45 – 3.93 (m, 9H), 3.64 – 3.36 (m, 6H), 2.42 (d, J = 12.4 Hz, 4H), 2.29 – 1.99 (m, 9H). LCMS: 705.6.

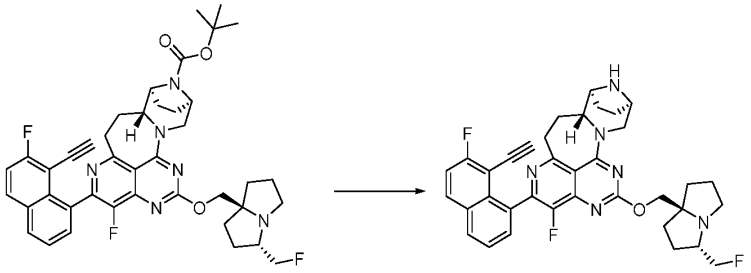
Example 165, Compound 165: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-(((3S,7aS)-3-(fluoromethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



165-2 165

[1104] Compound **165** was prepared in a manner analogous to Compound **36** using Intermediate **165-2** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.89 (ddt, J = 8.9, 5.8, 2.9 Hz, 1H), 7.41 – 7.30 (m, 2H), 7.23 (dd, J = 14.1, 2.6 Hz, 1H), 5.74 (td, J = 14.8, 3.0 Hz, 1H), 4.88 (s, 4H), 4.47 – 4.24 (m, 3H), 4.16 (s, 1H), 3.71 – 3.28 (m, 7H), 2.65 – 2.36 (m, 4H), 2.36 – 1.93 (m, 9H). LCMS: 641.3.

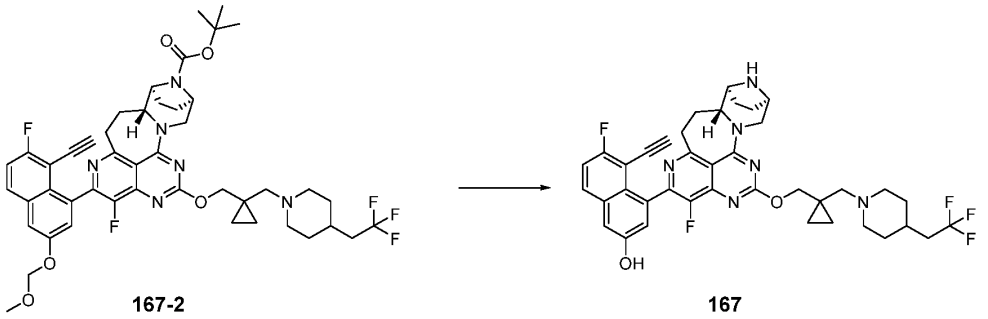
Example 166, Compound 166: (5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((3S,7aS)-3-(fluoromethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



166-1 166

[1105] Compound **166** was prepared in a manner analogous to Compound **36** using Intermediate **166-1** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.11 (m, 2H), 7.74 – 7.61 (m, 2H), 7.48 (td, J = 8.9, 4.5 Hz, 1H), 5.74 (td, J = 14.2, 3.0 Hz, 1H), 4.88 (s, 2H), 4.75 (dd, J = 12.3, 7.8 Hz, 1H), 4.68 – 4.64 (m, 1H), 4.45 – 4.29 (m, 3H), 4.17 (d, J = 6.0 Hz, 1H), 3.66 – 3.36 (m, 6H), 2.58 - 2.36 (m, 4H), 2.33 – 2.00 (m, 10H). LCMS: 625.3.

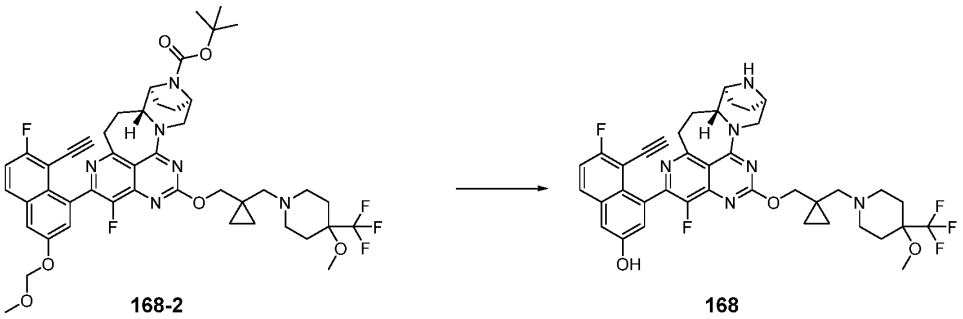
Example 167, Compound 167: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((1-((4-(2,2,2-trifluoroethyl)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



167-2 167

[1106] Compound **167** was prepared in a manner analogous to Compound **36** using Intermediate **167-2** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 (ddd, J = 9.1, 5.7, 3.4 Hz, 1H), 7.39 (d, J = 2.6 Hz, 1H), 7.35 (dt, J = 9.0, 4.5 Hz, 1H), 7.23 (dd, J = 17.2, 2.6 Hz, 1H), 5.68 (td, J = 14.6, 3.0 Hz, 1H), 4.63 – 4.28 (m, 4H), 4.14 (s, 1H), 3.95 (t, J = 11.9 Hz, 2H), 3.86 (s, 1H), 3.57 – 3.35 (m, 6H), 3.28 – 3.18 (m, 1H), 3.09 – 2.98 (m, 2H), 2.48 (dt, J = 18.9, 6.6 Hz, 2H), 2.26 – 1.96 (m, 8H), 1.72 (d, J = 13.0 Hz, 2H), 1.08 – 0.82 (m, 5H). LCMS: 719.3.

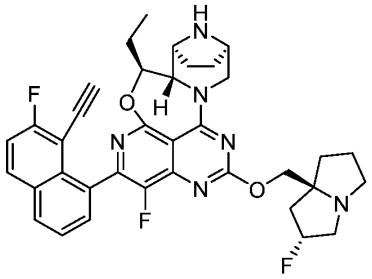
Example 168, Compound 168: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((1-((4-methoxy-4-(trifluoromethyl)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



168-2 168

[1107] Compound **168** was prepared in a manner analogous to Compound **36** using Intermediate **168-2** as the starting material. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.90 (ddd, J = 9.1, 5.7, 3.4 Hz, 1H), 7.40 – 7.38 (m, 1H), 7.35 (dt, J = 8.9, 4.5 Hz, 1H), 7.22 (dd, J = 15.4, 2.6 Hz, 1H), 4.61 (d, J = 11.9 Hz, 1H), 4.52 (s, 1H), 4.45 – 4.34 (m, 1H), 4.31 (s, 1H), 4.14 (s, 1H), 3.86 (d, J = 18.1 Hz, 2H), 3.59 – 3.35 (m, 9H), 3.21 (t, J = 12.6 Hz, 2H), 2.58 – 2.40 (m, 2H), 2.36 – 1.99 (m, 9H), 1.07 – 0.88 (m, 4H). LCMS: 735.4.

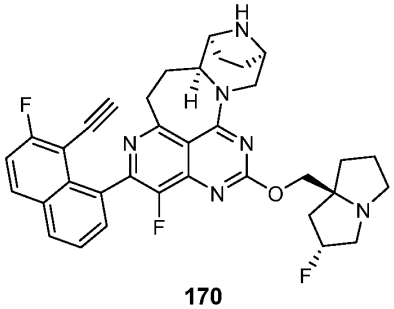
Example 169, Compound 169: (5*S*,5a*S*,6*S*,9*R*)-5-ethyl-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



169

[1108] Compound **169** was synthesized in a manner similar to Compound **13** using **Intermediate 116-3** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.06 (m, 2H), 7.71 – 7.51 (m, 2H), 7.46 (td, J = 8.9, 6.1 Hz, 1H), 5.75 – 5.37 (m, 2H), 4.79 – 4.65 (m, 2H), 4.60 – 4.43 (m, 2H), 4.39 – 4.25 (m, 2H), 4.12 – 3.80 (m, 2H), 3.80 – 3.42 (m, 3H), 2.82 – 1.75 (m, 12H), 1.18 (t, J = 7.2 Hz, 3H). LCMS: 641.1.

Example 170, Compound 170: (5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene

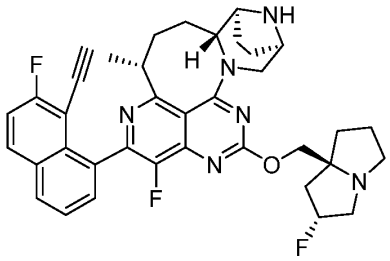


170

[1109] Intermediate **170-8** (40 mg, 0.06 mmol) was dissolved in acetonitrile (1 ml) and cooled to 0 °C. To it was added HCl solution (0.5 ml, 4.0 M in 1,4-dioxane). The resulting reaction mixture was stirred at 0 °C for 1 hour. Upon completion, the reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate aqueous solution, water and brine. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated to dryness. The residue was dissolved in acetonitrile/water and lyophilized to afford the title compound. ^{1}H NMR

(400 MHz, Methanol-d4) δ 8.17 – 8.07 (m, 2H), 7.74 – 7.56 (m, 2H), 7.46 (td, J = 9.0, 3.0 Hz, 1H), 5.33 (d, J = 53.7 Hz, 1H), 4.92 (d, J = 13.1 Hz, 1H), 4.89 (s, 1H), 4.36 (dd, J = 10.6, 3.8 Hz, 1H), 4.24 – 4.11 (m, 1H), 3.80 – 3.74 (m, 1H), 3.76 – 3.39 (m, 5H), 3.30 – 3.16 (m, 2H), 3.16 – 3.00 (m, 2H), 3.04 – 2.86 (m, 1H), 2.50 – 2.25 (m, 2H), 2.26 – 2.14 (m, 1H), 2.14 – 1.99 (m, 3H), 1.98 – 1.88 (m, 3H), 1.85 – 1.29 (m, 3H). LCMS: 611.3.

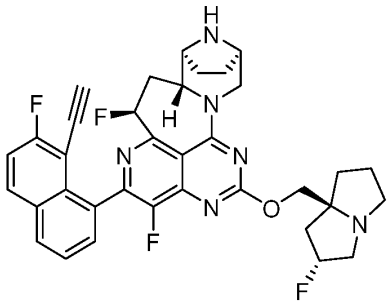
Example 171, Compound 171: (4R,6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



171

[1110] Hydrogen chloride solution (4.0 M in 1,4-dioxane, 12.2 mL, 48.7 mmol) was added via syringe to a vigorously stirred solution of **Intermediate 171-8** (223 mg, 0.302 mmol) in acetonitrile (12 mL) at 0°C. After 60 min, the resulting mixture was purified by reverse phase preparative HPLC (0.1% TFA in acetonitrile/water) to give Compound **171**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.09 (m, 2H), 7.74 – 7.54 (m, 2H), 7.52 – 7.42 (m, 1H), 5.70 – 5.46 (m, 2H), 4.77 – 4.69 (m, 2H), 4.38 – 3.41 (m, 9H), 2.93 – 1.57 (m, 14H), 1.39 (d, *J* = 6.4 Hz, 3H). LCMS: 639.1 $[M + H]^+$.

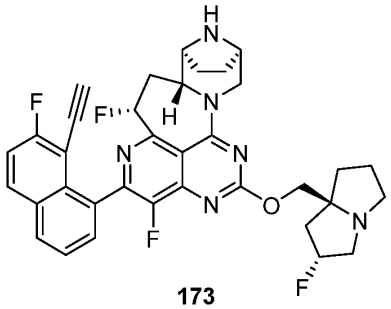
Example 172, Compound 172: (4*S*,5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1,4-difluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



172

[1111] Compound **172** was synthesized in a manner similar to Compound **13** using **Intermediate 172-6** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.28 – 8.06 (m, 2H), 7.75 – 7.57 (m, 2H), 7.47 (t, J = 9.0 Hz, 1H), 5.95 (ddd, J = 48.7, 8.0, 2.1 Hz, 1H), 5.81 (dd, J = 14.7, 3.1 Hz, 1H), 5.58 (d, J = 51.8 Hz, 1H), 4.79 – 4.55 (m, 3H), 4.43 – 4.11 (m, 2H), 4.11 – 3.76 (m, 3H), 3.60 – 3.52 (m, 1H), 3.52 – 3.43 (m, 2H), 3.00 – 1.94 (m, 12H). LCMS: 629.3.

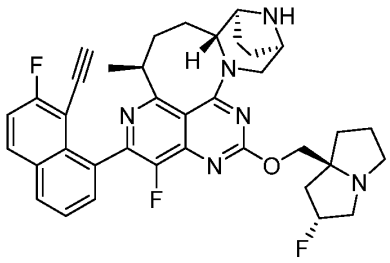
Example 173, Compound 173: (4*R*,5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1,4-difluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene



173

[1112] Compound **173** was synthesized in a manner similar to Compound **13** using **Intermediate 173-6** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.23 – 8.00 (m, 2H), 7.74 – 7.58 (m, 2H), 7.46 (td, J = 8.9, 3.3 Hz, 1H), 5.94 (dd, J = 47.3, 10.2 Hz, 1H), 5.69 – 5.40 (m, 2H), 4.78 – 4.65 (m, 2H), 4.53 (d, J = 11.5 Hz, 1H), 4.29 (d, J = 49.5 Hz, 2H), 4.13 – 3.78 (m, 3H), 3.69 – 3.35 (m, 3H), 2.95 – 1.63 (m, 12H). LCMS: 629.0.

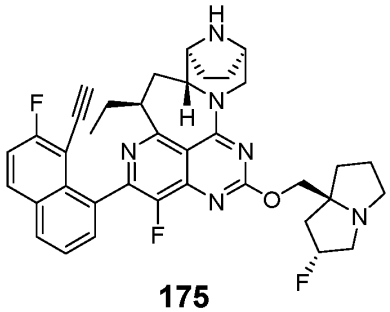
Example 174, Compound 174: (4S,6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



174

[1113] Compound **174** was synthesized in a manner similar to Compound **76** using **Intermediate 174-5** instead of **Intermediate 76-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.19 – 8.11 (m, 2H), 7.76 – 7.55 (m, 2H), 7.47 (dd, J = 9.0 Hz, 1H), 5.60 (d, J = 51.8 Hz, 1H), 4.80 – 4.72 (m, 2H), 4.45 – 4.20 (m, 3H), 4.05 – 3.45 (m, 6H), 2.85 – 2.13 (m, 8H), 1.99 – 1.84 (m, 2H), 1.40 (d, J = 6.5 Hz, 3H). LCMS: 639.1 $[M + H]^+$.

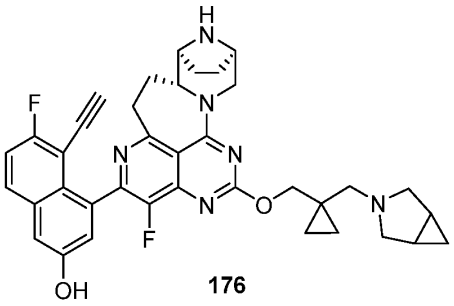
Example 175, Compound 175: (4S,5aR,6S,9R)-4-ethyl-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



175

[1114] Compound **175** was synthesized in a manner similar to Compound **76** using **Intermediate 175-5** instead of **Intermediate 76-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.23 – 8.10 (m, 2H), 7.75 – 7.61 (m, 2H), 7.52 – 7.44 (m, 1H), 5.92 – 5.75 (m, 1H), 5.59 (d, J = 51.9 Hz, 1H), 4.78 – 4.67 (m, 2H), 4.50 (dd, J = 13.1, 4.6 Hz, 1H), 4.37 (s, 1H), 4.17 – 3.83 (m, 4H), 3.62 – 3.35 (m, 5H), 2.80 – 1.69 (m, 17H), 1.19 – 0.96 (m, 3H). LCMS: 639.1 $[M + H]^+$.

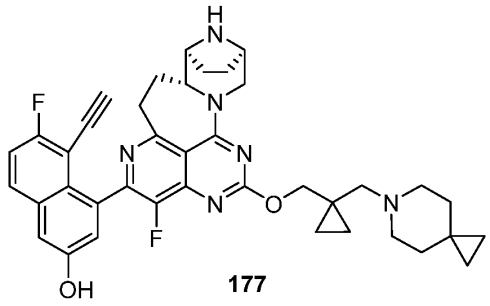
Example 176, Compound 176: 4-((5aR,6S,9R)-12-((1-((3-azabicyclo[3.1.0]hexan-3-yl)methyl)cyclopropyl)methoxy)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



176

[1115] Compound **176** was synthesized in a manner similar to Compound **106** using 3-azabicyclo[3.1.0]hexane instead of 4-(trifluoromethoxy)piperidine hydrochloride. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.91 – 7.85 (m, 1H), 7.38 – 7.30 (m, 2H), 7.23 – 7.17 (m, 1H), 5.74 – 5.59 (m, 1H), 4.53 – 4.29 (m, 3H), 4.28 – 3.91 (m, 3H), 3.58 – 3.36 (m, 5H), 2.83 (s, 1H), 2.52 – 2.36 (m, 2H), 2.14 – 1.96 (m, 5H), 1.86 (s, 3H), 0.97 – 0.72 (m, 7H). LCMS: 635.1.

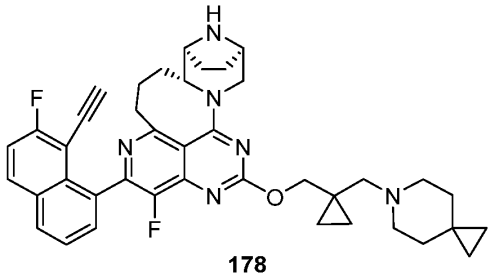
Example 177, Compound 177: 4-((5aR,6S,9R)-12-((1-((6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



177

[1116] Compound **177** was synthesized in a manner similar to Compound **106** using 6-azaspiro[2.5]octane instead of 4-(trifluoromethoxy)piperidine hydrochloride. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (ddd, J = 9.1, 5.7, 3.1 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.20 (dd, J = 15.6, 2.5 Hz, 1H), 5.66 (ddd, J = 18.1, 14.6, 3.1 Hz, 1H), 4.57 (t, J = 11.4 Hz, 1H), 4.48 – 4.29 (m, 3H), 4.16 – 4.10 (m, 1H), 3.88 – 3.76 (m, 2H), 3.58 – 3.32 (m, 6H), 3.18 – 3.08 (m, 2H), 2.53 – 2.39 (m, 2H), 2.31 – 2.18 (m, 2H), 2.15 – 1.95 (m, 4H), 1.33 – 1.15 (m, 2H), 1.04 – 0.95 (m, 2H), 0.95 – 0.84 (m, 2H), 0.57 – 0.39 (m, 4H). LCMS: 664.5.

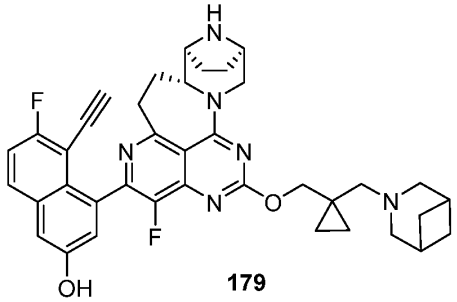
Example 178, Compound 178: (6aR,7S,10R)-13-((1-((6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



178

[1117] Compound **178** was synthesized in a manner similar to Compound **127** using 6-azaspiro[2.5]octane instead of 4-(trifluoromethoxy)piperidine hydrochloride. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.19 – 8.10 (m, 2H), 7.72 – 7.62 (m, 2H), 7.47 (td, J = 8.9, 3.0 Hz, 1H), 5.44 – 5.32 (m, 1H), 4.60 (dd, J = 17.9, 11.8 Hz, 1H), 4.47 (t, J = 11.4 Hz, 1H), 4.40 – 4.26 (m, 1H), 4.16 (d, J = 9.4 Hz, 1H), 4.07 (s, 1H), 3.95 – 3.77 (m, 2H), 3.70 – 3.62 (m, 1H), 3.54 – 3.33 (m, 3H), 3.17 – 2.67 (m, 4H), 2.37 – 2.18 (m, 3H), 2.16 – 1.65 (m, 7H), 1.31 – 1.17 (m, 2H), 1.00 (s, 2H), 0.90 (s, 2H), 0.55 – 0.37 (m, 4H). LCMS: 661.3.

Example 179, Compound 179: 4-((5aR,6S,9R)-12-((1-((3-azabicyclo[3.1.1]heptan-3-yl)methyl)cyclopropyl)methoxy)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol

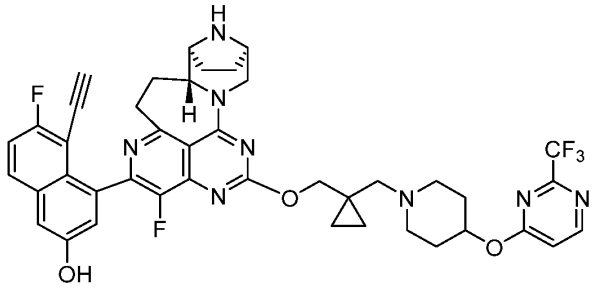


179

[1118] Compound **179** was synthesized in a manner similar to Compound **106** using 3-azabicyclo[3.1.1]heptane instead of 4-(trifluoromethoxy)piperidine hydrochloride. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.87 (ddd, J = 9.2, 5.7, 3.4 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.19 (dd, J = 14.8, 2.6 Hz, 1H), 5.62 (ddd, J = 18.0, 14.6, 3.0 Hz, 1H), 4.57 (dd, J = 11.8, 7.6 Hz, 1H), 4.47 (dd, J =

15.7, 11.8 Hz, 1H), 4.41 – 4.28 (m, 2H), 4.23 – 4.08 (m, 3H), 3.54 – 3.33 (m, 8H), 2.62 – 2.27 (m, 6H), 2.14 – 1.95 (m, 5H), 1.57 (t, *J* = 8.9 Hz, 1H), 1.03 – 0.87 (m, 4H). LCMS: 649.2.

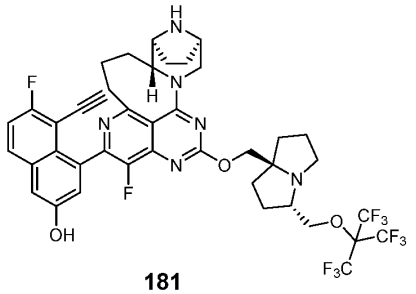
Example 180, Compound 180: 5-ethynyl-6-fluoro-4-((5aR,6S,9R)-1-fluoro-12-((1-((4-((2-(trifluoromethyl)pyrimidin-4-yl)oxy)piperidin-1-yl)methyl)cyclopropyl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol



180

[1119] Compound **180** was synthesized in a manner similar to Compound **122** using intermediate **180-4** instead of ((1*S*,7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol and using potassium bis(trimethylsilyl)amide instead of lithium bis(trimethylsilyl)amide. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.66 (d, J = 5.9 Hz, 1H), 7.88 (s, 1H), 7.44 – 7.16 (m, 2H), 7.06 (d, J = 20.5 Hz, 2H), 5.83 – 5.46 (m, 2H), 4.82 (m, 1H), 4.61 (d, J = 12.4 Hz, 1H), 4.47 (d, J = 11.2 Hz, 1H), 4.42 – 4.26 (m, 2H), 4.18 (d, J = 27.6 Hz, 1H), 3.93 (m, 1H), 3.85 (m, 1H), 3.79 – 3.59 (m, 1H), 3.59 – 3.41 (m, 2H), 3.38 (d, J = 6.2 Hz, 3H), 3.13 (m, 1H), 2.48 (m, 2H), 2.36 (m, 2H), 2.22 – 1.94 (m, 4H), 1.31 (m, 2H), 1.11 – 0.77 (m, 4H). LCMS: 799.4.

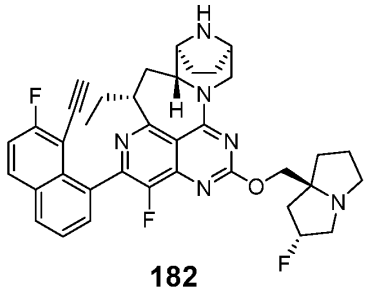
Example 181, Compound 181: 5-ethynyl-6-fluoro-4-((6a*R*,7*S*,10*R*)-1-fluoro-13-(((3*S*,7a*S*)-3-(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalen-2-yl)naphthalen-2-ol



181

[1120] Compound **181** was synthesized in a manner similar to Compound **63** using intermediate **181-2** instead of intermediate **63-7**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.97 – 7.87 (m, 1H), 7.47 – 7.33 (m, 2H), 7.31 – 7.18 (m, 1H), 5.47 – 5.36 (m, 1H), 4.81 – 4.69 (m, 2H), 4.64 – 4.47 (m, 2H), 4.46 – 4.22 (m, 2H), 4.22 – 4.05 (m, 2H), 4.00 – 3.13 (m, 4H), 3.12 – 2.87 (m, 2H), 2.66 – 1.60 (m, 16H), 1.96 (s, 6H). LCMS: 871.3.

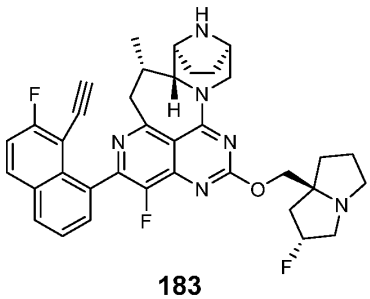
Example 182, Compound 182: (4R,5aR,6S,9R)-4-ethyl-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



182

[1121] Compound **182** was synthesized in a manner similar to Compound **76** using **Intermediate 182-5** instead of **Intermediate 76-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.18 – 8.11 (m, 2H), 7.71 – 7.62 (m, 2H), 7.52 – 7.42 (m, 1H), 5.86 – 5.72 (m, 1H), 5.68 – 5.49 (m, 1H), 4.74 – 4.64 (m, 1H), 4.43 (d, J = 12.5 Hz, 1H), 4.24 – 3.82 (m, 5H), 3.57 – 3.46 (m, 3H), 3.20 – 3.12 (m, 1H), 2.74 – 1.72 (m, 11H), 1.12 – 1.02 (m, 3H). LCMS: 639.1 $[M + H]^+$.

Example 183, Compound 183: (5S,5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene

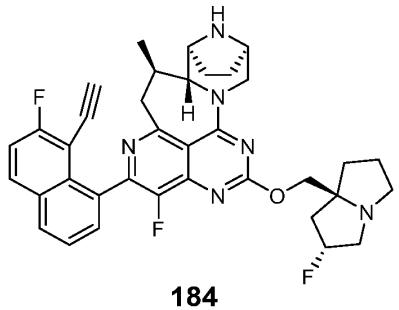


183

[1122] Compound **183** was synthesized in a manner similar to Compound **76** using **Intermediate 183-9** instead of **Intermediate 76-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.13 (m, 2H),

7.73 – 7.62 (m, 2H), 7.53 – 7.45 (m, 1H), 5.68 – 5.50 (m, 2H), 4.79 – 4.66 (m, 2H), 4.46 – 4.29 (m, 3H), 4.15 – 3.83 (m, 3H), 3.68 – 3.44 (m, 4H), 2.98 – 2.06 (m, 14H), 1.05 (dd, *J* = 18.1, 7.3 Hz, 3H). LCMS: 625.1 $[M+H]^+$

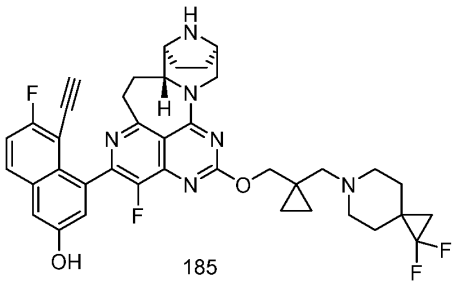
Example 184, Compound 184: (5R,5aR,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



184

[1123] Compound **184** was synthesized in a manner similar to Compound **76** using **Intermediate 184-5** instead of **Intermediate 76-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.21 - 8.11 (m, 2H), 7.74 – 7.62 (m, 2H), 7.53 – 7.44 (m, 1H), 5.79 – 5.49 (m, 2H), 4.78 – 4.66 (m, 2H), 4.34 (s, 2H), 4.13 – 3.86 (m, 4H), 3.65 – 3.46 (m, 2H), 3.27 – 3.14 (m, 1H), 2.82 – 1.77 (m, 12H), 1.44 – 1.33 (m, 3H). LCMS: 625.1 $[M+H]^+$.

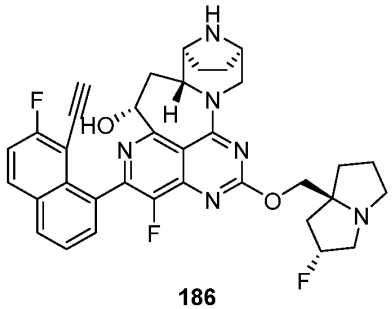
Example 185, Compound 185: 4-((5aR,6S,9R)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



185

[1124] Compound **185** was synthesized in a manner similar to Compound **78** using 1,1-difluoro-6-azaspiro[2.5]octane hydrochloride instead of 4,4-dimethyl-1,4-azasilepane hydrochloride. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 – 7.85 (m, 1H), 7.51 – 7.16 (m, 3H), 5.73 – 5.58 (m, 1H), 4.80 – 2.92 (m, 13H), 2.70 – 0.75 (m, 18H). LCMS: 699.1.

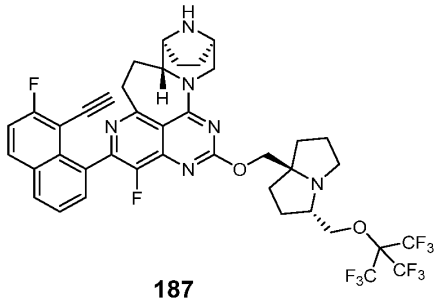
Example 186, Compound 186: (4*R*,5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-4-ol



186

[1125] Compound **186** was synthesized in a manner similar to Compound **13** using **Intermediate 186-6** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.24 – 8.06 (m, 2H), 7.74 – 7.61 (m, 2H), 7.46 (td, J = 9.0, 3.5 Hz, 1H), 5.77 (ddd, J = 14.6, 8.3, 3.0 Hz, 1H), 5.58 (d, J = 52.1 Hz, 1H), 5.01 (d, J = 17.6 Hz, 1H), 4.77 – 4.64 (m, 2H), 4.61 – 4.49 (m, 1H), 4.39 – 4.16 (m, 2H), 4.11 – 3.81 (m, 3H), 3.62 – 3.39 (m, 3H), 2.83 – 1.80 (m, 11H). LCMS: 627.1.

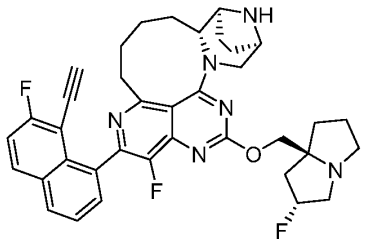
Example 187, Compound 187: (5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((3*S*,7a*S*)-3-(((1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene



187

[1126] Compound **187** was synthesized in a manner similar to Compound **113** using intermediate **63-4** instead of ((6'*R*,7a'*R*)-6'-fluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.25 – 8.11 (m, 2H), 7.75 – 7.62 (m, 2H), 7.54 – 7.43 (m, 1H), 5.82 – 5.65 (m, 1H), 4.81 – 4.66 (m, 2H), 4.65 – 4.29 (m, 5H), 4.23 – 4.11 (m, 1H), 4.01 – 3.20 (m, 4H), 2.65 – 1.23 (m, 16H), 1.96 (s, 6H). LCMS: 841.0.

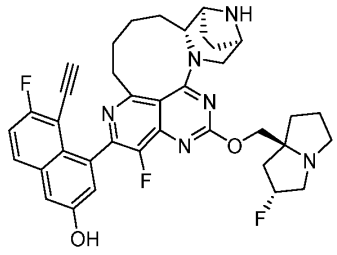
Example 188, Compound 188: (7a*R*,8*S*,11*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-14-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,6,7,7a,8,9,10,11,12-decahydro-3,12a,13,15,16-pentaaza-8,11-methanocyclohepta[4,5]cyclonona[1,2,3-*de*]naphthalene



188

[1127] Compound **188** was synthesized in a manner similar to Compound **13** using **Intermediate 188-8** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.14 (dd, J = 6.0, 3.4 Hz, 2H), 7.68 (q, J = 7.4 Hz, 2H), 7.46 (td, J = 9.0, 7.0 Hz, 1H), 5.60 (d, J = 51.6 Hz, 1H), 4.78 – 3.41 (m, 12H), 2.95 – 0.67 (m, 19H). LCMS: 639.1.

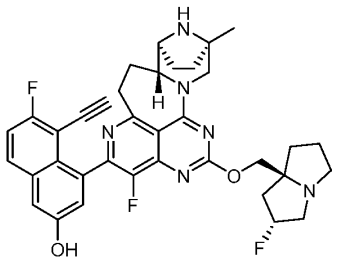
Example 189, Compound 189: 5-ethynyl-6-fluoro-4-((7a*R*,8*S*,11*R*)-1-fluoro-14-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4,5,6,7,7a,8,9,10,11,12-decahydro-3,12a,13,15,16-pentaaza-8,11-methanocyclohepta[4,5]cyclonona[1,2,3-*de*]naphthalen-2-yl)naphthalen-2-ol



189

[1128] Compound **189** was synthesized in a manner similar to Compound **13** using **Intermediate 189-2** instead of **Intermediate 13-11**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.99 – 7.74 (m, 1H), 7.46 – 7.10 (m, 3H), 5.75 – 5.21 (m, 1H), 4.97 – 4.88 (m, 2H), 4.83 (s, 2H), 4.80 – 4.60 (m, 1H), 4.50 – 3.42 (m, 5H), 2.97 – 0.58 (m, 22H). LCMS: 655.2.

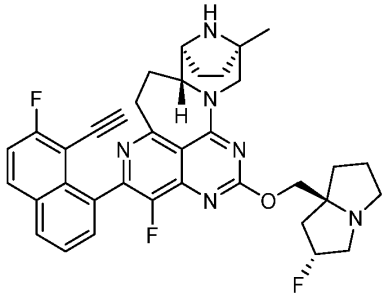
Example 190, Compound 190: 5-ethynyl-6-fluoro-4-((5a*R*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-9-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol



190

[1129] Compound **190** was synthesized in a manner similar to Compound **122** using intermediate **190-5** instead of intermediate **63-6**, using ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol instead of ((6'*R*,7a'*R*)-6'-fluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol, and using 0.1% acetic acid in acetonitrile/water instead of 0.1% trifluoroacetic acid in acetonitrile/water. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.95 – 7.78 (m, 1H), 7.40 – 7.27 (m, 2H), 7.27 – 7.09 (m, 1H), 5.62 – 5.28 (m, 2H), 4.57 – 4.30 (m, 2H), 4.26 – 4.07 (m, 1H), 3.83 – 2.98 (m, 7H), 2.65 – 1.51 (m, 14H), 1.96 (s, 6H), 1.50 (s, 3H). LCMS: 641.0.

Example 191, Compound 191: (5a*R*,6*S*,9*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-9-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene

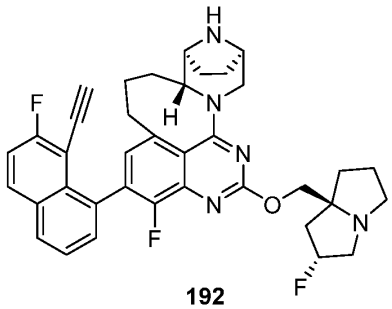


191

[1130] Compound **191** was synthesized in a manner similar to Compound **190** using ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane instead of ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.20 – 8.09

(m, 2H), 7.73 – 7.60 (m, 2H), 7.54 – 7.33 (m, 1H), 5.60 – 5.24 (m, 2H), 4.58 – 4.36 (m, 2H), 4.26 – 4.13 (m, 1H), 3.77 (t, J = 7.5 Hz, 1H), 3.72 – 3.08 (m, 6H), 2.55 – 1.57 (m, 14H), 1.96 (s, 6H), 1.51 (s, 3H). LCMS: 625.3.

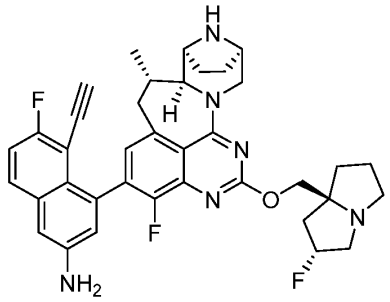
Example 192, Compound 192: (1S,4R,15aR)-11-(8-ethynyl-7-fluoronaphthalen-1-yl)-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,4,5,13,14,15,15a-octahydro-1H-1,4-epiminoazepino[1',2':1,8]azocino[2,3,4-de]quinazoline



192

[1131] Compound **192** was synthesized in a manner similar to Compound **2** using intermediate **192-3** instead of intermediate **2-1**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.19 – 7.99 (m, 2H), 7.62 (td, J = 7.6, 3.9 Hz, 1H), 7.52 (t, J = 8.3 Hz, 1H), 7.48 – 7.37 (m, 1H), 7.37 – 7.08 (m, 1H), 5.68 – 5.41 (m, 1H), 5.40 – 5.16 (m, 1H), 4.71 (d, J = 19.3 Hz, 2H), 4.39 – 4.13 (m, 1H), 4.13 – 3.75 (m, 5H), 3.64 (d, J = 14.7 Hz, 1H), 3.45 (s, 2H), 3.21 (d, J = 21.3 Hz, 1H), 2.98 (dt, J = 68.9, 12.2 Hz, 2H), 2.83 – 2.51 (m, 2H), 2.51 – 2.21 (m, 4H), 2.21 – 1.90 (m, 3H), 1.90 – 1.55 (m, 4H). ^{19}F NMR (376 MHz, Methanol- d_4) δ -77.69, -106.98 – -107.54 (m), -133.29 (dd, J = 309.7, 7.3 Hz), -173.89 – -175.96 (m). LCMS: 624.37.

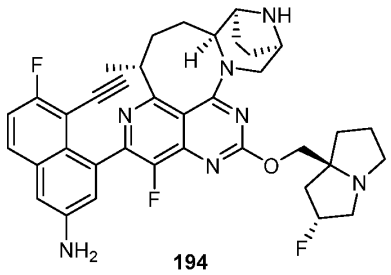
Example 193, Compound 193: 5-ethynyl-6-fluoro-4-((1S,4R,14S,14aS)-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-14-methyl-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)naphthalen-2-amine



193

[1132] A solution of intermediate **193-2** (11.42 mg, 12.6 umol) and 2,6-lutidine (6 uL, 51.8 umol) in MeCN (0.2 mL) was stirred at rt as trimethylsilyl trifluoromethanesulfonate (9 uL, 49.6 umol) was added. The reaction mixture was diluted with MeOH (1 mL) and then hydroxylammine hydrochloride (13.72 mg, 197 umol) and sodium acetate (12.62 mg, 210 umol) were added. The resulting mixture was stirred at rt for 45 min. After the reaction mixture was concentrated by rotorvap, the residue was dissolved in MeOH (0.5 mL), filtered, and purified by preparative HPLC (Gemini 5 um NX-C18 110 A LC Column 250 x 21.2 mm AX) eluting 5-60% acetonitrile (0.1% TFA) in water (0.1% TFA) over 20 min and the collected fractions were freeze-dried to give Compound **193**. ^{1}H NMR (400 MHz, Methanol-*d4*) δ 7.81 (ddd, J = 9.3, 5.8, 3.7 Hz, 1H), 7.36 – 7.24 (m, 2H), 7.17 (dd, J = 8.8, 6.4 Hz, 1H), 7.10 (t, J = 2.5 Hz, 1H), 5.67 – 5.40 (m, 1H), 5.11 (dd, J = 14.1, 1.6 Hz, 1H), 4.78 – 4.51 (m, 2H), 4.29 (d, J = 30.5 Hz, 2H), 3.98 (ddd, J = 37.1, 14.1, 3.1 Hz, 1H), 3.91 – 3.70 (m, 3H), 3.50 – 3.33 (m, 2H), 3.22 – 3.05 (m, 1H), 2.89 (q, J = 6.3, 5.8 Hz, 1H), 2.78 – 2.50 (m, 3H), 2.50 – 2.26 (m, 3H), 2.25 – 1.96 (m, 5H), 1.96 – 1.80 (m, 1H), 1.20 (dd, J = 6.5, 3.1 Hz, 3H). ^{19}F NMR (376 MHz, Methanol- *d4*) δ -77.69, -112.34 (d, J = 35.5 Hz), -134.70 (d, J = 6.8 Hz), -135.78 (d, J = 6.5 Hz), -174.89 (dt, J = 53.1, 20.1 Hz). LCMS: 639.4.

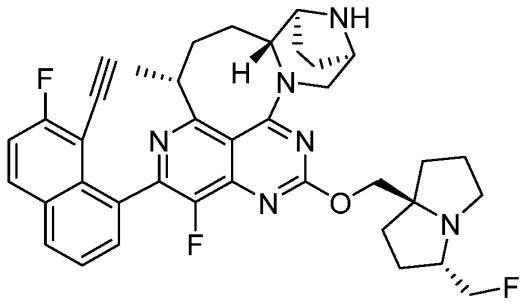
Example 194, Compound 194: 5-ethynyl-6-fluoro-4-((4R,6aS,7S,10R)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)naphthalen-2-amine



194

[1133] Intermediate **194-11** (19 mg, 0.025 mmol) was dissolved in 1.0 mL dichloromethane and treated with HCl solution (0.63 ml, 2.5 mmol, 4 N in 1,4-dioxane) at room temperature. After 30 minutes, hexane was added, and the precipitate was collected by vacuum filtration then dissolved in MeOH/H_2O and purified by RP-HPLC to afford Compound **194**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.87 (td, J = 9.3, 5.7 Hz, 1H), 7.42 (q, J = 2.4 Hz, 1H), 7.40 – 7.05 (m, 2H), 5.61 (d, J = 51.7 Hz, 1H), 5.21 (dd, J = 14.0, 9.0 Hz, 1H), 4.78 – 4.72 (m, 2H), 4.25 (d, J = 20.4 Hz, 1H), 4.09 – 3.89 (m, 4H), 3.88 – 3.55 (m, 2H), 3.56 – 3.43 (m, 2H), 2.88 – 2.56 (m, 2H), 2.44 – 2.35 (m, 5H), 2.21 (s, 1H), 2.14 – 1.93 (m, 6H), 1.50 – 1.22 (m, 4H). LCMS: 654.4.

Example 195, Compound 195: (4R,6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((3S,7aS)-3-(fluoromethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-methyl-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene

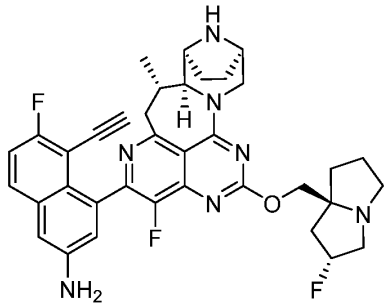


195

[1134] Compound **195** was synthesized in a manner similar to Compound **171** using **Intermediate 195-2** instead of **Intermediate 171-8**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.15

(dd, *J* = 9.1, 5.7 Hz, 2H), 7.75 – 7.54 (m, 2H), 7.47 (td, *J* = 9.0, 2.8 Hz, 1H), 5.57 – 5.45 (m, 1H), 4.79 – 4.62 (m, 2H), 4.41 – 4.04 (m, 4H), 3.66 (d, *J* = 13.7 Hz, 3H), 3.48 (t, *J* = 6.4 Hz, 0H), 2.90 (q, *J* = 9.7, 9.0 Hz, 1H), 2.52 – 1.96 (m, 7H), 1.84 – 1.60 (m, 3H), 1.39 (d, *J* = 6.4 Hz, 3H). LCMS: 653.1.

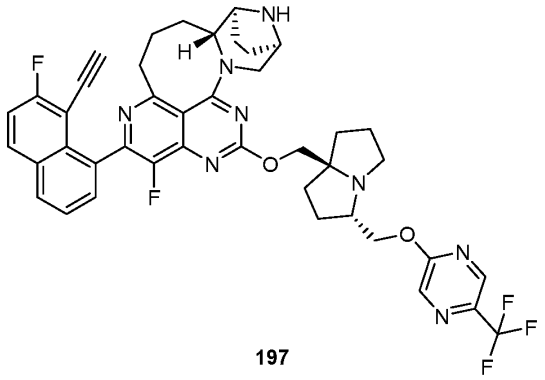
Example 196, Compound 196: 5-ethynyl-6-fluoro-4-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-amine



196

[1135] Compound **196** was synthesized in a manner similar to Compound **64** using intermediate **194-9** instead of ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane. ^{1}H NMR (400 MHz, Methanol-*d*$_4$) δ 7.93 (ddd, *J* = 8.9, 5.7, 3.1 Hz, 1H), 7.54 – 7.24 (m, 3H), 5.61 (d, *J* = 52.2 Hz, 1H), 5.50 – 5.37 (m, 1H), 4.94 – 4.88 (m, 1H), 4.84 – 4.81 (m, 1H), 4.80 – 4.67 (m, 1H), 4.49 – 4.20 (m, 2H), 4.12 (d, *J* = 6.2 Hz, 1H), 4.09 – 3.63 (m, 4H), 3.60 – 3.38 (m, 2H), 3.17 – 1.69 (m, 15H). LCMS: 641.0.

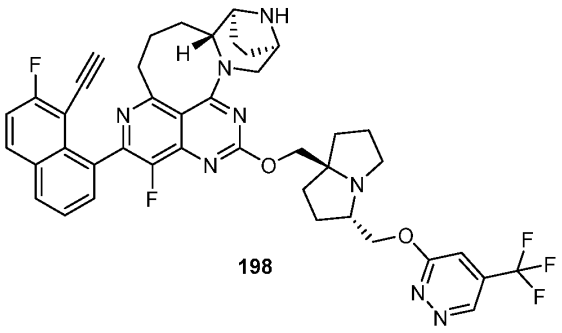
Example 197, Compound 197: (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((3S,7aS)-3-(((5-(trifluoromethyl)pyrazin-2-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



197

[1136] Compound **197** was synthesized in a manner similar to Compound **154** using intermediate **155-1** instead of intermediate **149-1**. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.60 (d, J = 13.1 Hz, 1H), 8.29 (d, J = 1.3 Hz, 1H), 8.17 (dd, J = 7.6, 2.0 Hz, 2H), 7.69 (p, J = 8.4, 7.8 Hz, 2H), 7.46 (dt, J = 18.2, 9.0 Hz, 1H), 5.42 (d, J = 13.8 Hz, 1H), 4.95 (dd, J = 12.9, 3.7 Hz, 1H), 4.79 – 4.68 (m, 3H), 4.43 (d, J = 39.4 Hz, 2H), 4.31 (s, 1H), 4.17 (d, J = 9.4 Hz, 1H), 4.10 (s, 1H), 3.69 (d, J = 15.2 Hz, 2H), 3.61 (s, 1H), 3.59 – 3.39 (m, 1H), 3.05 (d, J = 18.6 Hz, 1H), 3.01 – 2.91 (m, 1H), 2.53 – 2.40 (m, 2H), 2.33 (d, J = 12.8 Hz, 1H), 2.30 – 2.18 (m, 4H), 2.13 (dd, J = 12.6, 6.9 Hz, 2H), 2.04 (s, 2H), 1.96 (s, 1H), 1.80 (dd, J = 30.3, 13.0 Hz, 3H). LCMS:783.4.

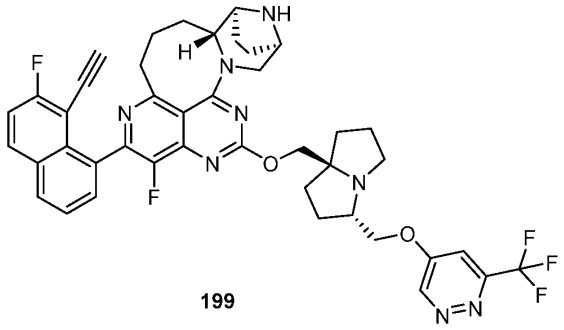
Example 198, Compound 198: (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((3S,7aS)-3-(((5-(trifluoromethyl)pyridazin-3-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



198

[1137] Lithium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 27.3 µL, 27.3 µmol) was added to a stirred reaction mixture of intermediate **115-3** (10.0 mg, 15.2 µmol), intermediate **198-1** (7.21 mg, 22.7 µmol), and tetrahydrofuran (0.5 mL) at 0 °C. Upon completion (about 5 min), added brine and extracted with ethyl acetate. The organic layer was wash with aqueous sodium carbonate and water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give Boc-protected product which was dissolved in acetonitrile (0.3 mL) and cooled to 0 °C. To it was added Hydrogen chloride solution (4.0 M in 1,4-dioxane, 250 µL, 1.0 mmol) and stirred for 1 hour. Upon completion, concentrated to dryness. The residue was purified by RP-HPLC (5% to 60 % 0.1% TFA in MeCN/0.1% TFA in H_2O). Fractions containing the product were pooled and lyophilized to yield Compound **198**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.25 (d, J = 2.1 Hz, 1H), 8.20 – 8.15 (m, 2H), 7.74 – 7.63 (m, 2H), 7.60 – 7.41 (m, 2H), 5.43 (t, J = 12.3 Hz, 1H), 5.13 (dd, J = 12.8, 3.8 Hz, 1H), 4.78 (d, J = 6.2 Hz, 3H), 4.54 (s, 2H), 4.32 (s, 1H), 4.18 (d, J = 9.3 Hz, 1H), 4.09 (s, 1H), 3.73 – 3.60 (m, 3H), 3.59 – 3.49 (m, 1H), 3.42 (d, J = 12.5 Hz, 1H), 3.26 – 2.71 (m, 3H), 2.62 – 2.26 (m, 3H), 2.34 – 2.05 (m, 4H), 1.96 (s, 3H), 1.88 – 1.71 (m, 3H). LCMS: 783.4.

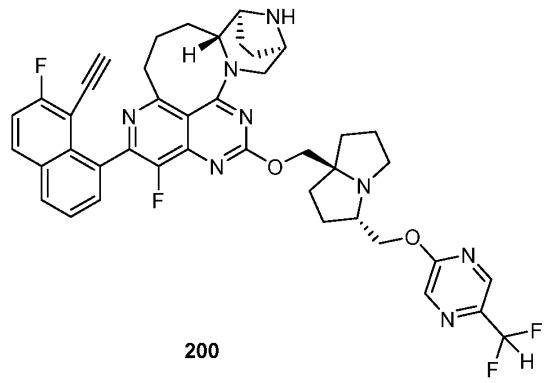
Example 199, Compound 199: (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((3S,7aS)-3-(((6-(trifluoromethyl)pyridazin-4-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



199

[1138] Compound **199** was synthesized in a manner similar to Compound **154** using intermediate **199-3** instead of intermediate **149-1**. ^{1}H NMR (400 MHz, Methanol-d4) δ 9.06 (d, J = 41.3 Hz, 1H), 8.17 (d, J = 7.6 Hz, 2H), 7.94 – 7.57 (m, 3H), 7.53 – 7.39 (m, 1H), 5.43 (d, J = 13.8 Hz, 1H), 5.06 – 4.91 (m, 1H), 4.91 (s, 0H), 4.78 (s, 2H), 4.63 (t, J = 10.6 Hz, 1H), 4.49 (s, 2H), 4.31 (s, 1H), 4.17 (d, J = 9.3 Hz, 1H), 4.10 (s, 1H), 3.70 (s, 1H), 3.62 (s, 1H), 3.48 (d, J = 17.8 Hz, 4H), 2.95 (s, 2H), 2.50 (s, 2H), 2.32 (d, J = 42.6 Hz, 5H), 2.15 (s, 4H), 1.81 (d, J = 27.0 Hz, 3H). LCMS: 783.4.

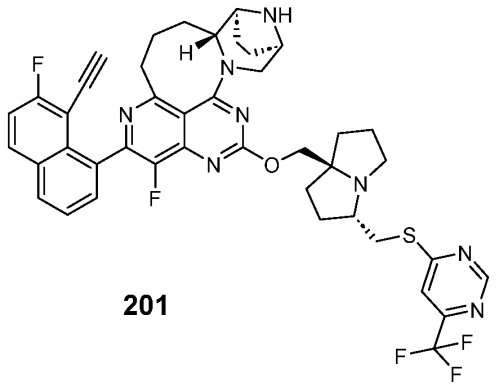
Example 200, Compound 200: (6aR,7S,10R)-13-(((3S,7aS)-3-(((5-(difluoromethyl)pyrazin-2-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



200

[1139] Compound **200** was synthesized in a manner similar to Compound **198** using 2-chloro-5-(difluoromethyl)pyrazine instead of 3-chloro-5-(trifluoromethyl)pyridazine. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.47 (d, J = 14.3 Hz, 1H), 8.17 (d, J = 8.6 Hz, 3H), 7.70 – 7.66 (m, 2H), 7.46 (dt, J = 18.1, 9.0 Hz, 1H), 6.80 (td, J = 54.7, 3.2 Hz, 1H), 5.43 (t, J = 11.7 Hz, 1H), 4.94 (dd, J = 13.0, 3.6 Hz, 1H), 4.83 – 4.65 (m, 4H), 4.39 (d, J = 66.1 Hz, 3H), 4.21 – 4.01 (m, 2H), 3.66 (dd, J = 23.1, 13.3 Hz, 3H), 3.54 (d, J = 10.8 Hz, 1H), 3.44 (s, 1H), 3.19 – 2.77 (m, 2H), 2.47 (d, J = 20.9 Hz, 2H), 2.33 (d, J = 13.5 Hz, 1H), 2.30 – 2.17 (m, 2H), 2.18 – 1.96 (m, 4H), 1.96 – 1.56 (m, 3H). LCMS: 765.4.

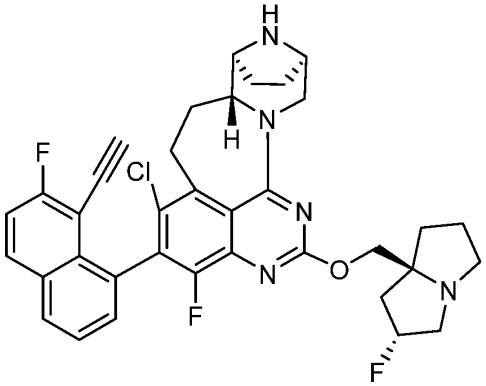
Example 201, Compound 201: (6aR,7S,10R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-13-(((3S,7aS)-3-(((6-(trifluoromethyl)pyrimidin-4-yl)thio)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



201

[1140] Compound **201** was synthesized in a manner similar to Compound **154** using intermediate **201-4** instead of intermediate **149-1**. ^{1}H NMR (400 MHz, Methanol-d4) δ 9.22 – 8.89 (m, 1H), 8.16 (t, J = 7.3 Hz, 2H), 7.98 – 7.77 (m, 1H), 7.70 (q, J = 7.0 Hz, 2H), 7.48 (t, J = 8.8 Hz, 1H), 5.38 (d, J = 14.1 Hz, 1H), 4.75 – 4.63 (m, 1H), 4.32 (d, J = 18.8 Hz, 2H), 4.20 – 4.04 (m, 1H), 3.79 (d, J = 7.0 Hz, 2H), 3.68 (s, 2H), 3.63 (d, J = 11.7 Hz, 1H), 3.46 (d, J = 6.3 Hz, 2H), 3.11 (d, J = 34.2 Hz, 1H), 2.88 (d, J = 13.0 Hz, 1H), 2.54 – 2.23 (m, 8H), 2.21 – 2.00 (m, 7H), 1.84 – 1.67 (m, 2H). LCMS: 799.4.

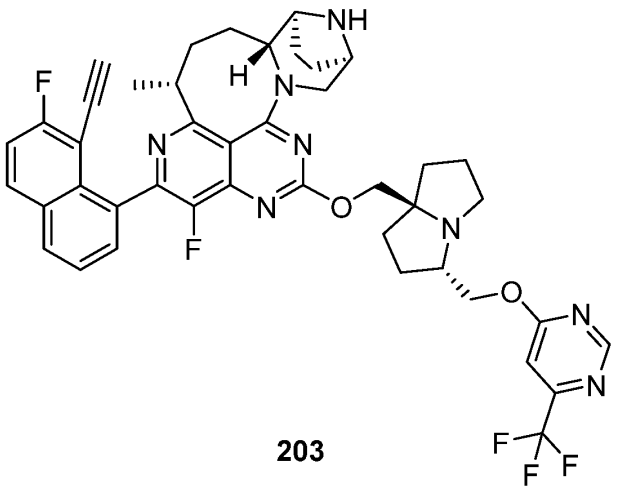
Example 202, Compound 202: (1S,4R,14aR)-12-chloro-11-(8-ethynyl-7-fluoronaphthalen-1-yl)-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazoline



202

[1141] Compound **202** was synthesized in a manner similar to Compound **204** using ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane instead of ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.18 – 8.09 (m, 2H), 7.72 – 7.63 (m, 1H), 7.52 – 7.41 (m, 2H), 5.66 – 5.44 (m, 2H), 4.80 – 4.59 (m, 2H), 4.39 – 4.28 (m, 2H), 4.16 – 3.78 (m, 5H), 3.60 – 3.40 (m, 3H), 3.19 – 3.05 (m, 1H), 2.73 – 1.97 (m, 13H). LCMS: 644.2.

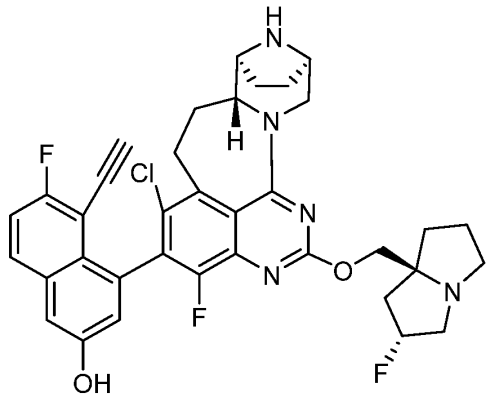
Example 203, Compound 203: (4*R*,6a*R*,7*S*,10*R*)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-4-methyl-13-(((3*S*,7a*S*)-3-((((6-(trifluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4*H*-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-*de*]naphthalene



203

[1142] Hydrogen chloride solution (4.0 M in 1,4-dioxane, 51.0 µL, 0.204 mmol) was added via syringe to a vigorously stirred solution of **Intermediate 203-2** (12.4 mg, 13.9 µmol) in acetonitrile (0.4 mL) at room temperature. After 110 min, the resulting mixture was purified by reverse phase preparative HPLC (0.1% trifluoroacetic acid in acetonitrile/water) to give Compound **203**. ^{1}H NMR (400 MHz, Methanol-*d*$_4$) δ 8.93 (d, *J* = 11.5 Hz, 1H), 8.20 – 8.04 (m, 2H), 7.75 – 7.52 (m, 2H), 7.43 (dt, *J* = 11.8, 9.0 Hz, 1H), 7.25 (dd, *J* = 16.2, 1.1 Hz, 1H), 5.55 – 5.41 (m, 1H), 5.00 (ddd, *J* = 13.5, 10.1, 3.6 Hz, 1H), 4.79 – 4.64 (m, 3H), 4.45 (s, 1H), 4.29 (s, 1H), 4.16 (d, *J* = 9.2 Hz, 1H), 4.05 (t, *J* = 6.1 Hz, 1H), 3.73 – 3.56 (m, 3H), 3.54 – 3.42 (m, 1H), 3.27 – 3.08 (m, 1H), 2.83 (q, *J* = 9.9, 9.1 Hz, 1H), 2.45 (dd, *J* = 13.9, 8.6 Hz, 2H), 2.37 – 1.92 (m, 7H), 1.69 (td, *J* = 26.6, 23.0, 13.9 Hz, 4H), 1.36 (dd, *J* = 6.5, 4.8 Hz, 3H). LCMS: 797.2.

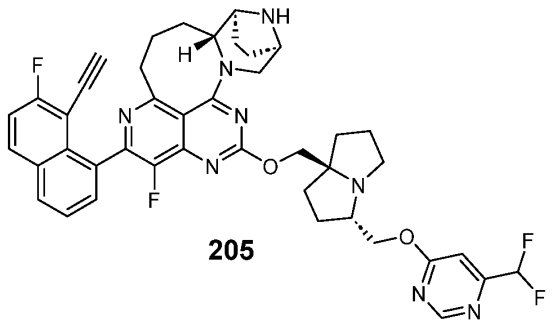
Example 204, Compound 204: 4-((1S,4R,14aR)-12-chloro-10-fluoro-8-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,4,5,13,14,14a-octahydro-1,4-epiminoazepino[1',2':1,7]azepino[2,3,4-de]quinazolin-11-yl)-5-ethynyl-6-fluoronaphthalen-2-ol



204

[1143] Compound **204** was synthesized in a manner similar to Compound **79** using intermediate **204-15** instead of intermediate **79-5**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.91-7.84 (m, 1H), 7.39 – 7.28 (m, 2H), 7.04 (dd, J = 14.4, 2.6 Hz, 1H), 5.65 – 5.44 (m, 2H), 4.78 – 4.60 (m, 2H), 4.41 – 4.27 (m, 2H), 4.21 – 3.43 (m, 8H), 3.18 – 3.05 (m, 1H), 2.72 – 1.99 (m, 15H). LCMS: 660.1.

Example 205, Compound 205: (6aR,7S,10R)-13-(((3S,7aS)-3-(((6-(difluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene

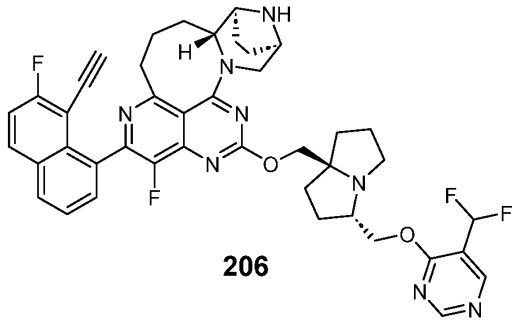


205

[1144] Compound **205** was synthesized in a manner similar to Compound **207** using intermediate **205-2** instead of intermediate **207-2**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.88 (m, 1H), 8.16 (m, 3H), 7.76 – 7.40 (m, 2H), 7.14 (m, 1H), 6.66 (td, J = 54.6, 6.3 Hz, 1H), 5.40 (m, 1H), 5.02 (m,

1H), 4.80 – 4.70 (m, 3H), 4.46 (m, 2H), 4.30 (m, 1H), 4.17 (m, 1H), 4.09 (m, 1H), 3.74 – 3.39 (m, 6H), 3.08 – 2.94 (m, 1H), 2.90 (m, 1H), 2.56 – 2.40 (m, 2H), 2.38 – 2.08 (m, 5H), 2.00 (m, 3H), 1.89 – 1.72 (m, 3H). LCMS: 765.4.

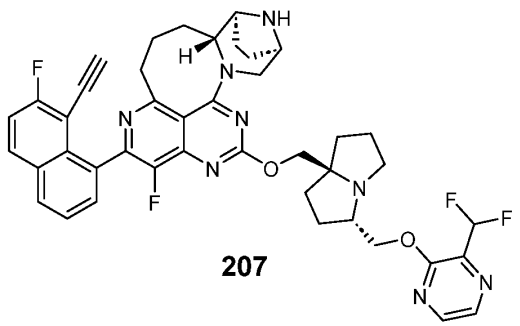
Example 206, Compound 206: (6aR,7S,10R)-13-(((3S,7aS)-3-(((5-(difluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



206

[1145] Compound **206** was synthesized in a manner similar to Compound **207** using intermediate **206-4** instead of intermediate **207-2**. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.90 (d, J = 14.7 Hz, 1H), 8.74 (d, J = 5.3 Hz, 1H), 8.20 – 8.10 (m, 3H), 7.69 (q, J = 9.8, 8.5 Hz, 3H), 7.53 – 7.41 (m, 1H), 7.05 (td, J = 54.0, 13.4 Hz, 1H), 5.42 (t, J = 12.8 Hz, 1H), 5.10 – 4.97 (m, 1H), 4.88 – 4.71 (m, 4H), 4.44 (d, J = 37.9 Hz, 2H), 4.30 (s, 1H), 4.17 (d, J = 9.2 Hz, 1H), 4.08 (s, 1H), 3.83 – 3.58 (m, 4H), 3.59 – 3.38 (m, 3H), 3.18 – 2.72 (m, 2H), 2.57 – 2.47 (m, 2H), 2.41 – 2.17 (m, 5H), 2.07 – 1.66 (m, 4H). LCMS: 765.4.

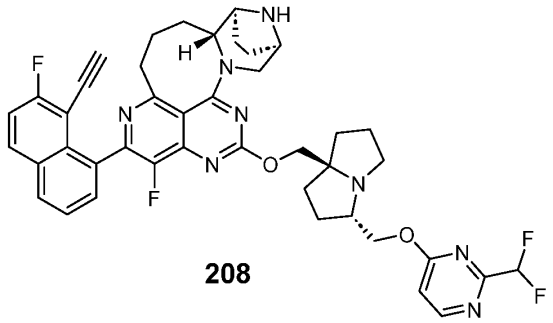
Example 207, Compound 207: (6aR,7S,10R)-13-(((3S,7aS)-3-(((3-(difluoromethyl)pyrazin-2-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



207

[1146] Intermediate **207-3** (13 mg, 15 μmol) was dissolved in acetonitrile (0.6 mL) and cooled to 0 °C. To it was added Hydrogen chloride solution (4.0 M in 1,4-dioxane, 500 μL, 2.0 mmol) and the mixture was stirred for 1 hour. Upon completion, the mixture was concentrated to dryness. The residue was purified by RP-HPLC (5% to 60 % 0.1% TFA in MeCN/0.1% TFA in H_2O). Fractions containing the product were pooled and lyophilized to yield Compound **207**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.36 (dd, J = 23.0, 2.8 Hz, 2H), 8.20 – 8.13 (m, 2H), 7.74 – 7.61 (m, 2H), 7.54 – 7.40 (m, 1H), 6.99 (td, J = 53.6, 14.8 Hz, 1H), 5.51 – 5.37 (m, 1H), 5.07 – 4.91 (m, 1H), 4.85 – 4.70 (m, 4H), 4.57 – 4.35 (m, 2H), 4.33 – 4.27 (m, 1H), 4.23 – 4.14 (m, 1H), 4.14 – 4.04 (m, 1H), 3.75 – 3.51 (m, 4H), 3.52 – 3.37 (m, 1H), 3.13 – 2.86 (m, 2H), 2.56 – 2.20 (m, 8H), 2.18 – 1.66 (m, 5H). LCMS: 765.4.

Example 208, Compound 208: (6aR,7S,10R)-13-(((3S,7aS)-3-(((2-(difluoromethyl)pyrimidin-4-yl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalene



208

[1147] Compound **208** was synthesized in a manner similar to Compound **207** using intermediate **208-2** instead of intermediate **207-2**. ^{1}H NMR (400 MHz, Methanol-d4) δ 8.59 – 8.46 (m, 1H), 8.23 – 8.10 (m, 2H), 7.82 – 7.64 (m, 2H), 7.56 – 7.40 (m, 1H), 6.97 – 6.90 (m, 1H), 6.68 (m, 1H), 5.52 – 5.32 (m, 1H), 5.06 – 4.90 (m, 1H), 4.86 – 4.66 (m, 3H), 4.51 – 4.23 (m, 3H), 4.24 – 4.00 (m, 2H), 3.78 – 3.39 (m, 3H), 3.58 – 3.37 (m, 3H), 3.21 – 2.81 (m, 2H), 2.63 – 2.19 (m, 5H), 2.18 – 2.06 (m, 2H), 2.07 – 1.84 (m, 3H), 1.84 – 1.71 (m, 3H). LCMS: 765.4.

IV. Biological Examples

Example A. KRAS G12D (GDP) Biochemical Assay

[1148] Compounds were tested for binding to GDP-loaded KRAS G12D in a 384-well assay format using a TR-FRET probe displacement assay in buffer consisting of 50 mM Hepes (pH 7.4), 150 mM NaCl, 5 mM $MgCl_2$ and 0.005% Tween-20. 0.5 nM enzyme was used in this assay with

0.25 nM Eu-streptavidin and 200 nM (2X K_D) Cy-5 labelled probe. Compounds were serially diluted (1:3) in DMSO. The LabCyte ECHO Acoustic dispenser system was used to pre-spot the assay plates (384-well Non-Binding Surface plates, Corning, Catalog #3824) with 50 nL of compound. The compounds were pre-incubated with 5 µL of 2X final enzyme concentration for 30 minutes before adding 5 µL of 2X final concentration of Eu-streptavidin and TR-FRET probe (10 µL final reaction volume). The plates were incubated at room temperature for 2 hours before measuring TR-FRET ratio on the Envision plate reader. IC_{50} values were defined as the compound concentration that causes a 50% decrease in TR-FRET ratio and were calculated using a sigmoidal dose-response model to generate curve fits.

Example B. 2D Cell Viability Assay

[1149] Compounds were tested in a 384-well format for their ability to inhibit the viability of GP2D (KRAS G12D) cells in 2D assays. Compounds were serially diluted (1:3) in DMSO. The LabCyte ECHO Acoustic dispenser system was used to pre-spot assay plates with 200 nL of test molecule per well. 1000 cells/well (40 µL volume per well) in RPMI medium with 10% FBS, and Penicillin-Streptomycin-Glutamine were plated in pre-spotted 384-well plates (Greiner, Catalog # 781076) on the BioTEK EL406 liquid dispenser with a 5 µL dispensing cassette (BioTek 7170011). The plates were incubated at 37°C, 5% CO_2 for 4 days before addition of CellTiter-Glo (CTG) reagent and measurement of luminescence signal. EC_{50} values were defined as the compound concentration that causes a 50% decrease in luminescence signal and were calculated using a sigmoidal dose-response model to generate curve fits.

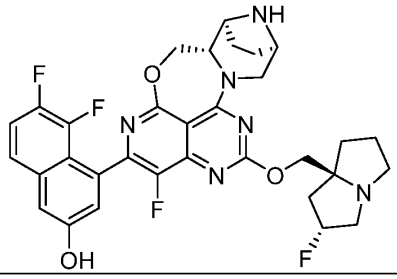
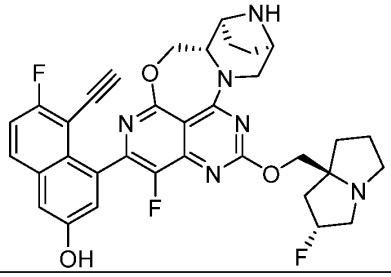
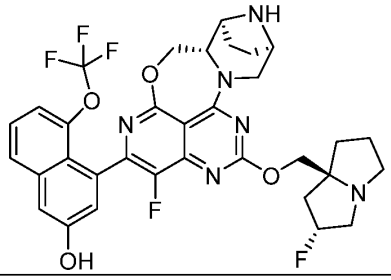
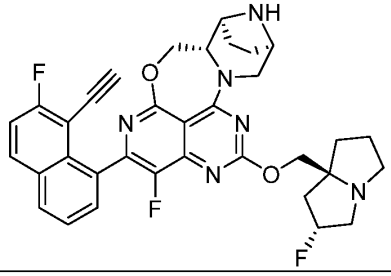
Example C. 3D Cell Viability Assay

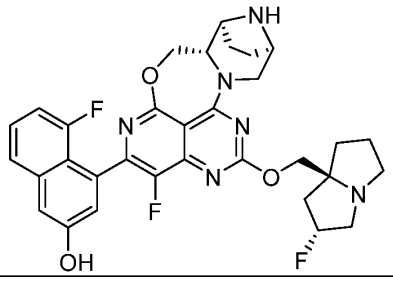
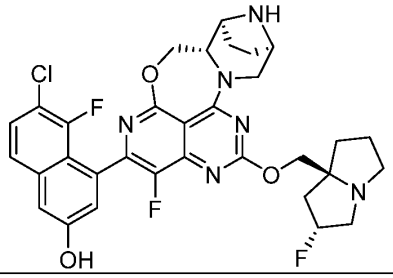
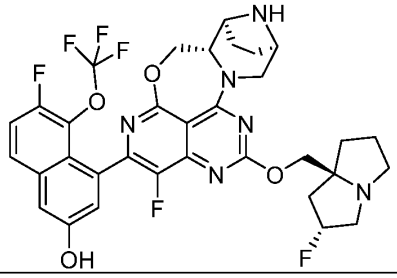
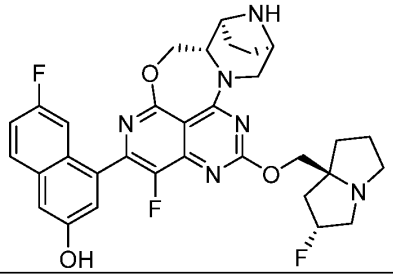
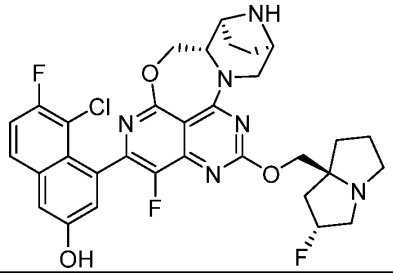
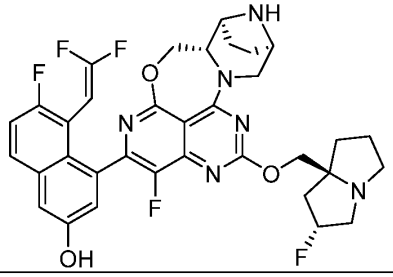
[1150] Compounds were tested in a 384-well format for their ability to inhibit the viability of AsPC-1 (KRAS G12D) cells in 3D assays. On day 0, 1000 cells/well (80 µL volume per well) in DMEM with 10% FBS, and Penicillin-Streptomycin-Glutamine were plated in 384-well Ultra-Low Attachment Spheroid Microplates (Corning, Catalog # 3830) on the BioTEK EL406 liquid dispenser with a 5 µL dispensing cassette (BioTek 7170011). The plates were incubated at 37°C, 5% CO_2 for 3 days to allow spheroid formation. On day 3, compounds were serially diluted (1:3) in DMSO. The Biomek FX was used to add 400 nL of test molecule per well. The plates were incubated at 37°C, 5% CO_2 for 4 days before addition of CellTiter-Glo 3D (Promega, Catalog # 9683) reagent and measurement of luminescence signal. EC_{50} values were defined as the compound concentration that causes a 50% decrease in luminescence signal and were calculated using a sigmoidal dose-response model to generate curve fits.

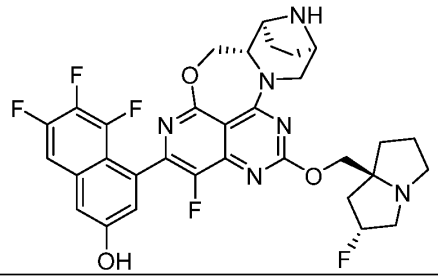
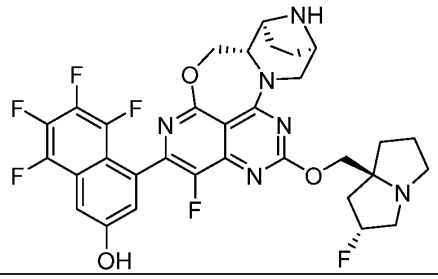
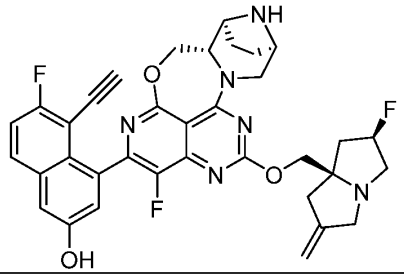
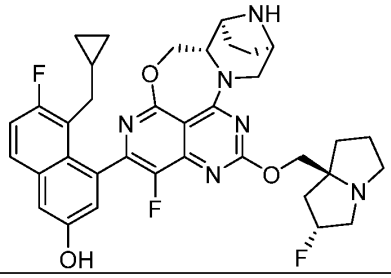
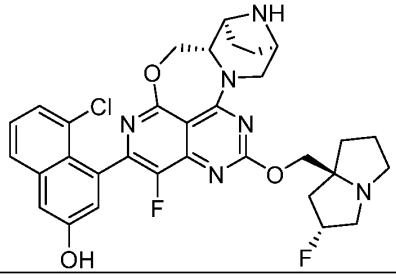
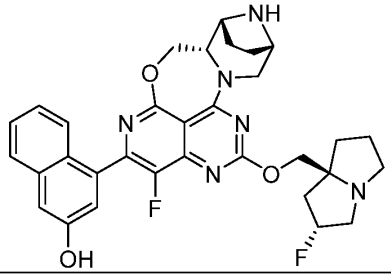
Biological Data

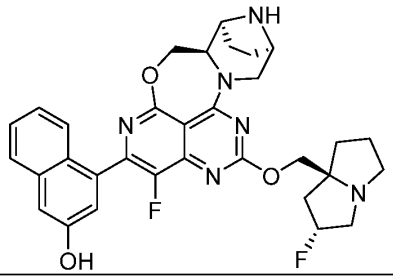
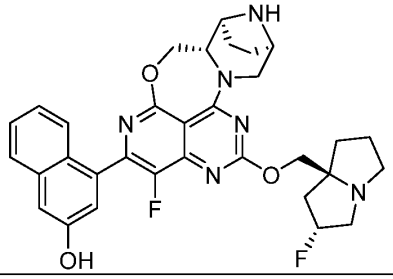
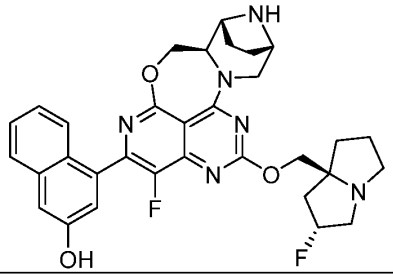
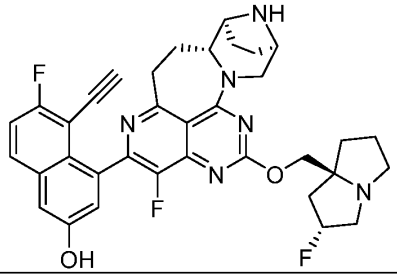
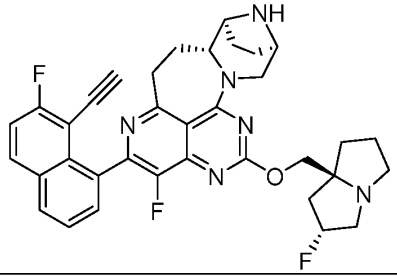
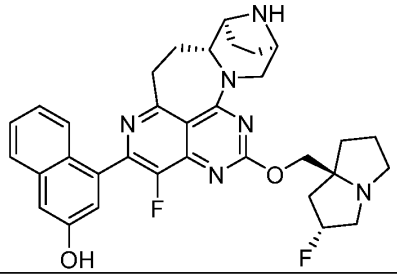
[1151] Provided below in Table 2 is data related to compounds disclosed herein.

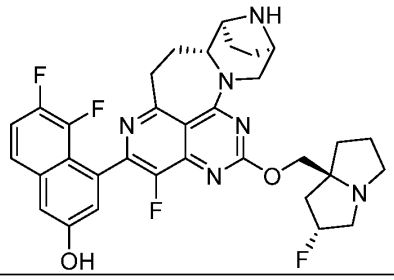
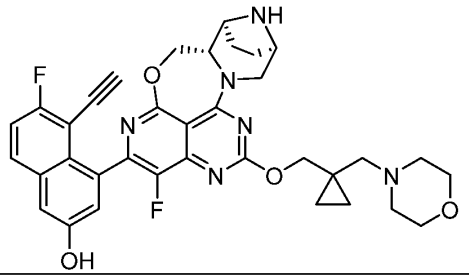
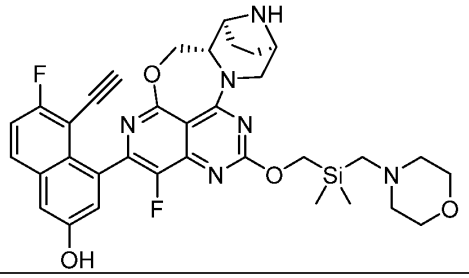
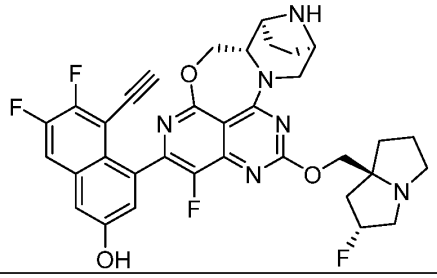
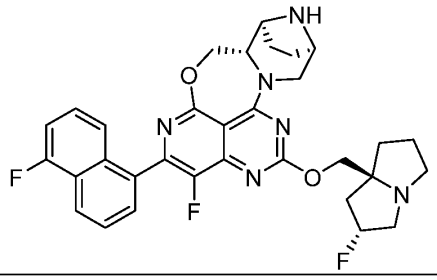
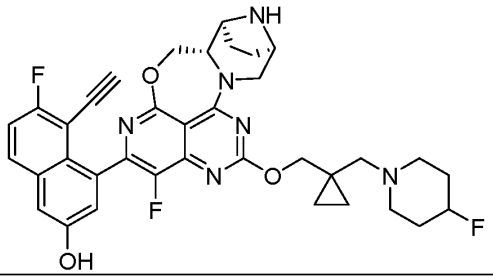
Table 2. Biological Data for Compounds Disclosed Herein

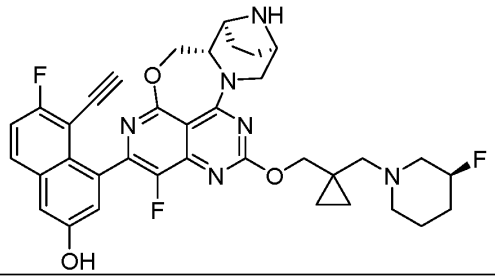
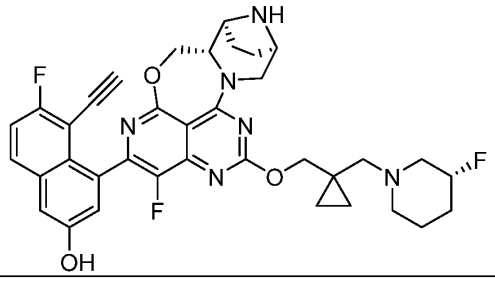
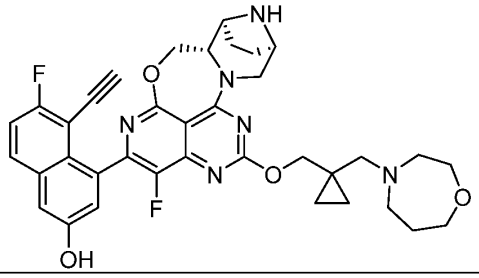
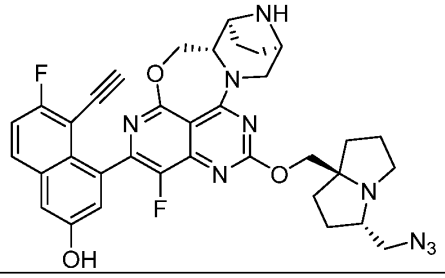
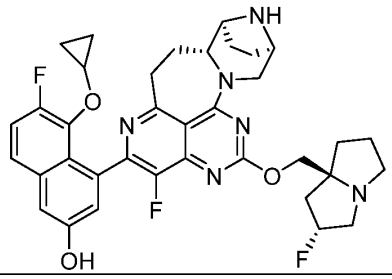
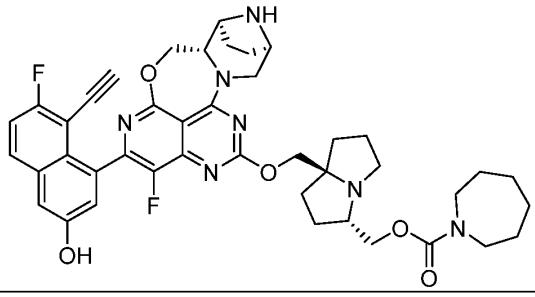
Example No.	Structure	G12D IC_{50} (nM)	G12D 2D EC_{50} (nM)	G12D 3D EC_{50} (nM)
1		0.5	19	170
2		0.2	6	42
3		2	24	160
4		4	45	92

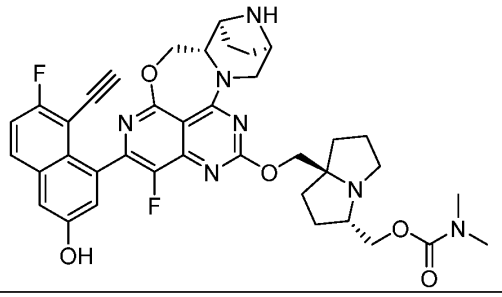
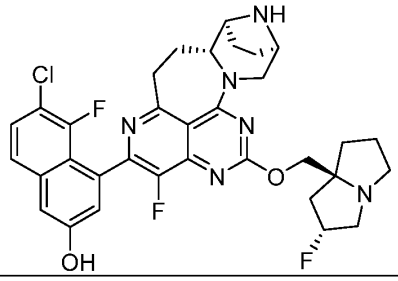
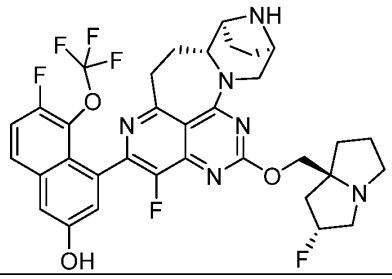
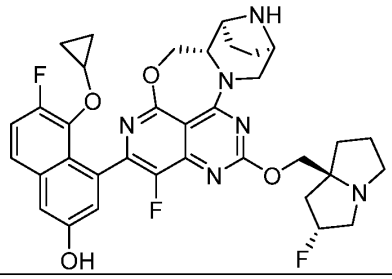
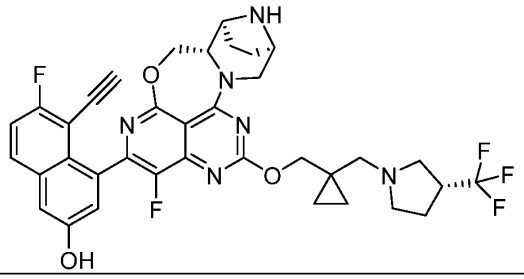
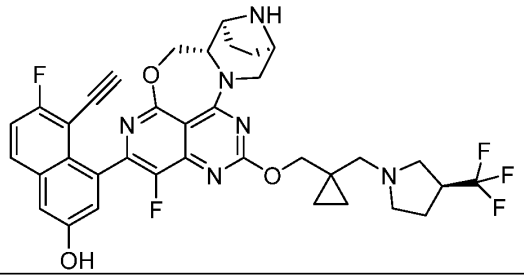
5		3	250	N/A
6		2	70	N/A
7		0.6	16	36
8		2	54	N/A
9		0.5	20	77
10		18	250	N/A

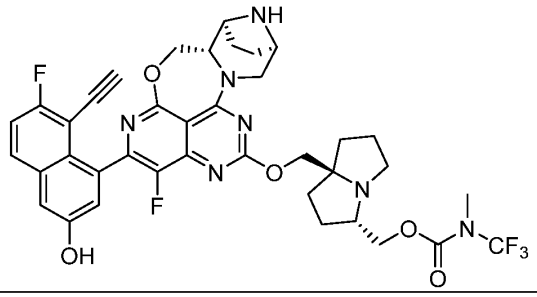
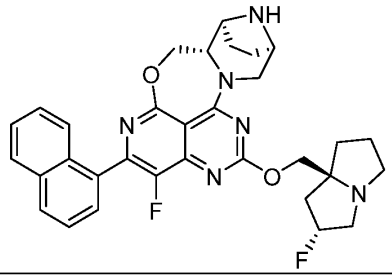
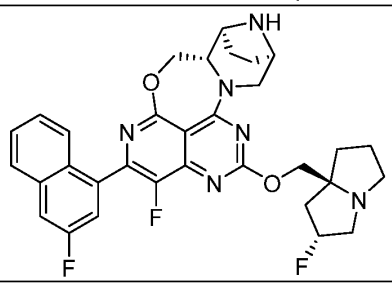
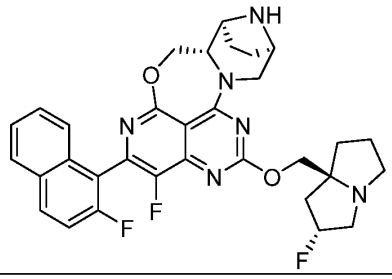
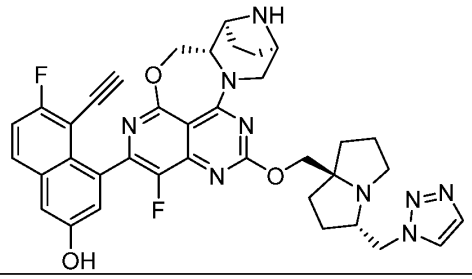
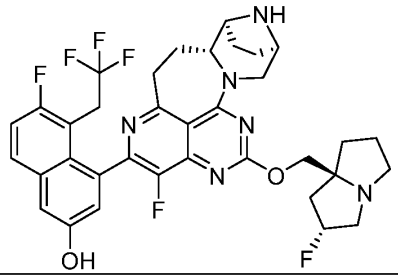
11		1	56	N/A
12		6	130	N/A
13		0.4	2	17
14		34	530	N/A
17		0.4	49	180
18		>1000	>10000	N/A

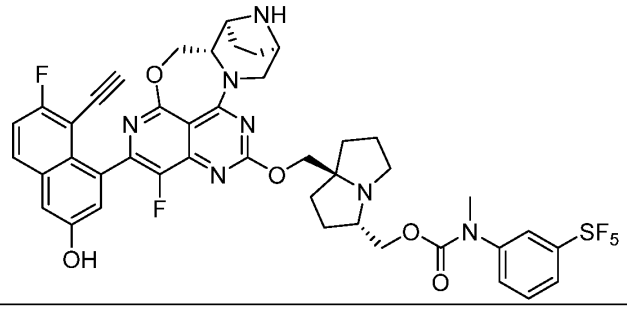
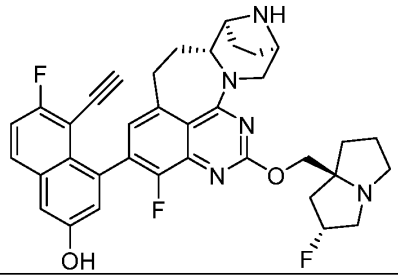
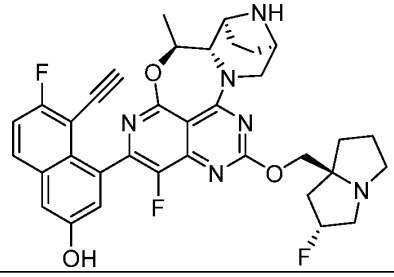
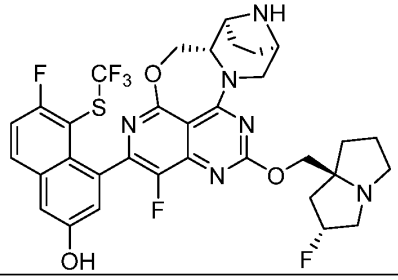
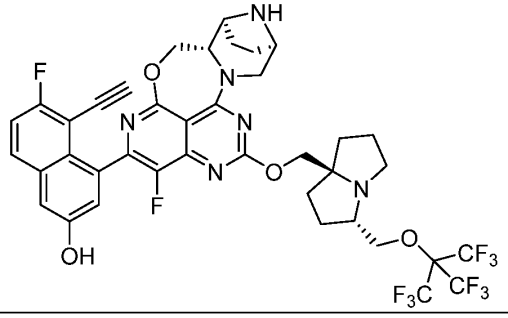
19		590	3300	N/A
20		7	210	>1000
21		2100	3100	N/A
22		0.1	0.6	2
23		1	9	31
24		1	17	190

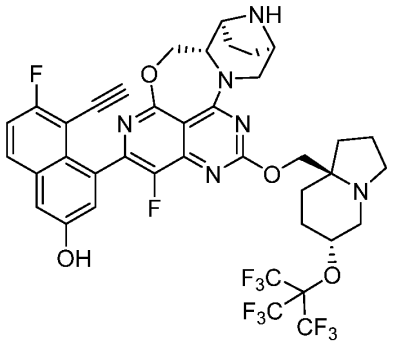
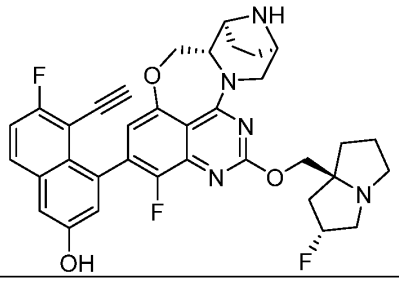
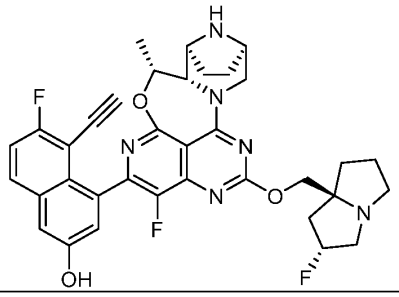
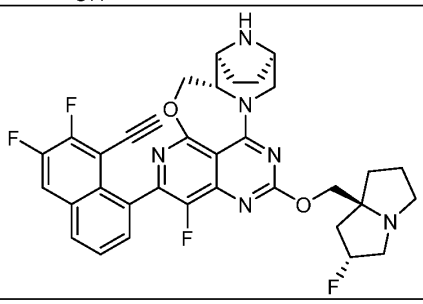
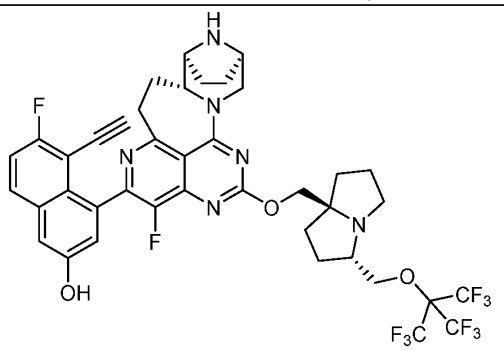
27		0.7	4	29
28		0.6	7	N/A
29		560	>1000	N/A
30		0.2	11	260
31		4900	>1000	N/A
32		0.2	2	N/A

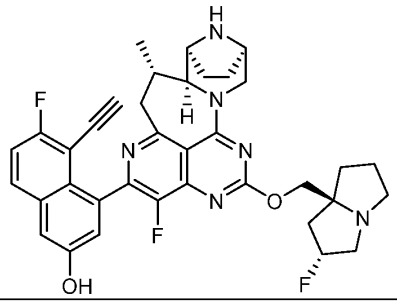
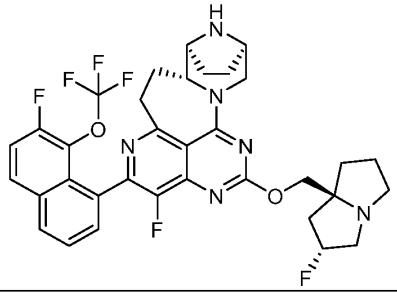
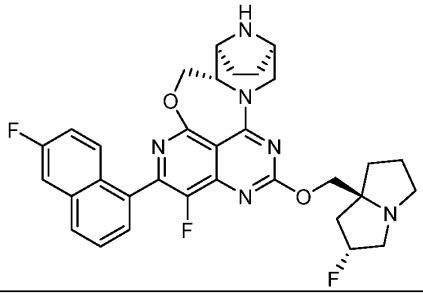
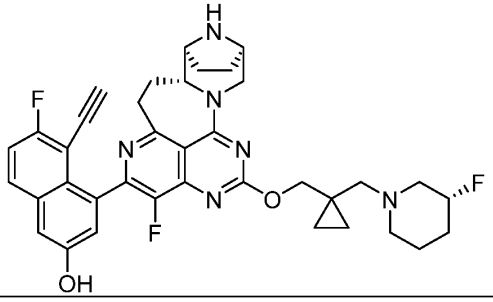
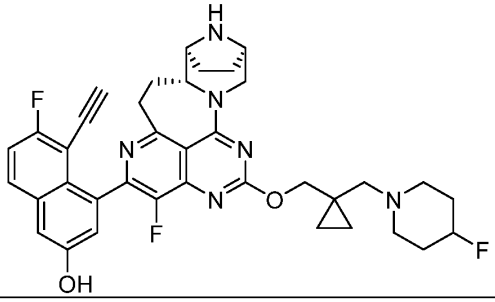
33		0.3	3	N/A
34		0.2	2	N/A
35		0.3	6	17
36		0.2	4	N/A
37		1	9	N/A
38		0.3	28	47

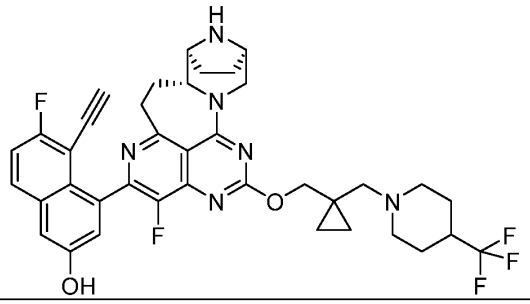
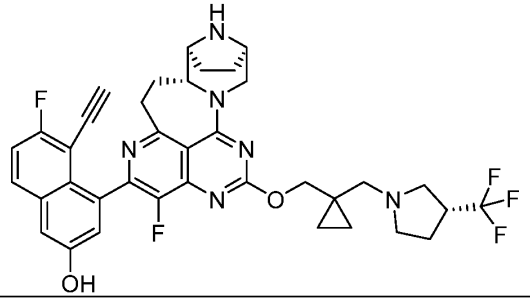
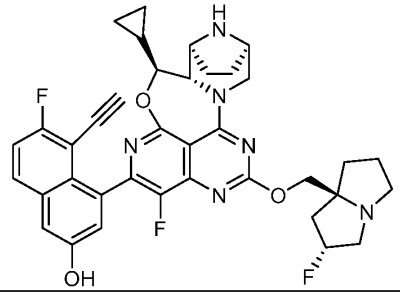
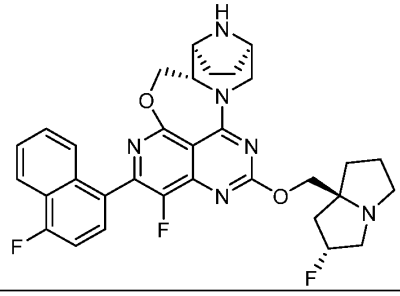
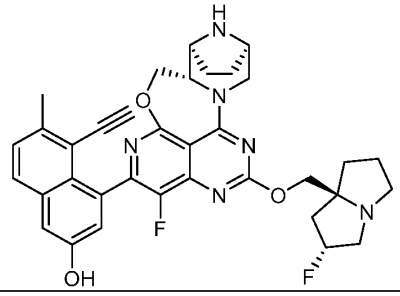
39		0.4	48	96
40		2	19	74
41		0.6	3	8
42		2	28	95
43		0.6	5	N/A
44		2	7	N/A

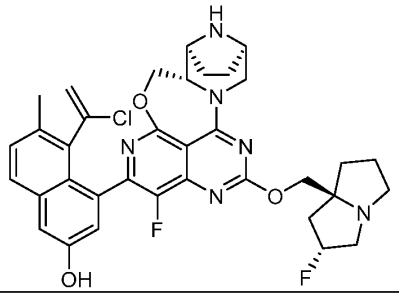
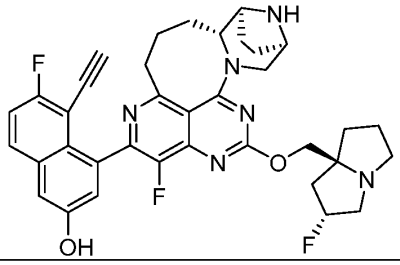
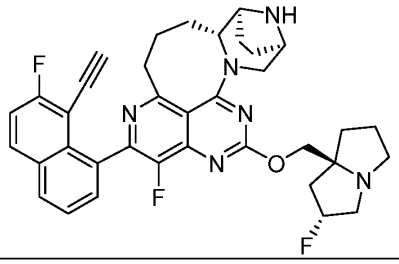
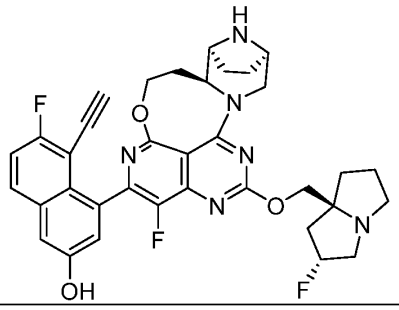
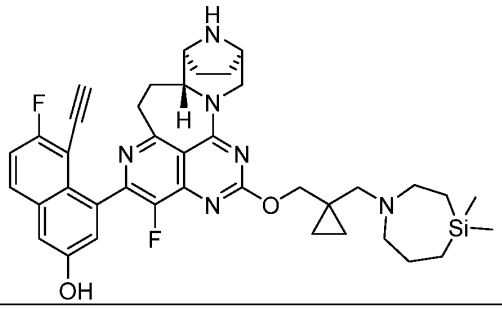
45		0.3	4	N/A
46		910	>1000	N/A
47		3400	>1000	N/A
48		2200	>1000	N/A
49		0.2	37	140
50		3	24	N/A

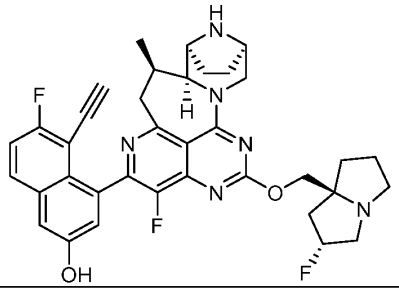
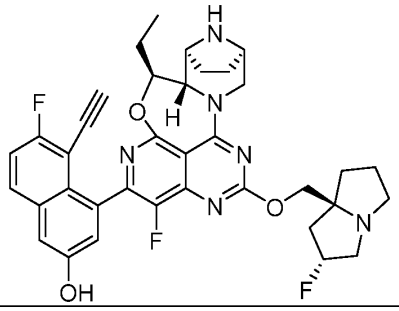
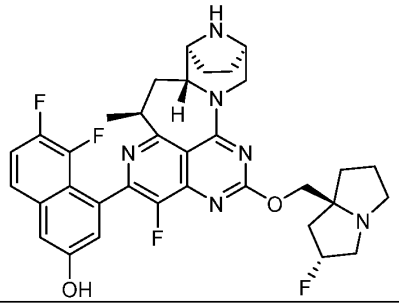
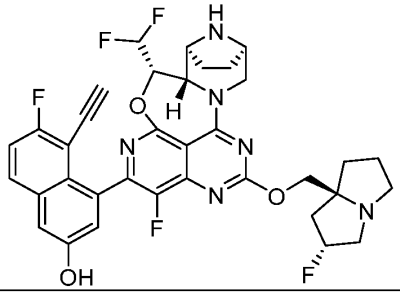
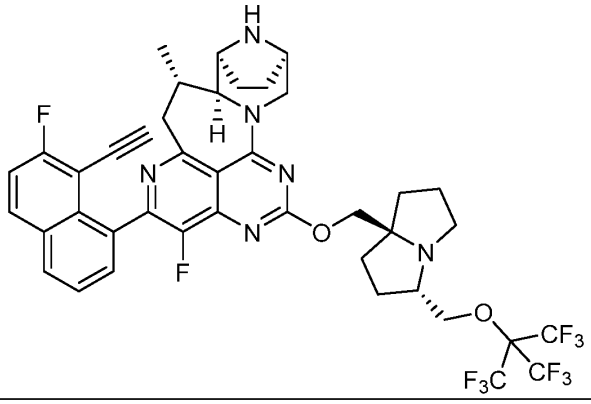
51		2	98	N/A
52		0.1	1	7
53		0.1	2	-
54		3	42	-
55		0.5	0.8	-

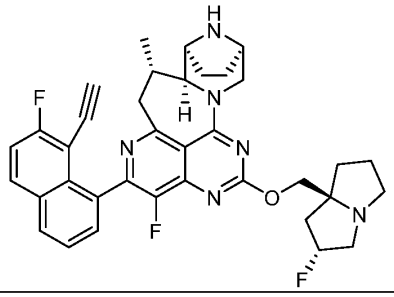
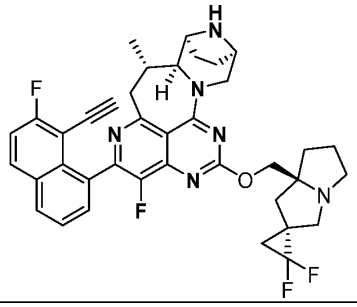
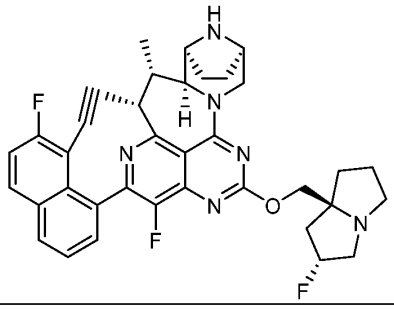
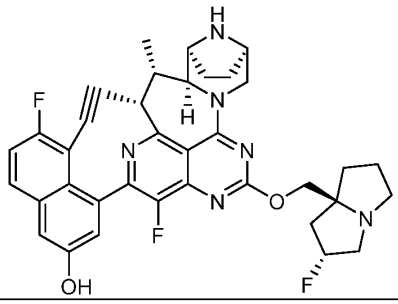
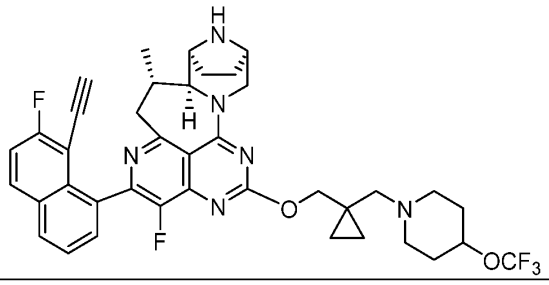
56		13	50	-
57		0.6	28	-
61		26	520	-
62		7	79	-
63		0.2	0.2	-

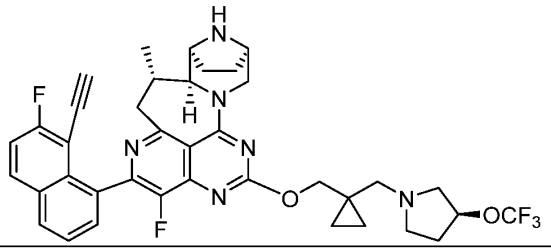
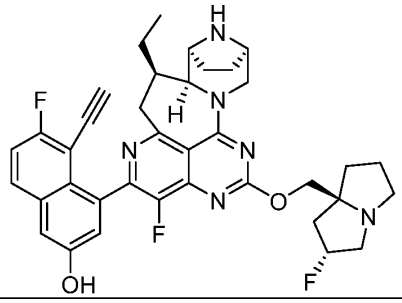
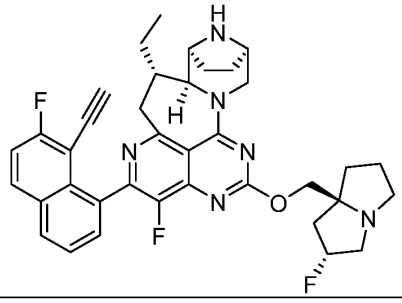
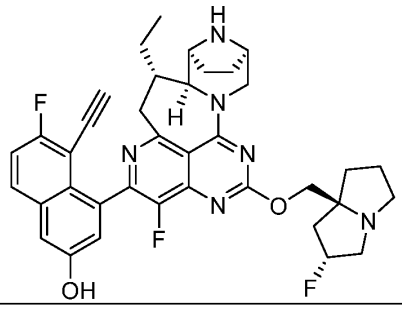
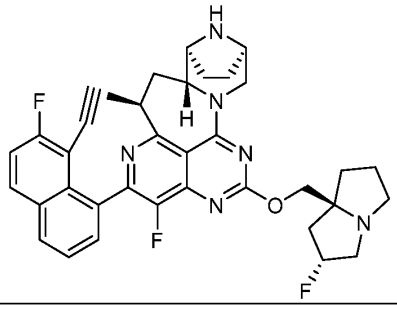
64		0.1	0.3	-
65		89	450	-
66		860	>1000	-
67		0.08	1	-
68		0.05	0.6	-

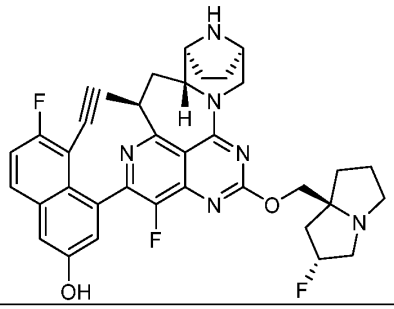
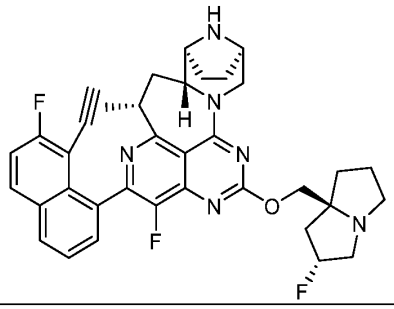
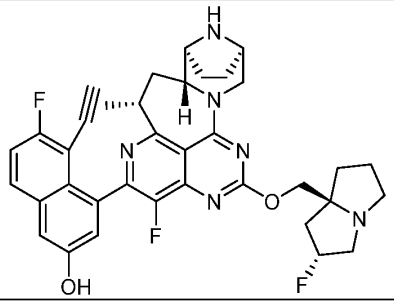
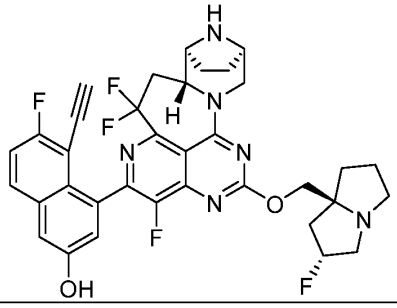
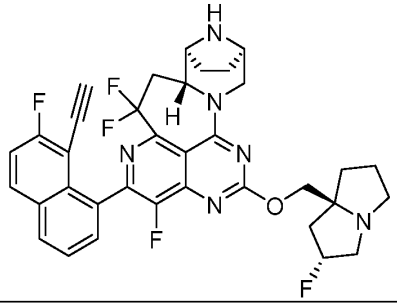
69		0.1	0.6	-
70		0.1	1	-
71		4	81	-
72		510	>1000	-
73		-	-	-

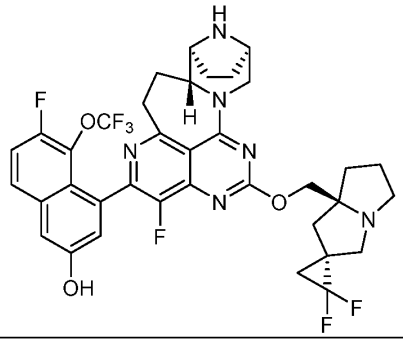
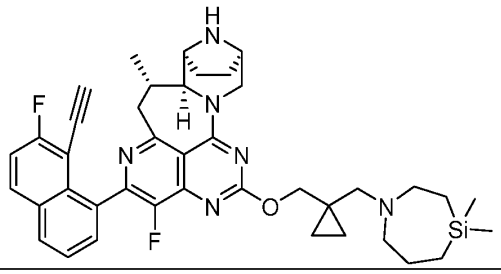
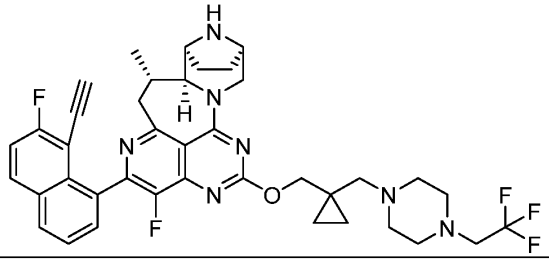
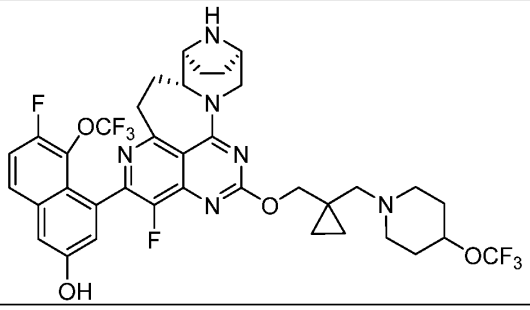
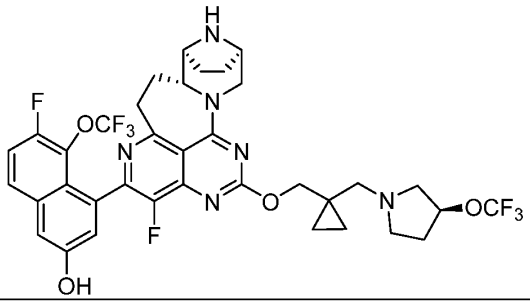
74		16	310	-
75		0.06	0.17	0.5
76		0.1	4	27
77		6	83	-
78		0.2	3.9	15

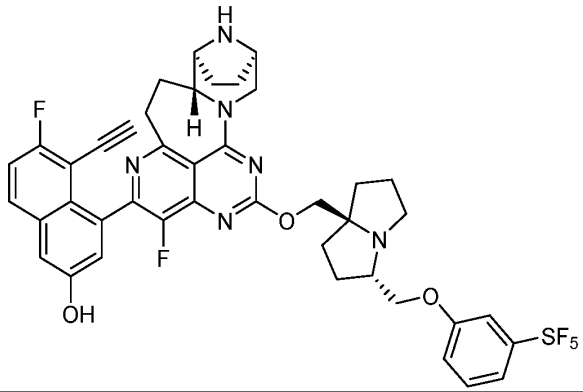
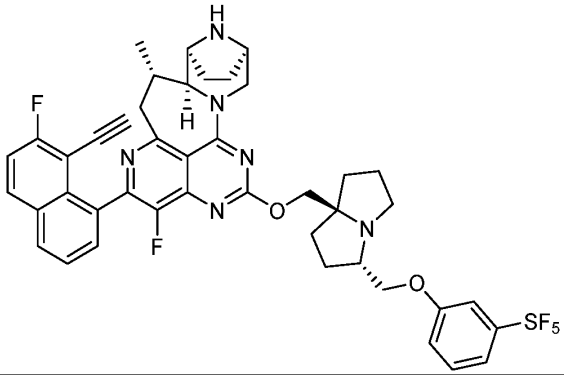
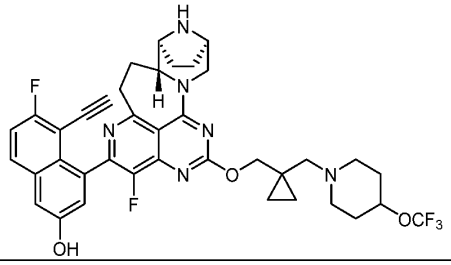
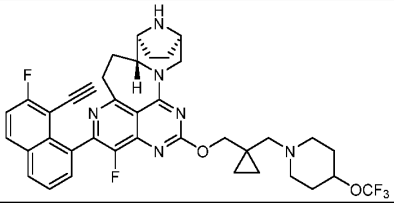
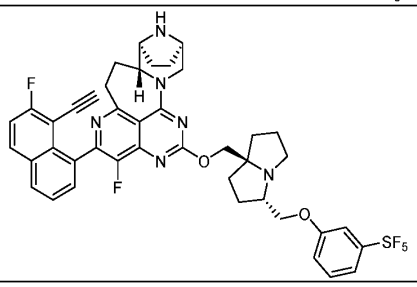
79		7	15.3	
80		0.1	2.2	2
81		0.2	2.8	18
82		11.4	104.4	
83		3.2	67.4	

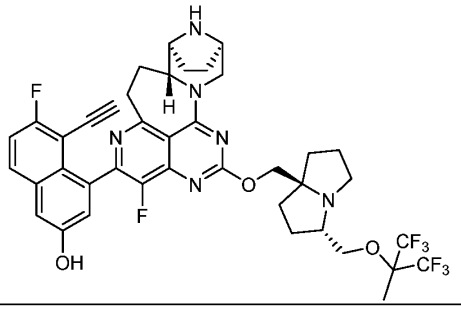
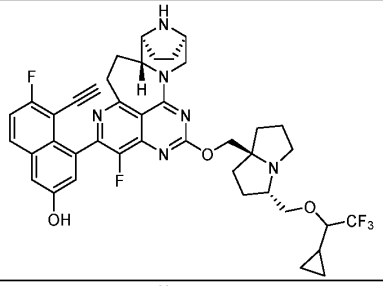
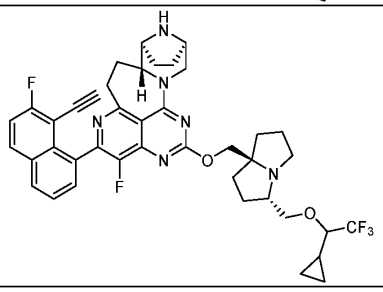
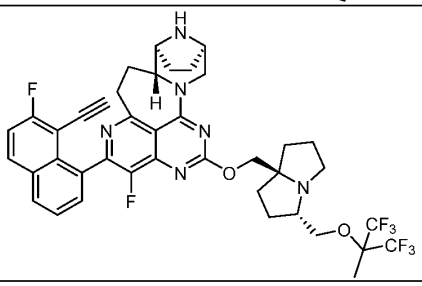
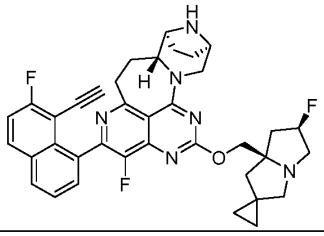
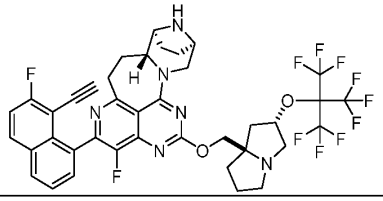
84		3.9	27.7	
85		6.8	58	
86		0.5	14.4	64
87		0.4	0.2	0.3
88		36.5	254.6	

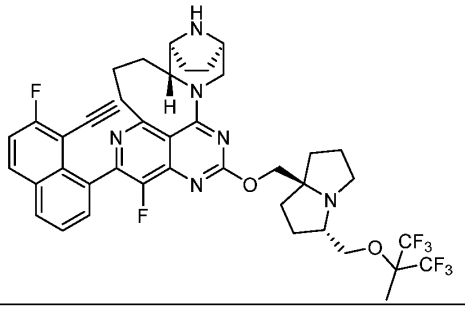
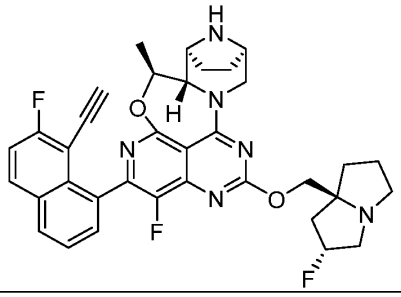
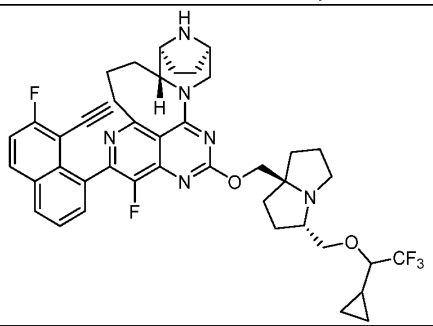
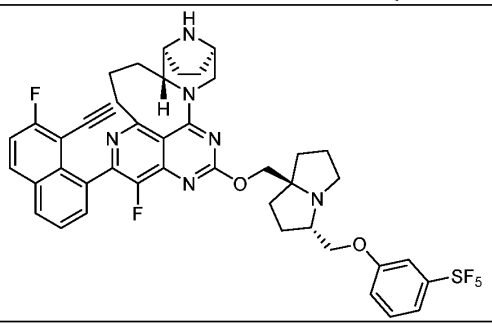
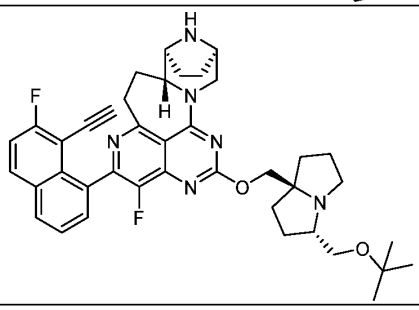
89		50.9	379.1	
90		100	1000	
91		100	1000	
92		1.9	17.3	52
93		2.5	26.6	82

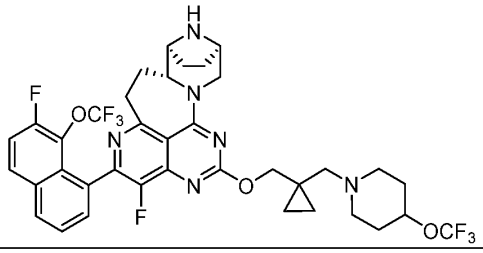
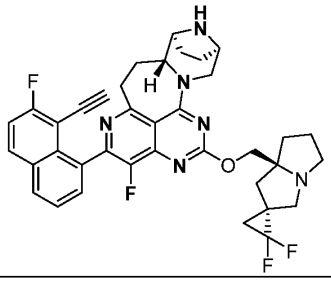
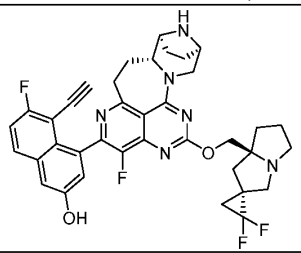
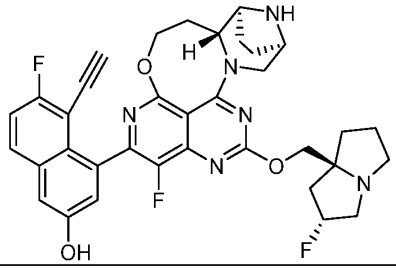
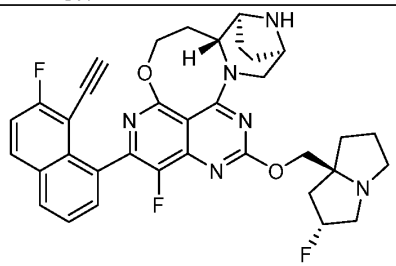
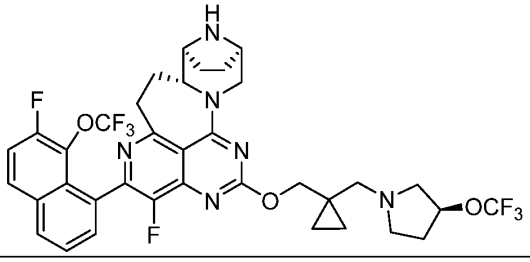
94		0.1	0.6	2.2
95		0.6	31.9	200
96		0.3	0.5	1.9
97		0.2	7.7	55
98		12.6	124.2	

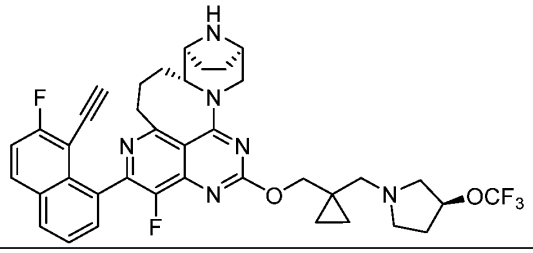
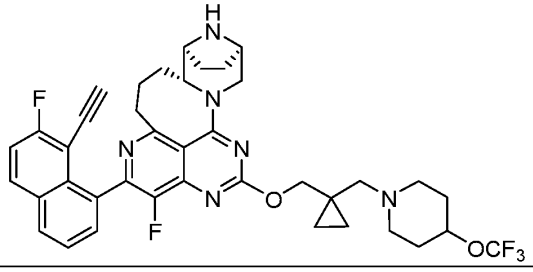
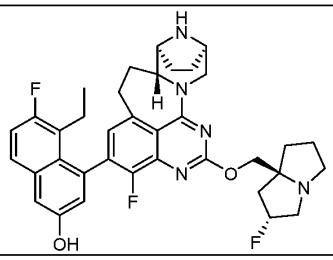
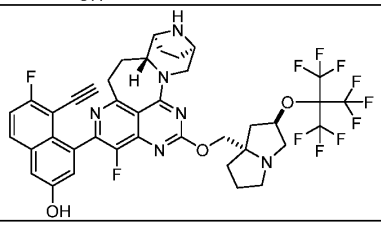
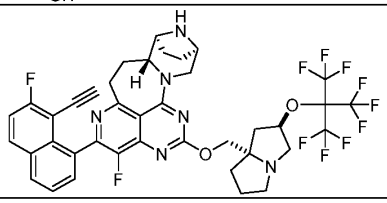
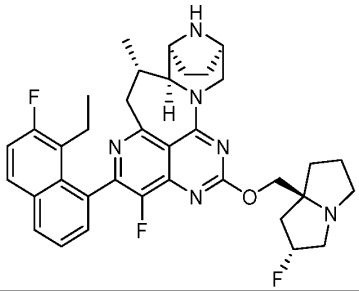
99		0.6	7.4	110
100		31.8	372.9	
101		12.7	175.2	
102		3.3	39.5	680
103		5.3	62.6	

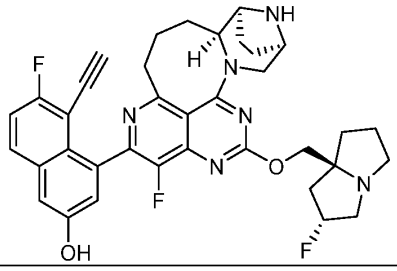
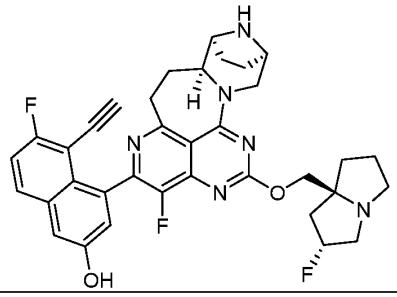
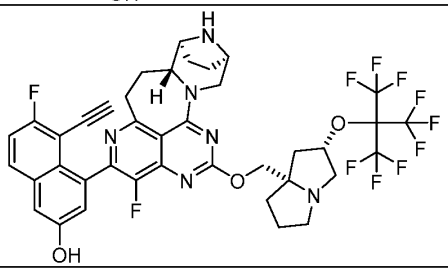
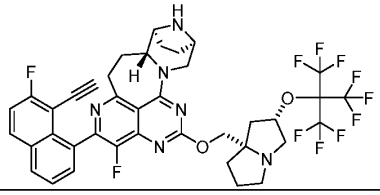
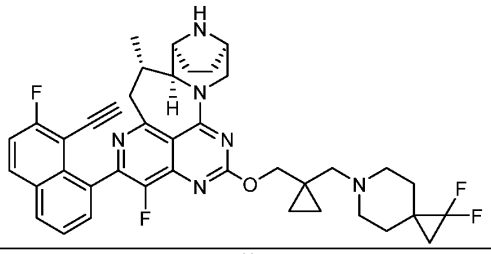
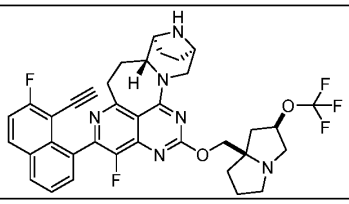
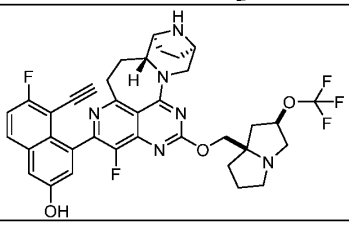
104		0.8	8.7	53
105		5.3	434.9	
106		0.2	1.9	8.2
107		7.2	460	
108		1.5	449.8	

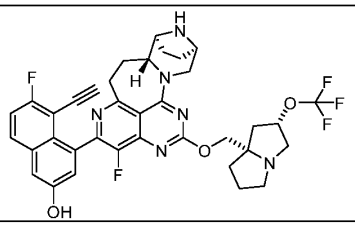
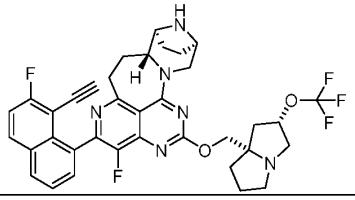
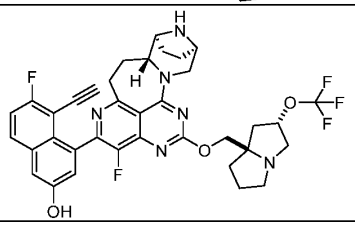
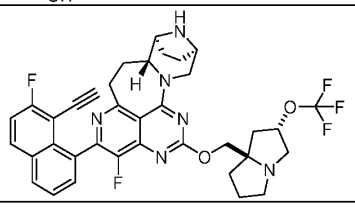
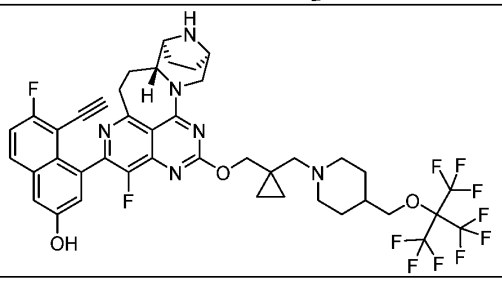
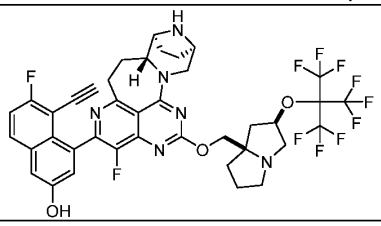
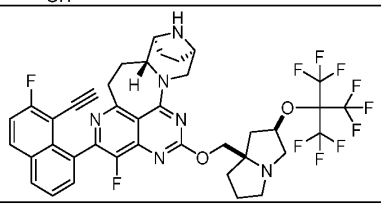
109		0.1	1.2	0.8
110		0.3	36.1	51
111		0.7	69.9	360
112		0.3	41	270
113		0.2	7.3	57
114		125	1000	

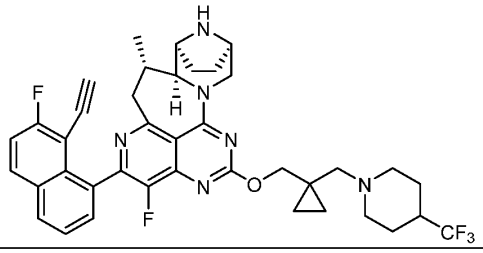
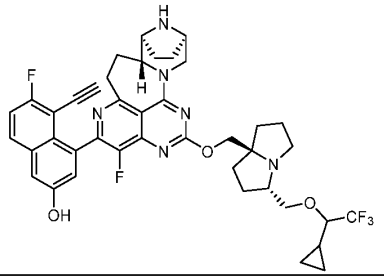
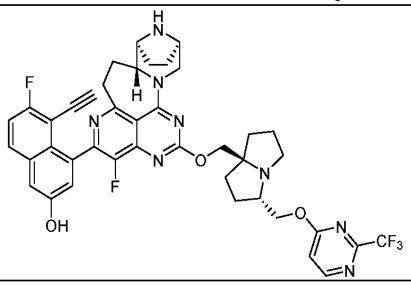
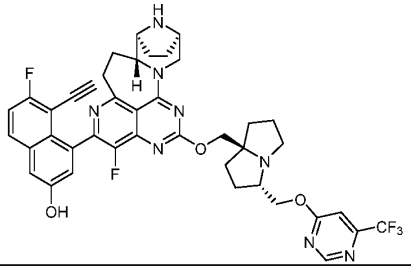
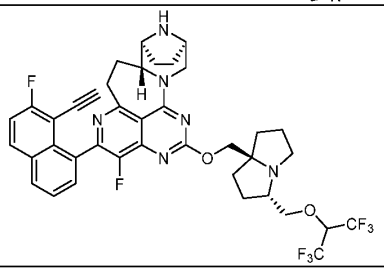
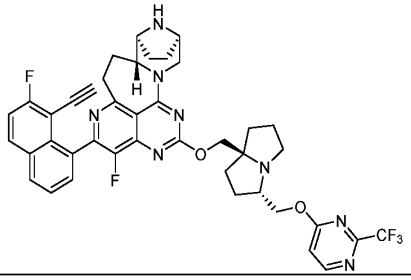
115		0.1	11.5	100
116		0.6	6	25
117		0.1	8.5	
118		0.4	72.7	
119		2.4	124.7	390

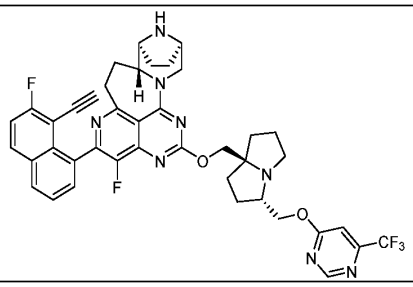
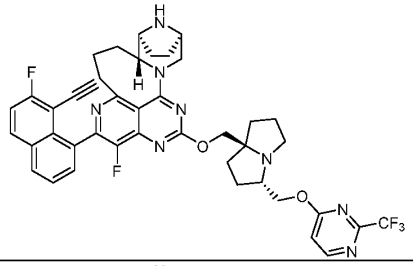
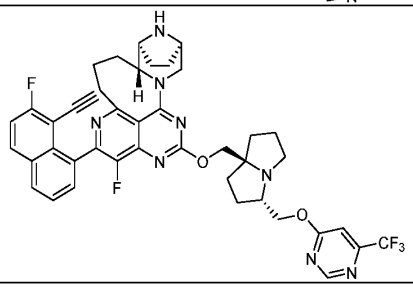
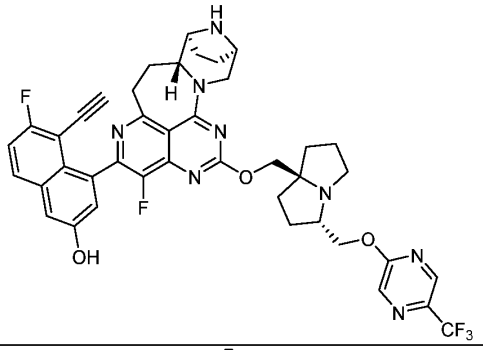
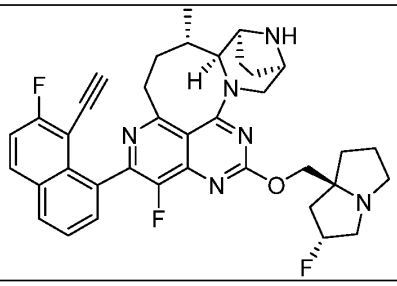
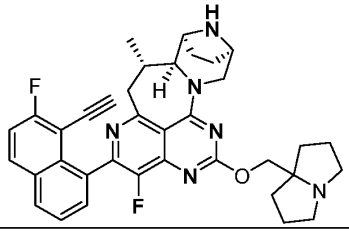
120		336.9	1000	
121		0.3	7	
122		<0.1	0.1	2.9
123		<0.1	0.5	3
124		0.5	26	81
125		416.6	1000	

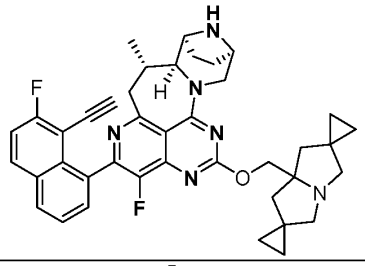
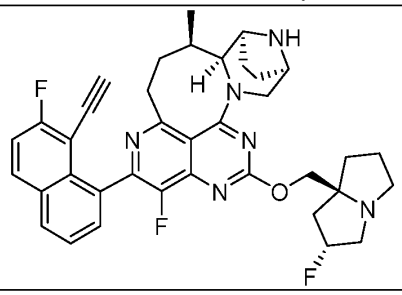
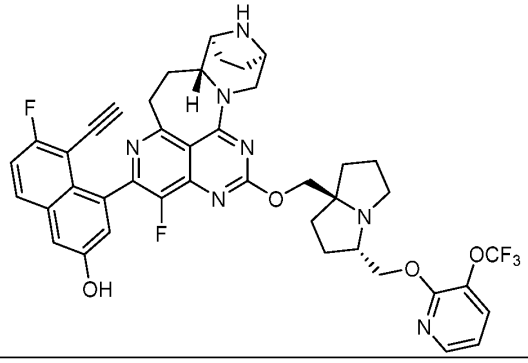
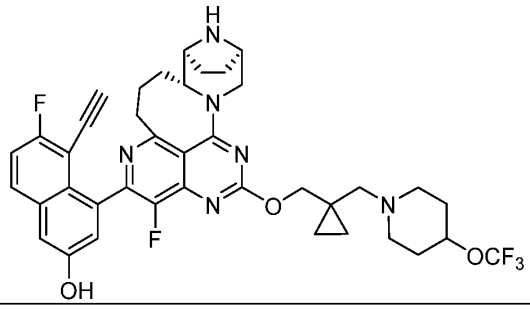
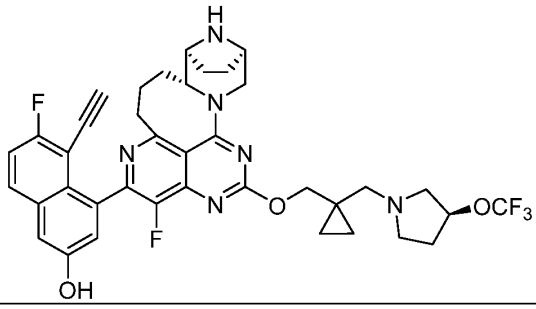
126		2	94.4	
127		1.6	88.9	
128		0.2	4.1	59
129		2.7	13.3	
130		100	100	
131		55.3	100	

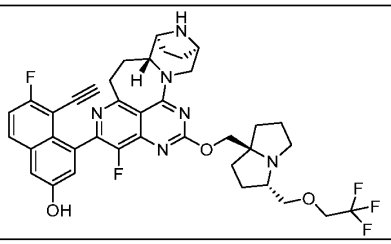
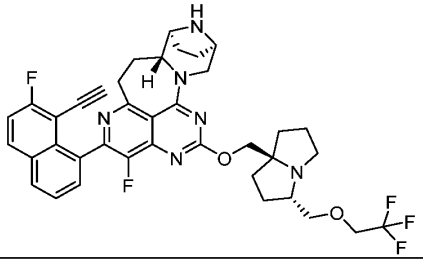
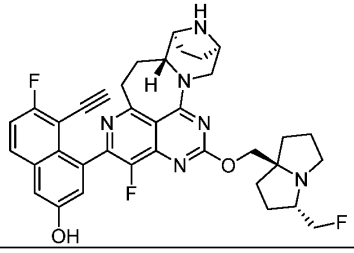
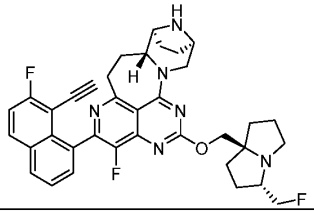
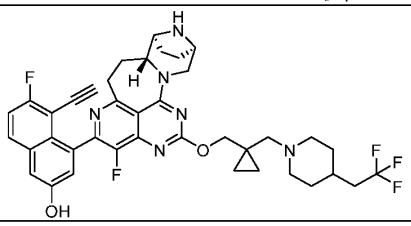
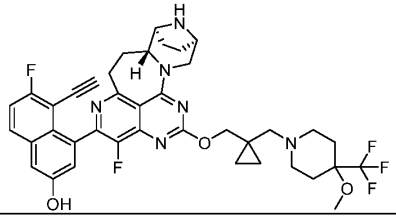
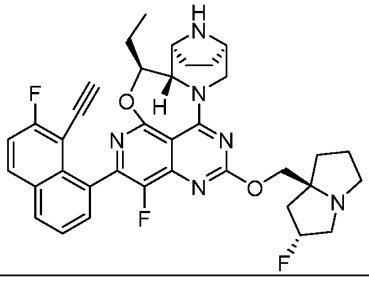
132		0.2	2.2	50
133		0.1	1.1	
134		0.5	2.2	31
135		88.1	100	
136		17.1	100	
137		24.5	100	
138		0.3	17.2	

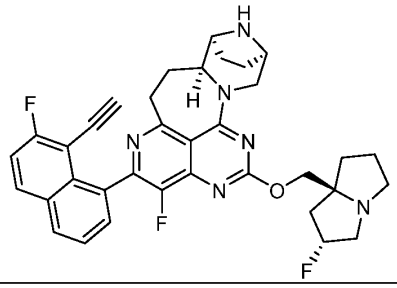
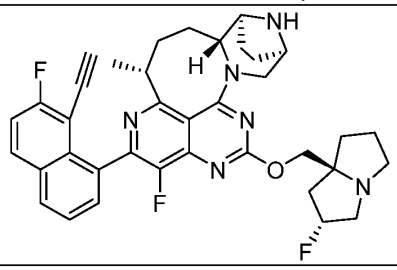
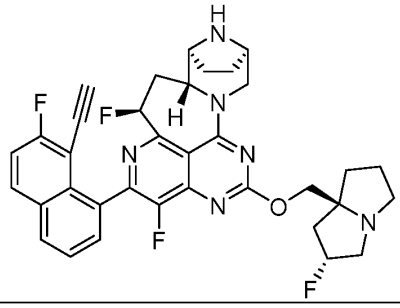
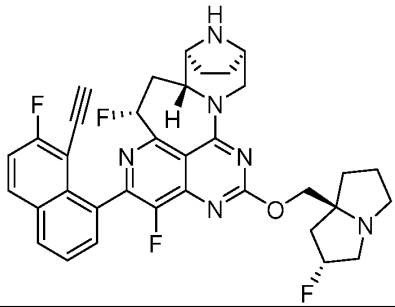
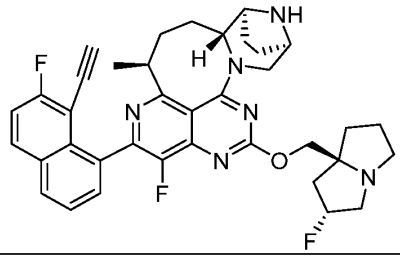
139		0.1	0.6	4.2
140		3.7	75.9	
141		0.2	0.4	3.7
142		3.6	94.8	
143		1.9	3.1	110
144		83.1	100	
145		100	100	

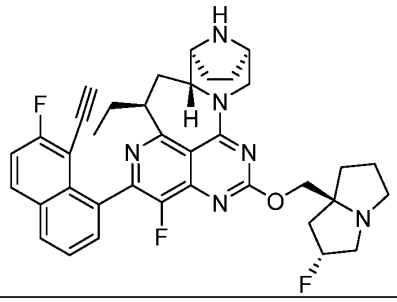
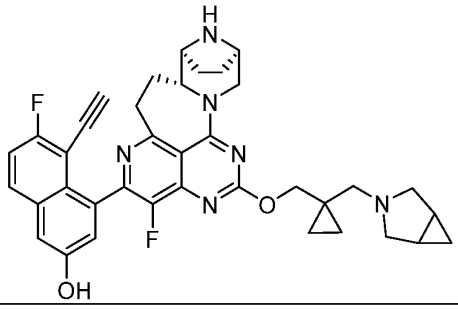
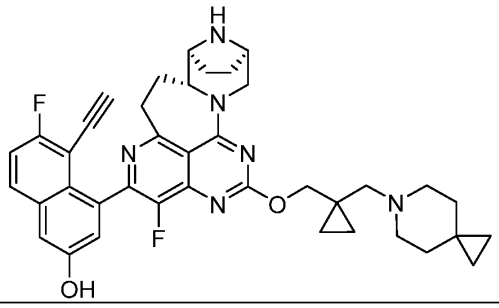
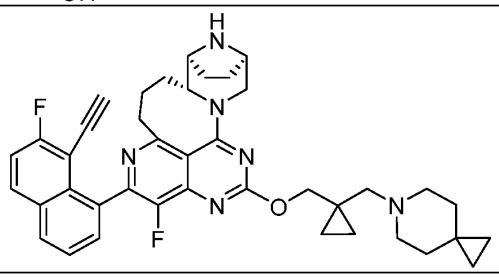
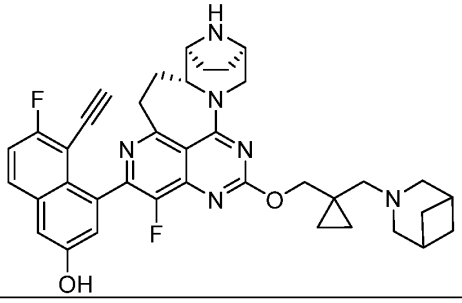
146		15.6	100	
147		<0.1	1.3	19
148		0.1	0.7	7.7
149		<0.1	0.3	
150		0.2	47.2	
151		0.1	5	

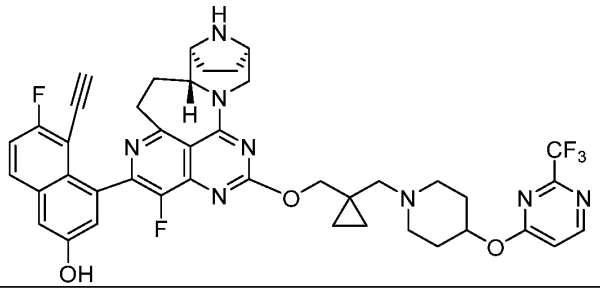
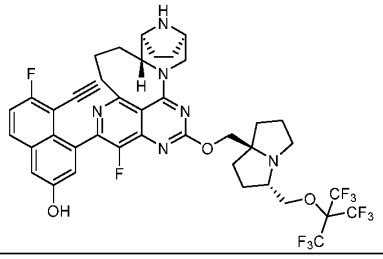
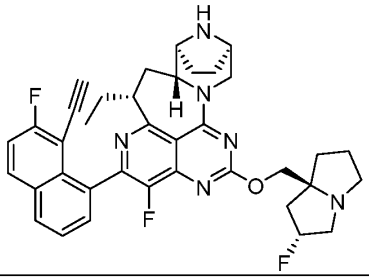
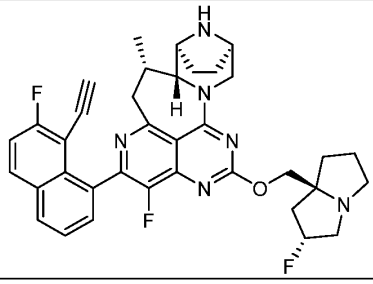
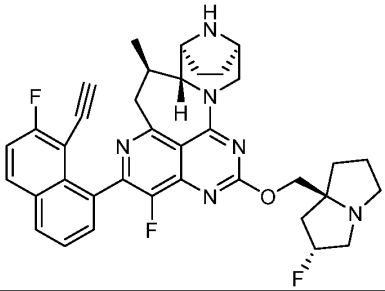
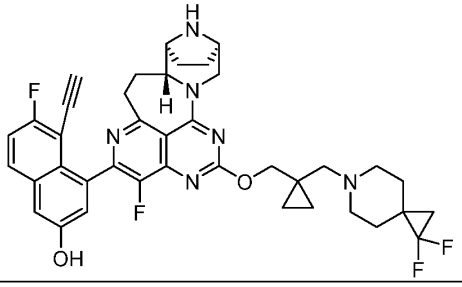
152		0.1	5.4	
153		0.3	4.3	
154		0.1	1	
155		0.1	0.3	5.2
156		100	100	
157		6.4	29.4	

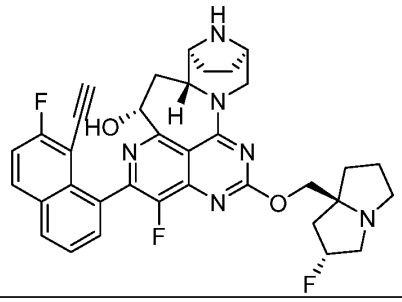
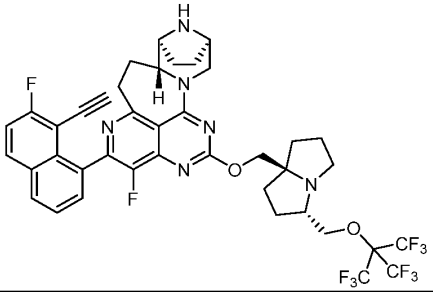
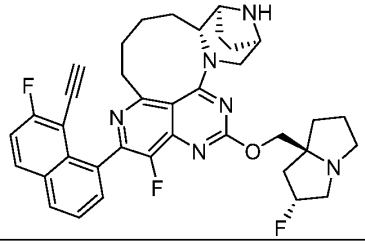
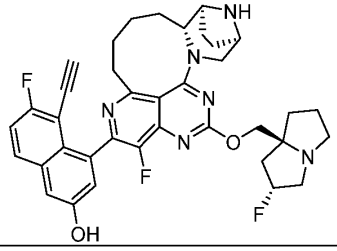
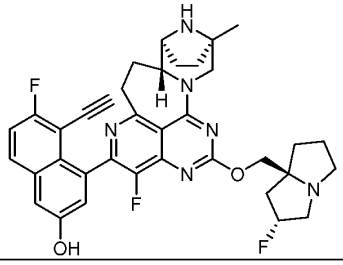
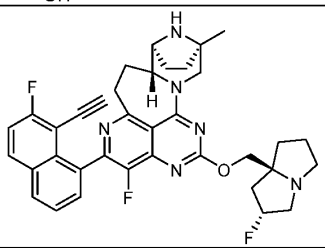
158		12.5	100	
159		100	100	
160		0.2	1.4	16
161		0.3	0.3	23
162		0.4	0.5	

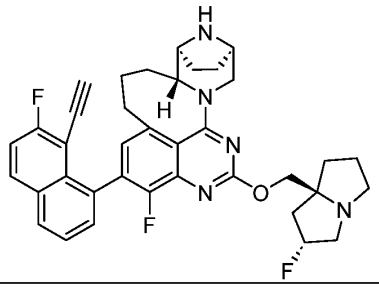
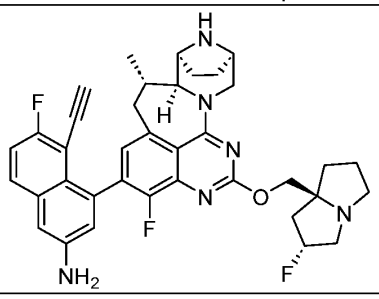
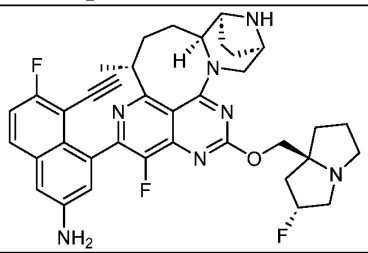
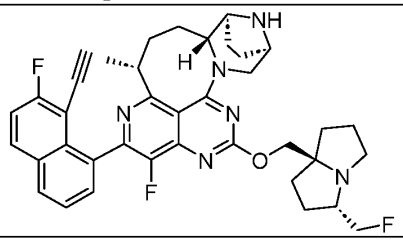
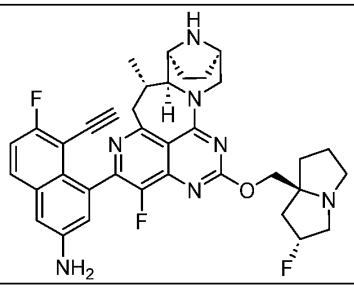
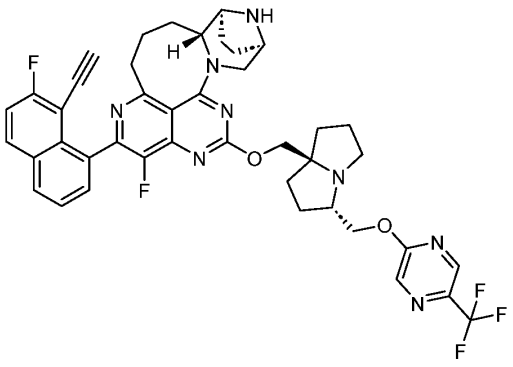
163		0.1	5.1	
164		0.3	38	
165		<0.1	0.7	3.9
166		0.3	3.5	110
167		<0.1	0.7	32
168		0.2	0.5	24
169		0.8	26.5	190

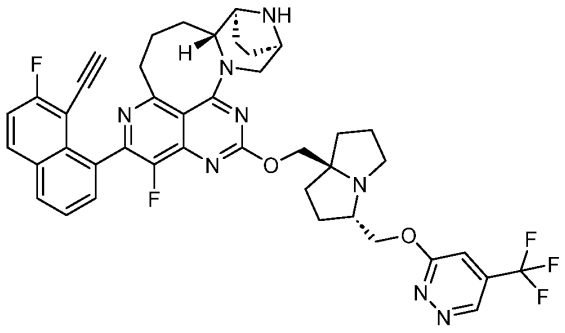
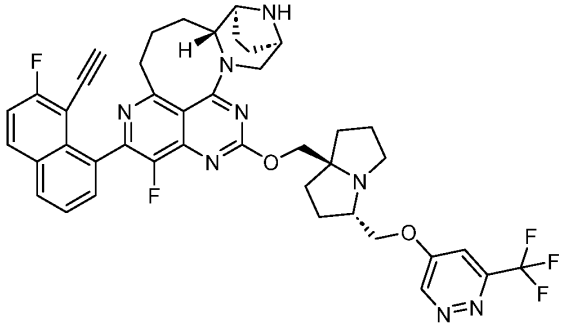
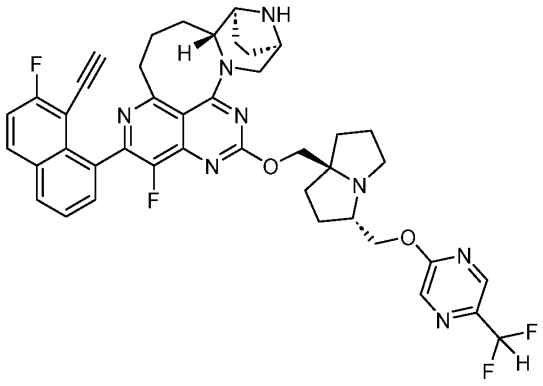
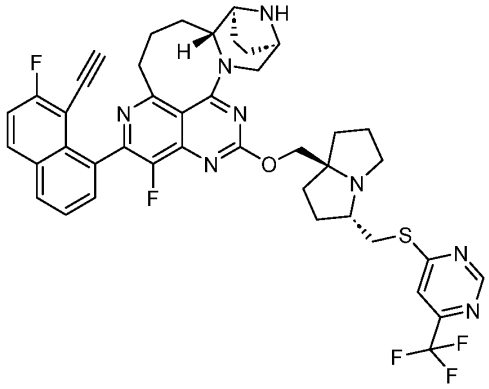
170		18.1	100	>1,000
171		<0.1	1.9	120
172		3.5	65.3	480
173		<0.1	4.2	100
174		5.7	100	

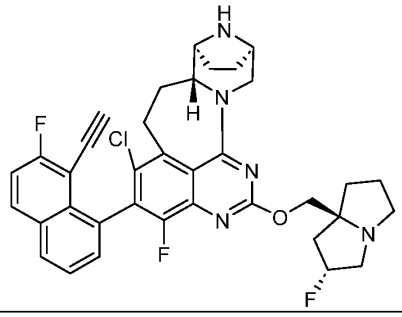
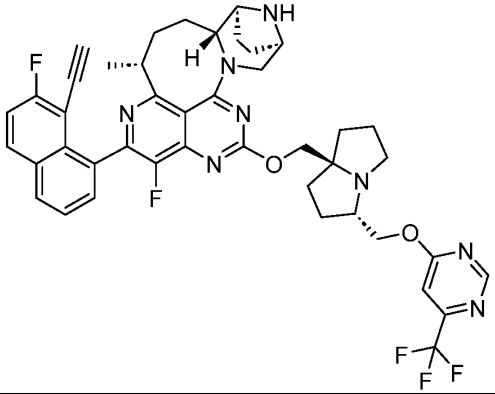
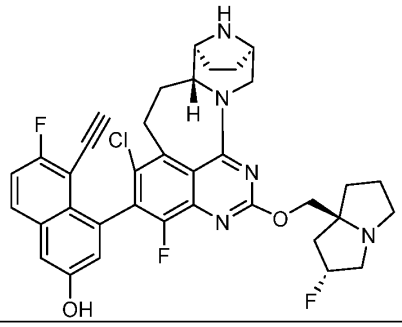
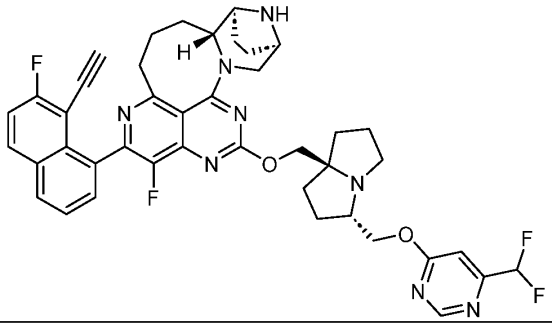
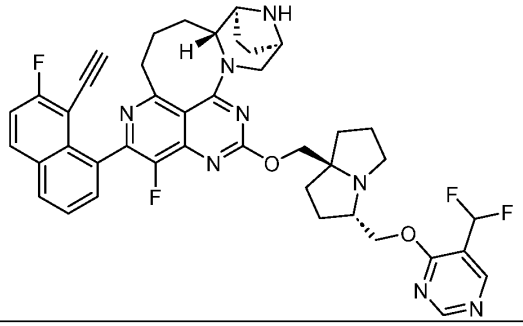
175		0.5	11.9	150
176		0.1	0.4	9.8
177		0.1	1.5	20
178		0.7	37.4	
179		0.1	0.4	7.7

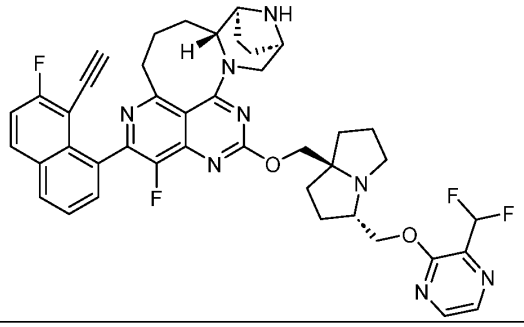
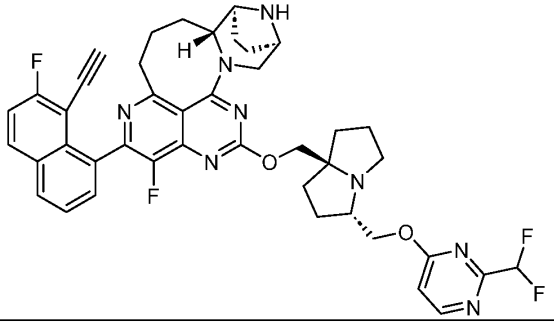
180		0.8	5.1	
181		0.5	0.3	6.9
182		0.4	87	
183		1.9	63	270
184		0.7	19	
185		0.4	2.7	23.1

186		0.2	13	
187		0.9	62	
188		0.2	100	
189		0.1	0.6	2.9
190		0.1	1.5	7.9
191		2	39.8	110

192		0.1	4.5	
193		0.05	4.9	
194		31	70	
195		0.07	1.5	
196		0.1	1.8	
197		0.04	2.4	

198		0.02	2.4	
199		0.07	3.2	
200		0.05	2.9	
201		0.02	10	

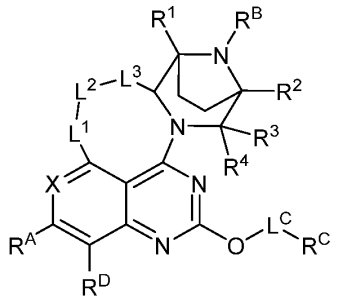
202		0.37	64	
203		0.12	1.2	
204		0.1	1.3	
205		0.06	2.2	
206		0.04	1.6	

207		0.06	1	
208		0.09	3.3	

[1152] The present disclosure provides reference to various embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the present disclosure. The description is made with the understanding that it is to be considered an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated.

CLAIMS

1. A compound of Formula I:



Formula I,

or a pharmaceutically acceptable salt thereof,

wherein

X is N, CH, or CR^x;

R^x is $(CH_2)_mCN$ or halo;

m is 0, 1, 2 or 3;

R^1, R^2, R^3, and R^4 are each independently H or C_1-C_3 alkyl;

L^1 is O, S, or $CR^{1a}R^{1b}$;

R^{1a} and R^{1b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{1a} and R^{1b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

L^2 is $CR^{2a}R^{2b}$;

alternatively, L^2 is O or S, and L^1 is $CR^{1a}R^{1b}$;

R^{2a} and R^{2b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{2a} and R^{2b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

alternatively, R^{1b} and R^{2b} can combine with the atoms to which they are attached to form a C_3-C_6 cycloalkyl;

L^3 is a bond or $CR^{3a}R^{3b}$;

R^{3a} and R^{3b} are each independently H, C_1-C_3 alkyl, C_1-C_3 alkoxy, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -CN, C_1-C_3 cyanoalkyl, or C_3-C_6 cycloalkyl;

alternatively, R^{3a} and R^{3b} can combine with the atom to which they are attached to form a C_3-C_6 cycloalkyl;

alternatively, R^{2b} and R^{3b} can combine with the atoms to which they are attached to form a C_3-C_6 cycloalkyl;

R^A is phenyl or naphthyl, wherein R^A is substituted with 0, 1, 2, 3, 4, or 5 R^{A2};

each R^{A2} is independently -OH, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} hydroxyalkyl, C_2-C_{10} alkoxyalkyl, C_1-C_6 alkyl-$N(R^{A2a})(R^{A2b})$, C_1-C_{10} thioalkyl, halo, C_1-C_6 haloalkyl, -CN, $-C(O)R^{A2a}$, $-C(O)OR^{A2a}$, $-OC(O)R^{A2a}$, $-OC(O)OR^{A2a}$, $-C(O)N(R^{A2a})(R^{A2b})$, $-N(R^{A2a})C(O)(R^{A2b})$, $-OC(O)N(R^{A2a})(R^{A2b})$, $-N(R^{A2a})C(O)(OR^{A2b})$, oxo, $-OR^{A2a}$, $-SR^{A2a}$, $-S(O)_2R^{A2a}$, $-S(O)_2OR^{A2a}$, $-N(R^{A2a})(R^{A2b})$, -(C_0-C_3 alkyl)-SF_5, $-OP(O)(OR^{A2a})(OR^{A2b})$, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), 3- to 14-membered heterocyclyl, -(C_1-C_6 alkyl)-(3- to 14-membered heterocyclyl), C_6-C_{14} aryl, -(C_1-C_6 alkyl)-(C_6-C_{14} aryl), 5- to 14-membered heteroaryl, or -(C_1-C_6 alkyl)-(5- to 14-membered heteroaryl), wherein each alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, and haloalkyl is substituted with 0, 1, 2, or 3 R^{A3}, and wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 R^{A4};

each R^{A2a} and R^{A2b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl;

each R^{A3} is independently halo, -CN, $-OR^{A3a}$, $-SR^{A3a}$, $-N(R^{A3a})(R^{A3b})$, C_3-C_8 cycloalkyl, or 5- to 14-membered heteroaryl;

each R^{A3a} and R^{A3b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl;

each R^{A4} is independently C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 haloalkylthio, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), halo, -CN, -OH, or -N(R^{A4a})(R^{A4b});

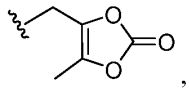
each R^{A4a} and R^{A4b} is independently H or C_1-C_6 alkyl;

alternatively, two R^{A2} can combine to form a C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, a 3- to 10-membered heterocyclyl, or 5- to 14-membered heteroaryl on two adjacent atoms on R^A;

R^B is H, -C(O)R^{B1}, or -C(O)OR^{B2};

R^{B1} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B1a};

R^{B2} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, (C_1-C_6 alkyl)-OC(O)R^{B3}, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, 5- to 14-membered heteroaryl, or



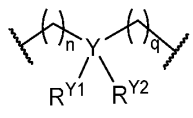
,

wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B2a};

R^{B3} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein the C_3-C_8 cycloalkyl, C_6-C_{14} aryl or 5- to 14-membered heteroaryl are substituted with 0, 1, 2, or 3 R^{B3a};

each R^{B1a}, R^{B2a} and R^{B3a} is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkoxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, oxo, -OH, -CN, or C_3-C_{10} cycloalkyl;

L^C is a bond or



;

Y is C or Si;

n is 0, 1, 2, or 3;

q is 0, 1, 2, or 3;

R^{Y1} is H or C_1-C_3 alkyl;

R^{Y2} is H or C_1-C_3 alkyl;

alternatively, R^{Y1} and R^{Y2} combine to form a C_3-C_{10} cycloalkyl or a 3- to 10-membered heterocyclyl;

R^C is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, C_2-C_6 alkoxyalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, -NH_2, -NHR^{C1}, -$N(R^{C1})_2$, C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-C_{14} aryl, or 5- to 14-membered heteroaryl, wherein each C_3-C_8 cycloalkyl, 3- to 14-membered heterocyclyl, C_6-C_{14} aryl, and 3- to 14-membered heteroaryl, is substituted with 0, 1, 2, 3, or 4 R^{C3};

each R^{C1} is independently selected from C_1-C_6 alkyl;

each R^{C3} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxyalkyl, C_1-C_6 hydroxyalkyl, halo, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, -(C_1-C_6 alkyl)-$N(R^{C3a})(R^{C3b})$, -CN, -$C(O)R^{C3a}$, -$C(O)OR^{C3a}$, -$C(O)N(R^{C3a})(R^{C3b})$, -$N(R^{C3a})C(O)(R^{C3b})$, -$OC(O)N(R^{C3a})(R^{C3b})$, -$N(R^{C3a})C(O)(OR^{C3b})$, =CH_2, =CF_2, oxo, -OR^{C3a}, -SR^{C3a}, -$N(R^{C3a})(R^{C3b})$, -N_3, SF_5, C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, -(C_1-C_6 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl),
wherein each alkyl is substituted with 0, 1, 2, or 3 -CN, -$C(O)OR^{C3a1}$, -$C(O)N(R^{C3a1})(R^{C3a2})$, -$N(R^{C3a1})C(O)(R^{C3a2})$, -$OC(O)N(R^{C3a1})(R^{C3a2})$, -$OR^{C3a1}$, -$SR^{C3a1}$, N_3, SF_5, or 3- to 10-membered heterocyclyl substituted with 0, 1, 2, or 3 R^{C3a2},
each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2},
each alkenyl is substituted with 0, 1, 2, or 3 halo, and
each alkoxyalkyl and alkynyl is substituted with 0, 1, 2, or 3 C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl substituted with 0 or 1 C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each R^{C3a} and R^{C3b} is independently H, C_1-C_{10} alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, or 5- to 10-membered heteroaryl, wherein each aryl and heteroaryl is substituted with 0, 1, 2, or 3 halo, -CN, or R^{C3a2};

alternatively, R^{C3a} and R^{C3b} together with the N to which they are attached form a 3- to 8-membered heterocycle;

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, halo, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, -(C_1-C_3 alkyl)-(C_3-C_8 cycloalkyl), 3- to 10-membered heterocyclyl, -(C_1-C_3 alkyl)-(3- to 10-membered heterocyclyl), C_6-C_{10} aryl, -(C_1-C_3 alkyl)-(C_6-C_{10} aryl), -(C_2-C_4 alkynyl)-(C_6-C_{10} aryl), 5- to 10-membered heteroaryl, -(C_1-C_3 alkyl)-(5- to 10-membered heteroaryl), or SF_5, wherein each cycloalkyl, alkyl-cycloalkyl, heterocyclyl, alkyl-heterocyclyl, aryl, alkyl-aryl, alkynyl-aryl, heteroaryl, and alkyl-heteroaryl is substituted with 0, 1, 2, or 3 halo, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, or SF_5;

alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle;

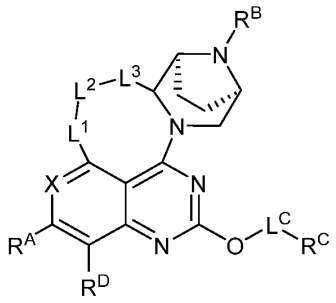
R^D is halo;

each heterocyclyl has 1, 2, 3, or 4 heteroatoms selected from N, O, S, and Si; and

each heteroaryl has 1, 2, 3, or 4 heteroatoms selected from N, O, and S.

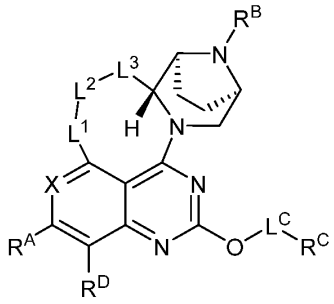
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and R^4 are each H.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, having the structure of Formula (I-1):



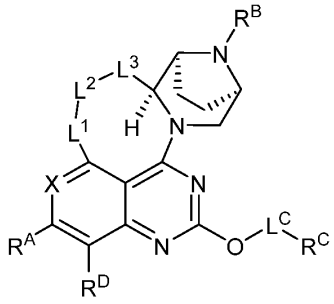
(I-1).

4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, having the structure of Formula (I-2):



(I-2).

5. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, having the structure of Formula (I-3):



(I-3).

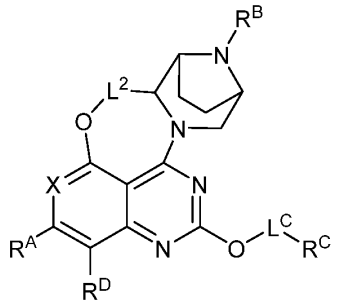
6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein X is N.

7. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein X is CH.

8. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein X is C-Cl.

9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein L^1 is O.

10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, having the structure of Formula (IIa):



(IIa).

11. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein L^1 is CHR^{1b}.

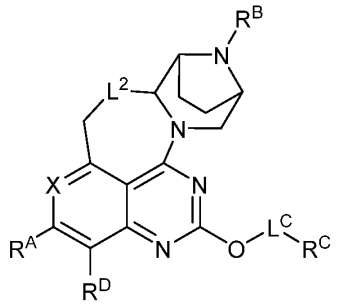
12. The compound of any one of claims 1 to 8 or 11, or a pharmaceutically acceptable salt thereof, wherein L^1 is CH_2.

13. The compound of any one of claims 1 to 8 or 11, or a pharmaceutically acceptable salt thereof, wherein R^{1a} and R^{1b} are each independently H, C_1-C_3 alkyl, or halo.

14. The compound of any one of claims 1 to 8, 11, or 13, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is C_1-C_3 alkyl or halo.

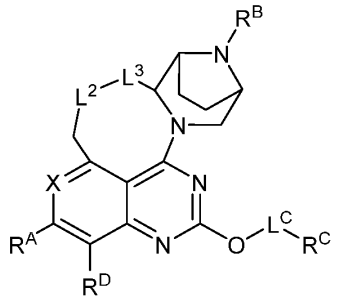
15. The compound of any one of claims 1 to 8, 11, or 13 to 14, or a pharmaceutically acceptable salt thereof, wherein R^{1b} is methyl.

16. The compound of any one of claims 1 to 8 or 11 to 13, or a pharmaceutically acceptable salt thereof, having the structure of Formula (IIb):



(IIb).

17. The compound of any one of claims 1 to 8 or 11 to 13, or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ib):



(Ib).

18. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein R^{2a} and R^{2b} are each independently H, C_1-C_3 alkyl, halo, or C_1-C_6 haloalkyl.

19. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein L^2 is CHR^{2b}.

20. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R^{2b} is H or C_1-C_3 alkyl.

21. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein R^{2b} is H.

22. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein R^{2b} is C_1-C_3 alkyl.

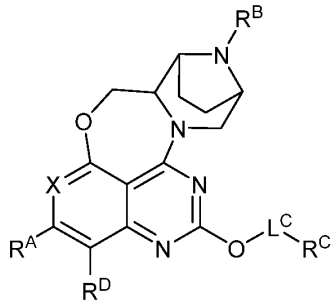
23. The compound of any one of claims 1 to 20 or 22, or a pharmaceutically acceptable salt thereof, wherein R^{2b} is methyl.

24. The compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, wherein L^3 is a bond.

25. The compound of any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, wherein L^3 is $CR^{3a}R^{3b}$.

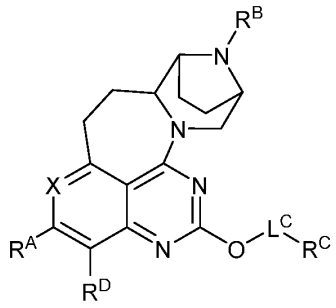
26. The compound of any one of claims 1 to 23 or 25, or a pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{3b} are H.

27. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, having the structure of Formula (IIa-1):



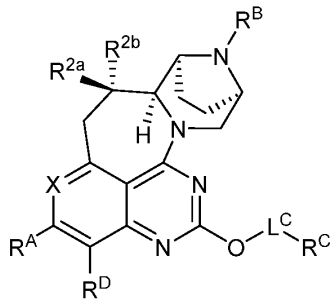
(IIa-1).

28. The compound of any one of claims 1 to 9, 11 to 13, or 16 to 21, or a pharmaceutically acceptable salt thereof, having the structure of Formula (IIb-1):



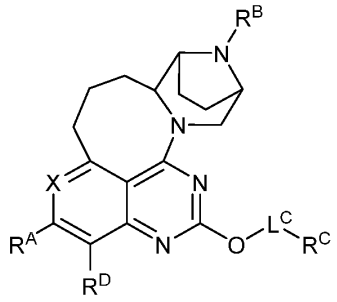
(IIb-1).

29. The compound of any one of claims 1 to 3, 5 to 8, 11 to 13, 16 to 21, or 24, or a pharmaceutically acceptable salt thereof, having the structure of Formula (IIb-2):



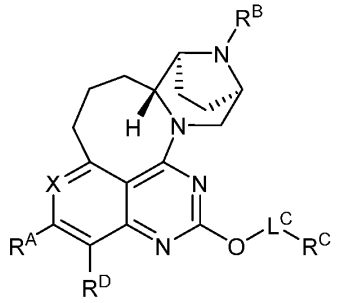
(IIb-2).

30. The compound of any one of claims 1 to 8, 11 to 13, 17 to 21, or 25 to 26, or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ib-1):



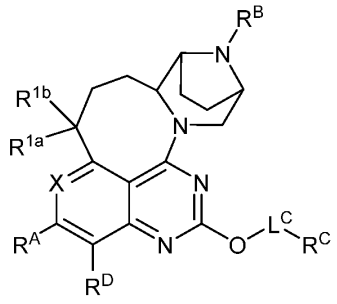
(Ib-1).

31. The compound of any one of claims 1 to 4, 6 to 8, 11 to 13, 17 to 21, or 25 to 26, or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ib-2):



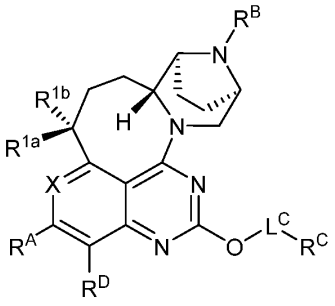
(Ib-2).

32. The compound of any one of claims 1 to 8, 11 to 15, 17 to 21, or 25 to 26, or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ib-3):



(Ib-3).

33. The compound of any one of claims 1 to 4, 6 to 8, 11 to 15, 17 to 21, or 25 to 26, or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ib-4):



(Ib-4).

34. The compound of any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof, wherein R^A is naphthyl substituted with 0, 1, 2, 3, 4, or 5 R^{A2}.

35. The compound of any one of claims 1 to 34, or a pharmaceutically acceptable salt thereof, wherein

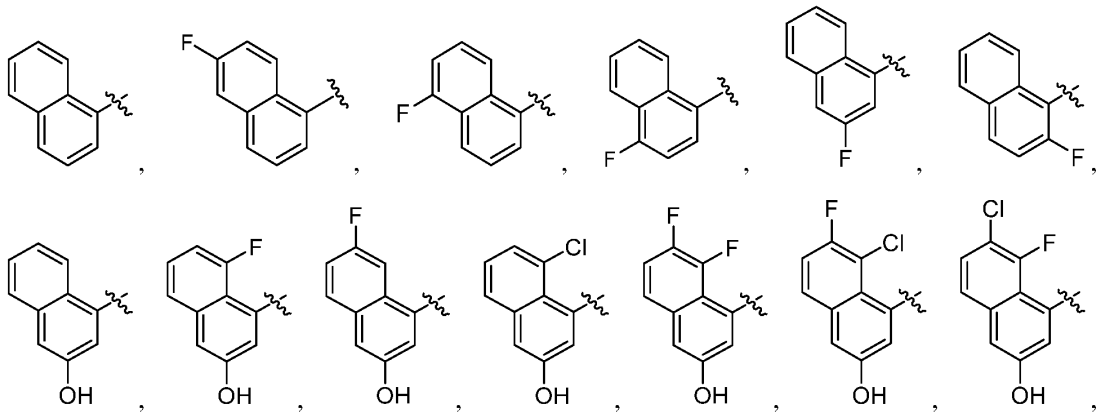
each R^{A2} is independently C_1-C_6 alkyl, -OH, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo, C_1-C_6 haloalkyl, -OR^{A2a}, -SR^{A2a}, or -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), wherein each alkenyl is substituted with 0, 1, 2, or 3 R^{A3};

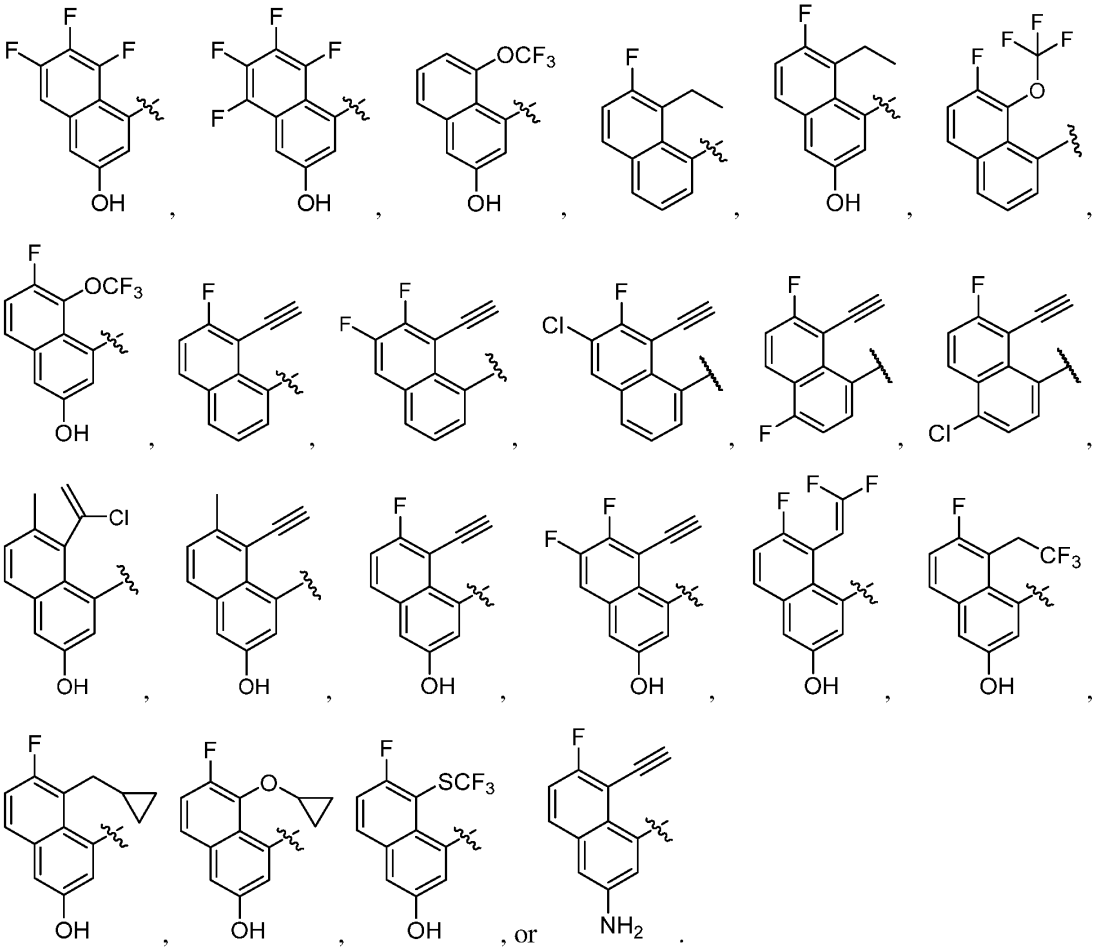
each R^{A2a} is independently C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl; and

each R^{A3} is independently halo.

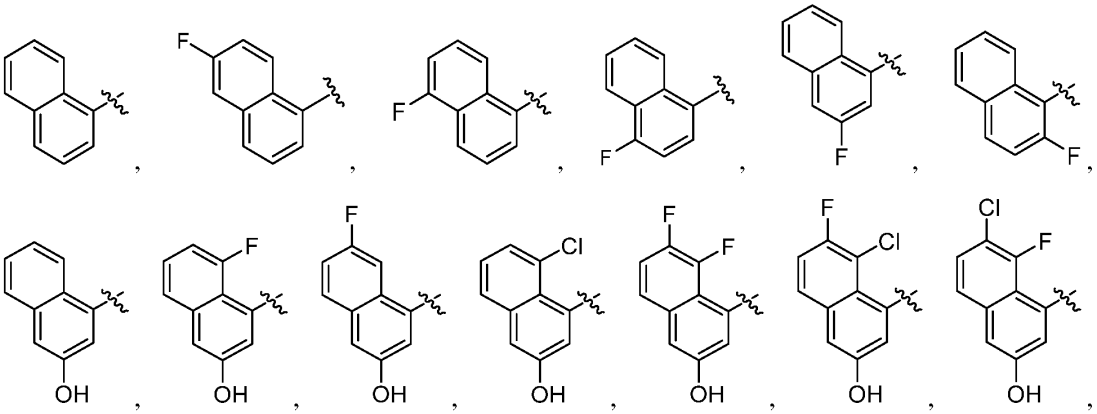
36. The compound of any one of claims 1 to 35, or a pharmaceutically acceptable salt thereof, wherein each R^{A2} is independently Me, -OH, -C(Cl)=CH_2, -CH=CHF_2, -C≡CH, F, Cl, -CH_2CF_3, -OCF_3, -O-cyclopropyl, -SCF_3, or –CH_2-cyclopropyl.

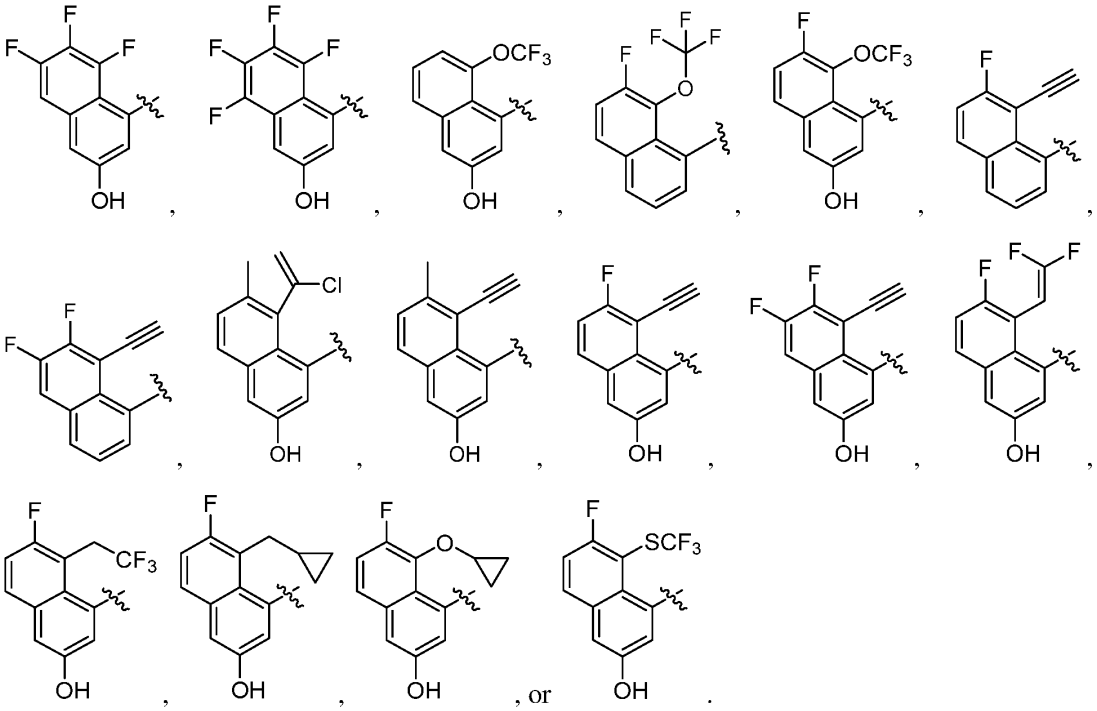
37. The compound of any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof, wherein R^A is



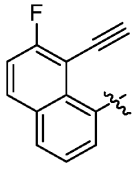


38. The compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt thereof, wherein R^A is





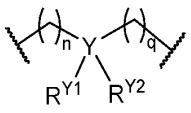
39. The compound of any one of claims 1 to 38, or a pharmaceutically acceptable salt thereof, wherein R^A is



40. The compound of any one of claims 1 to 39, or a pharmaceutically acceptable salt thereof, wherein R^B is H.

41. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein

L^C is



;

Y is C or Si;

n is 0 or 1;

q is 0 or 1;

R^{Y1} is H or Me; and

R^{Y2} is H or Me;

alternatively, R^{Y1} and R^{Y2} combine to form a cyclopropyl.

42. The compound of any one of claims 1 to 41, or a pharmaceutically acceptable salt thereof, wherein

R^C is 3- to 14-membered heterocyclyl, substituted with 0, 1, 2, or 3 R^{C3};

each R^{C3} is independently C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, $=CH_2$, $-OR^{C3a}$, or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl), wherein each alkyl is substituted with 1-$OC(O)N(R^{C3a1})(R^{C3a2})$, $-OR^{C3a1}$, or N_3;

each R^{C3a} is independently C_1-C_6 haloalkyl; and

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl wherein each aryl or heteroaryl is substituted with 0, 1, 2, 3, or 4 halo, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, or SF_5;

alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle.

43. The compound of any one of claims 1 to 42, or a pharmaceutically acceptable salt thereof, wherein

R^C is 3- to 14-membered heterocyclyl, substituted with 0, 1, 2, or 3 R^{C3};

each R^{C3} is independently C_1-C_6 alkyl, halo, C_1-C_6 haloalkyl, $=CH_2$, $-OR^{C3a}$, or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl), wherein each alkyl is substituted with 1-$OC(O)N(R^{C3a1})(R^{C3a2})$, $-OR^{C3a1}$, or N_3;

each R^{C3a} is independently C_1-C_6 haloalkyl; and

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, C_1-C_6 haloalkyl, or C_6-C_{10} aryl, wherein each aryl is substituted with 1 SF_5;

alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle.

44. The compound of any one of claims 1 to 43, or a pharmaceutically acceptable salt thereof, wherein L^C is $–CH_2-$.

45. The compound of any one of claims 1 to 44, or a pharmaceutically acceptable salt thereof, wherein

R^C is 8- to 14-membered heterocyclyl, is substituted with 0, 1, 2, or 3 R^{C3};

each R^{C3} is independently C_1-C_6 alkyl, halo, $=CH_2$, $-OR^{C3a}$, or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl),

wherein each alkyl is substituted with 1 $-OC(O)N(R^{C3a1})(R^{C3a2})$, $-OR^{C3a1}$, or N_3;

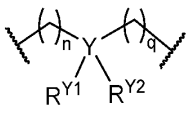
each R^{C3a} is independently C_1-C_6 haloalkyl; and

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, C_1-C_6 haloalkyl, or C_6-C_{10} aryl, wherein each aryl is substituted with 1 SF_5;

alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle.

46. The compound of any one of claims 1 to 43, or a pharmaceutically acceptable salt thereof, wherein

L^C is



;

Y is C or Si;

n is 1;

q is 1;

R^{Y1} is Me; and

R^{Y2} is Me;

alternatively, R^{Y1} and R^{Y2} combine to form a cyclopropyl.

47. The compound of any one of claims 1 to 43 or 46, or a pharmaceutically acceptable salt thereof, wherein

R^C is 3- to 7-membered heterocyclyl, substituted with 0, 1, or 2 R^{C3}; and

each R^{C3} is independently halo or C_1-C_6 haloalkyl.

48. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein

L^C is $–CH_2$-;

R^C is 3- to 14-membered heterocyclyl substituted with 1 R^{C3};

R^{C3} is C_1-C_6 alkyl substituted with one -OR^{C3a1} or -SR^{C3a1}; and

R^{C3a1} is 5- to 10-membered heteroaryl substituted with 0, 1, or 2 C_1-C_3 haloalkyl or C_1-C_3 haloalkoxy.

49. The compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein

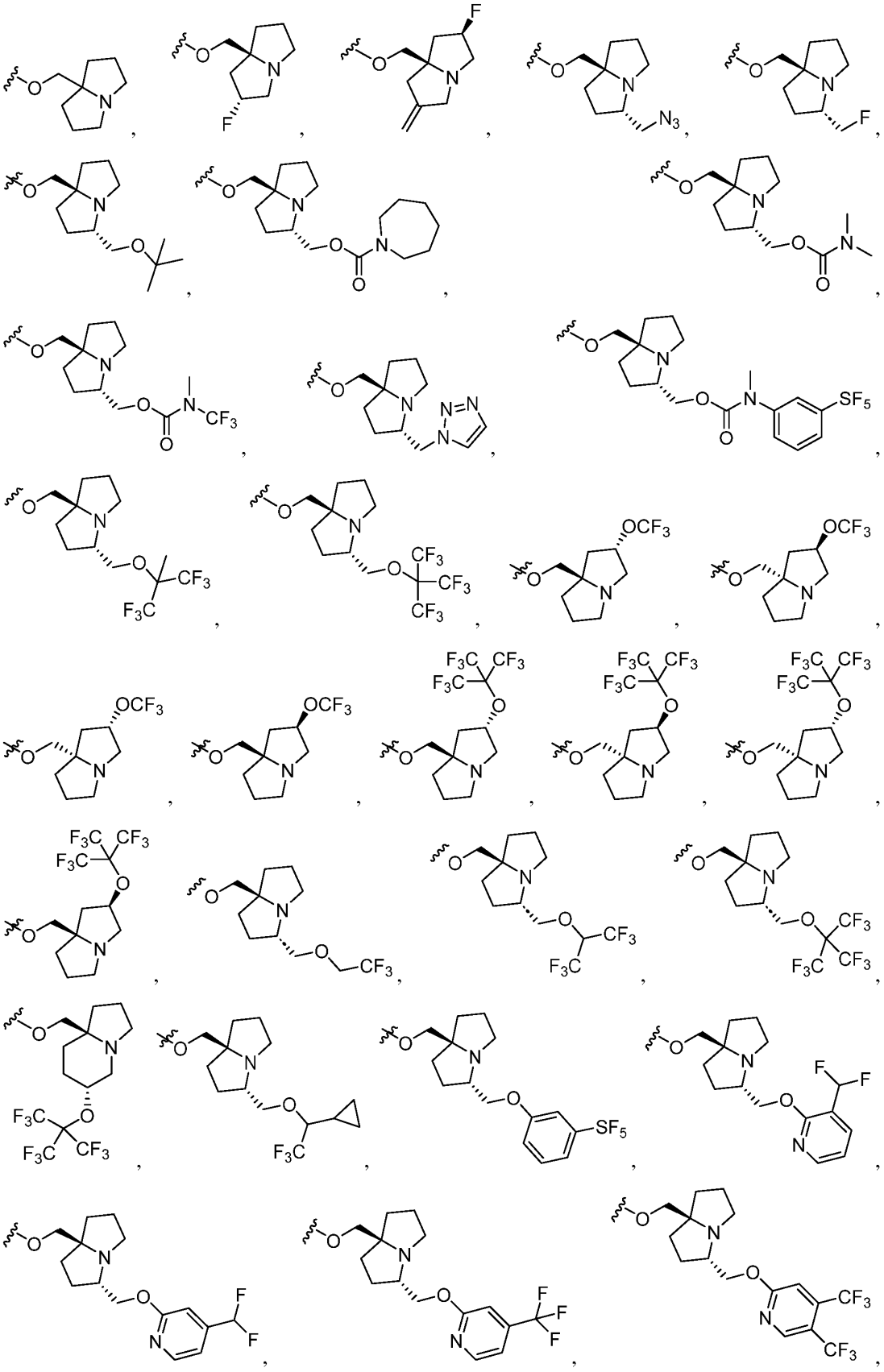
L^C is $–CH_2$-;

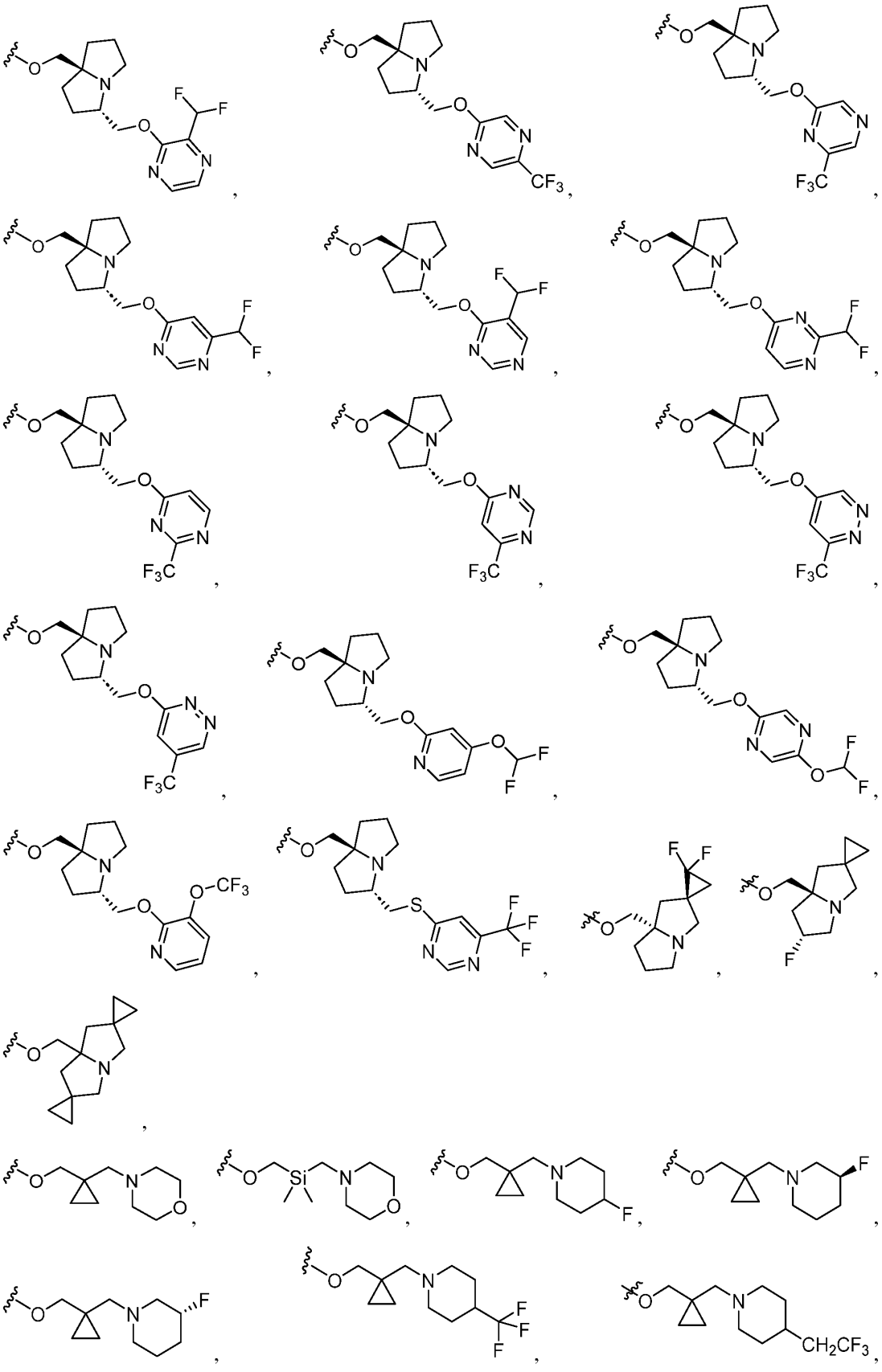
R^C is 4- to 8-membered heterocyclyl substituted with 1 R^{C3};

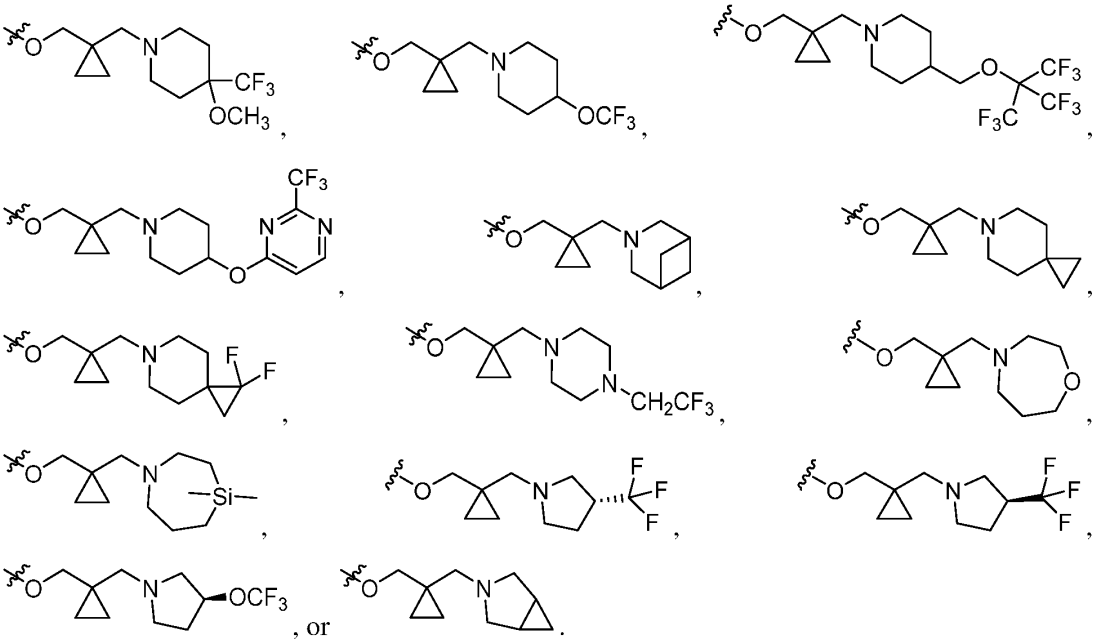
R^{C3} is -CH_2OR^{C3a1}; and

R^{C3a1} is a pyrimidine, wherein the pyrimidine is substituted with 1 trifluoromethyl group.

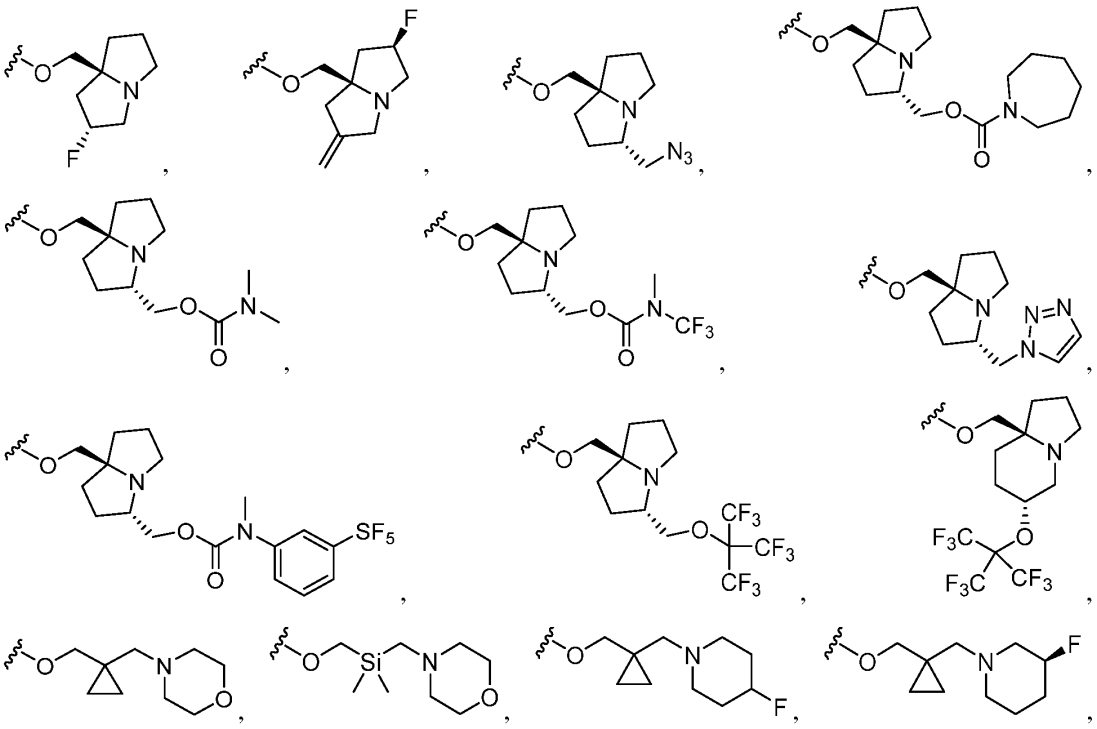
50. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein the –O-L^C-R^C moiety is

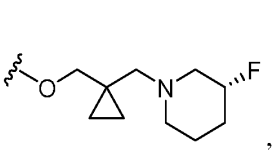
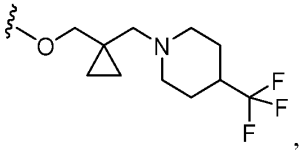
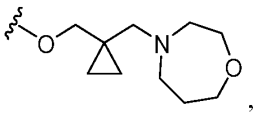
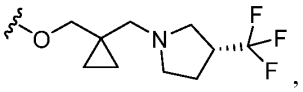
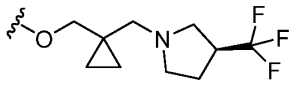




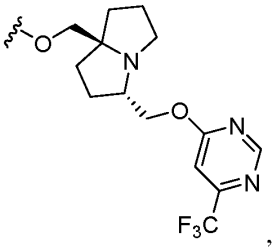
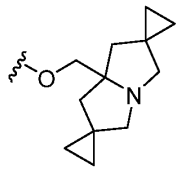
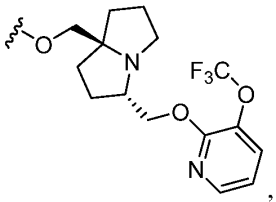
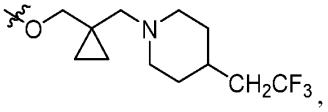
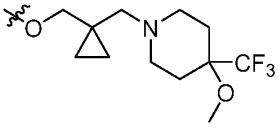
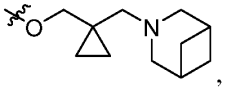
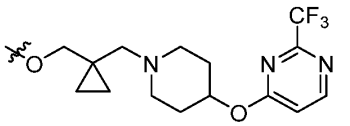
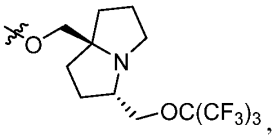
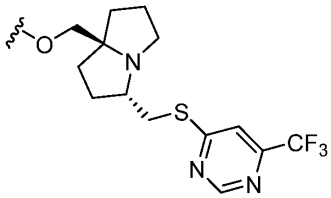
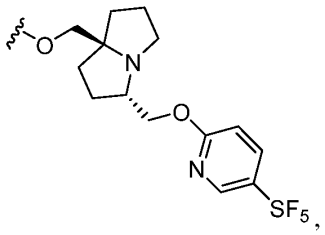
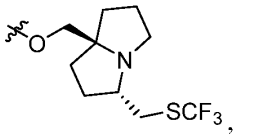
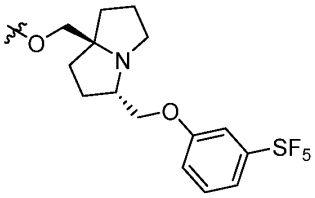
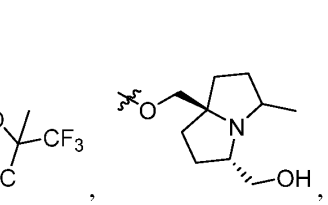
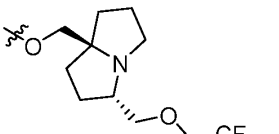
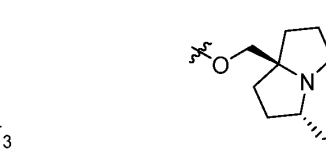


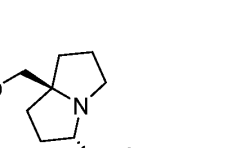
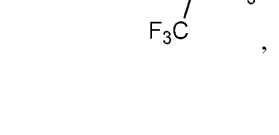
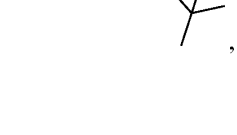
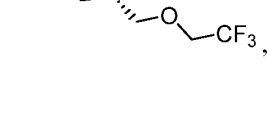
51. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein the –O-L^C-R^C moiety is

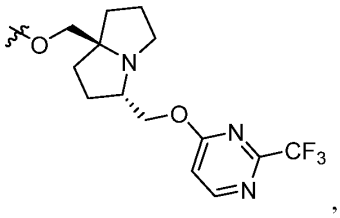
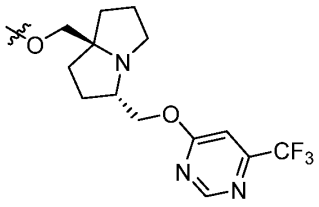
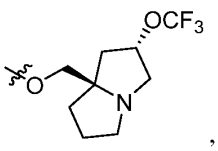
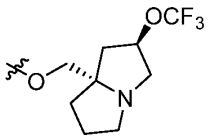
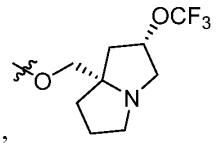
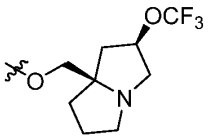
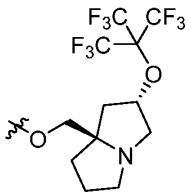
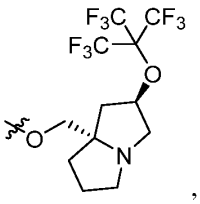
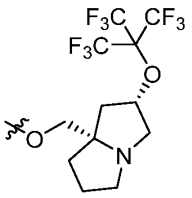
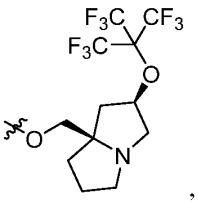
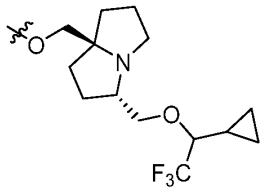
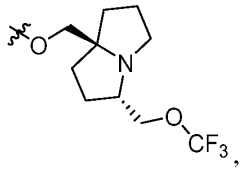
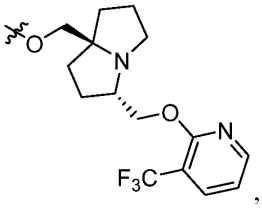
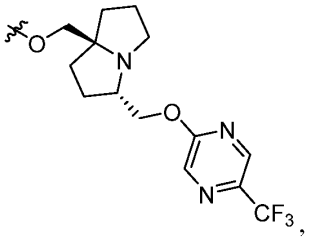
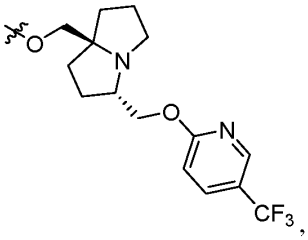
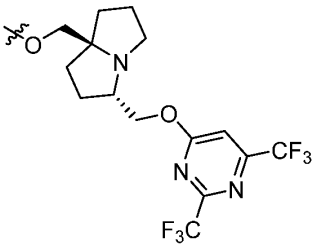
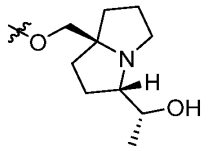
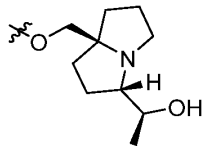
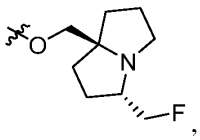
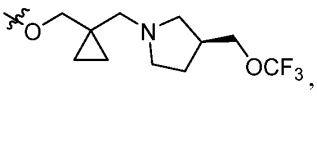
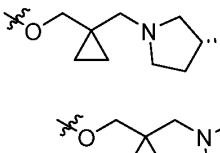


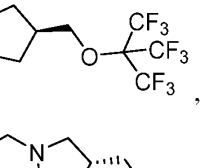
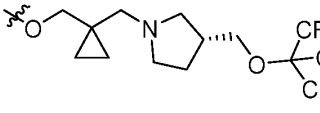

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52. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein the –O-L^C-R^C moiety is


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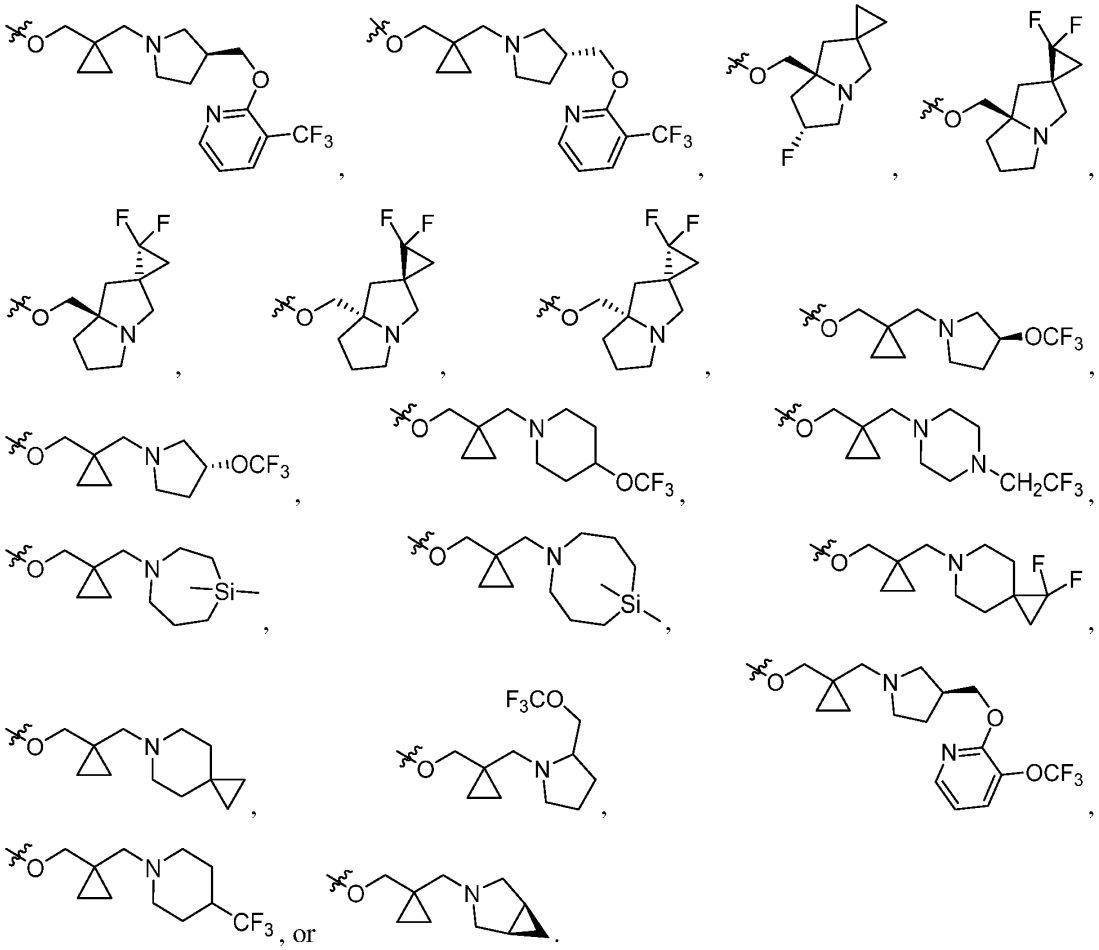
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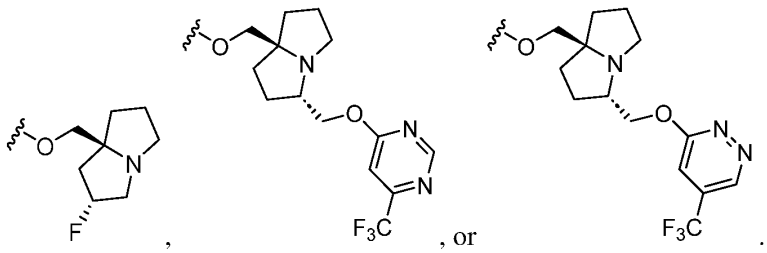
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53. The compound of any one of claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein the –O-L^C-R^C moiety is



54. The compound of any one of claims 1 to 53, or a pharmaceutically acceptable salt thereof, wherein R^D is F.

55. The compound of any one of claims 1 and 3 to 5, or a pharmaceutically acceptable salt thereof, wherein

X is N, CH, or CR^x;

R^x is halo;

L^1 is O or $CR^{1a}R^{1b}$;

R^{1a} and R^{1b} are each independently H, C_1-C_3 alkyl, or halo;

L^2 is $CR^{2a}R^{2b}$;

R^{2a} and R^{2b} are each independently H, C_1-C_3 alkyl, C_1-C_6 haloalkyl, or C_3-C_6 cycloalkyl;

L^3 is a bond or $CR^{3a}R^{3b}$;

R^{3a} and R^{3b} are each independently H or C_1-C_3 alkyl;

R^1, R^2, R^3, and R^4 are each H;

R^A is naphthyl, wherein R^A is substituted with 0, 1, 2, 3, 4, or 5 R^{A2};

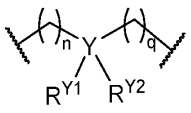
each R^{A2} is independently -OH, C_1-C_3 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, halo, C_1-C_6 haloalkyl, $-OR^{A2a}$, $-SR^{A2a}$, $-N(R^{A2a})(R^{A2b})$, or -(C_1-C_6 alkyl)-(C_3-C_8 cycloalkyl), wherein each alkyl, alkenyl, alkynyl, alkoxy, and haloalkyl is substituted with 0, 1, 2, or 3 R^{A3};

each R^{A2a} and R^{A2b} is independently H, C_1-C_6 haloalkyl, or C_3-C_8 cycloalkyl;

each R^{A3} is independently halo;

R^B is H;

L^C is a bond or



;

Y is C or Si;

n is 0 or 1;

q is 0 or 1;

R^{Y1} is H or C_1-C_3 alkyl;

R^{Y2} is H or C_1-C_3 alkyl;

alternatively, R^{Y1} and R^{Y2} combine to form a C_3-C_8 cycloalkyl;

R^C is 3- to 14-membered heterocyclyl, wherein each 3- to 14-membered heterocyclyl is substituted with 0, 1, 2, 3, or 4 R^{C3};

each R^{C3} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxyalkyl, halo, C_1-C_6 haloalkyl, $=CH_2$, $-OR^{C3a}$, wherein each alkyl is substituted with 0, 1, 2, or 3 $-OC(O)N(R^{C3a1})(R^{C3a2})$, $-OR^{C3a1}$, $-SR^{C3a1}$, or N_3;

R^{C3a} is C_1-C_6 alkyl, C_1-C_6 haloalkyl, or 5- to 10-membered heteroaryl, wherein the heteroaryl is substituted with 1 R^{C3a2};

each R^{C3a1} and R^{C3a2} is independently C_1-C_3 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is substituted with 1 or 2 halo, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, or SF_5;

alternatively, R^{C3a1} and R^{C3a2} together with the N to which they are attached form a 3- to 8-membered heterocycle; and

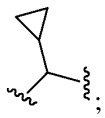
R^D is F.

56. The compound of any one of claims 1 and 3 to 5, or a pharmaceutically acceptable salt thereof, wherein

X is N, CH, or C-Cl;

L^1 is O, CH_2, $CHCH_3$, $CHCH_2CH_3$, CHF, or CF_2;

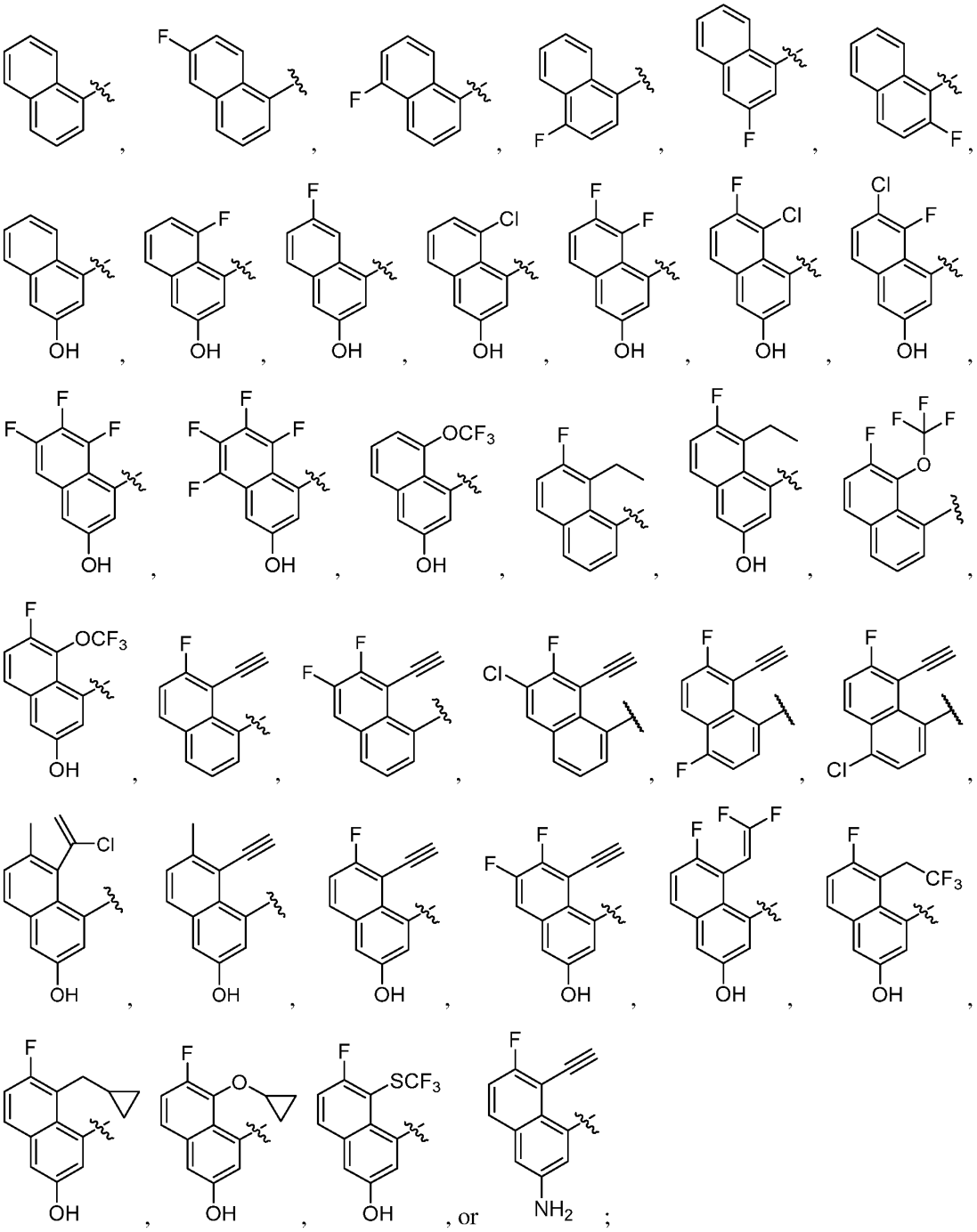
L^2 is CH_2, $CHCH_3$, $CHCH_2CH_3$, $CHCHF_2$, or

 ;

L^3 is a bond, CH_2, or $CHCH_3$;

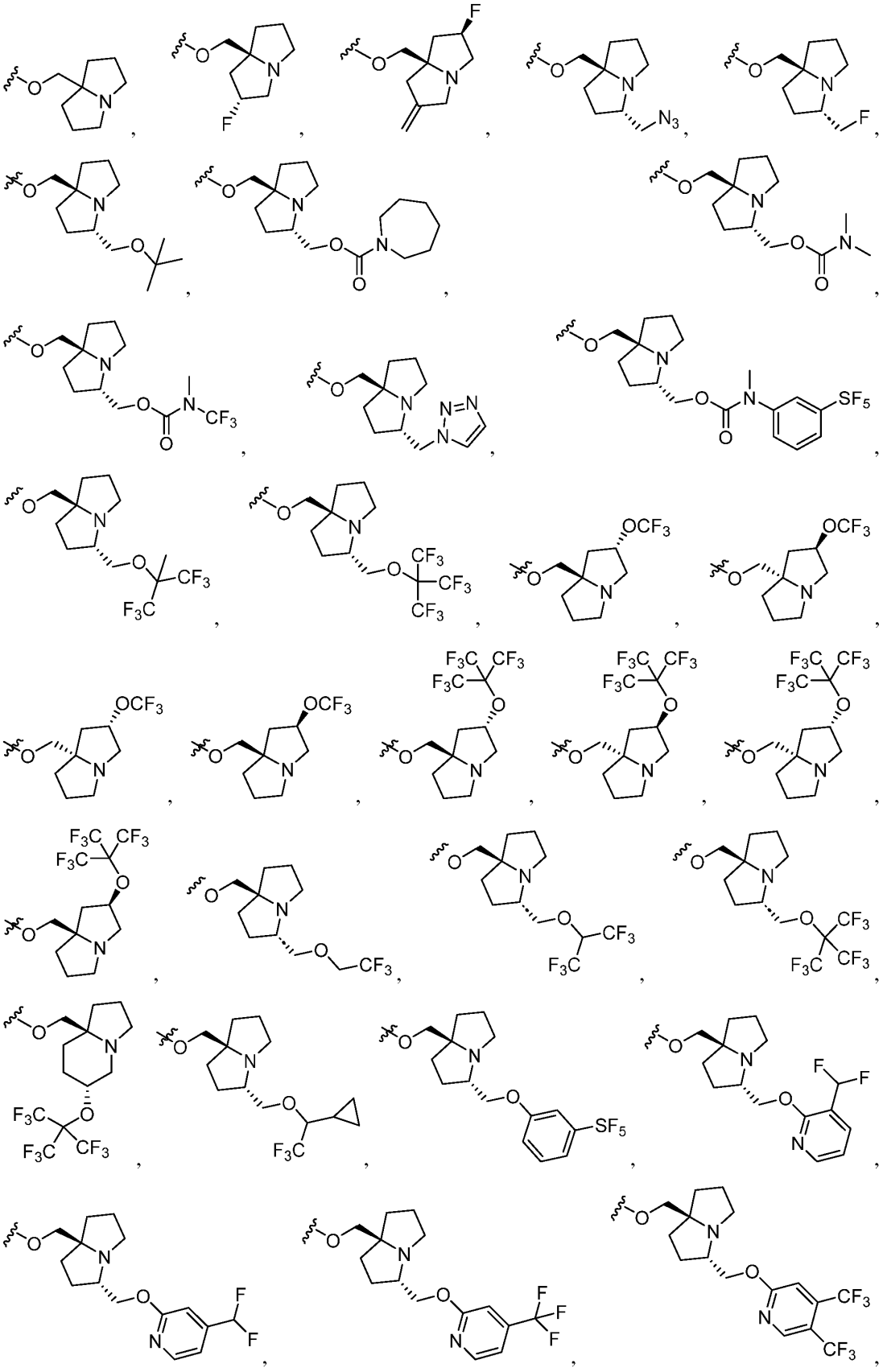
R^1, R^2, R^3, and R^4 are each H;

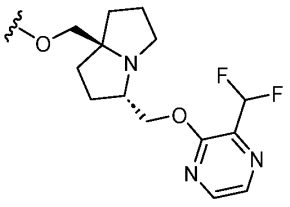
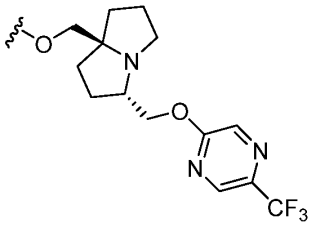
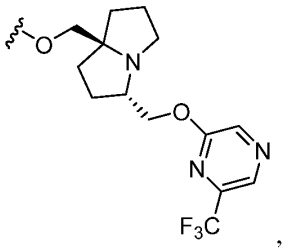
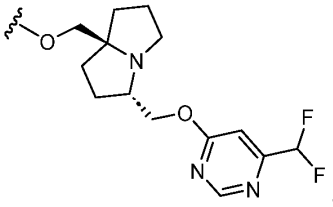
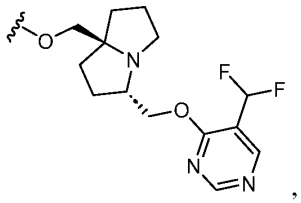
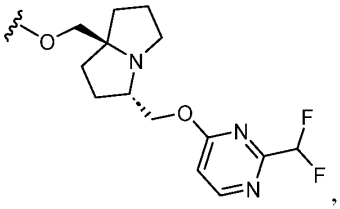
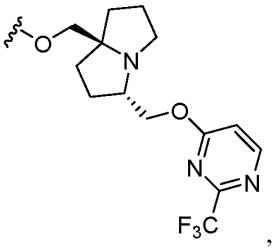
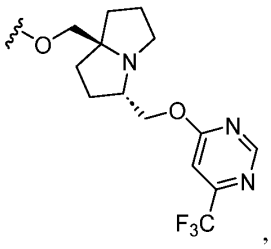
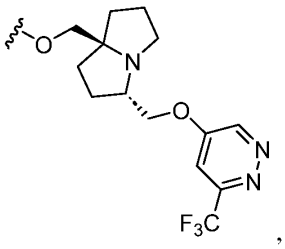
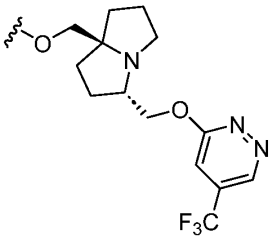
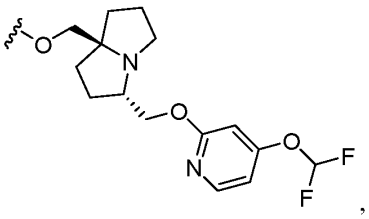
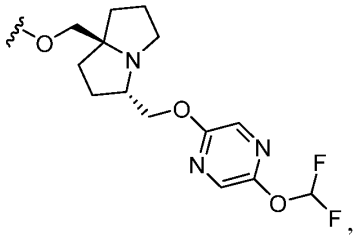
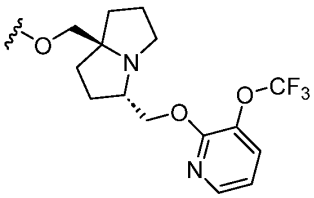
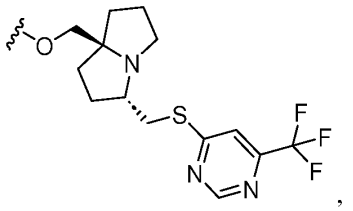
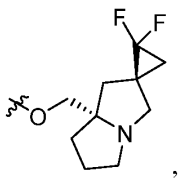
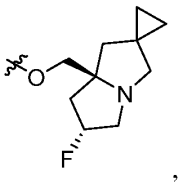
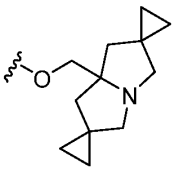
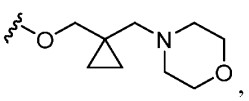
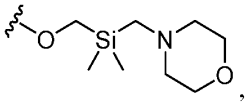
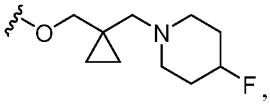
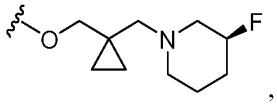
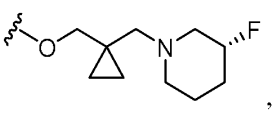
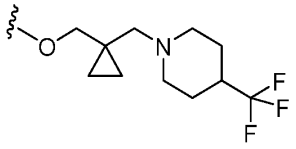
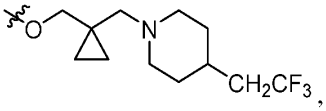
R^A is

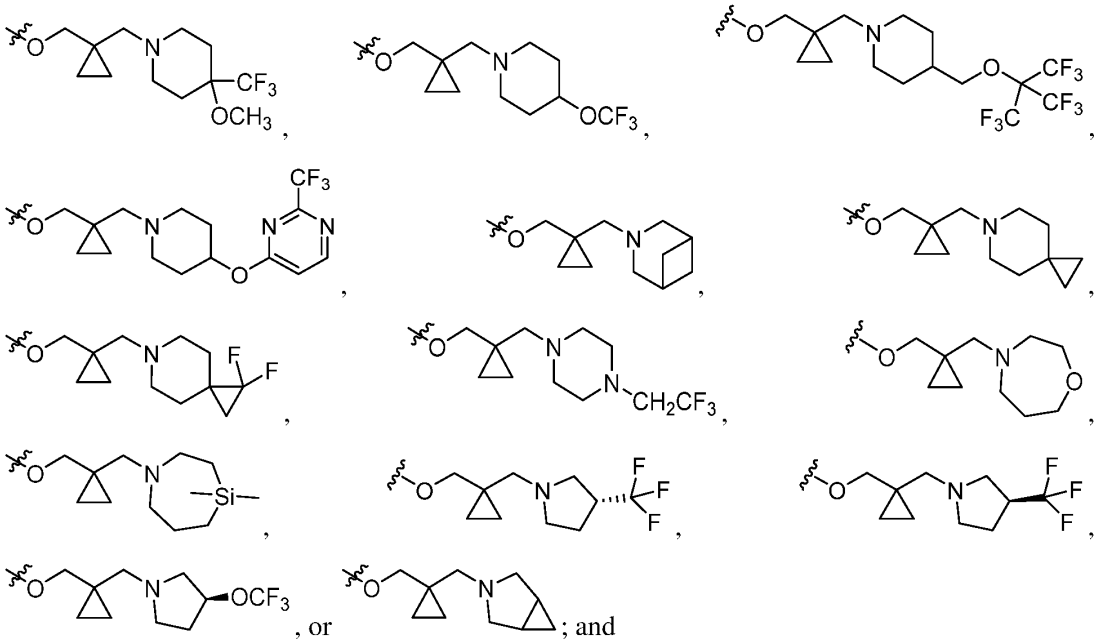


R^B is H;

the –O-L^C-R^C moiety is




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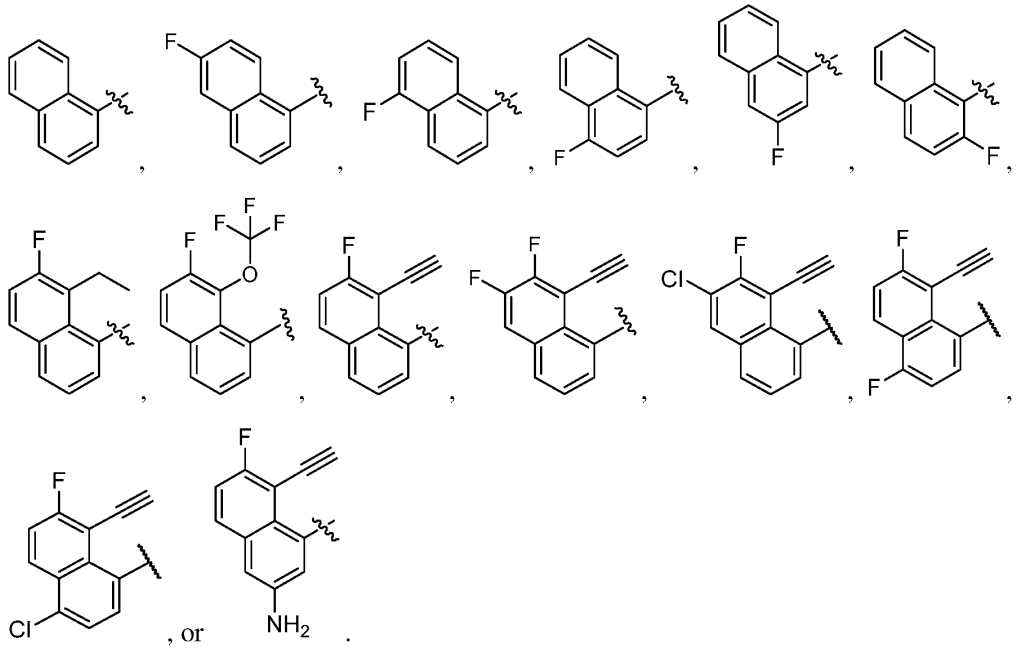


R^D is F.

57. The compound of claim 56, or a pharmaceutically acceptable salt thereof, wherein L^1 is CH_2, $CHCH_3$, $CHCH_2CH_3$, CHF, or CF_2.

58. The compound of claim 56 or 57, or a pharmaceutically acceptable salt thereof, wherein L^3 is CH_2 or $CHCH_3$.

59. The compound of any one of claims 56 to 58, or a pharmaceutically acceptable salt thereof, wherein R^A is



60. The compound of any one of claims 1 and 3 to 5, or a pharmaceutically acceptable salt thereof, wherein

X is N;

R^1, R^2, R^3, and R^4 are each H;

L^1 is $CR^{1a}R^{1b}$;

R^{1a} and R^{1b} are each independently H or C_1-C_3 alkyl;

L^2 is $CR^{2a}R^{2b}$;

R^{2a} and R^{2b} are each H;

L^3 is $CR^{3a}R^{3b}$;

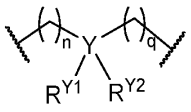
R^{3a} and R^{3b} are each H;

R^A is naphthyl, wherein R^A is substituted with 2 R^{A2};

each R^{A2} is independently C_2-C_6 alkynyl or halo;

R^B is H;

L^C is



;

Y is C;

n is 0;

q is 0;

R^{Y1} is H;

R^{Y2} is H;

R^C is 3- to 14-membered heterocyclyl, wherein the 3- to 14-membered heterocyclyl is substituted with 1 R^{C3};

R^{C3} is C_1-C_6 alkyl, halo, or C_1-C_6 haloalkyl, wherein the alkyl is substituted with 1 -OR^{C3a1};

R^{C3a1} is 5- to 10-membered heteroaryl, wherein the heteroaryl is substituted with 1 C_1-C_3 haloalkyl; and

R^D is F.

61. The compound of any one of claims 1 and 3 to 5, or a pharmaceutically acceptable salt thereof, wherein

X is N;

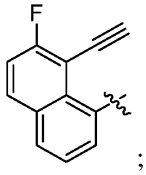
R^1, R^2, R^3, and R^4 are each H;

L^1 is CH_2 or $CHCH_3$;

L^2 is CH_2;

L^3 is CH_2;

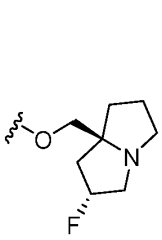
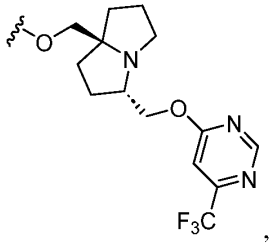
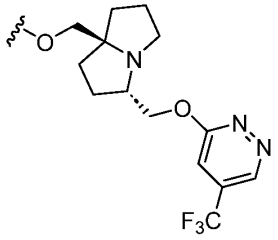
R^A is



;

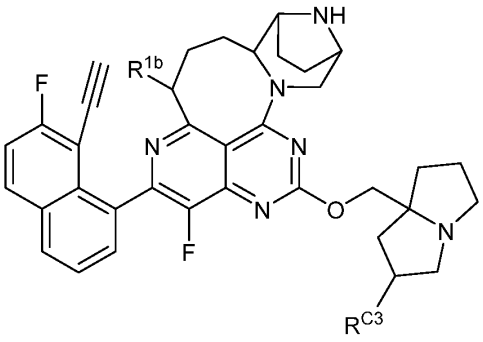
R^B is H;

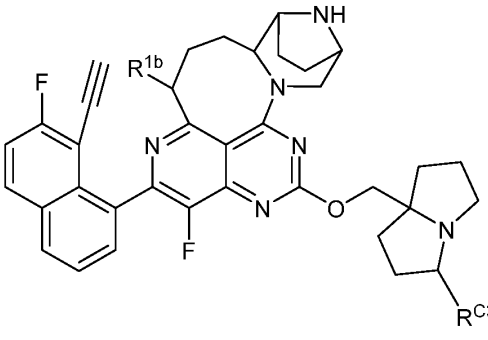
the -O-L^C-R^C moiety is


,

, or

; and

R^D is F.

62. The compound of any one of claims 1, 3 to 5, 17, and 30 to 33, or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ib-5) or Formula (Ib-6):


(Ib-5),


(Ib-6),

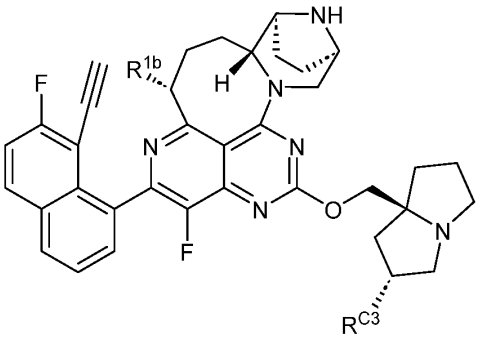
wherein

R^{1b} is H or methyl;

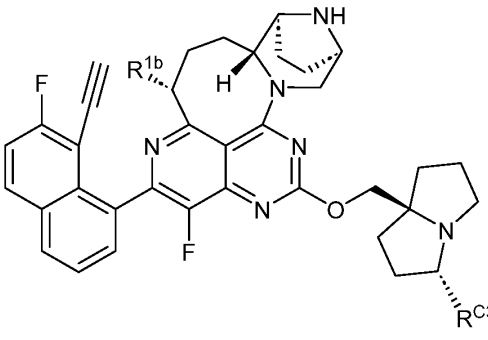
R^{C3} is -CH_2OR^{C3a1} or F; and

R^{C3a1} is 5- to 6-membered heteroaryl substituted with one halo or C_1-C_2 haloalkyl.

63. The compound of any one of claims 1, 3 to 5, 17, and 30 to 33, or a pharmaceutically acceptable salt thereof, having the structure of Formula (Ib-7) or Formula (Ib-8):



(Ib-7),



(Ib-8),

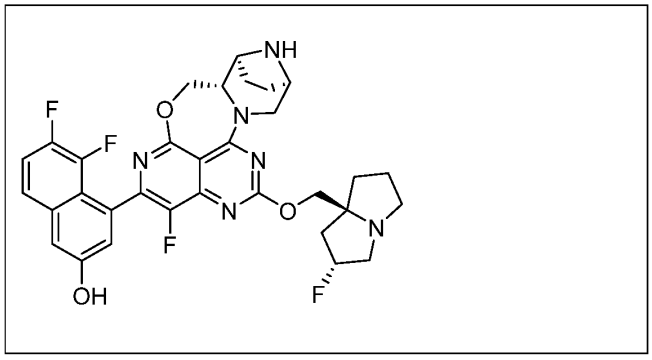
wherein

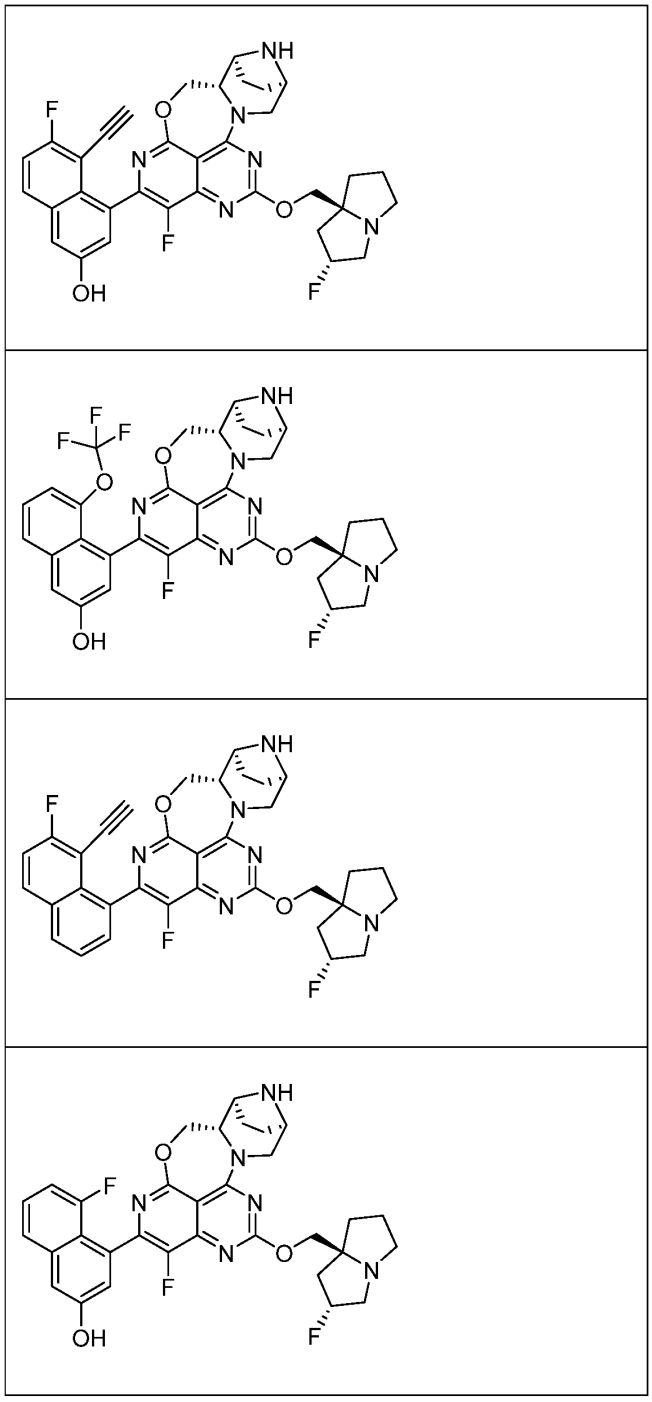
R^{1b} is H or methyl;

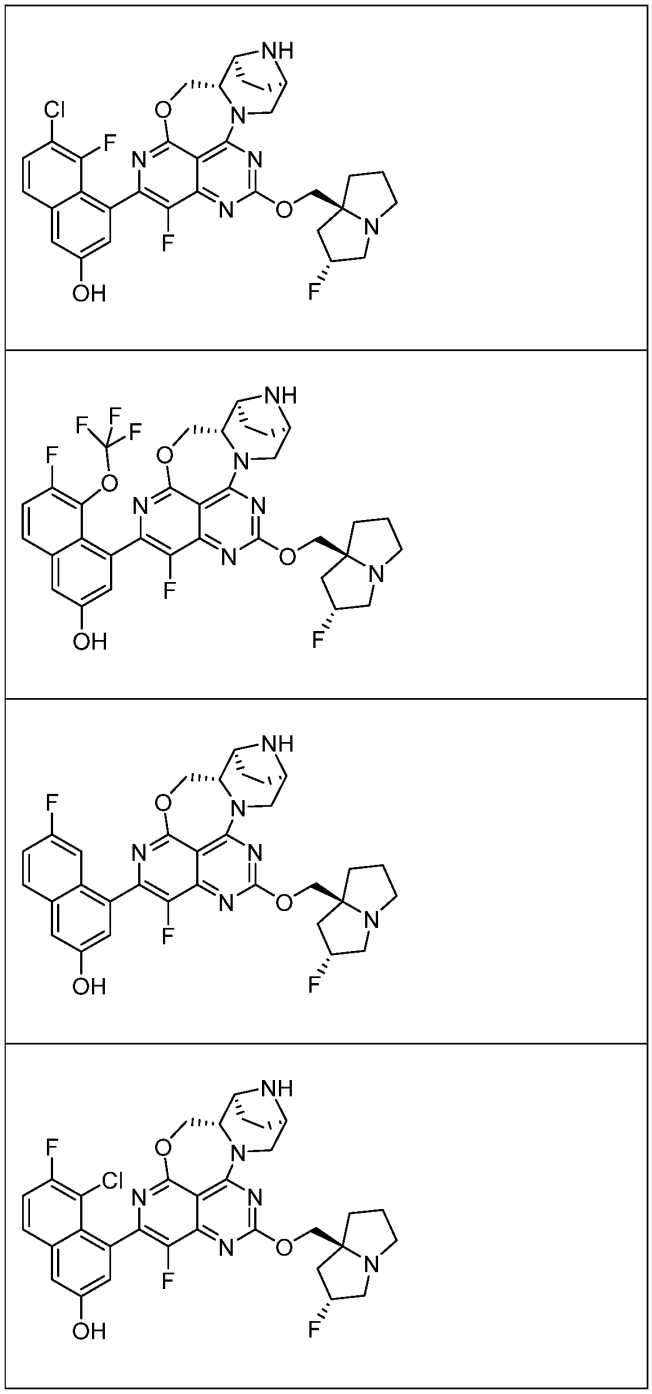
R^{C3} is $-CH_2OR^{C3a1}$ or F; and

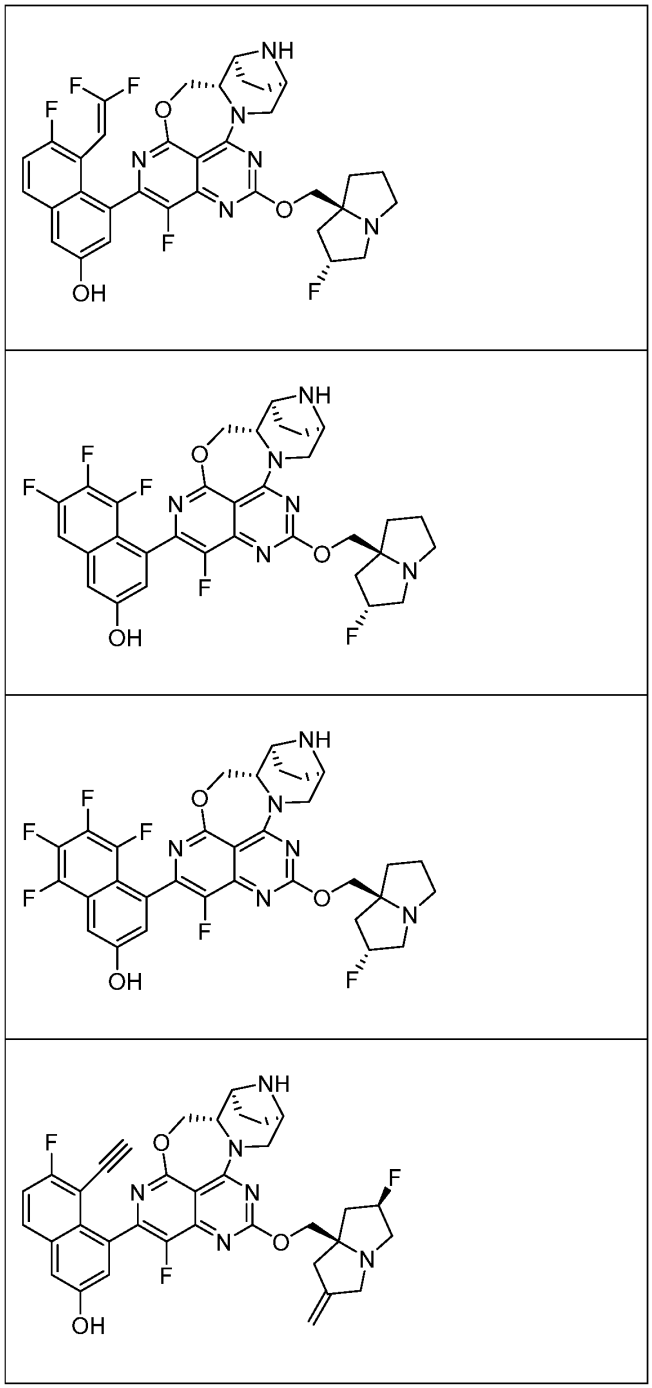
R^{C3a1} is 5- to 6-membered heteroaryl substituted with one halo or C_1-C_2 haloalkyl.

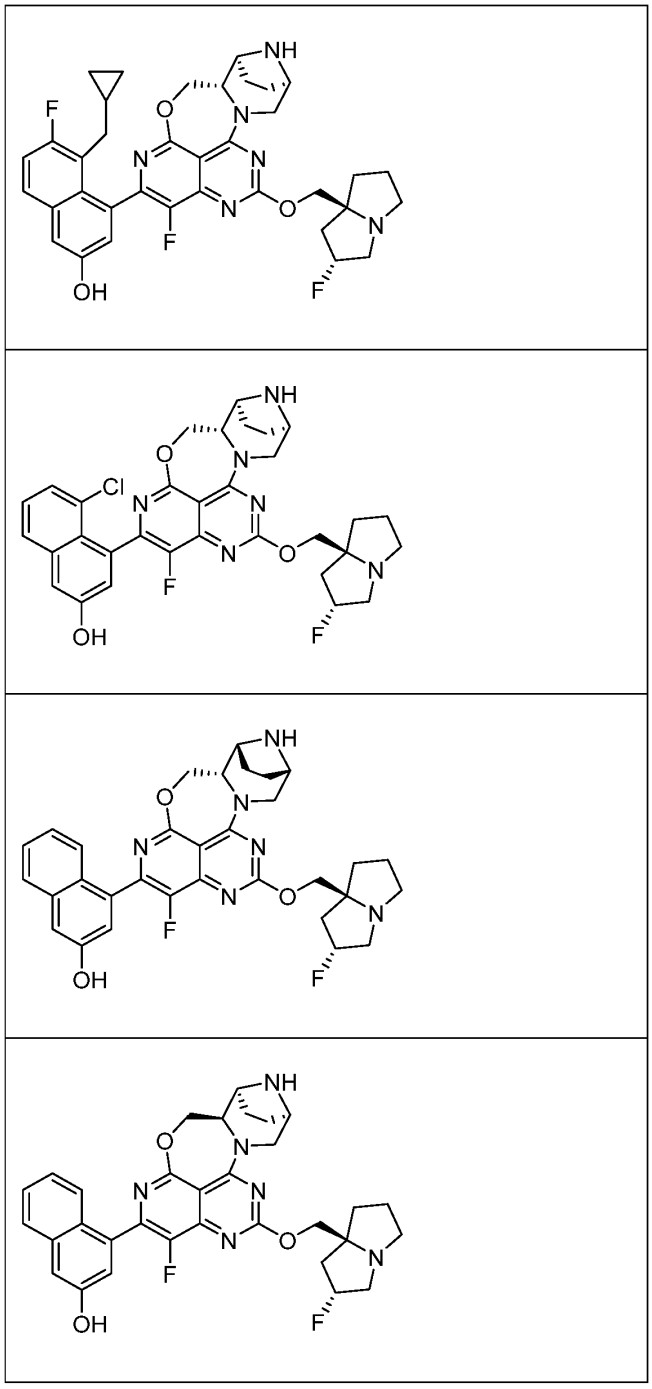
64. The compound of any one of claims 1 to 63, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure:

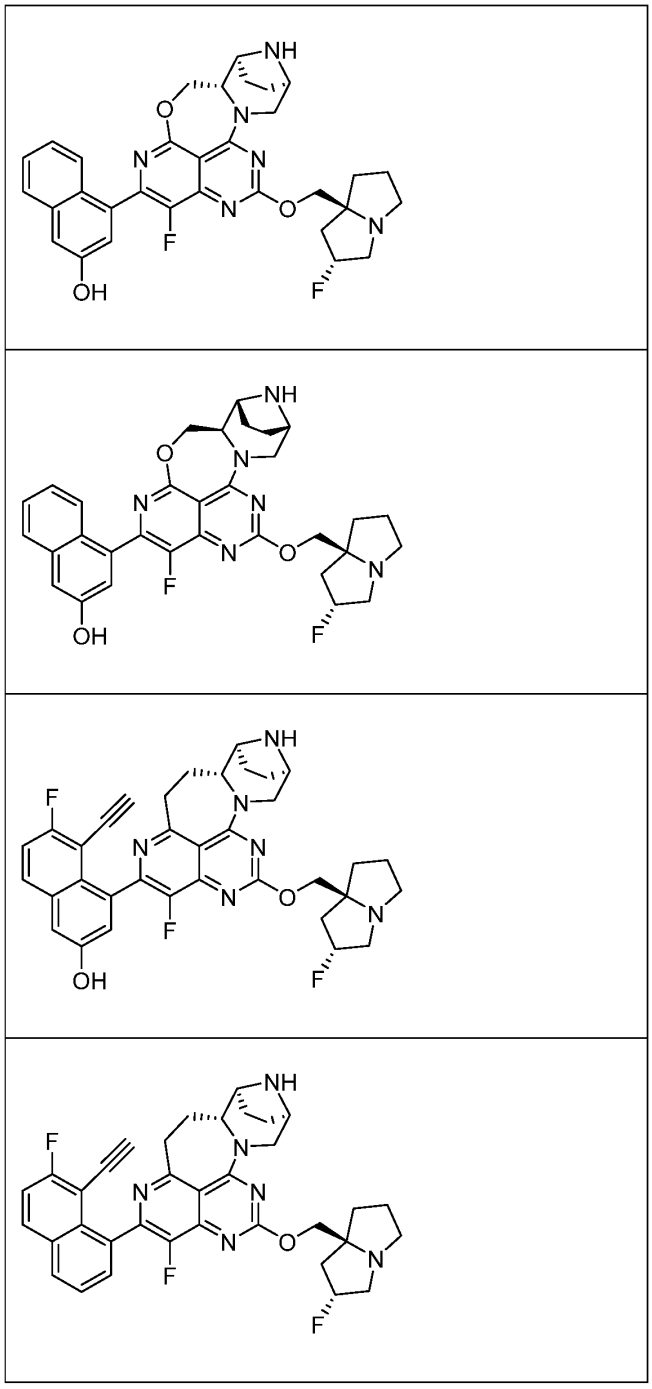


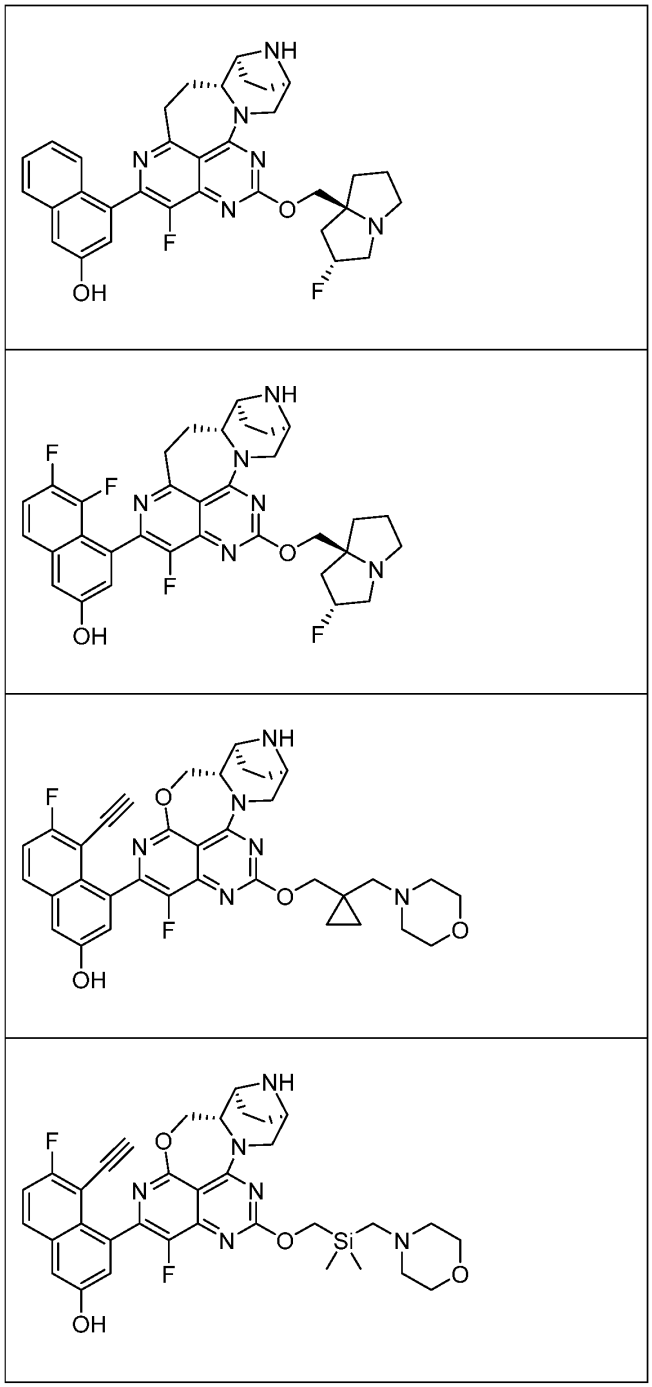


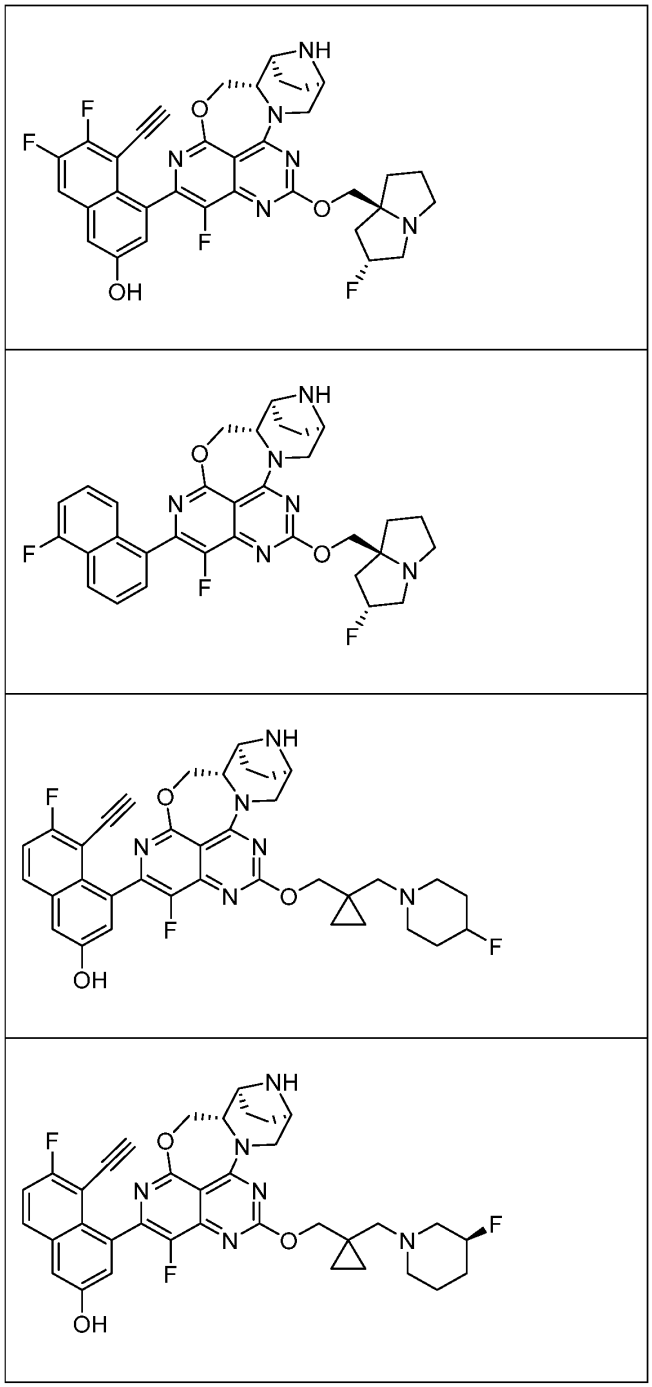


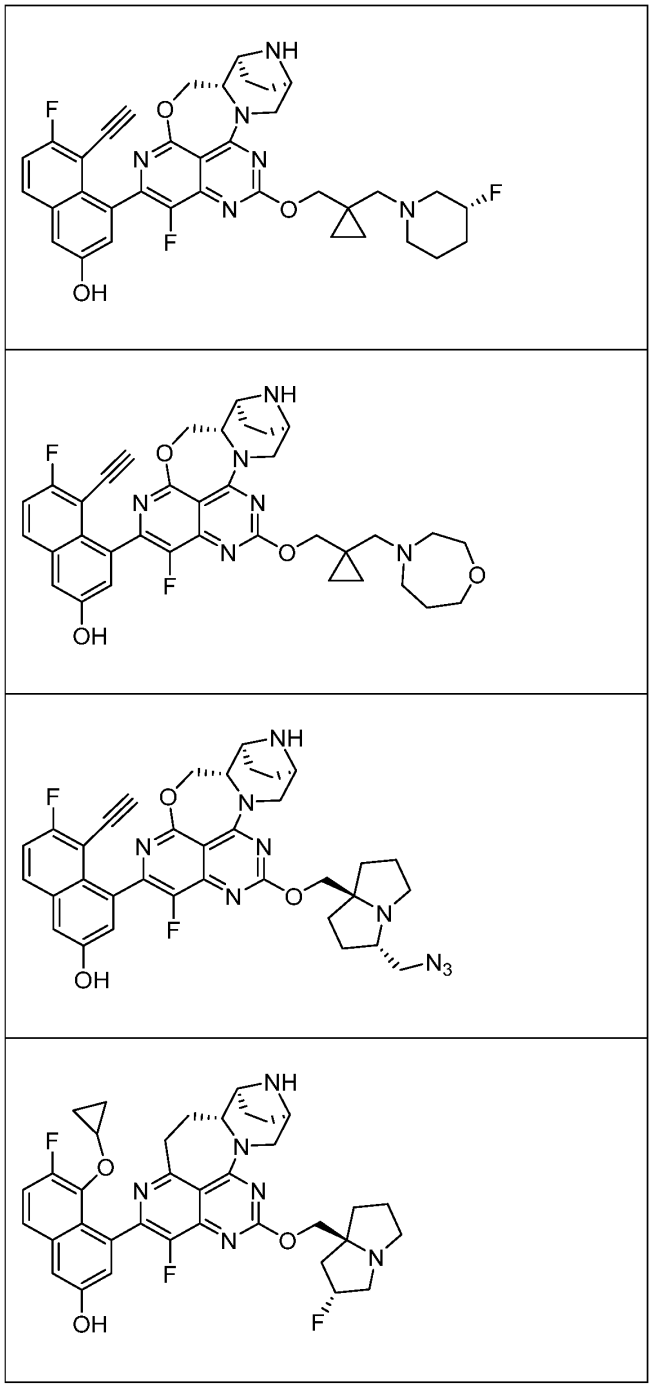


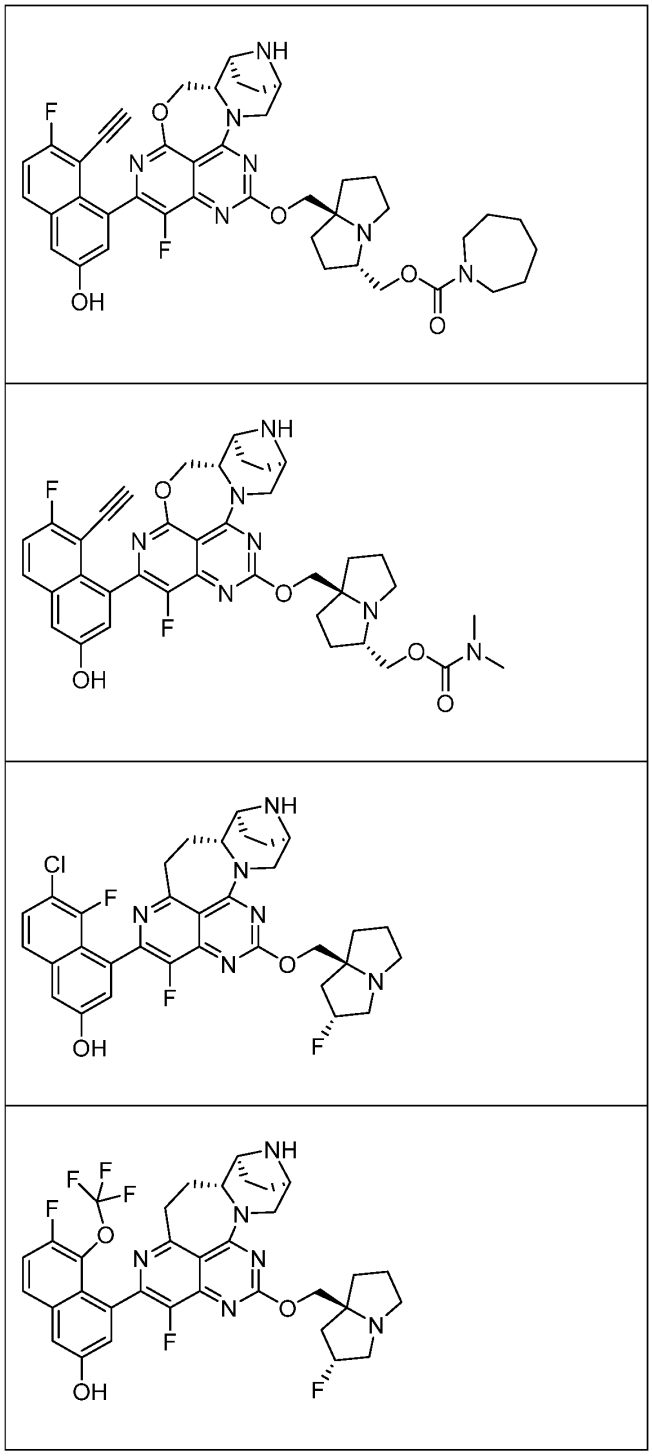


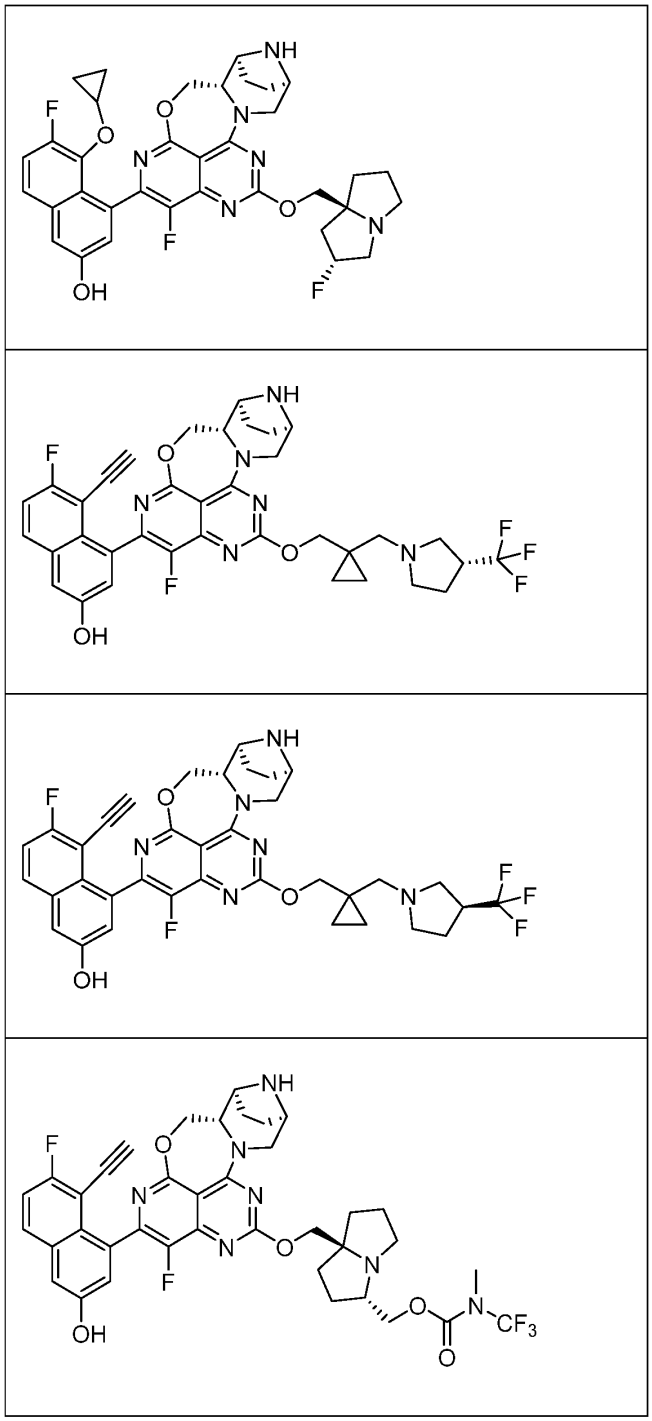


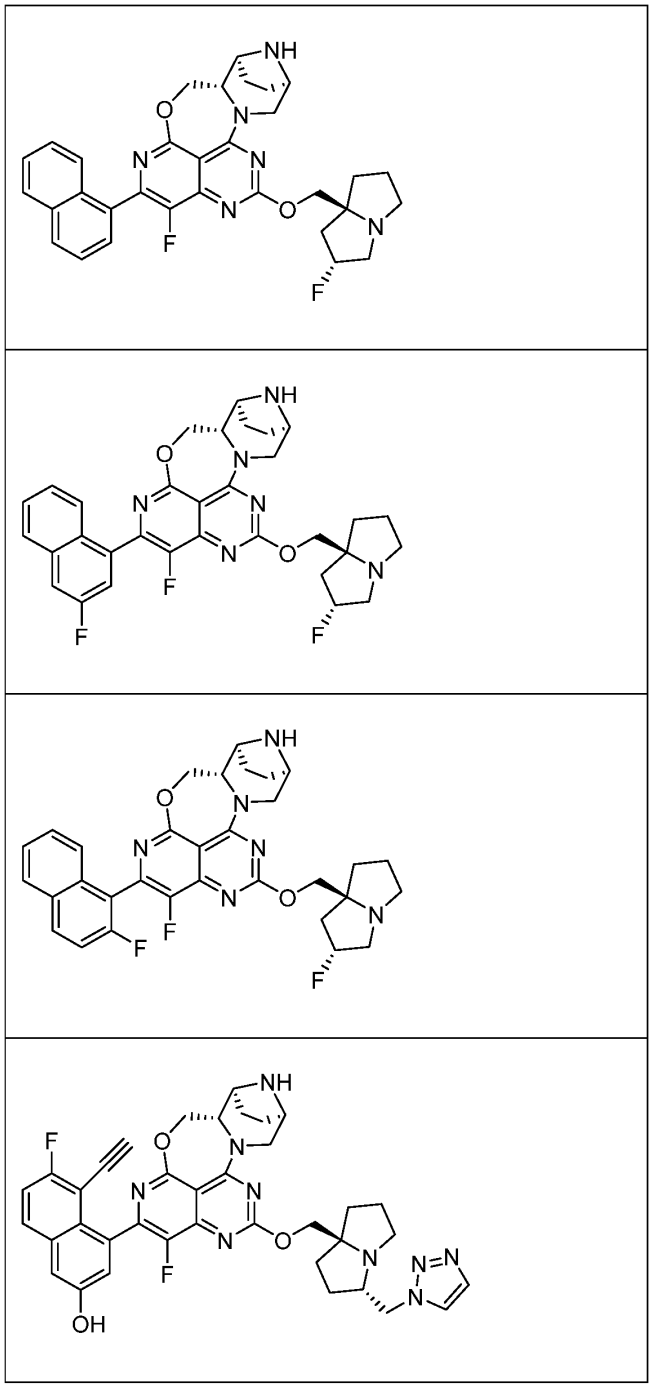


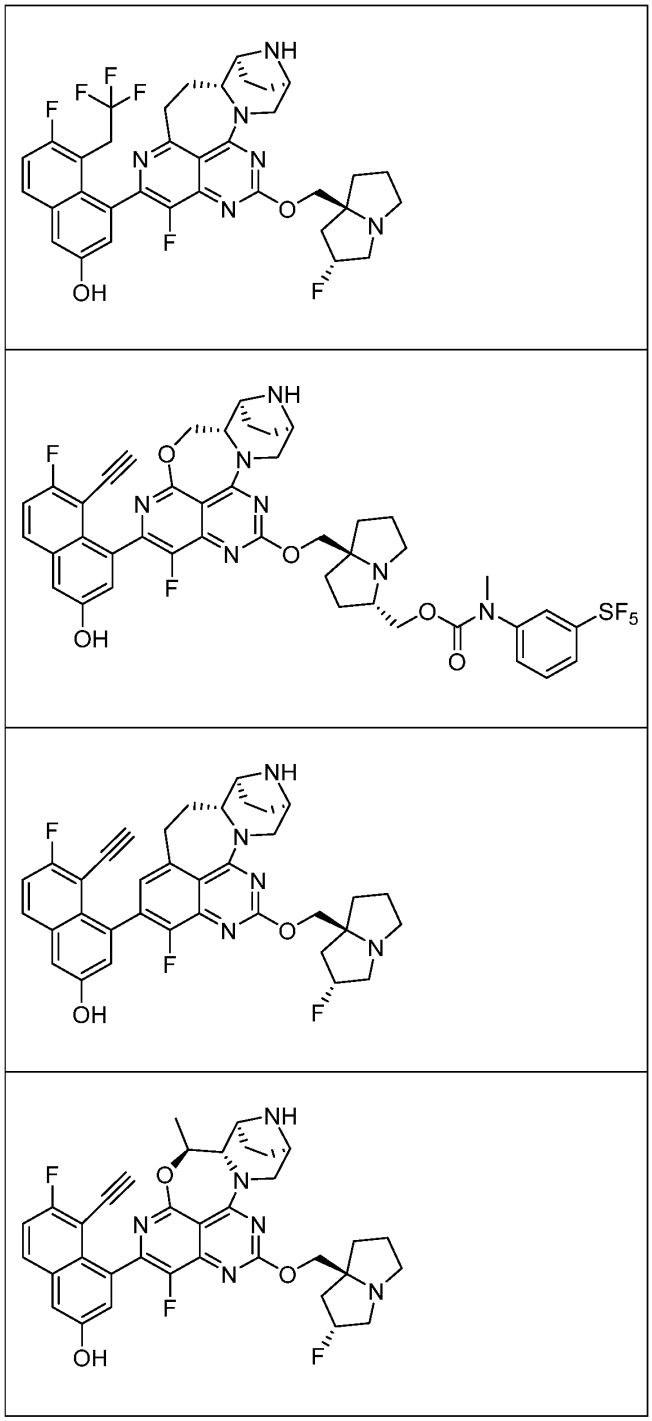


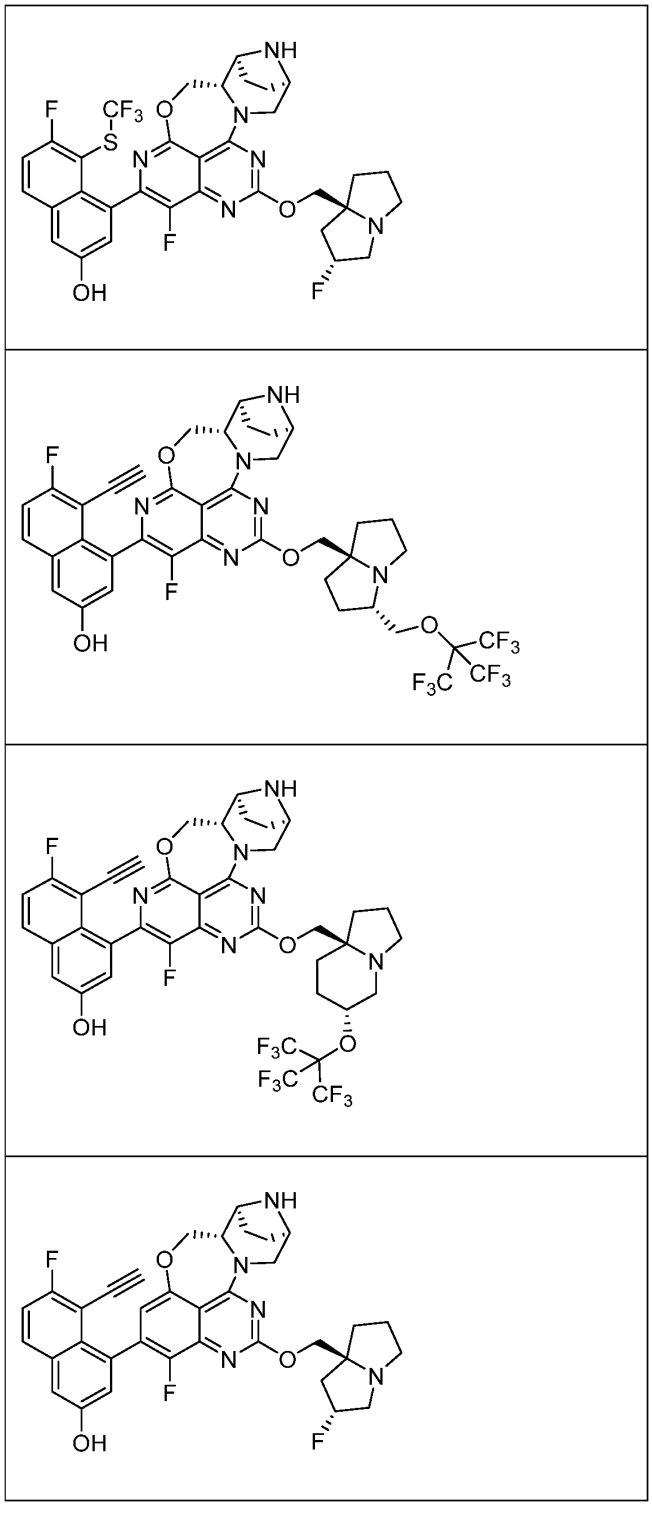


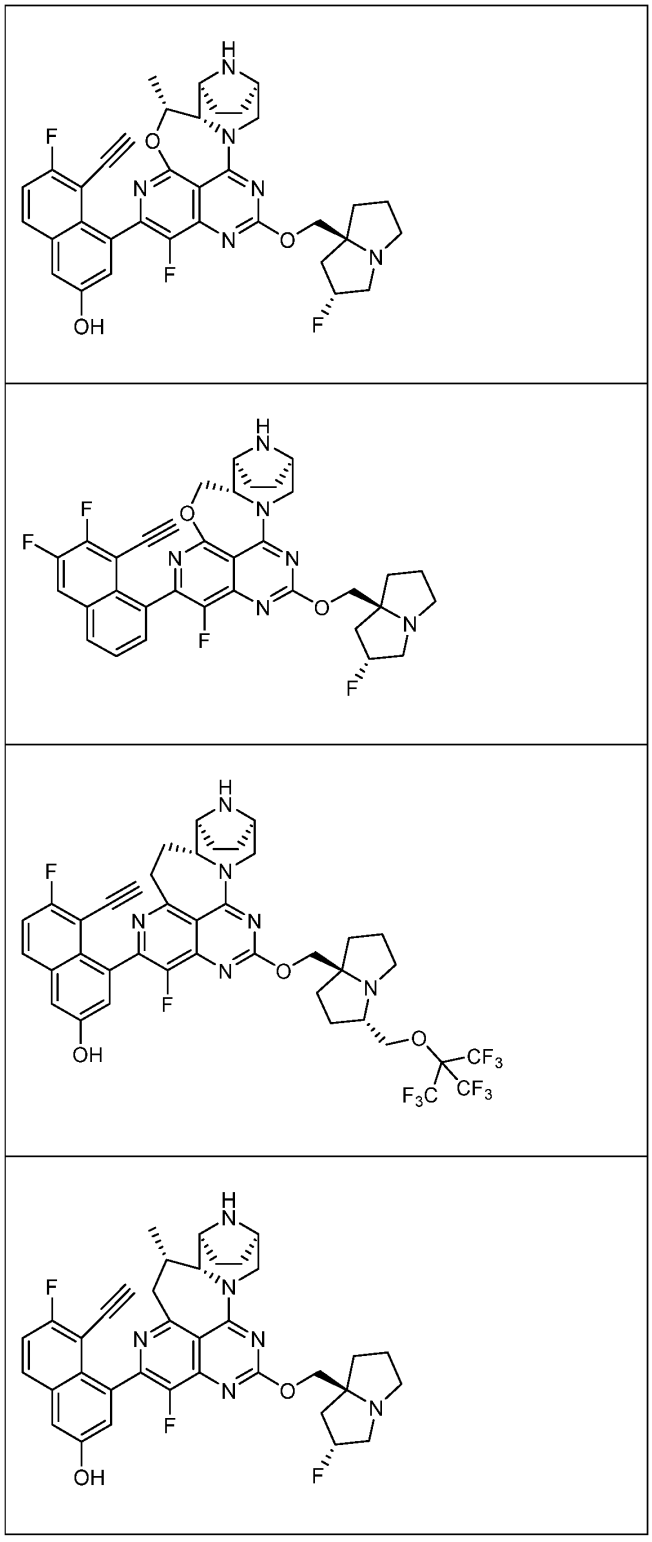


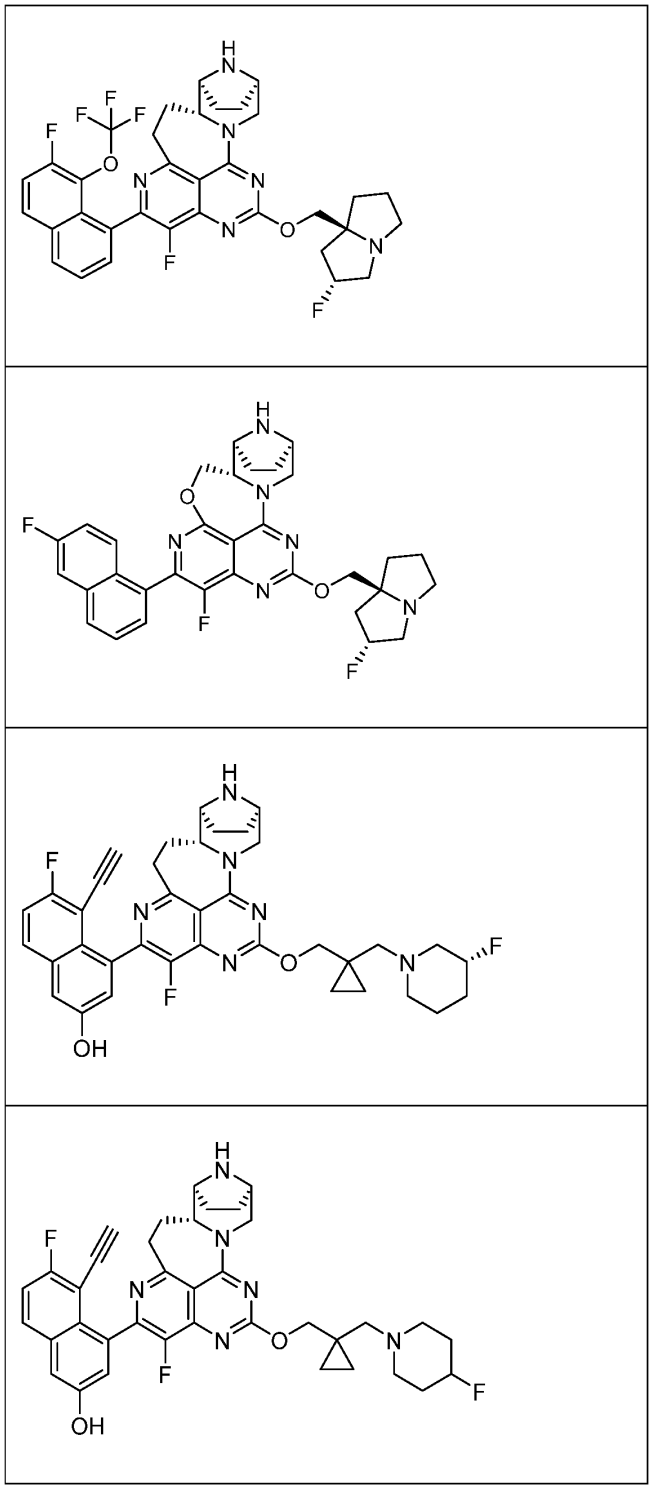


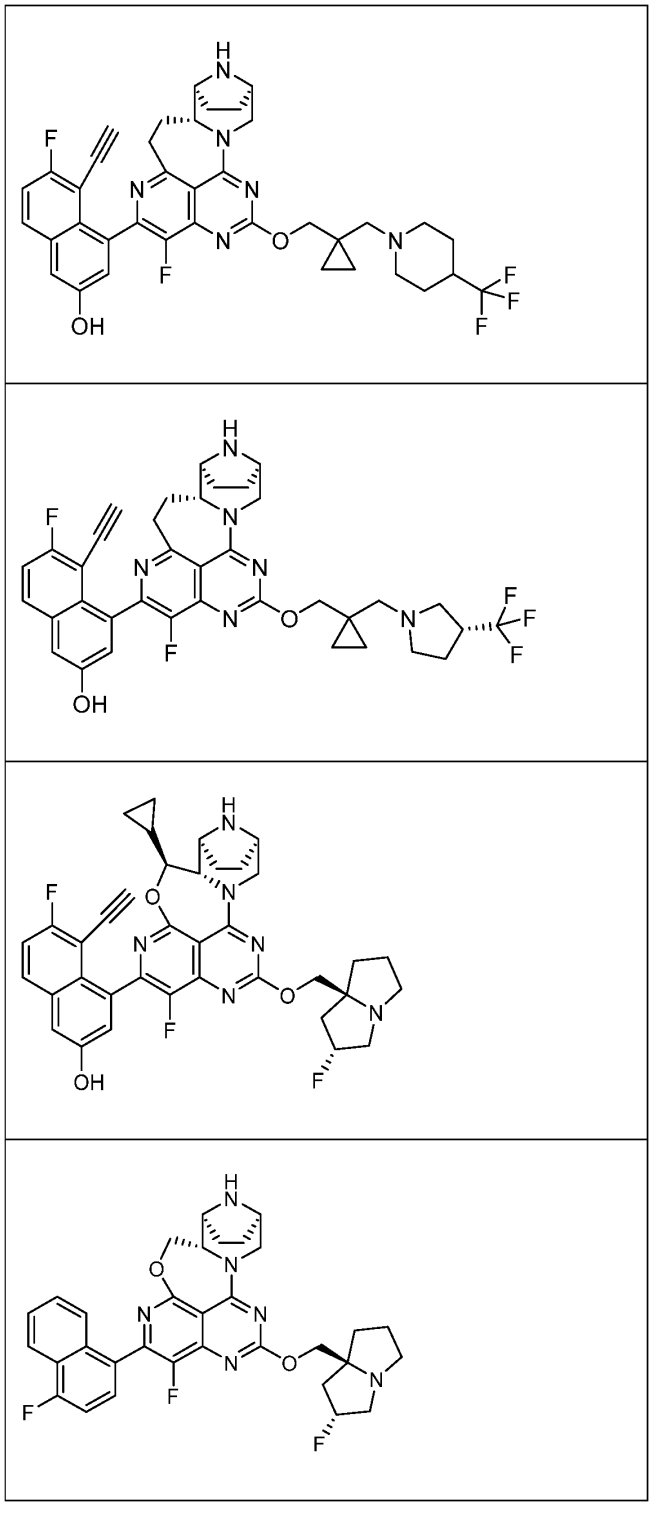


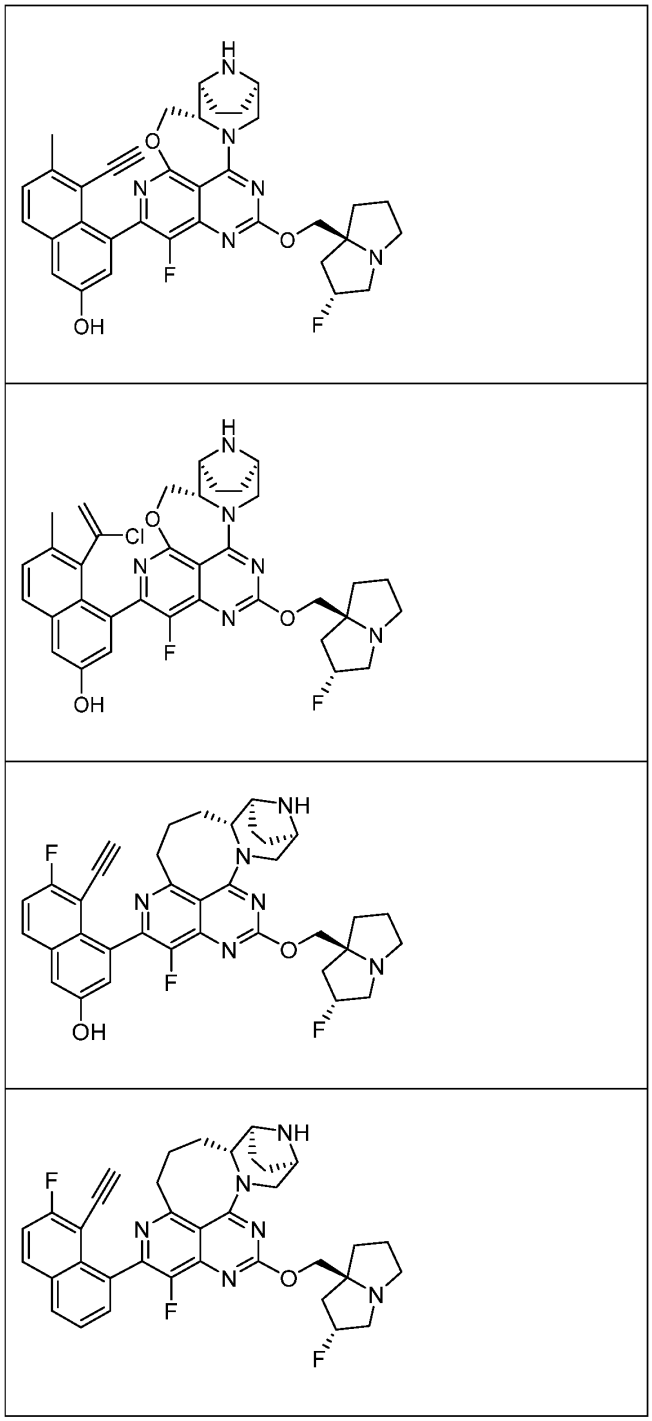


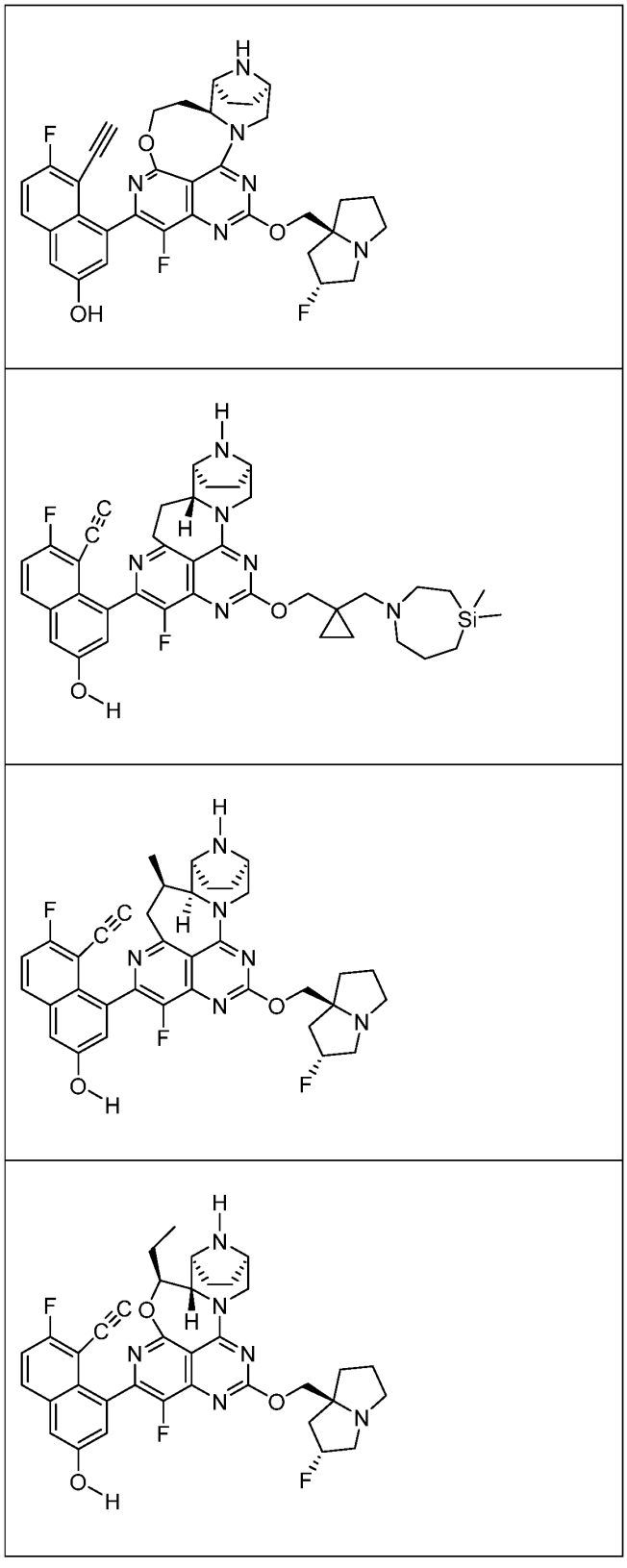


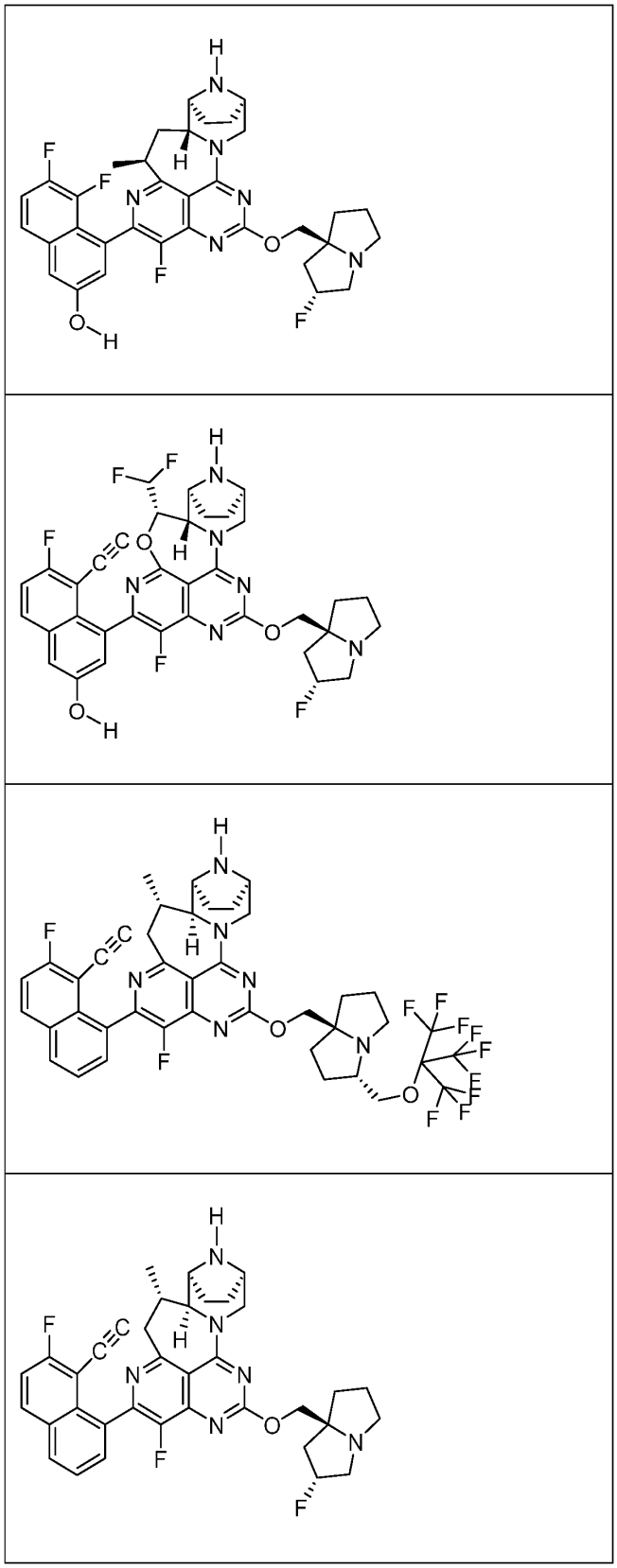


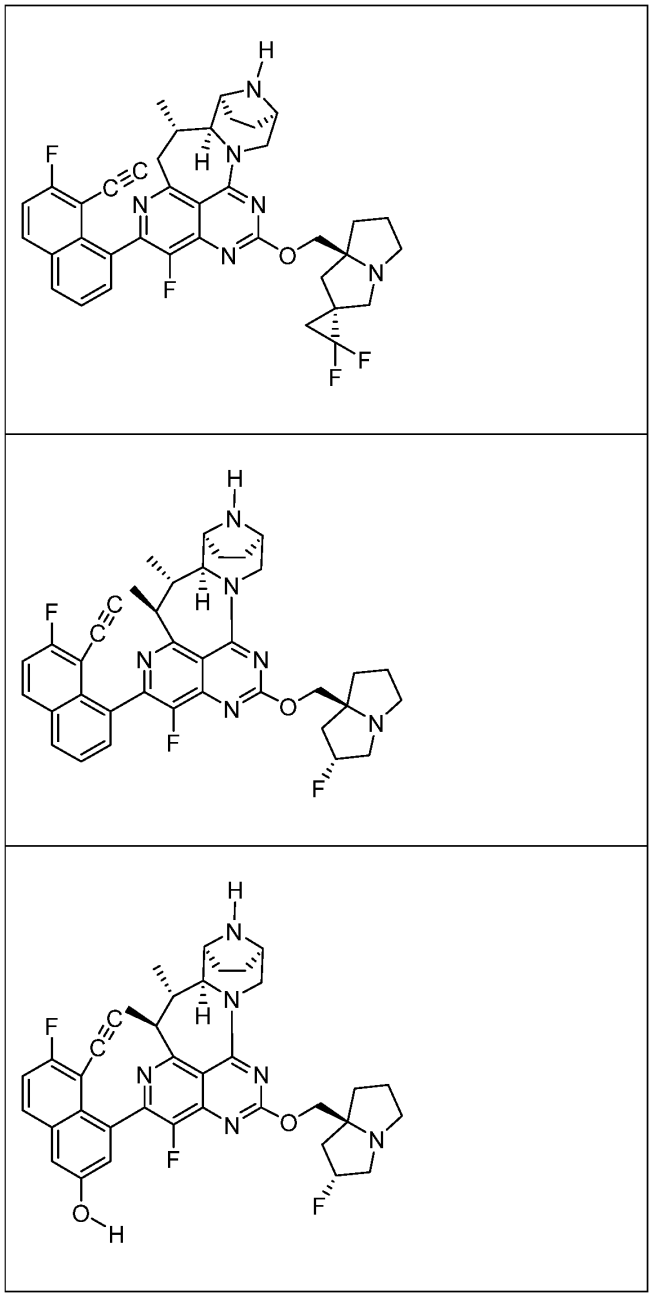


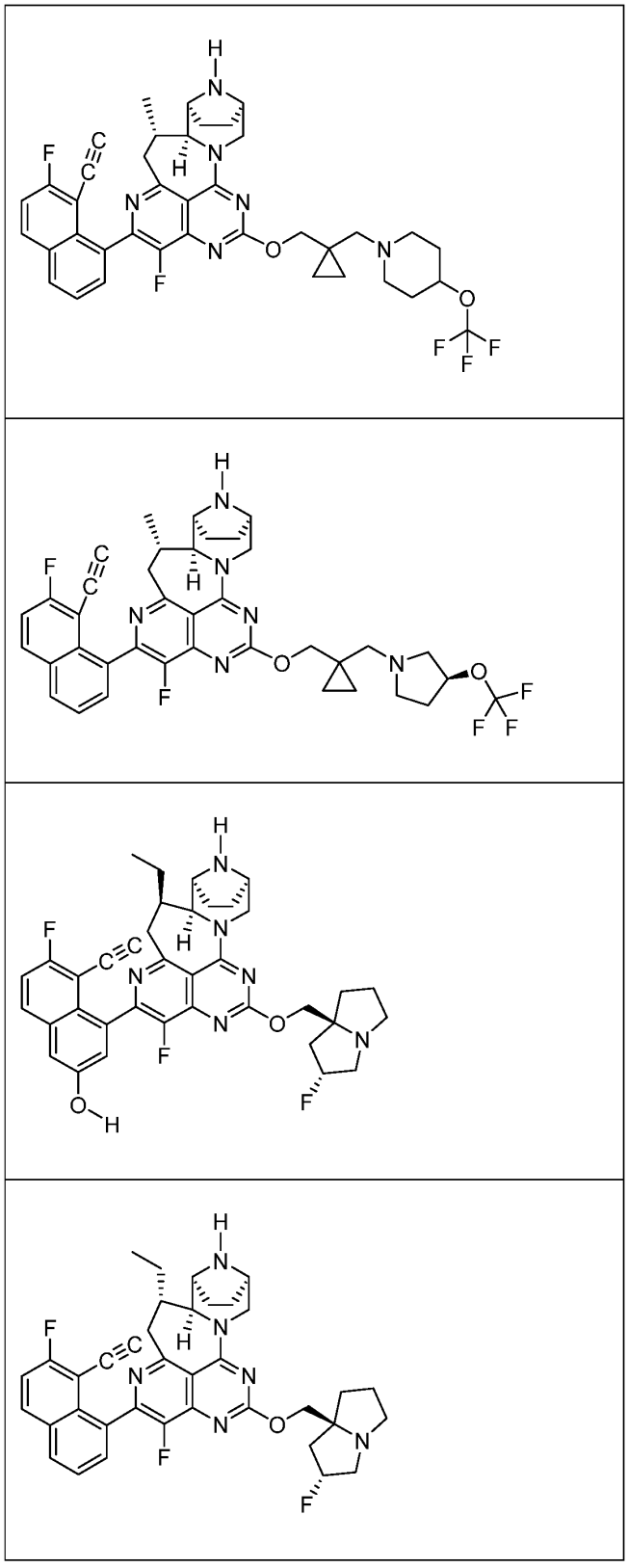


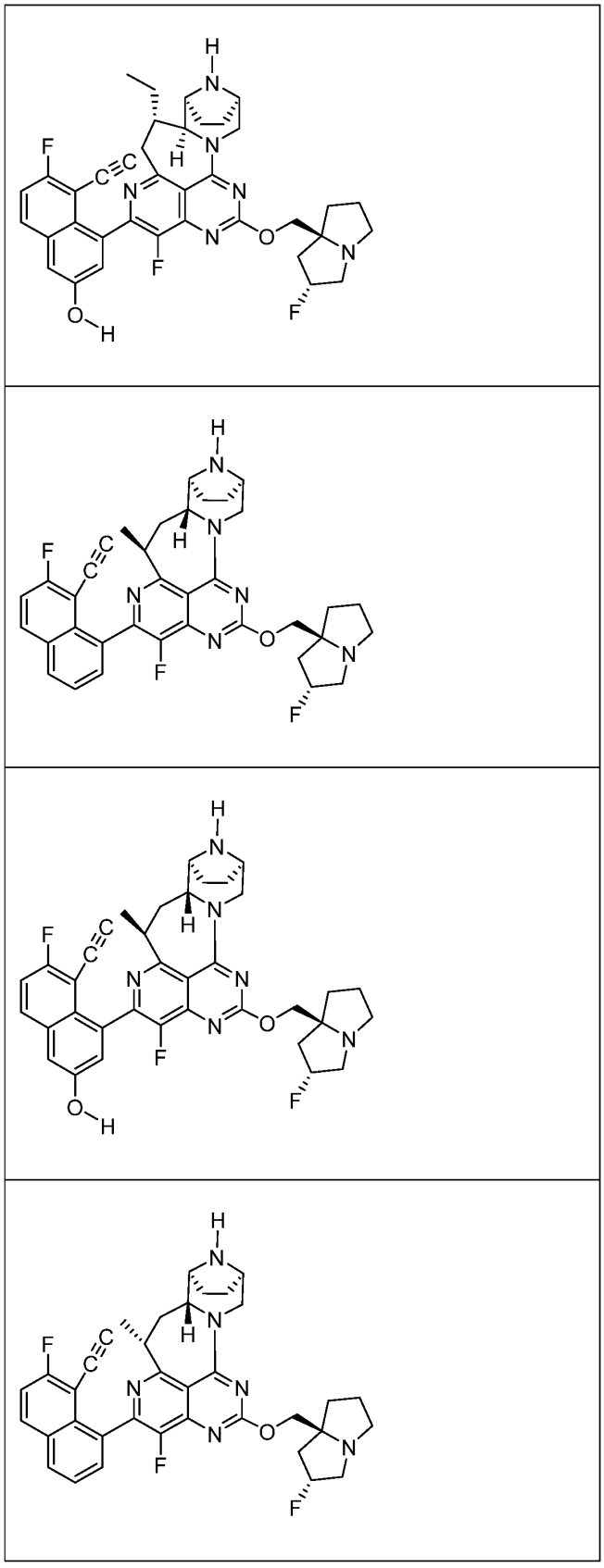


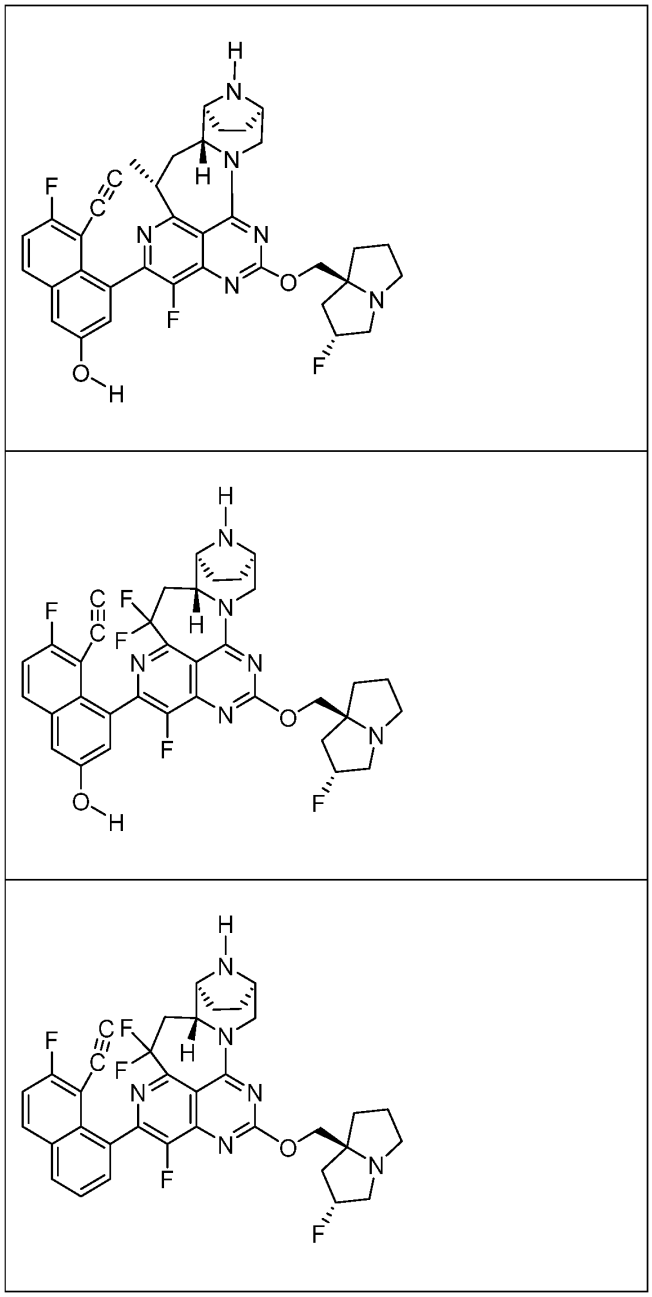


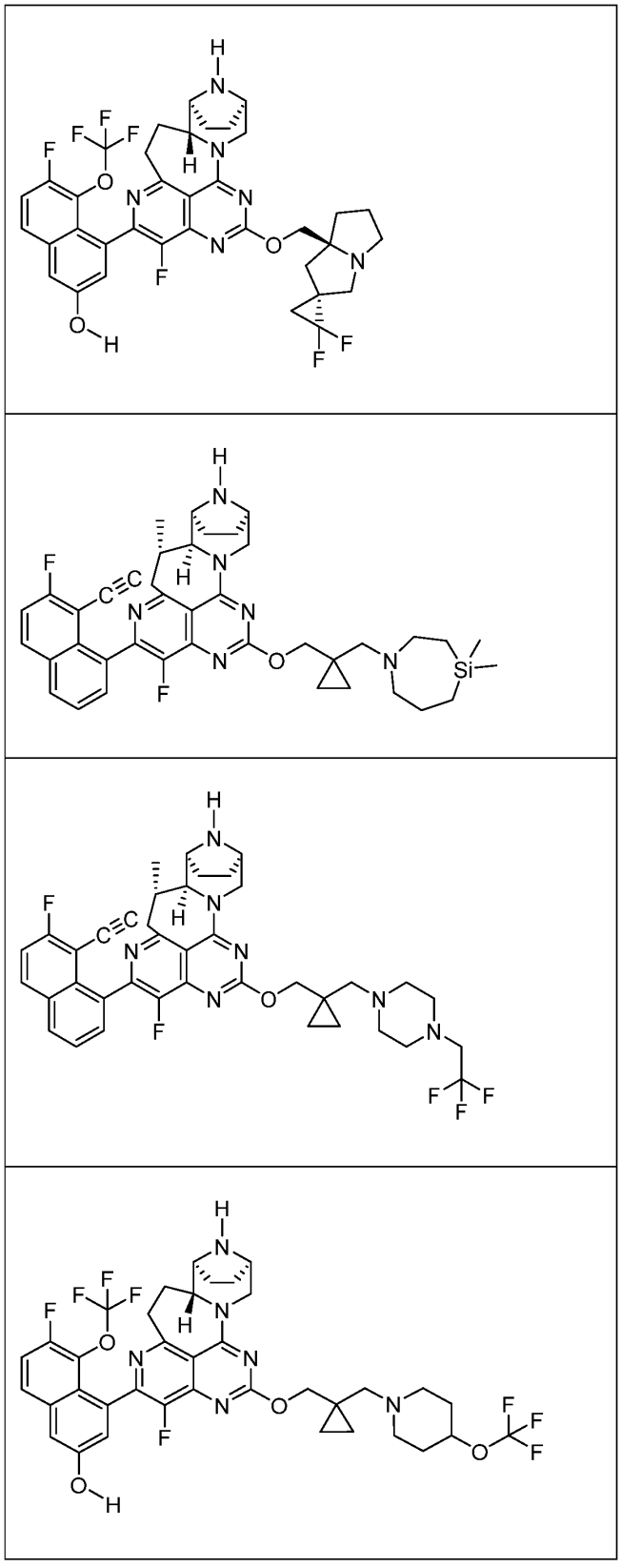


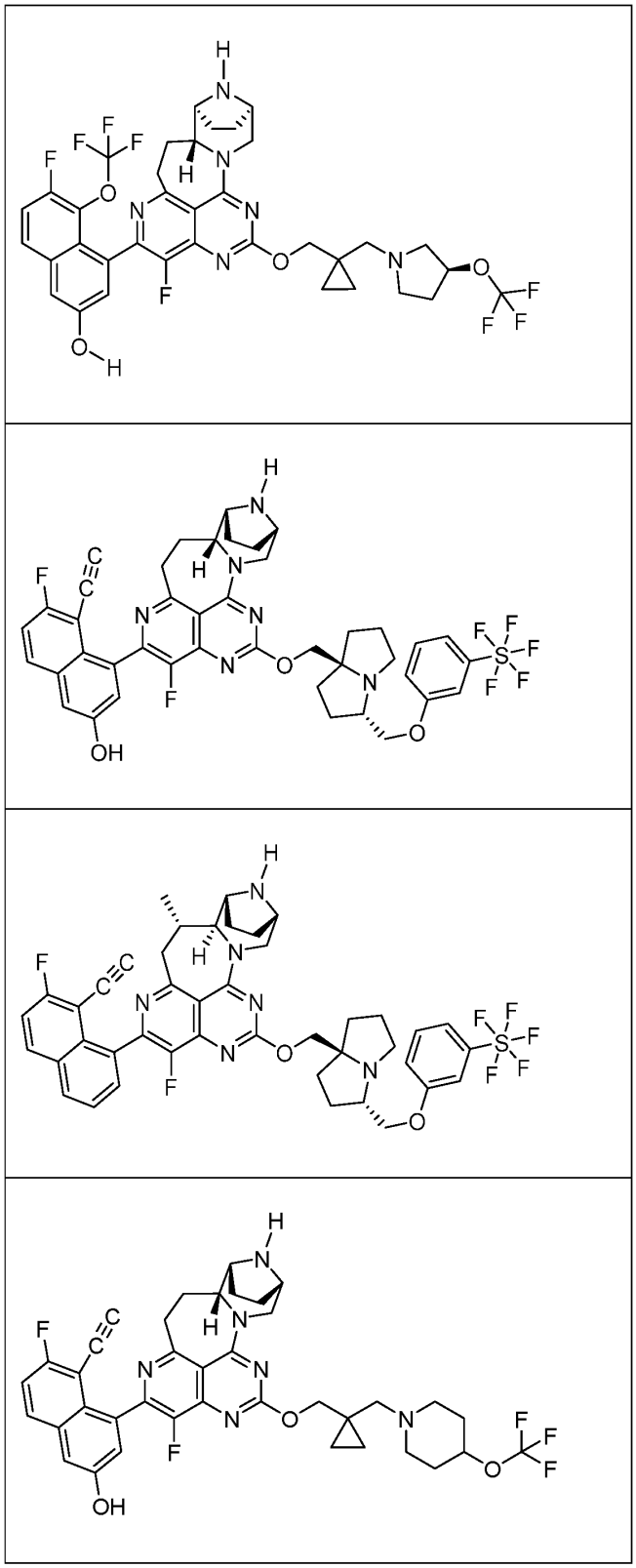


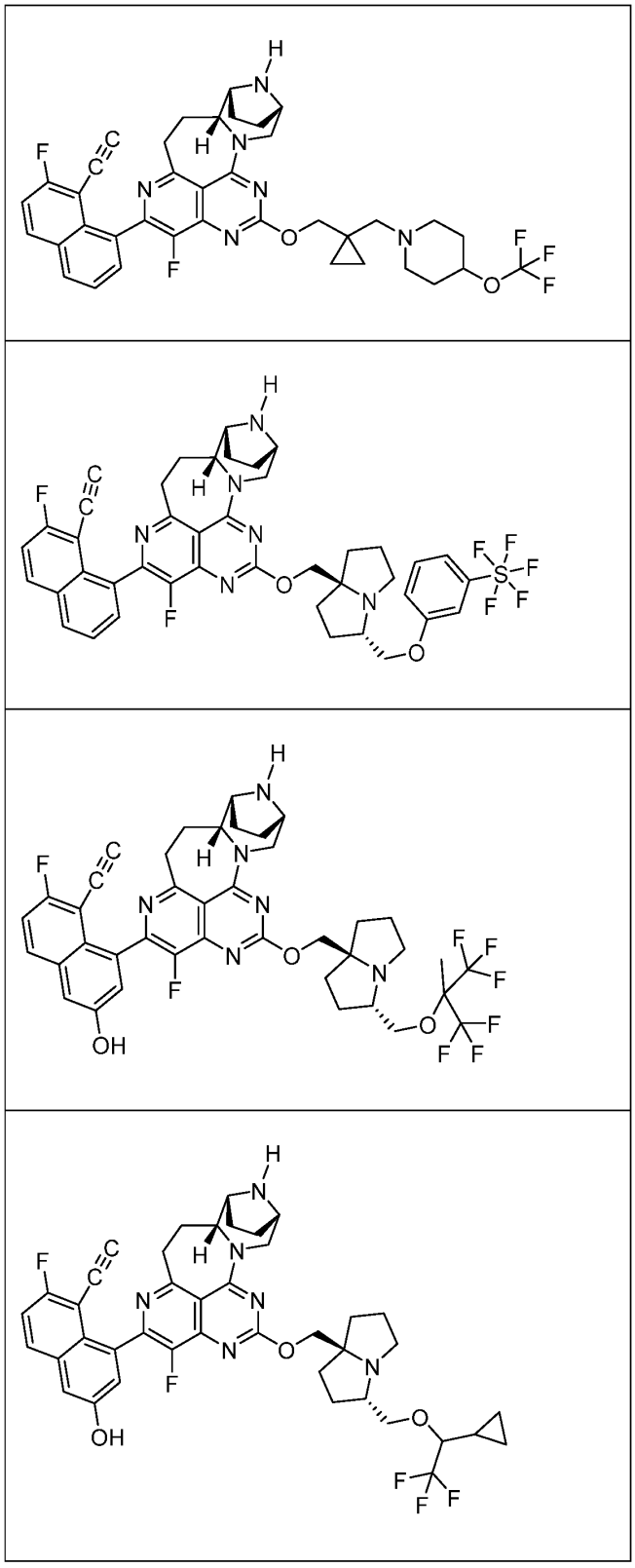


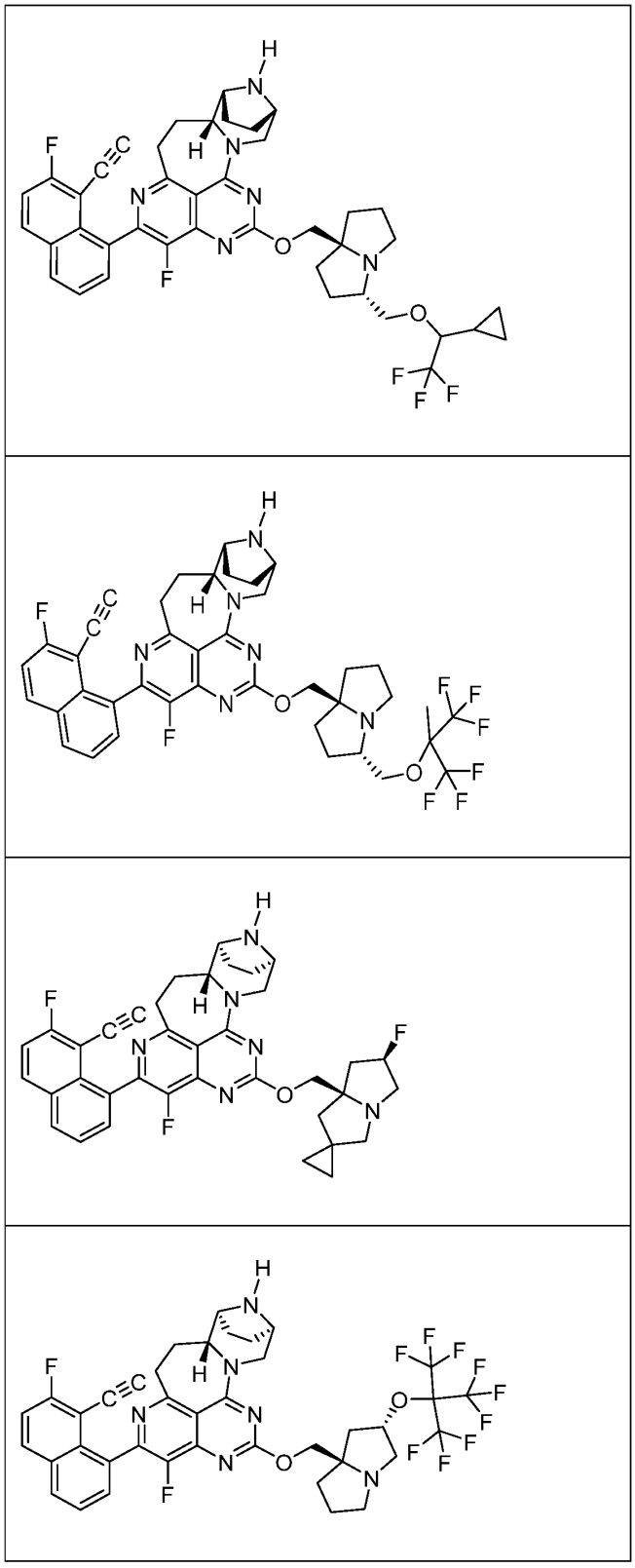


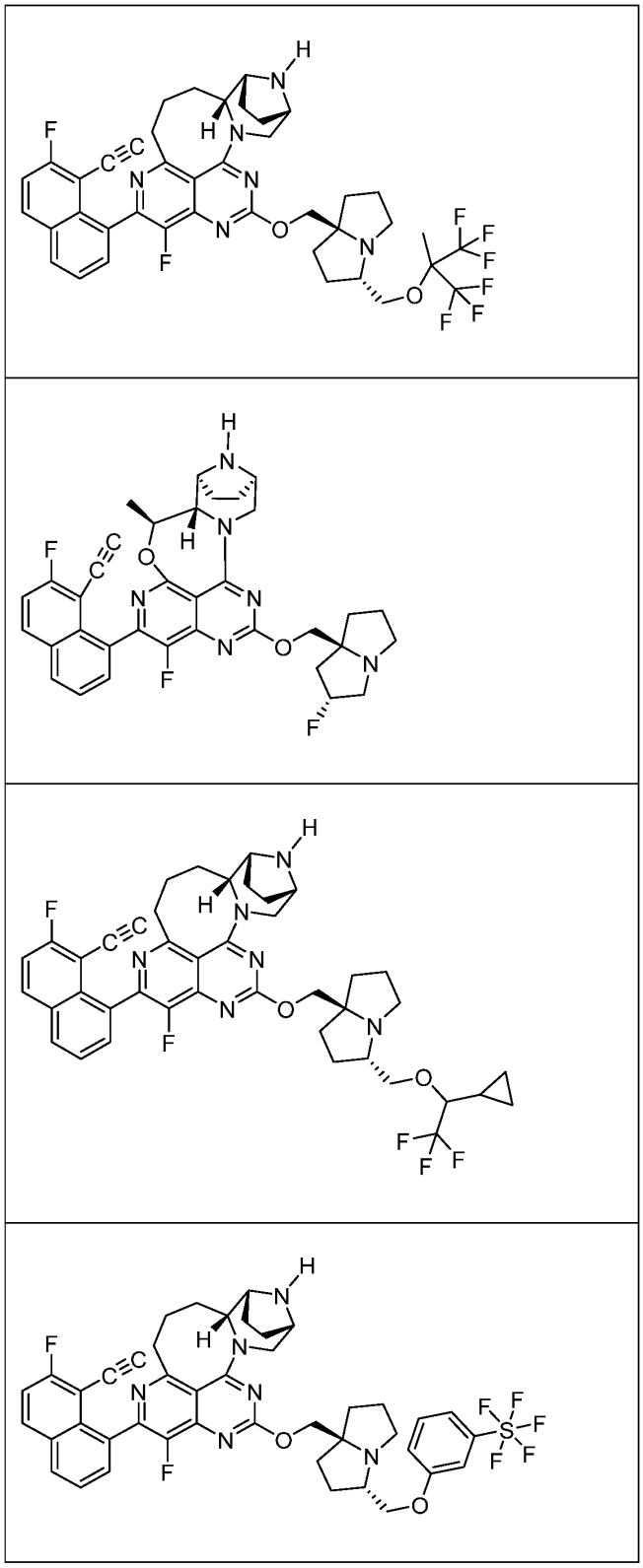


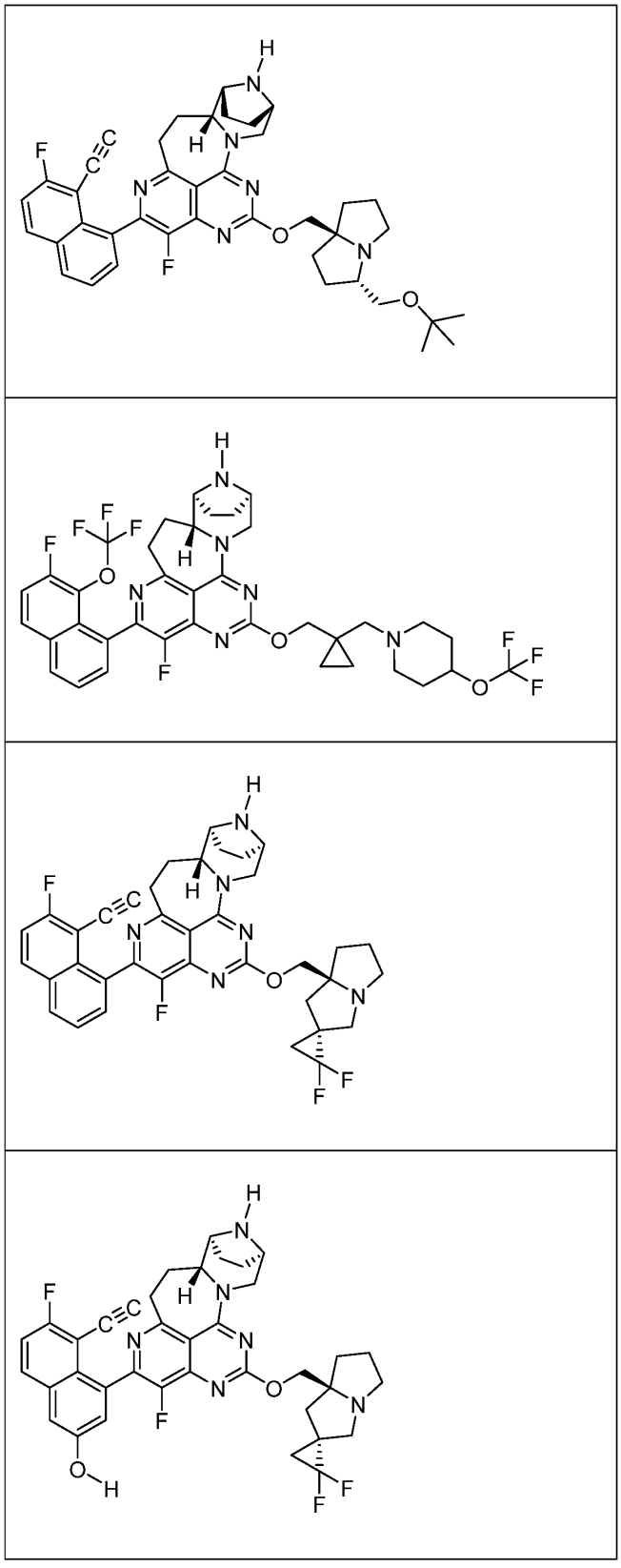


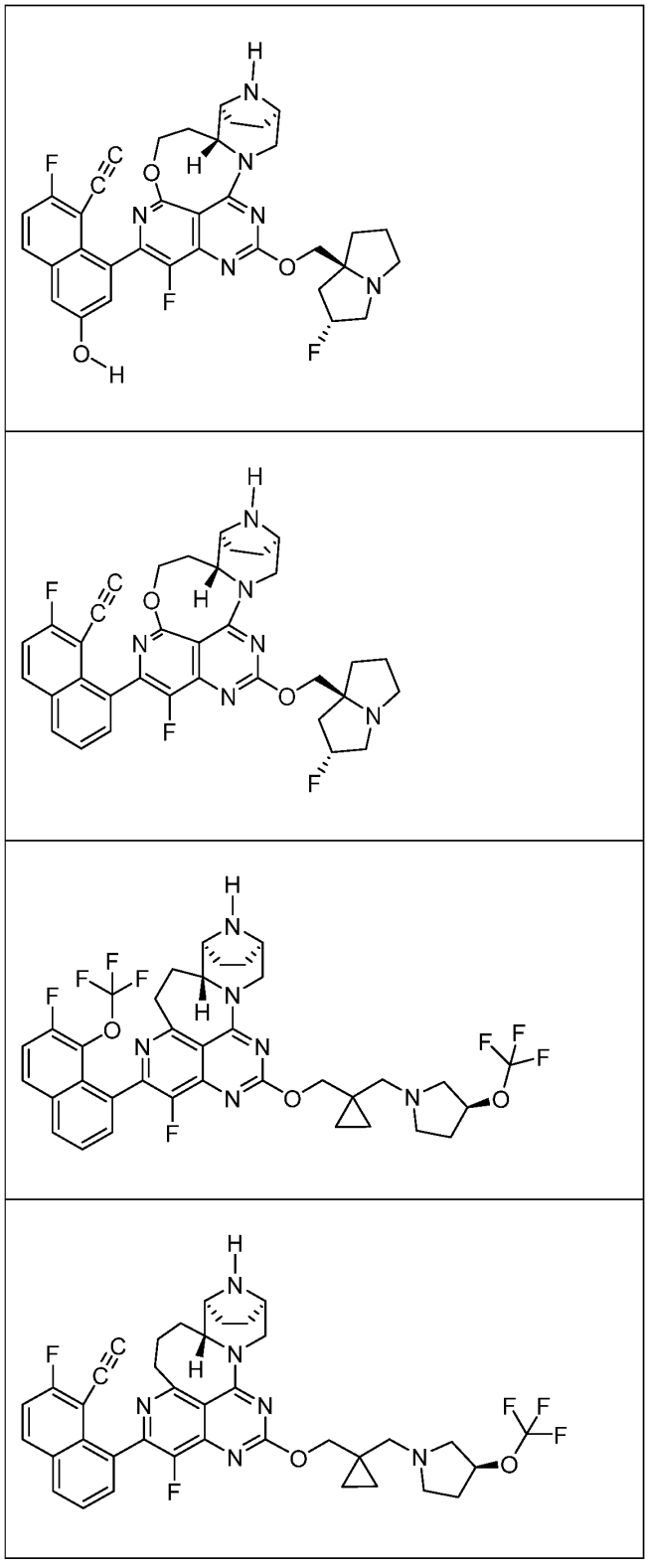


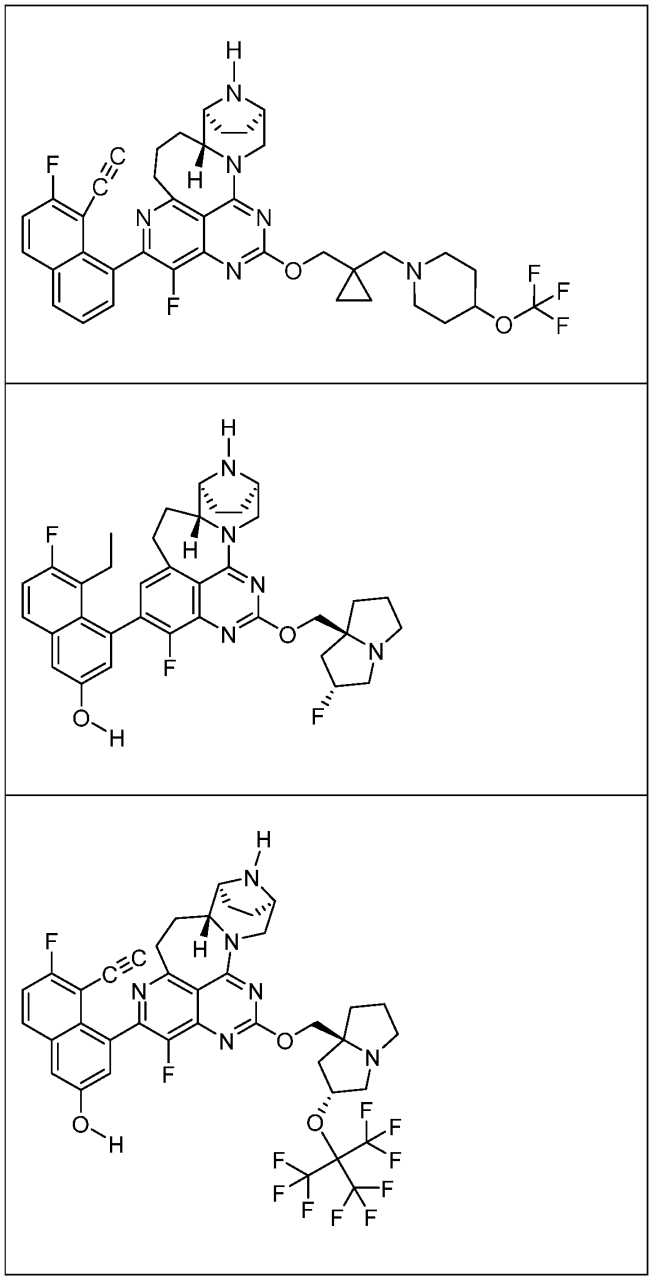


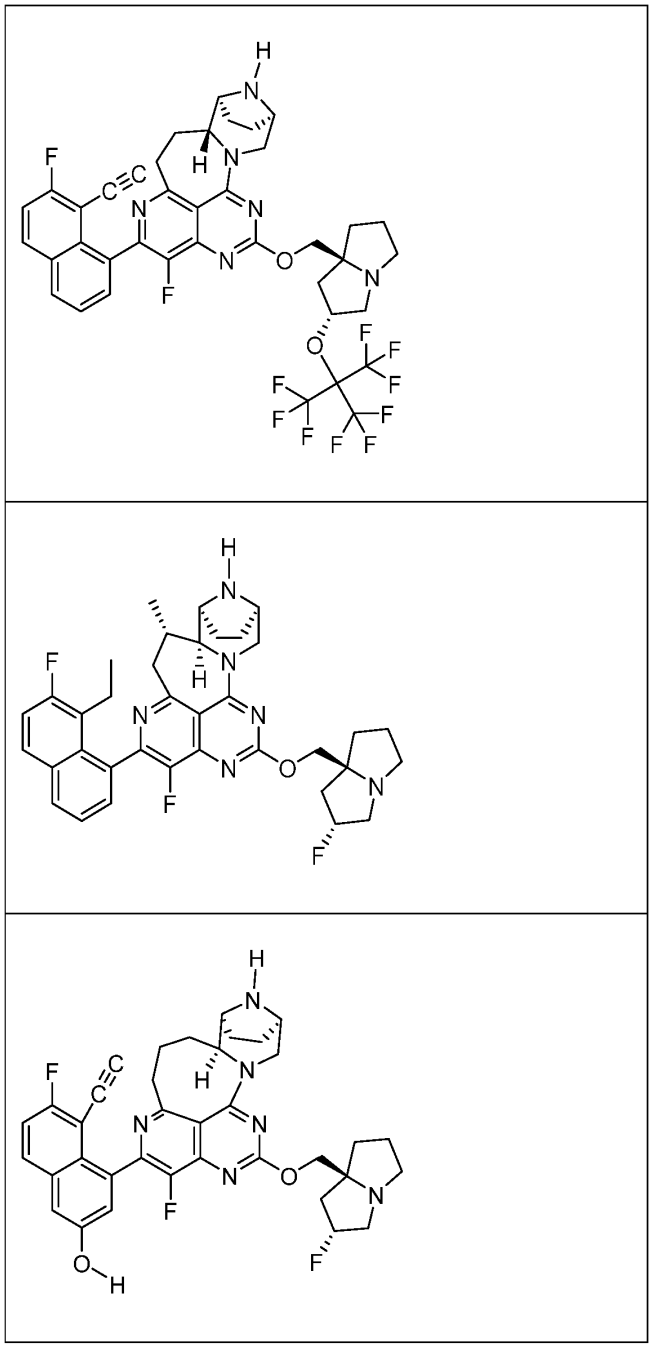


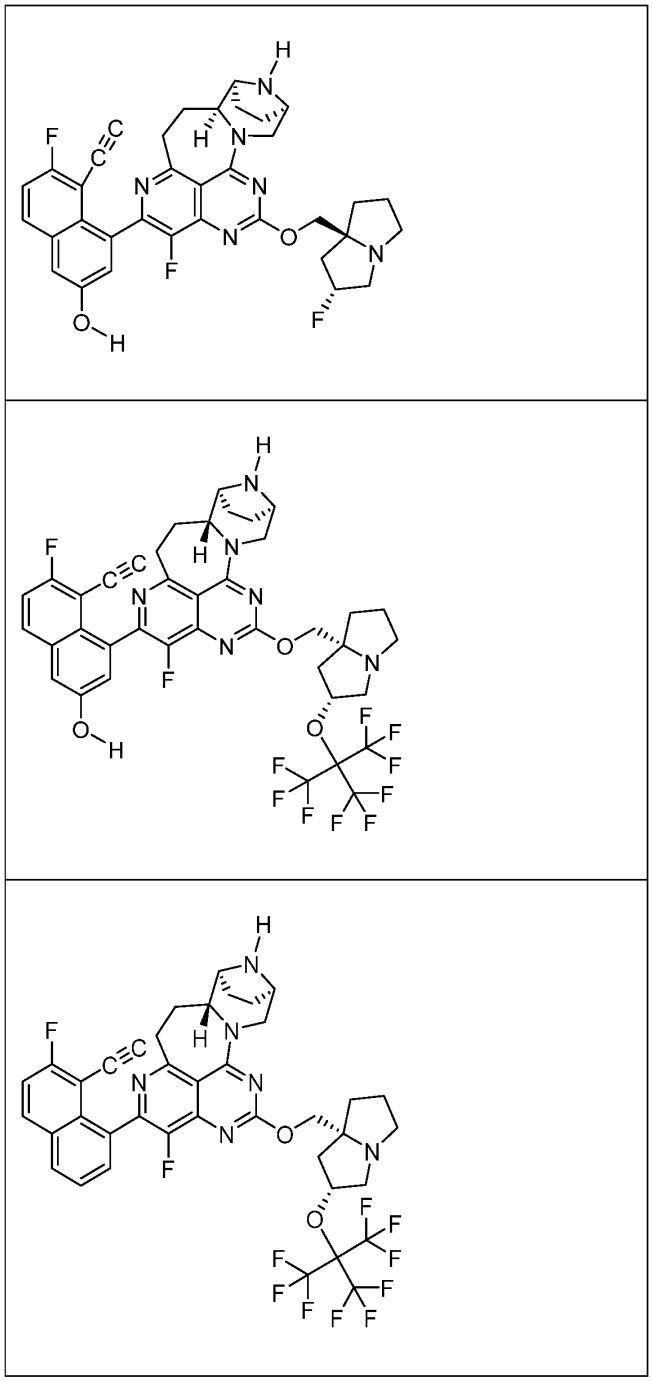


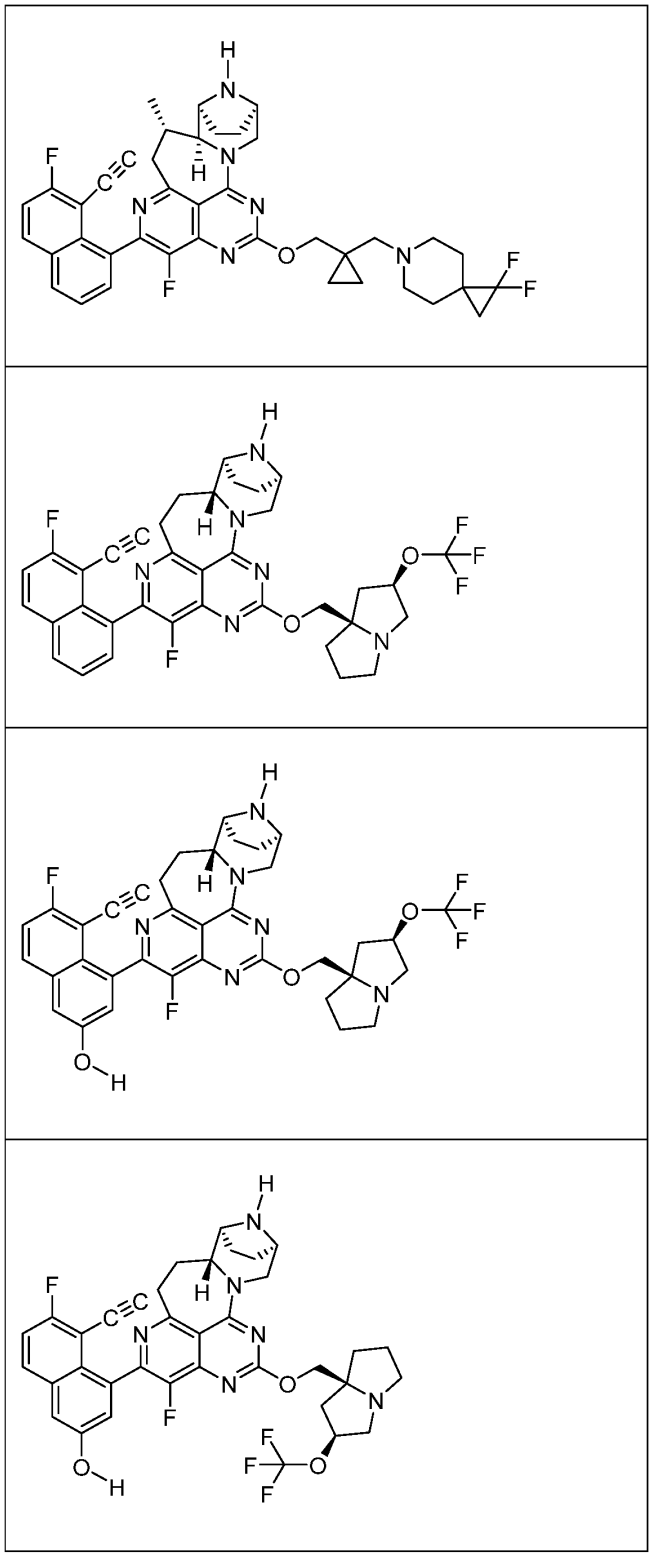


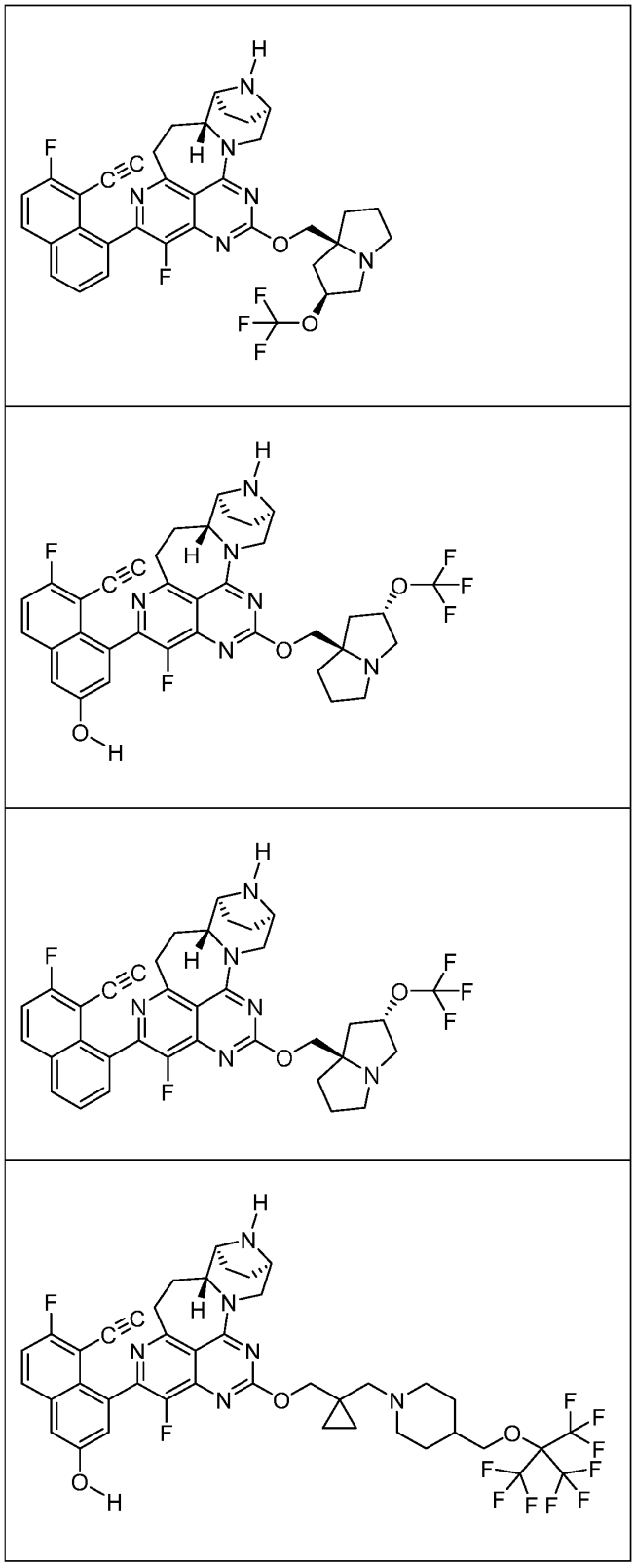


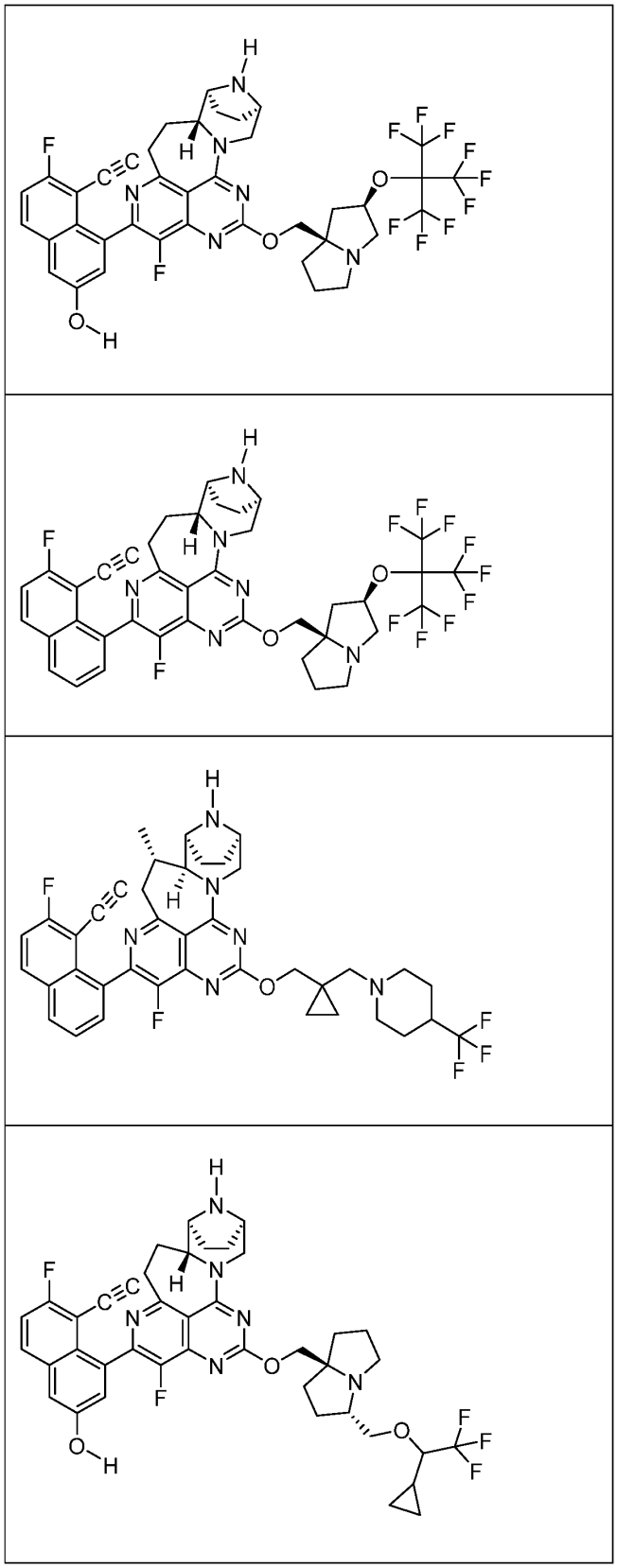


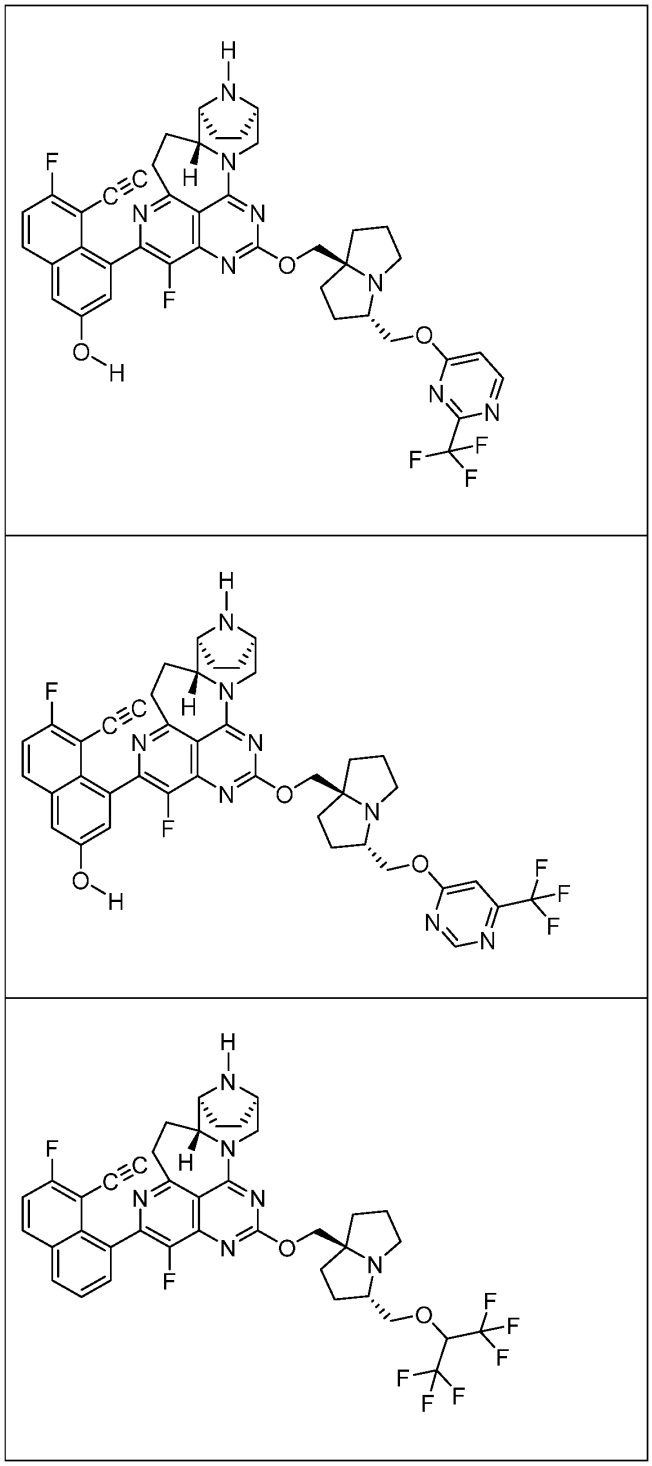


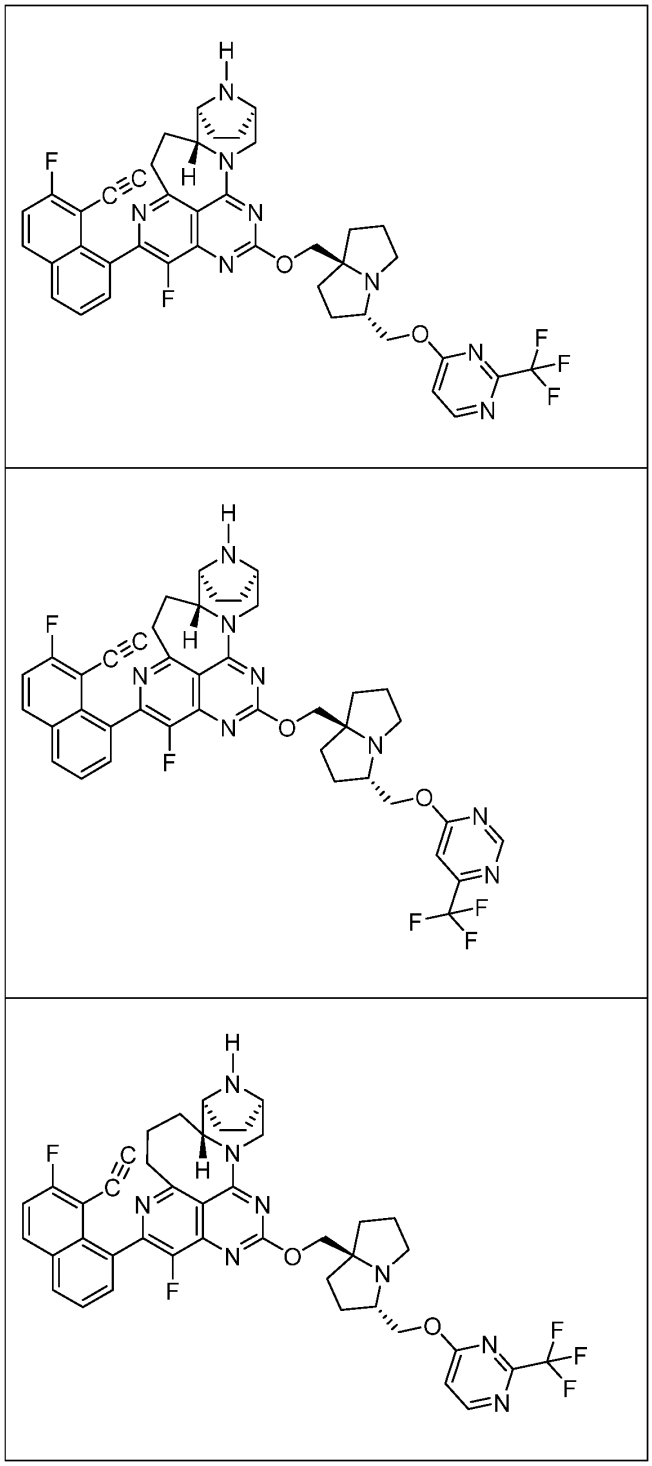


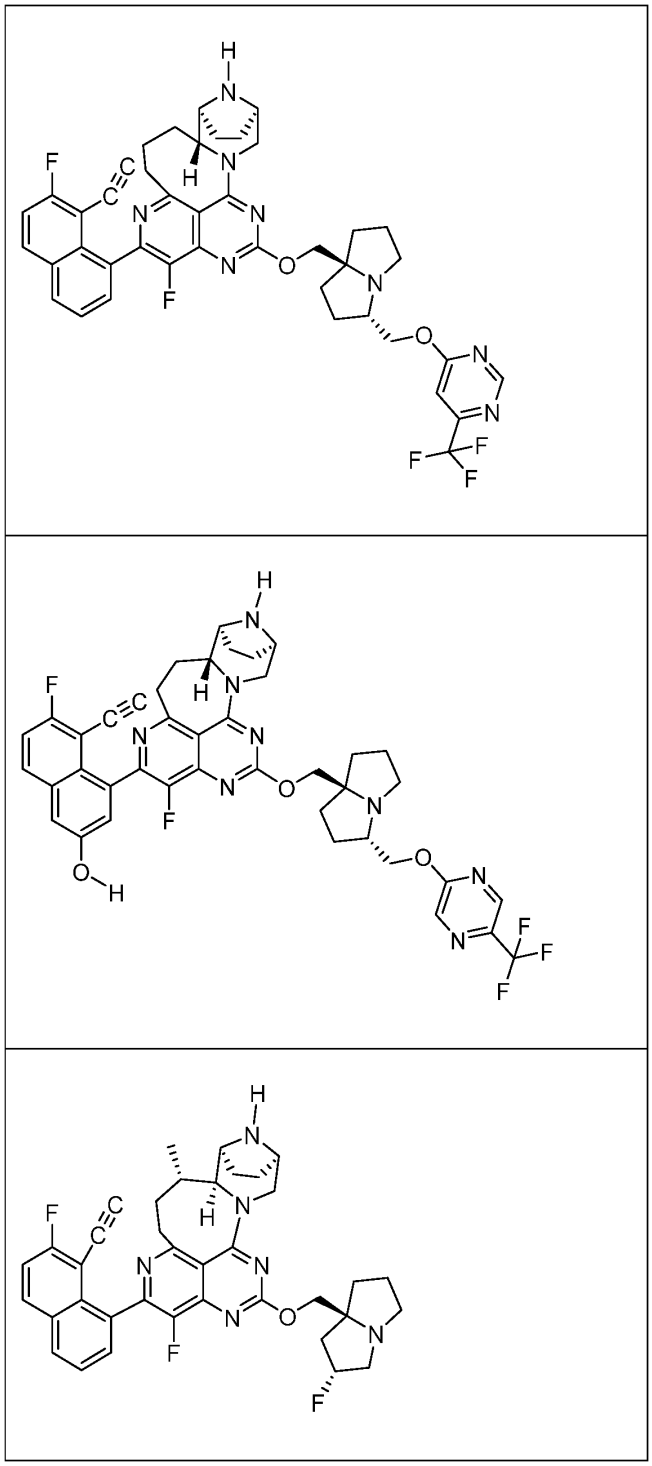


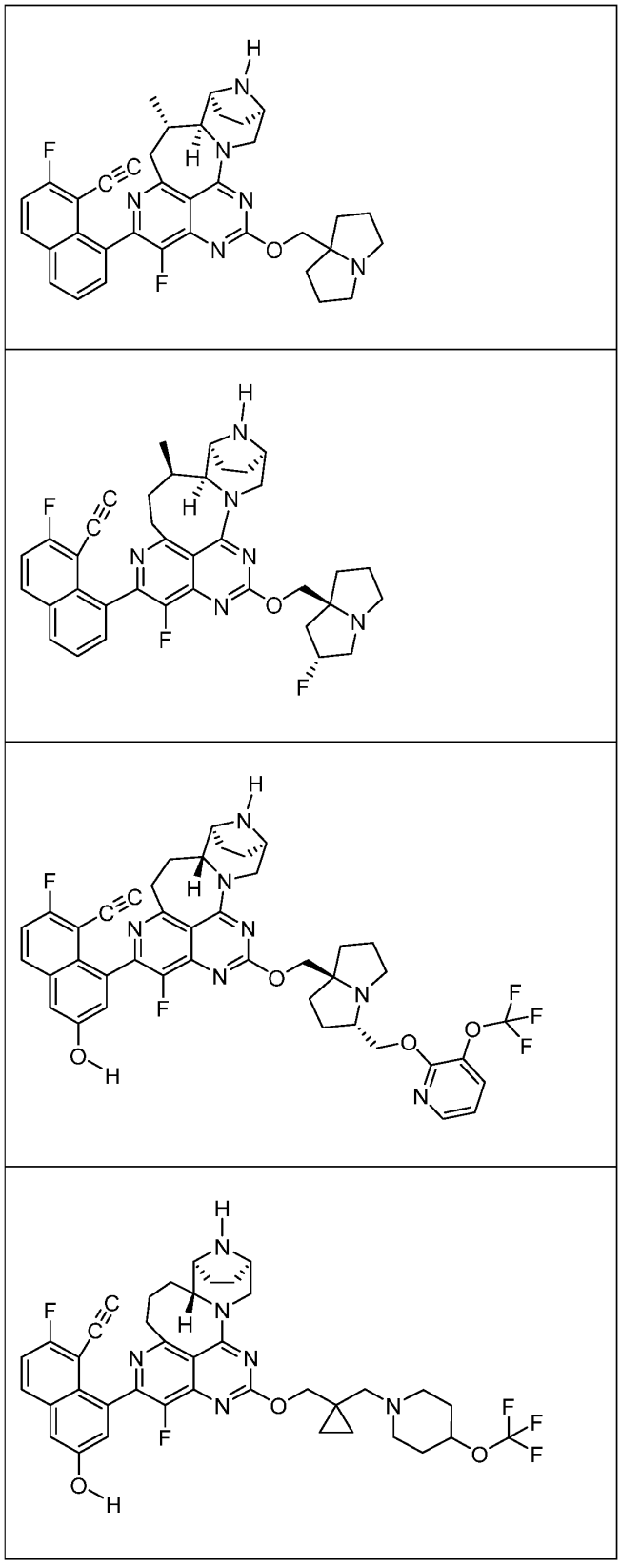


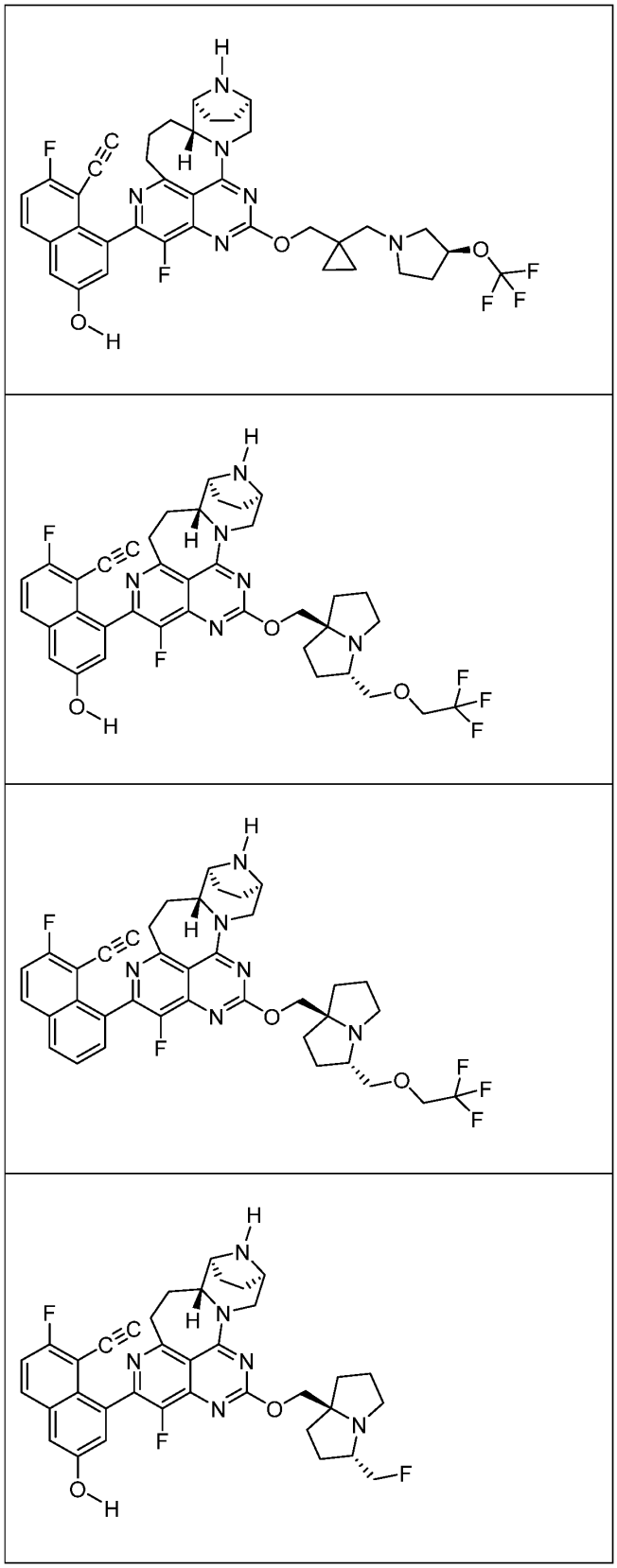


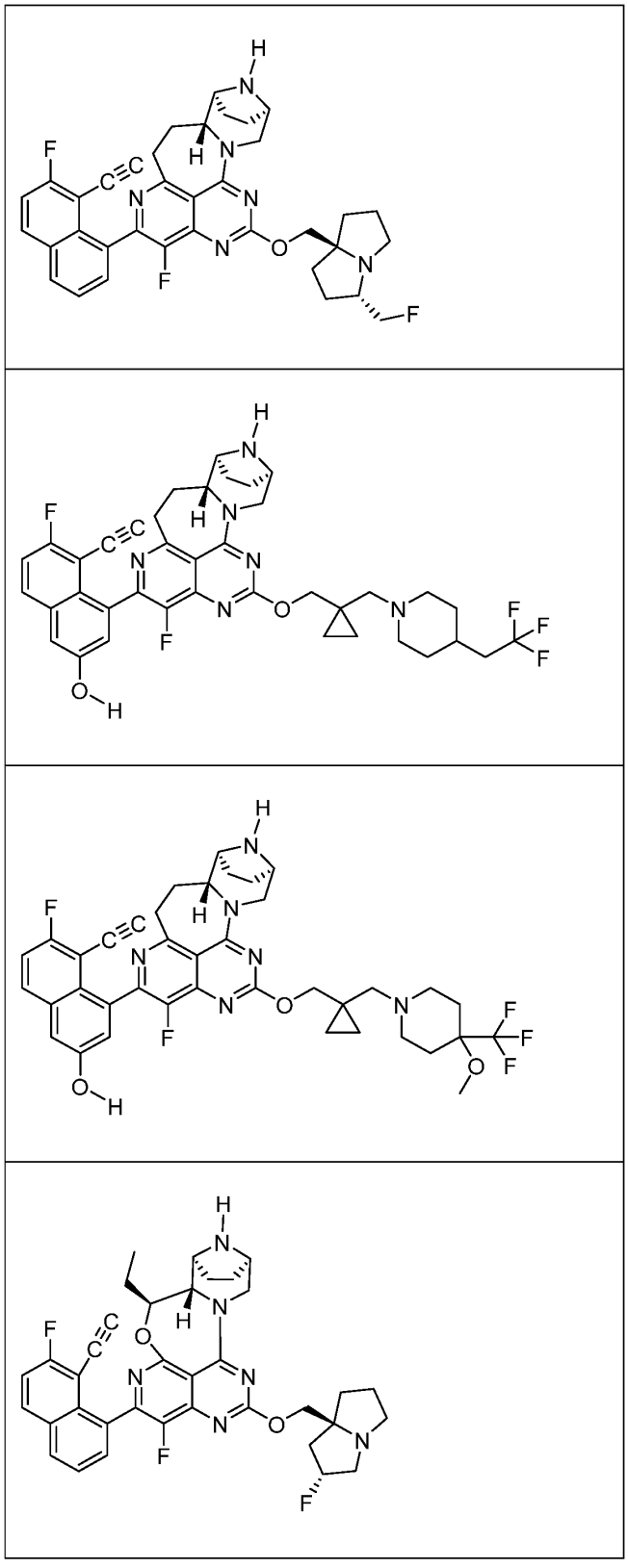


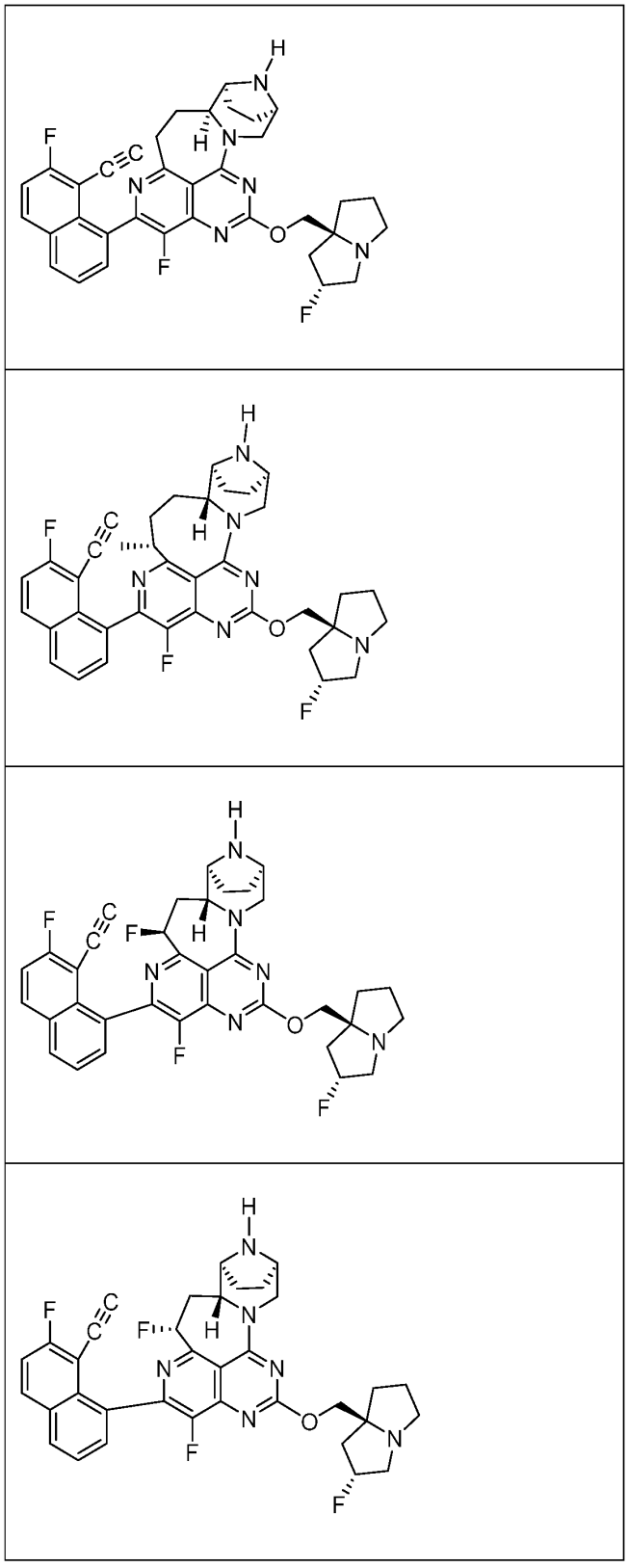


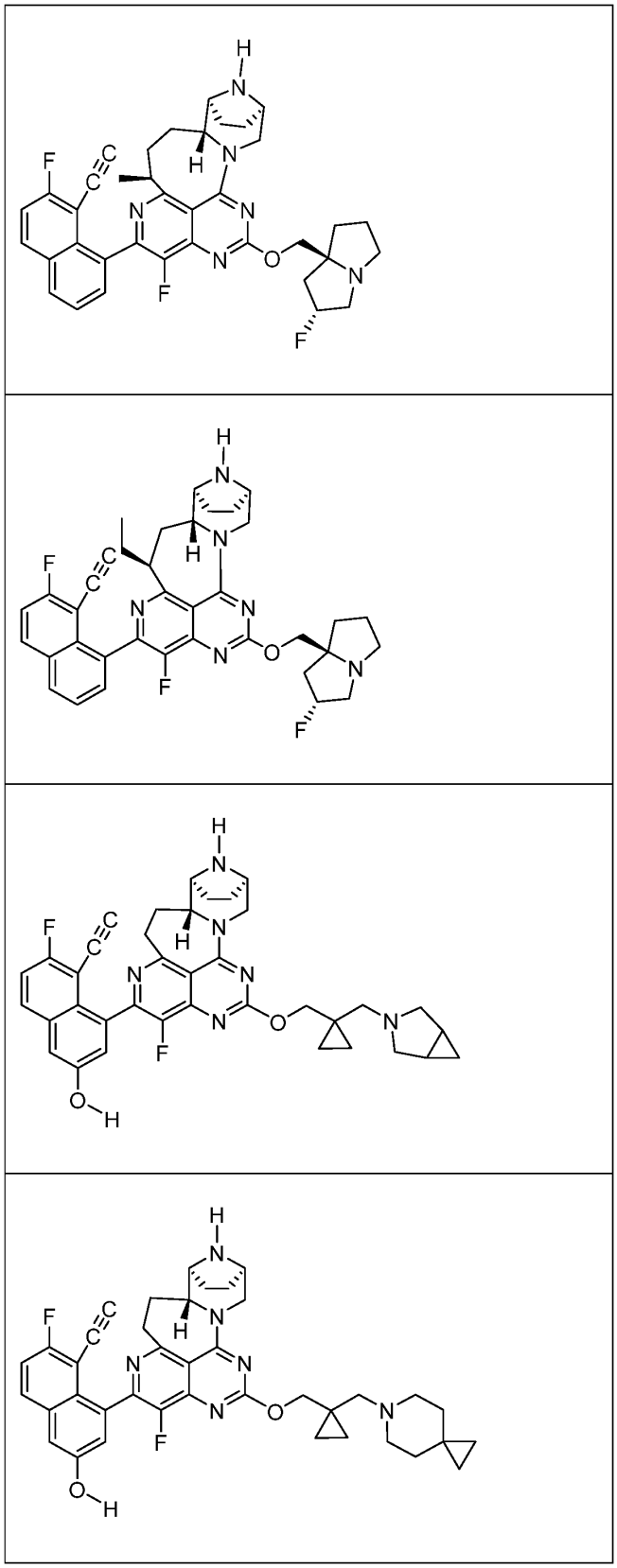


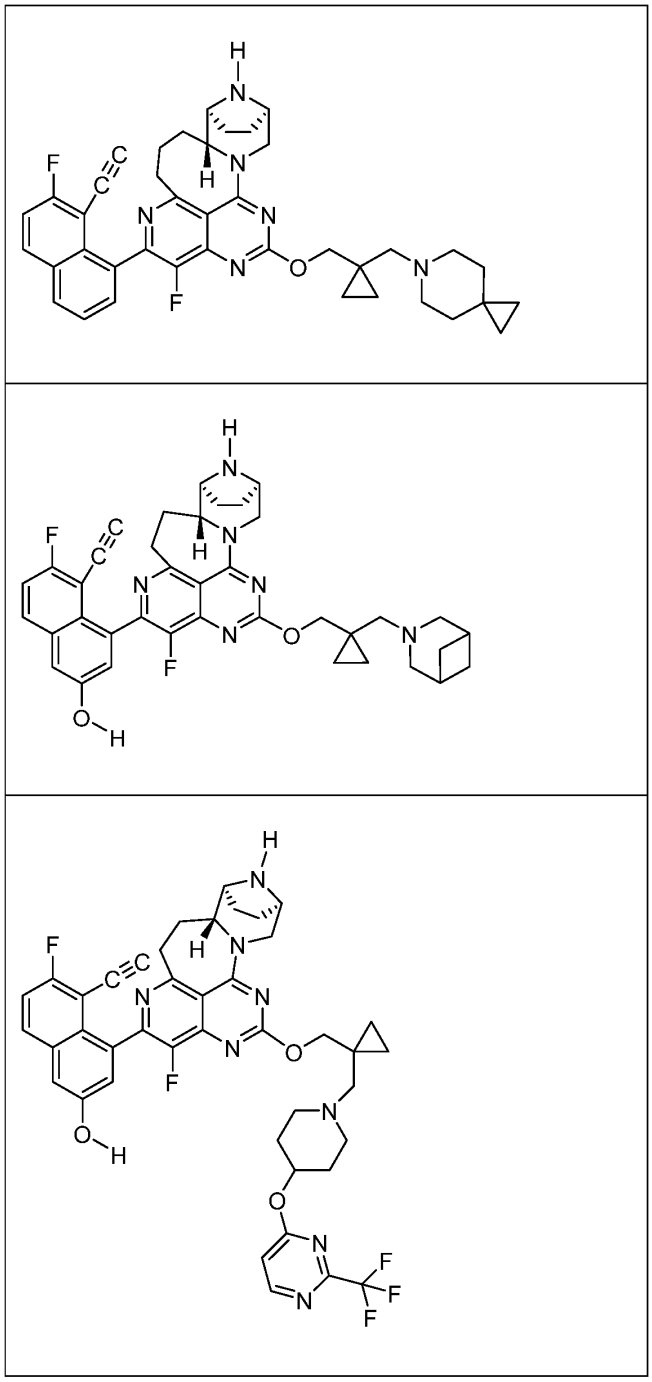


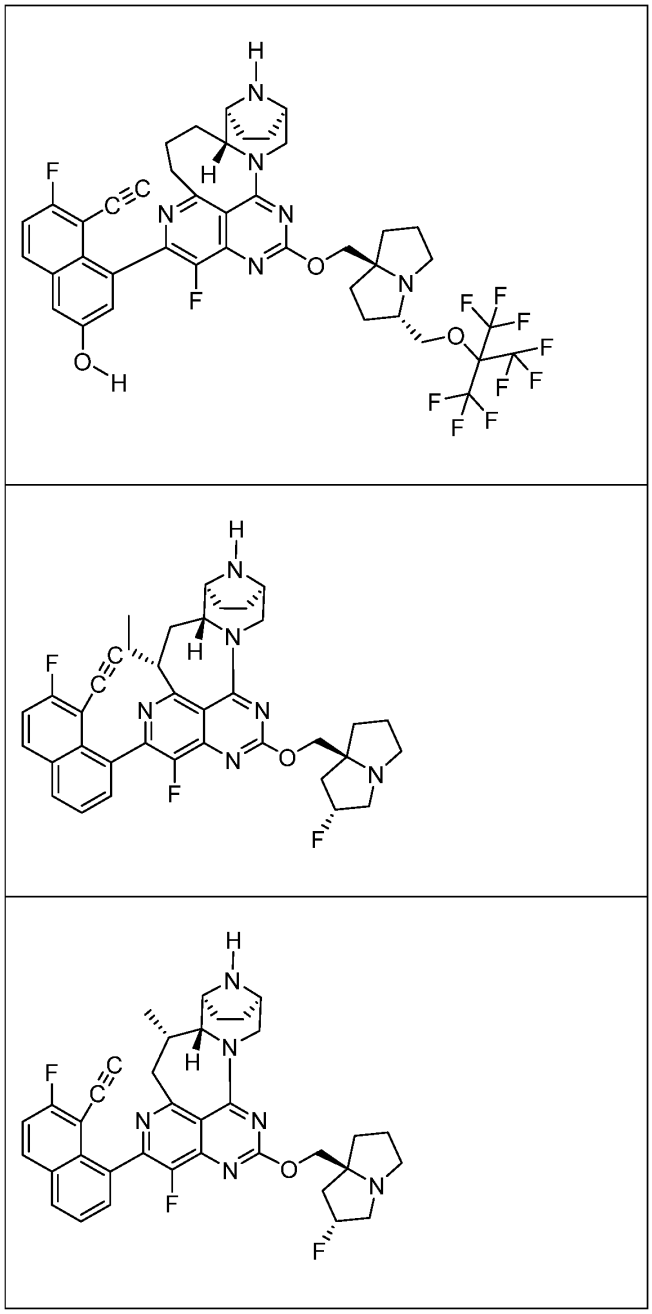


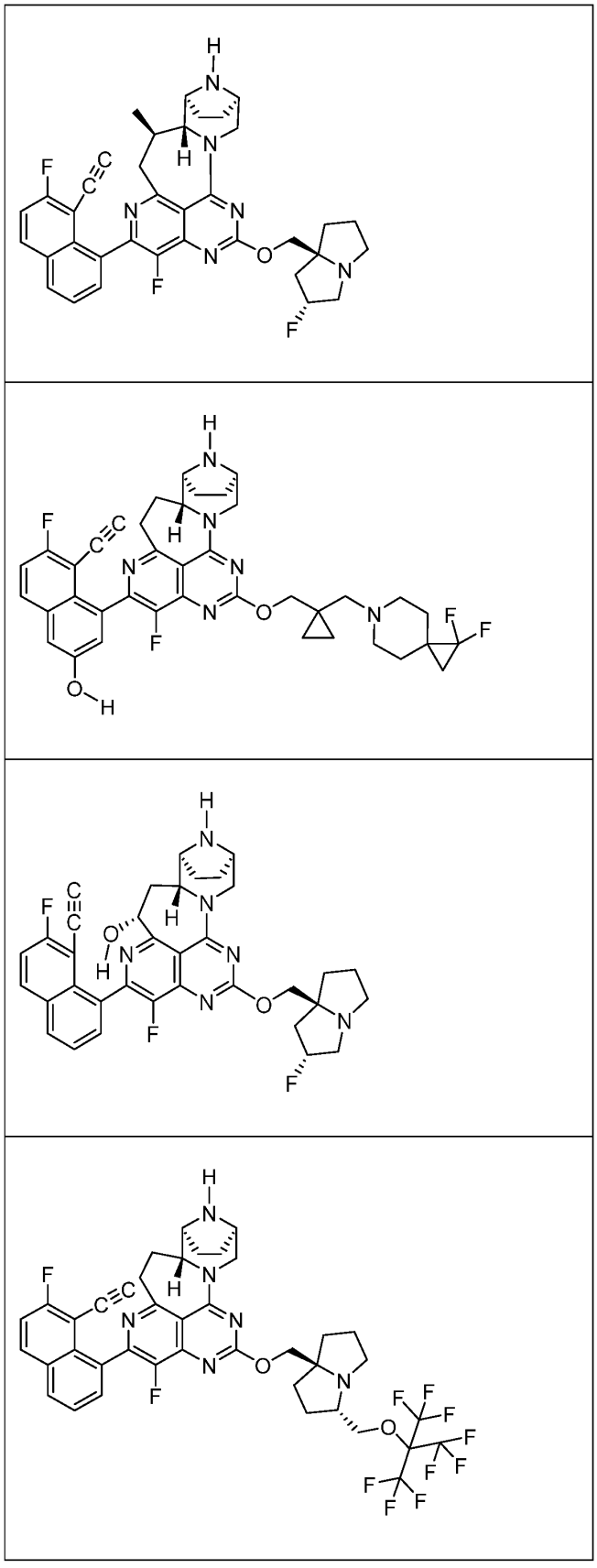


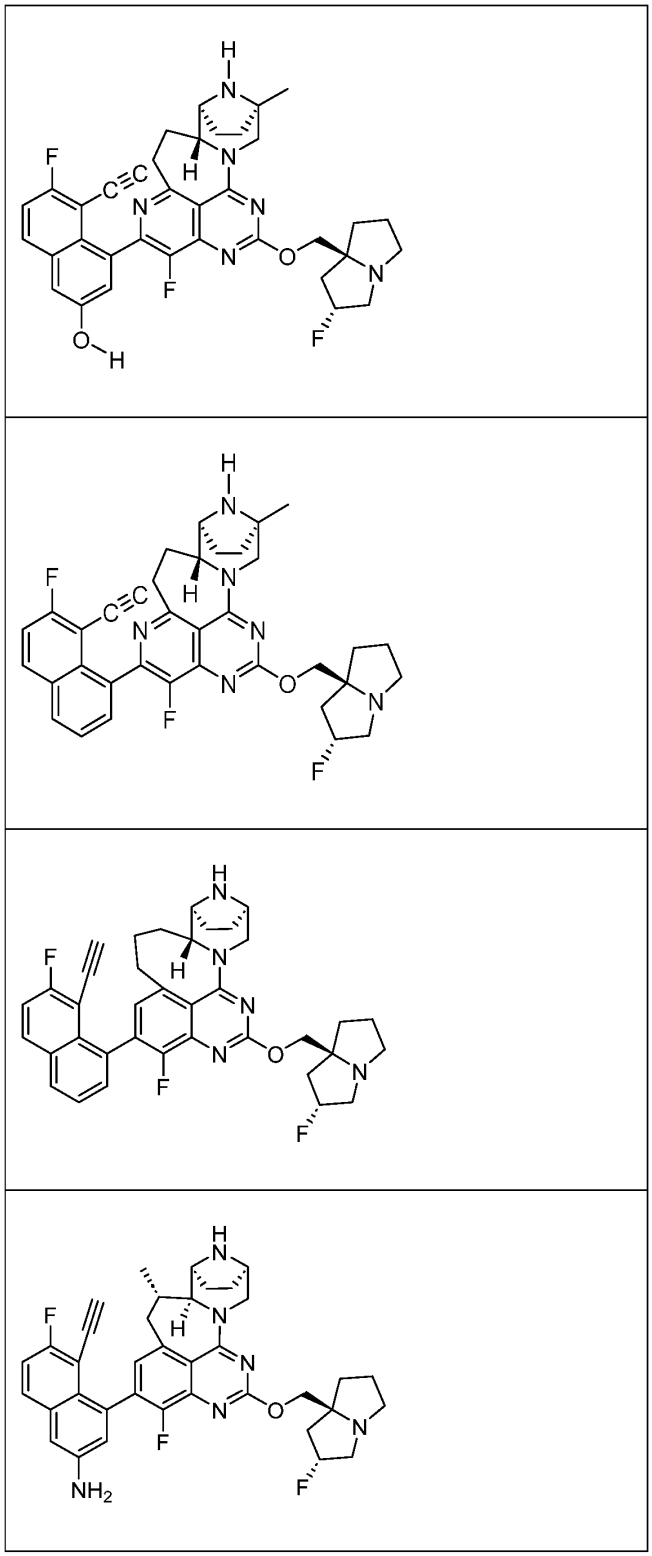


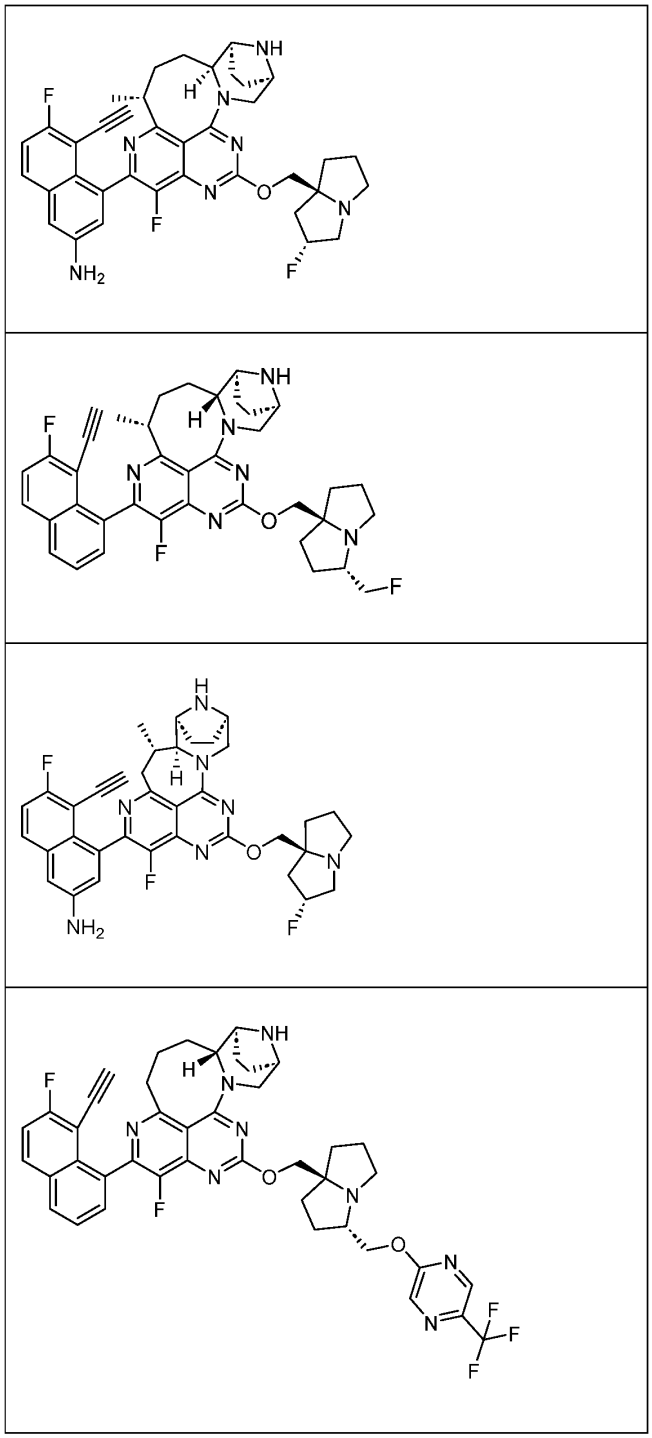


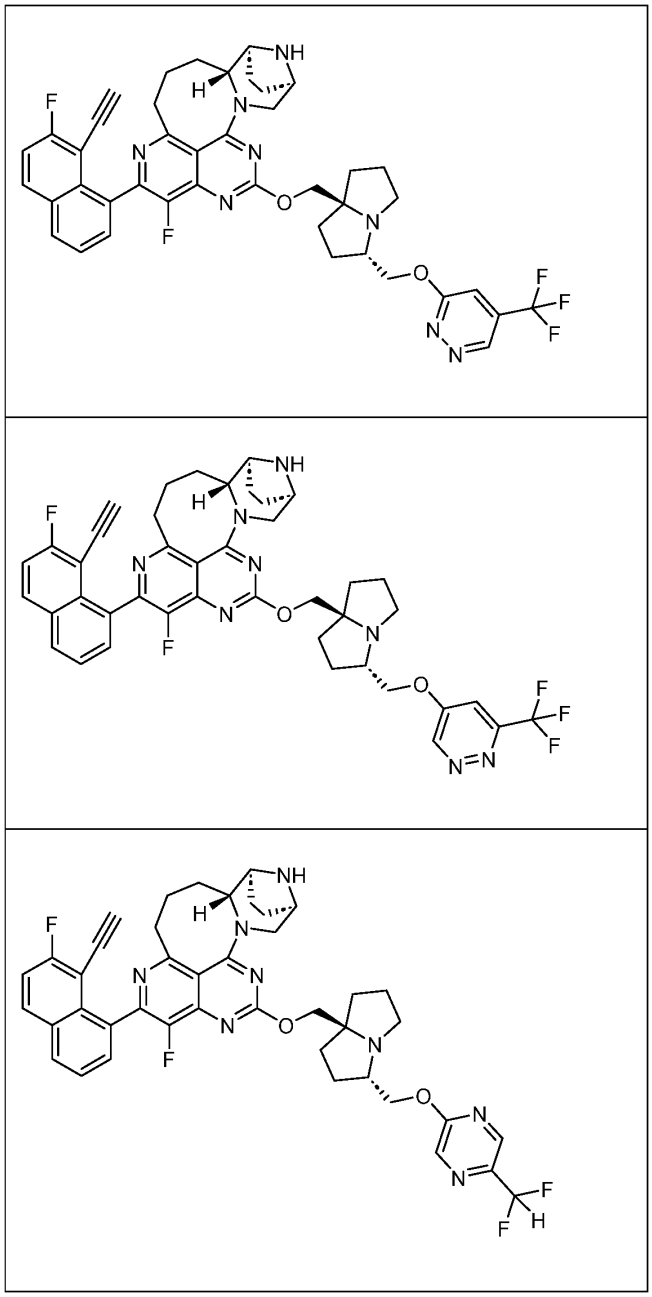


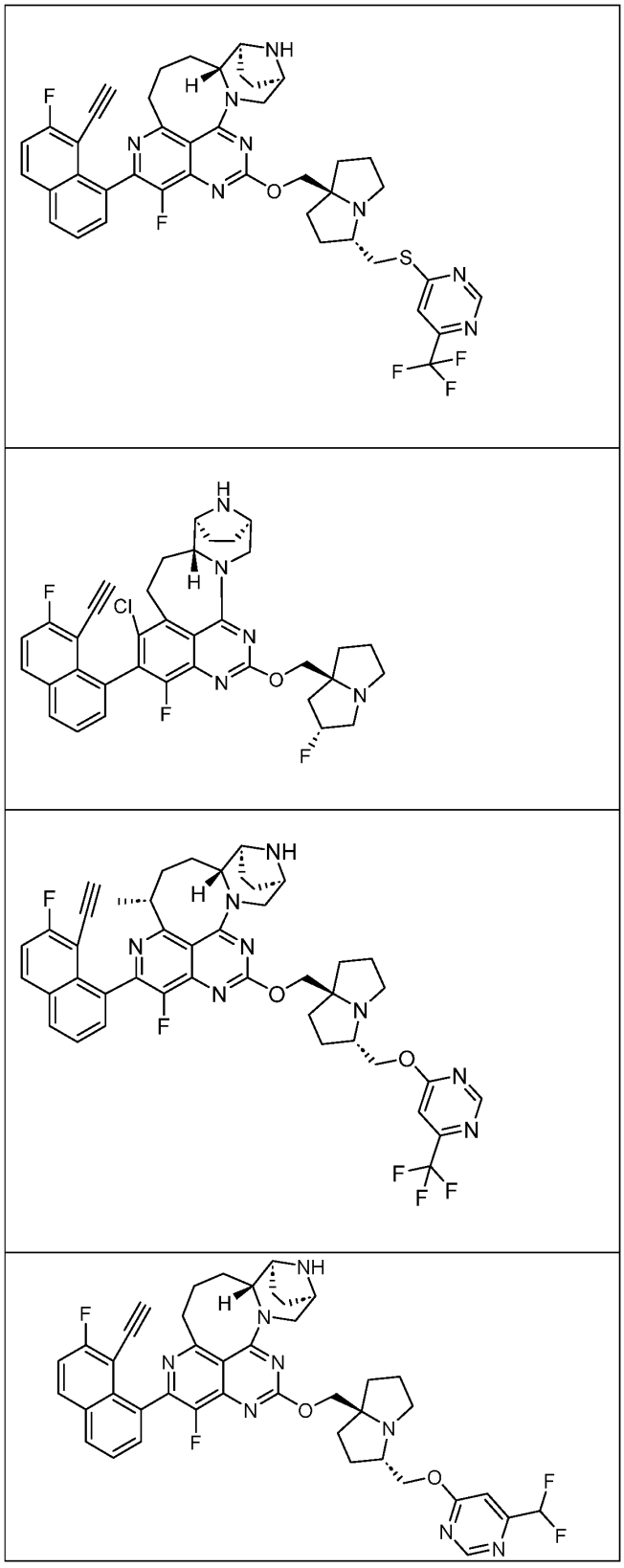


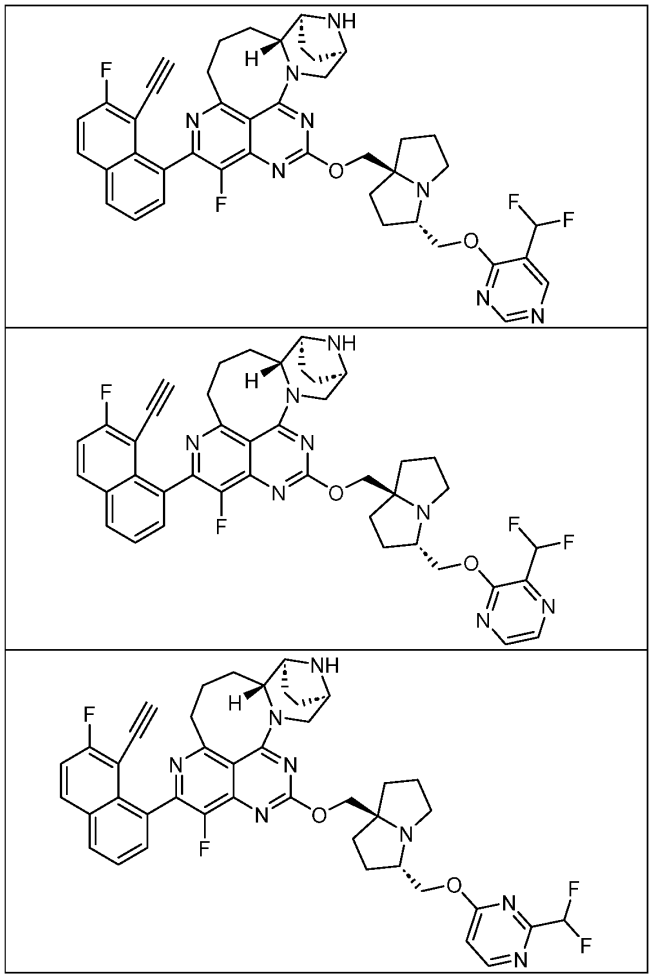




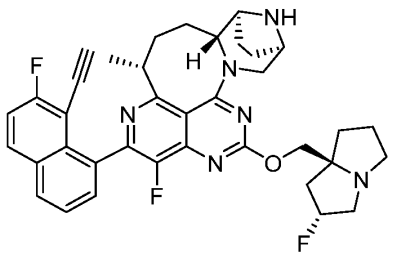




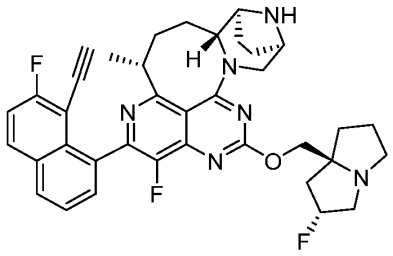




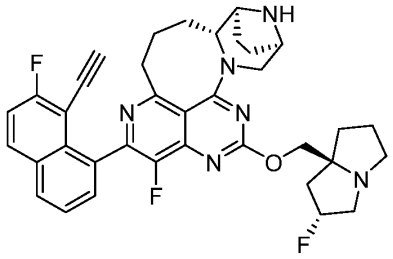
65. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure:



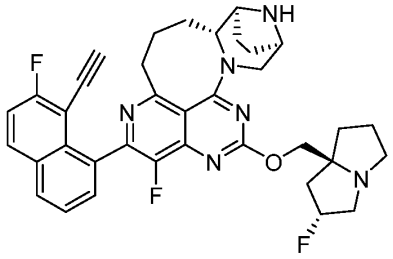
66. The compound of claim 1 having the structure:



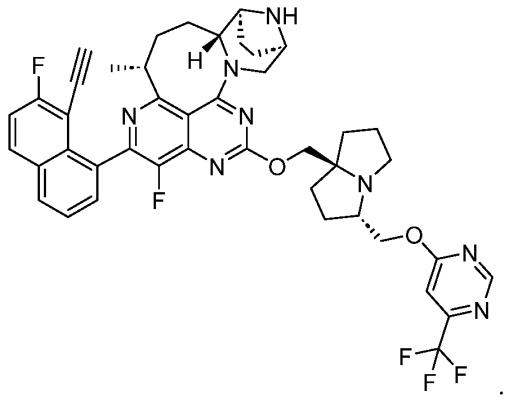
67. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure:



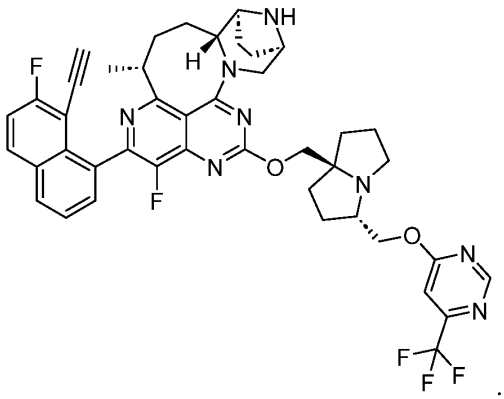
68. The compound of claim 1 having the structure:



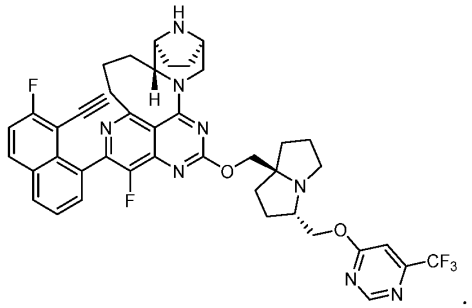
69. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure:



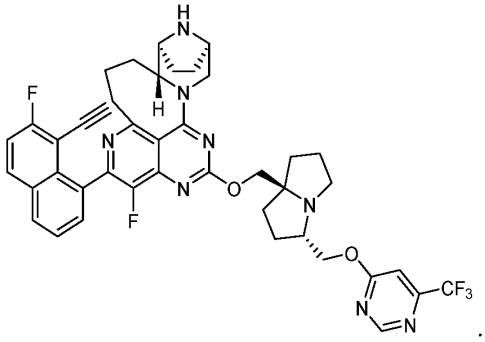
70. The compound of claim 1 having the structure:



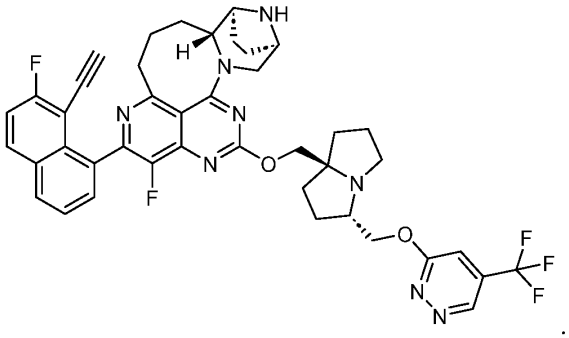
71. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure:



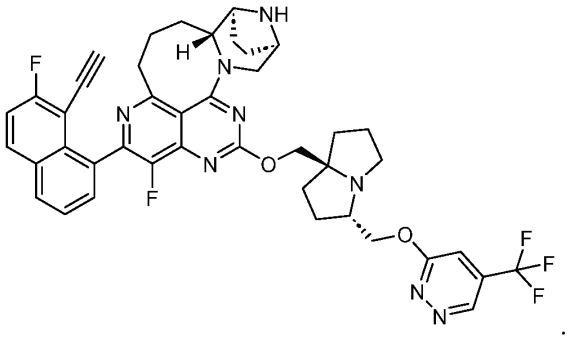
72. The compound of claim 1 having the structure:



73. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the structure:



74. The compound of claim 1 having the structure:



75. A pharmaceutical composition comprising a compound of any one of claims 1 to 74, and a pharmaceutically acceptable excipient.

76. The pharmaceutical composition of claim 75, further comprising one or more additional therapeutic agents.

77. A method of inhibiting KRAS G12D protein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 74, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claims 75 or 76.

78. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 74, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claims 75 or 76.

79. The method of claim 78, wherein the cancer is a KRAS G12D-associated cancer.

80. The method of claim 78 or 79, wherein the cancer is a hematological cancer selected from acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), B-cell ALL, myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), undifferentiated leukemia, small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), follicular lymphoma (FL), T-cell lymphoma, B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), marginal zone lymphoma (MZL), Waldestrom's macroglobulinemia (WM)) and multiple myeloma (MM).

81. The method of any one of claims 78 to 80, wherein the cancer is a solid tumor and is selected from lung cancer, colorectal cancer, stomach cancer, renal cancer, ovarian cancer, testicular cancer, uterine cancer, urinary bladder cancer, breast cancer, prostate cancer, cervical cancer, pancreatic cancer and head and neck cancer.

82. The method of any one of claims 78 to 81, wherein the cancer is pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, uterine cancer, gastric cancer, bile duct cancer, testicular cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft tissue sarcoma, non-small cell lung cancer, small-cell lung cancer, myelodysplastic syndrome, thyroid cancer, or colon cancer.

83. The method of any one of claims 78 to 82, wherein the cancer is pancreatic cancer, colorectal cancer, non-small cell lung cancer, endometrial cancer, uterine endometrical carcinoma, cholangio carcinoma, testicular germ cell cancer, cervical squamous carcinoma, or myelodysplastic syndrome.

84. The method of any one of claims 78 to 83, wherein the cancer is myelodysplastic syndrome.

85. The method of any one of claims 78 to 84, wherein the cancer is high risk myelodysplastic syndrome or low risk myelodysplastic syndrome.

86. The method of any one of claims 78 to 85, wherein the cancer is high risk myelodysplastic syndrome.

87. The method of any one of claims 78 to 85, wherein the cancer is low risk myelodysplastic syndrome.

88. The method of any one of claims 78 to 83, wherein the cancer is colorectal cancer.

89. The method of any one of claims 78 to 83, wherein the cancer is non-small cell lung cancer.

90. The method of any one of claims 78 to 83, wherein the cancer is pancreatic cancer.

91. The method of any one of claims 78 to 83, wherein the cancer is endometrial cancer.

92. The method of any one of claims 78 to 83, wherein the cancer is uterine endometrical carcinoma.

93. The method of any one of claims 78 to 83, wherein the cancer is testicular germ cell cancer.

94. The method of any one of claims 78 to 83, wherein the cancer is cervical squamous carcinoma.

95. The method of any one of claims 78 to 83, wherein the cancer is cholangio carcinoma.

96. The method of any one of claims 78 to 95, wherein the compound or pharmaceutically acceptable salt thereof is administered in combination with one or more additional therapeutic agent or therapeutic modality.

97. The pharmaceutical composition of claim 76, or the method of claim 96, wherein the one or more more additional therapeutic agent or additional therapeutic modality comprises one, two, three, or four additional therapeutic agents and/or therapeutic modalities.

98. The pharmaceutical composition or method of claim 97, wherein the additional therapeutic agent or therapeutic modalities are selected from an immune checkpoint modulator, an antibody-drug conjugate (ADC), an antiapoptotic agent, a targeted anticancer therapeutic, a chemotherapeutic agent, surgery, or radiation therapy.

99. The pharmaceutical composition or method of claim 98, wherein the immune checkpoint modulator is selected from an anti-PD-(L)1 antibody, an anti-TIGIT antibody, an anti-CTLA4 antibody, an anti-CCR8 antibody, an anti-TREM1 antibody, an anti-TREM2 antibody, a CD47 inhibitor, a DGKα inhibitor, an HPK1 inhibitor, a FLT3 agonist, an adenosine receptor antagonist, a CD39 inhibitor, a CD73 inhibitor, an IL-2 variant (IL-2v), and a CAR-T cell therapy.

100. The pharmaceutical composition or method of claim 99, wherein the anti-PD-(L)1 antibody is selected from pembrolizumab, nivolumab, cemiplimab, pidilizumab,

spartalizumab, atezolizumab, avelumab, durvalumab, cosibelimab, sasanlimab, tislelizumab, retifanlimab, balstilimab, toripalimab, cetrelimab, genolimzumab, prolgolimab, lodapolimab, camrelizumab, budigalimab, avelumab, dostarlimab, envafolimab, sintilimab, and zimberelimab.

101. The pharmaceutical composition or method of claim 99, wherein the anti-TIGIT antibody is selected from tiragolumab, vibostolimab, domvanalimab, AB308, AK127, BMS-986207, and etigilimab.

102. The pharmaceutical composition or method of claim 99, wherein the anti-CTLA4 antibody is selected from ipilimumab, tremelimumab, and zalifrelimab.

103. The pharmaceutical composition or method of claim 99, wherein the CD47 inhibitor is selected from magrolimab, letaplimab, lemzoparlimab, AL-008, RRx-001, CTX-5861, FSI-189 (GS-0189), ES-004, BI-765063, ADU1805, CC-95251, and Q-1801.

104. The pharmaceutical composition or method of claim 99, wherein the adenosine receptor antagonist is etrumadenant (AB928), taminadenant, TT-10, TT-4, or M1069.

105. The pharmaceutical composition or method of claim 99, wherein the CD39 inhibitor is TTX-030.

106. The pharmaceutical composition or method of claim 99, wherein the CD73 inhibitor is quemliclustat (AB680), uliledlimab, mupadolimab, ORIC-533, ATG-037, PT-199, AK131, NZV930, BMS-986179, or oleclumab.

107. The pharmaceutical composition or method of claim 99, wherein the IL-2v is aldesleukin (Proleukin), bempegaldesleukin (NKTR-214), nemvaleukin alfa (ALKS-4230), THOR-202 (SAR-444245), BNT-151, ANV-419, XTX-202, RG-6279 (RO-7284755), NL-201, STK-012, SHR-1916, or GS-4528.

108. The pharmaceutical composition or method of claim 99, wherein the ADC is selected from sacituzumab govitecan, datopotamab deruxtecan, enfortumab vedotin, and trastuzumab deruxtecan.

109. The pharmaceutical composition or method of claim 99, wherein the additional therapeutic agent is selected from idealisib, sacituzumab govitecan, magrolimab, GS-0189, GS-3583, zimberelimab, GS-4224, GS-9716, GS-6451, GS-1811 (JTX-1811),

quemliclustat (AB680), etrumadenant (AB928), domvanalimab, AB308, PY159, PY314, AGEN-1223, AGEN-2373, axicabtagene ciloleucel and brexucabtagene autoleucel.

110. The pharmaceutical composition or method of claim 97, wherein the one or more additional therapeutic agents is independently a chemotherapeutic agent, an immunotherapeutic agent, a hormonal agent, an anti-hormonal agent, a targeted therapy agent, or an anti-angiogenesis agent.

111. The pharmaceutical composition or method of claim 97, wherein the one or more additional therapeutic agents is independently SNS-301, 5-FU + leucovorin + oxaliplatin + irinotecan, 5-FU + nanoliposomal irinotecan, 5-FU, afatinib (Gilotrif®), aflibercept (Zaltrap®), aflibercept + FOLFIRI, albumin-bound paclitaxel, alectinib (Alecensa®), anastrozole (Arimidex®), atezolizumab, avelumab, azacitidine (Vidaza®), bevacizumab (Avastin®), bevacizumab + carboplatin + nab-paclitaxel, bevacizumab + carboplatin + pemetrexed, bevacizumab + FOLFIRI, bevacizumab + FOLFOX, bevacizumab + FOLFOXIRI, bevacizumab + leucovorin + 5-FU + oxaliplatin (FOLFOX), bevacizumab + XELOX, bevacizumab, BGB324, binimetinib + encorafenib + cetuximab, brigatinib, cabozantinib, canakinumab, capecitabine, carboplatin + nab-paclitaxel, carboplatin + pemetrexed, carboplatin, cemiplimab, cetuximab (Erbitux®), cetuximab + FOLFIRI, cisplatin + gemcitabine, cisplatin + pemetrexed, cisplatin, crizotinib (Xalkori®), cytarabine + daunorubicin, cytarabine + idarubicin, cytarabine, dabrafenib (Tafinlar®), dabrafenib + trametinib, datopotamab deruxtecan (DS-1062), datopotamab deruxtecan + durvalumab, datopotamab deruxtecan + pembrolizumab, daunorubicin, decitabine (Dacogen®), docetaxel, domvanalimab, dostarlimab (Jemperli®), doxorubicin, DSP-7888, durvalumab + tremelimumab, durvalumab, enasidenib, enfortumab vedotin (Padcev®), entrectinib (Tarceva®), erlotinib, etoposide, exemestane (Aromasin®), fluorouracil, FOLFIRI, FOLFIRINOX, FOLFOXIRI, gefitinib (Iressa®), gemcitabine + nab-paclitaxel, gemcitabine, guadecitabine, idarubicin, ifosfamide, imetelstat, irinotecan, ivosidenib, LB-100, lenalidomide (Revlimid®), lenalidomide, lenvatinib (Lenvima®), letrozole (Femara®), leucovorin + nanoliposomal irinotecan, leucovorin, Lonsurf (Orcantas®), luspatercept, nab-paclitaxel (Abraxane®), napabucasin + FOLFIRI + bevacizumab, nivolumab (Opdivo®), nivolumab + docetaxel, nivolumab + ipilimumab, nogapendekin alfa (N-803) + pembrolizumab, nogapendekin alfa, ociperlimab + tislelizumab, ociperlimab, osimertinib (Tagrisso®), oxaliplatin (FOLFOX), paclitaxel, panitumumab, pembrolizumab (Keytruda®), pembrolizumab + carboplatin + nab-paclitaxel, pembrolizumab + carboplatin + pemetrexed, pembrolizumab + lenvatinib + pemetrexed,

pembrolizumab + olaparib, pembrolizumab + pemetrexed + carboplatin, pemetrexed (Alimta®), pemetrexed + cisplatin + carboplatin, pevonedistat, progesterone, ramucirumab (Cyramza®), ramucirumab + docetaxel, regorafenib (Stivarga®), rigosertib, roxadustat, sabatolimab, selinexor, tiragolumab + atezolizumab, tiragolumab, trametinib (Mekinist®), trametinib + dabrafenib + panitumumab, trastuzumab + pertuzumab, trastuzumab deruxtecan (Enhertu®), trastuzumab, vandetanib, vemurafenib, venetoclax, vibostolimab + pembrolizumab, vibostolimab, vinblastine, vinorelbine, XELOX, or ziv-aflibercept.

112. A method for manufacturing a medicament for treating cancer in a subject in need thereof, characterized in that a compound of any one of claims 1 to 74, or a pharmaceutically acceptable salt thereof, is used.

113. A method for manufacturing a medicament for inhibiting cancer metastasis in a subject in need thereof, characterized in that a compound of any one of claims 1 to 74, or a pharmaceutically acceptable salt thereof, is used.

114. Use of the compound of any one of claims 1 to 74, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer in a subject.

115. Use of the compound of any one of claims 1 to 74, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for inhibiting cancer metastasis in a subject.

116. The compound of any one of claims 1 to 74, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a subject in need thereof.

117. The compound of any one of claims 1 to 74, or a pharmaceutically acceptable salt thereof, for use in inhibiting cancer metastasis in a subject in need thereof.

118. The compound of any one of claims 1 to 74, or a pharmaceutically acceptable salt thereof, for use in therapy.