DEGRADERS AND USES THEREOF

CROSS-REFERENCE

[001] This application claims the benefit of U.S. Provisional Application No. 63/595,640, filed November 2, 2023, U.S. Provisional Application No. 63/609,738, filed December 13, 2023, and U.S. Provisional Application No. 63/559,138, filed February 28, 2024, each incorporated herein by reference in its entirety.

SEQUENCE LISTING

[002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on October 25, 2024, is named 56690_774_601_SL.xml and is 15,018 bytes in size.

BACKGROUND

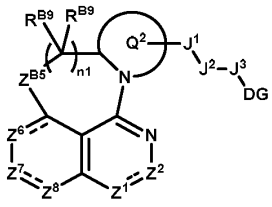
[003] Cancer (e.g., tumor, neoplasm, metastases) is the second leading cause of death worldwide estimated to be responsible for about 10 million deaths each year. Many types of cancers are marked with mutations in one or more proteins involved in various signaling pathways leading to unregulated growth of cancerous cells. In some cases, about 25 to 30 percent (%) of tumors are known to harbor Rat sarcoma (Ras) mutations. In particular, mutations in the Kirsten Ras oncogene (K-Ras) are one of the most frequent Ras mutations detected in human cancers, including lung adenocarcinomas (LUADs) and pancreatic ductal adenocarcinoma (PDAC).

[004] Ras proteins have long been considered "undruggable," due to, in part, high affinity to their substrate guanosine-5'-triphosphate (GTP) and/or their smooth surfaces without any obvious targeting region. The specific G12C Ras gene mutation has been identified as a druggable target to which a number of G12C specific inhibitors have been developed. However, such therapeutics are still of limited application, as the G12C mutation in Ras exhibits a much lower prevalence rate as compared to other known Ras mutations, such as G12D and G12V. Drug resistance and lack of durability impose further limitations to such therapeutics.

SUMMARY

[005] In view of the foregoing, there remains a considerable need for a new design of therapeutics and diagnostics that can specifically target Ras, including wildtype Ras, mutants and/or associated proteins of Ras to reduce Ras signaling output. Of particular interest are Ras inhibitors, including pan Ras inhibitors capable of inhibiting two or more Ras mutants and/or wildtype Ras, as well as mutant-selective inhibitors targeting mutant Ras proteins such as Ras G12D, G12C, G12S, G13D, and/or G12V, for the treatment of Ras-associated diseases (e.g., cancer). Of further interest are Ras-specific protein degrader compounds that are capable of binding to a Ras protein and enhancing the degradation of the Ras protein. Of additional interest are methods of synthesizing such Ras protein specific degraders along with new compounds that are useful in those synthetic methods. Such compositions and methods can be particularly useful for treating a variety of diseases including, but not limited to, cancers and neoplasia conditions. The present disclosure addresses these needs, and provides additional advantages applicable for diagnosis, prognosis, and/or treatment for a wide diversity of diseases.

[006] In an aspect is provided a compound of Formula (A0):



(A0),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^{B5} is selected from $C(R^{B9})_2$ and O;

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6}

alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

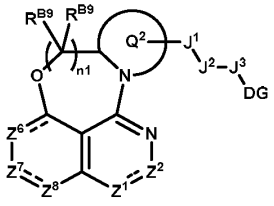
R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-}

$_{12}$ carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[007] In an aspect is provided a compound of Formula (A):



(A),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to

6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the

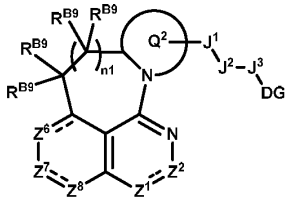
carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[008] In an aspect is provided a compound of Formula (A1):



(A1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and N(R^{B1b});

Z^2 is selected from C(R^{B2}) and C(O);

Z^6 is selected from C(R^{B6}), C(R^{B6})$_2$, N, and N(R^{B6b});

Z^7 is selected from C(R^{B7}) and N(R^{B7b});

Z^8 is selected from C(R^{B8}), C(R^{B8})$_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -N(R^{B12})-, -C(O)-, -N(R^{B12})C(O)-, -C(O)N(R^{B12})-, -S-, -S(O)$_2$-, -S(O)-, -P(O)R^{B12}-, -N(R^{B12})S(O)$_2$-, -N(R^{B12})S(O)-, -N(R^{B12})P(O)R^{B12}-, -S(O)$_2$N(R^{B12})-, -S(O)N(R^{B12})-, -P(O)R^{B12}N(R^{B12})-, -OS(O)$_2$-, -OS(O)-, -OP(O)R^{B12}-, -S(O)$_2$O-, -S(O)O-, and -P(O)R^{B12}O-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12}

carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -C(O)OR^{B12}, -C(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -$S(O)_2R^{B12}$, -S(O)(NR^{B12})R^{B12}, -$S(O)_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -N(R^{B12})(R^{B13}), -C(O)OR^{B12}, -OC(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)OR^{B12}, -N(R^{B12})$S(O)_2R^{B12}$, -C(O)R^{B12}, -S(O)R^{B12}, -OC(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)R^{B12}, -$S(O)_2R^{B12}$, -S(O)(NR^{B12})R^{B12}, -$S(O)_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), =NR^{B22}, =C(R^{B21})$_2$, -C(O)OR^{B22}, -OC(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)OR^{B22}, -N(R^{B22})$S(O)_2R^{B22}$, -C(O)R^{B22}, -S(O)R^{B22}, -OC(O)R^{B22}, -C(O)N(R^{B22})(R^{B23}), -C(O)C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)R^{B22}, -$S(O)_2R^{B22}$, -S(O)(NR^{B22})R^{B22}, -$S(O)_2$N(R^{B22})(R^{B23})-, and -S(=O)(=NR^{B22})N(R^{B22})(R^{B23}); wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), =NR^{B22}, =C(R^{B21})$_2$, -C(O)OR^{B22}, -OC(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)OR^{B22}, -N(R^{B22})$S(O)_2R^{B22}$, -C(O)R^{B22}, -S(O)R^{B22}, -OC(O)R^{B22}, -

$C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

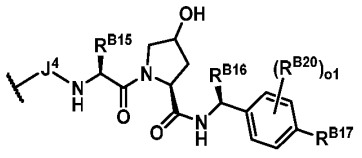
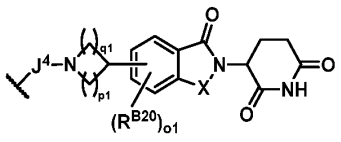
R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

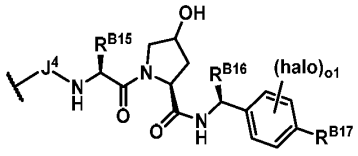
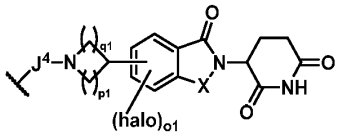
⎓ indicates a single or double bond such that all valences are satisfied.

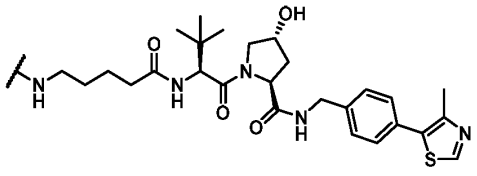
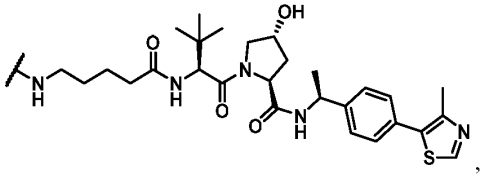
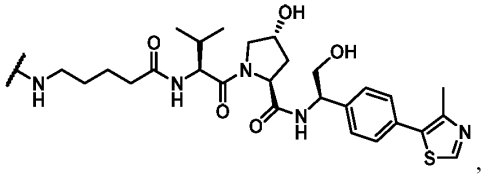
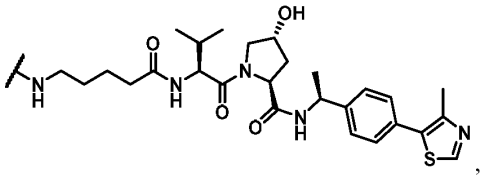
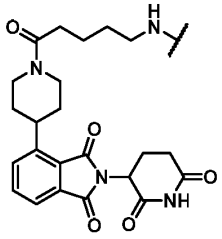
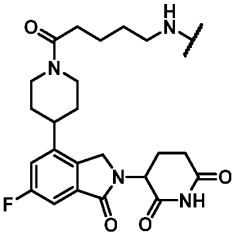
[009] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a salt or solvate thereof, the degradation enhancer is capable of binding a protein selected from E3A, mdm2, APC, EDD1, SOCS/BC-box/eloBC/CUL5/RING, LNXp80, CBX4, CBLL1, HACE1, HECTD1, HECTD2, HECTD3, HECTD4, HECW1, HECW2, HERC1, HERC2, HERC3, HERC4, HER5, HERC6, HUWE1, ITCH, NEDD4, NEDD4L, PPIL2, PRPF19, PIAS1, PIAS2, PIAS3, PIAS4, RANBP2, RNF4, RBX1, SMURF1, SMURF2, STUB1, TOPORS, TRIP12, UBE3A, UBE3B, UBE3C, UBE3D, UBE4A, UBE4B, UBOX5, UBR5, VHL (von-Hippel-Lindau ubiquitin ligase), WWP1, WWP2, Parkin, MKRN1, CMA (chaperon-mediated autophage), SCFb-TRCP (Skip-Cullin-F box (Beta-TRCP) ubiquitin complex), b-TRCP (b-transducing repeat-containing protein), cIAP1 (cellular inhibitor of apoptosis protein 1), APC/C (anaphase-promoting complex/cyclosome), CRBN (cereblon), CUL4-RBX1-DDB1-CRBN ($CRL4^{CRBN}$) ubiquitin ligase, XIAP, IAP, KEAP1, DCAF15, RNF114, DCAF16, AhR, SOCS2, KLHL12, UBR2, SPOP, KLHL3, KLHL20, KLHDC2, SPSB1, SPSB2, SPSB4, SOCS6, FBXO4, FBXO31, BTRC, FBW7, CDC20, PML, TRIM21, TRIM24, TRIM33, GID4, avadomide, iberdomide, and CC-885.

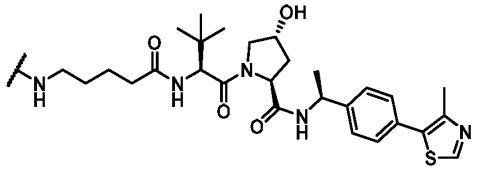
[010] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a salt or solvate thereof, the degradation enhancer is capable of binding a protein selected from UBE2A, UBE2B, UBE2C, UBE2D1, UBE2D2, UBE2D3, UBE2DR, UBE2E1, UBE2E2, UBE2E3, UBE2F, UBE2G1, UBE2G2, UBE2H, UBE2I, UBE2J1, UBE2J2, UBE2K, UBE2L3, UBE2L6, UBE2L1, UBE2L2, UBE2L4, UBE2M, UBE2N, UBE2O, UBE2Q1, UBE2Q2, UBE2R1, UBE2R2, UBE2S, UBE2T, UBE2U, UBE2V1, UBE2V2, UBE2W, UBE2Z, ATG3, BIRC6, and UFC1.

[011] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a salt or solvate thereof, DG is a monovalent form of a degradation enhancer. In some embodiments, DG is selected from:  and  ; wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, -

$C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O).

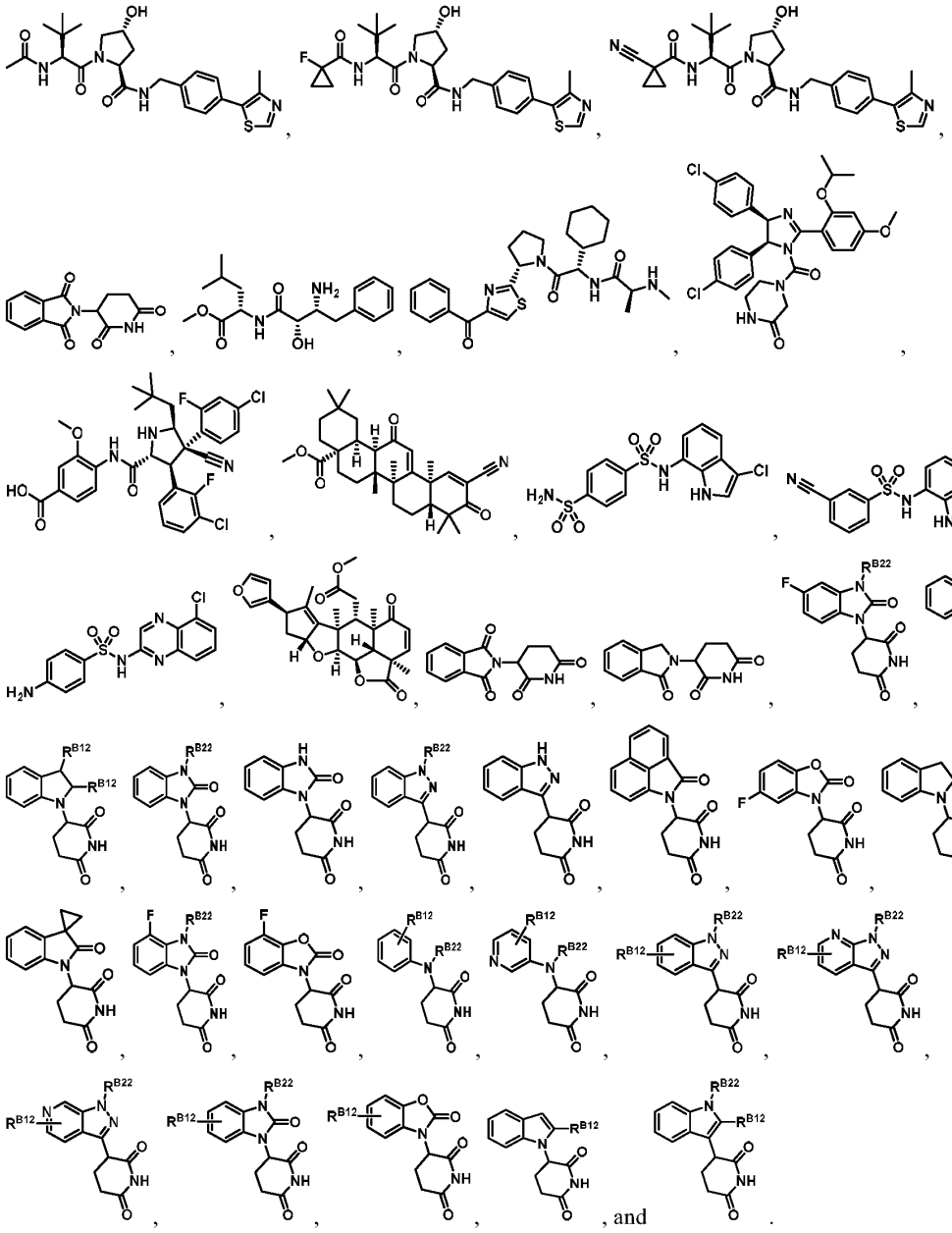
[012] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a salt or solvate thereof, DG is selected from:  and  ; wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from $-CH(CH_3)_2$ and $-C(CH_3)_3$; R^{B16} is selected from hydrogen, $-CH_3$, and $-CH_2OH$; R^{B17} is selected from methylthiazole and methylpyrazole; o1 is selected from 0 and 1; p1 and q1 are independently selected from 1 and 2; and X is selected from CH_2 and C(O).

[013] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a salt or solvate thereof, DG is selected from:  ,  ,  ,  ,  , and  .

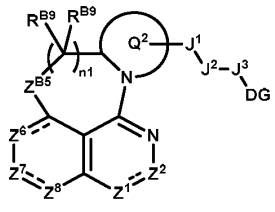
[014] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a salt or solvate thereof, DG is  .

[015] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a

salt or solvate thereof, DG comprises a monovalent form of a compound selected from



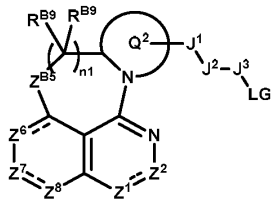
[016] In an aspect is provided a method of preparing a compound of Formula (A0):



(A0),

the method comprising:

(a) reacting a compound of Formula (a0):



(a0),

with a degradation enhancer under conditions to effect release of LG and production of the compound of Formula (A0), wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^{B5} is selected from $C(R^{B9})_2$ and O;

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})-$, -C(O)-, $-N(R^{B12})C(O)-$, $-C(O)N(R^{B12})-$, -S-, $-S(O)_2-$, -S(O)-, $-P(O)R^{B12}-$, $-N(R^{B12})S(O)_2-$, $-N(R^{B12})S(O)-$, $-N(R^{B12})P(O)R^{B12}-$, $-S(O)_2N(R^{B12})-$, $-S(O)N(R^{B12})-$, $-P(O)R^{B12}N(R^{B12})-$, $-OS(O)_2-$, -OS(O)-, $-OP(O)R^{B12}-$, $-S(O)_2O-$, -S(O)O-, and $-P(O)R^{B12}O-$, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

LG is a leaving group;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are

optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl,

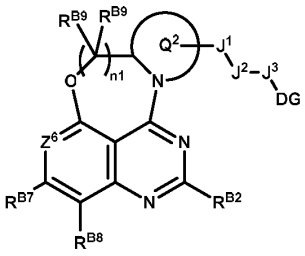
and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[017] In embodiments of a compound described herein (e.g., compound of Formula (A0) or (A)), or a salt or solvate thereof, the compound is a compound of Formula (A-1):



(A-1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

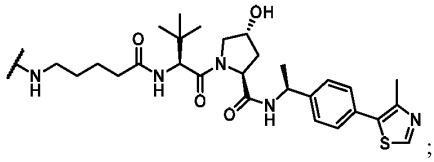
Z^6 is selected from C(R^{B6}) and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -N(R^{B12})-, -C(O)-, -N(R^{B12})C(O)-, and -C(O)N(R^{B12})-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, and -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, , wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)- and -C_{0-6} alkyl-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, each of which is optionally substituted with one or more R^{B20};

DG is  ;

n1 is 1;

R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), -O(C_{1-3} alkylene)-(4- to 5-membered heterocycle)-(C_{1-3} alkylene)-(4- to 10-membered heterocycle), or -O(C_{1-3} alkylene)-(C_{3-4} cycloalkyl)-(C_{1-3} alkylene)-(4- to 10-membered heterocycle), wherein C_{1-3} alkylene, C_{3-4} cycloalkyl, 4- to 5-membered heterocycle, and 4- to 10-membered heterocycle are each optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, -O-(C_{3-4} cycloalkyl), -NH_2, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and =C(R^{B21})$_2$;

R^{B6} is halogen or C_{1-3} haloalkyl;

R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one or more R^{B20};

R^{B8} is halogen;

R^{B9} is independently selected at each occurrence from hydrogen and methyl;

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

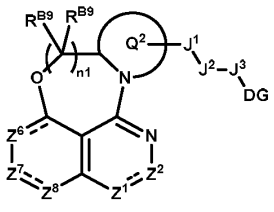
R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

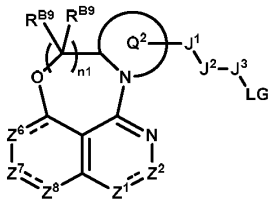
[018] In an aspect is provided a method of preparing a compound of Formula (A):



(A),

the method comprising:

(a) reacting a compound of Formula (a):



(a),

with a degradation enhancer under conditions to effect release of LG and production of the compound of Formula (A), wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

LG is a leaving group;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

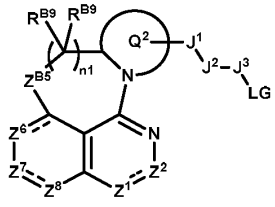
R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[019] In embodiments of the method of preparing a compound of Formula (A0), (A), and/or (A1), the reaction mixture comprises a base. In embodiments of the method, the reaction mixture comprises 5- to 12-equivalents of the base relative to the amount of degradation enhancer. In embodiments of the method, the base is *N*,*N*-diisopropylethylamine. In embodiments of the method, the compound of Formula (a0), (a), and/or (a1) and the degradation enhancer are heated to 40 to 100 °C for 2 to 48 hours. In embodiments of the method, the method further comprises (b) purifying the compound of Formula (A0), (A), and/or (A1). In embodiments of the method, the method may include the preparation of any embodiment of the compound of Formula (A0), (A), and/or (A1), including preparation of a compound of Formula (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6), or any embodiment thereof. In embodiments of the method, the method may include the use of any embodiment of the compound of Formula (a), including the use of a compound of Formula (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), or any embodiment thereof.

[020] In an aspect is provided a compound of Formula (a0):



(a0),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and N(R^{B1b});

Z^2 is selected from C(R^{B2}) and C(O);

Z^{B5} is selected from C(R^{B9})$_2$ and O;

Z^6 is selected from C(R^{B6}), C(R^{B6})$_2$, N, and N(R^{B6b});

Z^7 is selected from C(R^{B7}) and N(R^{B7b});

Z^8 is selected from C(R^{B8}), C(R^{B8})$_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -N(R^{B12})-, -C(O)-, -N(R^{B12})C(O)-, -C(O)N(R^{B12})-, -S-, -S(O)$_2$-, -S(O)-, -P(O)R^{B12}-, -N(R^{B12})S(O)$_2$-, -N(R^{B12})S(O)-, -N(R^{B12})P(O)R^{B12}-, -S(O)$_2$N(R^{B12})-, -S(O)N(R^{B12})-, -P(O)R^{B12}N(R^{B12})-, -OS(O)$_2$-, -OS(O)-, -OP(O)R^{B12}-, -S(O)$_2$O-, -S(O)O-, and -P(O)R^{B12}O-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-

, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

LG is selected from -$OS(O)_2R^{B4}$ and -$OS(O)(NR^{B4b})R^{B4}$;

n1 is selected from 1, 2, and 3;

R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and -$N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B1b}, R^{B4b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -$C(O)OR^{B12}$, -$C(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or

more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

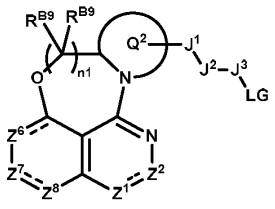
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[021] In an aspect is provided a compound of Formula (a):



(a),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -N(R^{B12})-, -C(O)-, -N(R^{B12})C(O)-, -C(O)N(R^{B12})-, -S-, -S(O)$_2$-, -S(O)-, -P(O)R^{B12}-, -N(R^{B12})S(O)$_2$-, -N(R^{B12})S(O)-, -N(R^{B12})P(O)R^{B12}-, -S(O)$_2$N(R^{B12})-, -S(O)N(R^{B12})-, -P(O)R^{B12}N(R^{B12})-, -OS(O)$_2$-, -OS(O)-, -OP(O)R^{B12}-, -S(O)$_2$O-, -S(O)O-, and -P(O)R^{B12}O-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

LG is selected from -OS(O)$_2R^{B4}$ and -OS(O)(NR^{B4b})R^{B4};

n1 is selected from 1, 2, and 3;

R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and -N(R^{B12})(R^{B13}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B1b}, R^{B4b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -C(O)OR^{B12}, -C(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -S(O)$_2R^{B12}$, -S(O)(NR^{B12})R^{B12}, -S(O)$_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -N(R^{B12})(R^{B13}), -C(O)OR^{B12}, -OC(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)OR^{B12}, -N(R^{B12})S(O)$_2R^{B12}$, -C(O)R^{B12}, -S(O)R^{B12}, -OC(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)R^{B12}, -S(O)$_2R^{B12}$, -S(O)(NR^{B12})R^{B12}, -S(O)$_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-

membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

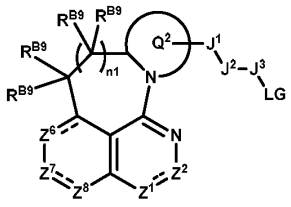
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[022] In an aspect is provided a compound of Formula (a1):



(a1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

LG is selected from $-OS(O)_2R^{B4}$ and $-OS(O)(NR^{B4b})R^{B4}$;

n1 is selected from 1, 2, and 3;

R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and $-N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B1b}, R^{B4b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and -

$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-OR^{B12}$, $-SR^{B12}$, $-N(R^{B12})(R^{B13})$, $-C(O)OR^{B12}$, $-OC(O)N(R^{B12})(R^{B13})$, $-N(R^{B12})C(O)N(R^{B12})(R^{B13})$, $-N(R^{B12})C(O)OR^{B12}$, $-N(R^{B12})S(O)_2R^{B12}$, $-C(O)R^{B12}$, $-S(O)R^{B12}$, $-OC(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-N(R^{B12})C(O)R^{B12}$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$-, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6}

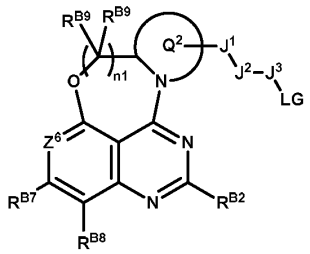
alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[023] In embodiments of a compound described herein (e.g., compound of Formula (a0) or (a)), or a salt or solvate thereof, the compound is a compound of Formula (a-1):



(a-1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^6 is selected from C(R^{B6}) and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -N(R^{B12})-, -C(O)-, -N(R^{B12})C(O)-, and -C(O)N(R^{B12})-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, and -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, , wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)- and -C_{0-6} alkyl-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, each of which is optionally substituted with one or more R^{B20};

LG is selected from -$OS(O)_2R^{B4}$;

R^{B4} is selected from C_{2-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and -N(R^{B12})(R^{B13}), wherein C_{2-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

n1 is 1;

R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), -O(C_{1-3} alkylene)-(4- to 5-membered

heterocycle)-(C_{1-3} alkylene)-(4- to 10-membered heterocycle), or -O(C_{1-3} alkylene)-(C_{3-4} cycloalkyl)-(C_{1-3} alkylene)-(4- to 10-membered heterocycle), wherein C_{1-3} alkylene, C_{3-4} cycloalkyl, 4- to 5-membered heterocycle, and 4- to 10-membered heterocycle are each optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, -O-(C_{3-4} cycloalkyl), -NH_2, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and =C(R^{B21})$_2$;

R^{B6} is halogen or C_{1-3} haloalkyl;

R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one or more R^{B20};

R^{B8} is halogen;

R^{B9} is independently selected at each occurrence from hydrogen and methyl;

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), =NR^{B22}, =C(R^{B21})$_2$, -C(O)OR^{B22}, -OC(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)OR^{B22}, -N(R^{B22})S(O)$_2R^{B22}$, -C(O)R^{B22}, -S(O)R^{B22}, -OC(O)R^{B22}, -C(O)N(R^{B22})(R^{B23}), -C(O)C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)R^{B22}, -S(O)$_2R^{B22}$, -S(O)(NR^{B22})R^{B22}, -S(O)$_2$N(R^{B22})(R^{B23})-, and -S(=O)(=NR^{B22})N(R^{B22})(R^{B23}); wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), =NR^{B22}, =C(R^{B21})$_2$, -C(O)OR^{B22}, -OC(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)OR^{B22}, -N(R^{B22})S(O)$_2R^{B22}$, -C(O)R^{B22}, -S(O)R^{B22}, -OC(O)R^{B22}, -C(O)N(R^{B22})(R^{B23}), -C(O)C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)R^{B22}, -S(O)$_2R^{B22}$, -S(O)(NR^{B22})R^{B22}, -S(O)$_2$N(R^{B22})(R^{B23}), and -S(=O)(=NR^{B22})N(R^{B22})(R^{B23});

R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl;

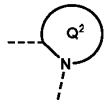
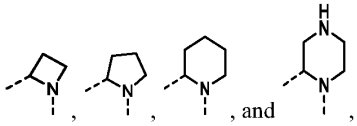
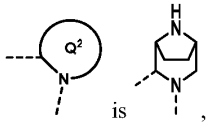
R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[024] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3),

(A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), or (a0-6)), Z^{B5} is $C(R^{B9})_2$. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), or (a0-6)), Z^{B5} is O.

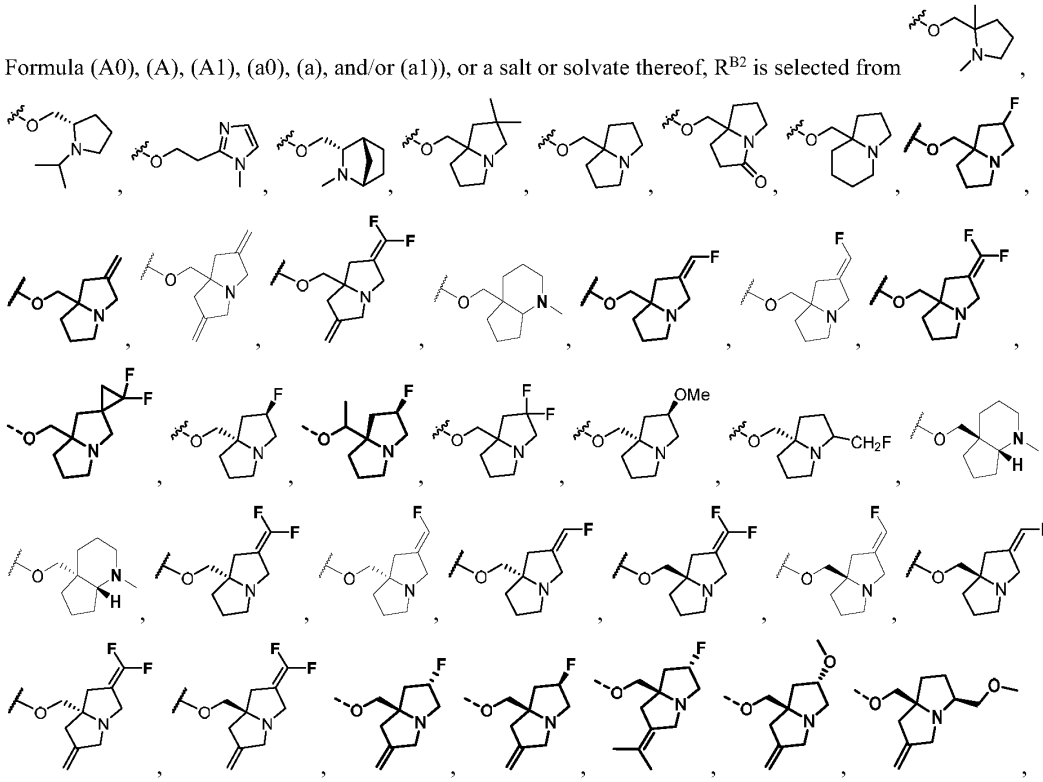
[025] In embodiments, n1 is 1. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, Q^2 is 4- to 6-membered monocyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, Q^2 is 7- to 9-membered bridged bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof,  is selected from  , and , each of which is optionally substituted with one or more R^{B20}. In embodiments of a compound described herein (e.g., compound of Formula (A) or (a)), or a salt or solvate thereof,  is , which is optionally substituted with one or more R^{B20}.

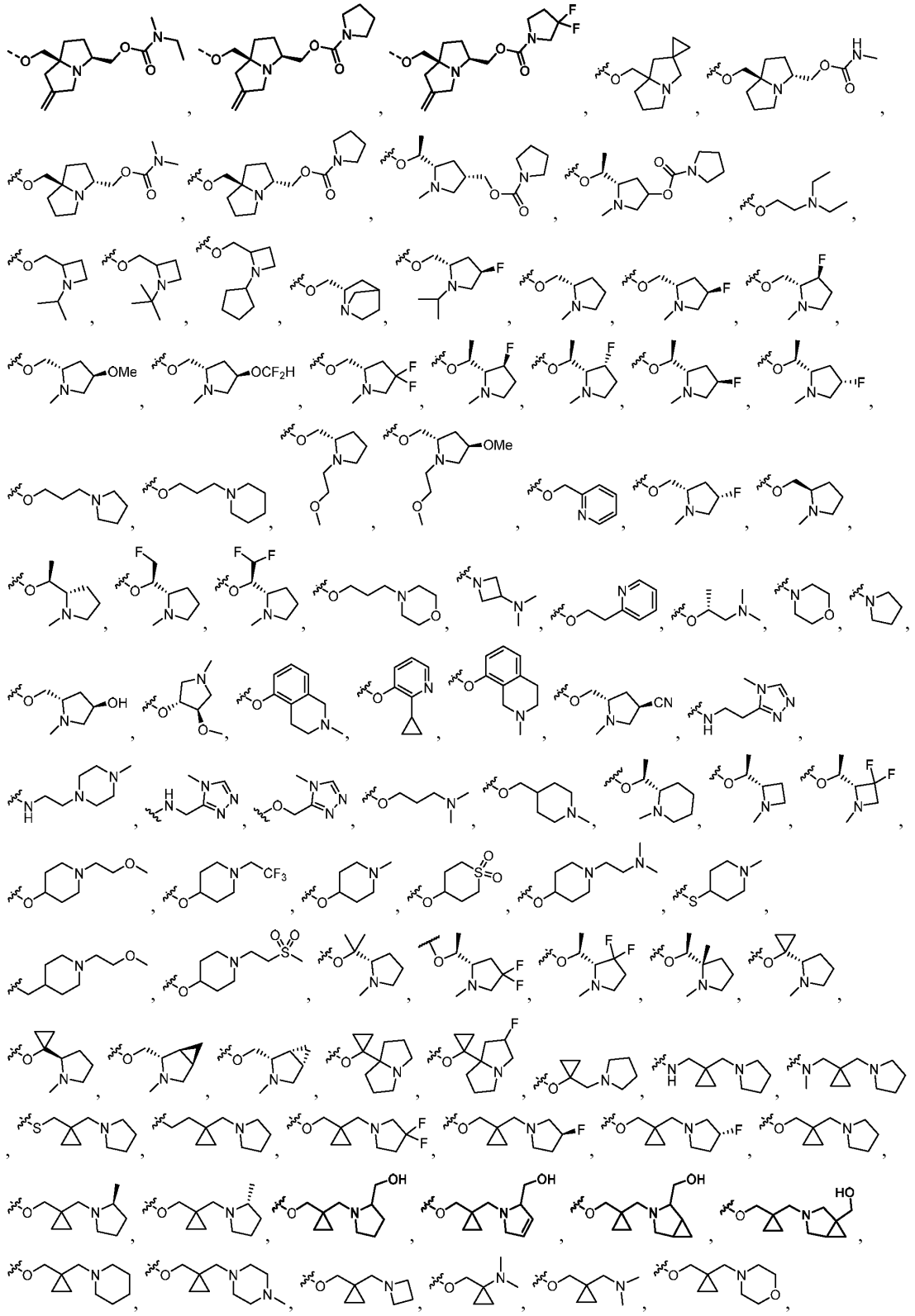
[026] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$; Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is N, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$; Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})_2$, Z^7 is $N(R^{B7b})$, and Z^8 is $C(R^{B8})_2$; or Z^1 is $N(R^{B1b})$, Z^2 is C(O), Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is N. In embodiments of a compound described herein (e.g., compound of Formula (a)), or a salt or solvate thereof, Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is N, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$.

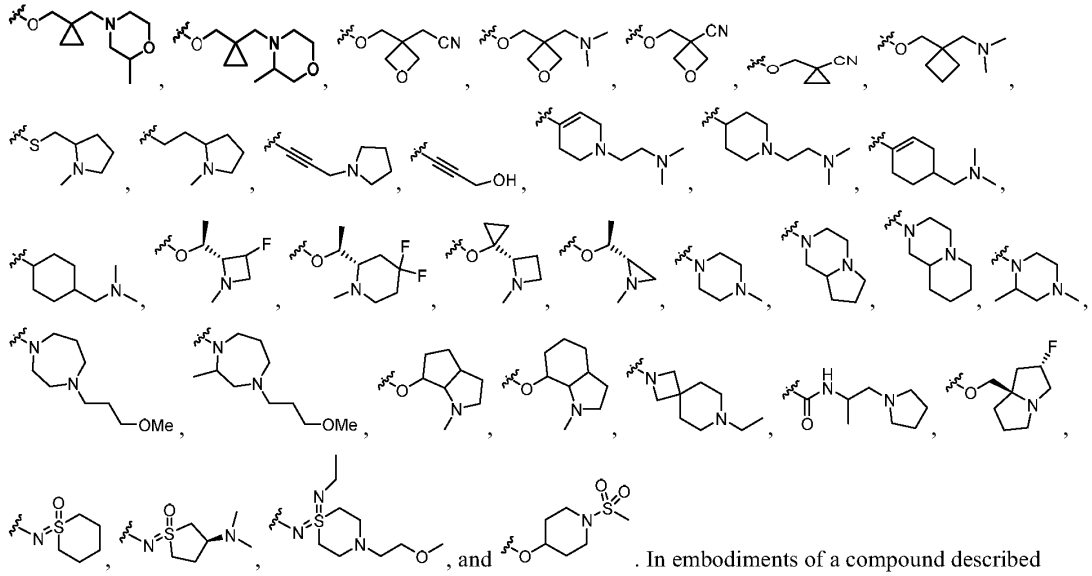
[027] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, J^1 is selected from a bond, C_{1-6} alkylene, 2- to 6-membered heteroalkylene, and -C(O)-, wherein C_{1-6} alkylene and 2- to 6-membered heteroalkylene are optionally substituted with one or more R^{B20}. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, J^1 is -C(O)-. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, and -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)- and -C_{0-6} alkyl-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20}. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, J^2 is a bond. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, J^3 is selected from C_{1-6} alkylene, 2- to 6-membered heteroalkylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20}. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, J^3 is selected from C_{1-6} alkylene and 2- to 6-membered heteroalkylene, each of which is optionally substituted with one or more R^{B20}. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate

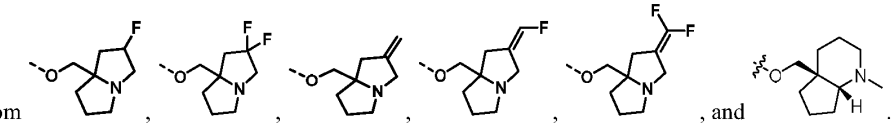
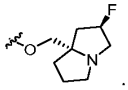
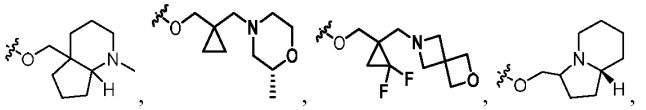
thereof, J^3 is selected from C_{1-6} alkylene and 2- to 6-membered heteroalkylene. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, J^1 is -C(O)-; J^2 is a bond; and J^3 is C_{1-6} alkylene. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, J^1 is a bond; J^2 is a bond; and J^3 is selected from C_{1-6} alkylene and 2- to 6-membered heteroalkylene, each of which is optionally substituted with one or more R^{B20}. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, J^1 is -C(O)-; J^2 is 3- to 12-membered heterocycle optionally substituted with one or more R^{B20}; and J^3 is C_{1-6} alkylene. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, J^3 is selected from -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and –(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20}. In embodiments, J^3 is selected from C_{1-6} alkylene and 2- to 6-membered heteroalkylene, each of which is optionally substituted with one or more R^{B20}. In embodiments, J^3 is selected from C_{1-6} alkylene and 2- to 6-membered heteroalkylene.

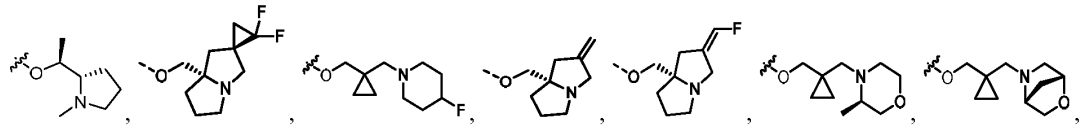
[028] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B2} is selected from

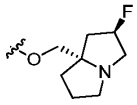
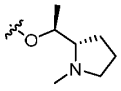
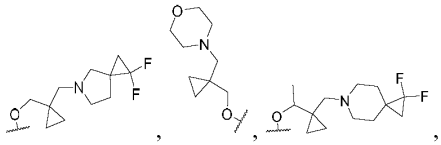


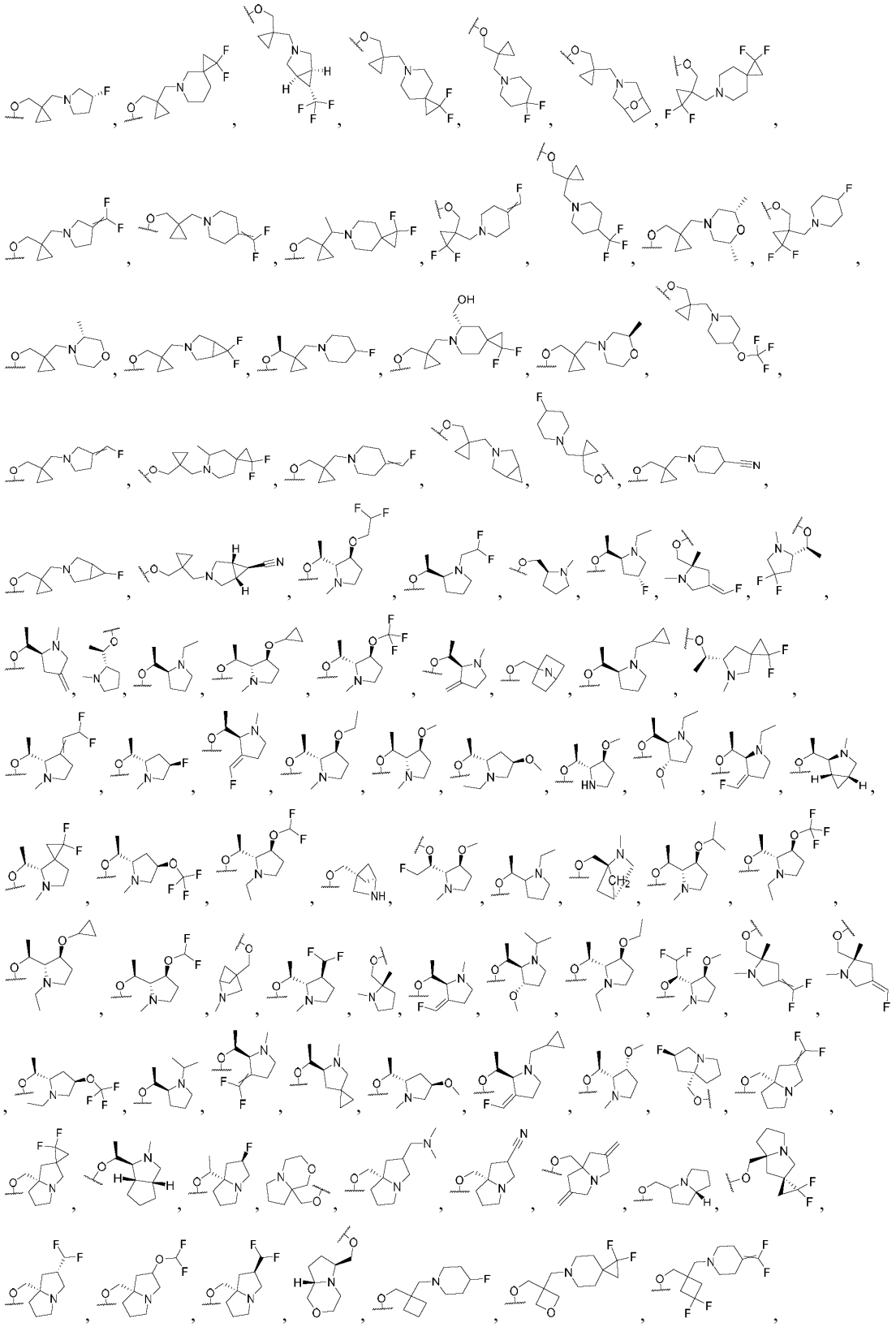


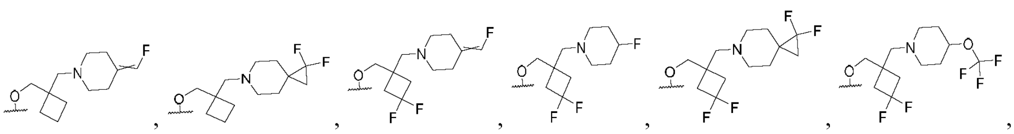


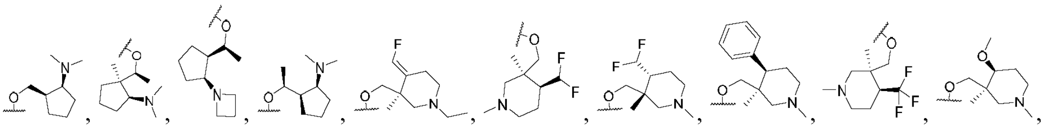
herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B2} is selected from  . In embodiments of a compound described herein (e.g., Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B2} is  . In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), R^{B2} is selected from 

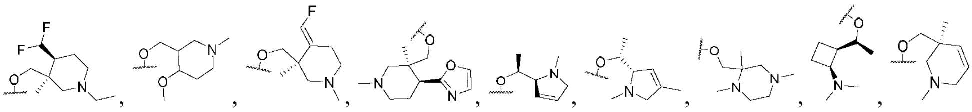


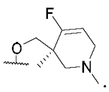
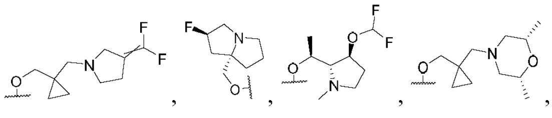
and  . In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), R^{B2} is  . In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), R^{B2} is selected from 

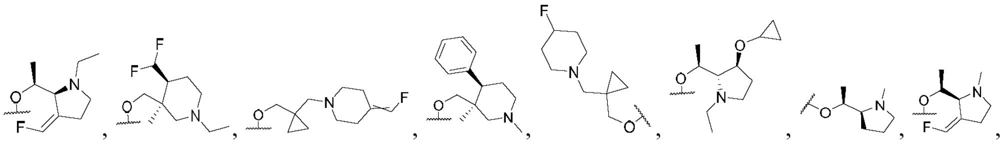


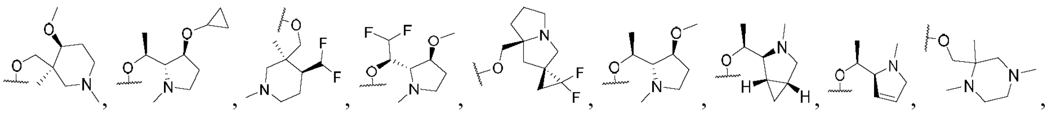


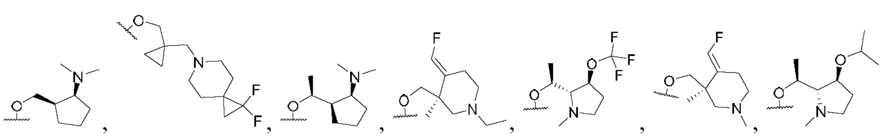
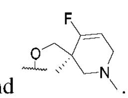
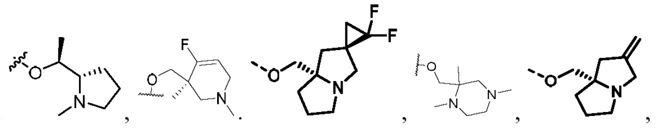


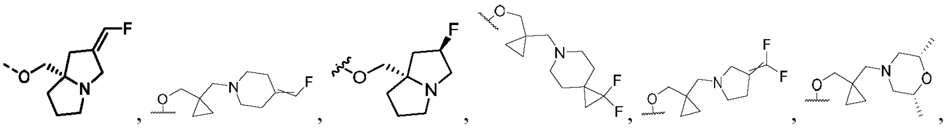
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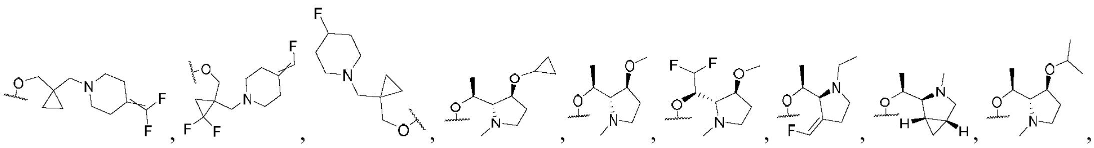
 . In some embodiments, R^{B2} is selected from 

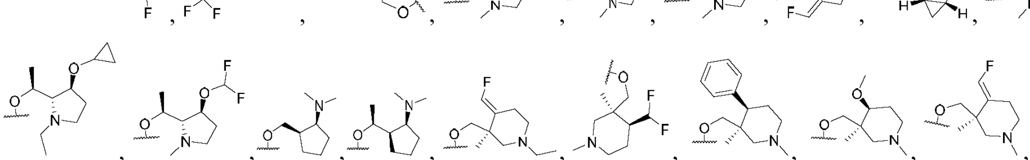


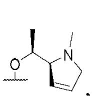
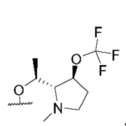
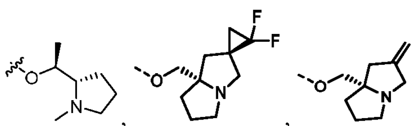


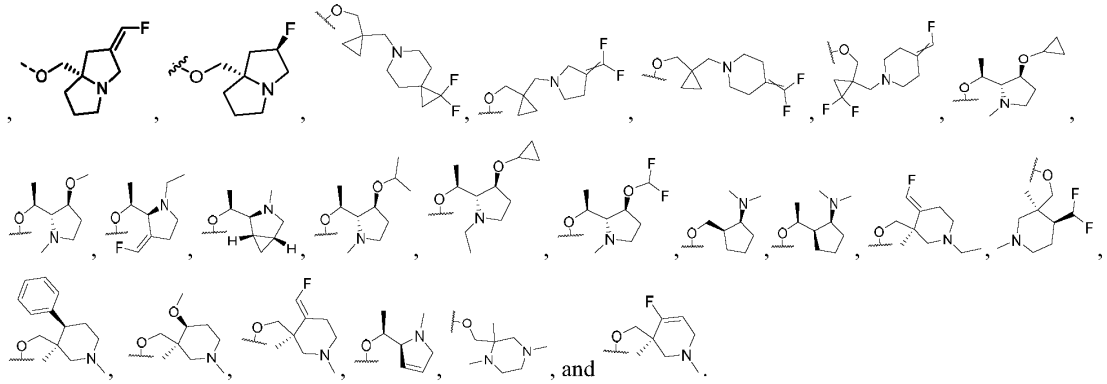
 , and  . In some embodiments, R^{B2} is selected from 





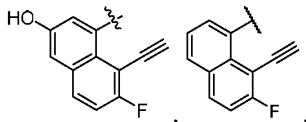


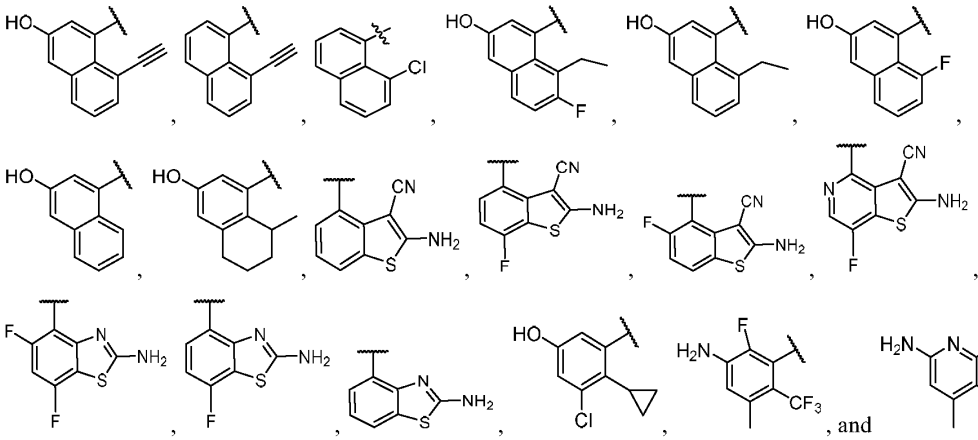
 , and  . In some embodiments, R^{B2} is selected from 



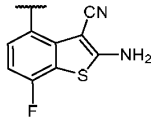
[029] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B6} is halogen. In embodiments, R^{B6} is halogen or C_{1-3} haloalkyl

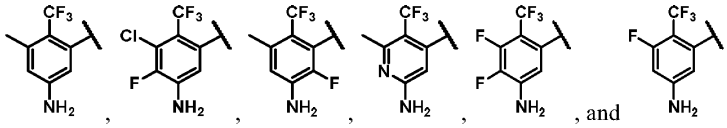
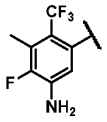
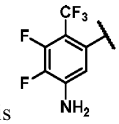
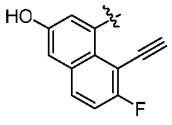
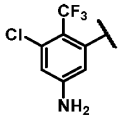
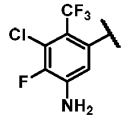
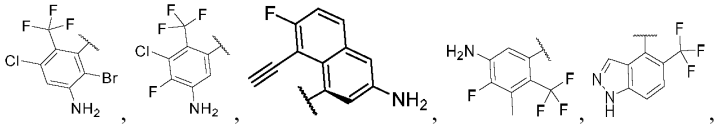
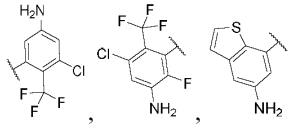
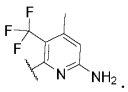
[030] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one or more R^{B20}. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OR^{B22}, -$N(R^{B22})(R^{B23})$, and C_{3-6} cycloalkyl. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, -CH_3, -CH_2CH_3, -$CH{=}CH_2$, -CF_3, -C≡CH, -OH, -NH_2, and -cyclopropyl. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B7} is selected from





. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or

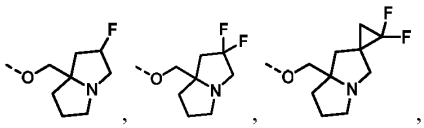
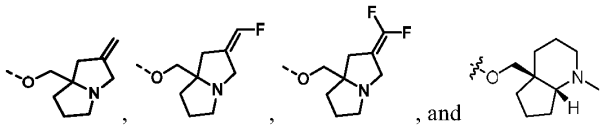
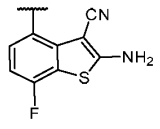
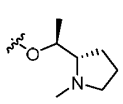
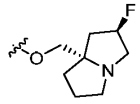
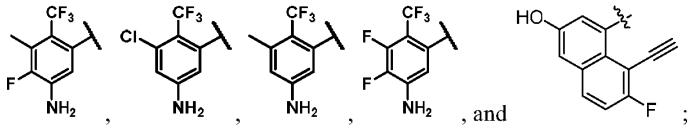


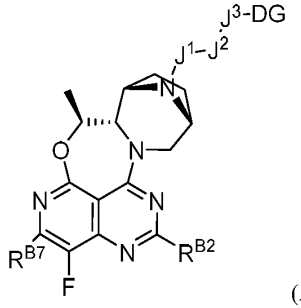
a salt or solvate thereof, R^{B7} is . In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), R^{B7} is selected from  ,  , and . In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), R^{B7} is  . In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), R^{B7} is  . In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), R^{B7} is  . In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), R^{B7} is  . In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), R^{B7} is  . In some embodiments, R^{B7} is selected from  ,  , and  .

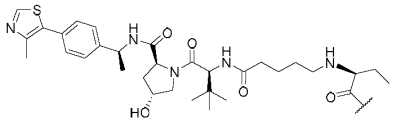
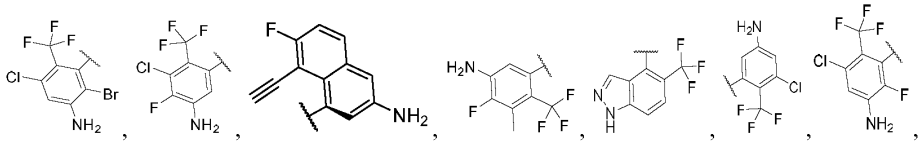
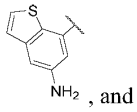
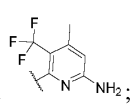
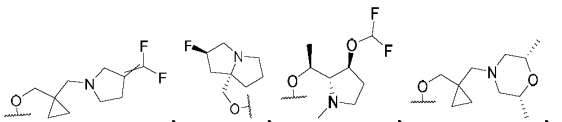
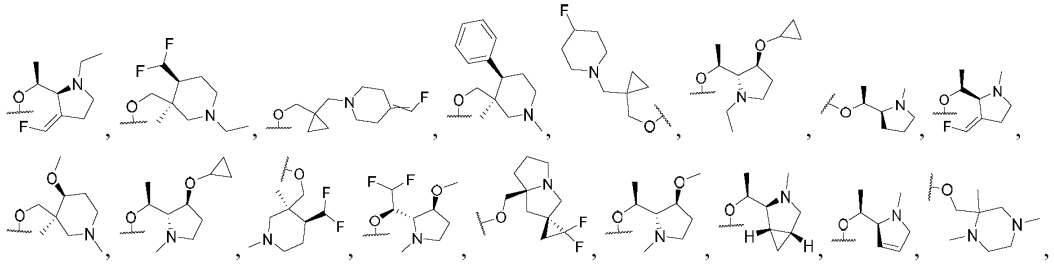
[031] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B8} is independently selected from hydrogen and halogen. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B8} is halogen.

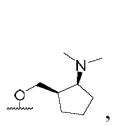
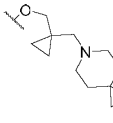
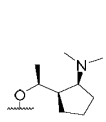
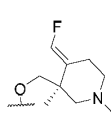
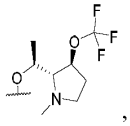
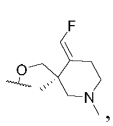
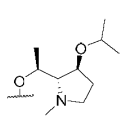
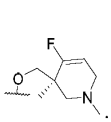
[032] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B6} is halogen; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl,

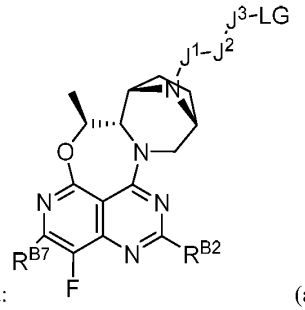
benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is halogen.

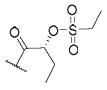
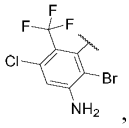
[033] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, R^{B2} is selected from  ,  , and ; R^{B6} is halogen; R^{B7} is  ; and R^{B8} is halogen. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), wherein: R^{B2} is selected from  and  ; R^{B6} is halogen; R^{B7} is selected from  , and ; and R^{B8} is halogen. In embodiments of a compound described herein (e.g., compound of Formula (A0) or (A)), the compound has the formula:

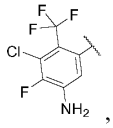
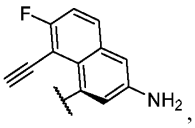
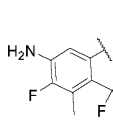
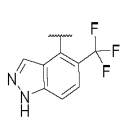
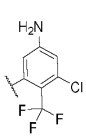
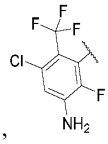
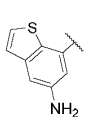
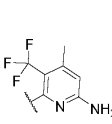
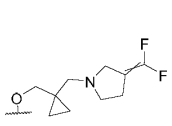


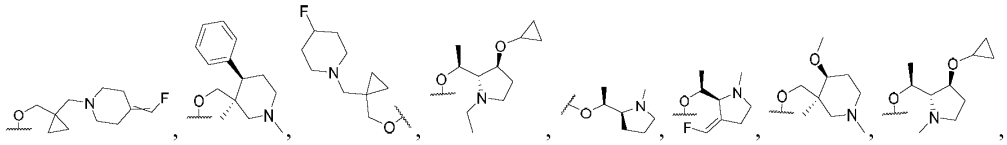
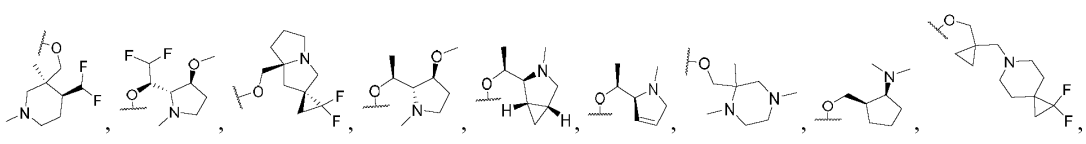
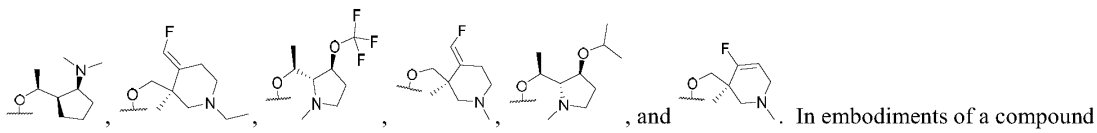
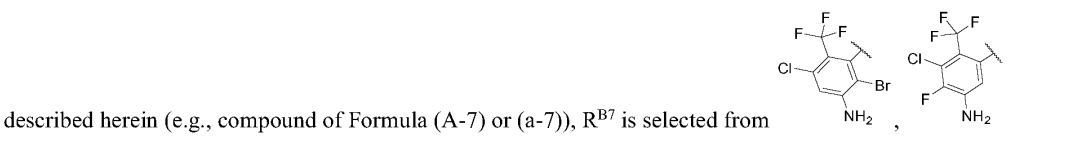
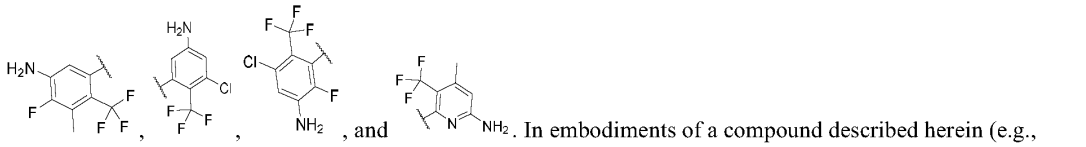
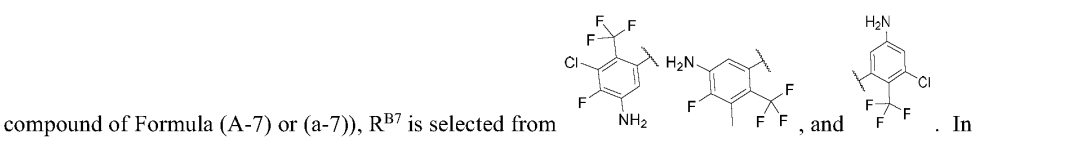
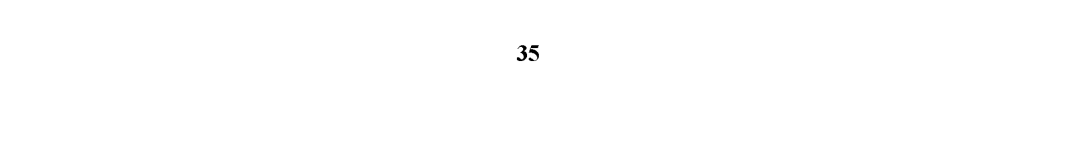
(A-7), wherein $-J^1-J^2-J^3-DG$ is  ; R^{B7} is selected from  ,  , and  ; and R^{B2} is selected from  , 









, and . In embodiments of a compound described herein (e.g., compound of Formula ((a0) and (a)), the compound has the formula:



(a-7); wherein -J^1-J^2-J^3-LG is  ; R^{B7} is selected from  ,

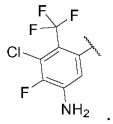
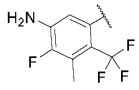
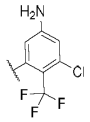
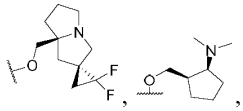
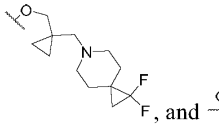
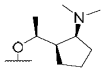
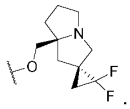
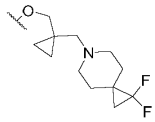
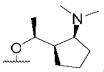







, and  ; and R^{B2} is selected from  ,

, and . In embodiments of a compound described herein (e.g., compound of Formula (A-7) or (a-7)), R^{B7} is selected from ,

, and . In embodiments of a compound described herein (e.g., compound of Formula (A-7) or (a-7)), R^{B7} is selected from

, and . In

embodiments of a compound described herein (e.g., compound of Formula (A-7) or (a-7)), R^{B7} is  . In embodiments of a compound described herein (e.g., compound of Formula (A-7) or (a-7)), R^{B7} is  . In embodiments of a compound described herein (e.g., compound of Formula (A-7) or (a-7)), R^{B7} is  . In embodiments of a compound described herein (e.g., compound of Formula (A-7) or (a-7)), R^{B2} is selected from  , ,  , and  . In embodiments of a compound described herein (e.g., compound of Formula (A-7) or (a-7)), R^{B2} is  . In embodiments of a compound described herein (e.g., compound of Formula (A-7) or (a-7)), R^{B2} is  . The compound, salt, solvate, or method of any one of claims 45 to 51, wherein R^{B2} is  . In embodiments of a compound described herein (e.g., Formula (A0), (A), (A1), (A-7) (a0), (a), (a1), or (a-7)), the compound is a compound selected from the compounds of Table 1.

[034] In an aspect is provided a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[035] In an aspect is provided a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof.

[036] In an aspect is provided a method of treating cancer in a subject comprising a Ras mutant protein, the method comprising: inhibiting the Ras mutant protein of said subject by administering to said subject a compound described herein, wherein the compound is characterized in that upon contacting the Ras mutant protein, said Ras mutant protein exhibits reduced Ras signaling output. In embodiments, the cancer is a solid tumor or a hematological cancer.

[037] In an aspect is provided a method of reducing signaling output of a Ras protein, comprising contacting a Ras protein with an effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, thereby reducing the signaling output of the Ras protein. In embodiments, the compound binds covalently or non-covalently to the Ras protein, thereby reducing the signaling output of the Ras protein.

[038] In an aspect is provided a method of inhibiting cell growth, comprising administering an effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, to a cell expressing a Ras protein, thereby inhibiting growth of said cells.

[039] In embodiments, a method described herein includes administering an additional agent. In embodiments,

the additional agent comprises (1) an inhibitor of MEK; (2) an inhibitor of epidermal growth factor receptor (EGFR) and/or mutants thereof; (3) an immunotherapeutic agent; (4) a taxane; (5) an anti-metabolite; (6) an inhibitor of FGFR1 and/or FGFR2 and/or FGFR3 and/or mutants thereof; (7) a mitotic kinase inhibitor; (8) an anti-angiogenic drug; (9) a topoisomerase inhibitor; (10) a platinum-containing compound; (11) an inhibitor of c-MET and/or mutants thereof; (12) an inhibitor of BCR-ABL and/or mutants thereof; (13) an inhibitor of ErbB2 (Her2) and/or mutants thereof; (14) an inhibitor of AXL and/or mutants thereof; (15) an inhibitor of NTRK1 and/or mutants thereof; (16) an inhibitor of RET and/or mutants thereof; (17) an inhibitor of A-Raf and/or B-Raf and/or C-Raf and/or mutants thereof; (18) an inhibitor of ERK and/or mutants thereof; (19) an MDM2 inhibitor; (20) an inhibitor of mTOR; (21) an inhibitor of IGF1/2 and/or IGF1-R; (22) an inhibitor of CDK9; (23) an inhibitor of farnesyl transferase; (24) an inhibitor of SHIP pathway; (25) an inhibitor of SRC; (26) an inhibitor of JAK; (27) a PARP inhibitor, (28) a ROS1 inhibitor; (29) an inhibitor of SHP pathway; (30) an inhibitor of Src, FLT3, HDAC, VEGFR, PDGFR, LCK, Bcr-Abl or AKT; (31) an inhibitor of KRAS G12C; (32) an SHC inhibitor; (33) a GAB inhibitor; (34) a PI-3 kinase inhibitor; (35) a MARPK inhibitor; (36) a CDK4/6 inhibitor; (37) a MAPK inhibitor; (38) a SHP2 inhibitor; (39) a checkpoint immune blockade agent; (40) a SOS1 inhibitor; or (41) a SOS2 inhibitor. In embodiments, the additional agent comprises an inhibitor of SHP2 selected RMC-4630, ERAS-601, TNO155, JAB-3068, IACS-13909/BBP-398, SHP099, and RMC-4550. In embodiments, the additional agent comprises an inhibitor of SOS selected from RMC-5845, BI-1701963, BI-3406, MRTX0902, and BAY-293.

INCORPORATION BY REFERENCE

[040] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[041] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[042] **FIG. 1** depicts a sequence alignment of various wild type Ras proteins including K-Ras, H-Ras, N-Ras, RalA, and RalB, from top to bottom.

DETAILED DESCRIPTION

[043] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs. In the event that there are a plurality of definitions for terms herein, those in this section prevail. All patents, patent applications, publications and published nucleotide and amino acid sequences (*e.g.*, sequences available in GenBank or other databases) referred to herein are incorporated by reference. Chemical structures are named herein according to IUPAC conventions as implemented in ChemDraw® software (Perkin Elmer, Inc., Cambridge, MA). The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. As used in the specification and claims, the singular forms "a", "an" and "the" include plural references unless the context clearly dictates otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes", and "included", is not limiting. The section headings used herein are for organizational

purposes only and are not to be construed as limiting the subject matter described.

[044] The term "C_{x-y}" or "C_x-C_y" when used in conjunction with a chemical moiety, such as alkyl, alkenyl, or alkynyl, is meant to include groups that contain from x to y carbons in the chain. For example, the term "C_{x-y} alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups, that contain from x to y carbons in the chain.

[045] "Alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including linear and branched alkyl groups. An alkyl group may contain from one to twelve carbon atoms (e.g., C_{1-12} alkyl), such as one to eight carbon atoms (C_{1-8} alkyl) or one to six carbon atoms (C_{1-6} alkyl). Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, septyl, octyl, nonyl, and decyl. An alkyl group is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more substituents such as those substituents described herein.

[046] "Haloalkyl" refers to an alkyl group that is substituted by one or more halogens. Exemplary haloalkyl groups include trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, and 1,2-dibromoethyl.

[047] "Alkenyl" refers to substituted or unsubstituted hydrocarbon groups, including linear and branched alkenyl groups, containing at least one double bond. An alkenyl group may contain from two to twelve carbon atoms (e.g., C_{2-12} alkenyl), such as two to eight carbon atoms (C_{2-8} alkenyl) or two to six carbon atoms (C_{2-6} alkenyl). Exemplary alkenyl groups include ethenyl (i.e., vinyl), prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more substituents such as those substituents described herein.

[048] "Alkynyl" refers to substituted or unsubstituted hydrocarbon groups, including linear and branched alkynyl groups, containing at least one triple bond. An alkynyl group may contain from two to twelve carbon atoms (e.g., C_{2-12} alkynyl), such as two to eight carbon atoms (C_{2-8} alkynyl) or two to six carbon atoms (C_{2-6} alkynyl). Exemplary alkynyl groups include ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more substituents such as those substituents described herein.

[049] "Alkylene" or "alkylene chain" refers to substituted or unsubstituted divalent saturated hydrocarbon groups, including linear alkylene and branched alkylene groups, that contain from one to twelve carbon atoms (e.g., C_{1-12} alkylene), such as one to eight carbon atoms (C_{1-8} alkylene) or one to six carbon atoms (C_{1-6} alkylene). Exemplary alkylene groups include methylene, ethylene, propylene, and n-butylene. Similarly, "alkenylene" and "alkynylene" refer to alkylene groups, as defined above, which comprise one or more carbon-carbon double or triple bonds, respectively. The points of attachment of the alkylene, alkenylene or alkynylene chain to the rest of the molecule can be through one carbon or any two carbons of the chain. Unless stated otherwise specifically in the specification, an alkylene, alkenylene, or alkynylene group is optionally substituted by one or more substituents such as those substituents described herein.

[050] "Heteroalkyl", "heteroalkenyl" and "heteroalkynyl" refer to substituted or unsubstituted alkyl, alkenyl and alkynyl groups, respectively, in which one or more, such as 1, 2 or 3, of the carbon atoms are replaced with a heteroatom, such as O, N, P, Si, S, or combinations thereof. Any nitrogen, phosphorus, and sulfur heteroatoms present in the chain may optionally be oxidized, and any nitrogen heteroatoms may optionally be quaternized. If given, a numerical range refers to the chain length in total. For example, a 3- to 8-membered heteroalkyl group has a

chain length of 3 to 8 atoms. Connection to the rest of the molecule may be through either a heteroatom or a carbon in the heteroalkyl, heteroalkenyl, or heteroalkynyl chain. Unless stated otherwise specifically in the specification, a heteroalkyl, heteroalkenyl, or heteroalkynyl group is optionally substituted by one or more substituents such as those substituents described herein.

[051] "Heteroalkylene", "heteroalkenylene" and "heteroalkynylene" refer to substituted or unsubstituted alkylene, alkenylene and alkynylene groups, respectively, in which one or more, such as 1, 2 or 3, of the carbon atoms are replaced with a heteroatom, such as O, N, P, Si, S, or combinations thereof. Any nitrogen, phosphorus, and sulfur heteroatoms present in the chain may optionally be oxidized, and any nitrogen heteroatoms may optionally be quaternized. If given, a numerical range refers to the chain length in total. For example, a 3- to 8-membered heteroalkylene group has a chain length of 3 to 8 atoms. The points of attachment of the heteroalkylene, heteroalkenylene or heteroalkynylene chain to the rest of the molecule can be through either one heteroatom or one carbon, or any two heteroatoms, any two carbons, or any one heteroatom and any one carbon in the heteroalkylene, heteroalkenylene or heteroalkynylene chain. Unless stated otherwise specifically in the specification, a heteroalkylene, heteroalkenylene, or heteroalkynylene group is optionally substituted by one or more substituents such as those substituents described herein.

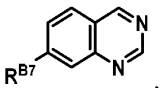
[052] "Carbocycle" refers to a saturated, unsaturated or aromatic ring in which each atom of the ring is a carbon atom. Carbocycle may include C_{3-10} monocyclic rings, C_{5-12} bicyclic rings, C_{5-18} polycyclic rings, C_{5-12} spirocyclic rings, and C_{5-12} bridged rings. Each ring of a bicyclic or polycyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. A polycyclic carbocycle contains a number or rings equal to the minimum number of scissions required to convert the carbocycle into an acyclic skeleton (e.g., bicyclic, tricyclic, tetracyclic, etc.). In some embodiments, the carbocycle is a C_{6-12} aryl group, such as C_{6-10} aryl. In some embodiments, the carbocycle is a C_{3-12} cycloalkyl group. In some embodiments, the carbocycle is a C_{5-12} cycloalkenyl group. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic rings, as valence permits, are included in the definition of carbocycle. A carbocycle may comprise a fused ring, a bridged ring, a spirocyclic ring, a saturated ring, an unsaturated ring, an aromatic ring, or any combination thereof. Exemplary carbocycles include cyclopentyl, cyclohexyl, cyclohexenyl, adamantly, phenyl, indanyl, and naphthyl. Unless state otherwise specifically in the specification, a carbocycle is optionally substituted by one or more substituents such as those substituents described herein.

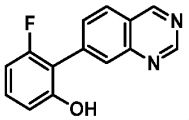
[053] "Heterocycle" refers to a saturated, unsaturated or aromatic ring comprising one or more heteroatoms, for example 1, 2, 3, or 4 heteroatoms selected from O, S, P, and N. Heterocycle may include 3- to 10-membered monocyclic rings, 5- to 12-membered bicyclic rings, 5- to 18-membered polycyclic rings, 5- to 12-membered spirocyclic rings, and 5- to 12-membered bridged rings. Each ring of a bicyclic or polycyclic heterocycle may be selected from saturated, unsaturated, and aromatic rings. A polycyclic heterocycle contains a number or rings equal to the minimum number of scissions required to convert the heterocycle into an acyclic skeleton (e.g., bicyclic, tricyclic, tetracyclic, etc.). The heterocycle may be attached to the rest of the molecule through any atom of the heterocycle, valence permitting, such as a carbon or nitrogen atom of the heterocycle. In some embodiments, the heterocycle is a 5- to 10-membered heteroaryl group, such as 5- or 6-membered heteroaryl. In some embodiments, the heterocycle is a 3- to 12-membered heterocycloalkyl group. A heterocycle may comprise a fused ring, a bridged ring, a spirocyclic ring, a saturated ring, an unsaturated ring, an aromatic ring, or any combination thereof. In an exemplary embodiment, a heterocycle, e.g., pyridyl, may be fused to a saturated or unsaturated ring, e.g.,

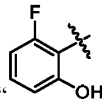
cyclohexane, cyclopentane, or cyclohexene. Exemplary heterocycles include pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, piperidinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiophenyl, oxazolyl, thiazolyl, morpholinyl, indazolyl, indolyl, benzothienyl, benzoxazolyl, and quinolinyl. Unless stated otherwise specifically in the specification, a heterocycle is optionally substituted by one or more substituents such as those substituents described herein.

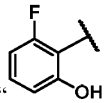
[054] "Heteroaryl" refers to an aromatic ring that comprises at least one heteroatom, for example 1, 2, 3, or 4 heteroatoms selected from O, S and N. Heteroaryl may include 5- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, 6- to 18-membered polycyclic rings, 5- to 12-membered spirocyclic rings, and 6- to 12-membered bridged rings. As used herein, the heteroaryl ring may be selected from monocyclic, bicyclic, or polycyclic—including fused, spirocyclic and bridged ring systems—wherein at least one of the rings in the ring system is aromatic and comprises at least one heteroatom. A polycyclic heteroaryl contains a number or rings equal to the minimum number of scissions required to convert the heteroaryl into an acyclic skeleton (e.g., bicyclic, tricyclic, tetracyclic, etc.). The heteroatom(s) in the heteroaryl may optionally be oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl may be attached to the rest of the molecule through any atom of the heteroaryl, valence permitting, such as a carbon or nitrogen atom of the heteroaryl. Examples of heteroaryl groups include, but are not limited to, azepinyl, benzimidazolyl, benzisothiazolyl, benzisoxazolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, furanyl, imidazolyl, indazolyl, indolyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, purinyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyridazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroquinolinyl, thiadiazolyl, thiazolyl, and thienyl groups. Unless stated otherwise specifically in the specification, a heteroaryl is optionally substituted by one or more substituents such as those substituents described herein.

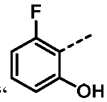
[055] Unless stated otherwise, hydrogen atoms are implied in structures depicted herein as necessary to satisfy the valence requirement.

[056] A waved line "〰" drawn across or at the end of a bond or a dashed bond "- - -" are used interchangeably herein to denote where a bond disconnection or attachment occurs. For example, in the structure 

, if R^{B7} is 2-fluoro-6-hydroxyphenyl as in 

, then R^{B7} may be depicted as " 

", " 

" or " 

".

[057] The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons or heteroatoms of the structure. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate

organic compounds. For purposes of this disclosure, heteroatoms such as nitrogen may have any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms.

[058] A compound disclosed herein, such as a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), is optionally substituted by one or more—such as 1, 2 or 3—substituents selected from:

halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two substituents attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein -C_{0-6} alkyl-(C_{3-12} carbocycle) and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl; and

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle.

[059] In some embodiments, a compound disclosed herein, such as a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), is optionally substituted by one or more—such as 1, 2 or 3—substituents selected from:

halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-}

$_{12}$ carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, and -$S(O)_2N(R^{B22})(R^{B23})$-, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, and =$C(R^{B21})_2$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein -C_{0-6} alkyl-(C_{3-12} carbocycle) and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle.

[060] In some embodiments, a compound disclosed herein, such as a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), is optionally substituted by one or more—such as 1, 2 or 3—substituents selected from halogen, oxo, =NH, -CN, -NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, -CH_2-(3- to 10-membered heterocycle), -OH, -OCH_3, -OCH_2CH_3, -NH_2, -$NHCH_3$, and -$NHCH_2CH_3$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, and -CH_2-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, -NO_2, -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -$C(CH_3)_3$, -OH, -OCH_3, -OCH_2CH_3, -NH_2, -$NHCH_3$, and -$NHCH_2CH_3$.

[061] It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as "unsubstituted", references to chemical moieties herein are understood to include substituted variants. For example, reference to a "heteroaryl" group or moiety implicitly includes both substituted and unsubstituted variants.

[062] Where bivalent substituent groups are specified herein by their conventional chemical formulae, written from left to right, they are intended to encompass the isomer that would result from writing the structure from right to left, e.g., -CH_2O- is also intended to encompass -OCH_2-.

[063] "Optional" or "optionally" means that the subsequently described event or circumstances may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, an "optionally substituted" group may be either unsubstituted or substituted.

[064] Compounds of the present disclosure also include crystalline and amorphous forms of those compounds, pharmaceutically acceptable salts, and active metabolites having the same type of activity, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, amorphous forms of the compounds, and mixtures thereof.

[065] The compounds described herein may exhibit their natural isotopic abundance, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure. For example, hydrogen has three naturally occurring isotopes, denoted ^{1}H (protium), ^{2}H (deuterium), and ^{3}H (tritium). Protium is the most abundant isotope of hydrogen in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increased in vivo half-life and/or exposure, or may provide a compound useful for investigating in vivo routes of drug elimination and metabolism. Examples of isotopes that may be incorporated into compounds of the present disclosure include, but are not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{36}Cl, and ^{18}F. Of particular interest are compounds of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) enriched in tritium or carbon-14, which can be used, for example, in tissue distribution studies; compounds of the disclosure enriched in deuterium—especially at a site of metabolism—resulting, for example, in compounds having greater metabolic stability; and compounds of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) enriched in a positron emitting isotope, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, which can be used, for example, in Positron Emission Topography (PET) studies. Isotopically-enriched compounds may be prepared by conventional techniques well known to those skilled in the art.

[066] As used herein, the phrase "of the formula", "having the formula" or "having the structure" is not intended to be limiting and is used in the same way that the term "comprising" is commonly used. For example, if one structure is depicted, it is understood that all stereoisomer and tautomer forms are encompassed, unless stated otherwise.

[067] Certain compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms, the asymmetric centers of which can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. In some embodiments, in order to optimize the therapeutic activity of the compounds of the disclosure, e.g., to treat cancer, it may be desirable that the carbon atoms have a particular configuration (e.g., (R,R), (S,S), (S,R), or (R,S)) or are enriched in a stereoisomeric form having such configuration. The compounds of the disclosure may be provided as racemic mixtures. Accordingly, the disclosure relates to racemic mixtures, pure stereoisomers (e.g., enantiomers and diastereomers), stereoisomer-enriched mixtures, and the like, unless otherwise indicated. When a chemical structure is depicted herein without any stereochemistry, it is understood that all possible stereoisomers are encompassed by such structure. Similarly, when a particular stereoisomer is shown or named herein, it will be understood by those skilled in the art that minor amounts of other stereoisomers may be present in the compositions of the disclosure unless otherwise indicated, provided that the utility of the composition as a whole is not eliminated by the presence of such other isomers. Individual stereoisomers may be obtained by numerous methods that are known in the art, including preparation using chiral synthons or chiral reagents, resolution using chiral chromatography using a suitable chiral stationary phase or support, or by chemically converting them into diastereomers, separating the diastereoisomers by conventional means such as chromatography or recrystallization, then regenerating the original stereoisomer.

[068] Additionally, where applicable, all *cis-trans* or *E/Z* isomers (geometric isomers), tautomeric forms and

topoisomeric forms of the compounds described herein are included with the scope of the disclosure unless otherwise specified.

[069] The term "pharmaceutically acceptable" refers to a material that is not biologically or otherwise unacceptable when used in the subject compositions and methods. For example, the term "pharmaceutically acceptable carrier" refers to a material—such as an adjuvant, excipient, glidant, sweetening agent, diluent, preservative, dye, colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent or emulsifier—that can be incorporated into a composition and administered to a patient without causing unacceptable biological effects or interacting in an unacceptable manner with other components of the composition. Such pharmaceutically acceptable materials typically have met the required standards of toxicological and manufacturing testing, and include those materials identified as suitable inactive ingredients by the U.S. Food and Drug Administration.

[070] The terms "salt" and "pharmaceutically acceptable salt" refer to a salt prepared from a base or an acid. Pharmaceutically acceptable salts are suitable for administration to a patient, such as a mammal (for example, salts having acceptable mammalian safety for a given dosage regime). Salts can be formed from inorganic bases, organic bases, inorganic acids and organic acids. In addition, when a compound contains both a basic moiety, such as an amine, pyridine or imidazole, and an acidic moiety, such as a carboxylic acid or tetrazole, zwitterions may be formed and are included within the term "salt" as used herein. Preferred pharmaceutically acceptable salts of the compounds described herein are pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

[071] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc., and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrates, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science,* 66:1-19 (1997)). Acid addition salts of basic compounds are, in some embodiments, prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

[072] "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Pharmaceutically acceptable base addition salts are, in some embodiments, formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron,

zinc, copper, manganese, aluminum salts and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chloroprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. See Berge et al., *supra*.

[073] The term "effective amount" or "therapeutically effective amount" refers to the amount of an agent that is sufficient to effect beneficial or desired results. The therapeutically effective amount may vary depending upon one or more of: the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. An effective amount of an active agent may be administered in a single dose or in multiple doses. A component may be described herein as having at least an effective amount, or at least an amount effective, such as that associated with a particular goal or purpose, such as any described herein. The term "effective amount" also applies to a dose that will provide an image for detection by an appropriate imaging method. The specific dose may vary depending on one or more of: the particular agent chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to be imaged, and the physical delivery system in which it is carried.

[074] As used herein, "treating" or "treatment" refers to an approach for obtaining beneficial or desired results with respect to a disease, disorder, or medical condition (such as cancer) in a subject, including but not limited to the following: (a) ameliorating the disease or medical condition, e.g., eliminating or causing regression of the disease or medical condition in a subject; (b) suppressing the disease or medical condition, e.g., slowing or arresting the development of the disease or medical condition in a subject; or (c) alleviating symptoms of the disease or medical condition in a subject. For example, "treating cancer" would include preventing cancer from reoccurring, ameliorating cancer, suppressing cancer, and alleviating the symptoms of cancer. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder.

[075] A "therapeutic effect", as that term is used herein, encompasses a therapeutic benefit and/or prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[076] The terms "antagonist" and "inhibitor" are used interchangeably, and they refer to a compound having the ability to inhibit a biological function (e.g., activity, expression, binding, protein-protein interaction) of a target protein (e.g., K-Ras). Accordingly, the terms "antagonist" and "inhibitor" are defined in the context of the biological role of the target protein. While preferred antagonists herein specifically interact with (e.g., bind to) the target, compounds that inhibit a biological activity of the target protein by interacting with other members of the signal transduction pathway of which the target protein is a member are also specifically included within this definition.

[077] The term "selective inhibition" or "selectively inhibit" refers to the ability of a biologically active agent to preferentially reduce the target signaling activity as compared to off-target signaling activity, via direct or indirect interaction with the target.

[078] The terms "subject" and "patient" refer to an animal, such as a mammal, for example a human. The methods described herein can be useful in both human therapeutics and veterinary applications. In some embodiments, the subject is a mammal, such as a human. "Mammal" includes humans and both domestic animals such as laboratory animals and household pets (e.g., cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

[079] The terms "therapeutic agent", "therapeutic capable agent" or "treatment agent" are used interchangeably and refer to a molecule or compound that confers some beneficial effect upon administration to a subject. The beneficial effect includes enablement of diagnostic determinations; amelioration of a disease, symptom, disorder, or pathological condition; reducing or preventing the onset of a disease, symptom, disorder or condition; and generally counteracting a disease, symptom, disorder or pathological condition.

[080] The terms "polypeptide", "peptide" and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation, such as conjugation with a labeling component. As used herein the term "amino acid" refers to either natural and/or unnatural or synthetic amino acids, including glycine and both the D or L optical isomers, and amino acid analogs and peptidomimetics.

[081] The terms "polynucleotide", "nucleotide sequence", "nucleic acid" and "oligonucleotide" are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Polynucleotides may have any three-dimensional structure, and may perform any function, known or unknown. The following are non-limiting examples of polynucleotides: coding or non-coding regions of a gene or gene fragment, loci (locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, short interfering RNA (siRNA), short-hairpin RNA (shRNA), micro-RNA (miRNA), ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. A polynucleotide may comprise one or more modified nucleotides, such as methylated nucleotides and nucleotide analogs, such as peptide nucleic acid (PNA), morpholino and locked nucleic acid (LNA), glycol nucleic acid (GNA), threose nucleic acid (TNA), 2'-fluoro, 2'-OMe, and phosphorothiolated DNA. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component or other conjugation target.

[082] As used herein, "expression" refers to the process by which a polynucleotide is transcribed from a DNA template (such as into an mRNA or other RNA transcript) and/or the process by which a transcribed mRNA is subsequently translated into peptides, polypeptides, or proteins. Transcripts and encoded polypeptides may be collectively referred to as "gene product." If the polynucleotide is derived from genomic DNA, expression may include splicing of the mRNA in a eukaryotic cell.

[083] An "antigen" is a moiety or molecule that contains an epitope, and, as such, also specifically binds to an antibody. An "antigen binding unit" may be whole or a fragment (or fragments) of a full-length antibody, a structural variant thereof, a functional variant thereof, or a combination thereof. A full-length antibody may be, for example, a monoclonal, recombinant, chimeric, deimmunized, humanized and human antibody. Examples of a fragment of a full-length antibody may include, but are not limited to, variable heavy (VH), variable light (VL), a

heavy chain found in camelids, such as camels, llamas, and alpacas (VHH or V_HH), a heavy chain found in sharks (V-NAR domain), a single domain antibody (sdAb, e.g., "nanobody") that comprises a single antigen-binding domain, Fv, Fd, Fab, Fab', F(ab')2, and "r IgG" (or half antibody). Examples of modified fragments of antibodies may include, but are not limited to scFv, di-scFv or bi(s)-scFv, scFv-Fc, scFv-zipper, scFab, Fab2, Fab3, diabodies, single chain diabodies, tandem diabodies (Tandab's), tandem di-scFv, tandem tri-scFv, minibodies (e.g., (VH-VL-CH3)2, (scFv-CH3)2, ((scFv)2-CH3+CH3), ((scFv)2-CH3) or (scFv-CH3-scFv)2), and multibodies (e.g., triabodies or tetrabodies).

[084] The term "antibody" and "antibodies" encompass any antigen binding units, including without limitation: monoclonal antibodies, human antibodies, humanized antibodies, camelised antibodies, chimeric antibodies, and any other epitope-binding fragments.

[085] "Prodrug" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein (e.g., a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)). Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. In some aspects, a prodrug is inactive when administered to a subject but is converted in vivo to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, e.g., Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam); Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," (1987) A.C.S. Symposium Series, Vol. 14; and Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press each of which is incorporated in full by reference herein). The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound in vivo when such prodrug is administered to a mammalian subject. Prodrugs of an active compound, as described herein, are typically prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of a hydroxy functional group, or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound, and the like.

[086] The term "in vivo" refers to an event that takes place in a subject's body. The term "ex vivo" refers to an event that first takes place outside of the subject's body for a subsequent in vivo application into a subject's body. For example, an ex vivo preparation may involve preparation of cells outside of a subject's body for the purpose of introduction of the prepared cells into the same or a different subject's body. The term "in vitro" refers to an event that takes place outside of a subject's body. For example, an in vitro assay encompasses any assay run outside of a subject's body. In vitro assays encompass cell-based assays in which cells alive or dead are employed. In vitro assays also encompass a cell-free assay in which no intact cells are employed.

[087] The disclosure is also meant to encompass the in vivo metabolic products of the disclosed compounds. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the disclosure includes compounds produced by a process comprising administering a compound disclosed herein to a mammal for a period

of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabeled compound of the disclosure in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to a human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

[088] The term "Ras" or "RAS" refers to a protein in the Rat sarcoma (Ras) superfamily of small GTPases, such as in the Ras subfamily. The Ras superfamily includes, but is not limited to, the Ras subfamily, Rho subfamily, Rab subfamily, Rap subfamily, Arf subfamily, Ran subfamily, Rheb subfamily, RGK subfamily, Rit subfamily, Miro subfamily, and Unclassified subfamily. In some embodiments, a Ras protein is selected from the group consisting of KRAS (also used interchangeably herein as K-Ras, K-ras, or Kras), HRAS (or H-Ras), NRAS (or N-Ras), MRAS (or M-Ras), ERAS (or E-Ras), RRAS2 (or R-Ras2), RALA (or RalA), RALB (or RalB), RIT1, and any combination thereof, such as from KRAS, HRAS, NRAS, RALA, RALB, and any combination thereof.

[089] The terms "mutant Ras" and "Ras mutant", as used interchangeably herein, refer to a Ras protein with one or more amino acid mutations, such as with respect to a common reference sequence such as a wild-type (WT) sequence. In some embodiments, a mutant Ras is selected from a mutant KRAS, mutant HRAS, mutant NRAS, mutant MRAS, mutant ERAS, mutant RRAS2, mutant RALA, mutant RALB, mutant RIT1, and any combination thereof, such as from a mutant KRAS, mutant HRAS, mutant NRAS, mutant RALA, mutant RALB, and any combination thereof. In some embodiments, a mutation can be an introduced mutation, a naturally occurring mutation, or a non-naturally occurring mutation. In some embodiments, a mutation can be a substitution (e.g., a substituted amino acid), insertion (e.g., addition of one or more amino acids), or deletion (e.g., removal of one or more amino acids). In some embodiments, two or more mutations can be consecutive, non-consecutive, or a combination thereof. In some embodiments, a mutation can be present at any position of Ras. In some embodiments, a mutation can be present at position 12, 13, 62, 92, 95, 96 (e.g., Y96D), or any combination thereof of Ras relative to SEQ ID No. 1 when optimally aligned. In some embodiments, a mutant Ras may comprise about or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, or more than 50 mutations. In some embodiments, a mutant Ras may comprise up to about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, or 50 mutations. In some embodiments, the mutant Ras is about or up to about 500, 400, 300, 250, 240, 233, 230, 220, 219, 210, 208, 206, 204, 200, 195, 190, 189, 188, 187, 186, 185, 180, 175, 174, 173, 172, 171, 170, 169, 168, 167, 166, 165, 160, 155, 150, 125, 100, 90, 80, 70, 60, 50, or fewer than 50 amino acids in length. In some embodiments, an amino acid of a mutation is a proteinogenic, natural, standard, non-standard, non-canonical, essential, non-essential, or non-natural amino acid. In some embodiments, an amino acid of a mutation has a positively charged side chain, a negatively charged side chain, a polar uncharged side chain, a non-polar side chain, a hydrophobic side chain, a hydrophilic side chain, an aliphatic side chain, an aromatic side chain, a cyclic side chain, an acyclic side chain, a basic side chain, or an acidic side chain. In some embodiments, a mutation comprises a reactive moiety. In some embodiments, a substituted amino acid comprises a reactive moiety. In some embodiments, a mutant Ras can be further modified, such as by conjugation with a detectable label. In some embodiments, a mutant Ras is a full-length or truncated polypeptide. For example, a mutant Ras can be a truncated polypeptide comprising residues 1-169 or residues 11-183 (e.g., residues 11-183 of a mutant RALA or mutant RALB).

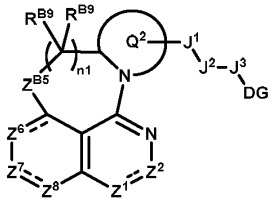
[090] As used herein, the term "corresponding to" or "corresponds to" as applied to an amino acid residue in a polypeptide sequence refers to the correspondence of such amino acid relative to a reference sequence when optimally aligned (e.g., taking into consideration of gaps, insertions and mismatches; wherein alignment may be

primary sequence alignment or three-dimensional structural alignment of the folded proteins). For instance, the serine residue in a K-Ras G12S mutant refers to the serine corresponding to residue 12 of SEQ ID No. 4, which can serve as a reference sequence. For instance, the aspartate residue in a K-Ras G12D mutant refers to the aspartate corresponding to residue 12 of SEQ ID No. 2, which can serve as a reference sequence. When an amino acid of a mutant Ras protein corresponds to an amino acid position in the WT Ras protein, it will be understood that although the mutant Ras protein amino acid may be a different amino acid (e.g., G12D, wherein the wildtype G at position 12 is replaced by an aspartate at position 12 of SEQ ID. No. 1), the mutant amino acid is at the position corresponding to the wildtype amino acid (e.g., of SEQ ID No. 1). In embodiments, a modified Ras mutant protein disclosed herein may comprise truncations at the C-terminus, or truncations at the N-terminal end preceding the serine residue. The serine residue in such N-terminal truncated modified mutant is still considered corresponding to position 12 of SEQ ID No. 1. In addition, an aspartate residue at position 12 of SEQ ID No. 2 finds a corresponding residue in SEQ ID Nos. 6 and 8.

[091] A "degradation enhancer" is a compound capable of binding a ubiquitin ligase protein (e.g., E3 ubiquitin ligase protein) or a compound capable of binding a protein that is capable of binding to a ubiquitin ligase protein to form a protein complex capable of conjugating a ubiquitin protein to a target protein. In some embodiments, the degradation enhancer is capable of binding to an E3 ubiquitin ligase protein or a protein complex comprising an E3 ubiquitin ligase protein. In some embodiments, the degradation enhancer is capable of binding to an E2 ubiquitin-conjugating enzyme. In some embodiments, the degradation enhancer is capable of binding to a protein complex comprising an E2 ubiquitin-conjugating enzyme and an E3 ubiquitin ligase protein.

Methods of Preparing Degrader Compounds

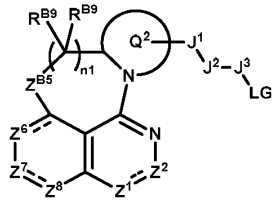
[092] In an aspect is provided a method of preparing a compound of Formula (A0):



(A0),

the method comprising:

(a) reacting a compound of Formula (a0):



(a0),

with a degradation enhancer under conditions to effect release of LG and production of the compound of Formula (A0), wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^{B5} is selected from $C(R^{B9})_2$ and O;

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})-$, -C(O)-, $-N(R^{B12})C(O)-$, $-C(O)N(R^{B12})-$, -S-, $-S(O)_2-$, -S(O)-, $-P(O)R^{B12}-$, $-N(R^{B12})S(O)_2-$, $-N(R^{B12})S(O)-$, $-N(R^{B12})P(O)R^{B12}-$, $-S(O)_2N(R^{B12})-$, $-S(O)N(R^{B12})-$, $-P(O)R^{B12}N(R^{B12})-$, $-OS(O)_2-$, -OS(O)-, $-OP(O)R^{B12}-$, $-S(O)_2O-$, -S(O)O-, and $-P(O)R^{B12}O-$, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

LG is a leaving group;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-OR^{B12}$, $-SR^{B12}$, $-N(R^{B12})(R^{B13})$, $-C(O)OR^{B12}$, $-OC(O)N(R^{B12})(R^{B13})$, $-N(R^{B12})C(O)N(R^{B12})(R^{B13})$, $-N(R^{B12})C(O)OR^{B12}$, $-N(R^{B12})S(O)_2R^{B12}$, $-C(O)R^{B12}$, $-S(O)R^{B12}$, $-OC(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-N(R^{B12})C(O)R^{B12}$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

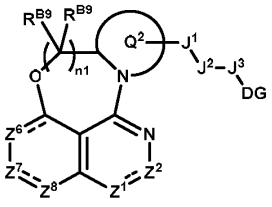
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

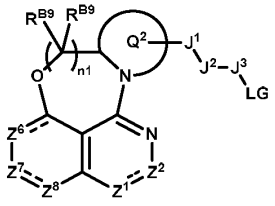
[093] In an aspect is provided a method of preparing a compound of Formula (A):



(A),

the method comprising:

(a) reacting a compound of Formula (a):



(a),

with a degradation enhancer under conditions to effect release of LG and production of the compound of Formula (A), wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

LG is a leaving group;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$

alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is

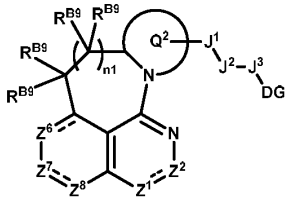
optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

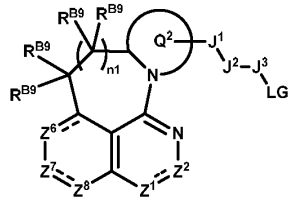
[094] In an aspect is provided a method of preparing a compound of Formula (A1):



(A1),

the method comprising:

(a) reacting a compound of Formula (a1):



(a1),

with a degradation enhancer under conditions to effect release of LG and production of the compound of Formula (A1), wherein:

Z^1 is selected from N and N(R^{B1b});

Z^2 is selected from C(R^{B2}) and C(O);

Z^6 is selected from C(R^{B6}), C(R^{B6})$_2$, N, and N(R^{B6b});

Z^7 is selected from C(R^{B7}) and N(R^{B7b});

Z^8 is selected from C(R^{B8}), C(R^{B8})$_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -N(R^{B12})-, -C(O)-, -N(R^{B12})C(O)-, -C(O)N(R^{B12})-, -S-, -S(O)$_2$-, -S(O)-, -P(O)R^{B12}-, -N(R^{B12})S(O)$_2$-, -N(R^{B12})S(O)-, -N(R^{B12})P(O)R^{B12}-, -S(O)$_2$N(R^{B12})-, -S(O)N(R^{B12})-, -P(O)R^{B12}N(R^{B12})-, -OS(O)$_2$-, -OS(O)-, -OP(O)R^{B12}-, -S(O)$_2$O-, -S(O)O-, and -P(O)R^{B12}O-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

LG is a leaving group;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -C(O)OR^{B12}, -C(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -S(O)$_2R^{B12}$, -S(O)(NR^{B12})R^{B12}, -S(O)$_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -N(R^{B12})(R^{B13}), -C(O)OR^{B12}, -OC(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)OR^{B12}, -N(R^{B12})S(O)$_2R^{B12}$, -C(O)R^{B12}, -S(O)R^{B12}, -OC(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)R^{B12}, -S(O)$_2R^{B12}$, -S(O)(NR^{B12})R^{B12}, -S(O)$_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), =NR^{B22}, =C(R^{B21})$_2$, -C(O)OR^{B22}, -OC(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)OR^{B22}, -N(R^{B22})S(O)$_2R^{B22}$, -C(O)R^{B22}, -S(O)R^{B22}, -OC(O)R^{B22}, -C(O)N(R^{B22})(R^{B23}), -C(O)C(O)N(R^{B22})(R^{B23}), -

$N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$-, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

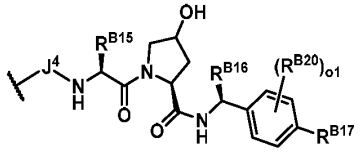
R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

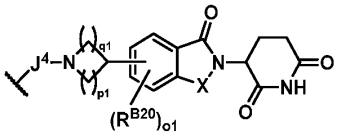
------ indicates a single or double bond such that all valences are satisfied.

[095] In embodiments of the method of preparing a compound of Formula (A0), (A), and/or (A1), the reaction mixture comprises a base. In embodiments of the method of preparing a compound of Formula (A0), (A), and/or (A1), the reaction mixture comprises 5- to 12-equivalents of the base relative to the amount of degradation enhancer. In embodiments of the method of preparing a compound of Formula (A0), (A), and/or (A1), the base is *N*,*N*-diisopropylethylamine. In embodiments of the method of preparing a compound of Formula (A0), (A), and/or (A1), the compound of Formula (a0), (a), and/or (a1) and the degradation enhancer are heated to 40 to 100 °C for 2 to 48 hours. In embodiments of the method of preparing a compound of Formula (A0), (A), and/or (A1), the method further comprises (b) purifying the compound of Formula (A0), (A), and/or (A1). In embodiments of the method of preparing a compound of Formula (A0), (A), and/or (A1), the method may include the preparation of any embodiment of the compound of Formula (A0), (A), and/or (A1), including preparation of a compound of Formula (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), or any embodiment thereof. In embodiments of the method of preparing a compound of Formula (A0), (A), and/or (A1), the method may include the use of any embodiment of the compound of Formula (a0), (a), and/or (a1) including the use of a compound of Formula (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), or any embodiment thereof.

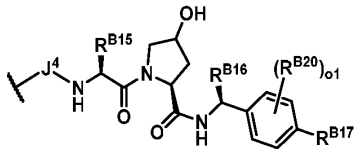
[096] In embodiments of the method of preparing a compound of Formula (A0), (A), and/or (A1), the degradation enhancer is selected from:



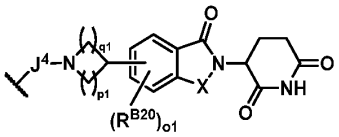
and



; wherein J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O). In embodiments of the method of preparing a compound of Formula (A0), (A), and/or (A1), DG is selected from



and

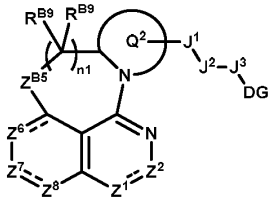


; wherein J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O). In embodiments of the method of preparing a compound of Formula (A0), (A), and/or (A1), LG is selected from -Cl, -Br, -I, -OBt, $-OS(O)_2R^{B4}$ and $-OS(O)(NR^{B4b})R^{B4}$; R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and $-N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20}; R^{B4b} is selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and -

$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20}; and $R^{B12})(R^{B13})$, and R^{B20} are as described for a compound of Formula (a0), (a), and/or (a1) or embodiments thereof. The term "-OBt" is -O-benzotriazole.

Compounds

[097] In an aspect is provided a compound of Formula (A0):



(A0),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^{B5} is selected from $C(R^{B9})_2$ and O;

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -C(O)OR^{B12}, -C(O)R^{B12}, -C(O)$N(R^{B12})(R^{B13})$, -C(O)C(O)$N(R^{B12})(R^{B13})$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -S(=O)(=$NR^{B12}$)$N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -C(O)OR^{B12}, -OC(O)$N(R^{B12})(R^{B13})$, -$N(R^{B12})$C(O)$N(R^{B12})(R^{B13})$, -$N(R^{B12})$C(O)OR^{B12}, -$N(R^{B12})S(O)_2R^{B12}$, -C(O)R^{B12}, -S(O)R^{B12}, -OC(O)R^{B12}, -C(O)$N(R^{B12})(R^{B13})$, -C(O)C(O)$N(R^{B12})(R^{B13})$, -$N(R^{B12})$C(O)R^{B12}, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -S(=O)(=$NR^{B12}$)$N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -C(O)OR^{B22}, -OC(O)$N(R^{B22})(R^{B23})$, -$N(R^{B22})$C(O)$N(R^{B22})(R^{B23})$, -$N(R^{B22})$C(O)OR^{B22}, -$N(R^{B22})S(O)_2R^{B22}$, -C(O)R^{B22}, -S(O)R^{B22}, -OC(O)R^{B22}, -C(O)$N(R^{B22})(R^{B23})$, -C(O)C(O)$N(R^{B22})(R^{B23})$, -$N(R^{B22})$C(O)R^{B22}, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -S(=O)(=$NR^{B22}$)$N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -C(O)OR^{B22}, -OC(O)$N(R^{B22})(R^{B23})$, -

$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

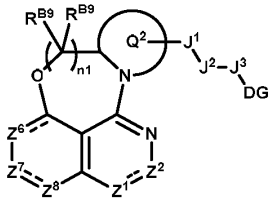
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[098] In an aspect is provided a compound of Formula (A):



(A),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered

heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -C(O)OR^{B12}, -C(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -S(O)$_2$$R^{B12}$, -S(O)(N$R^{B12}$)$R^{B12}$, -S(O)$_2$N($R^{B12}$)($R^{B13}$), and -S(=O)(=N$R^{B12}$)N($R^{B12}$)($R^{B13}$), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -N(R^{B12})(R^{B13}), -C(O)OR^{B12}, -OC(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)OR^{B12}, -N(R^{B12})S(O)$_2$$R^{B12}$, -C(O)$R^{B12}$, -S(O)$R^{B12}$, -OC(O)$R^{B12}$, -C(O)N($R^{B12}$)($R^{B13}$), -C(O)C(O)N($R^{B12}$)($R^{B13}$), -N($R^{B12}$)C(O)$R^{B12}$, -S(O)$_2$$R^{B12}$, -S(O)(N$R^{B12}$)$R^{B12}$, -S(O)$_2$N($R^{B12}$)($R^{B13}$), and -S(=O)(=N$R^{B12}$)N($R^{B12}$)($R^{B13}$), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), =NR^{B22}, =C(R^{B21})$_2$, -C(O)OR^{B22}, -OC(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)OR^{B22}, -N(R^{B22})S(O)$_2$$R^{B22}$, -C(O)$R^{B22}$, -S(O)$R^{B22}$, -OC(O)$R^{B22}$, -C(O)N($R^{B22}$)($R^{B23}$), -C(O)C(O)N($R^{B22}$)($R^{B23}$), -N($R^{B22}$)C(O)$R^{B22}$, -S(O)$_2$$R^{B22}$, -S(O)(N$R^{B22}$)$R^{B22}$, -S(O)$_2$N($R^{B22}$)($R^{B23}$)-, and -S(=O)(=N$R^{B22}$)N($R^{B22}$)($R^{B23}$); wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-}

$_{12}$ carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

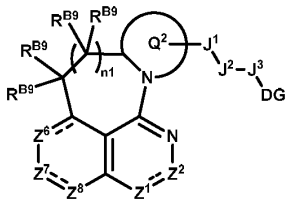
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[099] In an aspect is provided a compound of Formula (A1):



(A1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -$N(R^{B12})$-, -C(O)-, -$N(R^{B12})C(O)$-, -$C(O)N(R^{B12})$-, -S-, -$S(O)_2$-, -S(O)-, -$P(O)R^{B12}$-, -$N(R^{B12})S(O)_2$-, -$N(R^{B12})S(O)$-, -$N(R^{B12})P(O)R^{B12}$-, -$S(O)_2N(R^{B12})$-, -$S(O)N(R^{B12})$-, -$P(O)R^{B12}N(R^{B12})$-, -$OS(O)_2$-, -OS(O)-, -$OP(O)R^{B12}$-, -$S(O)_2O$-, -S(O)O-, and -$P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered

heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -C(O)OR^{B12}, -C(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -S(O)$_2R^{B12}$, -S(O)(NR^{B12})R^{B12}, -S(O)$_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -N(R^{B12})(R^{B13}), -C(O)OR^{B12}, -OC(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)OR^{B12}, -N(R^{B12})S(O)$_2R^{B12}$, -C(O)R^{B12}, -S(O)R^{B12}, -OC(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)R^{B12}, -S(O)$_2R^{B12}$, -S(O)(NR^{B12})R^{B12}, -S(O)$_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), =NR^{B22}, =C(R^{B21})$_2$, -C(O)OR^{B22}, -OC(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)OR^{B22}, -N(R^{B22})S(O)$_2R^{B22}$, -C(O)R^{B22}, -S(O)R^{B22}, -OC(O)R^{B22}, -C(O)N(R^{B22})(R^{B23}), -C(O)C(O)N(R^{B22})(R^{B23}), -

$N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$-, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle);

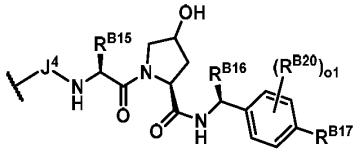
R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

$\overset{\text{------}}{=}$ indicates a single or double bond such that all valences are satisfied.

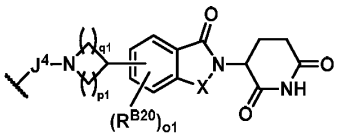
[100] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a salt or solvate thereof, the degradation enhancer is capable of binding a protein selected from E3A, mdm2, APC, EDD1, SOCS/BC-box/eloBC/CUL5/RING, LNXp80, CBX4, CBLL1, HACE1, HECTD1, HECTD2, HECTD3, HECTD4, HECW1, HECW2, HERC1, HERC2, HERC3, HERC4, HER5, HERC6, HUWE1, ITCH, NEDD4, NEDD4L, PPIL2, PRPF19, PIAS1, PIAS2, PIAS3, PIAS4, RANBP2, RNF4, RBX1, SMURF1, SMURF2, STUB1, TOPORS, TRIP12, UBE3A, UBE3B, UBE3C, UBE3D, UBE4A, UBE4B, UBOX5, UBR5, VHL (von-Hippel-Lindau ubiquitin ligase), WWP1, WWP2, Parkin, MKRN1, CMA (chaperon-mediated autophage), SCFb-TRCP (Skip-Cullin-F box (Beta-TRCP) ubiquitin complex), b-TRCP (b-transducing repeat-containing protein), cIAP1 (cellular inhibitor of apoptosis protein 1), APC/C (anaphase-promoting complex/cyclosome), CRBN (cereblon), CUL4-RBX1-DDB1-CRBN ($CRL4^{CRBN}$) ubiquitin ligase, XIAP, IAP, KEAP1, DCAF15, RNF114, DCAF16, AhR, SOCS2, KLHL12, UBR2, SPOP, KLHL3, KLHL20, KLHDC2, SPSB1, SPSB2, SPSB4, SOCS6, FBXO4, FBXO31, BTRC, FBW7, CDC20, PML, TRIM21, TRIM24, TRIM33, GID4, avadomide, iberdomide, and CC-885.

[101] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a salt or solvate thereof, the degradation enhancer is capable of binding a protein selected from UBE2A, UBE2B, UBE2C, UBE2D1, UBE2D2, UBE2D3, UBE2DR, UBE2E1, UBE2E2, UBE2E3, UBE2F, UBE2G1, UBE2G2, UBE2H, UBE2I, UBE2J1, UBE2J2, UBE2K, UBE2L3, UBE2L6, UBE2L1, UBE2L2, UBE2L4, UBE2M, UBE2N, UBE2O, UBE2Q1, UBE2Q2, UBE2R1, UBE2R2, UBE2S, UBE2T, UBE2U, UBE2V1, UBE2V2, UBE2W, UBE2Z, ATG3, BIRC6, and UFC1.

[102] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a

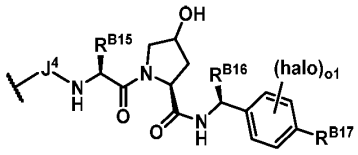


salt or solvate thereof, DG is selected from:

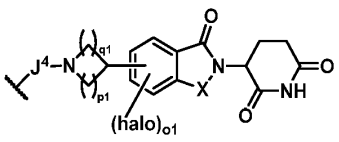


; wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O).

[103] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a

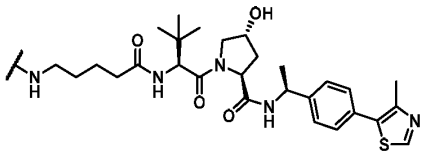


salt or solvate thereof, DG is selected from:

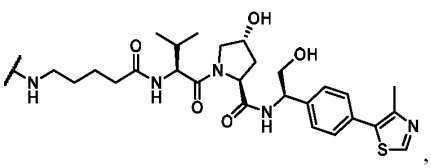


; wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from $-CH(CH_3)_2$ and $-C(CH_3)_3$; R^{B16} is selected from hydrogen, $-CH_3$, and $-CH_2OH$; R^{B17} is selected from methylthiazole and methylpyrazole; o1 is selected from 0 and 1; p1 and q1 are independently selected from 1 and 2; and X is selected from CH_2 and C(O).

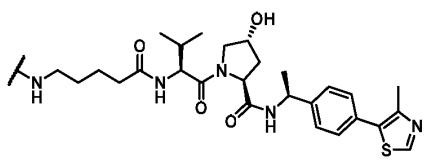
[104] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a



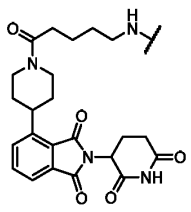
salt or solvate thereof, DG is selected from:



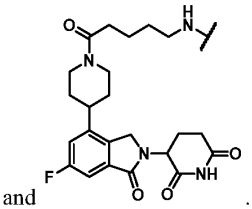
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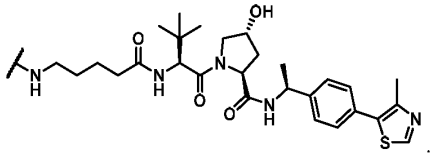
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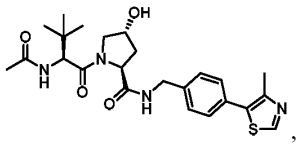
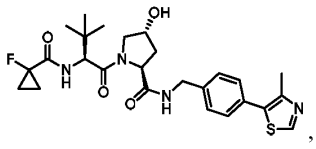
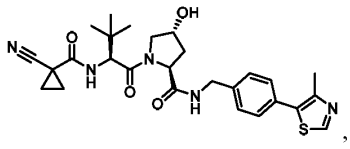
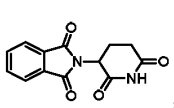
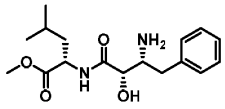
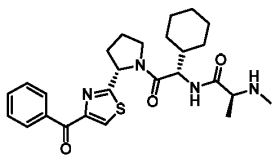
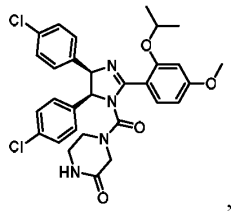
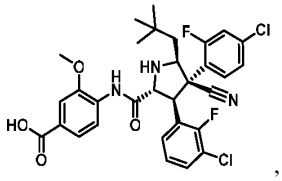
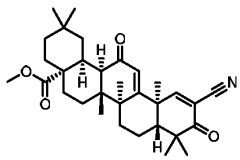
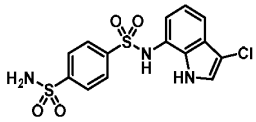
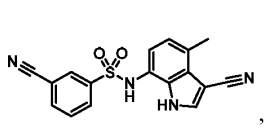
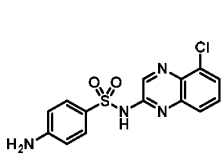
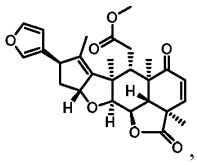
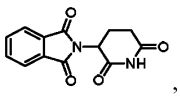
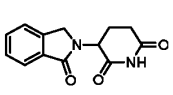
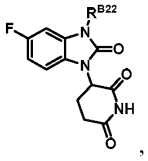
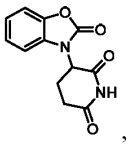
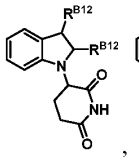
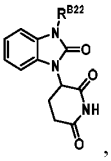
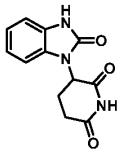
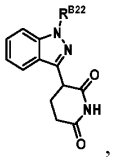
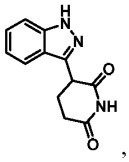
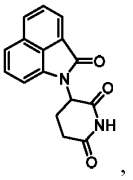
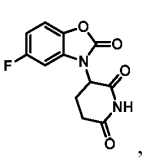
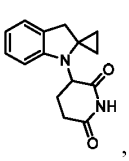
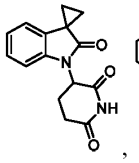
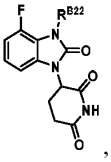
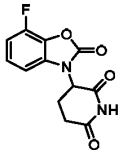
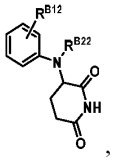
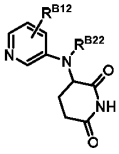
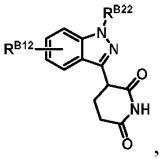
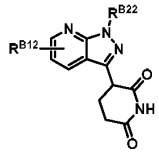
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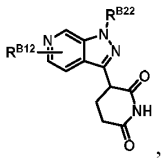
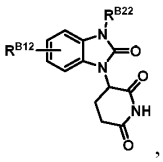
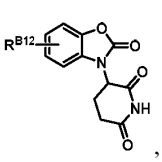
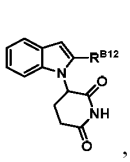
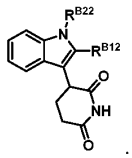


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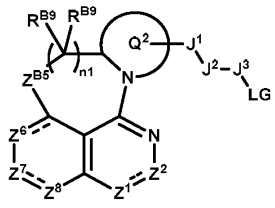
[105] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a salt or solvate thereof, DG is  .

[106] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), and/or (A1)), or a salt or solvate thereof, DG comprises a monovalent form of a compound selected from

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[107] In an aspect is provided a compound of Formula (a0):


(a0),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^{B5} is selected from $C(R^{B9})_2$ and O;

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

LG is selected from $-OS(O)_2R^{B4}$ and $-OS(O)(NR^{B4b})R^{B4}$;

n1 is selected from 1, 2, and 3;

R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and $-N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered

heterocycle) are optionally substituted with one or more R^{B20};

R^{B1b}, R^{B4b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -$C(O)OR^{B12}$, -$C(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more

substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

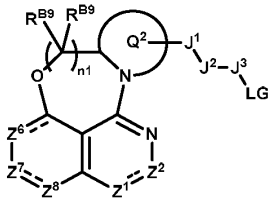
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[108] In an aspect is provided a compound of Formula (a):



(a),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to

6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

LG is selected from -$OS(O)_2R^{B4}$ and -$OS(O)(NR^{B4b})R^{B4}$;

n1 is selected from 1, 2, and 3;

R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and -$N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B1b}, R^{B4b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -$C(O)OR^{B12}$, -$C(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6}

alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

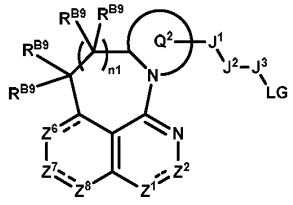
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

[109] In an aspect is provided a compound of Formula (a1):



(a1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -$N(R^{B12})$-, -C(O)-, -$N(R^{B12})C(O)$-, -$C(O)N(R^{B12})$-, -S-, -$S(O)_2$-, -S(O)-, -$P(O)R^{B12}$-, -$N(R^{B12})S(O)_2$-, -$N(R^{B12})S(O)$-, -$N(R^{B12})P(O)R^{B12}$-, -

$S(O)_2N(R^{B12})$-, -$S(O)N(R^{B12})$-, -$P(O)R^{B12}N(R^{B12})$-, -$OS(O)_2$-, -OS(O)-, -$OP(O)R^{B12}$-, -$S(O)_2O$-, -S(O)O-, and -$P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

LG is selected from -$OS(O)_2R^{B4}$ and -$OS(O)(NR^{B4b})R^{B4}$;

n1 is selected from 1, 2, and 3;

R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and -$N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B1b}, R^{B4b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -$C(O)OR^{B12}$, -$C(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

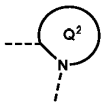
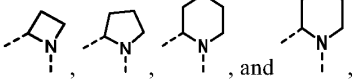
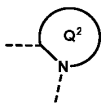
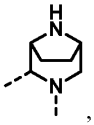
R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

$\overset{\text{------}}{=}$ indicates a single or double bond such that all valences are satisfied.

[110] In embodiments of a compound described herein (e.g., compound of Formula (a0), (a), and/or (a1)), or a salt or solvate thereof, LG is -$OS(O)_2R^{B4}$.

[111] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, n1 is 1. In embodiments, n1 is 2. In embodiments, n1 is 3. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, Q^2 is 4- to 6-membered monocyclic heterocycloalkyl optionally substituted with one or

more R^{B20}. In embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof,  is selected from  , each of which is optionally substituted with one or more R^{B20}. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof,  is  , each of which is optionally substituted with one or more R^{B20}.

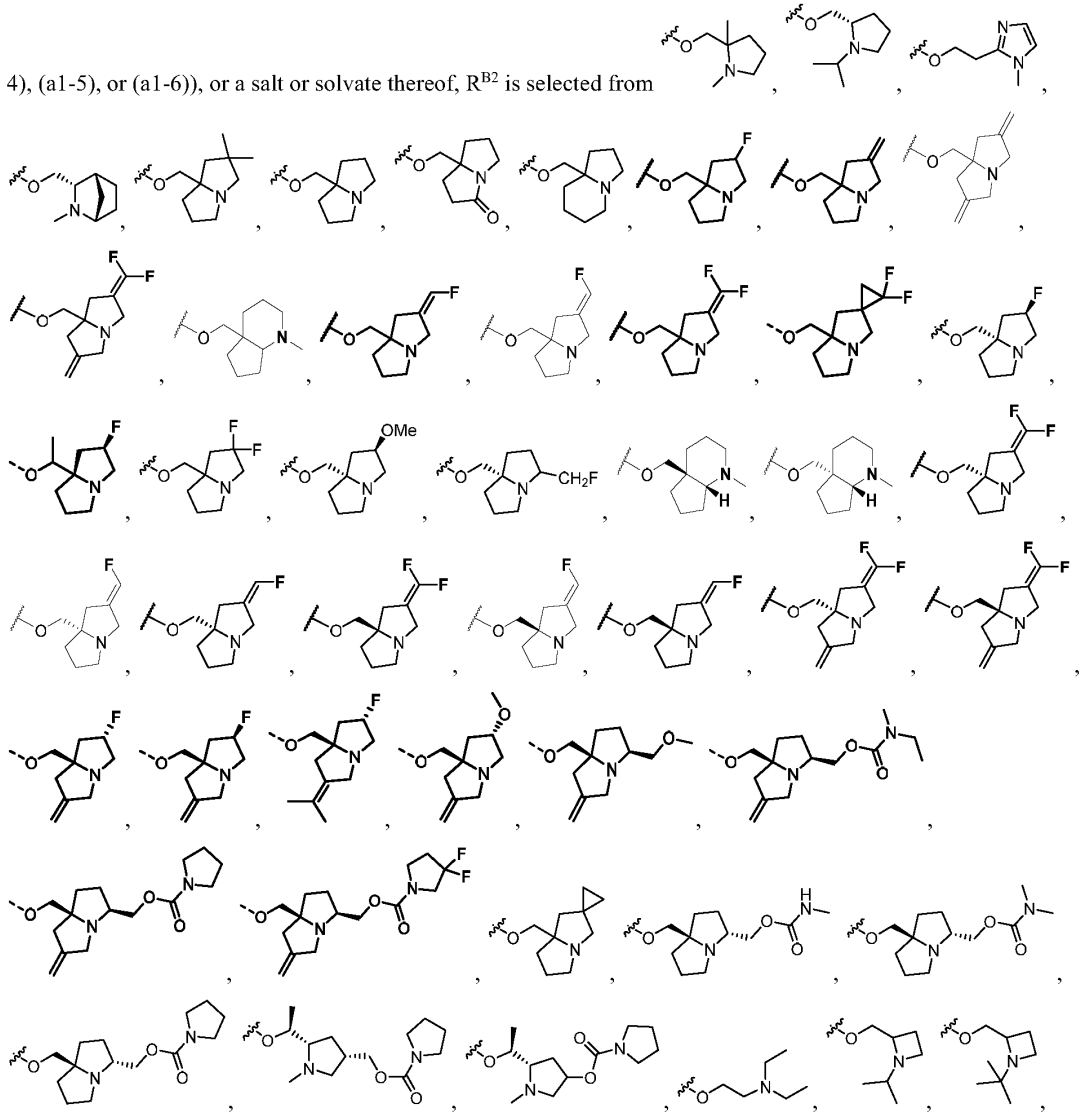
[112] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1)), or a salt or solvate thereof, Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$; Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is N, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$; Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})_2$, Z^7 is $N(R^{B7b})$, and Z^8 is $C(R^{B8})_2$; or Z^1 is $N(R^{B1b})$, Z^2 is C(O), Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is N. In embodiments of a compound described herein (e.g., compound of Formula (a)), or a salt or solvate thereof, Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$. In embodiments of a compound described herein (e.g., compound of Formula (a)), or a salt or solvate thereof, Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is N, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$.

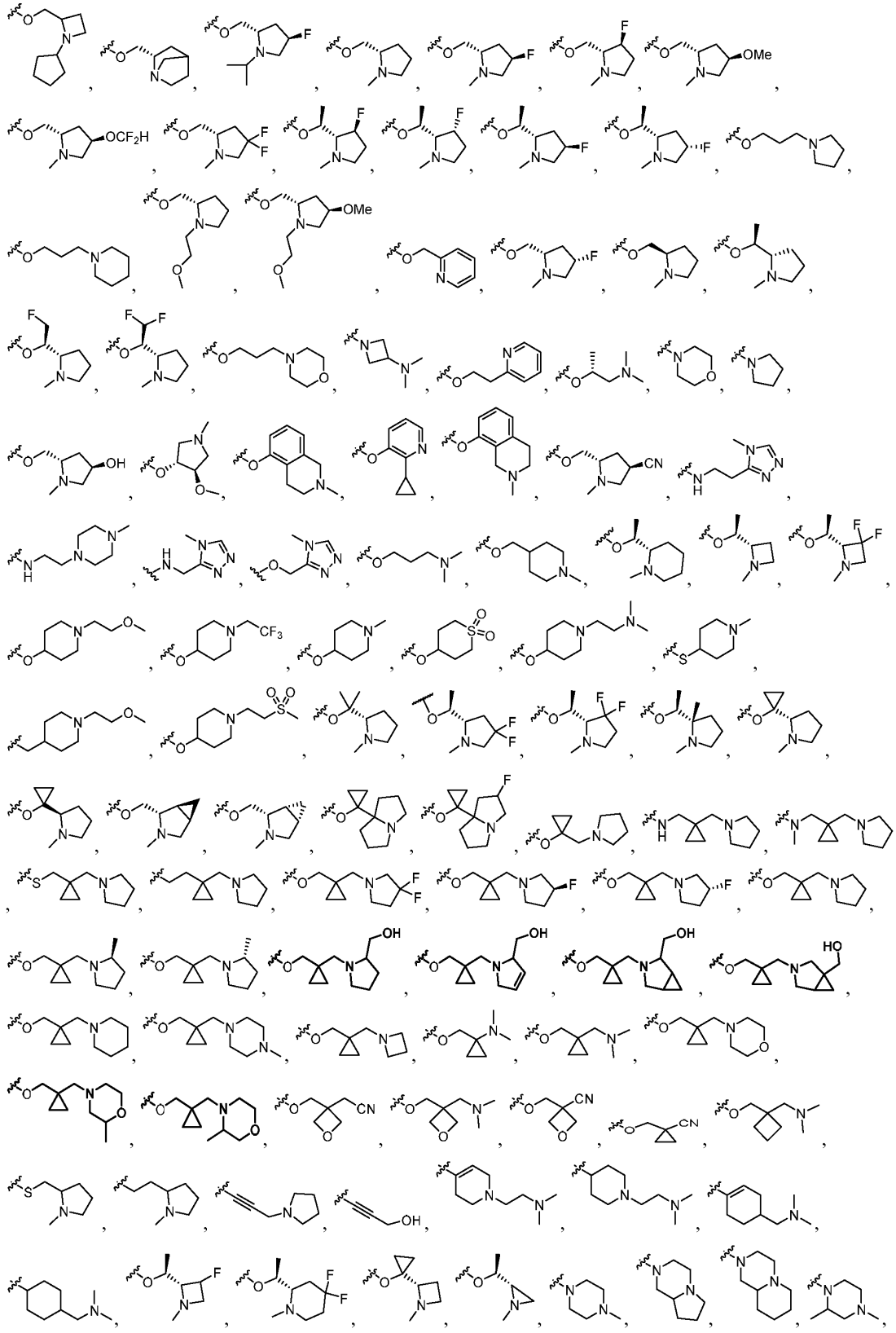
[113] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a salt or solvate thereof, J^1 is selected from a bond, C_{1-6} alkylene, 2- to 6-membered heteroalkylene, and -C(O)-, wherein C_{1-6} alkylene and 2- to 6-membered heteroalkylene are optionally substituted with one or more R^{B20}. In embodiments, J^1 is -C(O)-. In embodiments, J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, and -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)- and -C_{0-6} alkyl-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20}. In embodiments, J^2 is a bond. In embodiments, J^3 is selected from C_{1-6} alkylene, 2- to 6-membered heteroalkylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20}. In embodiments, J^3 is selected from C_{1-6} alkylene and 2- to 6-membered heteroalkylene, each of which is optionally substituted with one or more R^{B20}. In embodiments, J^3 is selected from C_{1-6} alkylene and 2- to 6-membered heteroalkylene. In embodiments, J^3 is selected from -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and –(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20}.

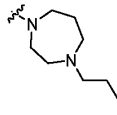
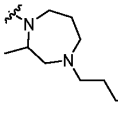
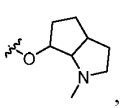
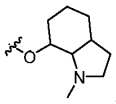
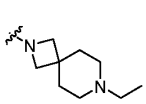
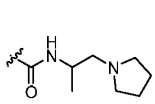
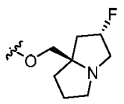
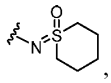
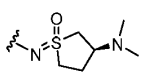
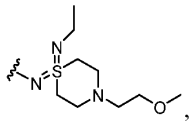
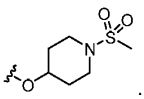
[114] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a salt or solvate thereof, J^1 is -C(O)-; J^2 is a bond; and J^3 is C_{1-6} alkylene. In embodiments, J^1 is a bond; J^2 is a bond; and J^3 is selected from C_{1-6} alkylene and 2- to 6-

membered heteroalkylene, each of which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is -C(O)-; J^2 is 3- to 12-membered heterocycle optionally substituted with one or more R^{B20}; and J^3 is C_{1-6} alkylene.

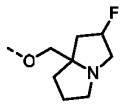
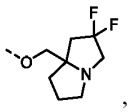
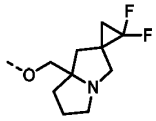
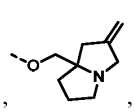
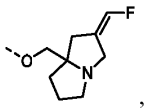
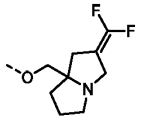
[115] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a salt or solvate thereof, R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a salt or solvate thereof, R^{B2} is selected from



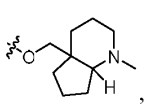
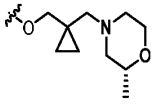
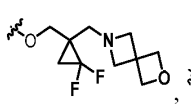
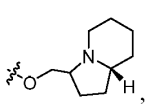


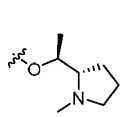
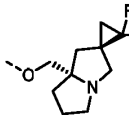
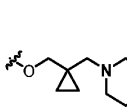
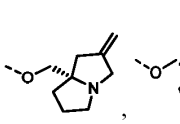
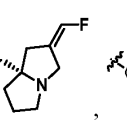
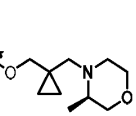
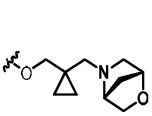
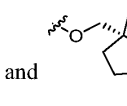
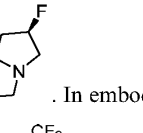
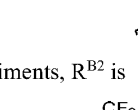
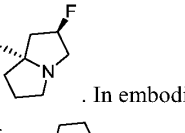
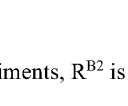
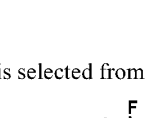
, and . In embodiments, R^{B2} is selected from

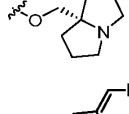
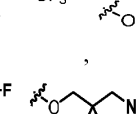
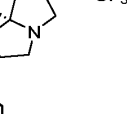
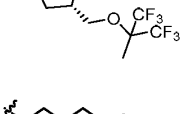
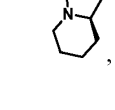
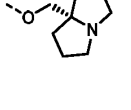
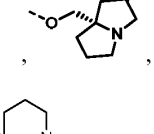







, and . In some embodiments, R^{B2} is selected from

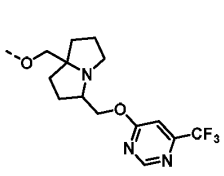
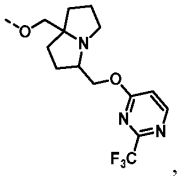
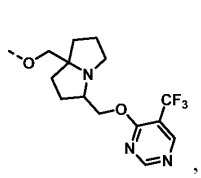





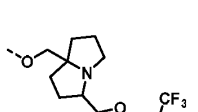
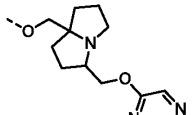
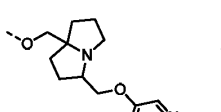
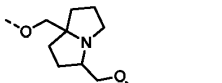
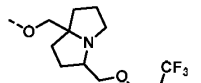
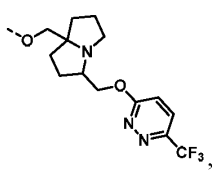
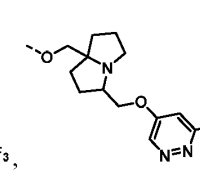
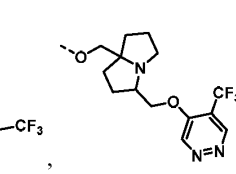
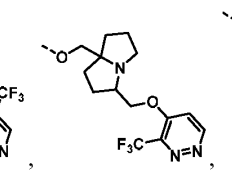
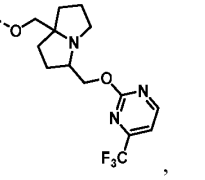
and . In embodiments, R^{B2} is . In embodiments, R^{B2} is selected from

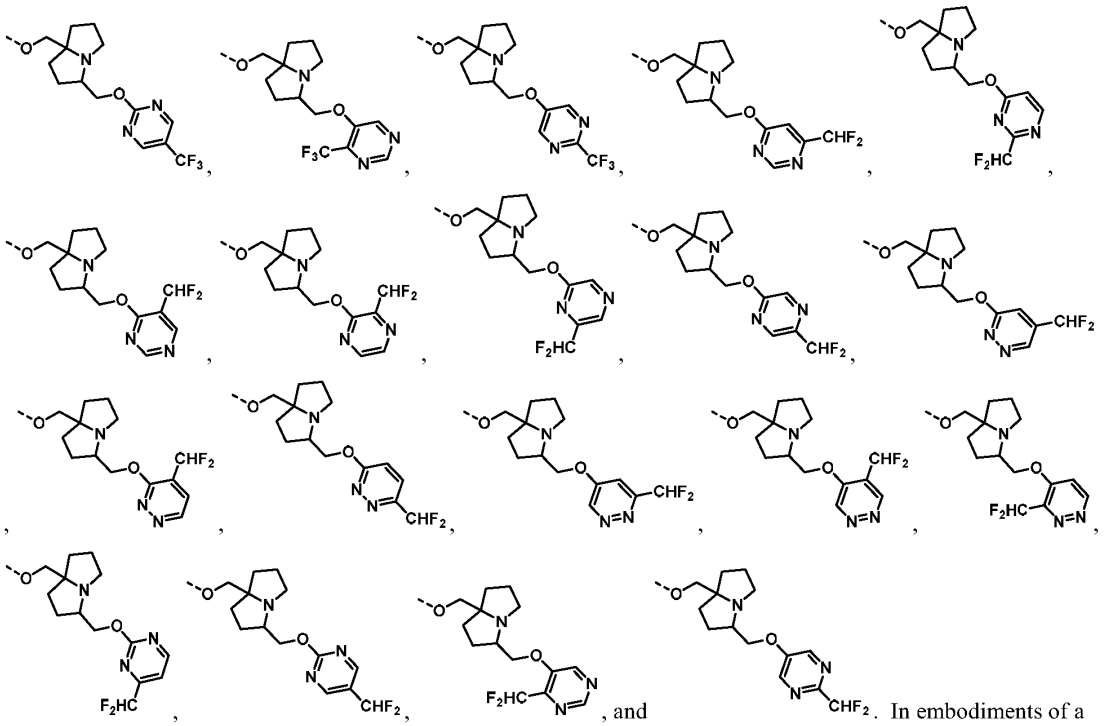








, and . In some embodiments, R^{B2} is selected from

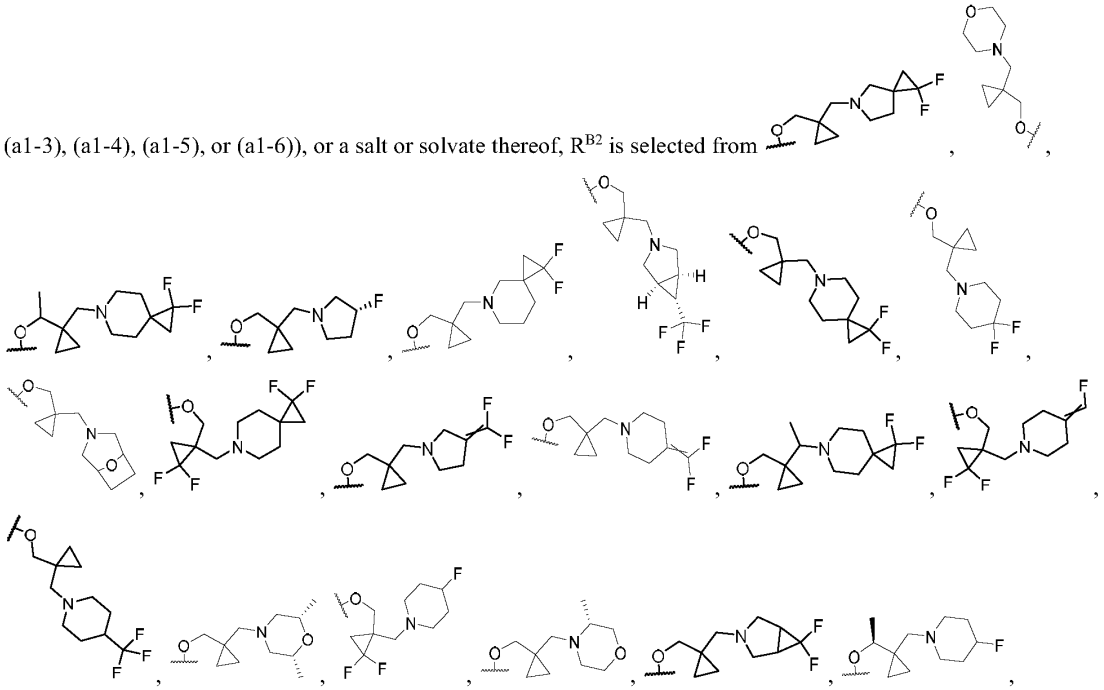




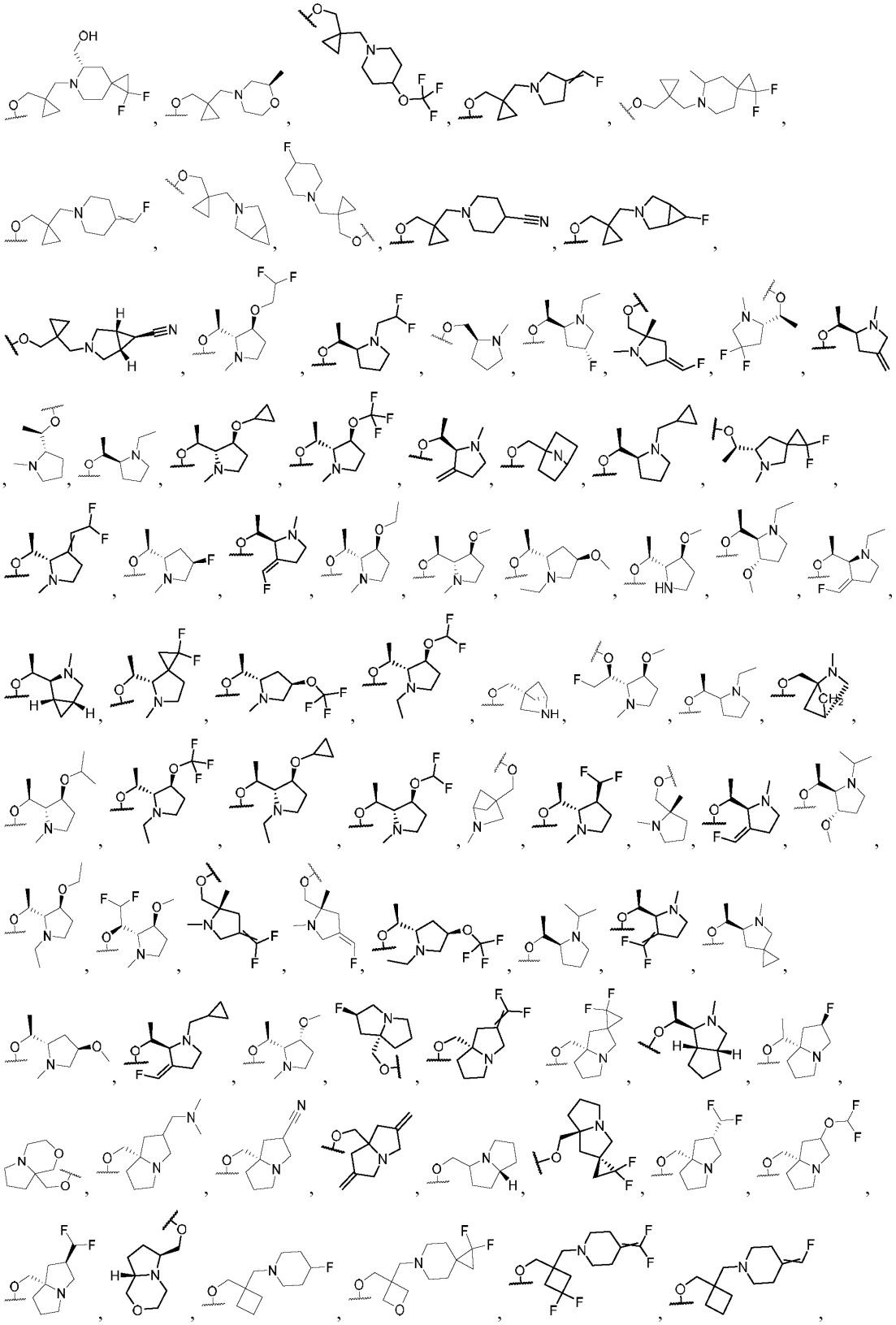











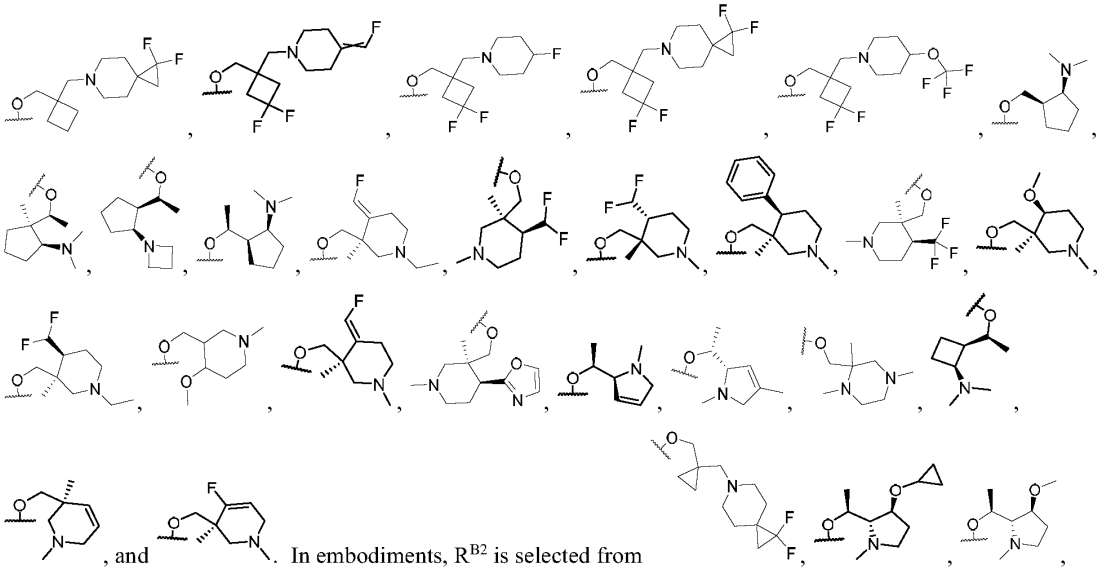




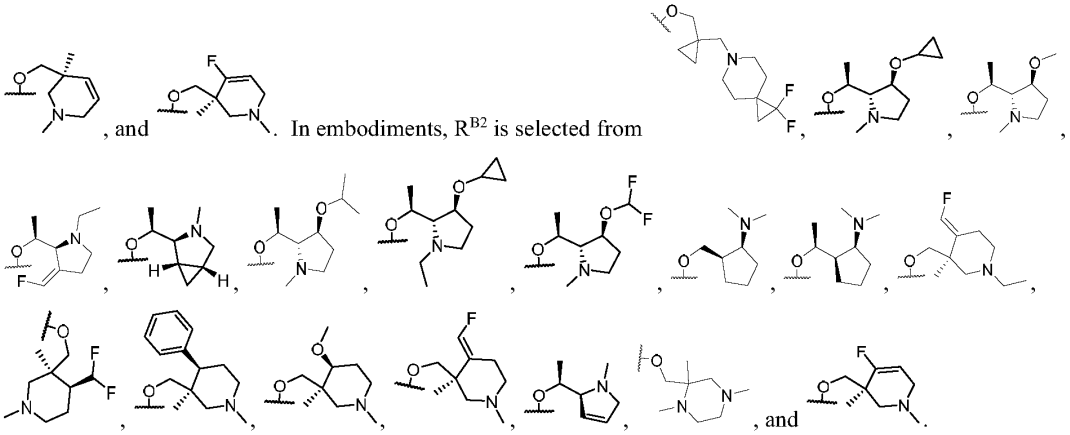
compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a salt or solvate thereof, R^{B2} is selected from



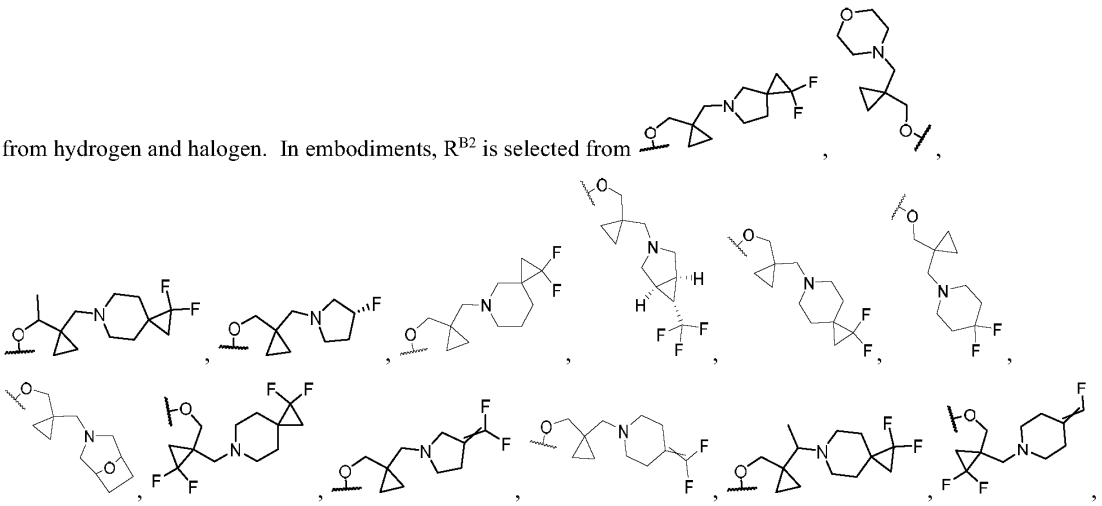


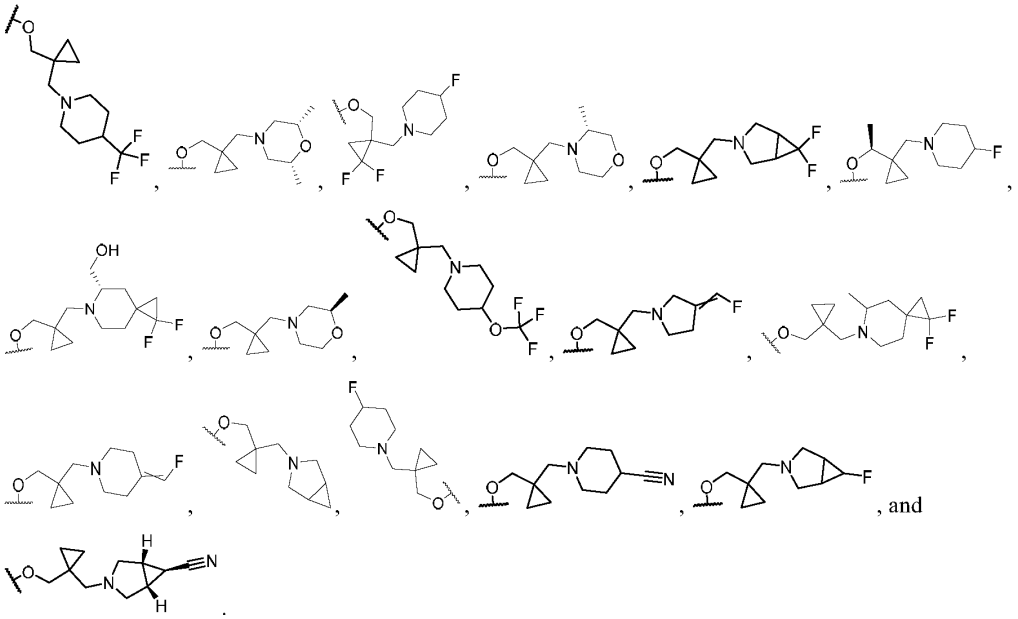


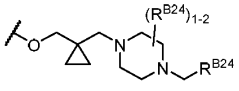
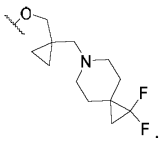
, and . In embodiments, R^{B2} is selected from

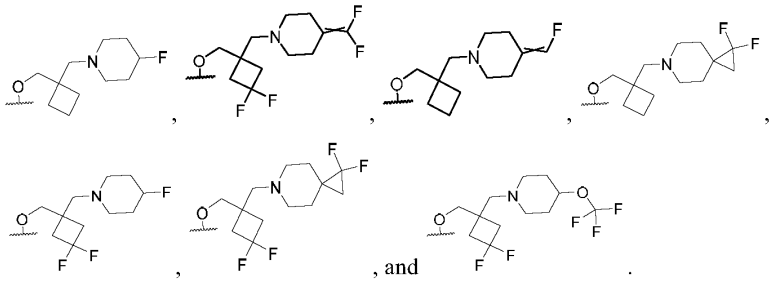


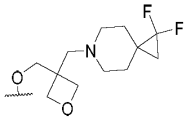
[116] In embodiments, R^{B2} is -O-(C_{1-3} alkylene)-(C_{3-4} carbocycle)-(C_{1-3} alkylene)-(4- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from R^{B20}; and R^{B20} is as described in Formula (A0), (A0-1), (A0-2), (A0-3), (a0), (a0-1), (a0-2), (a0-3), (A), (A-1), (A-2), (A-3), (a), (a-1), (a-2), (a-3), or any embodiment thereof. In embodiments, R^{B2} is -O-CH_2-(cyclopropyl)-CH_2-(4- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, =C(R^{B21})$_2$, C_{1-3} alkoxy, C_{1-3} haloalkoxy, and C_{1-3} alkyl optionally substituted with one or more substituents selected from halogen, -OH, and -NH_2; and R^{B21} is independently selected at each occurrence from hydrogen and halogen. In embodiments, R^{B2} is selected from





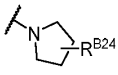
[117] In embodiments, R^{B2} is  ; and R^{B24} is independently selected from hydrogen, halogen, -CN, -OH, $-NH_2$, C_{1-3} alkoxy, and C_{1-3} haloalkoxy. In embodiments, R^{B2} is  .

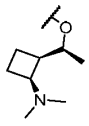
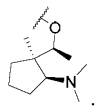
[118] In embodiments, R^{B2} is $-O-CH_2-$(cyclobutyl)$-CH_2-$(5- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, $=C(R^{B21})_2$, C_{1-3} alkoxy, C_{1-3} haloalkoxy, and C_{1-3} alkyl optionally substituted with one or more substituents selected from halogen, -OH, and $-NH_2$; and R^{B21} is independently selected at each occurrence from hydrogen and halogen. In embodiments, R^{B2} is selected from  .

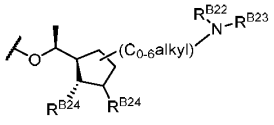
[119] In embodiments, R^{B2} is $-O-CH_2-$(3- to 4-membered heterocycle)$-CH_2-$(5- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, $=C(R^{B21})_2$, C_{1-3} alkoxy, C_{1-3} haloalkoxy, and C_{1-3} alkyl optionally substituted with one or more substituents selected from halogen, -OH, and $-NH_2$; and R^{B21} is independently selected at each occurrence from hydrogen and halogen. In embodiments, R^{B2} is  .

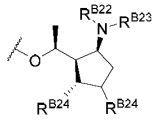
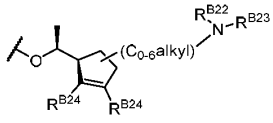
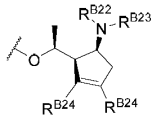
[120] In embodiments, R^{B2} is -(4- to 7-membered nitrogen containing heterocycle) optionally substituted with

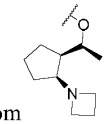
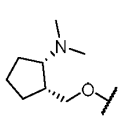
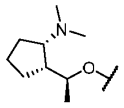
one or more substituents independently selected from R^{B20}; and R^{B20} is as described in Formula (A0), (A0-1), (A0-2), (A0-3), (a0), (a0-1), (a0-2), (a0-3), (A), (A-1), (A-2), (A-3), (a), (a-1), (a-2), (a-3), or any embodiment thereof.

In embodiments, R^{B2} is  ; and R^{B24} is independently selected from hydrogen, halogen, -CN, -OH, $-NH_2$, C_{1-3} alkoxy, and C_{1-3} haloalkoxy.

[121] In embodiments, R^{B2} is -O-(C_{1-3} alkylene)-(C_{4-6} carbocycle) optionally substituted with one or more substituents independently selected from R^{B20}; and R^{B20} is as described in Formula (A0), (A0-1), (A0-2), (A0-3), (a0), (a0-1), (a0-2), (a0-3), (A), (A-1), (A-2), (A-3), (a), (a-1), (a-2), (a-3), or any embodiment thereof. In embodiments, R^{B2} is selected from  and  .

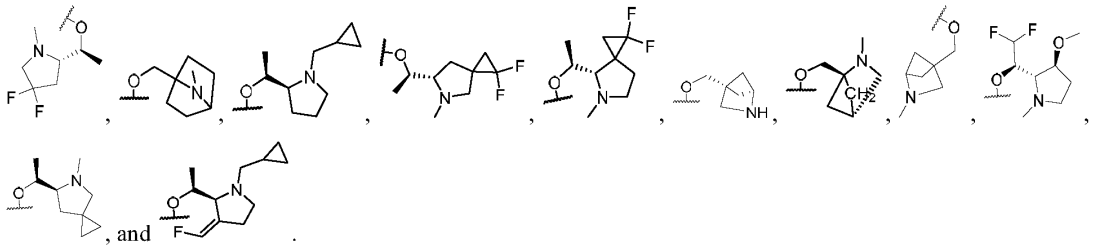
[122] In embodiments, R^{B2} is -O-CH_2-(C_5 carbocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), $-OR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, and $=C(R^{B21})_2$; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, and -C_{0-6} alkyl-(C_{3-12} carbocycle) are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, and $-N(R^{B22})(R^{B23})$; R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle. In embodiments, R^{B2} is selected from  ,

 ,  , and  ; R^{B24} is independently selected from hydrogen, halogen, -CN, $-OR^{B22}$, $-N(R^{B22})(R^{B23})$, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle.

In embodiments, R^{B2} is selected from  ,  and  .

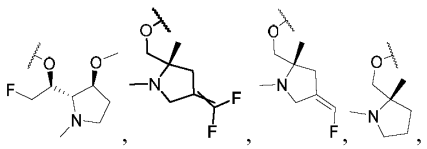
[123] In embodiments, R^{B2} is -O-(C_{1-3} alkylene)-(4- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from R^{B20}; and R^{B20} is as described in Formula (A0), (A0-1), (A0-2), (A0-3), (a0), (a0-1), (a0-2), (a0-3), (A), (A-1), (A-2), (A-3), (a), (a-1), (a-2), (a-3), or any embodiment thereof. In embodiments, R^{B2} is -O-(C_{1-3} alkylene)-(4- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered

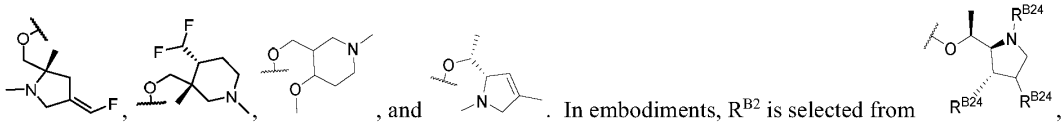
heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -OR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, and =$C(R^{B21})_2$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, and -$N(R^{B22})(R^{B23})$; R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle. In embodiments, R^{B2} is selected from



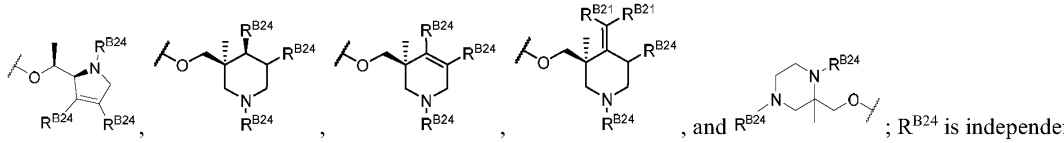
, and .

[124] In embodiments, R^{B2} is -O-(C_{1-3} alkylene)-(4- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, =$C(R^{B21})_2$, -OR^{B22}, -$N(R^{B22})(R^{B23})$, phenyl, 5 membered heteroaryl, and C_{1-3} alkyl optionally substituted with one or more substituents selected from halogen, -OH, and -NH_2; R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle. In embodiments, R^{B2} is selected from

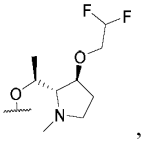
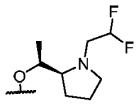
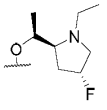
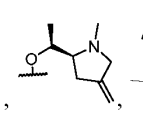
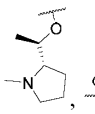
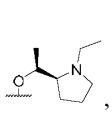
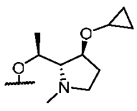
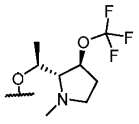
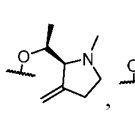
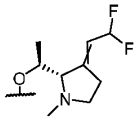
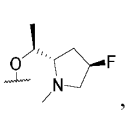
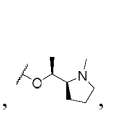
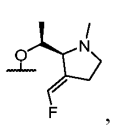
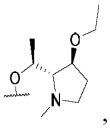
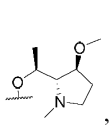
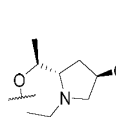
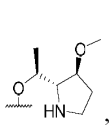
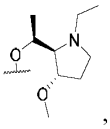
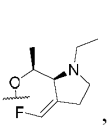
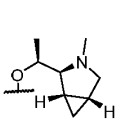
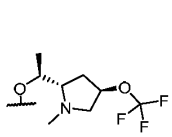
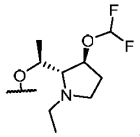
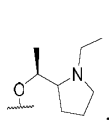
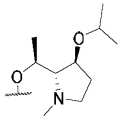
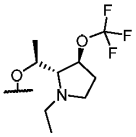
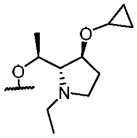
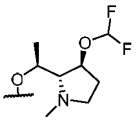
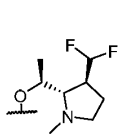
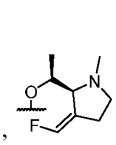
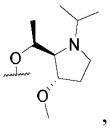
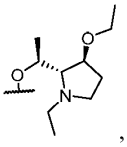
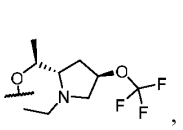
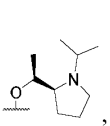
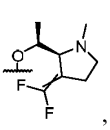
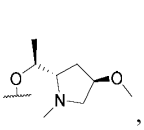
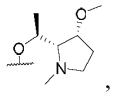
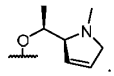
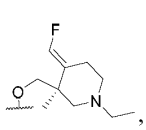
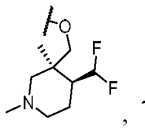
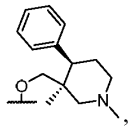
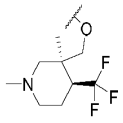
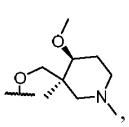
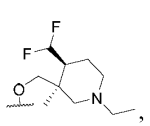
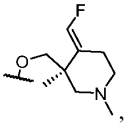
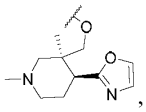
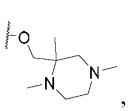
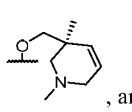
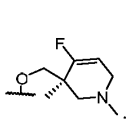
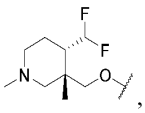
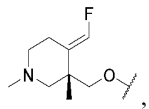
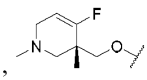
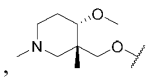
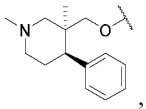
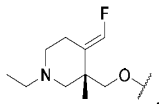
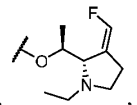
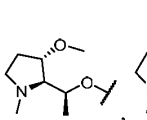
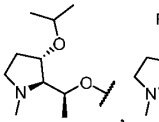
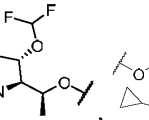
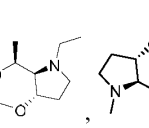
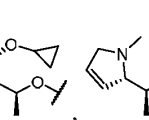
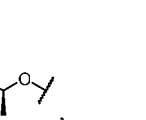
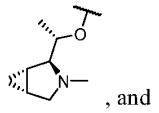
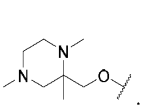
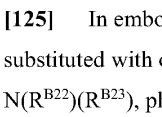
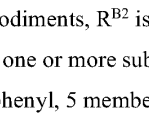
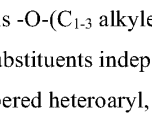
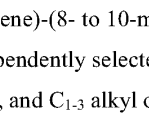
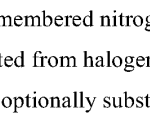
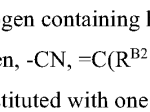
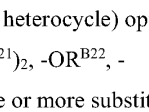
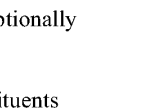
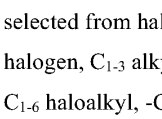
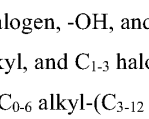




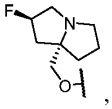
, and . In embodiments, R^{B2} is selected from

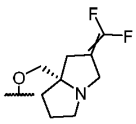
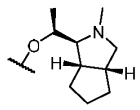
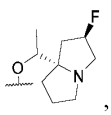
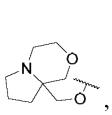
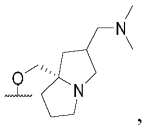
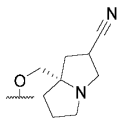
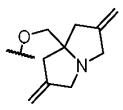
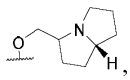


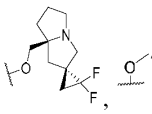
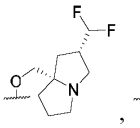
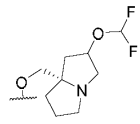
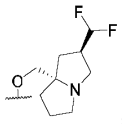
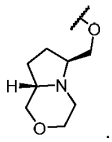
; R^{B24} is independently selected from hydrogen, halogen, -CN, -OR^{B22}, -$N(R^{B22})(R^{B23})$, =$C(R^{B21})_2$, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, phenyl, and 5 membered heteroaryl; or two R^{B24} are joined to form a C_{3-6} carbocycle or 3- to 5-membered heterocycle; R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10

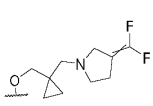
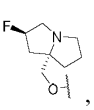
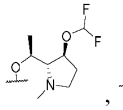
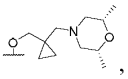
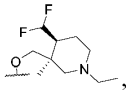
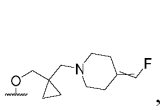
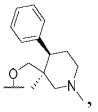
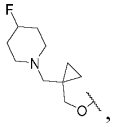
membered heterocycle. In embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , , , ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

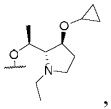
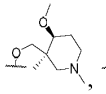
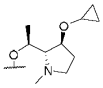
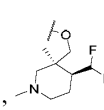
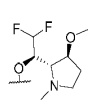
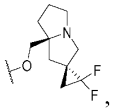
[125] In embodiments, R^{B2} is -O-(C_{1-3} alkylene)-(8- to 10-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, =C(R^{B21})$_2$, -OR^{B22}, -N(R^{B22})(R^{B23}), phenyl, 5 membered heteroaryl, and C_{1-3} alkyl optionally substituted with one or more substituents selected from halogen, -OH, and -N(R^{B22})(R^{B23}); R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same

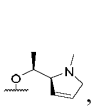
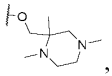
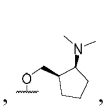
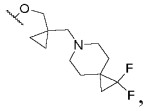
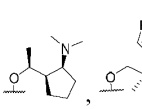
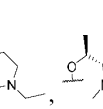
nitrogen atom form 3- to 10 membered heterocycle. In embodiments, R^{B2} is selected from  ,

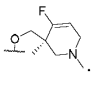
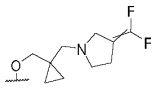
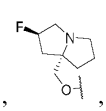
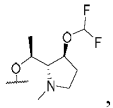
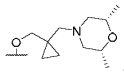
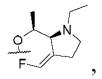
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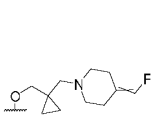
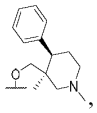
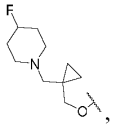
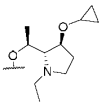
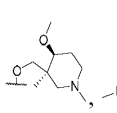
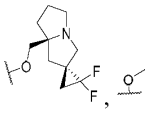
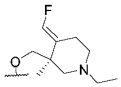
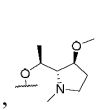
 ,  ,  ,  , and  . In embodiments, R^{B2} is selected from

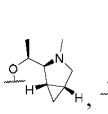
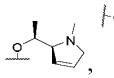
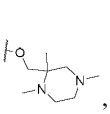
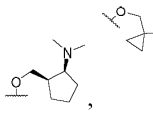
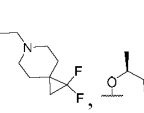
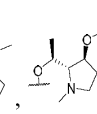
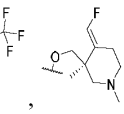
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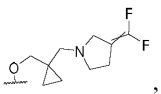
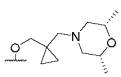
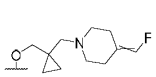
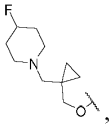
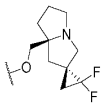
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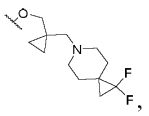
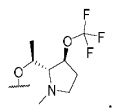
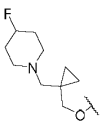
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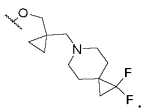
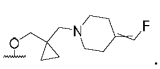
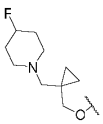
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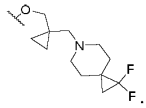
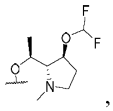
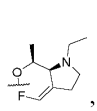
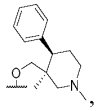
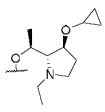
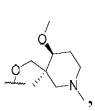
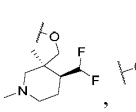
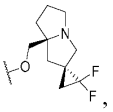
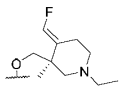
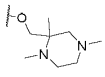
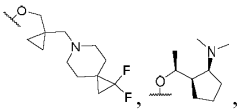
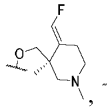
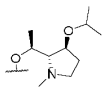
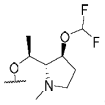
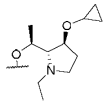
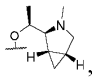
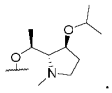
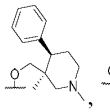
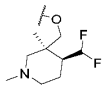
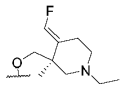
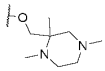
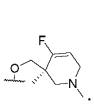
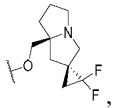
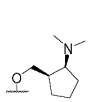
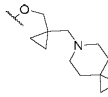
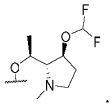
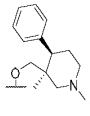
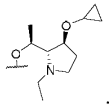
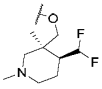
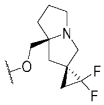
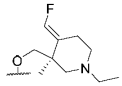
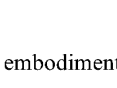
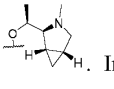
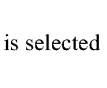
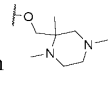
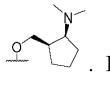
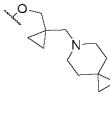
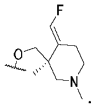
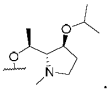
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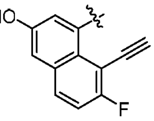
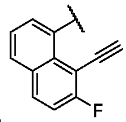
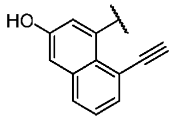
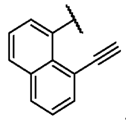
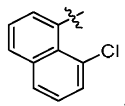
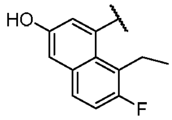
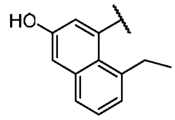
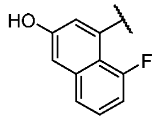
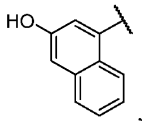
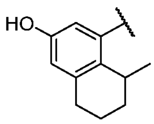
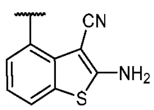
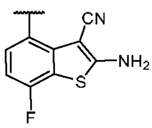
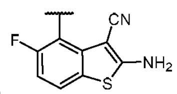
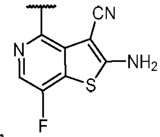
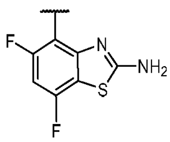
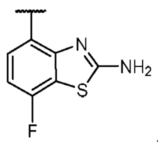
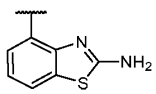
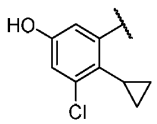
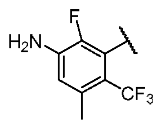
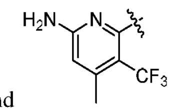
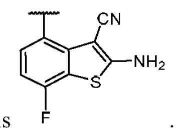
 , and  . In embodiments, R^{B2} is selected from ,  , and

 . In embodiments, R^{B2} is  . In embodiments, R^{B2} is  . In embodiments, R^{B2}

is  . In embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  , and  . In embodiments, R^{B2} is selected from  ,  ,  ,  ,  , and  . In embodiments, R^{B2} is selected from  ,  ,  , and  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  . In embodiments, R^{B2} is selected from  .

[126] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-

6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a salt or solvate thereof, R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl. In embodiments, R^{B6} is halogen.

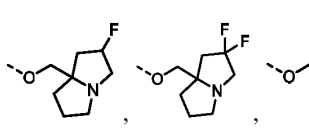
[127] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a salt or solvate thereof, R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one or more R^{B20}. In embodiments, R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}. In embodiments, R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, $-OR^{B22}$, $-N(R^{B22})(R^{B23})$, and C_{3-6} cycloalkyl. In embodiments, R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, $-CH_3$, $-CH_2CH_3$, $-CH=CH_2$, $-CF_3$, -C≡CH, -OH, $-NH_2$, and -cyclopropyl. In embodiments, R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In embodiments, R^{B7} is  .

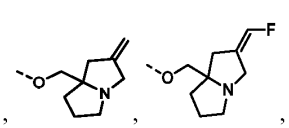
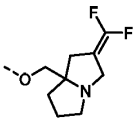
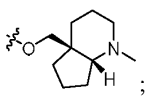
[128] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a salt or solvate thereof, R^{B8} is independently selected from hydrogen and halogen. In embodiments, R^{B8} is halogen.

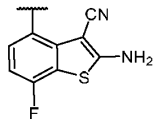
[129] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a salt or solvate thereof, R^{B6} is halogen; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of

which is optionally substituted with one or more R^{B20}; and R^{B8} is halogen.

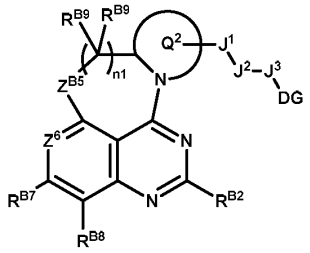
[130] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a salt or solvate thereof, R^{B2} is selected from

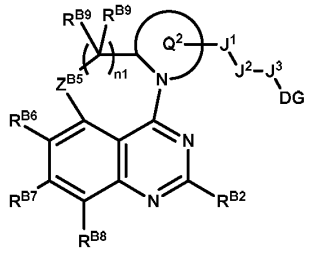


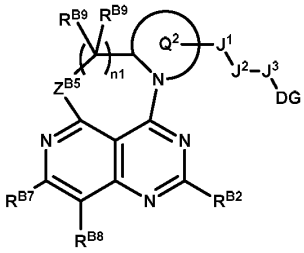



, and ; R^{B6} is


halogen; R^{B7} is ; and R^{B8} is halogen.

[131] In some embodiments, the present disclosure provides a compound of Formula (A0-1), (A0-2), or (A0-3):

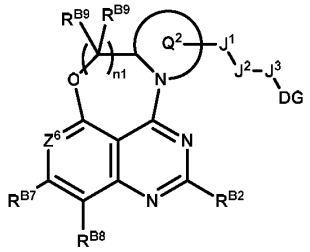

(A0-1),

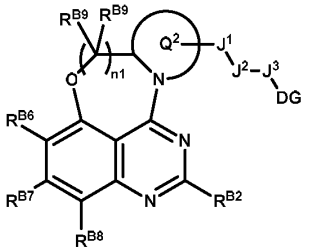

(A0-2),

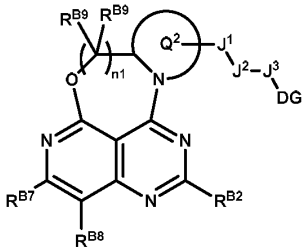

(A0-3),

or a pharmaceutically acceptable salt or solvate thereof, wherein all variables above are as described for Formula (A0), or any embodiment thereof.

[132] In some embodiments, the present disclosure provides a compound of Formula (A-1), (A-2), or (A-3):

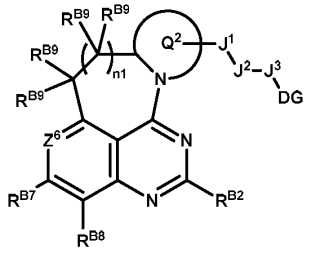

(A-1),

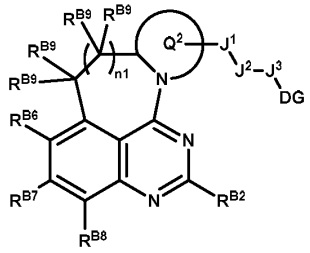

(A-2),

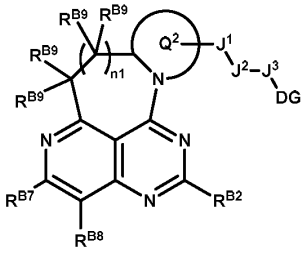

(A-3),

or a pharmaceutically acceptable salt or solvate thereof, wherein all variables above are as described for Formula (A), or any embodiment thereof.

[133] In some embodiments, the present disclosure provides a compound of Formula (A1-1), (A1-2), or (A1-3):


(A1-1),


(A1-2),



(A1-3),

or a pharmaceutically acceptable salt or solvate thereof, wherein all variables above are as described for Formula (A1), or any embodiment thereof.

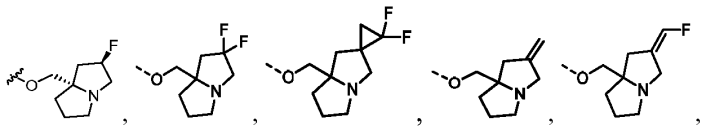
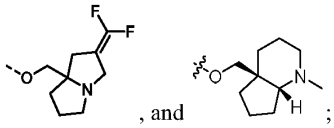
[134] In some embodiments, the present disclosure provides a compound of Formula (A0-1), (A0-2), (A0-3), (A-1), (A-2), (A-3), (A1-1), (A1-2), or (A1-3), or a pharmaceutically acceptable salt or solvate thereof, wherein:

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, -C(O)-, -N(R^{B12})C(O)-, and C_{1-6} alkylene, wherein C_{1-6} alkylene is optionally substituted with one, two, or three R^{B20};

J^2 is selected from a bond, C_{1-6} alkylene, and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, wherein C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)- are optionally substituted with one, two, or three R^{B20};

J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, wherein C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)- are optionally substituted with one, two, or three R^{B20};

R^{B2} is selected from  ,  , and ;

R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl.

R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OR^{B22}, -N(R^{B22})(R^{B23}), and C_{3-6} cycloalkyl;

R^{B8} is halogen;

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

n1 is selected from 1, 2, and 3; and

DG is as described for a compound of Formula (A).

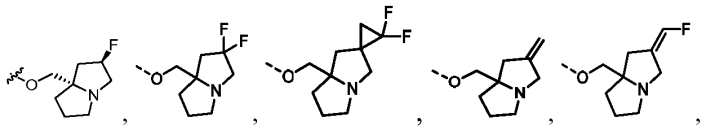
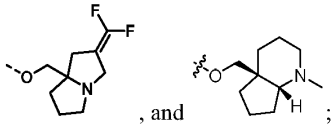
[135] In some embodiments of a compound of Formula (A0-1), (A0-2), (A0-3), (A-1), (A-2), (A-3), (A1-1), (A1-2), or (A1-3), or a pharmaceutically acceptable salt or solvate thereof:

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, -N(R^{B12})C(O)-, and -C(O)-;

J^2 is a bond;

J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, wherein C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)- are optionally substituted with one, two, or three R^{B20};

R^{B2} is selected from  ,  , and ;

R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl.

R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, $-OR^{B22}$, $-N(R^{B22})(R^{B23})$, and C_{3-6} cycloalkyl;

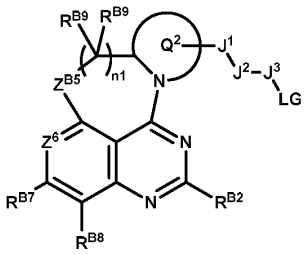
R^{B8} is halogen;

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

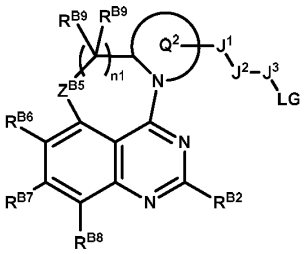
n1 is selected from 1, 2, and 3; and

DG is as described for a compound of Formula (A).

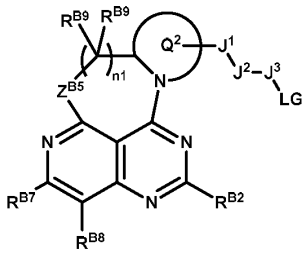
[136] In some embodiments, the present disclosure provides a compound of Formula (a0-1), (a0-2), or (a0-3):



(a0-1),



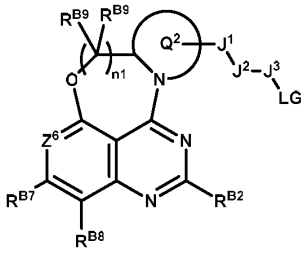
(a0-2),



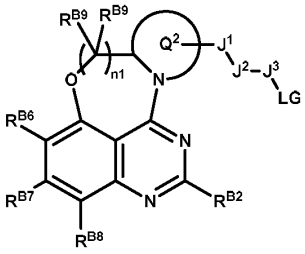
(a0-3),

or a pharmaceutically acceptable salt or solvate thereof, wherein all variables above are as described for Formula (a0), or any embodiment thereof.

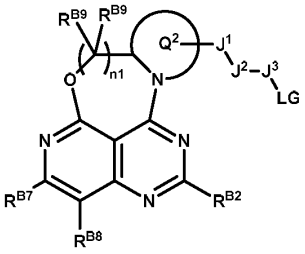
[137] In some embodiments, the present disclosure provides a compound of Formula (a-1), (a-2), or (a-3):



(a-1),



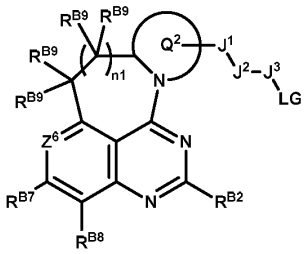
(a-2),



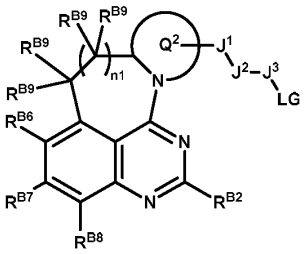
(a-3),

or a pharmaceutically acceptable salt or solvate thereof, wherein all variables above are as described for Formula (a), or any embodiment thereof.

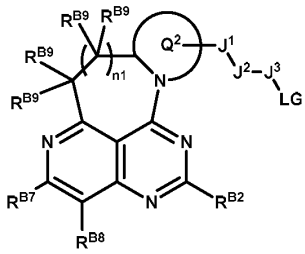
[138] In some embodiments, the present disclosure provides a compound of Formula (a1-1), (a1-2), or (a1-3):



(a1-1),



(a1-2),



(a1-3),

or a pharmaceutically acceptable salt or solvate thereof, wherein all variables above are as described for Formula (a1), or any embodiment thereof.

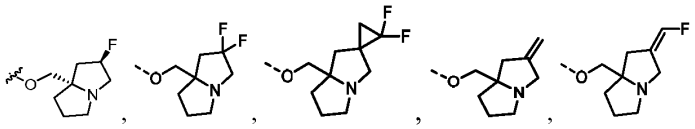
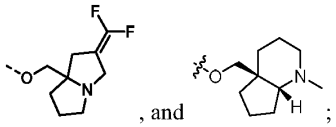
[139] In some embodiments, the present disclosure provides a compound of Formula (a0-1), (a0-2), (a0-3), (a-1), (a-2), (a-3), (a1-1), (a1-2), or (a1-3), or a pharmaceutically acceptable salt or solvate thereof, wherein:

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, -C(O)-, -N(R^{B12})C(O)-, and C_{1-6} alkylene, wherein C_{1-6} alkylene is optionally substituted with one, two, or three R^{B20};

J^2 is selected from a bond, C_{1-6} alkylene, and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, wherein C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)- are optionally substituted with one, two, or three R^{B20};

J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, wherein C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)- are optionally substituted with one, two, or three R^{B20};

R^{B2} is selected from  , and  ;

R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl.

R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OR^{B22}, -N(R^{B22})(R^{B23}), and C_{3-6} cycloalkyl;

R^{B8} is halogen;

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

n1 is selected from 1, 2, and 3; and

LG is as described for a compound of Formula (a).

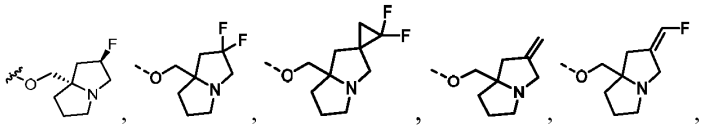
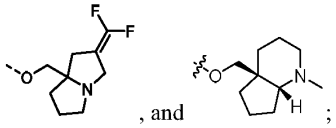
[140] In some embodiments of a compound of Formula (a0-1), (a0-2), (a0-3), (a-1), (a-2), (a-3), (a1-1), (a1-2), or (a1-3), or a pharmaceutically acceptable salt or solvate thereof:

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, -N(R^{B12})C(O)-, and -C(O)-;

J^2 is a bond;

J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, wherein C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)- are optionally substituted with one, two, or three R^{B20};

R^{B2} is selected from  , and  ;

R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl.

R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OR^{B22}, -N(R^{B22})(R^{B23}), and C_{3-6} cycloalkyl;

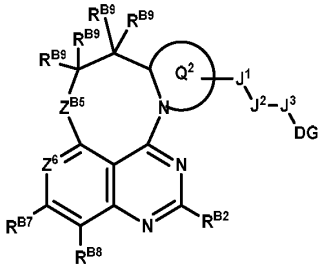
R^{B8} is halogen;

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

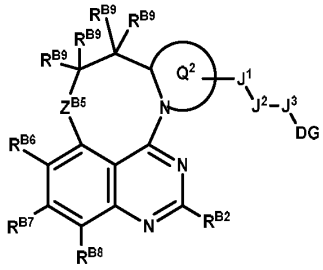
n1 is selected from 1, 2, and 3; and

LG is as described for a compound of Formula (a).

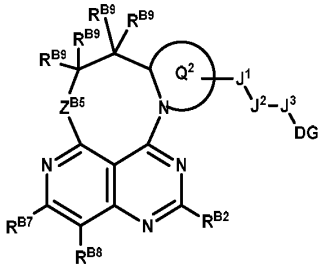
[141] In some embodiments, the present disclosure provides a compound of Formula (A0-4), (A0-5), or (A0-6):



(A0-4),



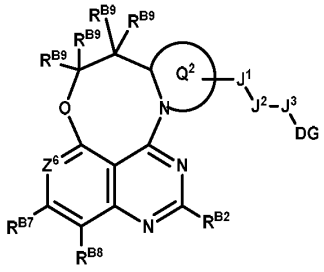
(A0-5),



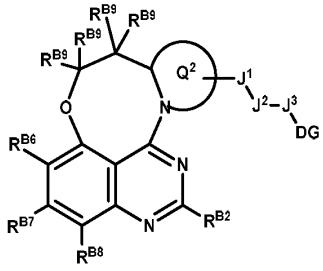
(A0-6),

or a pharmaceutically acceptable salt or solvate thereof, wherein all variables above are as described for Formula (A0), or any embodiment thereof.

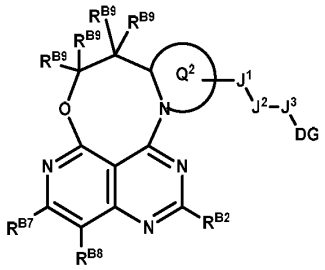
[142] In some embodiments, the present disclosure provides a compound of Formula (A-4), (A-5), or (A-6):



(A-4),



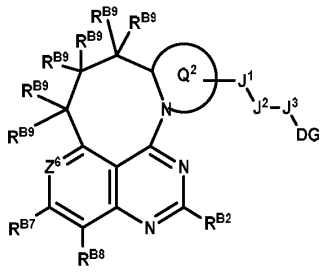
(A-5),



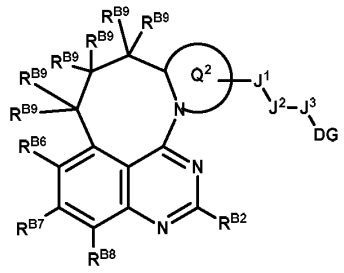
(A-6),

or a pharmaceutically acceptable salt or solvate thereof, wherein all variables above are as described for Formula (A), or any embodiment thereof.

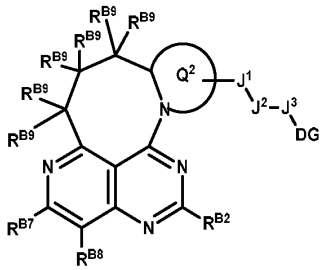
[143] In some embodiments, the present disclosure provides a compound of Formula (A1-4), (A1-5), or (A1-6):



(A1-4),



(A1-5),



(A1-6),

or a pharmaceutically acceptable salt or solvate thereof, wherein all variables above are as described for Formula (A1), or any embodiment thereof.

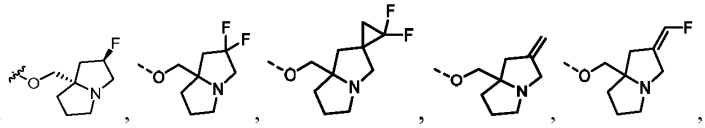
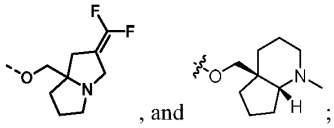
[144] In some embodiments, the present disclosure provides a compound of Formula (A0-4), (A0-5), (A0-6), (A-4), (A-5), (A-6), (A1-4), (A1-5), or (A1-6), or a pharmaceutically acceptable salt or solvate thereof, wherein:

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, -C(O)-, -N(R^{B12})C(O)-, and C_{1-6} alkylene, wherein C_{1-6} alkylene is optionally substituted with one, two, or three R^{B20};

J^2 is selected from a bond, C_{1-6} alkylene, and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, wherein C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)- are optionally substituted with one, two, or three R^{B20};

J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, wherein C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)- are optionally substituted with one, two, or three R^{B20};

R^{B2} is selected from  , and  ;

R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl.

R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OR^{B22}, -N(R^{B22})(R^{B23}), and C_{3-6} cycloalkyl;

R^{B8} is halogen;

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

n1 is selected from 1, 2, and 3; and

DG is as described for a compound of Formula (A).

[145] In some embodiments of a compound of Formula (A0-4), (A0-5), (A0-6), (A-4), (A-5), (A-6), (A1-4), (A1-

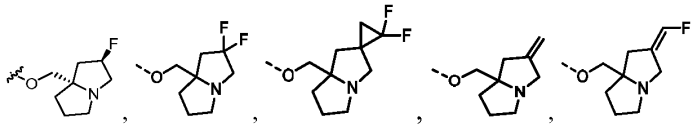
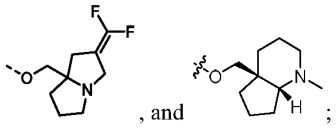
5), or (A1-6), or a pharmaceutically acceptable salt or solvate thereof:

B is selected from a 4- to 8-membered monocyclic heterocycle and 6- to 10-membered bridged bicyclic heterocycle, each of which (i) comprises at least two ring heteroatoms and (ii) is optionally substituted with one or more R^{B20};

J^1 is selected from a bond, -N(R^{B12})C(O)-, and -C(O)-;

J^2 is a bond;

J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, wherein C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)- are optionally substituted with one, two, or three R^{B20};

R^{B2} is selected from  , and  ;

R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl.

R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OR^{B22}, -N(R^{B22})(R^{B23}), and C_{3-6} cycloalkyl;

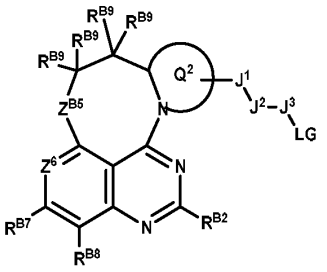
R^{B8} is halogen;

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

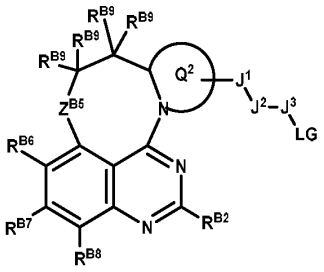
n1 is selected from 1, 2, and 3; and

DG is as described for a compound of Formula (A).

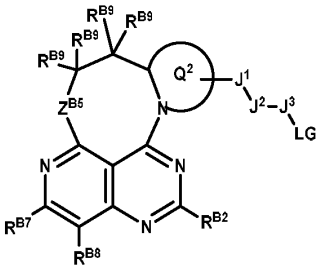
[146] In some embodiments, the present disclosure provides a compound of Formula (a0-4), (a0-5), or (a0-6):



(a0-4),



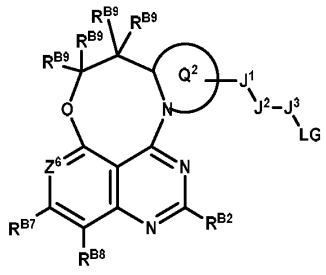
(a0-5),



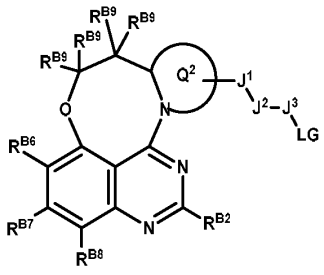
(a0-6),

or a pharmaceutically acceptable salt or solvate thereof, wherein all variables above are as described for Formula (a0), or any embodiment thereof.

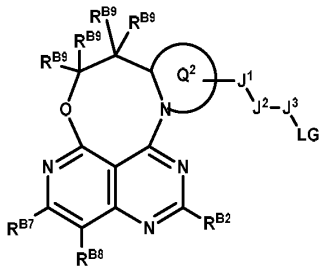
[147] In some embodiments, the present disclosure provides a compound of Formula (a-4), (a-5), or (a-6):



(a-4),



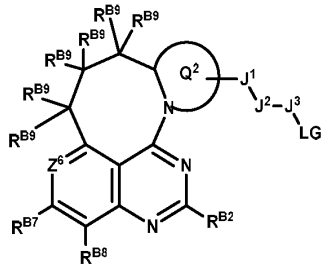
(a-5),



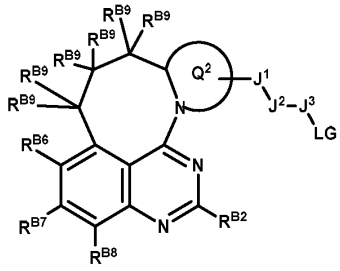
(a-6),

or a pharmaceutically acceptable salt or solvate thereof, wherein all variables above are as described for Formula (a), or any embodiment thereof.

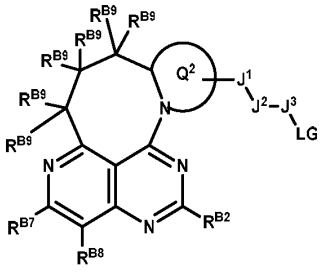
[148] In some embodiments, the present disclosure provides a compound of Formula (a1-4), (a1-5), or (a1-6):



(a1-4),



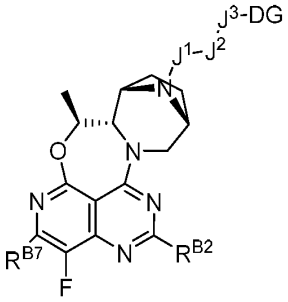
(a1-5),



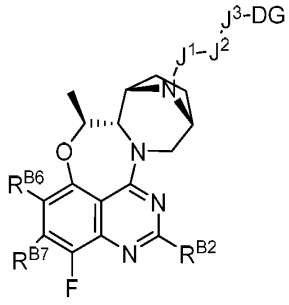
(a1-6),

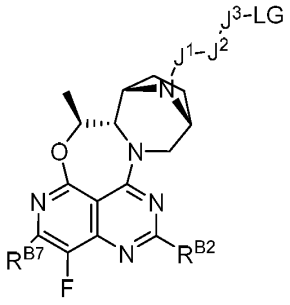
or a pharmaceutically acceptable salt or solvate thereof, wherein all variables above are as described for Formula (a1), or any embodiment thereof.

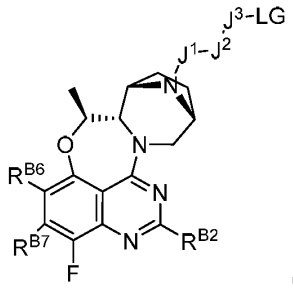
[149] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (a0), (a0-1), (a0-2), (a0-3), (A), (A-1), (A-2), (A-3), (a), (a-1), (a-2), or (a-3), the compound has the formula



(A-



7), 

(A-8), 

(a-7), or (a-8);

wherein all variables of the formulae above are as described in Formula (A0), (A0-1), (A0-2), (A0-3), (a0), (a0-1), (a0-2), (a0-3), (A), (A-1), (A-2), (A-3), (a), (a-1), (a-2), (a-3), or any embodiment thereof. In some embodiments, the compound has formula (A-7). In some embodiments, the compound has formula (a-7). In some embodiments, the compound has formula (A-8). In some embodiments, the compound has formula (a-8).

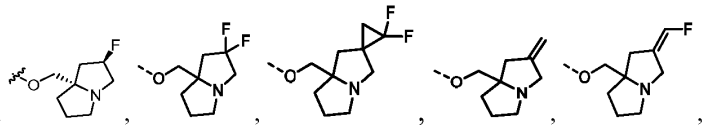
[150] In some embodiments, the present disclosure provides a compound of Formula (a0-4), (a0-5), (a0-6), (a-4), (a-5), (a-6), (a1-4), (a1-5), or (a1-6), or a pharmaceutically acceptable salt or solvate thereof, wherein:

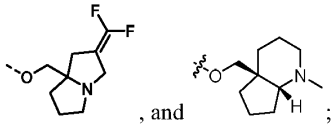
Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, -C(O)-, -N(R^{B12})C(O)-, and C_{1-6} alkylene, wherein C_{1-6} alkylene is optionally substituted with one, two, or three R^{B20};

J^2 is selected from a bond, C_{1-6} alkylene, and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, wherein C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)- are optionally substituted with one, two, or three R^{B20};

J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, wherein C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)- are optionally substituted with one, two, or three R^{B20};

R^{B2} is selected from 



;

R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl.

R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OR^{B22}, -N(R^{B22})(R^{B23}), and C_{3-6} cycloalkyl;

R^{B8} is halogen;

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

n1 is selected from 1, 2, and 3; and

LG as described for a compound of Formula (a).

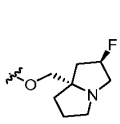
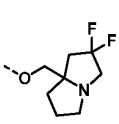
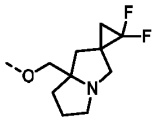
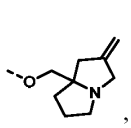
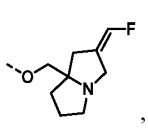
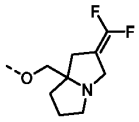
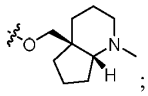
[151] In some embodiments of a compound of Formula (a0-4), (a0-5), (a0-6), (a-4), (a-5), (a-6), (a1-4), (a1-5), or (a1-6), or a pharmaceutically acceptable salt or solvate thereof:

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, -N(R^{B12})C(O)-, and -C(O)-;

J^2 is a bond;

J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, wherein C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)- are optionally substituted with one, two, or three R^{B20};

R^{B2} is selected from  ,  ,  ,  ,  ,  , and  ;

R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl.

R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OR^{B22}, -$N(R^{B22})(R^{B23})$, and C_{3-6} cycloalkyl;

R^{B8} is halogen;

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

n1 is selected from 1, 2, and 3; and

LG is as described for a compound of Formula (a).

[152] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), or (a0-6)), Z^{B5} is $C(R^{B9})_2$. In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), or (a0-6)), Z^{B5} is O.

[153] In some embodiments, for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), R^{B6b} is selected from hydrogen, -CN, C_{1-6} alkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20}. In some embodiments, R^{B6b} is selected from C_{1-6} alkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), each of which is optionally substituted with one or more R^{B20}. In some embodiments, R^{B6b} is selected from C_{1-6} alkyl and C_{3-12} carbocycle, each of which is optionally substituted with one or more R^{B20}. In some embodiments, R^{B6b} is C_{3-12} carbocycle, such as cyclopropyl.

[154] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), Z^7 is selected from $C(R^{B7})$ and $C(R^{B7})(R^{B7a})$. In some embodiments, Z^7 is $C(R^{B7})$. In some embodiments, Z^8 is selected from $C(R^{B8})$ and $C(R^{B8})_2$. In some embodiments, Z^8 is $C(R^{B8})$, such as CF. In some embodiments, R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one or more R^{B20}. In some embodiments, R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}. In some embodiments, R^{B7} is benzothiophenyl optionally substituted with one or more R^{B20}. In some embodiments, R^{B8} is selected from hydrogen and halogen. In some embodiments, R^{B8} is halogen, such as fluorine. In some embodiments, for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), R^{B6b} is selected from C_{1-6} alkyl and C_{3-12} carbocycle, each of which is optionally substituted with one or more R^{B20}; Z^7 is $C(R^{B7})$; Z^8 is $C(R^{B8})$; R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one or

more R^{B20}; and R^{B8} is halogen.

[155] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-4), (a0), (a0-1), (a0-4), (A), (A-1), (A-4), (a), (a-1), (a-4), (A1), (A1-1), (A1-4), (a1), (a1-1), or (a1-4)), Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$. In some embodiments, Z^6 is selected from $C(R^{B6})$ and $C(R^{B6})_2$. In some embodiments, Z^6 is selected from N and $N(R^{B6b})$. In some embodiments, Z^6 is selected from $C(R^{B6})$ and N. In some embodiments, Z^6 is selected from $C(R^{B6})_2$ and $N(R^{B6b})$. In some embodiments, Z^6 is $C(R^{B6})$. In some embodiments, Z^6 is $C(R^{B6})_2$. In some embodiments, Z^6 is N. In some embodiments, Z^6 is $N(R^{B6b})$.

[156] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$. In some embodiments, Z^7 is $C(R^{B7})$. In some embodiments, Z^7 is $N(R^{B7b})$.

[157] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), Z^8 is selected from $C(R^{B8})$, N, and $C(R^{B8})_2$. In some embodiments, Z^8 is selected from $C(R^{B8})$ and $C(R^{B8})_2$. In some embodiments, Z^8 is $C(R^{B8})$. In some embodiments, Z^8 is $C(R^{B8})_2$. In some embodiments, Z^8 is N.

[158] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$; Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$; and Z^8 is selected from $C(R^{B8})$, N, and $C(R^{B8})_2$. In some embodiments, Z^6 is $C(R^{B6})$; Z^7 is $C(R^{B7})$; and Z^8 is $C(R^{B8})$. In some embodiments, Z^6 is CCl; Z^7 is $C(R^{B7})$; and Z^8 is CF. In some embodiments, Z^6 is CCF_3; Z^7 is $C(R^{B7})$; and Z^8 is CF. In some embodiments, Z^6 is N; Z^7 is $C(R^{B7})$; and Z^8 is $C(R^{B8})$. In some embodiments, Z^6 is N; Z^7 is $C(R^{B7})$; and Z^8 is CF. In some embodiments, Z^6 is $C(R^{B6})_2$; Z^7 is $N(R^{B7b})$; and Z^8 is $C(R^{B8})_2$. In some embodiments, Z^6 is CH_2; Z^7 is $N(R^{B7b})$; and Z^8 is CH_2. In some embodiments, Z^6 is $N(R^{B6b})$; Z^7 is $C(R^{B7})$; and Z^8 is $C(R^{B8})$. In some embodiments, Z^6 is $N(R^{B6b})$; Z^7 is $C(R^{B7})$; and Z^8 is CF.

[159] In some embodiments, for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), Z^1 is selected from N and $N(R^{B1b})$; Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$; Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$; and Z^8 is selected from $C(R^{B8})$, N, and $C(R^{B8})_2$. In some embodiments, for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), Z^1 is N; Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$; Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$; and Z^8 is selected from $C(R^{B8})$, N, and $C(R^{B8})_2$. In some embodiments, Z^1 is N; Z^6 is $C(R^{B6})$; Z^7 is $C(R^{B7})$; and Z^8 is $C(R^{B8})$. In some embodiments, Z^1 is N; Z^6 is CCl; Z^7 is $C(R^{B7})$; and Z^8 is CF. In some embodiments, Z^1 is N; Z^6 is N; Z^7 is $C(R^{B7})$; and Z^8 is $C(R^{B8})$. In some embodiments, Z^1 is N; Z^6 is N; Z^7 is $C(R^{B7})$; and Z^8 is CF. In some embodiments, Z^1 is N; Z^6 is $C(R^{B6})_2$; Z^7 is $N(R^{B7b})$; and Z^8 is $C(R^{B8})_2$. In some embodiments, Z^1 is N; Z^6 is CH_2; Z^7 is $N(R^{B7b})$; and Z^8 is CH_2. In some embodiments, Z^1 is N; Z^6 is $N(R^{B6b})$; Z^7 is $C(R^{B7})$; and Z^8 is $C(R^{B8})$. In some embodiments, Z^1 is N; Z^6 is $N(R^{B6b})$; Z^7 is $C(R^{B7})$; and Z^8 is CF. In some embodiments, Z^1 is $N(R^{B1b})$; Z^6 is $C(R^{B6})$; Z^7 is $C(R^{B7})$; and Z^8 is N.

[160] In some embodiments, for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), Z^1 is selected from N and $N(R^{B1b})$; Z^2 is selected from $C(R^{B2})$ and C(O); X^3 is N; Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$; Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$; and Z^8 is selected from $C(R^{B8})$, N, and $C(R^{B8})_2$. In some

embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$; Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$; and Z^8 is selected from $C(R^{B8})$ and $C(R^{B8})_2$. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is $C(R^{B6})$; Z^7 is $C(R^{B7})$; and Z^8 is $C(R^{B8})$. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is CCl; Z^7 is $C(R^{B7})$; and Z^8 is CF. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is N; Z^7 is $C(R^{B7})$; and Z^8 is $C(R^{B8})$. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is N; Z^7 is $C(R^{B7})$; and Z^8 is CF. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is $C(R^{B6})_2$; Z^7 is $N(R^{B7b})$; and Z^8 is $C(R^{B8})_2$. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is CH_2; Z^7 is $N(R^{B7b})$; and Z^8 is CH_2. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is $N(R^{B6b})$; Z^7 is $C(R^{B7})$; and Z^8 is $C(R^{B8})$. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is $N(R^{B6b})$; Z^7 is $C(R^{B7})$; and Z^8 is CF. In some embodiments, Z^1 is $N(R^{B1b})$; Z^2 is C(O); Z^6 is $C(R^{B6})$; Z^7 is $C(R^{B7})$; and Z^8 is N.

[161] In some embodiments, for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), Z^1 is N; Z^2 is selected from $C(R^{B2})$ and C(O); Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$; Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$; and Z^8 is selected from $C(R^{B8})$, N, and $C(R^{B8})_2$. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$; Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$; and Z^8 is selected from $C(R^{B8})$ and $C(R^{B8})_2$. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is $C(R^{B6})$; Z^7 is $C(R^{B7})$; and Z^8 is $C(R^{B8})$. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is CCl; Z^7 is $C(R^{B7})$; and Z^8 is CF. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is CCF_3; Z^7 is $C(R^{B7})$; and Z^8 is CF. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is N; Z^7 is $C(R^{B7})$; and Z^8 is $C(R^{B8})$. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is N; Z^7 is $C(R^{B7})$; and Z^8 is CF. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is $C(R^{B6})_2$; Z^7 is $N(R^{B7b})$; and Z^8 is $C(R^{B8})_2$. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is CH_2; Z^7 is $N(R^{B7b})$; and Z^8 is CH_2. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is $N(R^{B6b})$; Z^7 is $C(R^{B7})$; and Z^8 is $C(R^{B8})$. In some embodiments, Z^1 is N; Z^2 is $C(R^{B2})$; Z^6 is $N(R^{B6b})$; Z^7 is $C(R^{B7})$; and Z^8 is CF. In some embodiments, Z^1 is $N(R^{B1b})$; Z^2 is C(O); Z^6 is $C(R^{B6})$; Z^7 is $C(R^{B7})$; and Z^8 is N.

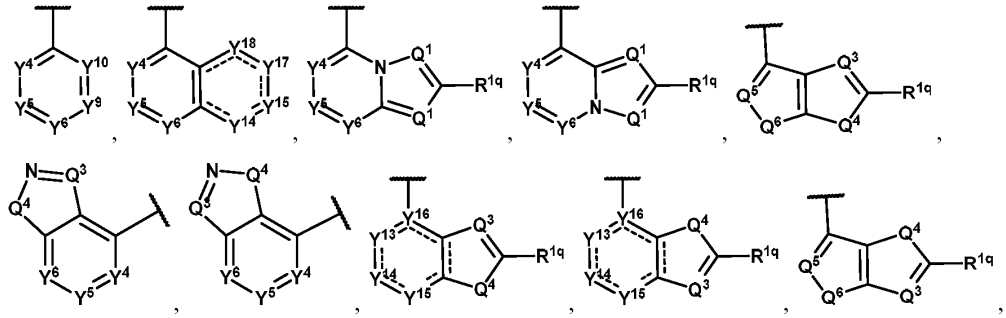
[162] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-4), (A0-5), (a0), (a0-1), (a0-2),] (a0-4), (a0-5), (A), (A-1), (A-2), (A-4), (A-5), (a), (a-1), (a-2), (a-4), (a-5), (A1), (A1-1), (A1-2), (A1-4), (A1-5), (a1), (a1-1), (a1-2), (a1-4), or (a1-5), R^{B6} is selected from hydrogen, halogen, -CN, C_{1-6} alkyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), $-OR^{B12}$, and $-N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20}. In some embodiments, R^{B6} is selected from hydrogen, halogen, and C_{1-3} alkyl. In some embodiments, R^{B6} is selected from hydrogen and halogen. In some embodiments, R^{B6} is hydrogen. In some embodiments, R^{B6} is halogen, such as chlorine. In some embodiments, R^{B6} is -Cl. In some embodiments, R^{B6} is -F. In some embodiments, R^{B6} is fluorine. In some embodiments, R^{B6} is C_{1-6} alkyl optionally substituted with one or more independently selected halogen. In some embodiments, R^{B6} is $-CF_3$. In some embodiments, Z^6 is $C(R^{B6})_2$ and each R^{B6} is hydrogen.

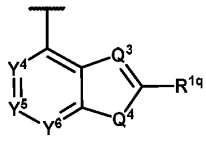
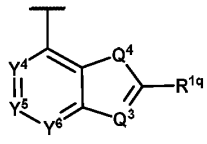
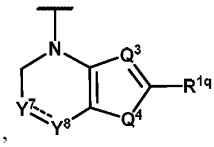
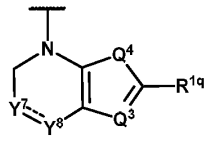
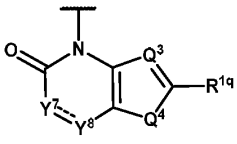
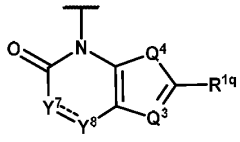
[163] In some embodiments (e.g., a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), R^{B7} is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{B20}; and R^{B7b} is selected from C_{3-12} carbocycle, -C(O)-(C_{3-12} carbocycle), 6- to 12-membered heterocycle, and -C(O)-(3- to 12-membered heterocycle), each of which is optionally substituted with one or more R^{B20}.

[164] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-

1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one or more R^{B20}. In some embodiments, R^{B7} is selected from C_{10} aryl and 9-membered heteroaryl, each of which is optionally substituted with one, two, or three R^{B20}. In some embodiments, R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}. In some embodiments, R^{B7} is selected from naphthalenyl and benzothiophenyl, each of which is optionally substituted with one, two, or three R^{B20}. In some embodiments, R^{B7} is selected from C_{3-10} cycloalkyl, 3- to 10-membered heterocycloalkyl, C_{6-10} aryl, and 5- to 10-membered heteroaryl, each of which is optionally substituted with one, two, or three R^{B20}. In some embodiments, R^{B7} is selected from bicyclic C_{4-10} cycloalkyl, bicyclic 4- to 10-membered heterocycloalkyl, bicyclic C_{7-10} aryl, and bicyclic 7- to 10-membered heteroaryl, each of which is optionally substituted with one, two, or three R^{B20}. In some embodiments, R^{B7} is selected from bridged bicyclic C_{4-10} cycloalkyl, bridged bicyclic 4- to 10-membered heterocycloalkyl, bridged bicyclic C_{7-10} aryl, and bridged bicyclic 7- to 10-membered heteroaryl, each of which is optionally substituted with one, two, or three R^{B20}. In some embodiments, R^{B7} is selected from fused bicyclic C_{4-10} cycloalkyl, fused bicyclic 4- to 10-membered heterocycloalkyl, fused bicyclic C_{7-10} aryl, and fused bicyclic 7- to 10-membered heteroaryl, each of which is optionally substituted with one, two, or three R^{B20}. In some embodiments, R^{B7} is selected from C_{6-10} aryl and 5- to 10-membered heteroaryl, each of which is optionally substituted with one, two, three, four, or five R^{B20}. In some embodiments, R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}. In some embodiments, R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, $-OR^{B22}$, $-N(R^{B22})(R^{B23})$, and C_{3-6} cycloalkyl. In some embodiments, R^{B7} is selected from C_6 aryl and 6-membered heteroaryl, each of which is substituted with one, two, three, four, or five R^{B20}. In some embodiments, R^{B7} is phenyl substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, $-OR^{B22}$, $-N(R^{B22})(R^{B23})$, and C_{3-6} cycloalkyl. In some embodiments, R^{B7} is phenyl substituted with one, two, three, or four substituents independently selected from -F, -Cl, -CN, $-CH_3$, $-CH_2CH_3$, $-CH{=}CH_2$, $-CF_3$, $-C{\equiv}CH$, -OH, $-NH_2$, and -cyclopropyl. In some embodiments, R^{B7} is optionally substituted with one or more R^{B20}, such as one, two, three, four, five, six, or seven R^{B20}.

[165] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B7} is selected from:



, and , wherein:

Q^1, Q^3, and Q^5 are independently selected from N and $C(R^{1q})$;

Q^4 and Q^6 are independently selected from O, S, $C(R^{1q})_2$, and $N(R^{1r})$;

Y^4, Y^5, Y^6, Y^9, and Y^{10} are independently selected from $C(R^{1q})$ and N;

Y^7 and Y^8 are independently selected from $C(R^{1q})$, $C(R^{1q})_2$, N, and $N(R^{1r})$;

Y^{13} is selected from a bond, $C(R^{1q})$, N, C(O), $C(R^{1q})_2$, $C(O)C(R^{1q})_2$, $C(R^{1q})_2C(R^{1q})_2$, $C(R^{1q})_2N(R^{1r})$, and $N(R^{1r})$;

Y^{14}, Y^{15}, Y^{17}, and Y^{18} are independently selected from C(O), $C(R^{1q})$, N, $C(R^{1q})_2$, and $N(R^{1r})$;

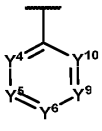
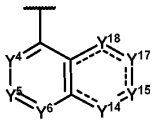
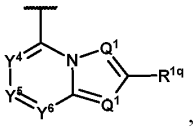
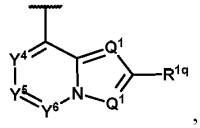
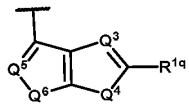
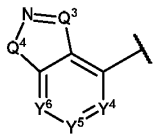
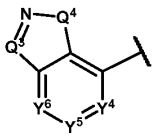
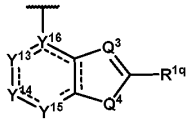
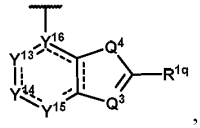
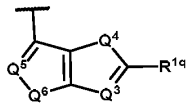
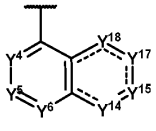
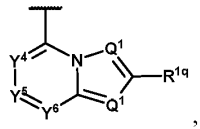
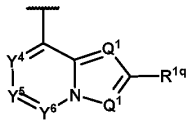
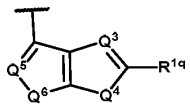
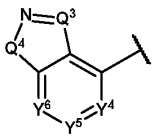
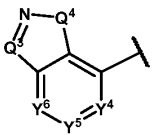
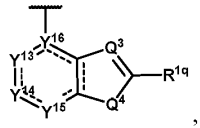
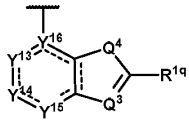
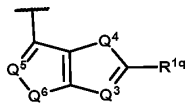
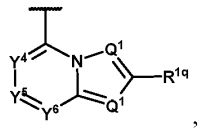
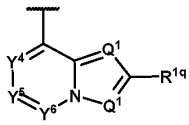
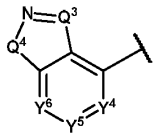
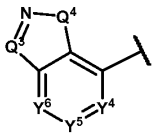
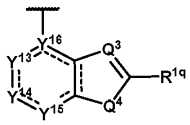
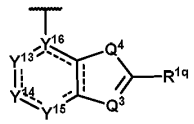
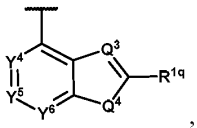
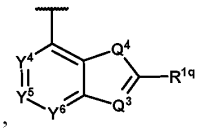
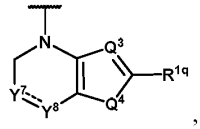
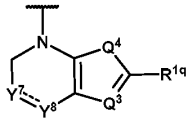
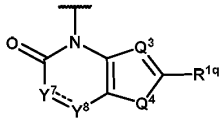
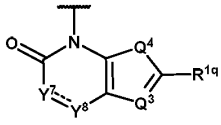
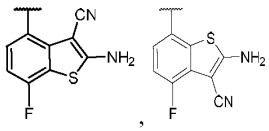
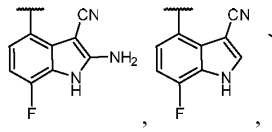
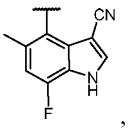
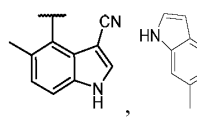
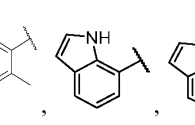
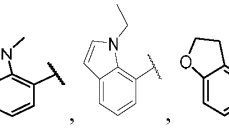
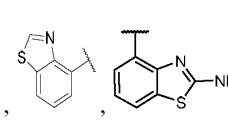
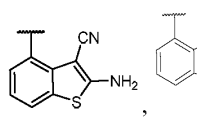
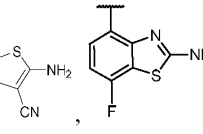
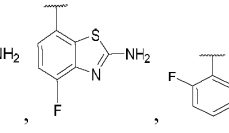
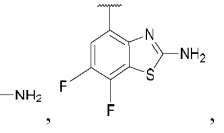
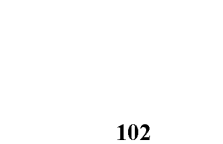
Y^{16} is selected from C, N, and $C(R^{1q})$;

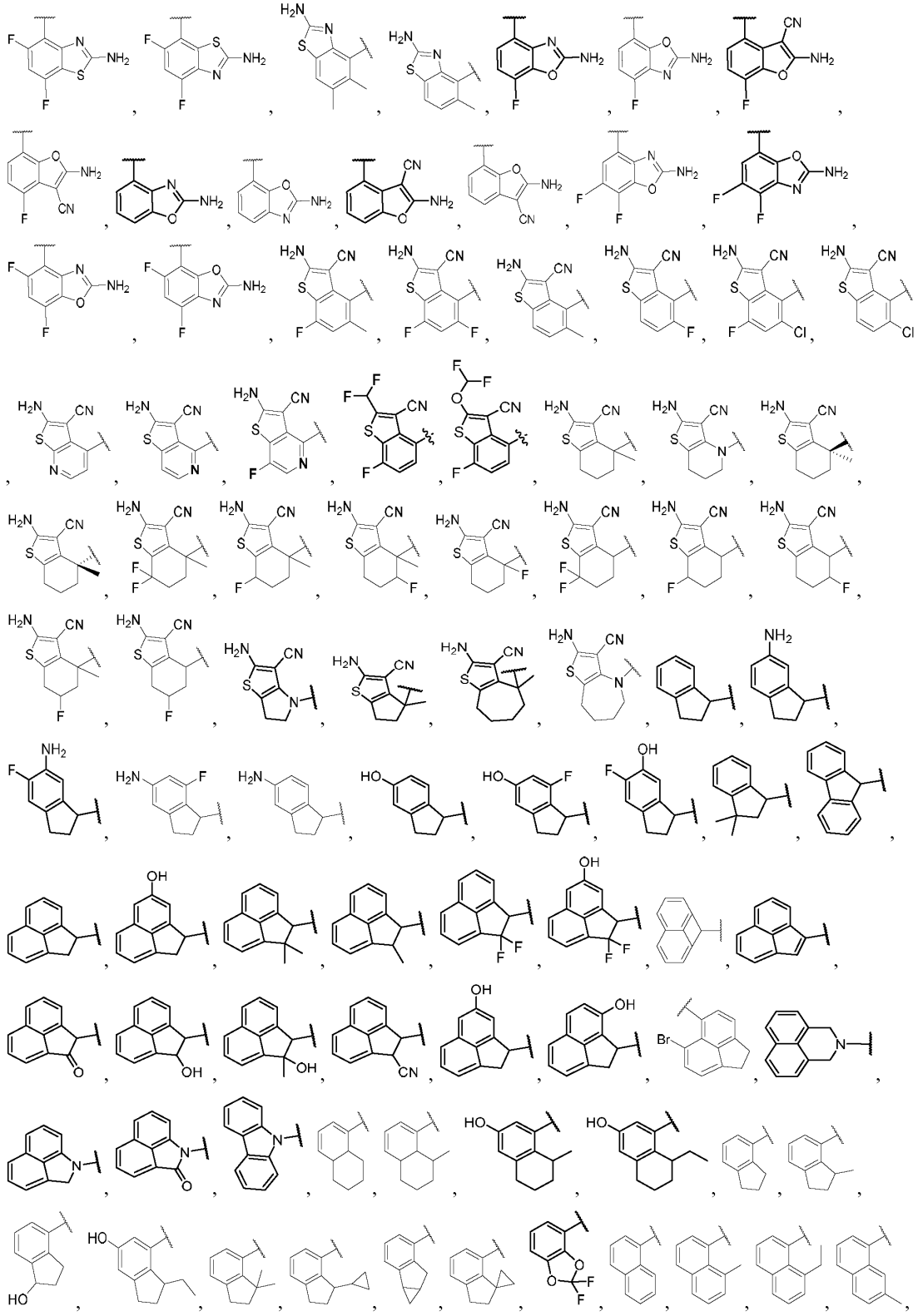
each R^{1q} is independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20}; or two R^{1q} bonded to the same carbon are joined to form 3- to 10-membered heterocycle or C_{3-10} carbocycle, wherein 3- to 10-membered heterocycle and C_{3-10} carbocycle are optionally substituted with one, two, or three R^{B20}; or two R^{1q} bonded to adjacent atoms are joined to form 3- to 10-membered heterocycle or C_{3-10} carbocycle, wherein 3- to 10-membered heterocycle and C_{3-10} carbocycle are optionally substituted with one, two, or three R^{B20}; or one R^{1q} and one R^{1r} are joined to form 3- to 10-membered heterocycle or C_{3-10} carbocycle, wherein 3- to 10-membered heterocycle and C_{3-10} carbocycle are optionally substituted with one, two, or three R^{B20};

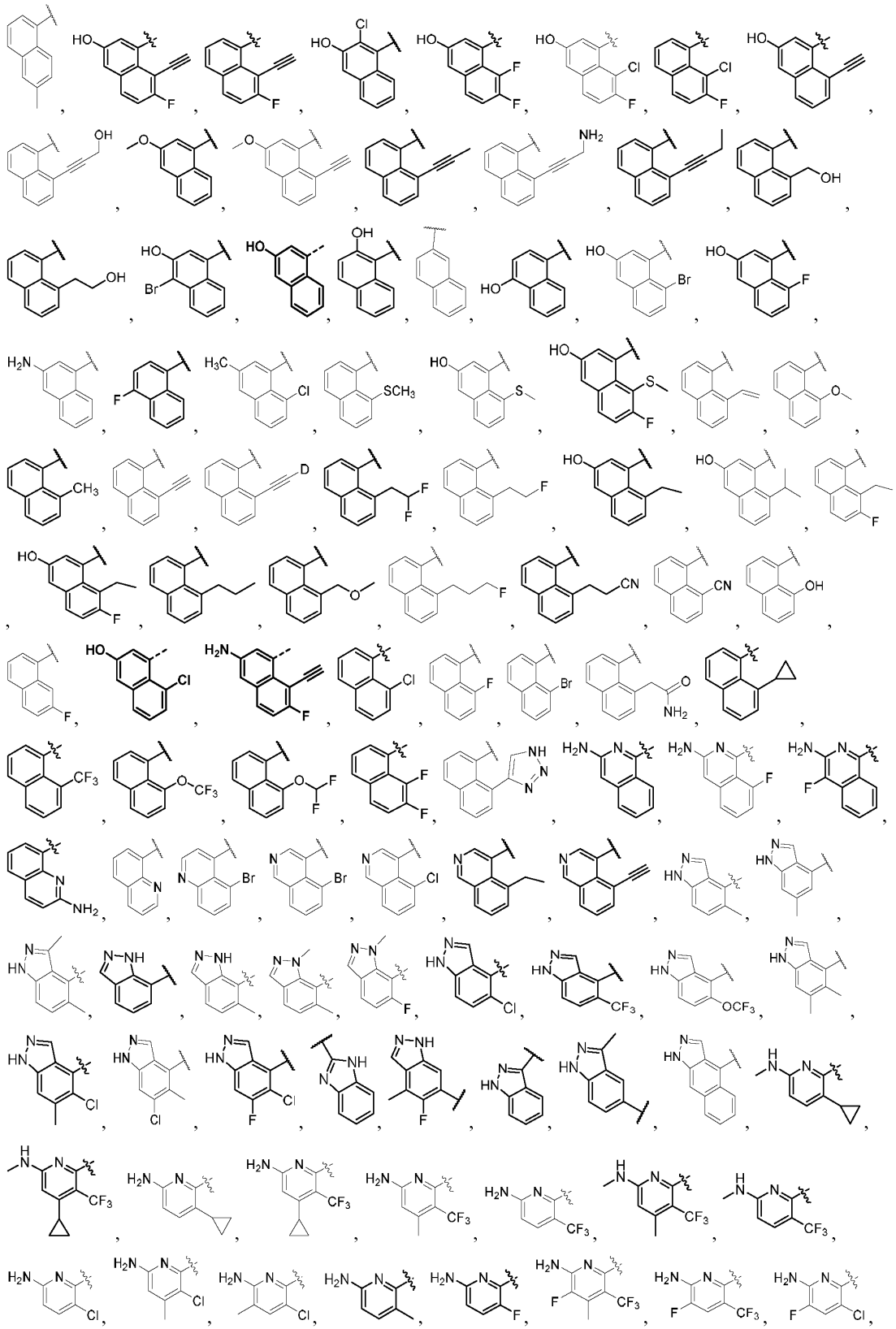
each R^{1r} is independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 10-membered heterocycle, and C_{3-10} carbocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 3- to 10-membered heterocycle, and C_{3-10} carbocycle are optionally substituted with one, two, or three R^{B20}; and

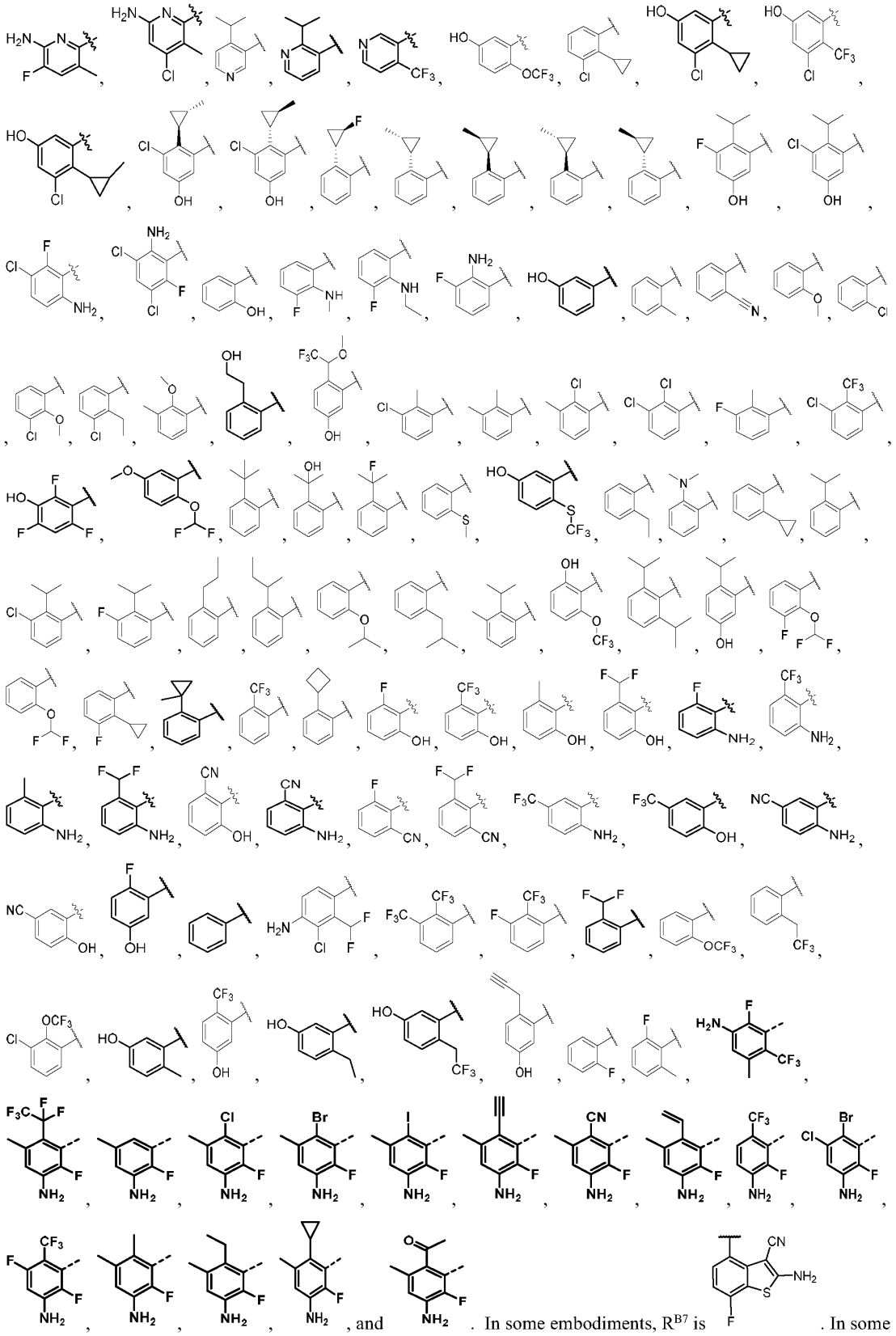
------ indicates a single or double bond such that all valences are satisfied.

[166] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1),

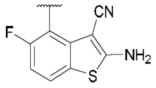
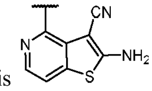
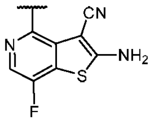
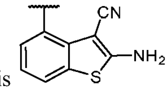
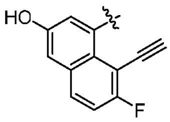
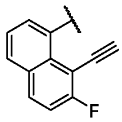
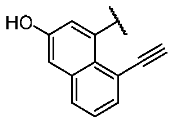
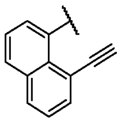
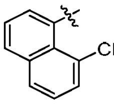
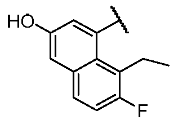
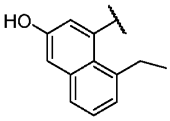
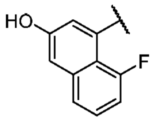
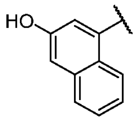
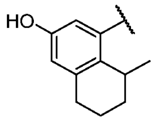
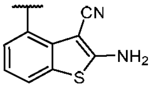
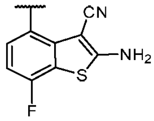
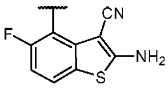
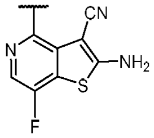
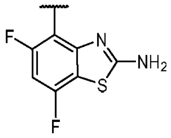
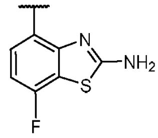
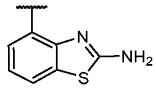
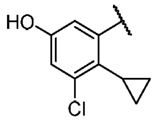
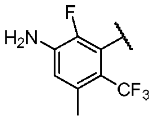
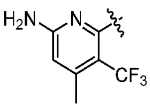
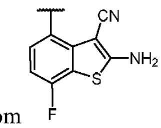
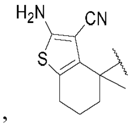
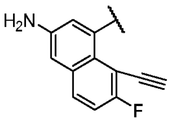
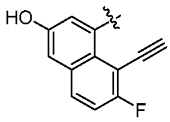
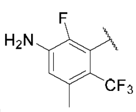
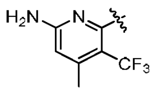
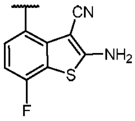
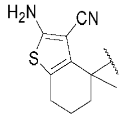
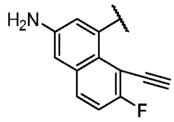
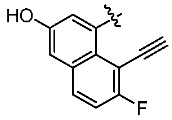
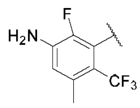
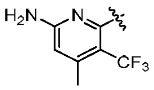
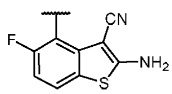
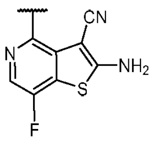
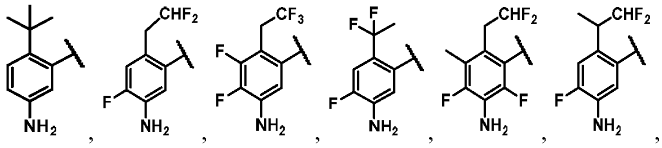
(a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^{B7} is selected from  ,  ,  ,  ,  , and  . In some embodiments, R^{B7} is selected from  ,  ,  ,  ,  , and  . In some embodiments, R^{B7} is selected from  , ,  , ,  ,  ,  ,  ,  ,  ,  ,  ,  , , ,  , , , , , , , , , .

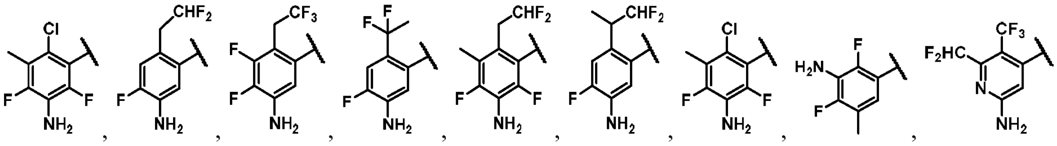


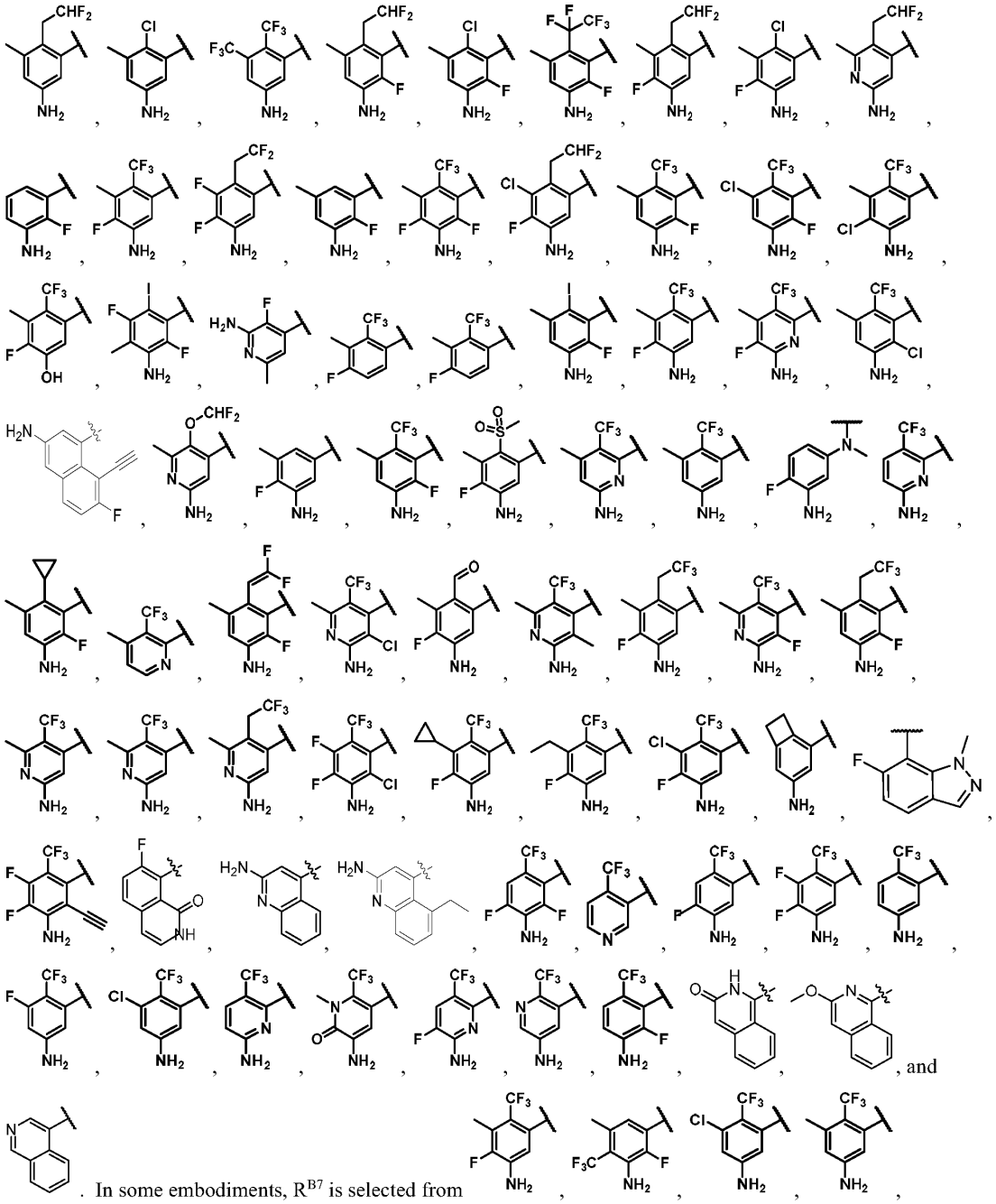




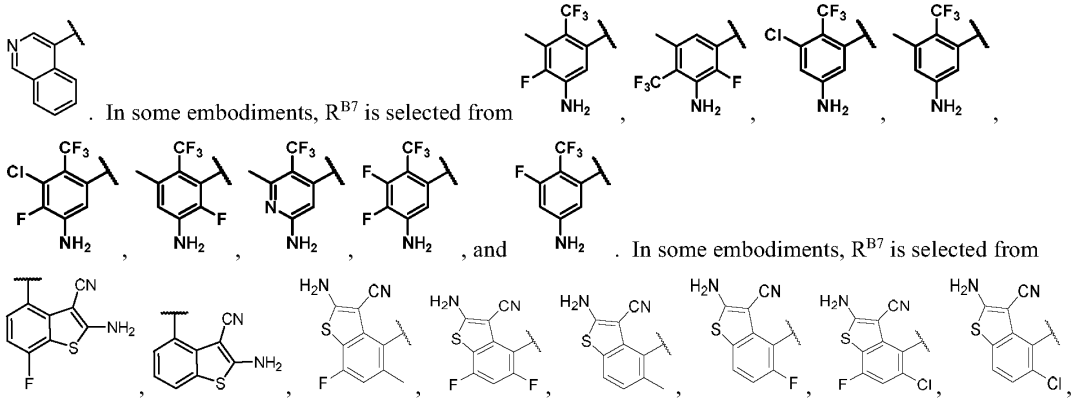
. In some embodiments, R^{B7} is . In some

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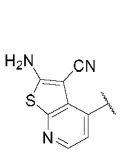
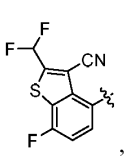
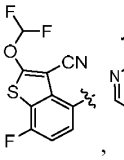
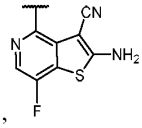
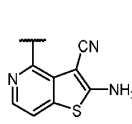
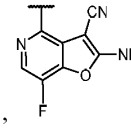
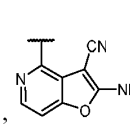
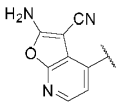
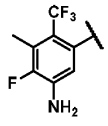
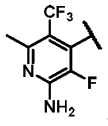
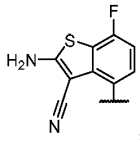
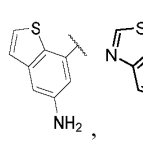
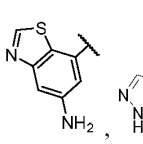
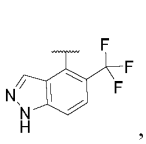
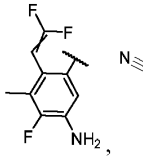
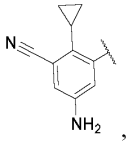
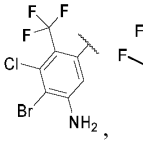
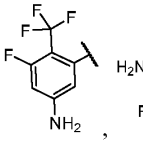
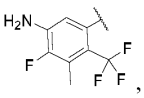
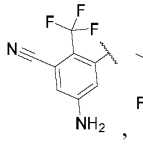
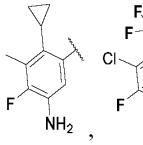
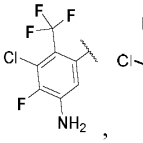
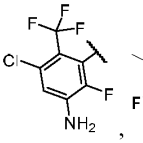
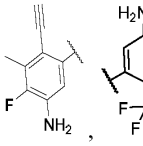
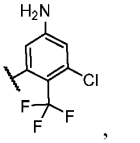
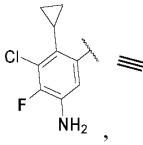
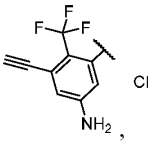
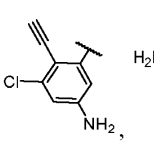
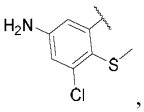
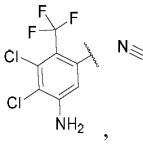
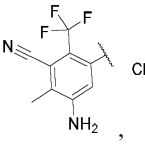
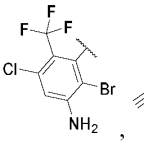
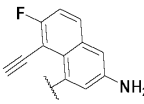
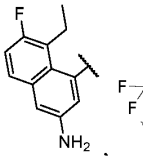
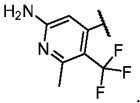
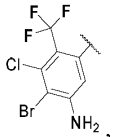
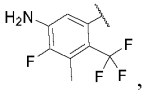
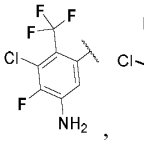
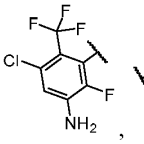
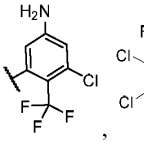
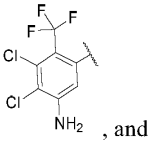
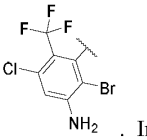
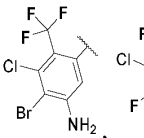
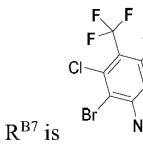
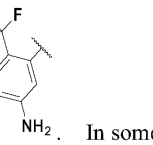
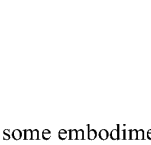
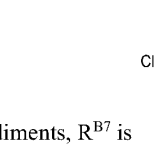
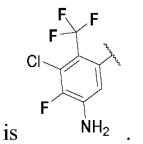


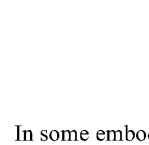


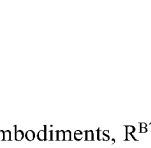
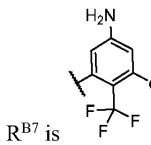
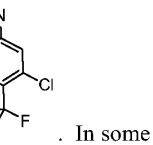
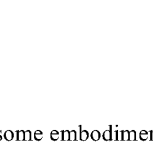
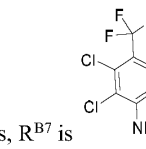
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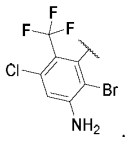





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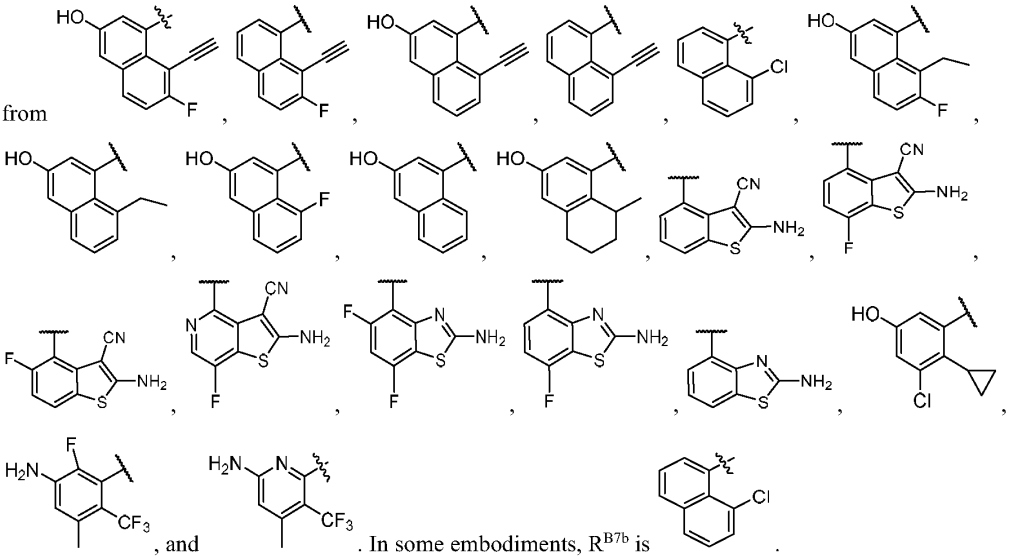
. In some

embodiments, R^{B7} is  .

[167] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, $-OR^{B22}$, $-SR^{B22}$, and $-N(R^{B22})(R^{B23})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{3-6} cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and $-OR^{B22}$. In some embodiments, R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, $-OR^{B22}$, $-N(R^{B22})(R^{B23})$, and C_{3-6} cycloalkyl. In some embodiments, R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, $-CH_3$, $-CH_2CH_3$, $-CH=CH_2$, $-CF_3$, $-C\equiv CH$, -OH, $-NH_2$, and -cyclopropyl. In some embodiments, R^{B7} is substituted with one, two, three, or four substituents independently selected from -F, -Cl, -CN, $-CH_3$, $-CH_2CH_3$, $-CH=CH_2$, $-CF_3$, $-C\equiv CH$, -OH, $-NH_2$, and -cyclopropyl. In some embodiments, R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, $-OR^{B22}$, and $-N(R^{B22})(R^{B23})$. In some embodiments, R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, $-CH_3$, $-C\equiv CH$, -OH, and $-NH_2$. In some embodiments, R^{B7} is substituted with -F, -CN, and $-NH_2$. In some embodiments, R^{B7} is substituted with -F, $-C\equiv CH$, and -OH. In some embodiments, R^{B7} is substituted with $-CF_3$, $-CH_3$, and $-NH_2$. In some embodiments, R^{B7} is substituted with $-CF_3$ and $-NH_2$. In some embodiments, R^{B7} is substituted with $-CF_3$, $-CH_3$, -F, and $-NH_2$. In some embodiments, R^{B7} is substituted with $-CF_3$, -F, and $-NH_2$. In some embodiments, R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, $-CH_3$, $-CH_2CH_3$, $-CH=CH_2$, $-CF_3$, $-C\equiv CH$, -OH, $-NH_2$, and -cyclopropyl.

[168] In some embodiments, for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), R^{B7b} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one or more R^{B20}. In some embodiments, R^{B7b} is selected from C_{10} aryl and 9-membered heteroaryl, each of which is optionally substituted with one, two, or three R^{B20}. In some embodiments, R^{B7b} is selected from naphthalenyl and benzothiophenyl, each of which is optionally substituted with one, two, or three R^{B20}. In some embodiments, R^{B7b} is selected from C_{3-10} cycloalkyl, 3- to 10-membered heterocycloalkyl, C_{6-10} aryl, and 5- to 10-membered heteroaryl, each of which is optionally substituted with one, two, or three R^{B20}. In some embodiments, R^{B7b} is selected from bicyclic C_{4-10} cycloalkyl, bicyclic 4- to 10-membered heterocycloalkyl, bicyclic C_{7-10} aryl, and bicyclic 7- to 10-membered heteroaryl, each of which is optionally substituted with one, two, or three R^{B20}. In some embodiments, R^{B7b} is selected from bridged bicyclic C_{4-10} cycloalkyl, bridged bicyclic 4- to 10-membered heterocycloalkyl, bridged bicyclic C_{7-10} aryl, and bridged bicyclic 7- to 10-membered heteroaryl, each of which is optionally substituted with one, two, or three R^{B20}. In some embodiments, R^{B7b} is selected from fused bicyclic C_{4-10} cycloalkyl, fused bicyclic 4- to 10-membered heterocycloalkyl, fused bicyclic C_{7-10} aryl, and fused bicyclic 7- to 10-membered heteroaryl, each of which is optionally substituted with one, two, or three R^{B20}. In some embodiments, R^{B7b} is selected from C_{6-10} aryl and 5- to 10-membered heteroaryl, each of which is optionally substituted with one, two, three, four, or five R^{B20}. In some embodiments, R^{B7b} is selected from naphthyl, isoquinolinyl, indazolyl,

benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}. In some embodiments, R^{B7b} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, $-OR^{B22}$, $-N(R^{B22})(R^{B23})$, and C_{3-6} cycloalkyl. In some embodiments, R^{B7b} is selected from C_6 aryl and 6-membered heteroaryl, each of which is substituted with one, two, three, four, or five R^{B20}. In some embodiments, R^{B7b} is optionally substituted with one or more R^{B20}, such as one, two, three, four, five, six, or seven R^{B20}.

[169] In some embodiments, for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), R^{B7b} is selected from  . In some embodiments, R^{B7b} is .

[170] In some embodiments, for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), R^{B7b} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, $-OR^{B22}$, $-SR^{B22}$, and $-N(R^{B22})(R^{B23})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{3-6} cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, and $-OR^{B22}$. In some embodiments, R^{B7b} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, $-OR^{B22}$, and $-N(R^{B22})(R^{B23})$. In some embodiments, R^{B7b} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, $-CH_3$, -C≡CH, -OH, and $-NH_2$. In some embodiments, R^{B7b} is substituted with -F, -CN, and $-NH_2$. In some embodiments, R^{B7b} is substituted with -F, -C≡CH, and -OH. In some embodiments, R^{B7b} is substituted with $-CF_3$, $-CH_3$, and $-NH_2$. In some embodiments, R^{B7b} is substituted with $-CF_3$ and $-NH_2$. In some embodiments, R^{B7b} is substituted with $-CF_3$, $-CH_3$, -F, and $-NH_2$. In some embodiments, R^{B7b} is substituted with $-CF_3$, -F, and $-NH_2$. In some embodiments, R^{B7b} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, $-CH_3$, $-CH_2CH_3$, $-CH=CH_2$, $-CF_3$, -C≡CH, -OH, $-NH_2$, and -cyclopropyl. In some embodiments, R^{B7b} is substituted with -Cl.

[171] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B8} is selected from hydrogen, halogen, -CN, C_{1-6} alkyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), $-OR^{B12}$, and $-N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered

heterocycle) are optionally substituted with one or more R^{B20}. In some embodiments, R^{B8} is selected from hydrogen, halogen, and C_{1-3} alkyl. In some embodiments, R^{B8} is selected from hydrogen and halogen. In some embodiments, R^{B8} is hydrogen. In some embodiments, R^{B8} is halogen, such as chlorine. In some embodiments, R^{B8} is -Cl. In some embodiments, R^{B8} is -F. In some embodiments, R^{B8} is $-CF_3$. In some embodiments, R^{B8} is C_{1-6} alkyl optionally substituted with one or more halogen. In some embodiments, R^{B8} is fluorine. In some embodiments, Z^8 is $C(R^{B8})_2$ and each R^{B8} is hydrogen.

[172] In some embodiments (e.g., embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), for a compound described herein, R^{B6} is halogen; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is halogen.

[173] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), Q^2 is 4- to 10-membered heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 4-membered heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 5-membered heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 6-membered heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 7-membered heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 8-membered heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 9-membered heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 10-membered heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, a heterocycle recited in this paragraph is fully saturated or partially unsaturated. In some embodiments, a heterocycle recited in this paragraph is fully saturated. In some embodiments, a heterocycle recited in this paragraph is partially unsaturated. In some embodiments, a heterocycle recited in this paragraph comprises at least one ring nitrogen atom. In some embodiments, a heterocycle recited in this paragraph comprises at least two ring nitrogen atoms. In some embodiments, a heterocycle recited in this paragraph comprises exactly two ring nitrogen atoms. In some embodiments, a heterocycle recited in this paragraph comprises at least one ring oxygen atom. In some embodiments, a heterocycle recited in this paragraph comprises one ring nitrogen atom and one ring oxygen atom.

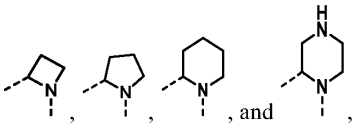
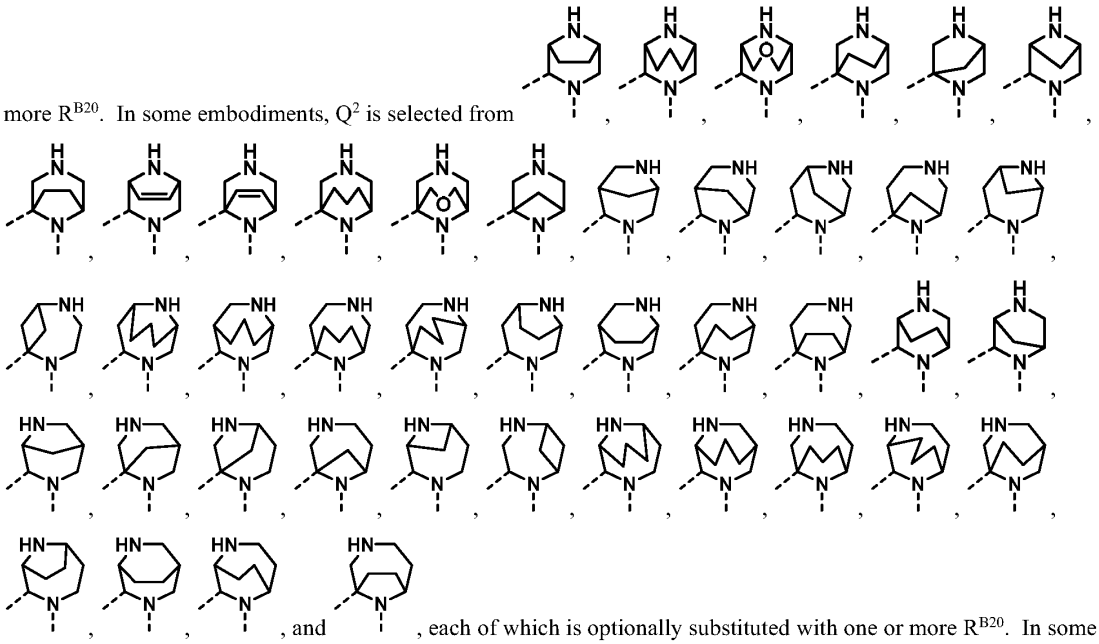
[174] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), Q^2 is 4- to 7-membered monocyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 4-membered monocyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 5-membered monocyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 6-membered monocyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 7-membered monocyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is 4- to 7-membered monocyclic heterocycloalkyl, which (i) comprises only one ring heteroatom and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 4-

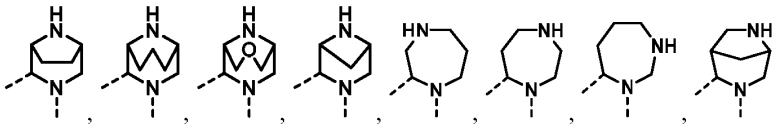
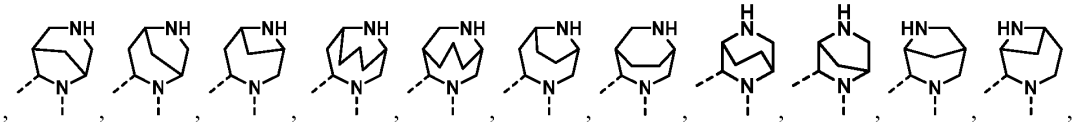
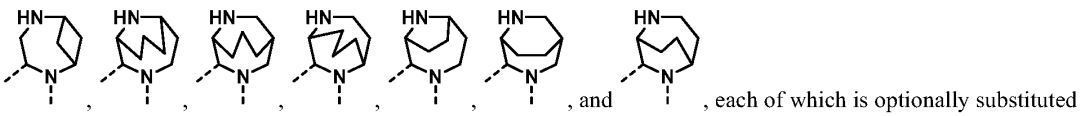
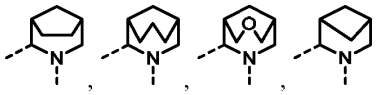
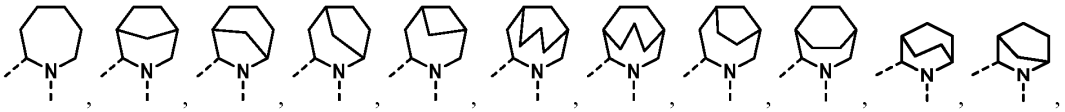
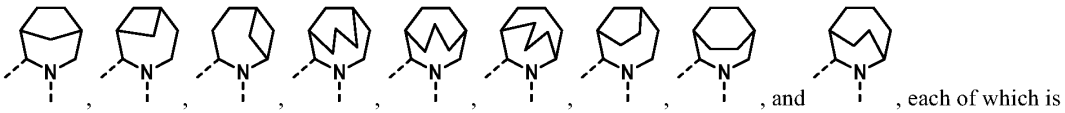
membered monocyclic heterocycloalkyl, which (i) comprises only one ring heteroatom and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 5-membered monocyclic heterocycloalkyl, which (i) comprises only one ring heteroatom and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 6-membered monocyclic heterocycloalkyl, which (i) comprises only one ring heteroatom and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 7-membered monocyclic heterocycloalkyl, which (i) comprises only one ring heteroatom and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is 4- to 7-membered monocyclic heterocycloalkyl, which (i) comprises at least two ring heteroatoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 4-membered monocyclic heterocycloalkyl, which (i) comprises at least two ring heteroatoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 5-membered monocyclic heterocycloalkyl, which (i) comprises at least two ring heteroatoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 6-membered monocyclic heterocycloalkyl, which (i) comprises at least two ring heteroatoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 7-membered monocyclic heterocycloalkyl, which (i) comprises at least two ring heteroatoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, a heterocycle recited in this paragraph is fully saturated or partially unsaturated. In some embodiments, a heterocycle recited in this paragraph is fully saturated. In some embodiments, a heterocycle recited in this paragraph is partially unsaturated. In some embodiments, a heterocycle recited in this paragraph comprises at least one ring nitrogen atom. In some embodiments, a heterocycle recited in this paragraph comprises at least two ring nitrogen atoms. In some embodiments, a heterocycle recited in this paragraph comprises exactly two ring nitrogen atoms. In some embodiments, a heterocycle recited in this paragraph comprises at least one ring oxygen atom. In some embodiments, a heterocycle recited in this paragraph comprises one ring nitrogen atom and one ring oxygen atom.

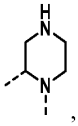
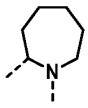
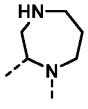
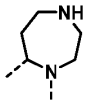
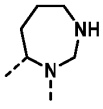
[175] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), Q^2 is 4- to 7-membered monocyclic heterocycloalkyl, which (i) comprises two ring nitrogen atoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 4-membered monocyclic heterocycloalkyl, which (i) comprises two ring nitrogen atoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 5-membered monocyclic heterocycloalkyl, which (i) comprises two ring nitrogen atoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 6-membered monocyclic heterocycloalkyl, which (i) comprises two ring nitrogen atoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 7-membered monocyclic heterocycloalkyl, which (i) comprises two ring nitrogen atoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is 6- to 9-membered bridged bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 6-membered bridged bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 7-membered bridged bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 8-membered bridged bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 9-membered bridged bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is 6- to 9-membered bridged bicyclic heterocycloalkyl, which (i) comprises only one ring heteroatom and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 6-membered bridged bicyclic heterocycloalkyl, which (i) comprises only one ring heteroatom and (ii) is

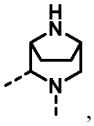
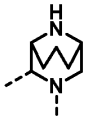
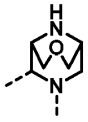
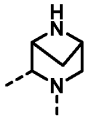
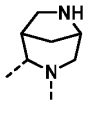
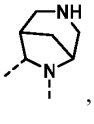
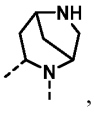
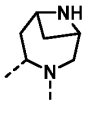
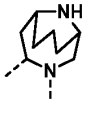
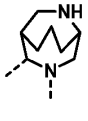
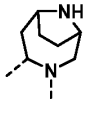
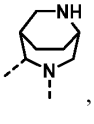
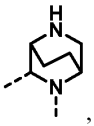
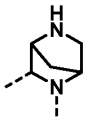
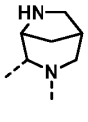
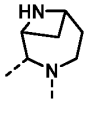
optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 7-membered bridged bicyclic heterocycloalkyl, which (i) comprises only one ring heteroatom and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 8-membered bridged bicyclic heterocycloalkyl, which (i) comprises only one ring heteroatom and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 9-membered bridged bicyclic heterocycloalkyl, which (i) comprises only one ring heteroatom and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is 6- to 9-membered bridged bicyclic heterocycloalkyl, which (i) comprises at least two ring heteroatoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 6-membered bridged bicyclic heterocycloalkyl, which (i) comprises at least two ring heteroatoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 7-membered bridged bicyclic heterocycloalkyl, which (i) comprises at least two ring heteroatoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 8-membered bridged bicyclic heterocycloalkyl, which (i) comprises at least two ring heteroatoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 9-membered bridged bicyclic heterocycloalkyl, which (i) comprises at least two ring heteroatoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, a heterocycle recited in this paragraph is fully saturated or partially unsaturated. In some embodiments, a heterocycle recited in this paragraph is fully saturated. In some embodiments, a heterocycle recited in this paragraph is partially unsaturated. In some embodiments, a heterocycle recited in this paragraph comprises at least one ring nitrogen atom. In some embodiments, a heterocycle recited in this paragraph comprises at least two ring nitrogen atoms. In some embodiments, a heterocycle recited in this paragraph comprises exactly two ring nitrogen atoms. In some embodiments, a heterocycle recited in this paragraph comprises at least one ring oxygen atom. In some embodiments, a heterocycle recited in this paragraph comprises one ring nitrogen atom and one ring oxygen atom. In some embodiments, Q^2 is 6- to 9-membered bridged bicyclic heterocycloalkyl, which (i) comprises two ring nitrogen atoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 6-membered bridged bicyclic heterocycloalkyl, which (i) comprises two ring nitrogen atoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 7-membered bridged bicyclic heterocycloalkyl, which (i) comprises two ring nitrogen atoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 8-membered bridged bicyclic heterocycloalkyl, which (i) comprises two ring nitrogen atoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 9-membered bridged bicyclic heterocycloalkyl, which (i) comprises two ring nitrogen atoms and (ii) is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is 6- to 10-membered fused bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 6-membered fused bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 7-membered fused bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 8-membered fused bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 9-membered fused bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 10-membered fused bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, a heterocycle recited in this paragraph is fully saturated or partially unsaturated. In some embodiments, a heterocycle recited in this paragraph is fully saturated. In some embodiments, a heterocycle recited in this paragraph is partially unsaturated. In some embodiments, a heterocycle recited in this paragraph comprises at least one ring nitrogen atom. In some embodiments, a heterocycle recited in this paragraph comprises at least two ring nitrogen atoms. In some embodiments, a heterocycle recited in this paragraph comprises exactly two ring nitrogen atoms. In some

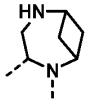
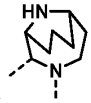
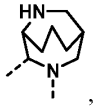
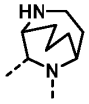
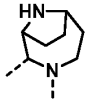
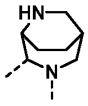
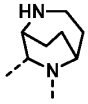
embodiments, a heterocycle recited in this paragraph comprises at least one ring oxygen atom. In some embodiments, a heterocycle recited in this paragraph comprises one ring nitrogen atom and one ring oxygen atom. In some embodiments, Q^2 is 6- to 12-membered spirocyclic bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 6-membered spirocyclic bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 7-membered spirocyclic bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 8-membered spirocyclic bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 9-membered spirocyclic bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is a 10-membered spirocyclic bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}. In some embodiments, a heterocycle recited in this paragraph is fully saturated or partially unsaturated. In some embodiments, a heterocycle recited in this paragraph is fully saturated. In some embodiments, a heterocycle recited in this paragraph is partially unsaturated. In some embodiments, a heterocycle recited in this paragraph comprises at least one ring nitrogen atom. In some embodiments, a heterocycle recited in this paragraph comprises at least two ring nitrogen atoms. In some embodiments, a heterocycle recited in this paragraph comprises exactly two ring nitrogen atoms. In some embodiments, a heterocycle recited in this paragraph comprises at least one ring oxygen atom. In some embodiments, a heterocycle recited in this paragraph comprises one ring nitrogen atom and one ring oxygen atom.

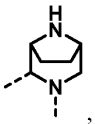
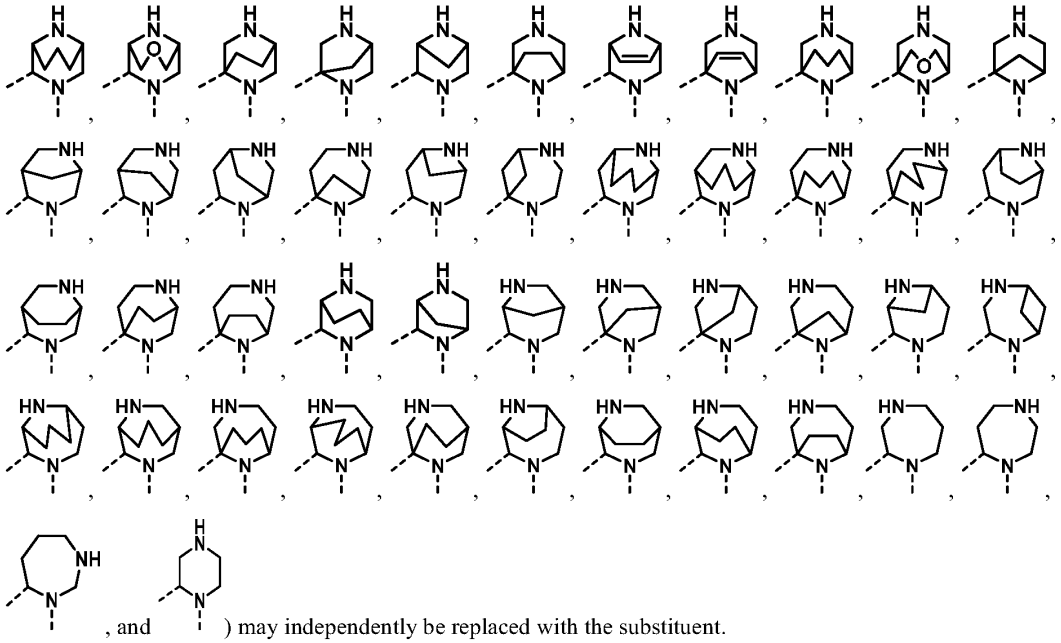
[176] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), Q^2 is selected from  , each of which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is selected from  , each of which is optionally substituted with one or more R^{B20}. In some

embodiments, Q^2 is selected from  ,  ,  , and , each of which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is selected from  ,  ,  , and , each of which is optionally substituted with one or more R^{B20}.

[177] In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is


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R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is  , which is optionally substituted with one or more R^{B20}.

[178] It will be understood that when Q^2 is substituted (e.g., by $-J^1-J^2-J^3-DG$, $-J^1-J^2-J^3-LG$, and/or one or more R^{B20}), any hydrogen on one or more carbon and/or nitrogen atoms of the embodiments above, (e.g.,  ,  , and) may independently be replaced with the substituent.

[179] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1),

(a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently halogen. In embodiments, R^{B20} is independently -F. In embodiments, R^{B20} is independently -Cl. In embodiments, R^{B20} is independently -Br. In embodiments, R^{B20} is independently -I. In embodiments, R^{B20} is independently oxo. In embodiments, R^{B20} is independently -CN. In embodiments, R^{B20} is independently C_{1-6} alkyl. In embodiments, R^{B20} is independently C_{2-6} alkenyl. In embodiments, R^{B20} is independently C_{2-6} alkynyl. In embodiments, R^{B20} is independently 2- to 6-membered heteroalkyl. In embodiments, R^{B20} is independently 3- to 6-membered heteroalkenyl. In embodiments, R^{B20} is independently 3- to 6-membered heteroalkynyl. In embodiments, R^{B20} is independently -C_{0-6} alkyl-(C_{3-12} carbocycle). In embodiments, R^{B20} is independently -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle). In embodiments, R^{B20} is independently -C_{0-6} alkyl-(3- to 12-membered heterocycle). In embodiments, R^{B20} is independently -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle). In embodiments, R^{B20} is independently -OR^{B22}. In embodiments, R^{B20} is independently -SR^{B22}. In embodiments, R^{B20} is independently -$N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently =NR^{B22}. In embodiments, R^{B20} is independently =$C(R^{B21})_2$. In embodiments, R^{B20} is independently -$C(O)OR^{B22}$. In embodiments, R^{B20} is independently -$OC(O)N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently -$N(R^{B22})C(O)OR^{B22}$. In embodiments, R^{B20} is independently -$N(R^{B22})S(O)_2R^{B22}$. In embodiments, R^{B20} is independently -$C(O)R^{B22}$. In embodiments, R^{B20} is independently -$S(O)R^{B22}$. In embodiments, R^{B20} is independently -$OC(O)R^{B22}$. In embodiments, R^{B20} is independently -$C(O)N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently -$C(O)C(O)N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently -$N(R^{B22})C(O)R^{B22}$. In embodiments, R^{B20} is independently -$S(O)_2R^{B22}$. In embodiments, R^{B20} is independently -$S(O)(NR^{B22})R^{B22}$. In embodiments, R^{B20} is independently -$S(O)_2N(R^{B22})(R^{B23})$-. In embodiments, R^{B20} is independently -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle. In embodiments, two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, wherein C_{3-12} carbocycle and 3- to 12-membered heterocycle optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -

$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_{1-6} alkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_{2-6} alkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_{2-6} alkynyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently 2- to 6-membered heteroalkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently 3- to 6-membered heteroalkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently 3- to 6-membered heteroalkynyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently $-C_{0-6}$ alkyl-(C_{3-12} carbocycle) optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle) optionally substituted with

one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle) optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_1 alkyl. In embodiments, R^{B20} is independently C_2 alkyl. In embodiments, R^{B20} is independently C_3 alkyl. In embodiments, R^{B20} is independently C_4 alkyl. In embodiments, R^{B20} is independently C_5 alkyl. In embodiments, R^{B20} is independently C_6 alkyl. In embodiments, R^{B20} is independently C_1 alkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_2 alkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_3 alkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_4 alkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_5 alkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl,

C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_6 alkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_2 alkenyl. In embodiments, R^{B20} is independently C_3 alkenyl. In embodiments, R^{B20} is independently C_4 alkenyl. In embodiments, R^{B20} is independently C_5 alkenyl. In embodiments, R^{B20} is independently C_6 alkenyl. In embodiments, R^{B20} is independently C_2 alkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_3 alkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_4 alkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_5 alkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_6 alkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_2 alkynyl. In embodiments, R^{B20} is independently C_3 alkynyl. In embodiments, R^{B20} is independently C_4 alkynyl. In embodiments, R^{B20} is independently C_5 alkynyl. In embodiments, R^{B20} is independently C_6 alkynyl. In embodiments, R^{B20} is independently C_2 alkynyl optionally substituted with one or more substituents independently selected from halogen,

oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_3 alkynyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_4 alkynyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_5 alkynyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently C_6 alkynyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B20} is independently -OH. In embodiments, R^{B20} is independently -SH. In embodiments, R^{B20} is independently -NH_2. In embodiments, R^{B20} is independently =NH. In embodiments, R^{B20} is independently =CH_2. In embodiments, R^{B20} is independently -$C(O)OH$. In embodiments, R^{B20} is independently -$C(O)CH_3$. In embodiments, R^{B20} is independently -$S(O)R^{B22}$. In embodiments, R^{B20} is independently -$OC(O)CH_3$. In embodiments, R^{B20} is independently -$C(O)NH_2$. In embodiments, R^{B20} is independently -$N(R^{B22})C(O)CH_3$. In embodiments, R^{B20} is independently -OCH_3. In embodiments, R^{B20} is independently -SCH_3. In embodiments, R^{B20} is independently -$N(CH_3)_2$.

[180] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B9} is independently hydrogen. In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B9} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to

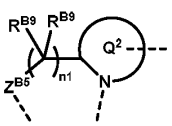
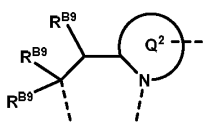
12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$-, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently halogen. In embodiments, R^{B9} is independently -F. In embodiments, R^{B9} is independently -Cl. In embodiments, R^{B9} is independently -Br. In embodiments, R^{B9} is independently-I. In embodiments, R^{B9} is independently oxo. In embodiments, R^{B9} is independently -CN. In embodiments, R^{B9} is independently C_{1-6} alkyl. In embodiments, R^{B9} is independently C_{2-6} alkenyl. In embodiments, R^{B9} is independently C_{2-6} alkynyl. In embodiments, R^{B9} is independently 2- to 6-membered heteroalkyl. In embodiments, R^{B9} is independently 3- to 6-membered heteroalkenyl. In embodiments, R^{B9} is independently 3- to 6-membered heteroalkynyl. In embodiments, R^{B9} is independently $-C_{0-6}$ alkyl-(C_{3-12} carbocycle). In embodiments, R^{B9} is independently -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle). In embodiments, R^{B9} is independently $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle). In embodiments, R^{B9} is independently -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle). In embodiments, R^{B9} is independently $-OR^{B22}$. In embodiments, R^{B9} is independently $-SR^{B22}$. In embodiments, R^{B9} is independently $-N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently $=NR^{B22}$. In embodiments, R^{B9} is independently $=C(R^{B21})_2$. In embodiments, R^{B9} is independently $-C(O)OR^{B22}$. In embodiments, R^{B9} is independently $-OC(O)N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently $-N(R^{B22})C(O)OR^{B22}$. In embodiments, R^{B9} is independently $-N(R^{B22})S(O)_2R^{B22}$. In embodiments, R^{B9} is independently $-C(O)R^{B22}$. In embodiments, R^{B9} is independently $-S(O)R^{B22}$. In embodiments, R^{B9} is independently $-OC(O)R^{B22}$. In embodiments, R^{B9} is independently $-C(O)N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently $-C(O)C(O)N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently $-N(R^{B22})C(O)R^{B22}$. In embodiments, R^{B9} is independently $-S(O)_2R^{B22}$. In embodiments, R^{B9} is independently $-S(O)(NR^{B22})R^{B22}$. In embodiments, R^{B9} is independently $-S(O)_2N(R^{B22})(R^{B23})$-. In embodiments, R^{B9} is independently $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, two R^{B9} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle. In embodiments, two R^{B9} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, wherein C_{3-12} carbocycle and 3- to 12-membered heterocycle optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_{1-6} alkyl optionally substituted with one or

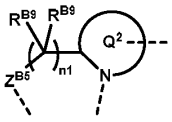
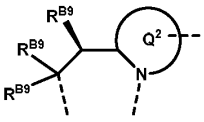
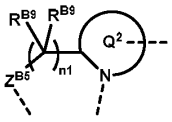
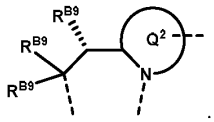
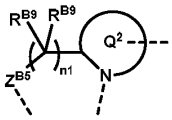
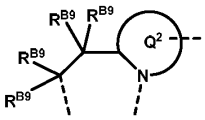
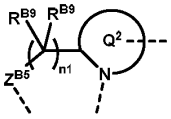
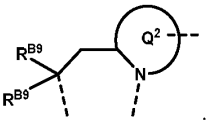
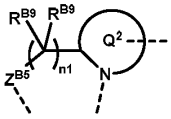
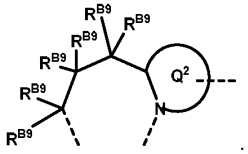
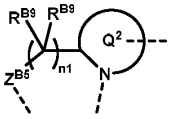
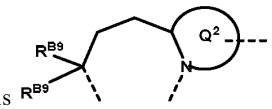
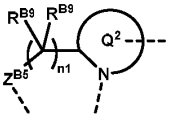
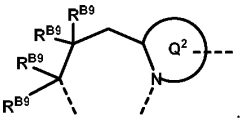
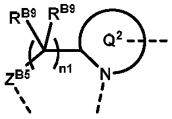
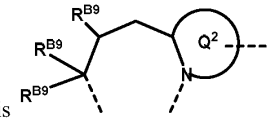
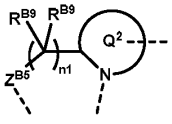
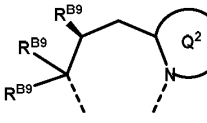
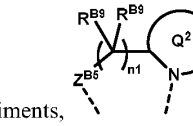
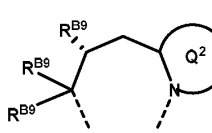
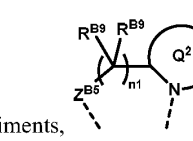
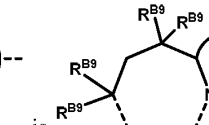
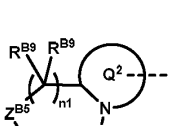
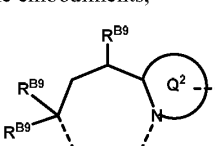
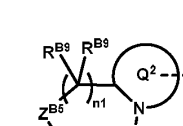
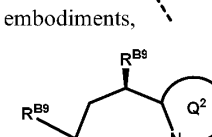
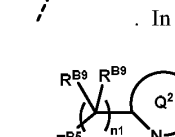
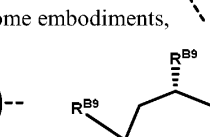
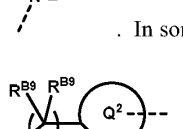
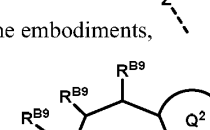
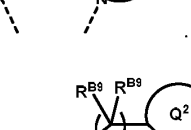
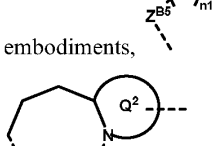
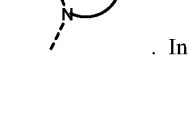
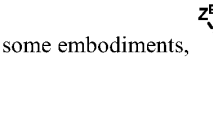
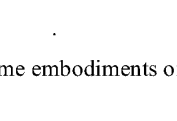
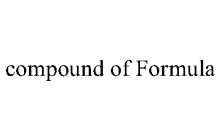
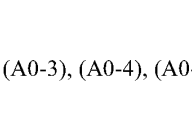
more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_{2-6} alkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_{2-6} alkynyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently 2- to 6-membered heteroalkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently 3- to 6-membered heteroalkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently 3- to 6-membered heteroalkynyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently $-C_{0-6}$ alkyl-(C_{3-12} carbocycle) optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle) optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, -

$OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle) optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_1 alkyl. In embodiments, R^{B9} is independently C_2 alkyl. In embodiments, R^{B9} is independently C_3 alkyl. In embodiments, R^{B9} is independently C_4 alkyl. In embodiments, R^{B9} is independently C_5 alkyl. In embodiments, R^{B9} is independently C_6 alkyl. In embodiments, R^{B9} is independently unsubstituted C_1 alkyl. In embodiments, R^{B9} is independently unsubstituted C_2 alkyl. In embodiments, R^{B9} is independently unsubstituted C_3 alkyl. In embodiments, R^{B9} is independently unsubstituted C_4 alkyl. In embodiments, R^{B9} is independently unsubstituted C_5 alkyl. In embodiments, R^{B9} is independently unsubstituted C_6 alkyl. In embodiments, R^{B9} is independently C_1 alkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_2 alkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_3 alkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_4 alkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_5 alkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl,

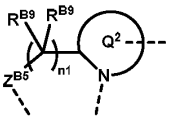
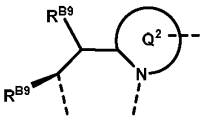
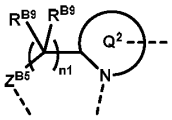
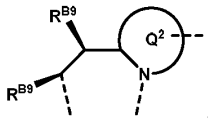
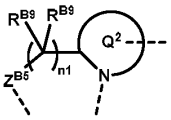
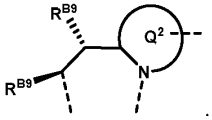
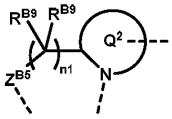
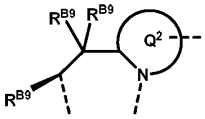
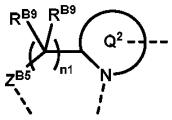
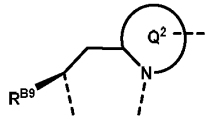
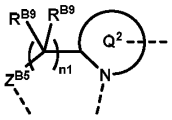
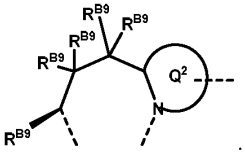
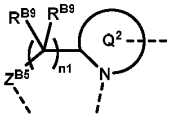
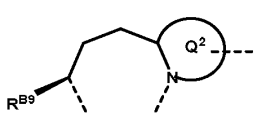
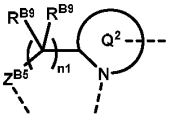
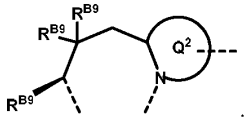
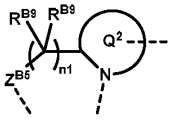
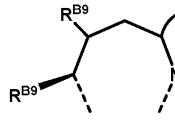
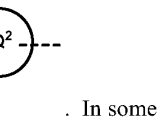
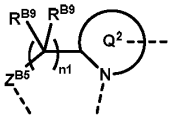
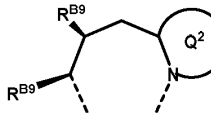
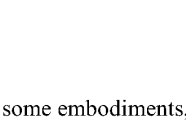
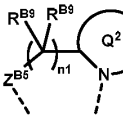
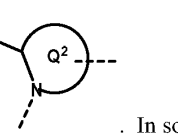
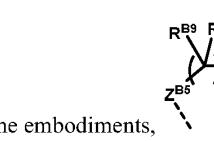
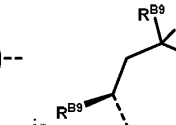
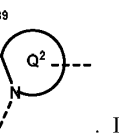
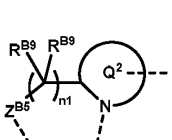
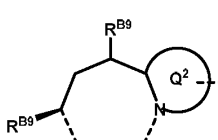
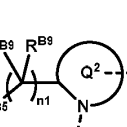
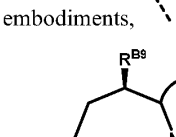
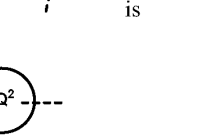
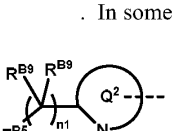
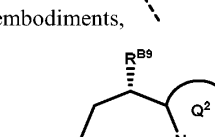
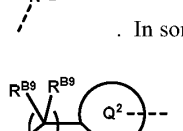
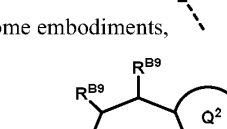
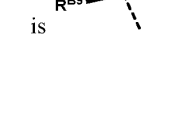
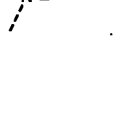
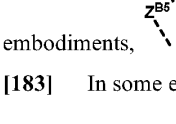
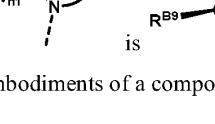
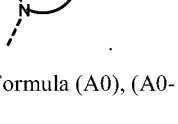
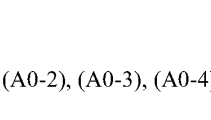
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In embodiments, R^{B9} is independently C_6 alkyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_2 alkenyl. In embodiments, R^{B9} is independently C_3 alkenyl. In embodiments, R^{B9} is independently C_4 alkenyl. In embodiments, R^{B9} is independently C_5 alkenyl. In embodiments, R^{B9} is independently C_6 alkenyl. In embodiments, R^{B9} is independently unsubstituted C_2 alkenyl. In embodiments, R^{B9} is independently unsubstituted C_3 alkenyl. In embodiments, R^{B9} is independently unsubstituted C_4 alkenyl. In embodiments, R^{B9} is independently unsubstituted C_5 alkenyl. In embodiments, R^{B9} is independently unsubstituted C_6 alkenyl. In embodiments, R^{B9} is independently C_2 alkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_3 alkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_4 alkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_5 alkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_6 alkenyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_2 alkynyl. In embodiments, R^{B9} is independently C_3 alkynyl. In embodiments,

R^{B9} is independently C_4 alkynyl. In embodiments, R^{B9} is independently C_5 alkynyl. In embodiments, R^{B9} is independently C_6 alkynyl. In embodiments, R^{B9} is independently unsubstituted C_2 alkynyl. In embodiments, R^{B9} is independently unsubstituted C_3 alkynyl. In embodiments, R^{B9} is independently unsubstituted C_4 alkynyl. In embodiments, R^{B9} is independently unsubstituted C_5 alkynyl. In embodiments, R^{B9} is independently unsubstituted C_6 alkynyl. In embodiments, R^{B9} is independently C_2 alkynyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_3 alkynyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_4 alkynyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_5 alkynyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently C_6 alkynyl optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$. In embodiments, R^{B9} is independently -OH. In embodiments, R^{B9} is independently -SH. In embodiments, R^{B9} is independently $-NH_2$. In embodiments, R^{B9} is independently =NH. In embodiments, R^{B9} is independently $=CH_2$. In embodiments, R^{B9} is independently -C(O)OH. In embodiments, R^{B9} is independently $-C(O)CH_3$. In embodiments, R^{B9} is independently $-S(O)R^{B22}$. In embodiments, R^{B9} is independently $-OC(O)CH_3$. In embodiments, R^{B9} is independently $-C(O)NH_2$. In embodiments, R^{B9} is independently $-N(R^{B22})C(O)CH_3$. In embodiments, R^{B9} is independently $-OCH_3$. In embodiments, R^{B9} is independently $-SCH_3$. In embodiments, R^{B9} is independently $-N(CH_3)_2$.

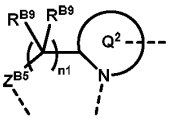
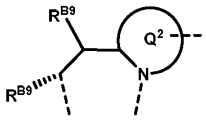
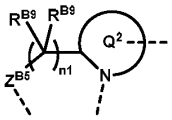
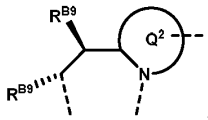
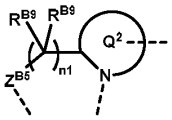
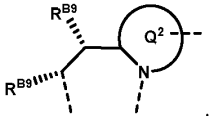
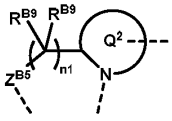
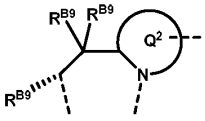
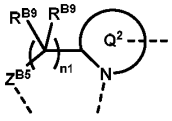
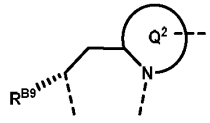
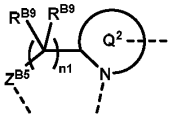
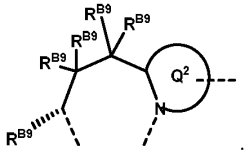
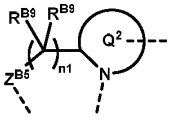
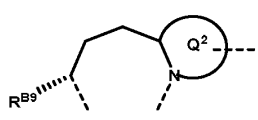
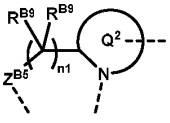
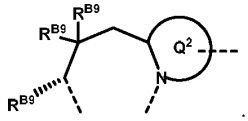
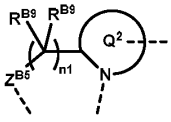
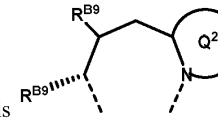
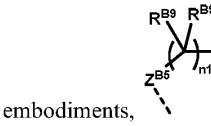
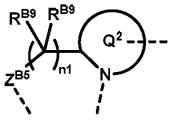
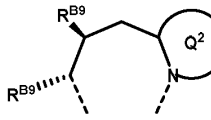
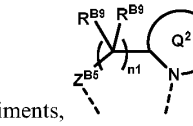
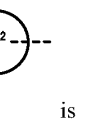
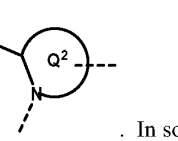
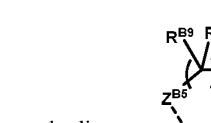
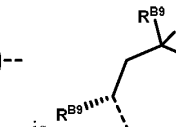
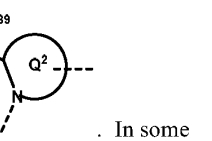
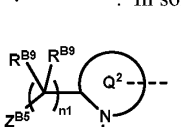
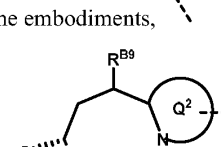
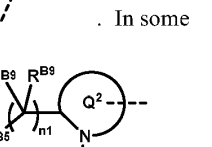
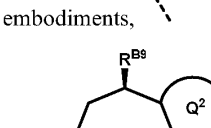
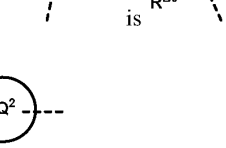
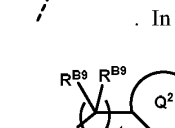
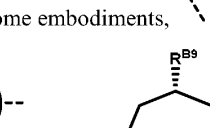
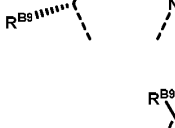
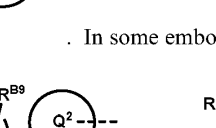
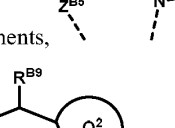
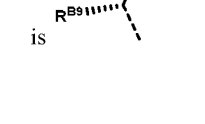
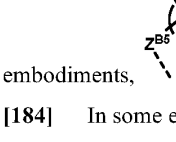
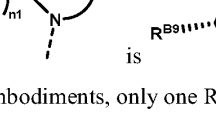
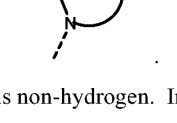
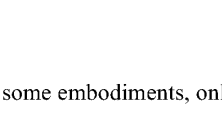
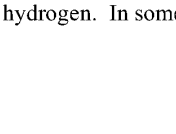
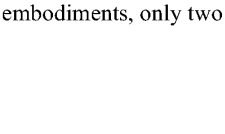
[181] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), or (a0-6),  is  . In some

[182] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6),

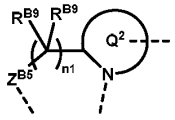
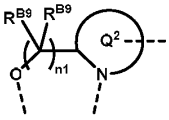
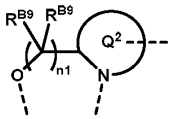
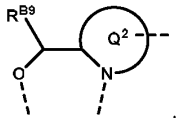
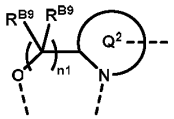
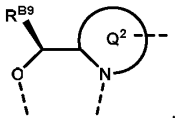
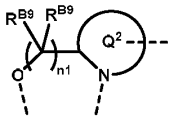
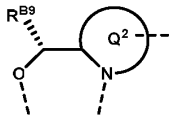
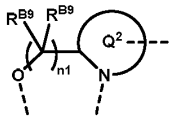
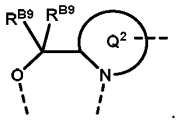
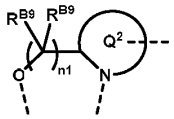
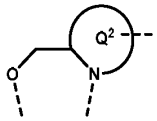
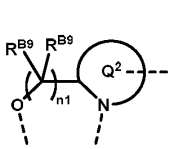
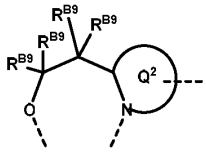
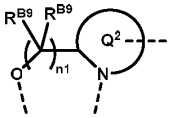
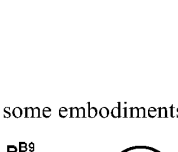
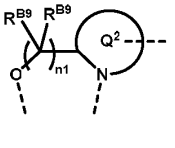
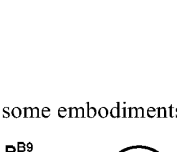
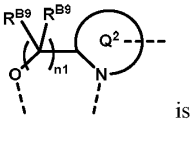
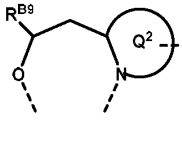
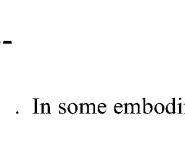
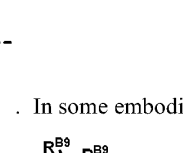
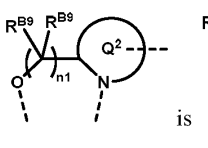
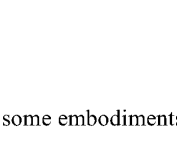
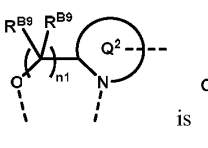
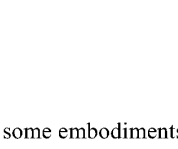
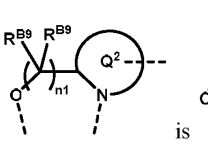
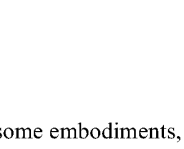
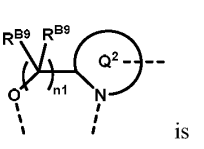
(a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), or (a0-6),  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  .  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments, is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments, is  . In some embodiments, is . In some embodiments, is .

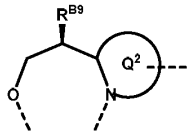
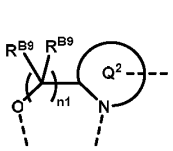
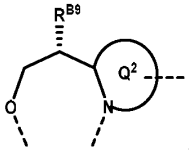
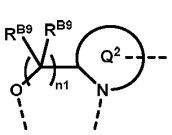
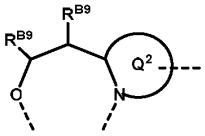
[183] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6),

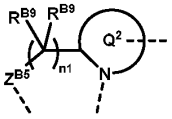
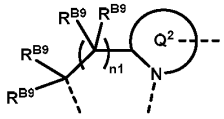
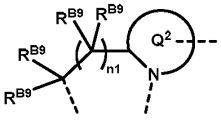
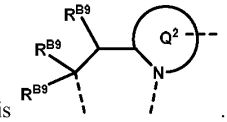
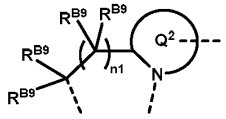
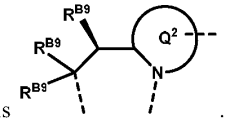
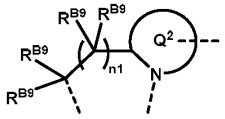
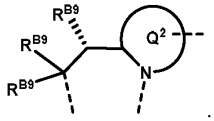
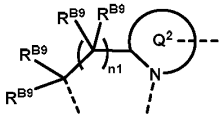
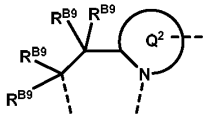
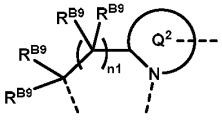
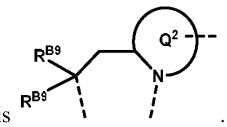
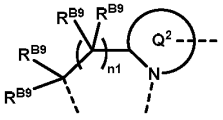
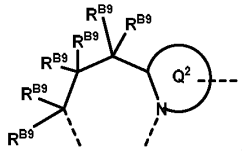
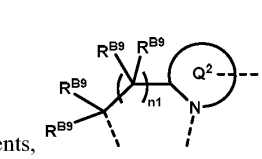
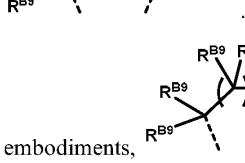
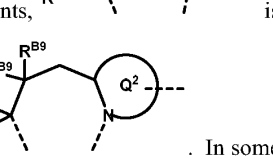
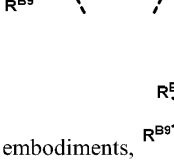
(a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), or (a0-6),  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments, is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  .

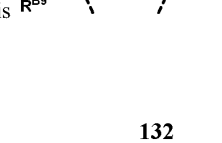
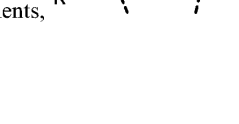
[184] In some embodiments, only one R^{B9} is non-hydrogen. In some embodiments, only two R^{B9} are non-hydrogen. In some embodiments, only two R^{B9} bonded to the same carbon atom are non-hydrogen. In some

embodiments, only two R^{B9} bonded to different carbon atoms are non-hydrogen. In some embodiments, only three R^{B9} are non-hydrogen. In some embodiments, only four R^{B9} are non-hydrogen. In some embodiments, only five R^{B9} are non-hydrogen. In some embodiments, only six R^{B9} are non-hydrogen. In some embodiments, all R^{B9} are hydrogen.

[185] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), or (a0-6),  is  . In some embodiments of a compound of Formula (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), or (a-6),  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments, is . In some embodiments, is


. In some embodiments,

is

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is

. In some embodiments, only one R^{B9} is non-hydrogen. In some embodiments, only two R^{B9} are non-hydrogen. In some embodiments, only two R^{B9} bonded to the same carbon atom are non-hydrogen. In some embodiments, only two R^{B9} bonded to different carbon atoms are non-hydrogen. In some embodiments, only three R^{B9} are non-hydrogen. In some embodiments, only four R^{B9} are non-hydrogen. In some embodiments, only five R^{B9} are non-hydrogen. In some embodiments, only six R^{B9} are non-hydrogen. In some embodiments, all R^{B9} are hydrogen.

[186] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), or (a0-6),

is

. In some embodiments of a compound of Formula (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6),

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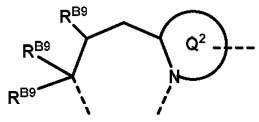
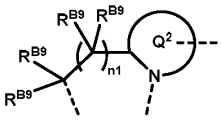
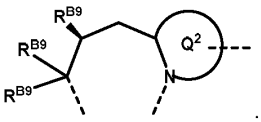
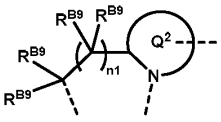
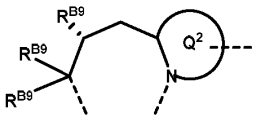
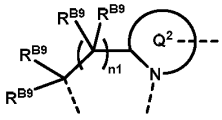
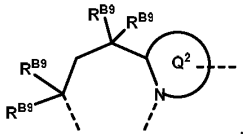
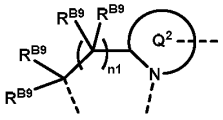
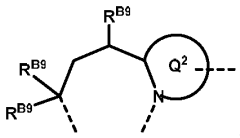
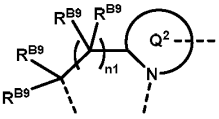
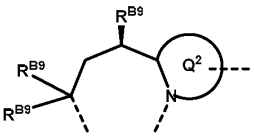
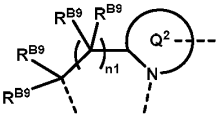
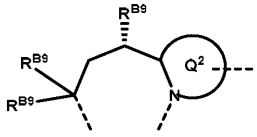
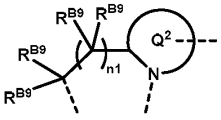
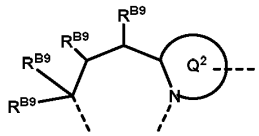
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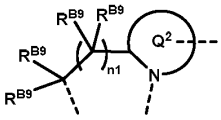
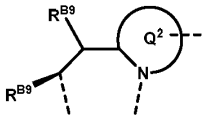
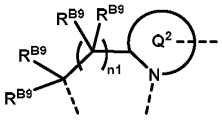
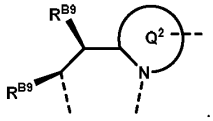
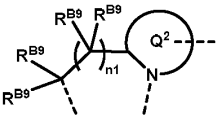
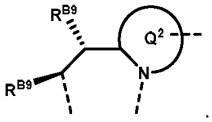
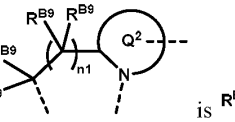
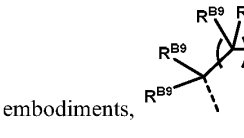
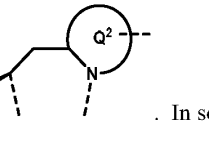
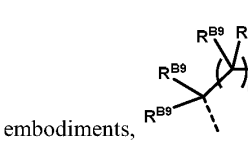
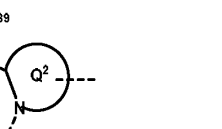
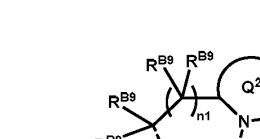
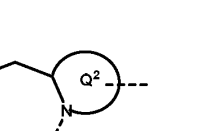
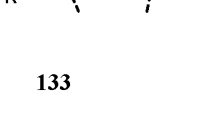
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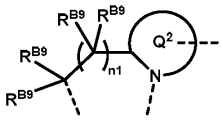
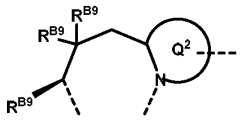
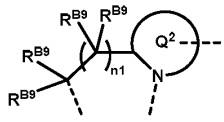
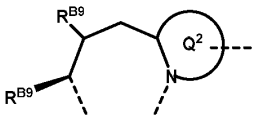
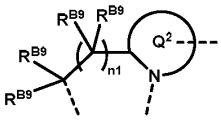
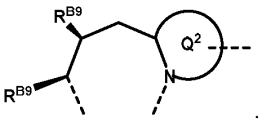
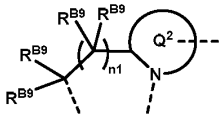
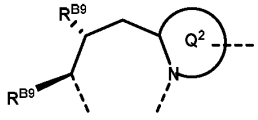
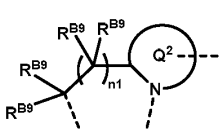
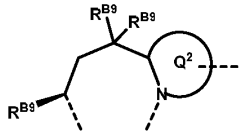
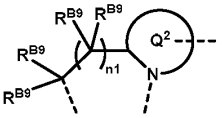
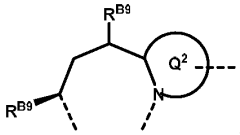
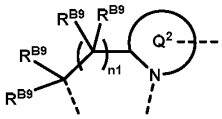
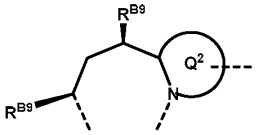
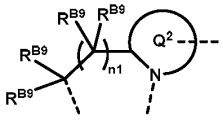
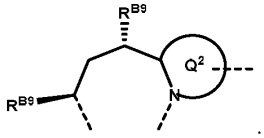
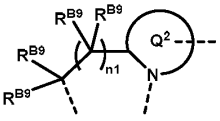
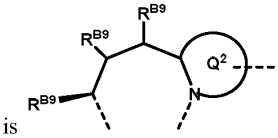
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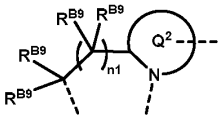
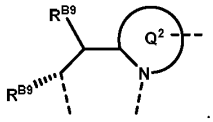
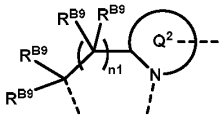
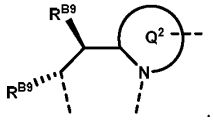
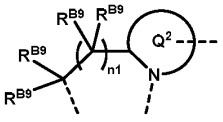
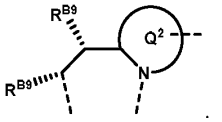
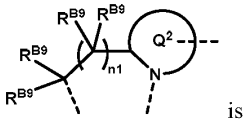
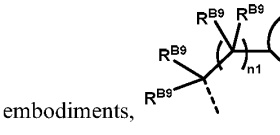
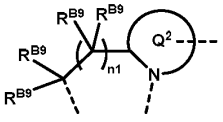
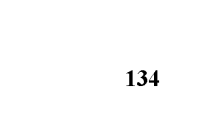
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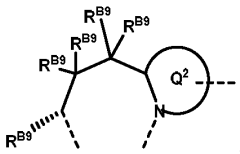
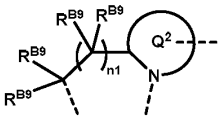
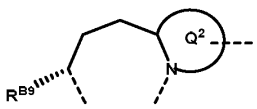
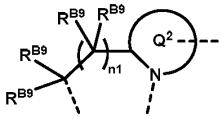
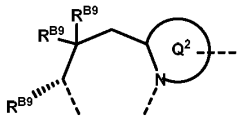
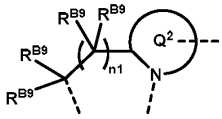
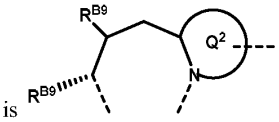
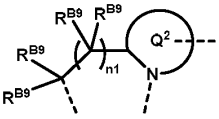
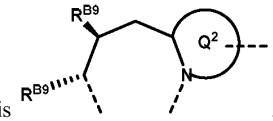
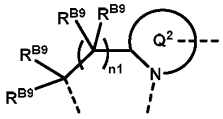
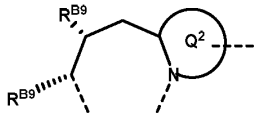
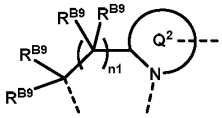
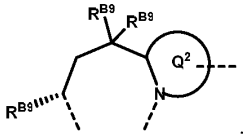
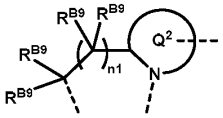
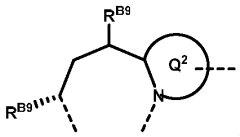
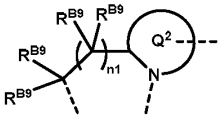
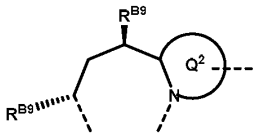
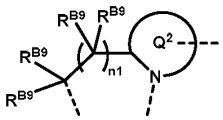
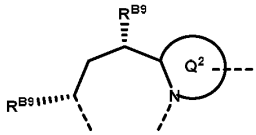
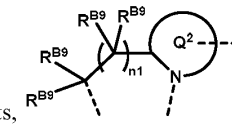
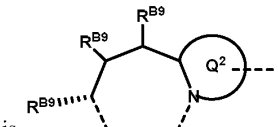
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[187] In some embodiments of a compound of Formula (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6),  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is . In some embodiments,  is . In some embodiments, is . In some embodiments, is . In some embodiments, is . In some

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[188] In some embodiments of a compound of Formula (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6),  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is . In some embodiments,  is . In some embodiments, is . In some embodiments, is .

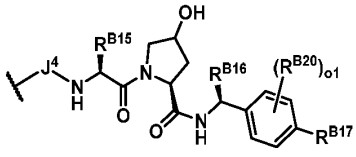
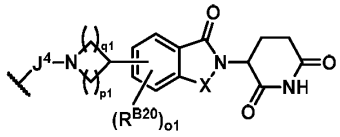

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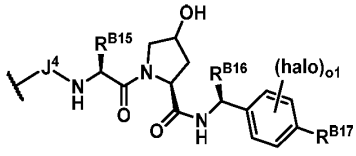
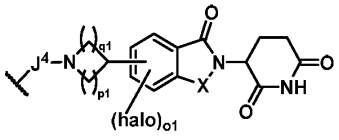
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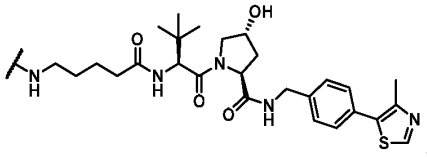
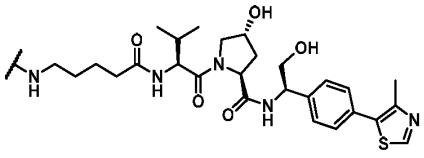
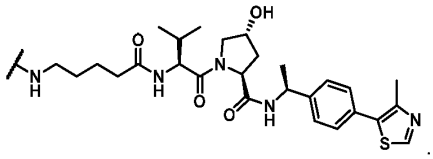
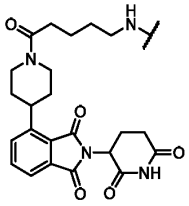
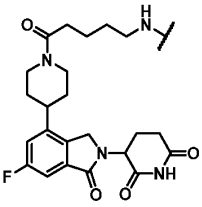
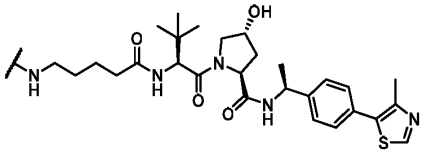
[189] In some embodiments, only one R^{B9} is non-hydrogen. In some embodiments, only two R^{B9} are non-hydrogen. In some embodiments, only two R^{B9} bonded to the same carbon atom are non-hydrogen. In some embodiments, only two R^{B9} bonded to different carbon atoms are non-hydrogen. In some embodiments, only three R^{B9} are non-hydrogen. In some embodiments, only four R^{B9} are non-hydrogen. In some embodiments, only five R^{B9} are non-hydrogen. In some embodiments, only six R^{B9} are non-hydrogen. In some embodiments, all R^{B9} are hydrogen.

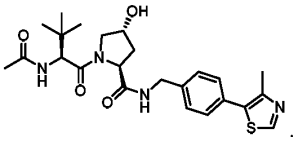
[190] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), J^1 is a bond, J^2 is a bond, and J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -

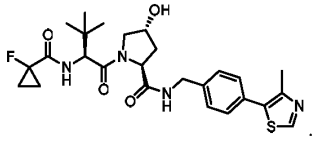
C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a bond, J^2 is a bond, and J^3 is C_{1-6} alkylene, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a bond, J^2 is a bond, and J^3 is ethylene, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a bond, J^2 is a bond, and J^3 is propylene, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a bond, J^2 is a bond, and J^3 is unsubstituted ethylene. In embodiments, J^1 is a bond, J^2 is a bond, and J^3 is unsubstituted propylene. In embodiments, J^1 is a bond, J^2 is a bond, and J^3 is -C_{0-6} alkyl-(C_{3-12} carbocycle)-, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a bond, J^2 is a bond, and J^3 is C_{3-12} carbocycle, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a bond, J^2 is a bond, and J^3 is C_{3-6} carbocycle, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a bond, J^2 is a bond, and J^3 is C_{4-6} carbocycle, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a bond, J^2 is a bond, and J^3 is cyclobutylene, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a bond, J^2 is a bond, and J^3 is cyclobutylene.

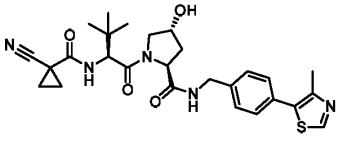
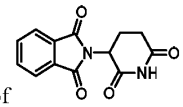
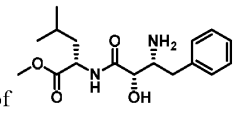
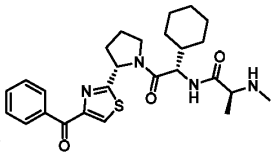
[191] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6)), or a salt or solvate thereof, DG is  ; wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, -OR^{B12}, -$C(O)OR^{B12}$, and -$C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and -$S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O). In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6)), or a salt or solvate thereof, DG is  ; wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, -OR^{B12}, -$C(O)OR^{B12}$, and -$C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and -$S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6}

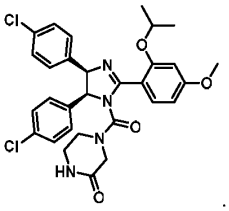
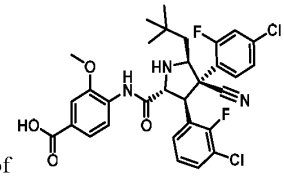
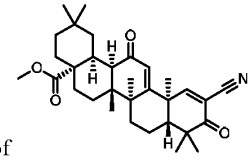
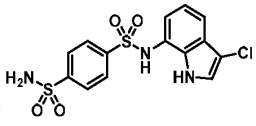
carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O). In embodiments, DG is  ; wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from $-CH(CH_3)_2$ and $-C(CH_3)_3$; R^{B16} is selected from hydrogen, $-CH_3$, and $-CH_2OH$; R^{B17} is selected from methylthiazole and methylpyrazole; o1 is selected from 0 and 1; p1 and q1 are independently selected from 1 and 2; and X is selected from CH_2 and C(O). In embodiments, DG is  ; wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from $-CH(CH_3)_2$ and $-C(CH_3)_3$; R^{B16} is selected from hydrogen, $-CH_3$, and $-CH_2OH$; R^{B17} is selected from methylthiazole and methylpyrazole; o1 is selected from 0 and 1; p1 and q1 are independently selected from 1 and 2; and X is selected from CH_2 and C(O).

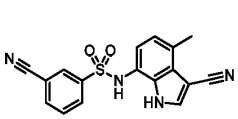
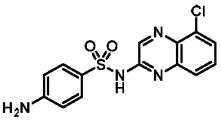
[192] In embodiments of a compound described herein (e.g., compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6)), or a salt or solvate thereof, DG is  . In embodiments, DG is  . In embodiments, DG is  . In embodiments, DG is  . In embodiments, DG is  . In embodiments, DG is  . In embodiments, DG comprises a monovalent form of


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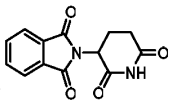
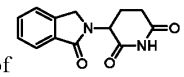
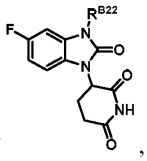
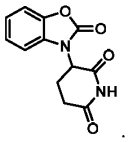
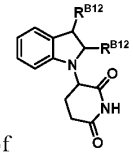
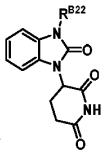
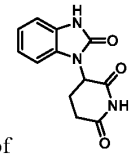
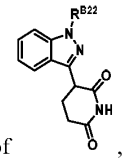
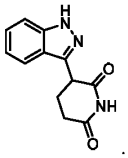
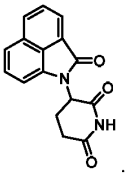
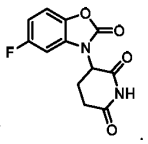
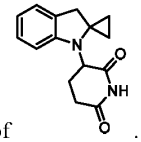
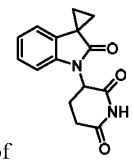
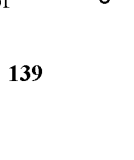

. In embodiments, DG comprises a monovalent form of

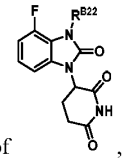
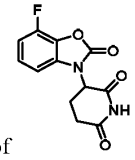
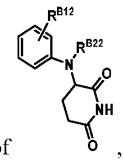
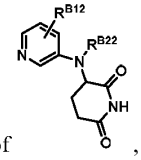
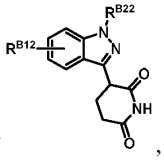
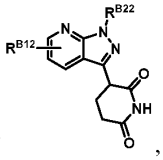
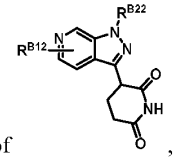
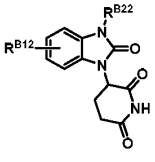

. In embodiments, DG comprises a monovalent form of 
. In embodiments, DG comprises a monovalent form of 
. In embodiments, DG comprises a monovalent form of 
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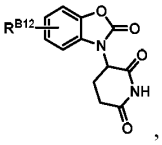
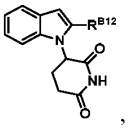
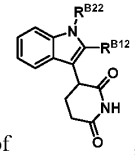

. In embodiments, DG comprises a monovalent form of 
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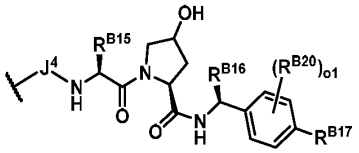
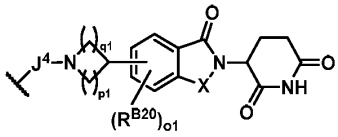

. In embodiments, DG comprises a monovalent form of 
. In embodiments, DG comprises a monovalent form of
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. In embodiments, DG comprises a monovalent form of

monovalent form of  . In embodiments, DG comprises a monovalent form of  . In embodiments, DG comprises a monovalent form of  , R^{B22} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof. In embodiments, DG comprises a monovalent form of  . In embodiments, DG comprises a monovalent form of  , R^{B12} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof; and R^{B22} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof. In embodiments, DG comprises a monovalent form of  , R^{B22} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof. In embodiments, DG comprises a monovalent form of  . In embodiments, DG comprises a monovalent form of  , R^{B22} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof. In embodiments, DG comprises a monovalent form of  . In embodiments, DG comprises a monovalent form of  . In embodiments, DG comprises a monovalent form of  . In embodiments, DG comprises a monovalent form of  . In embodiments, DG comprises a monovalent form of  . In embodiments, DG comprises a monovalent form of  . In embodiments, DG comprises a monovalent

form of  , R^{B22} is as described for a compound of Formula (A) or (a), or any embodiment thereof. In embodiments, DG comprises a monovalent form of  . In embodiments, DG comprises a monovalent form of  , R^{B12} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof; and R^{B22} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof. In embodiments, DG comprises a monovalent form of  , R^{B12} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof; and R^{B22} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof. In embodiments, DG comprises a monovalent form of  , R^{B12} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof; and R^{B22} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof. In embodiments, DG comprises a monovalent form of  , R^{B12} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof; and R^{B22} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof. In embodiments, DG comprises a monovalent form of  , R^{B12} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof; and R^{B22} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof. In embodiments, DG comprises a monovalent form of  , R^{B12} is as described for a

compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof; and R^{B22} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof. In embodiments, DG comprises a monovalent form of  , R^{B12} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof. In embodiments, DG comprises a monovalent form of  , R^{B12} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof. In embodiments, DG comprises a monovalent form of  , R^{B12} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof; and R^{B22} is as described for a compound of Formula (A0), (A), (A1), (a0), (a), and/or (a1), or any embodiment thereof.

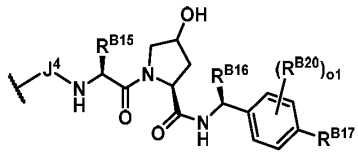
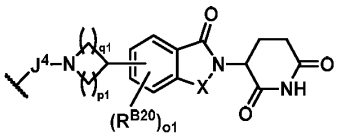
[193] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6), J^1 is a bond; J^2 is a bond; J^3 is unsubstituted ethylene; DG is selected from  and  ; J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O). In embodiments, J^1 is a bond; J^2 is a bond; J^3 is unsubstituted propylene; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In embodiments, J^1 is a bond; J^2 is a bond; J^3 is cyclobutylene; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph.

[194] In some embodiments of a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), J^1 is a bond; J^2 is a bond; J^3 is unsubstituted ethylene; LG is selected from $-OS(O)_2R^{B4}$, $-OS(O)(NH)R^{B4}$, and $-OS(O)(NCN)R^{B4}$; and R^{B4} is

selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle. In embodiments, J^1 is a bond; J^2 is a bond; J^3 is unsubstituted propylene; LG is selected from -OS(O)$_2R^{B4}$, -OS(O)(NH)R^{B4}, and -OS(O)(NCN)R^{B4}; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle. In embodiments, J^1 is a bond; J^2 is a bond; J^3 is cyclobutylene; LG is selected from -OS(O)$_2R^{B4}$, -OS(O)(NH)R^{B4}, and -OS(O)(NCN)R^{B4}; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle.

[195] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), J^1 is -C(O)-, J^2 is a bond, and J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is C_{1-6} alkylene, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is methylene, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is unsubstituted methylene. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is ethylene (e.g., -$CH(CH_3)$-), which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is unsubstituted ethylene (e.g., -$CH(CH_3)$-). In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is propylene (e.g., -$CH(CH_2CH_3)$-), which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is unsubstituted propylene (e.g., -$CH(CH_2CH_3)$-). In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is butylene (e.g., -$CH(CH(CH_3)_2)$-), which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is unsubstituted butylene (e.g., -$CH(CH(CH_3)_2)$-). In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is methylene, which is substituted with one or more unsubstituted C_{3-6} carbocycle. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is methylene, which is substituted with one or more unsubstituted C_{3-4} carbocycle. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is methylene, which is substituted with one or more unsubstituted cyclopropyl. .In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is C_2 alkylene (e.g., -$CH(CH_3)$-), which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is unsubstituted C_2 alkylene (e.g., -$CH(CH_3)$-). In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is C_3 alkylene (e.g., -$CH(CH_2CH_3)$-), which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is unsubstituted C_3 alkylene (e.g., -$CH(CH_2CH_3)$-). In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is C_4 alkylene (e.g., -$CH(CH(CH_3)_2)$-), which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is unsubstituted C_4 alkylene (e.g., -$CH(CH(CH_3)_2)$-). In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is C_1 alkylene, which is substituted with one or more unsubstituted C_{3-6} carbocycle. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is C_1 alkylene, which is substituted with one or more unsubstituted C_{3-4} carbocycle. In embodiments, J^1 is a -C(O)-, J^2 is a bond, and J^3 is C_1 alkylene, which is substituted with one or more unsubstituted cyclopropyl.

[196] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6), J^1 is a -C(O)-;

J^2 is a bond; J^3 is unsubstituted methylene; DG is selected from  and  ; J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O). In embodiments, J^1 is a -C(O)-; J^2 is a bond; J^3 is unsubstituted ethylene (e.g., $-CH(CH_3)-$; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In embodiments, J^1 is a -C(O)-; J^2 is a bond; J^3 is unsubstituted propylene (e.g., $-CH(CH_2CH_3)-$; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In embodiments, J^1 is a -C(O)-; J^2 is a bond; J^3 is unsubstituted butylene (e.g., $-CH(CH(CH_3)_2)-$; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In embodiments, J^1 is a -C(O)-; J^2 is a bond; J^3 is methylene, which is substituted with one unsubstituted cyclopropyl; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph.

[197] In some embodiments of a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), J^1 is a -C(O)-; J^2 is a bond; J^3 is unsubstituted methylene; LG is selected from $-OS(O)_2R^{B4}$, $-OS(O)(NH)R^{B4}$, and $-OS(O)(NCN)R^{B4}$; and R^{B4} is selected from $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle. In embodiments, J^1 is a -C(O)-; J^2 is a bond; J^3 is unsubstituted ethylene (e.g., $-CH(CH_3)-$; LG is selected from $-OS(O)_2R^{B4}$, $-OS(O)(NH)R^{B4}$, and $-OS(O)(NCN)R^{B4}$; and R^{B4} is selected from $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle. In embodiments, J^1 is a -C(O)-; J^2 is a bond; J^3 is unsubstituted propylene (e.g., $-CH(CH_2CH_3)-$; LG is selected from $-OS(O)_2R^{B4}$, $-OS(O)(NH)R^{B4}$, and $-OS(O)(NCN)R^{B4}$; and R^{B4} is selected from $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle. In embodiments, J^1 is a -C(O)-; J^2 is a bond; J^3 is unsubstituted butylene (e.g., $-CH(CH(CH_3)_2)-$; LG is selected from $-OS(O)_2R^{B4}$, $-OS(O)(NH)R^{B4}$, and $-OS(O)(NCN)R^{B4}$; and R^{B4} is selected from $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle. In embodiments, J^1 is a -C(O)-; J^2 is a bond; J^3 is methylene, which is substituted with one unsubstituted cyclopropyl; LG is selected from $-OS(O)_2R^{B4}$, $-OS(O)(NH)R^{B4}$, and $-OS(O)(NCN)R^{B4}$; and R^{B4} is selected from $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle.

[198] In some embodiments, for a compound described herein (e.g., compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), LG is selected from $-OS(O)_2R^{B4}$, $-OS(O)(NH)R^{B4}$, and $-OS(O)(NCN)R^{B4}$. In some embodiments, LG is -

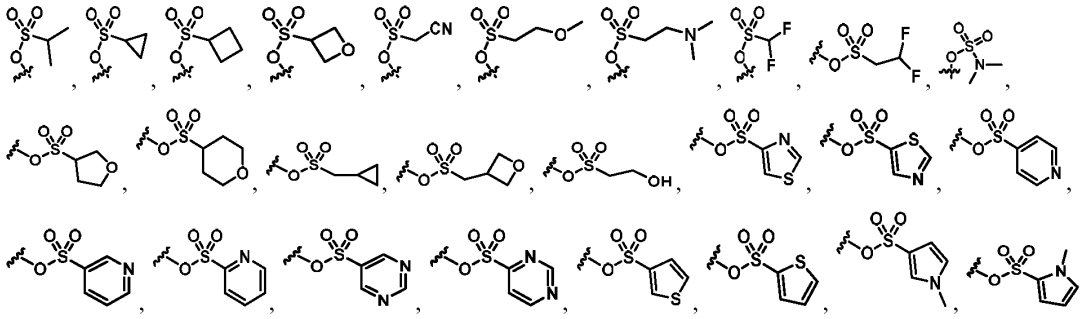
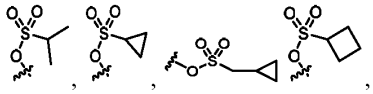
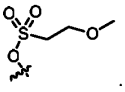
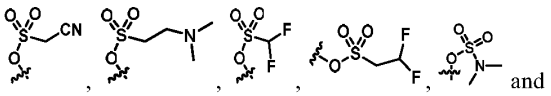
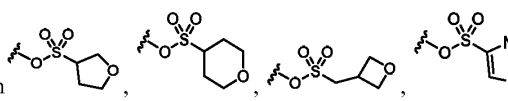
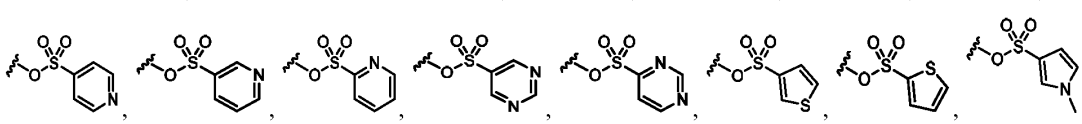
$OS(O)_2R^{B4}$. In some embodiments, LG is $-OS(O)(NR^{B4b})R^{B4}$.

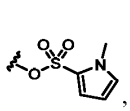
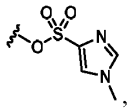
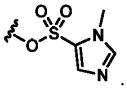
[199] In some embodiments, LG is not mesylate or tosylate. In some embodiments, LG is not mesylate, triflate, or tosylate. In some embodiments, R^{B4} is not $-CH_3$ or *p*-methylphenyl. In some embodiments, R^{B4} is not $-CH_3$, CF_3, or *p*-methylphenyl. In some embodiments, R^{B4} is not $-CH_3$, unsubstituted phenyl, penta-substituted phenyl, or *p*-methylphenyl. In some embodiments, R^{B4} is not $-CH_3$, $-CF_3$, unsubstituted phenyl, penta-substituted phenyl, or *p*-methylphenyl.

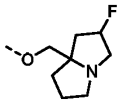
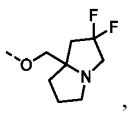
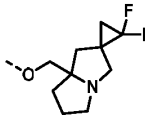
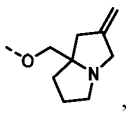
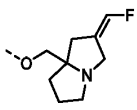
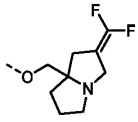
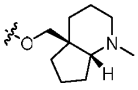
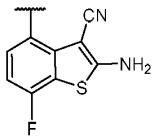
[200] In some embodiments, for a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), –(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and $-N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20}. In some embodiments, R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and –(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), each of which is optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle) are optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4} is selected from C_{1-6} alkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle) are optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4} is selected from C_{1-6} alkyl and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), each of which is optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4} is selected from C_{1-6} alkyl and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), each of which is optionally substituted with one, two, three, or four R^{B20}, wherein the C_{3-12} carbocycle is not phenyl. In some embodiments, R^{B4} is selected from C_{1-6} alkyl and $-C_{0-6}$ alkyl-(C_{3-12} cycloalkyl), each of which is optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4} is C_{1-6} alkyl optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4} is C_{1-6} alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, or pentyl. In some embodiments, R^{B4} is selected from ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, and pentyl. In some embodiments, R^{B4} is ethyl. In some embodiments, R^{B4} is not methyl, phenyl or *p*-methylphenyl. In some embodiments, R^{B4} is 2- to 6-membered heteroalkyl optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4} is $-N(R^{B12})(R^{B13})$. In some embodiments, R^{B4} is $-NH(R^{B12})$. In some embodiments, R^{B4} is $-NH_2$. In some embodiments, R^{B4} is $-NH(C_{1-6}$ alkyl). In some embodiments, R^{B4} is $-NH(C_{1-3}$ alkyl). In some embodiments, R^{B4} is $-N(C_{1-6}$ alkyl$)_2$. In some embodiments, R^{B4} is $-N(C_{1-3}$ alkyl$)_2$. In some embodiments, R^{B4} is $-N(CH_3)_2$. In some embodiments, R^{B4} is $-N(CH_2CH_3)_2$. In some embodiments, R^{B4} is $-NH(CH_2CH_3)$. In some embodiments, R^{B4} is $-NH(CH_3)$.

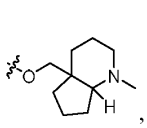
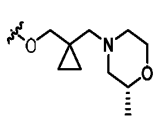
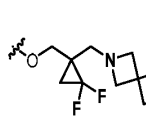
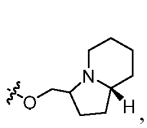
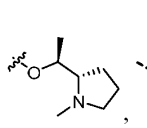
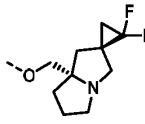
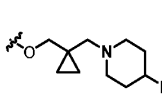
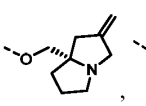
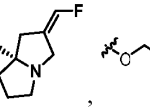
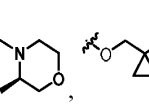
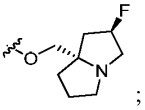
[201] In some embodiments, for a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B4b} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and –(2- to 6-membered heteroalkyl)-

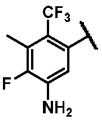
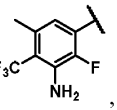
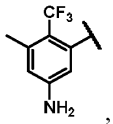
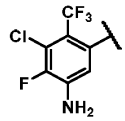
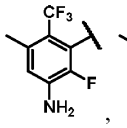
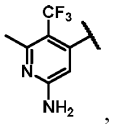
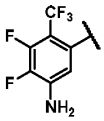
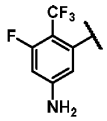
(3- to 12-membered heterocycle), each of which is optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4b} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4b} is selected from C_{1-6} alkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4b} is selected from C_{1-6} alkyl and -C_{0-6} alkyl-(C_{3-12} carbocycle), each of which is optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4b} is selected from C_{1-6} alkyl and -C_{0-6} alkyl-(C_{3-12} cycloalkyl), each of which is optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4b} is C_{1-6} alkyl optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4b} is C_{1-6} alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, or pentyl. In some embodiments, R^{B4b} is selected from ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, and pentyl. In some embodiments, R^{B4b} is 2- to 6-membered heteroalkyl optionally substituted with one, two, three, or four R^{B20}. In some embodiments, R^{B4b} is hydrogen. In some embodiments, R^{B4b} is -CN. In some embodiments, R^{B4b} is -C(O)OR^{B12}. In some embodiments, R^{B4b} is -C(O)R^{B12}. In some embodiments, R^{B4b} is -S(O)$_2R^{B12}$.

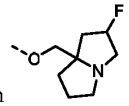
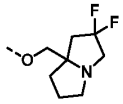
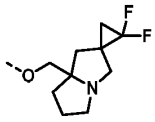
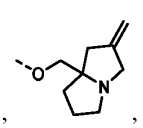
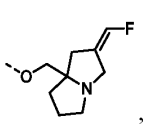
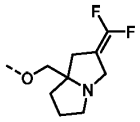
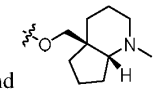
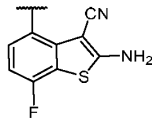
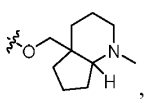
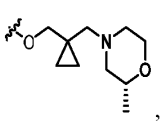
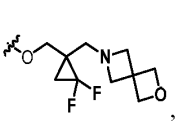
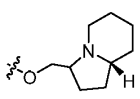
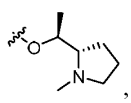
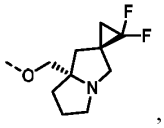
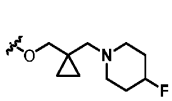
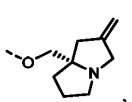
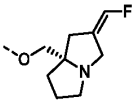
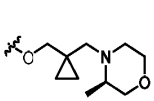
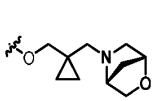
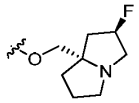
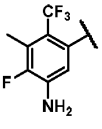
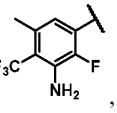
[202] In some embodiments, for a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), LG is selected from  ,  , and  . In some embodiments, LG is selected from  , and  . In some embodiments, LG is  . In some embodiments, LG is selected from  . In some embodiments, LG is selected from  . In some embodiments, LG is selected from  .

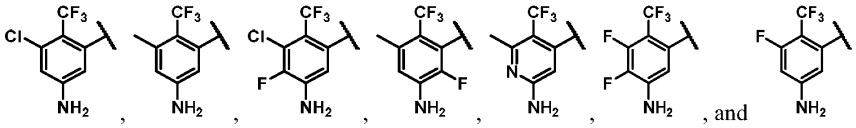
 ,  , and  . In some embodiments, LG is selected from  ,  , and  .

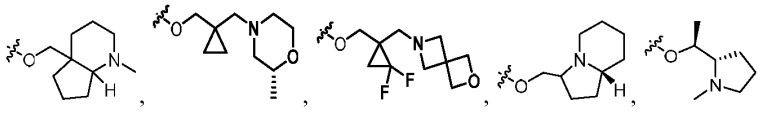
[203] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-4), (A0-5), (a0), (a0-1), (a0-2), (a0-4), (a0-5), (A), (A-1), (A-2), (A-4), (A-5), (a), (a-1), (a-2), (a-4), (a-5), (A1), (A1-1), (A1-2), (A1-4), (A1-5), (a1), (a1-1), (a1-2), (a1-4), or (a1-5), R^{B6} is halogen or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), each of which is optionally substituted with one, two, three, or four R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is halogen. In some embodiments, R^{B6} is selected from hydrogen, halogen, and $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), each of which is optionally substituted with one, two, three, or four R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is selected from hydrogen and halogen. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), each of which is optionally substituted with one, two, three, or four R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), each of which is optionally substituted with one, two, three, or four R^{B20}; R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  , and  ; R^{B6} is halogen or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is  ; and R^{B8} is halogen. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), each of which is optionally substituted with one, two, three, or four R^{B20}; R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from

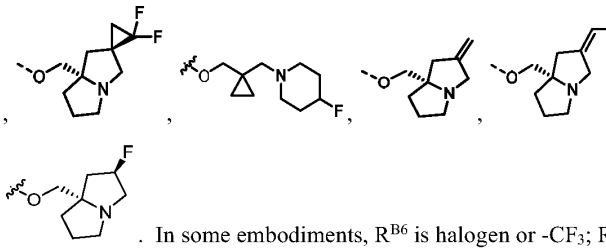
 ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ; R^{B6} is

halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; and R^{B8} is halogen.

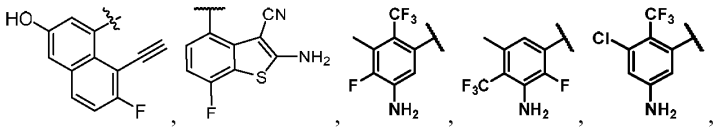
[204] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-4), (A0-5), (a0), (a0-1), (a0-2), (a0-4), (a0-5), (A), (A-1), (A-2), (A-4), (A-5), (a), (a-1), (a-2), (a-4), (a-5), (A1), (A1-1), (A1-2), (A1-4), (A1-5), (a1), (a1-1), (a1-2), (a1-4), or (a1-5), R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is halogen. In some embodiments, R^{B6} is selected from hydrogen, halogen, and -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is selected from hydrogen and halogen. In some embodiments, R^{B6} is chloro or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B6} is chloro or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  , and  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is  ; and R^{B8} is halogen. In some embodiments, R^{B6} is chloro or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from  ,  ,

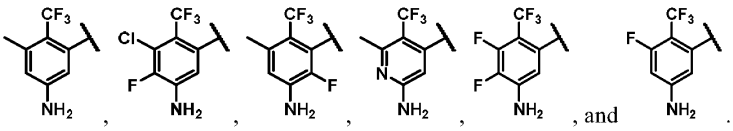

, and ; and R^{B8} is halogen. In some embodiments, R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B8} is halogen; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from




, and

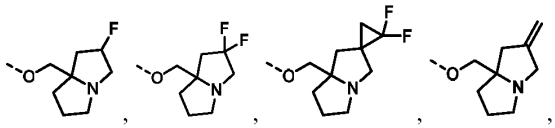
. In some embodiments, R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B8} is halogen; R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from

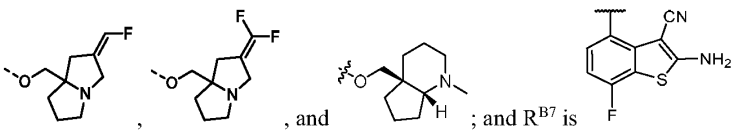



, and

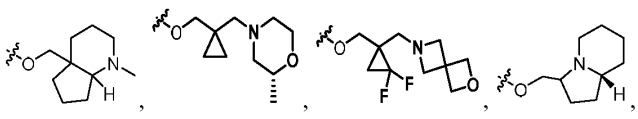
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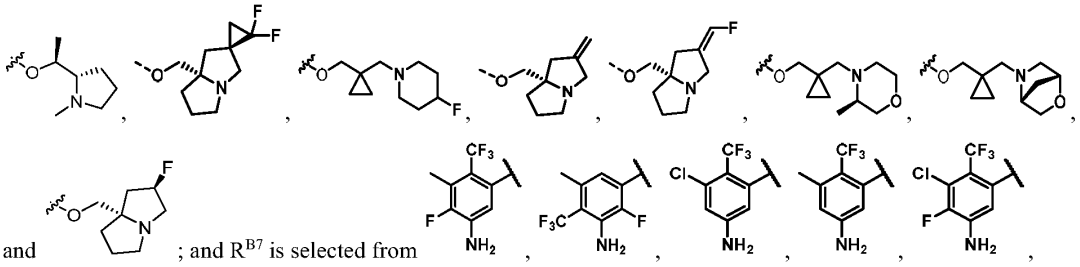
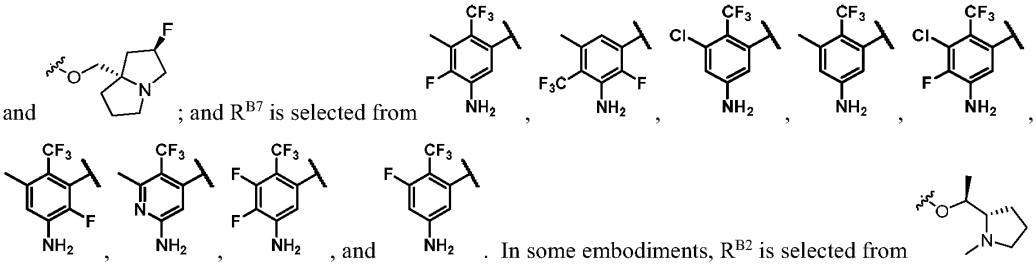
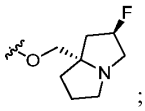
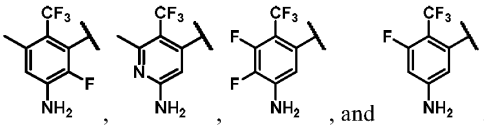
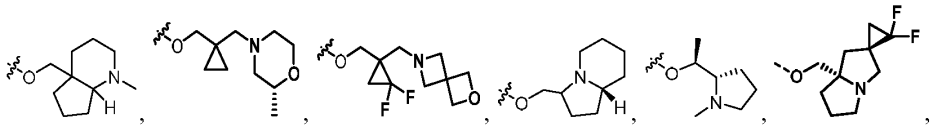
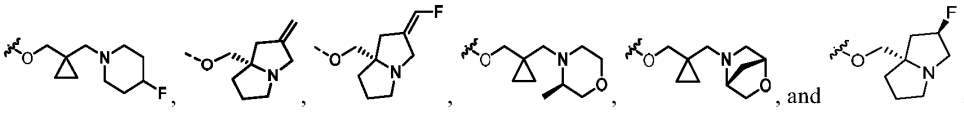
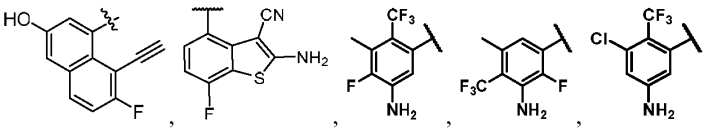
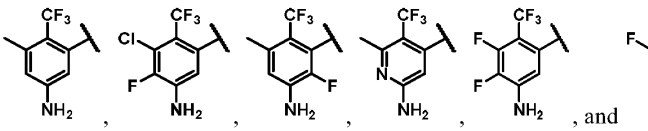
[205] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-4), (A0-5), (a0), (a0-1), (a0-2), (a0-4), (a0-5), (A), (A-1), (A-2), (A-4), (A-5), (a), (a-1), (a-2), (a-4), (a-5), (A1), (A1-1), (A1-2), (A1-4), (A1-5), (a1), (a1-1), (a1-2), (a1-4), or (a1-5), R^{B6} is chloro or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from



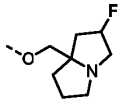
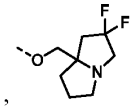
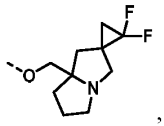
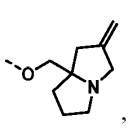
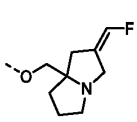
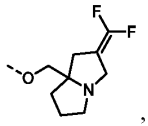
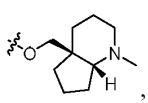
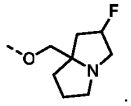
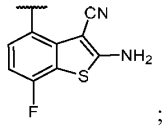
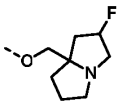
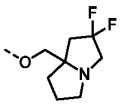
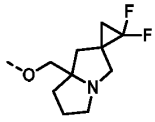
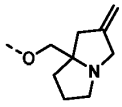
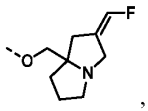
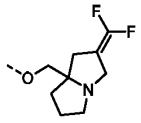
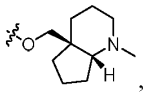
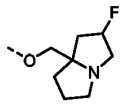
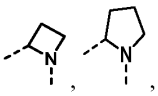
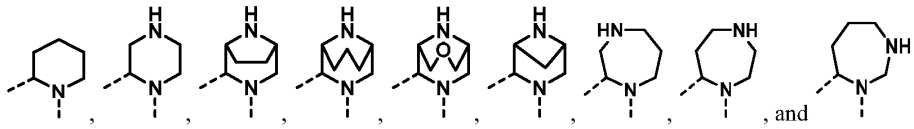
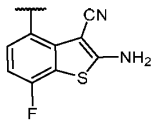
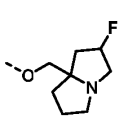
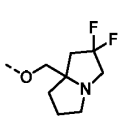
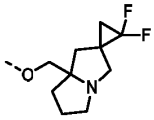
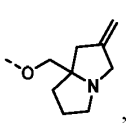
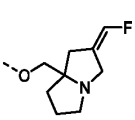
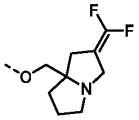
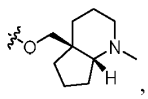
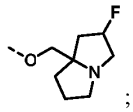
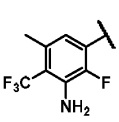
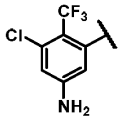
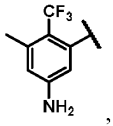

, and ; and R^{B7} is

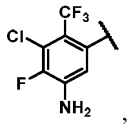
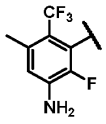
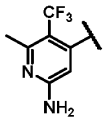
. In some embodiments, R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from

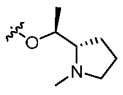
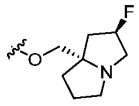
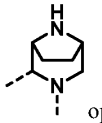
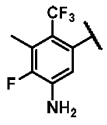
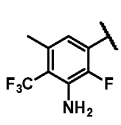
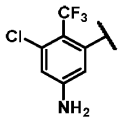
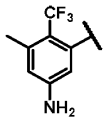
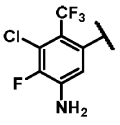
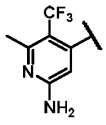
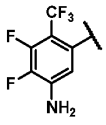
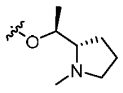
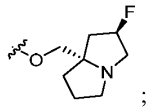
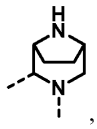
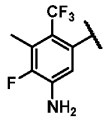
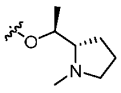
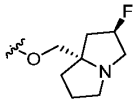
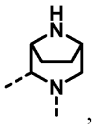
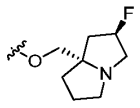
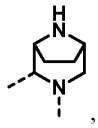
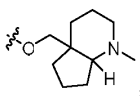
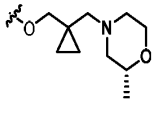
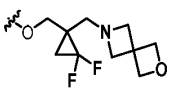
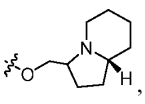
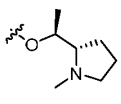
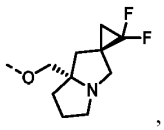
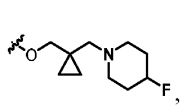
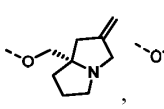
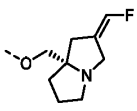
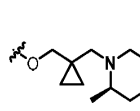
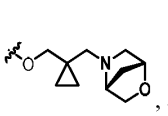


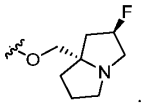
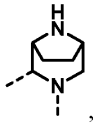
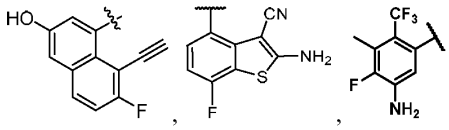
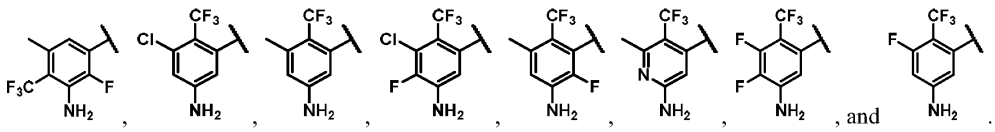

and ; and R^{B7} is selected from 
, and . In some embodiments, R^{B2} is selected from
and 
; and R^{B7} is selected from 

, and . In some embodiments, R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from 

. In some embodiments, R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from 

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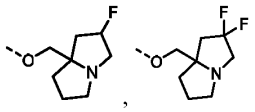
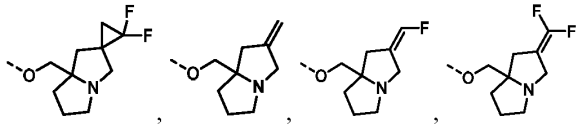
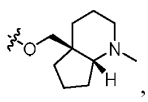
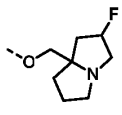
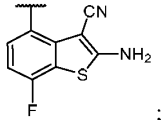
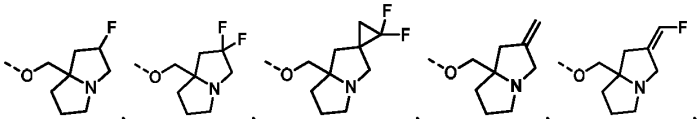
[206] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), Q^2 is 6- to 10-membered heterocycle that is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; and R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}. In

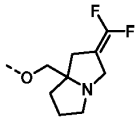
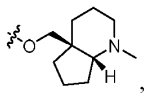
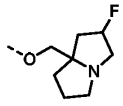
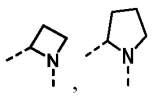
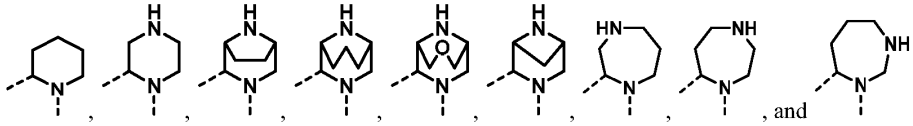
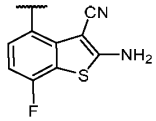
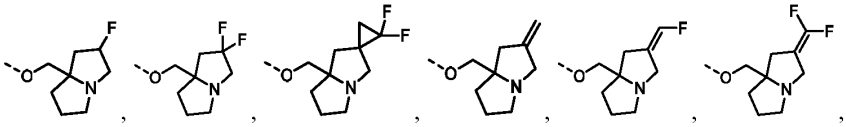
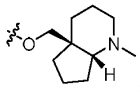
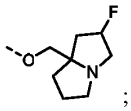
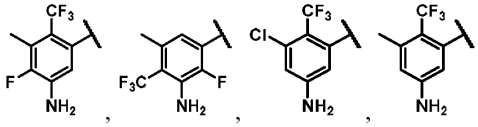
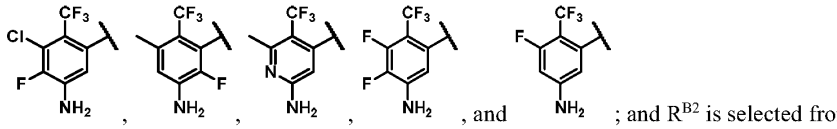
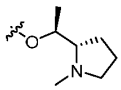
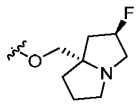
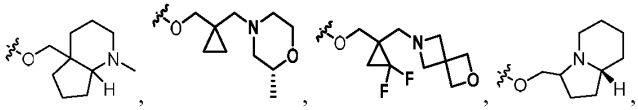
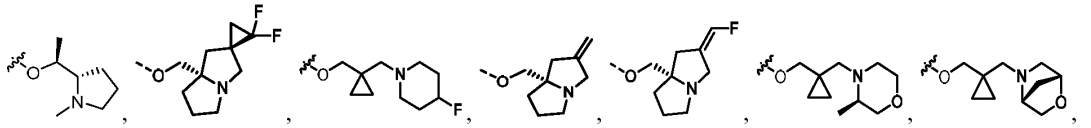
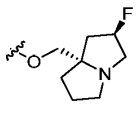
some embodiments, Q^2 is 7- to 9-membered heterocycle that is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms and is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}; and R^{B2} is selected from  ,  ,  ,  ,  ,  ,  , and  , such as . In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; and R^{B2} is selected from  ,  ,  ,  ,  ,  , and  , such as  . In some embodiments, Q^2 is selected from  ,  , and , each of which is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; R^{B2} is selected from  ,  ,  ,  ,  ,  , and  , such as  ; and Z^1 is N. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from  ,  ,  ,  ,

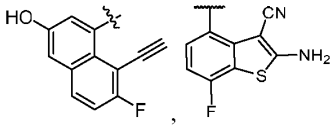
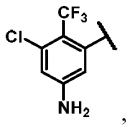
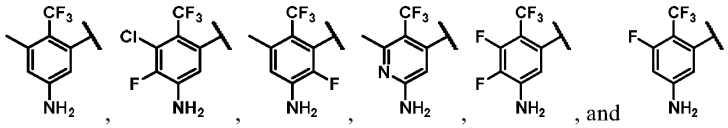




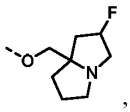
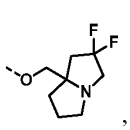
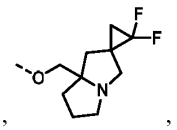
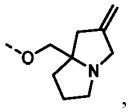
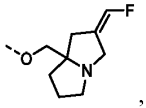
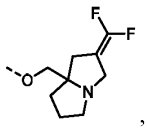
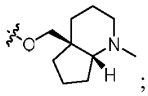
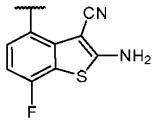
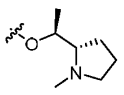
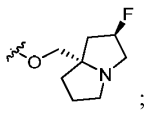
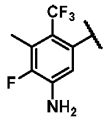
, and 
; and R^{B2} is selected from 
and 
. In some embodiments, Q^2 is 
optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from 




, 


, and 
; R^{B2} is selected from 
and 
; and Z^1 is N. In some embodiments, Q^2 
, optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is 
; R^{B2} is selected from 
and 
; and Z^1 is N. In some embodiments, Q^2 
, optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is 
; R^{B2} is 
; and Z^1 is N. In some embodiments, Q^2 
, optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; Z^1 is N; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from 




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, and

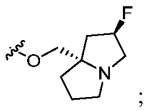
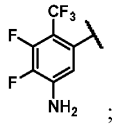
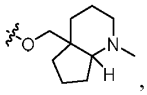
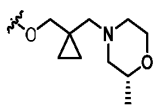
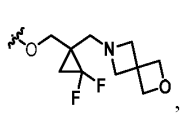
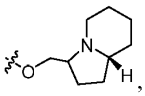
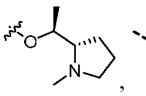
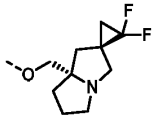
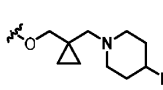
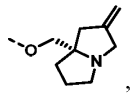
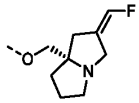
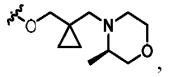
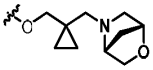
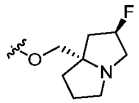
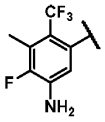
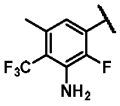
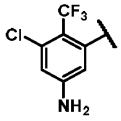
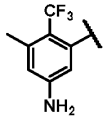
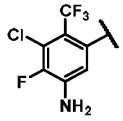
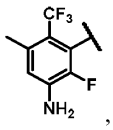
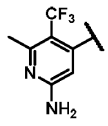
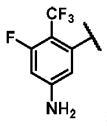
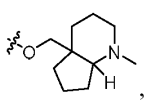
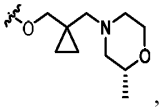
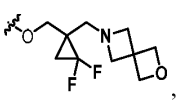
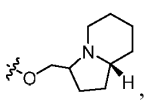
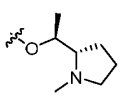
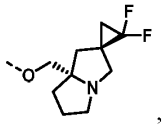
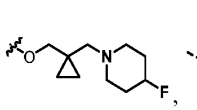
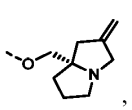
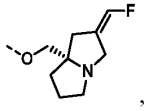
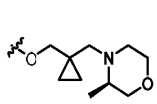
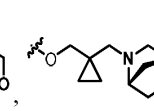
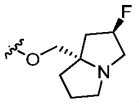
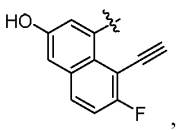
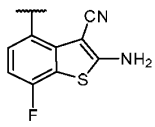
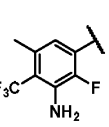
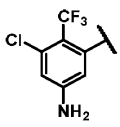
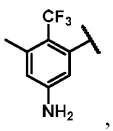
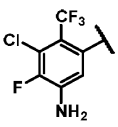
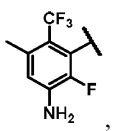
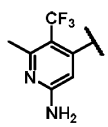
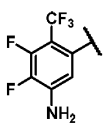

. In some embodiments, Q^2  , optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; Z^1 is N; R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from  ,  , and .

[207] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), Q^2 is 6- to 10-membered heterocycle that is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; and R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}. In some embodiments, Q^2 is 7- to 9-membered heterocycle that is optionally substituted with one or more R^{B20}. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}; and R^{B2} is selected from  ,  , and  , such as  . In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; and R^{B2} is selected from  ,

 , and  , such as  . In some embodiments, Q^2 is selected from  ,  , and , each of which is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; R^{B2} is selected from  , and  , such as  ; and Z^1 is N. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from  ,  , and ; and R^{B2} is selected from  and  . In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from  ,  , and  . In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at

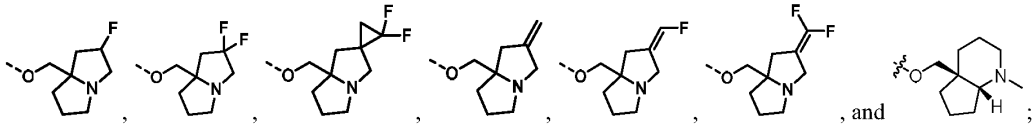
least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from      and .

[208] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is halogen. In some embodiments, R^{B6} is selected from hydrogen, halogen, and -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is selected from hydrogen and halogen. In some embodiments, R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  , and  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is  ; and R^{B8} is halogen. In some embodiments, R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  and  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from  ; and R^{B8} is halogen. In

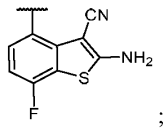
some embodiments, R^{B2} is  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from  ; and R^{B8} is halogen. In some embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; and R^{B8} is halogen. In some embodiments, R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B8} is halogen; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B8} is halogen; R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

[209] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-3), (A0-4), (A0-6), (a0), (a0-1), (a0-3), (a0-4), (a0-6), (A), (A-1), (A-3), (A-4), (A-6), (a), (a-1), (a-3), (a-4), (a-6), (A1), (A1-1), (A1-3), (A1-4), (A1-6),

(a1), (a1-1), (a1-3), (a1-4), or (a1-6), R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is halogen. In some embodiments, R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is selected from hydrogen and halogen. In some embodiments, R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from



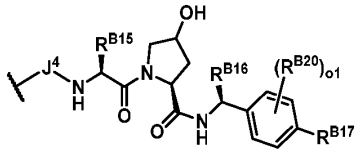
; R^{B6} is halogen or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is



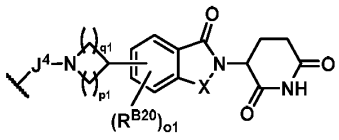
; and R^{B8} is halogen. In some embodiments, R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro.

[210] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-3), (A0-4), (A0-6), (a0), (a0-1), (a0-3), (a0-4), (a0-6), (A), (A-1), (A-3), (A-4), (A-6), (a), (a-1), (a-3), (a-4), (a-6), (A1), (A1-1), (A1-3), (A1-4), (A1-6), (a1), (a1-1), (a1-3), (a1-4), or (a1-6), R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro.

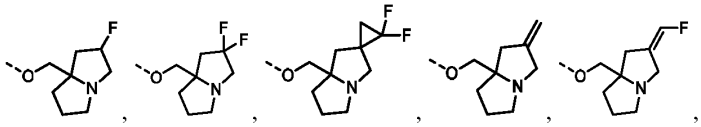
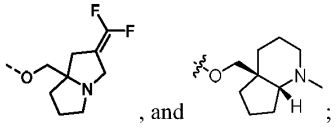
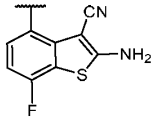
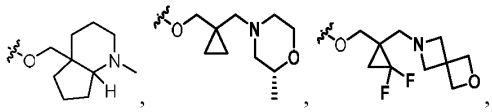
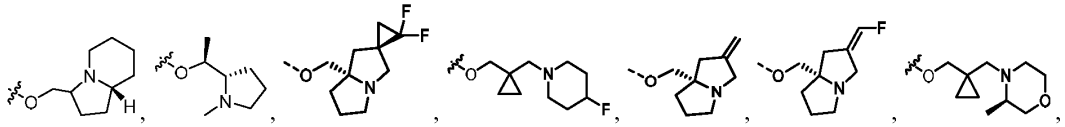
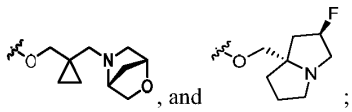
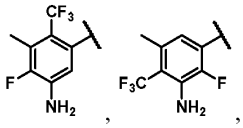
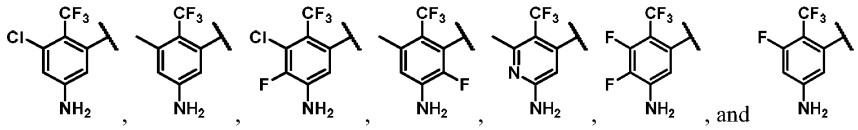
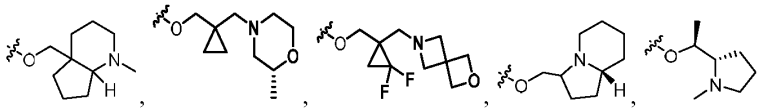
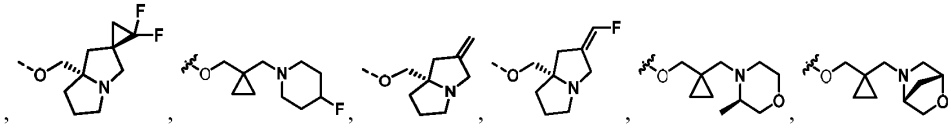
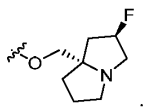
[211] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A), (A-1), (A-2), (A1), (A1-1), or (A1-2), R^{B6} is halogen or $-CF_3$; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; DG is selected from

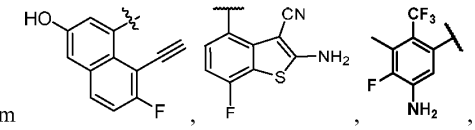
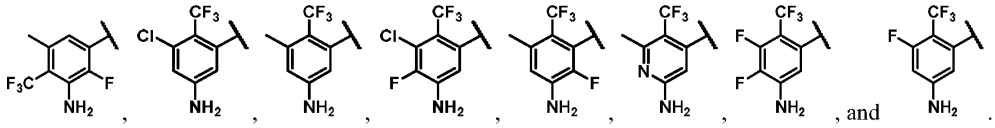


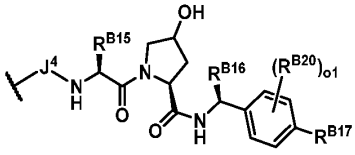
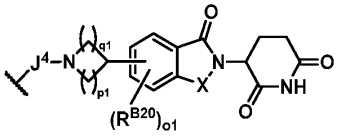
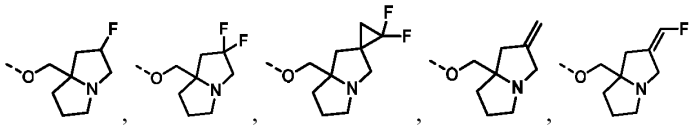
and

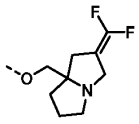
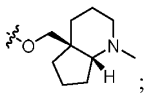
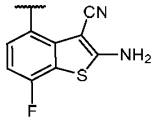
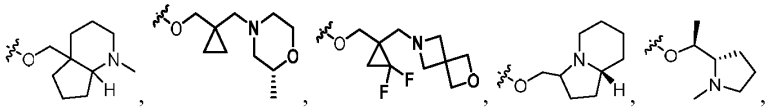
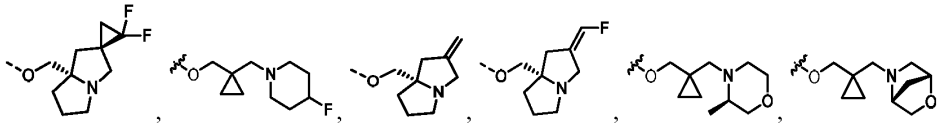
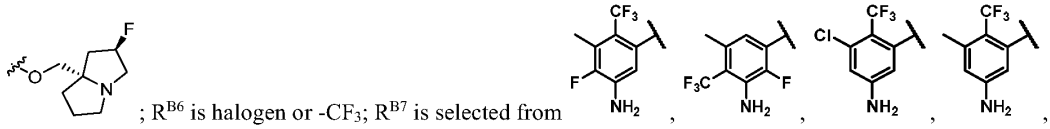
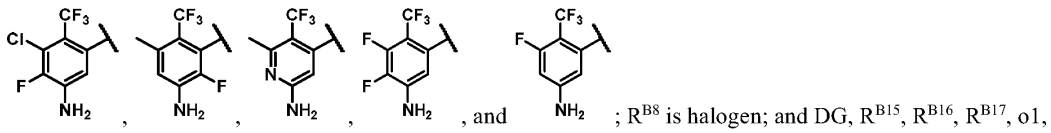


, wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and R^{B8} is halogen. In some embodiments, R^{B6} is selected from hydrogen, halogen, and $-CF_3$; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally

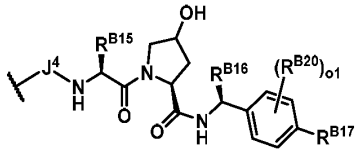
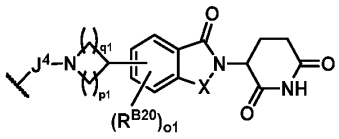
substituted with one or more R^{B20}; R^{B8} is selected from hydrogen and halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  , and  ; R^{B6} is halogen or $-CF_3$; R^{B7} is  ; R^{B8} is halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  ,  , and  ; R^{B6} is halogen or $-CF_3$; R^{B7} is selected from  , and  ; R^{B8} is halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B6} is halogen or $-CF_3$; R^{B8} is halogen; DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from  ,  , and  . In some embodiments, R^{B6} is halogen or $-CF_3$; R^{B8} is halogen; DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph; R^{B2} is $-O(C_{1-3}$ alkylene)(4- to 10-membered heterocycle), wherein 4- to

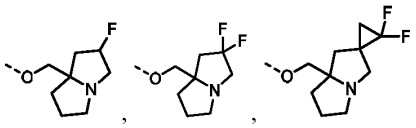
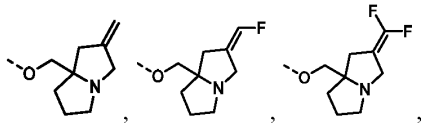
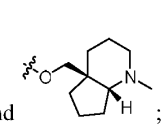
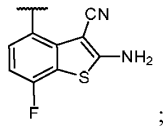
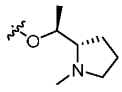
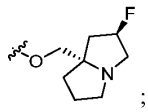
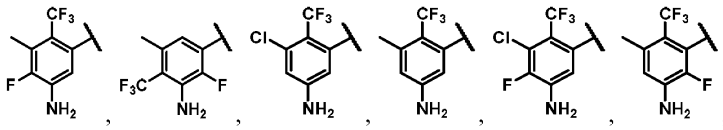
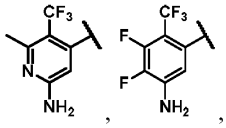
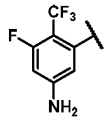
10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and $=C(R^{B21})_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from  ,  , and .

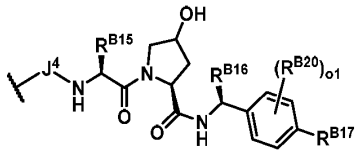
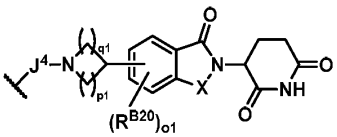
[212] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A), (A-1), (A-2), (A1), (A1-1), or (A1-2), R^{B6} is halogen or $-CF_3$; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B6} is selected from hydrogen, halogen, and $-CF_3$; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is selected from hydrogen and halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; DG is selected from  and  , wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and R^{B8} is fluoro. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B2} is selected from  .

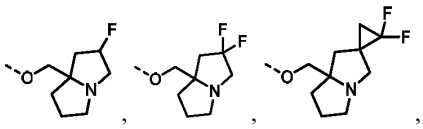
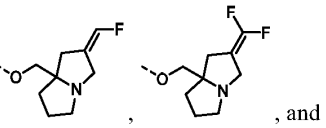
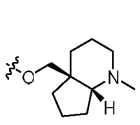
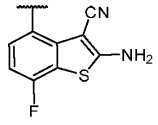
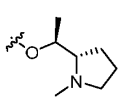
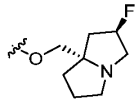
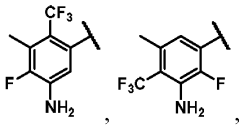
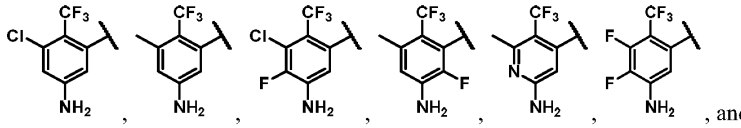
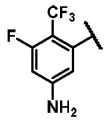

, and 
; R^{B6} is halogen or -CF_3; R^{B7} is 
; R^{B8} is halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B6} is chloro or -CF_3; R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B2} is selected from 

, and 
; R^{B6} is halogen or -CF_3; R^{B7} is selected from 

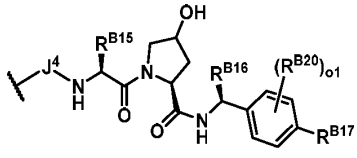
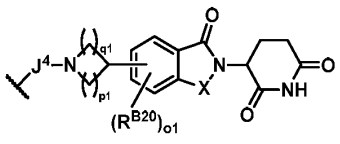
; R^{B8} is halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph.

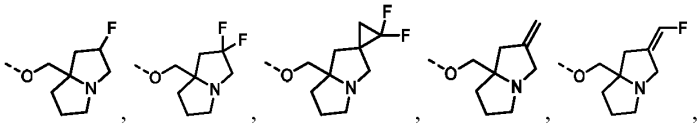
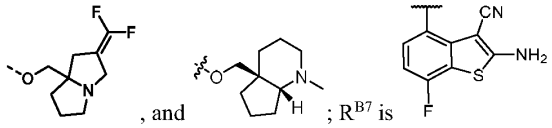
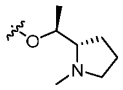
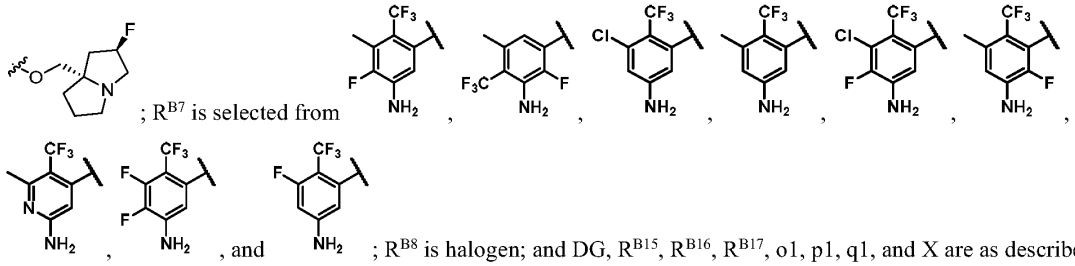
[213] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A), (A-1), (A-2), (A1), (A1-1), or (A1-2)), R^{B6} is chloro or -CF_3; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; DG is selected from 
and 
, wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, -OR^{B12}, -$C(O)OR^{B12}$, and -$C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and -$S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and R^{B8} is fluoro. In some embodiments, R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above

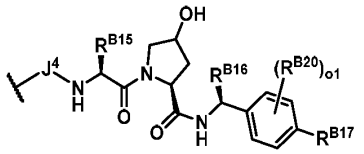
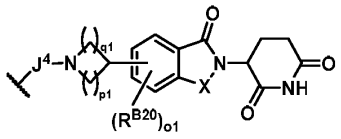
in this paragraph. In some embodiments, R^{B2} is selected from  ,  , and  ; R^{B7} is  ; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B2} is selected from  and  ; R^{B7} is selected from  ,  , and  ; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph.

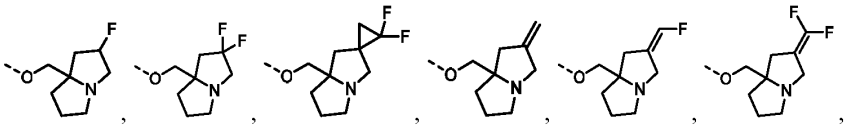
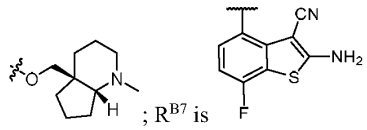
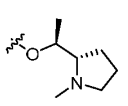
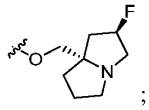
[214] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-3), (A0-6), (A), (A-1), (A-3), (A-6), (A1), (A1-1), (A1-3), or (A1-6), R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; DG is selected from  and  , wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and R^{B8} is halogen. In some embodiments, R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is selected from hydrogen and halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B7} is

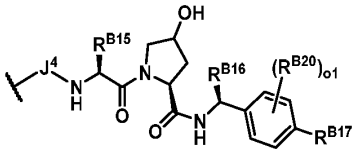
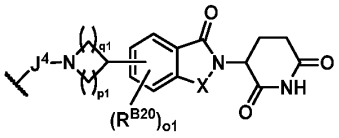
selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  ,  , and  ; R^{B7} is  ; R^{B8} is halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  and  ; R^{B7} is selected from  ,  , and  ; R^{B8} is halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph.

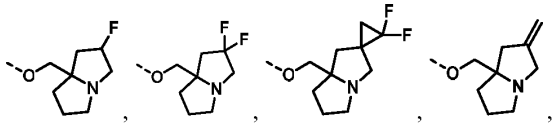
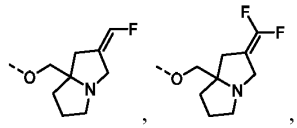
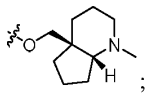
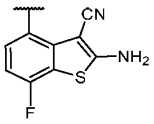
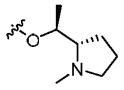
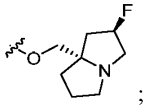
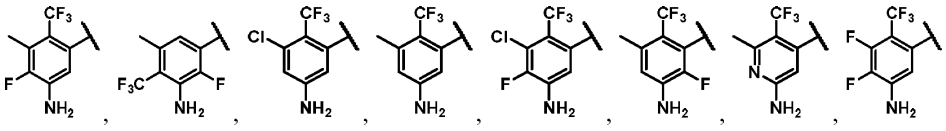
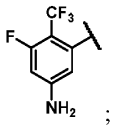
[215] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A), (A-1), (A-2), (A1), (A1-1), or (A1-2), R^{B6} is halogen or $-CF_3$; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; DG is selected from  and  , wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and R^{B8} is halogen. In some embodiments, R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is selected from hydrogen and halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some

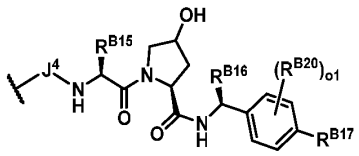
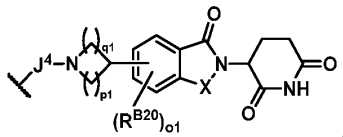
embodiments, R^{B2} is selected from  , and  ; R^{B7} is ; R^{B8} is halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B2} is selected from  and  ; R^{B7} is selected from ; R^{B8} is halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph.

[216] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6), R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; DG is selected from  and  , wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and R^{B8} is fluoro. In some embodiments, R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments,

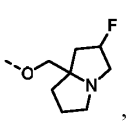
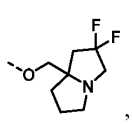
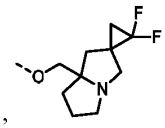
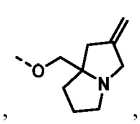
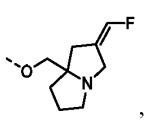
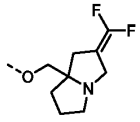
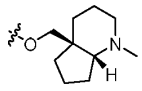
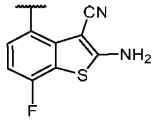
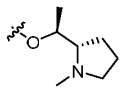
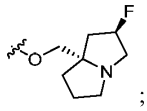
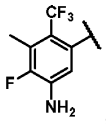
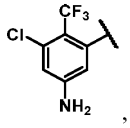
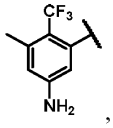
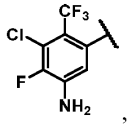
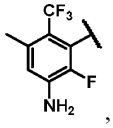
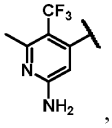
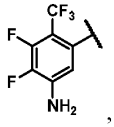
R^{B2} is selected from  , and  ; R^{B7} is ; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B2} is selected from  and  ; R^{B7} is selected from  ; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph.

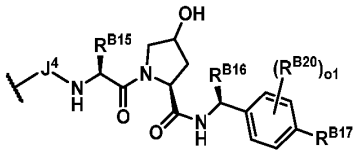
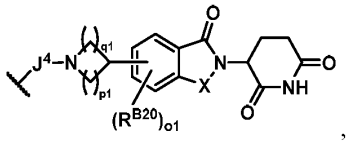
[217] In some embodiments, for a compound of Formula (A0), (A0-4), (A0-5), (A), (A-4), (A-5), (A1), (A1-4), or (A1-5), R^{B6b} is selected from C_{1-6} alkyl and -C_{0-6} alkyl-(C_{3-12} carbocycle), wherein C_{1-6} alkyl and -C_{0-6} alkyl-(C_{3-12} carbocycle) are optionally substituted with one, two, three, or four R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; DG is selected from  and  , wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, -OR^{B12}, -$C(O)OR^{B12}$, and -$C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and -$S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and R^{B8} is halogen. In some embodiments, R^{B6b} is selected from C_{1-6} alkyl and -C_{0-6} alkyl-(C_{3-12} carbocycle), wherein C_{1-6} alkyl and -C_{0-6} alkyl-(C_{3-12} carbocycle) are optionally substituted with one, two, three, or four R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is selected from hydrogen and halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this

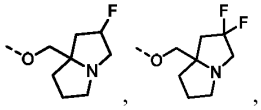
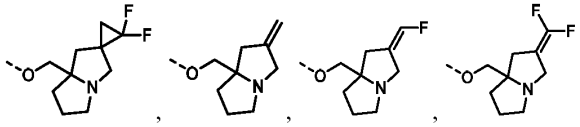
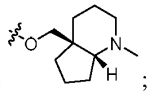
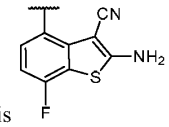
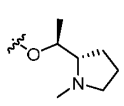
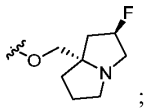
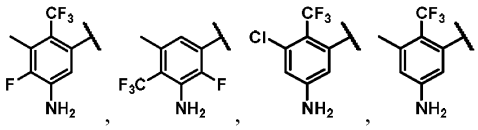
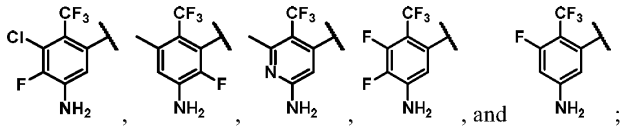
paragraph. In some embodiments, R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  ,  , and  ; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is  ; R^{B8} is halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  and  ; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from  ; and  ; R^{B8} is halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph.

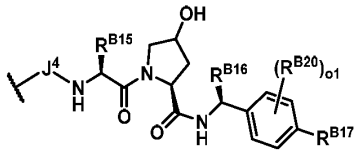
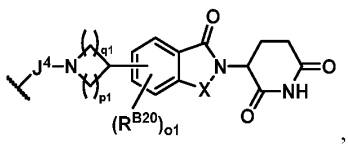
[218] In some embodiments, for a compound of Formula (A0), (A0-4), (A0-5), (A), (A-4), (A-5), (A1), (A1-4), or (A1-5), R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; DG is selected from  and  , wherein:

J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein

C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and R^{B8} is halogen. In some embodiments, R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is selected from hydrogen and halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  , and  ; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is  ; R^{B8} is halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B2} is selected from  and  ; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; R^{B8} is halogen; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph.

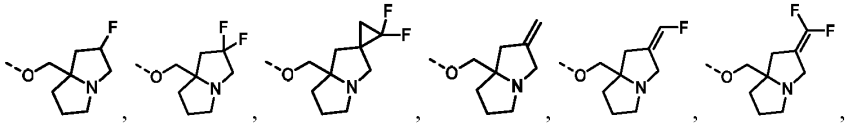
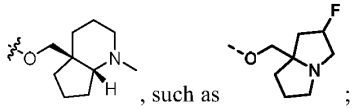
[219] In some embodiments, for a compound of Formula (A0), (A0-4), (A0-5), (A), (A-4), (A-5), (A1), (A1-4), or (A1-5), R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; DG is selected from  and  , wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-

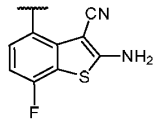
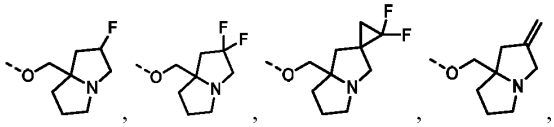
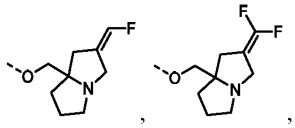
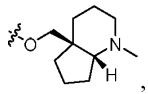
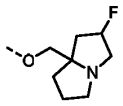
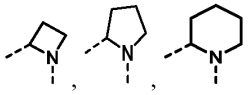
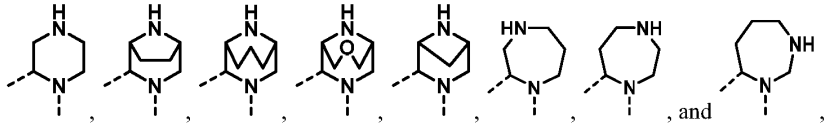
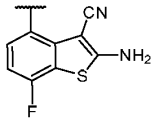
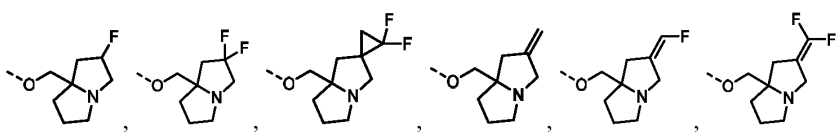
membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and R^{B8} is fluoro. In some embodiments, R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B2} is selected from  ,  , and  ; R^{B7} is  ; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, R^{B2} is selected from  and  ; R^{B7} is selected from  ,  , and ; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph.

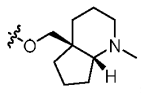
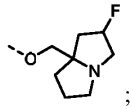
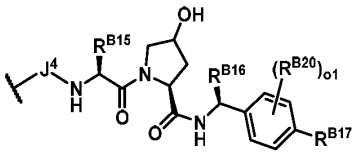
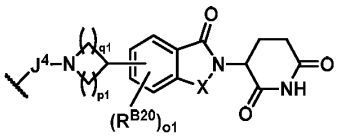
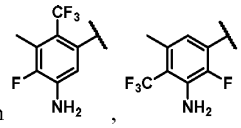
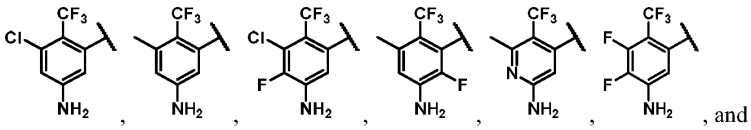
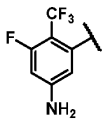
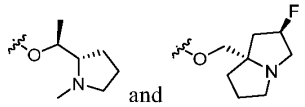
[220] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6), Q^2 is 6- to 10-membered heterocycle that is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; DG is selected from  and  , wherein:

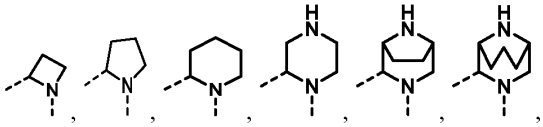
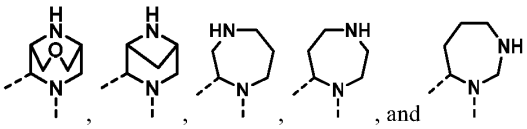
J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17}

is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}. In some embodiments, Q^2 is 7- to 9-membered heterocycle that is optionally substituted with one or more R^{B20}; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms and is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20};

R^{B2} is selected from  , and  , such as ; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20};

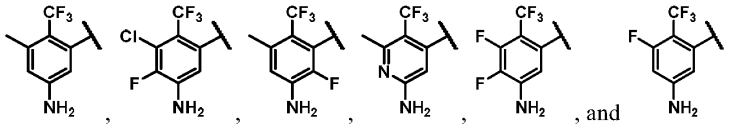
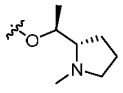
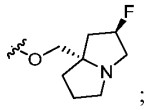
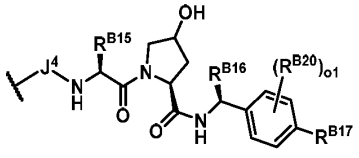
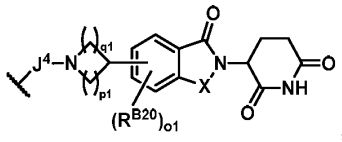
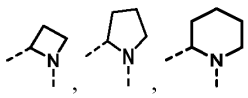
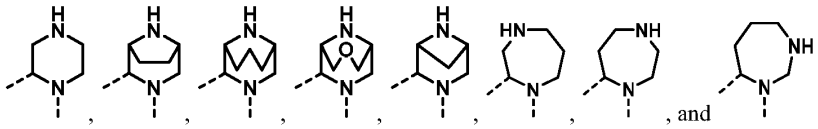
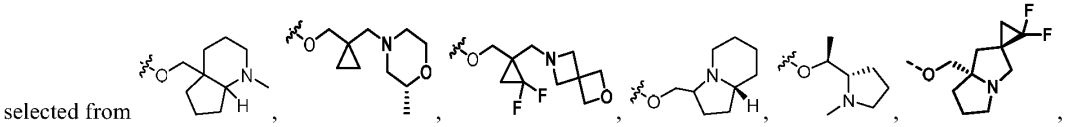
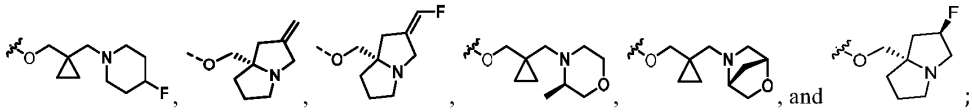
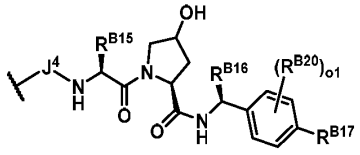
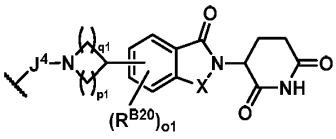
R^{B7} is  ; R^{B2} is selected from  ,  , and  , such as  ; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, Q^2 is selected from  ,  , and , each of which is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; R^{B2} is selected from  , and

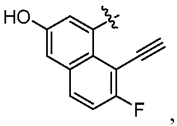
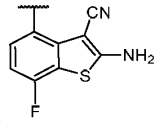
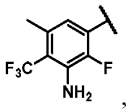
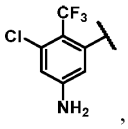
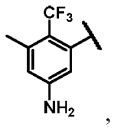
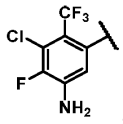
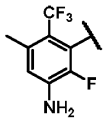
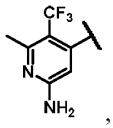
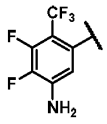
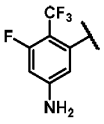
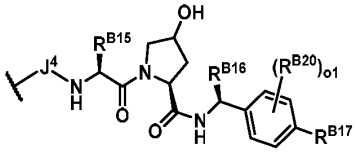
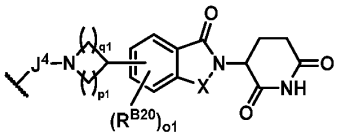

, such as

; DG is selected from

and

, wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and Z^1 is N. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from

,

, and

; R^{B2} is selected from

and

; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, Q^2 is selected from

,

, and

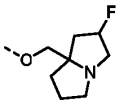
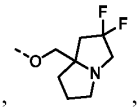
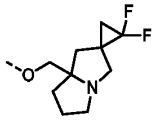
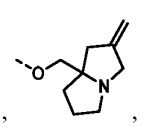
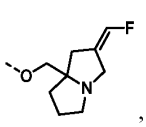
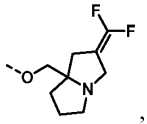
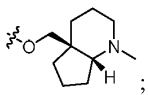
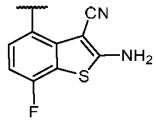
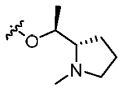
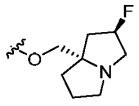
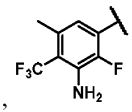
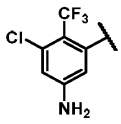
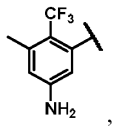
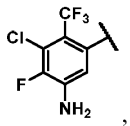
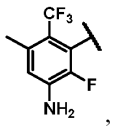
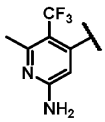
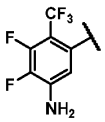
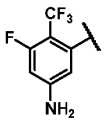
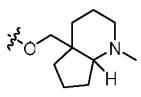
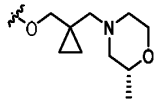
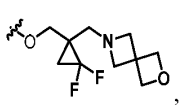
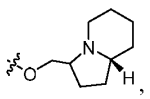
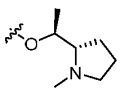
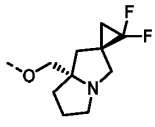
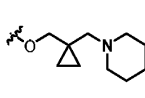
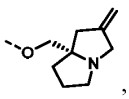
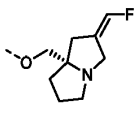
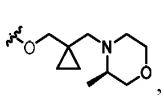
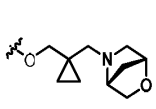
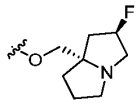
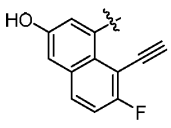
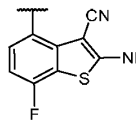
, each of which is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from

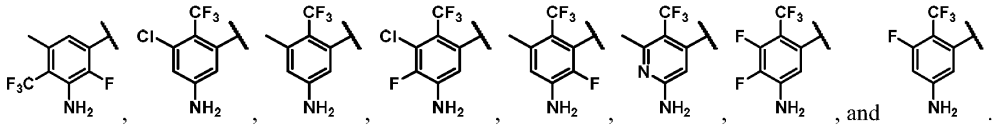
,


, and ; R^{B2} is selected from  and  ; DG is selected from  and  , wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and Z^1 is N. In some embodiments, Q^2 is selected from  ,  , and , each of which is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B2} is selected from  ,  , and ; DG is selected from  and  , wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, -

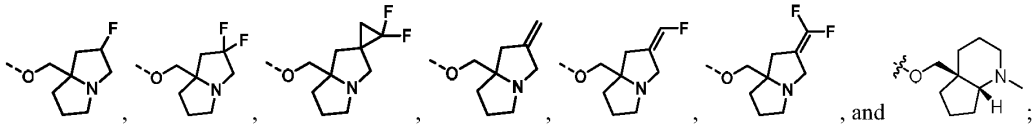
$C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and Z^1 is N. In some embodiments, R^{B2} is $-O(C_{1-3}$ alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and $=C(R^{B21})_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from            ; DG is selected from  and  , wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and Z^1 is N.

[221] In some embodiments, for a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B6} is halogen or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), wherein C_{1-6} alkyl and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle) are optionally substituted with one, two, three, or four R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B6} is selected from hydrogen, halogen, and $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is selected from hydrogen and halogen. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), wherein C_{1-6} alkyl and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle) are optionally substituted with one, two, three, or four R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted

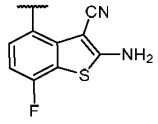
C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  , and  ; R^{B6} is halogen or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is  ; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  and  ; R^{B6} is halogen or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B6} is chloro or $-CF_3$; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; R^{B8} is fluoro; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^{B6} is chloro or $-CF_3$; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; R^{B8} is fluoro; R^{B2} is $-O(C_{1-3}$ alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and $=C(R^{B21})_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from  ,  ,  ,



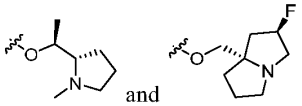
[222] In some embodiments, for a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B6} is halogen or $-CF_3$; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B6} is selected from hydrogen, halogen, and $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is selected from hydrogen and halogen. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from



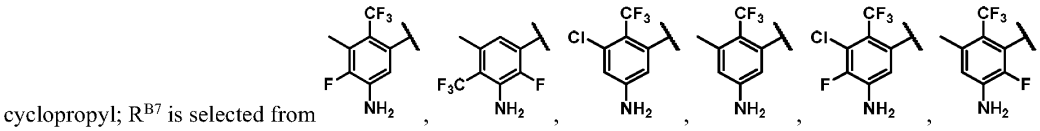
; R^{B6} is halogen or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is

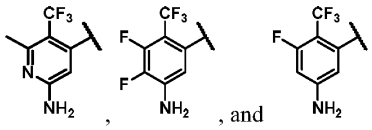


; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from

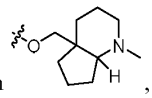


; R^{B6} is halogen or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from

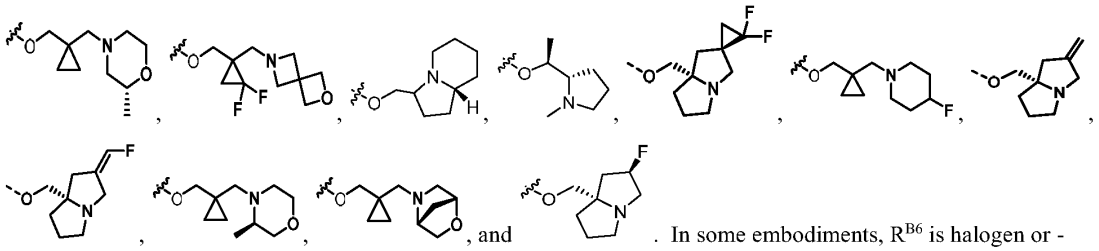




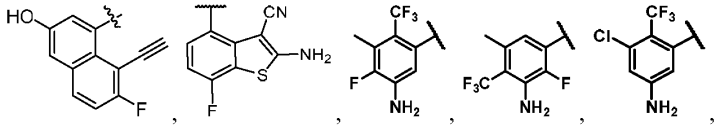
; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B6} is halogen or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; R^{B8} is halogen; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from

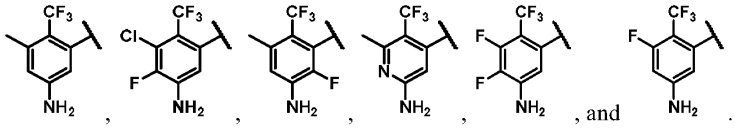


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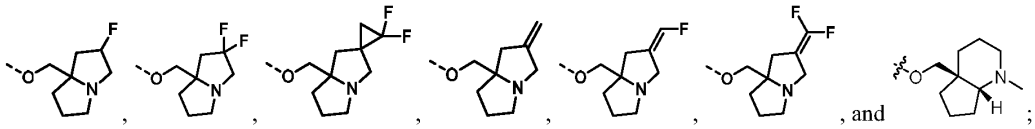


. In some embodiments, R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; R^{B8} is halogen; R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and =$C(R^{B21})_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from

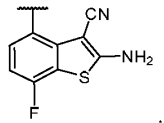




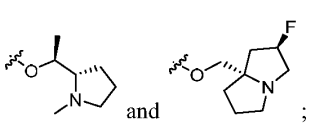
[223] In some embodiments, for a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B6} is chloro or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from



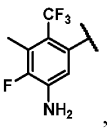
; and R^{B7} is

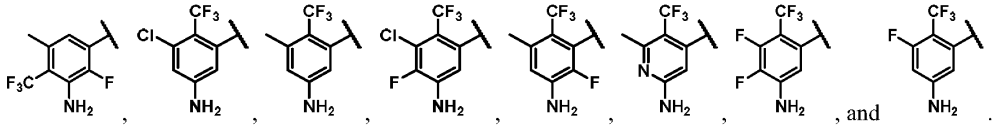


. In some embodiments, R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from

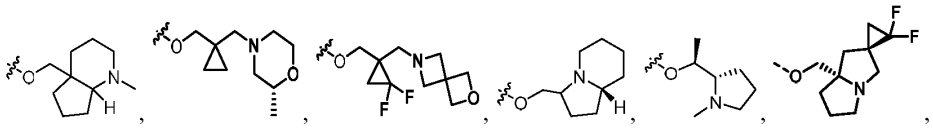
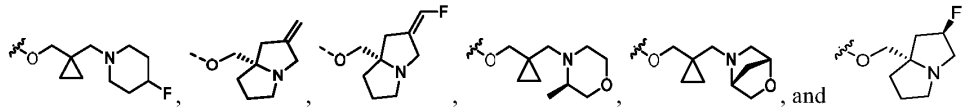
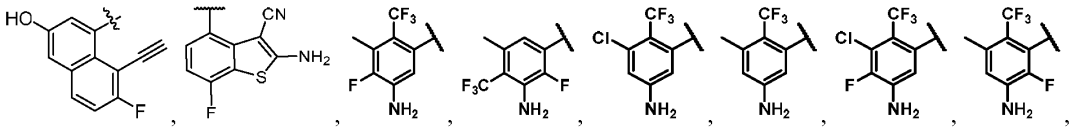
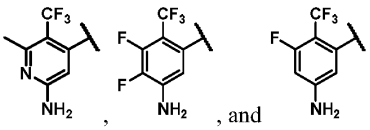


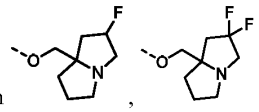
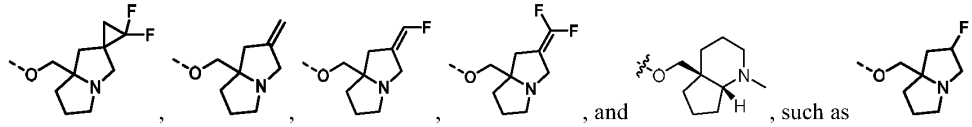
; and R^{B7} is selected from

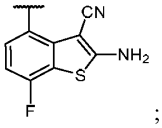
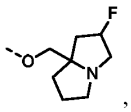
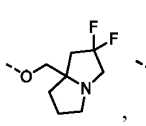
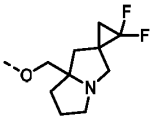
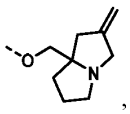
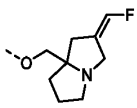
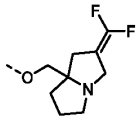
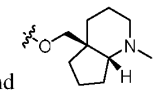
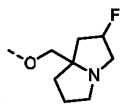
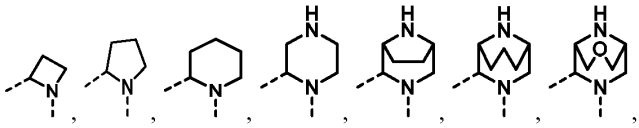
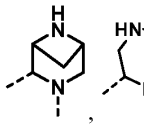
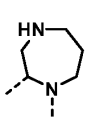
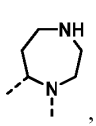
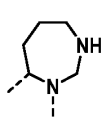
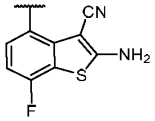
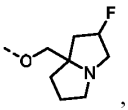
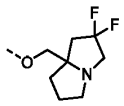
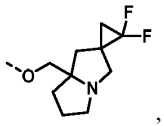
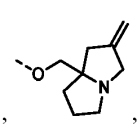
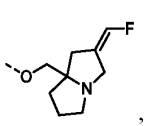
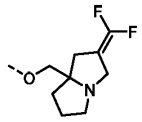
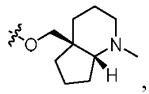
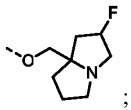
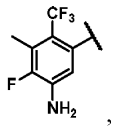
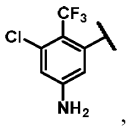
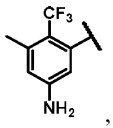
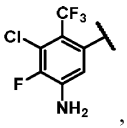
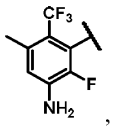
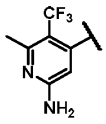
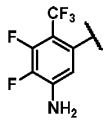
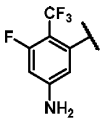
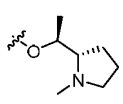
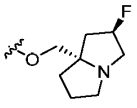
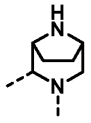


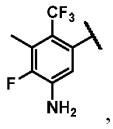
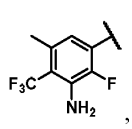
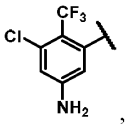
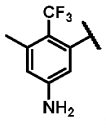
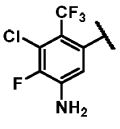
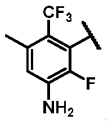
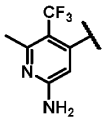
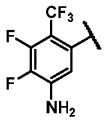
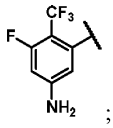
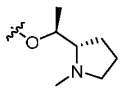
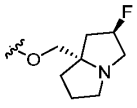
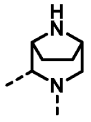
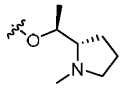
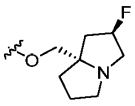
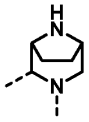
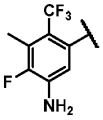
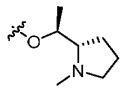
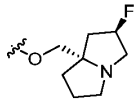
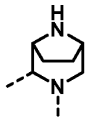
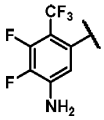
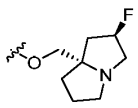
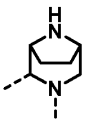
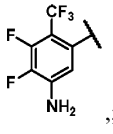
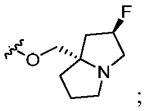


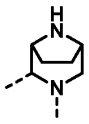
. In some embodiments, LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; R^{B8} is fluoro; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is

selected from  ,  , and . In some embodiments, LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; R^{B8} is fluoro; R^{B2} is $-O(C_{1-3}$ alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and $=C(R^{B21})_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from  ,  , and .

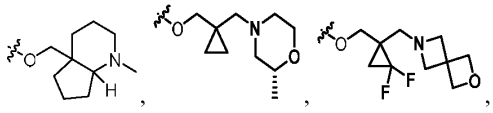
[224] In some embodiments, for a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), Q^2 is 6- to 10-membered heterocycle that is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}. In some embodiments, Q^2 is 7- to 9-membered heterocycle that is optionally substituted with one or more R^{B20}; LG is $-OS(O)_2R^{B4}$; and R^{B4} is unsubstituted C_{2-4} alkyl. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms and is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B2} is selected from  ,  , and , such as . In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is

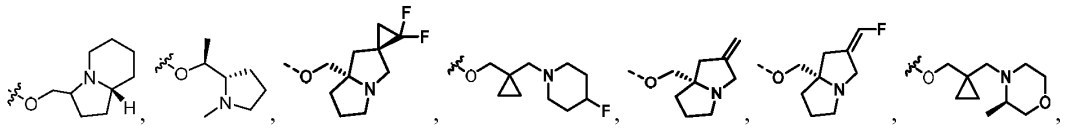

; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B2} is selected from  ,  ,  ,  ,  ,  , and  , such as  . In some embodiments, Q^2 is selected from  ,  ,  ,  , and  , each of which is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; R^{B2} is selected from  ,  ,  ,  ,  ,  , and  , such as  ; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and Z^1 is N. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B2} is selected from  and  . In some embodiments, Q^2 is  optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected

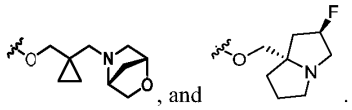
from  ,  ,  ,  ,  ,  ,  ,  , and  ; R^{B2} is selected from  and  ; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and Z^1 is N. In some embodiments, Q^2 is  optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{1-6} alkylene optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; R^{B2} is selected from  and  ; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and Z^1 is N. In some embodiments, Q^2 is  optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{1-6} alkylene optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; R^{B2} is selected from  and  ; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{3-4} carbocycle; and Z^1 is N. In some embodiments, Q^2 is  optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{1-6} alkylene optionally substituted with one, two, or three R^{B20}; R^{B7} is  ,; R^{B2} is  ; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and Z^1 is N. In some embodiments, Q^2 is  optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{1-6} alkylene optionally substituted with one, two, or three R^{B20}; R^{B7} is  ,; R^{B2} is  ; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{3-4} carbocycle; and Z^1 is N. In some



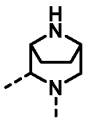
embodiments, Q^2 is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{1-6} alkylene optionally substituted with one, two, or three R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{3-4} carbocycle; Z^1 is N; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from



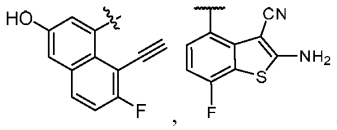


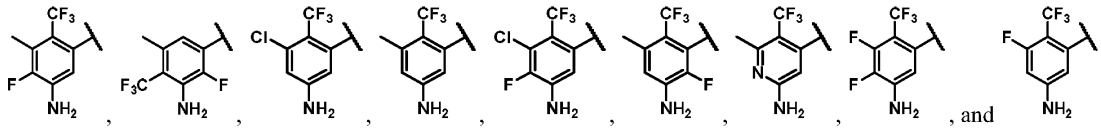


and



. In some embodiments, Q^2 is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{1-6} alkylene optionally substituted with one, two, or three R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{3-4} carbocycle; Z^1 is N; R^{B2} is $-O(C_{1-3}$ alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and $=C(R^{B21})_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from

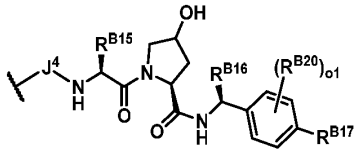




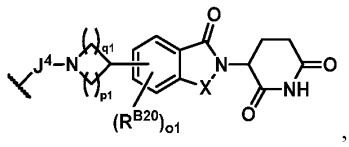
and

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[225] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6), Q^2 is 6- to 10-membered heterocycle that is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; DG is selected from



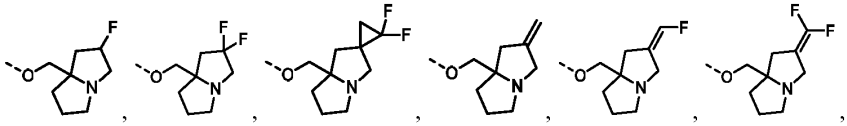
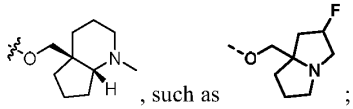
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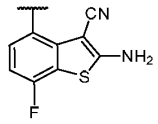
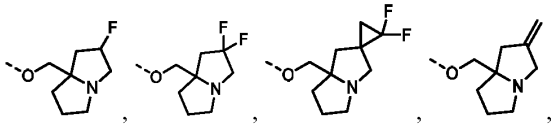
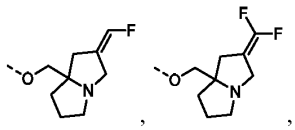
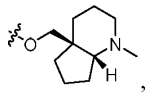
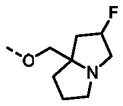
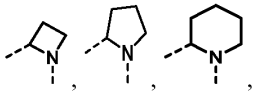
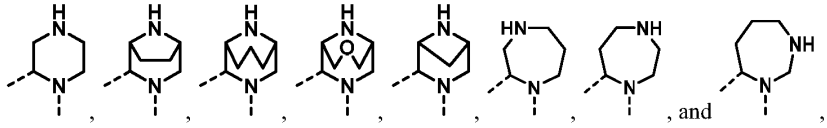
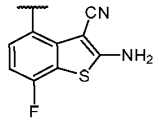
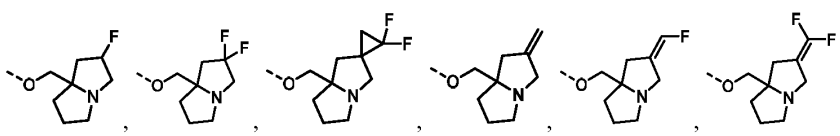


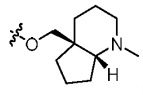
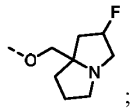
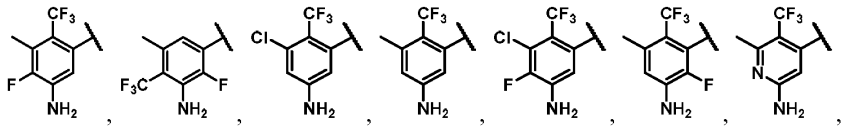
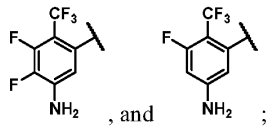
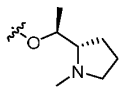
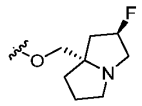
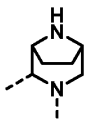
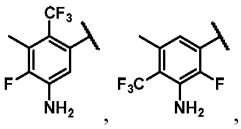
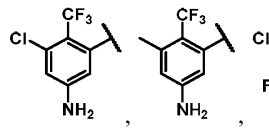
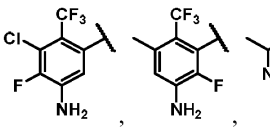
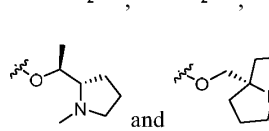
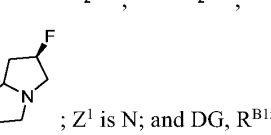
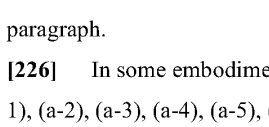
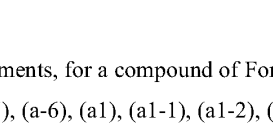
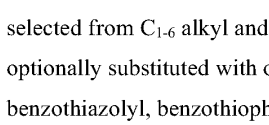
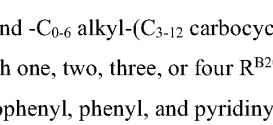
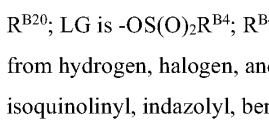
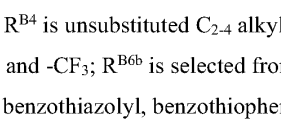
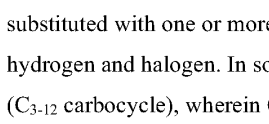
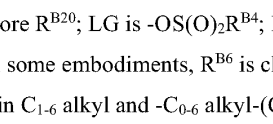
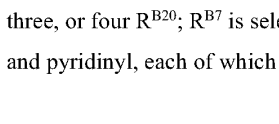
, wherein:

J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17}

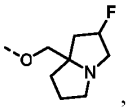
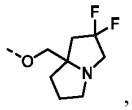
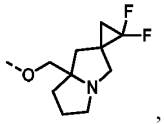
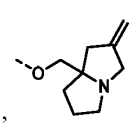
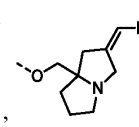
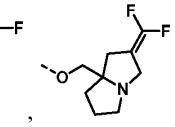
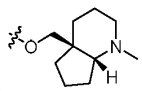
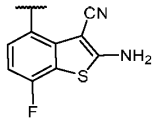
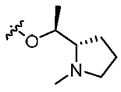
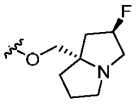
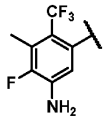
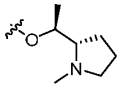
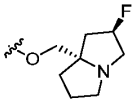
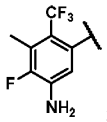
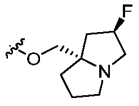
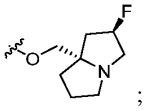
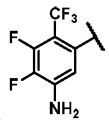
is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}. In some embodiments, Q^2 is 7- to 9-membered heterocycle that is optionally substituted with one or more R^{B20}; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20};

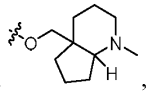
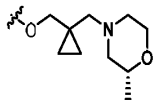
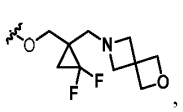
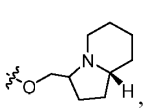
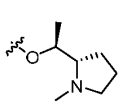
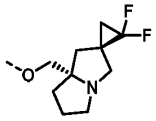
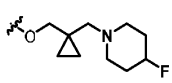
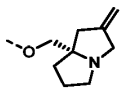
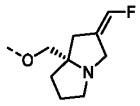
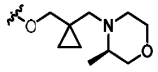
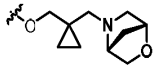
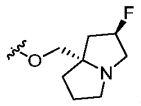
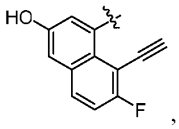
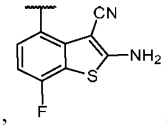
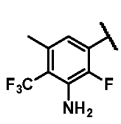
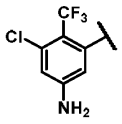
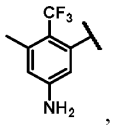
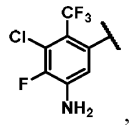
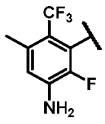
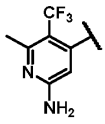
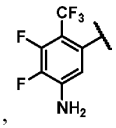
R^{B2} is selected from  , and  , such as ; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20};

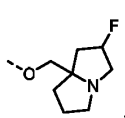
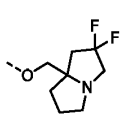
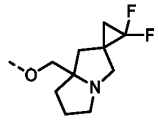
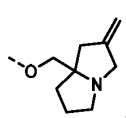
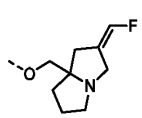
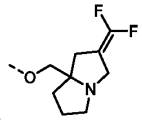
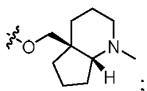
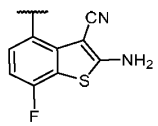
R^{B7} is  ; R^{B2} is selected from  ,  , and  , such as  ; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, Q^2 is selected from  ,  , and , each of which is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; R^{B2} is selected from  , and

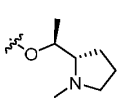
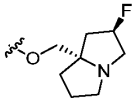
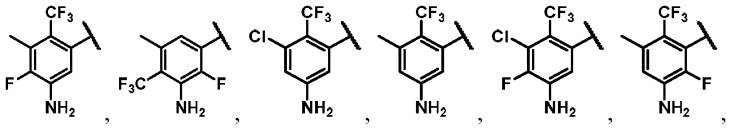
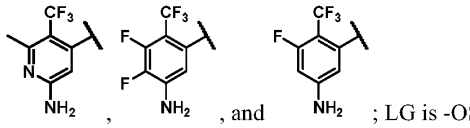
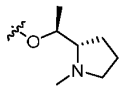
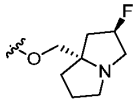
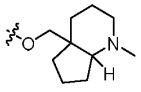
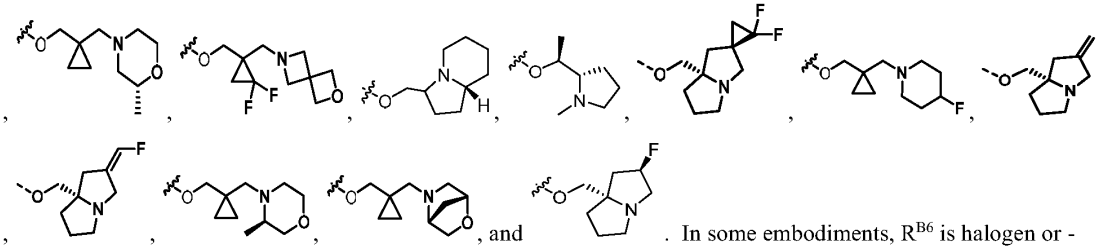
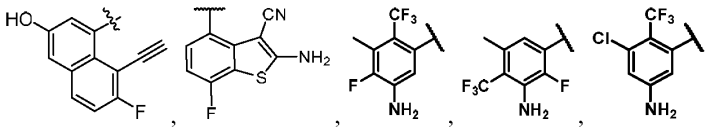
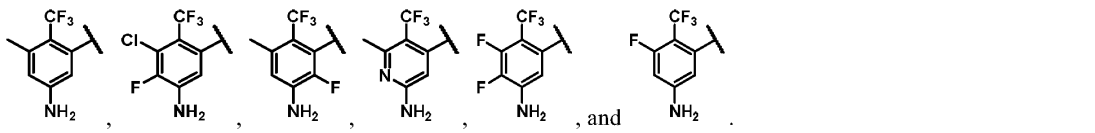

, such as 
; Z^1 is N; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from 
, and 
; R^{B2} is selected from 
and 
; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, Q^2 is 
optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from 
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, and 
; R^{B2} is selected from
and
; Z^1 is N; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph.

[226] In some embodiments, for a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -C_{0-6} alkyl-(C_{3-12} carbocycle), wherein C_{1-6} alkyl and -C_{0-6} alkyl-(C_{3-12} carbocycle) are optionally substituted with one, two, three, or four R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B6} is selected from hydrogen, halogen, and -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is selected from hydrogen and halogen. In some embodiments, R^{B6} is chloro or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -C_{0-6} alkyl-(C_{3-12} carbocycle), wherein C_{1-6} alkyl and -C_{0-6} alkyl-(C_{3-12} carbocycle) are optionally substituted with one, two, three, or four R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted

C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B6} is chloro or -CF_3; R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  , and  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is  ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B6} is chloro or -CF_3; R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  and  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is  ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B2} is selected from  and  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is  ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted cyclopropyl; and R^{B8} is halogen. In some embodiments, R^{B2} is  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is  ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B2} is  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is  ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted cyclopropyl; and R^{B8} is halogen. In some embodiments, R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted cyclopropyl; R^{B8} is halogen; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl,

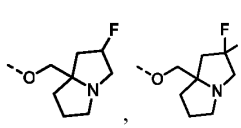
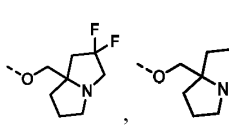
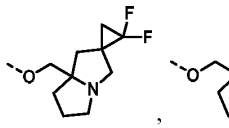
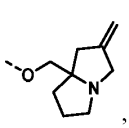
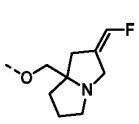
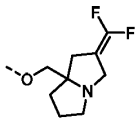
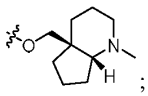
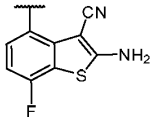
each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted cyclopropyl; R^{B8} is halogen; R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and $=C(R^{B21})_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

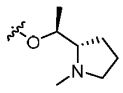
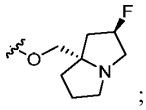
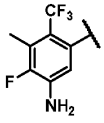
[227] In some embodiments, for a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B6} is halogen or -CF_3; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B6} is selected from hydrogen, halogen, and -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is selected from hydrogen and halogen. In some embodiments, R^{B6} is chloro or -CF_3; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B6} is chloro or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  ,  ,  ,  ,  ,  , and  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is  ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B6} is chloro or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or

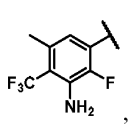
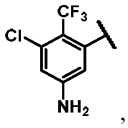
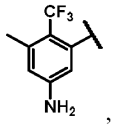
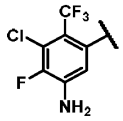
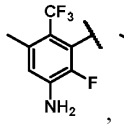
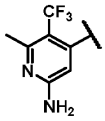
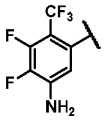
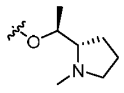
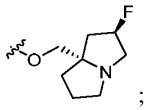
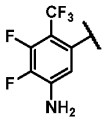
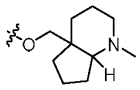
more R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  and  ; R^{B6} is halogen or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from  ,  , and ; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B2} is selected from  and  ; R^{B6} is halogen or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is  ; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is halogen. In some embodiments, R^{B6} is halogen or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; R^{B8} is halogen; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from  ,  , and . In some embodiments, R^{B6} is halogen or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and cyclopropyl; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; R^{B8} is halogen; R^{B2} is $-O(C_{1-3}$ alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and $=C(R^{B21})_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from  ,  , and .

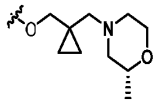
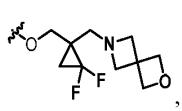
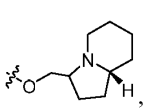
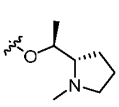
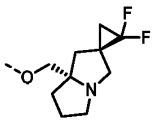
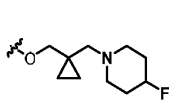
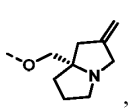
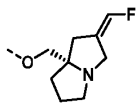
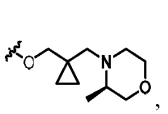
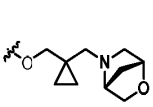
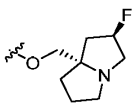
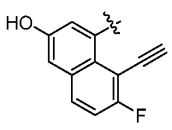
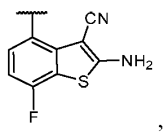
[228] In some embodiments, for a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), R^{B6} is chloro or $-CF_3$; R^{B6b} is

selected from C_{1-6} alkyl and cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B7} is selected from benzothiazolyl and benzothiophenyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from







, and  ; and 

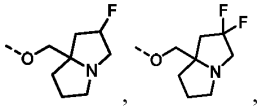
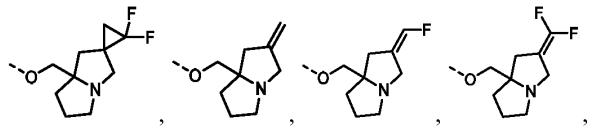
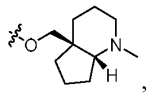
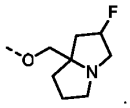
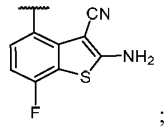
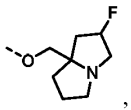
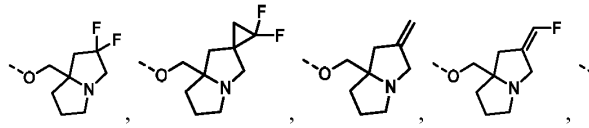
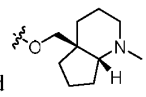
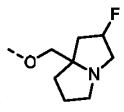
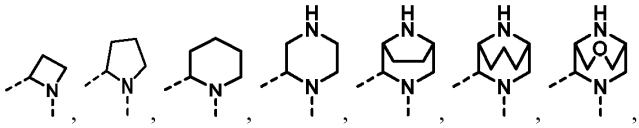
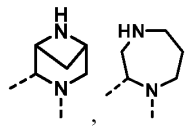
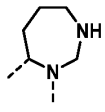
R^{B7} is . In some embodiments, R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  and  ; and R^{B7} is selected from  ,

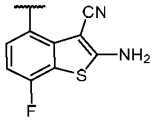
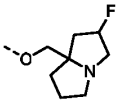
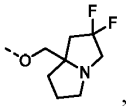
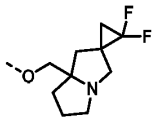
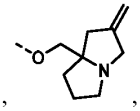
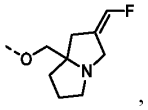
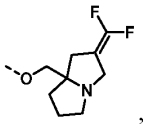
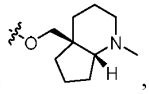
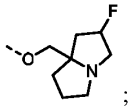
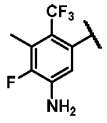
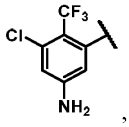
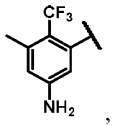
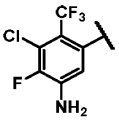
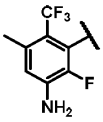
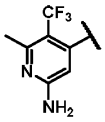
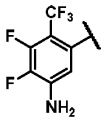
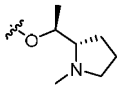
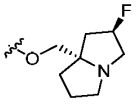
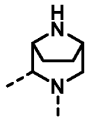
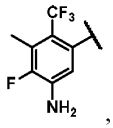
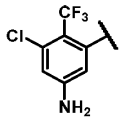
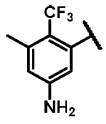
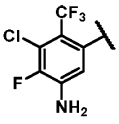
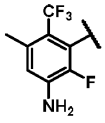
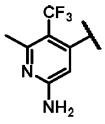
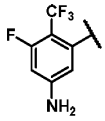
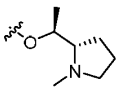
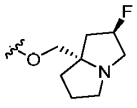
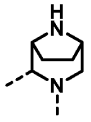
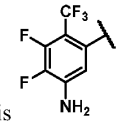
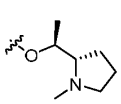
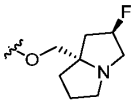







, and  . In some embodiments, R^{B7} is selected from phenyl and pyridinyl, each of which is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro. In some embodiments, R^{B2} is selected from  and  ; and R^{B7} is  . In some embodiments, LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from  ,

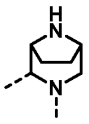
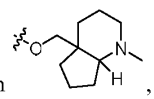
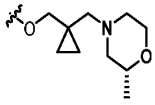
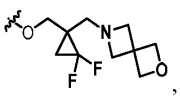
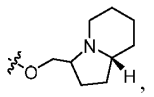
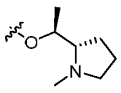
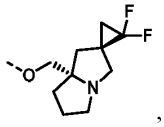
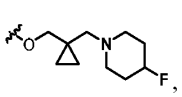
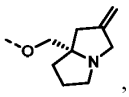
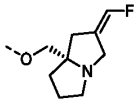
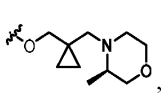
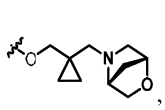
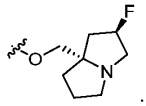
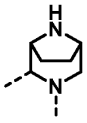
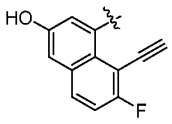
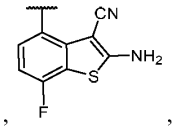
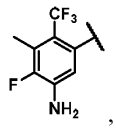
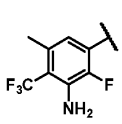
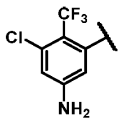
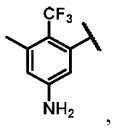
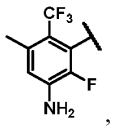
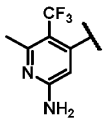
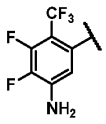
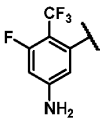










, and  . In some embodiments, LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B8} is fluoro; R^{B2} is -$O(C_{1-3}$ alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and $=C(R^{B21})_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from  ,  ,



.

[229] In some embodiments, for a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), Q^2 is 6- to 10-membered heterocycle that is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}. In some embodiments, Q^2 is 7- to 9-membered heterocycle that is optionally substituted with one or more R^{B20}; LG is -$OS(O)_2R^{B4}$; and R^{B4} is unsubstituted C_{2-4} alkyl. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B2} is selected from  ,  , and  , such as  . In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B2} is selected from  ,  , and  , such as  . In some embodiments, Q^2 is selected from  ,  , and  , each of which is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally

substituted with one, two, or three R^{B20}; R^{B7} is  ; R^{B2} is selected from  ,  ,  ,  ,  ,  , and  , such as  ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and Z^1 is N. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} i is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B2} is selected from  and  . In some embodiments, Q^2 is  optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; R^{B2} is selected from  and  ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and Z^1 is N. In some embodiments, Q^2 is  optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; R^{B2} is selected from  and  ; LG is -$OS(O)_2R^{B4}$;

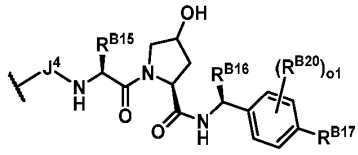
R^{B4} is unsubstituted C_{2-4} alkyl; and Z^1 is N. In some embodiments, Q^2 is  optionally substituted with one or more R^{B20}; J^1 is -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; LG is -OS(O)$_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; Z^1 is N; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from             and  . In some embodiments, Q^2 is optionally substituted with one or more R^{B20}; J^1 is -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; LG is -OS(O)$_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; Z^1 is N; R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from           , and  .

[230] In some embodiments of a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), J^1 is a -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is unsubstituted ethylene; LG is selected from -OS(O)$_2R^{B4}$, -OS(O)(NH)R^{B4}, and -OS(O)(NCN)R^{B4}; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle. In embodiments, J^1 is a bond; J^2 is a bond; J^3 is unsubstituted propylene; LG is selected from -OS(O)$_2R^{B4}$, -OS(O)(NH)R^{B4}, and -OS(O)(NCN)R^{B4}; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle. In embodiments, J^1 is a -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is cyclobutylene; LG is selected from -OS(O)$_2R^{B4}$, -OS(O)(NH)R^{B4}, and -OS(O)(NCN)R^{B4}; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle.

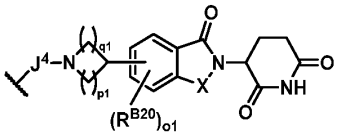
[231] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), J^1 is -N(C_{1-3} alkyl)C(O)-, J^2 is a bond, and J^3 is selected from C_{1-6} alkylene,

C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a -N(C_{1-3} alkyl)C(O)-, J^2 is a bond, and J^3 is C_{1-6} alkylene, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is -N(CH_3)C(O)-, J^2 is a bond, and J^3 is methylene, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is -N(CH_3)C(O)-, J^2 is a bond, and J^3 is unsubstituted methylene. In embodiments, J^1 is -N(CH_3)C(O)-, J^2 is a bond, and J^3 is ethylene (e.g., -CH(CH_3)-, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is -N(CH_3)C(O)-, J^2 is a bond, and J^3 is unsubstituted ethylene (e.g., -CH(CH_3)-. In embodiments, J^1 is -N(CH_3)C(O)-, J^2 is a bond, and J^3 is propylene (e.g., -CH(CH_2CH_3)-, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is -N(CH_3)C(O)-, J^2 is a bond, and J^3 is unsubstituted propylene (e.g., -CH(CH_2CH_3)-. In embodiments, J^1 is -N(CH_3)C(O)-, J^2 is a bond, and J^3 is butylene (e.g., -CH(CH(CH_3)$_2$)-, which is optionally substituted with one or more R^{B20}. In embodiments, J^1 is a -N(CH_3)C(O)-, J^2 is a bond, and J^3 is unsubstituted butylene (e.g., -CH(CH(CH_3)$_2$)-. In embodiments, J^1 is -N(CH_3)C(O)-, J^2 is a bond, and J^3 is methylene, which is substituted with one or more unsubstituted C_{3-6} carbocycle. In embodiments, J^1 is -N(CH_3)C(O)-, J^2 is a bond, and J^3 is methylene, which is substituted with one or more unsubstituted C_{3-4} carbocycle. In embodiments, J^1 is -N(CH_3)C(O)-, J^2 is a bond, and J^3 is methylene, which is substituted with one or more unsubstituted cyclopropyl.

[232] In some embodiments of a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6), J^1 is a -C(O)-; J^2 is a bond; J^3 is unsubstituted methylene; DG is selected from



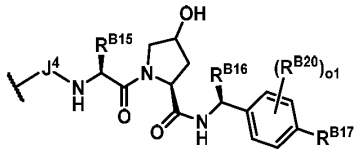
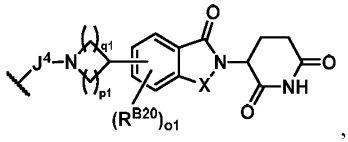
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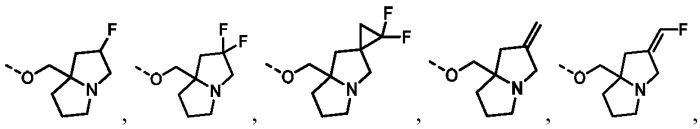
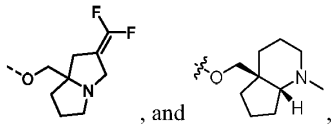
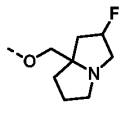
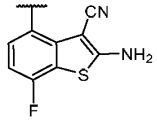
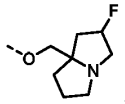
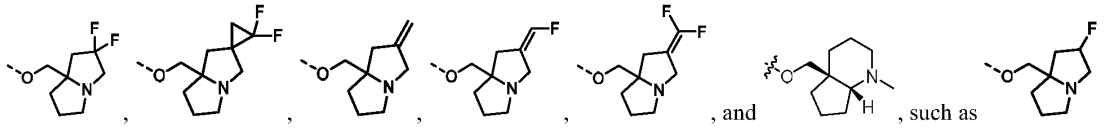
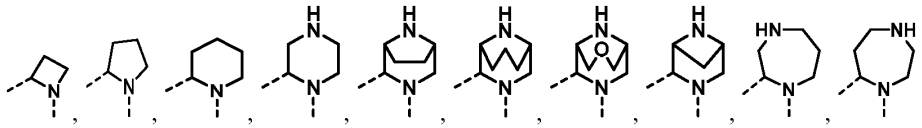
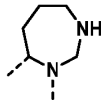
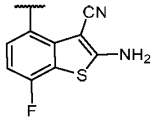
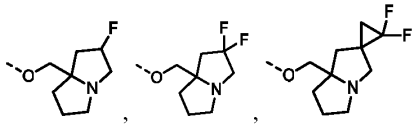
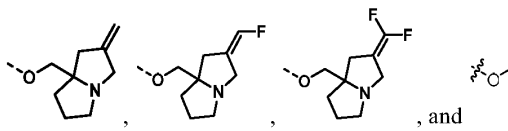
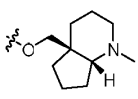
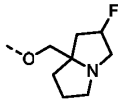
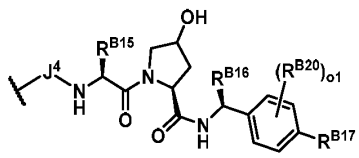
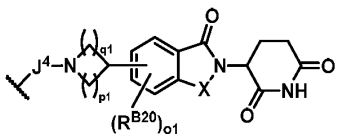


; J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, -OR^{B12}, -C(O)OR^{B12}, and -C(O)R^{B12}, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and -$S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O). In embodiments, J^1 is -N(CH_3)C(O)-; J^2 is a bond; J^3 is unsubstituted ethylene (e.g., -CH(CH_3)-; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In embodiments, J^1 is -N(CH_3)C(O)-; J^2 is a bond; J^3 is unsubstituted propylene (e.g., -CH(CH_2CH_3)-; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In embodiments, J^1 is -N(CH_3)C(O)-; J^2 is a bond; J^3 is unsubstituted butylene (e.g., -CH(CH(CH_3)$_2$)-; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1,

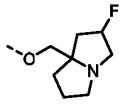
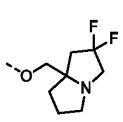
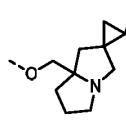
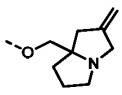
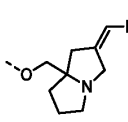
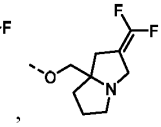
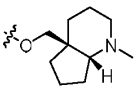
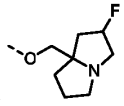
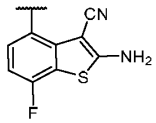
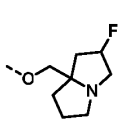
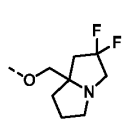
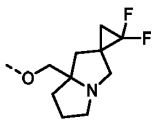
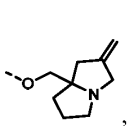
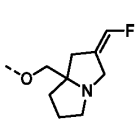
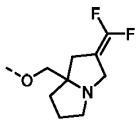
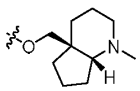
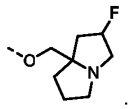
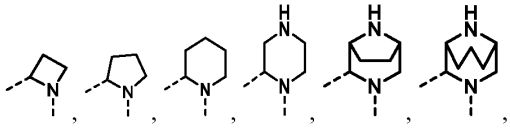
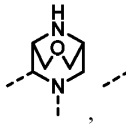
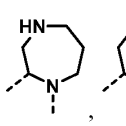
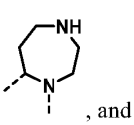
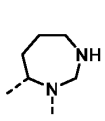
and X are as described above in this paragraph. In embodiments, J^1 is -N(CH_3)C(O)-; J^2 is a bond; J^3 is methylene, which is substituted with one unsubstituted cyclopropyl; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph.

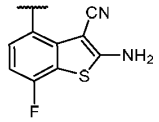
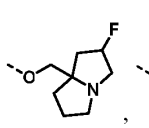
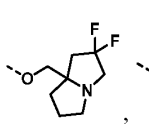
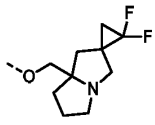
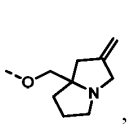
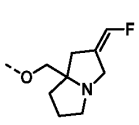
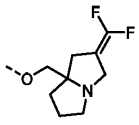
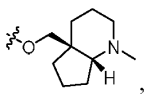
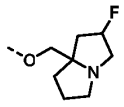
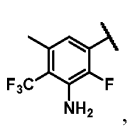
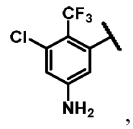
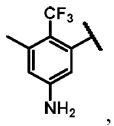
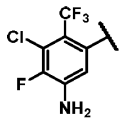
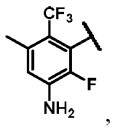
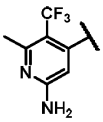
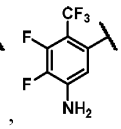
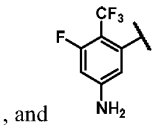
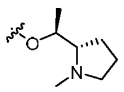
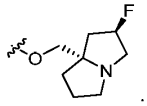
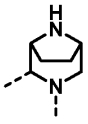
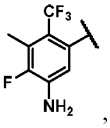
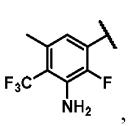
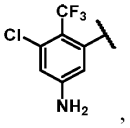
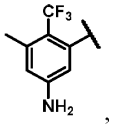
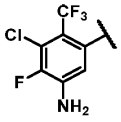
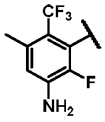
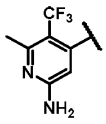
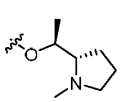
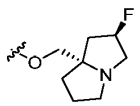
[233] In some embodiments of a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), J^1 is -N(CH_3)C(O)-; J^2 is a bond; J^3 is unsubstituted methylene; LG is selected from -OS(O)$_2R^{B4}$, -OS(O)(NH)R^{B4}, and -OS(O)(NCN)R^{B4}; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle. In embodiments, J^1 is -N(CH_3)C(O)-; J^2 is a bond; J^3 is unsubstituted ethylene (e.g., -CH(CH_3)-; LG is selected from -OS(O)$_2R^{B4}$, -OS(O)(NH)R^{B4}, and -OS(O)(NCN)R^{B4}; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle. In embodiments, J^1 is -N(CH_3)C(O)-; J^2 is a bond; J^3 is unsubstituted propylene (e.g., -CH(CH_2CH_3)-; LG is selected from -OS(O)$_2R^{B4}$, -OS(O)(NH)R^{B4}, and -OS(O)(NCN)R^{B4}; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle. In embodiments, J^1 is -N(CH_3)C(O)-; J^2 is a bond; J^3 is unsubstituted butylene (e.g., -CH(CH(CH_3)$_2$)-; LG is selected from -OS(O)$_2R^{B4}$, -OS(O)(NH)R^{B4}, and -OS(O)(NCN)R^{B4}; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle. In embodiments, J^1 is -N(CH_3)C(O)-; J^2 is a bond; J^3 is methylene, which is substituted with one unsubstituted cyclopropyl; LG is selected from -OS(O)$_2R^{B4}$, -OS(O)(NH)R^{B4}, and -OS(O)(NCN)R^{B4}; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle.

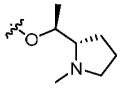
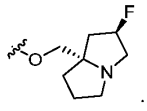
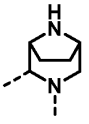
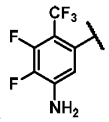
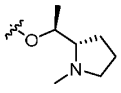
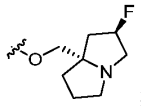
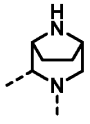
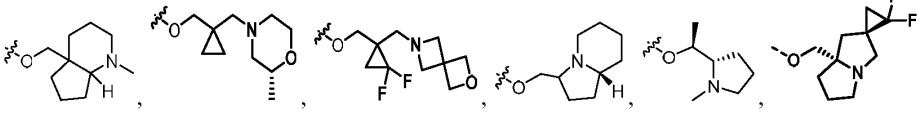
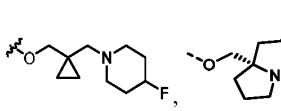
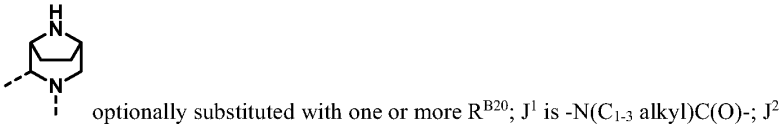
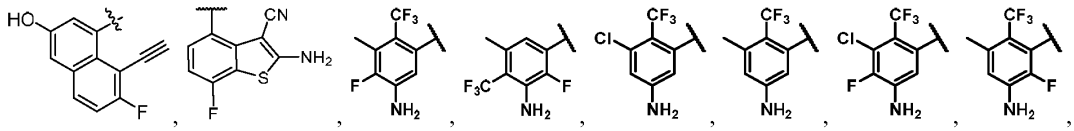
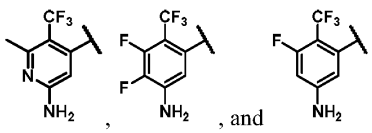
[234] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6), Q^2 is 6- to 10-membered heterocycle that is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; DG is selected from  and  , wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, -OR^{B12}, -C(O)OR^{B12}, and -C(O)R^{B12}, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and -S(O)$_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}. In some embodiments, Q^2 is 7- to 9-membered heterocycle that is optionally substituted with one or more R^{B20}; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms and is optionally substituted with one or more R^{B20}; J^1 is -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl,

benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}; R^{B2} is selected from  , and  , such as  ; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; R^{B2} is selected from  ,  , and , such as ; and DG, R^{B15}, R^{B16}, R^{B17}, o1, p1, q1, and X are as described above in this paragraph. In some embodiments, Q^2 is selected from  , and  , each of which is optionally substituted with one or more R^{B20}; J^1 is -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; R^{B2} is selected from  ,  , and  , such as  ; DG is selected from  , and  , wherein: J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered

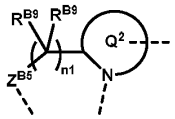
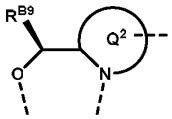
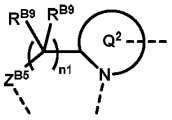
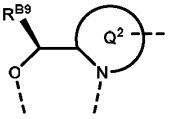
heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O); and Z^1 is N.

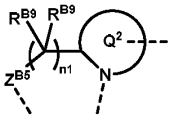
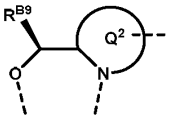
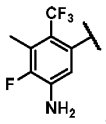
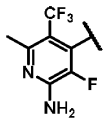
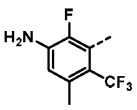
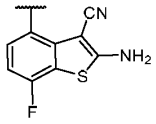
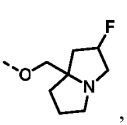
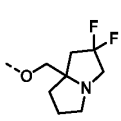
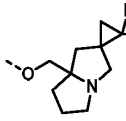
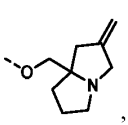
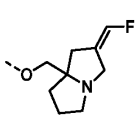
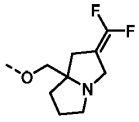
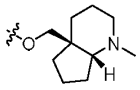
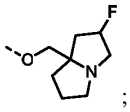
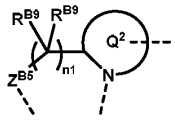
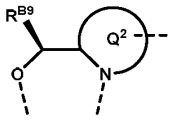
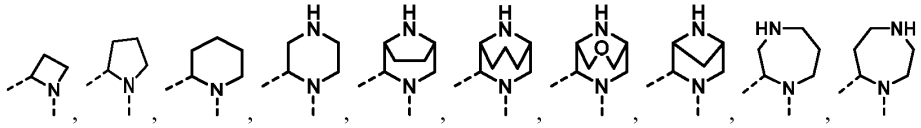
[235] In some embodiments, for a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), Q^2 is 6- to 10-membered heterocycle that is optionally substituted with one or more R^{B20}; J^1 is $-N(C_{1-3}$ alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}. In some embodiments, Q^2 is 7- to 9-membered heterocycle that is optionally substituted with one or more R^{B20}; LG is $-OS(O)_2R^{B4}$; and R^{B4} is unsubstituted C_{2-4} alkyl. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms and is optionally substituted with one or more R^{B20}; J^1 is $-N(C_{1-3}$ alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B2} is selected from  ,  ,  ,  ,  ,  , and  , such as  . In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is $-N(C_{1-3}$ alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; LG is $-OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B2} is selected from  ,  ,  ,  ,  ,  , and  , such as  . In some embodiments, Q^2 is selected from  ,  , , ,  ,  , and  , each of which is optionally substituted with one or more

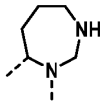
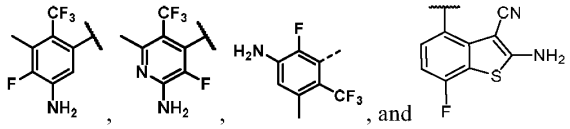
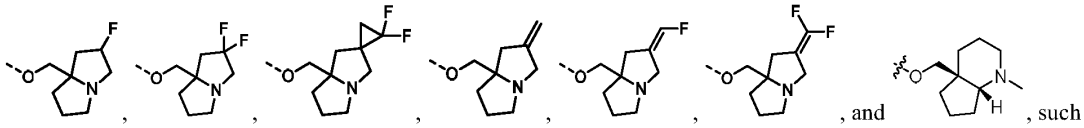
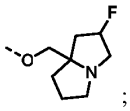
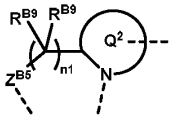
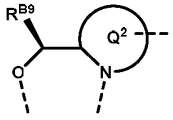
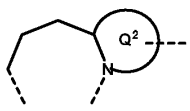
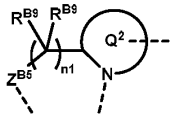
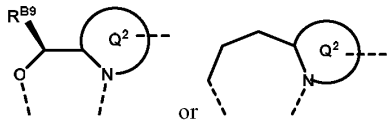
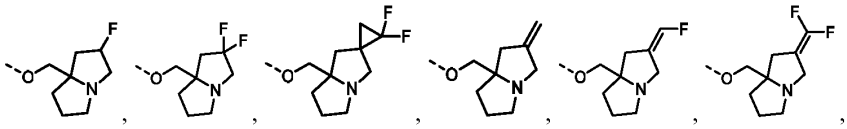
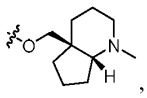
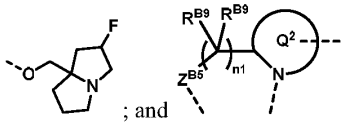
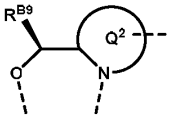
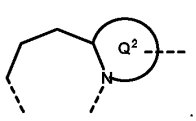
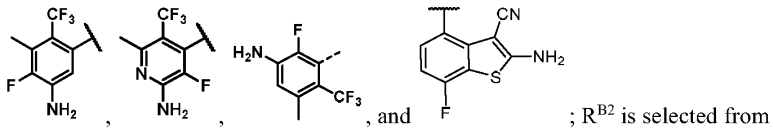
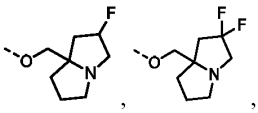
R^{B20}; J^1 is -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; R^{B2} is selected from  ,  ,  ,  ,  ,  , and  , such as  ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and Z^1 is N. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  , and ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and R^{B2} is selected from  and  . In some embodiments, Q^2 is  optionally substituted with one or more R^{B20}; J^1 is -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  , and ; R^{B2} is selected from  and  ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and Z^1 is N. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; LG is -$OS(O)_2R^{B4}$; R^{B4} is unsubstituted C_{2-4}

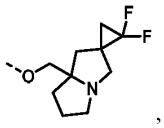
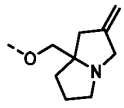
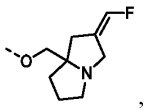
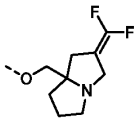
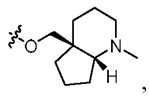
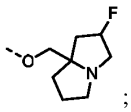
alkyl; and R^{B2} is selected from  and  . In some embodiments, Q^2 is  optionally substituted with one or more R^{B20}; J^1 is -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is  ; R^{B2} is selected from  and  ; LG is -OS(O)$_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; and Z^1 is N. In some embodiments, Q^2 is  optionally substituted with one or more R^{B20}; J^1 is -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; LG is -OS(O)$_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; Z^1 is N; R^{B7} is selected from phenyl, naphthyl, benzothiophenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and R^{B2} is selected from  ,  , and  . In some embodiments, Q^2 is optionally substituted with one or more R^{B20}; J^1 is -N(C_{1-3} alkyl)C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; LG is -OS(O)$_2R^{B4}$; R^{B4} is unsubstituted C_{2-4} alkyl; Z^1 is N; R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl; and R^{B7} is selected from  , and  .

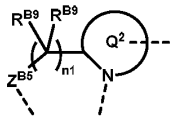
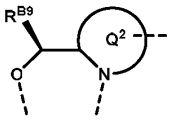
[236] In some embodiments, for a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), or (a0-6), R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -C_{0-6} alkyl-(C_{3-12} carbocycle), each of which is optionally substituted with one, two, three, or four R^{B20}; R^{B7} is selected

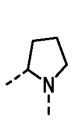
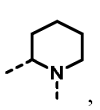
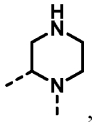
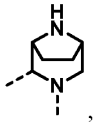
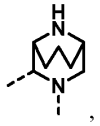
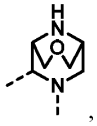
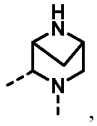
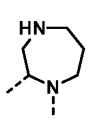
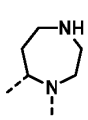
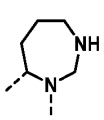
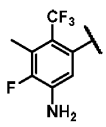
from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is halogen; and  is  or  . In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), each of which is optionally substituted with one, two, three, or four R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and  is  or  .

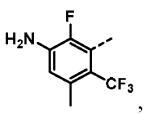
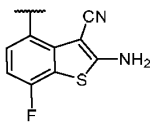
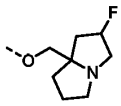
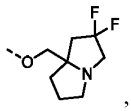
[237] In some embodiments, R^{B6} is chloro or $-CF_3$; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; R^{B8} is fluoro; and  is  or  . In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from  ,  ,  , and  ; R^{B2} is selected from  ,  ,  ,  ,  ,  , and  , such as  ; and  is  or  . In some embodiments, Q^2 is selected from  , and

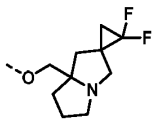
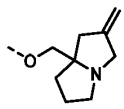
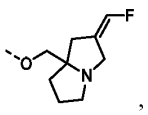
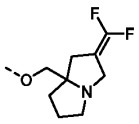
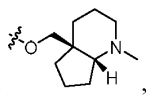
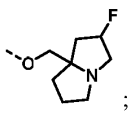

, each of which is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from 
; R^{B2} is selected from 
, such as 
; Z^1 is N; and 
is 
or 
. In some embodiments, Q^2 is 6- to 10-membered heterocycle that is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}; and 
is 
. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}; R^{B2} is selected from 
, such as 
; and 
is 
or 
. In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from 
; R^{B2} is selected from 
,

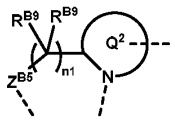
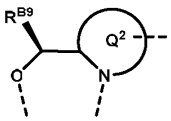
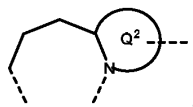




, and  , such as  ; and

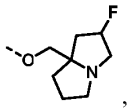
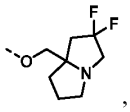
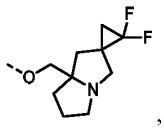
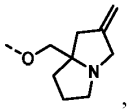
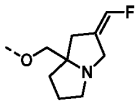
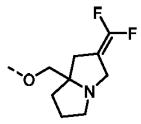
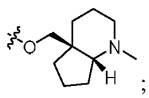

is 
or  . In some embodiments, Q^2 is selected from  ,










, and  , each of which is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from 

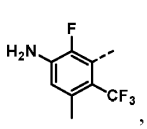
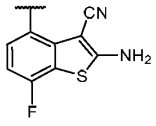
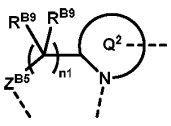
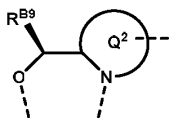

, and  ; R^{B2} is selected from 

,

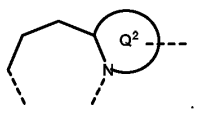
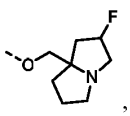
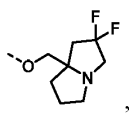
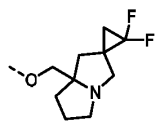




, and  , such as  ; Z^1 is N; and

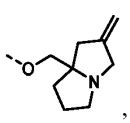
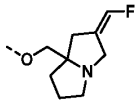
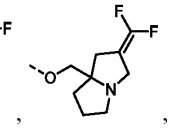
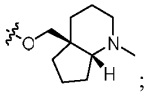

is 
or  . In some embodiments, R^{B2} is selected from

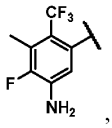
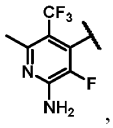
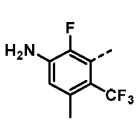
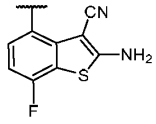
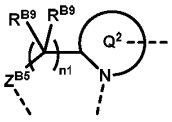
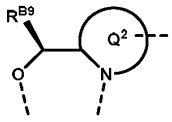






, and  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6} alkyl and -cyclopropyl; R^{B7} is selected from 

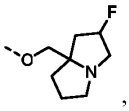
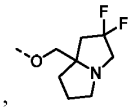
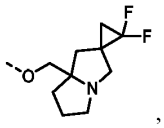
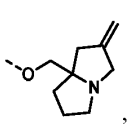
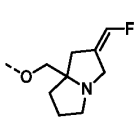
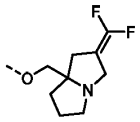
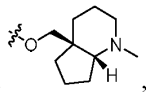
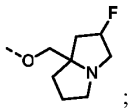
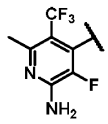
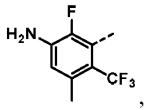
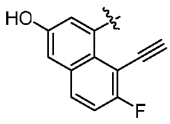
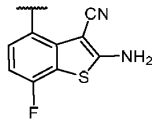
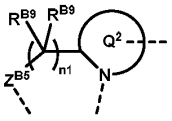
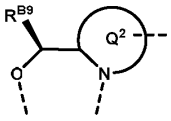
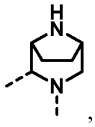
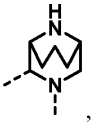
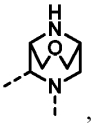
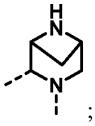
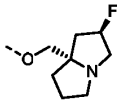
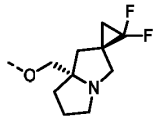
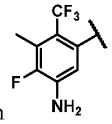
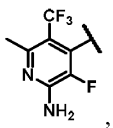
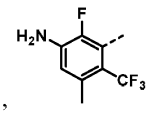
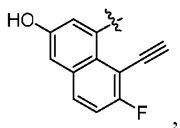
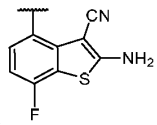
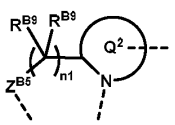
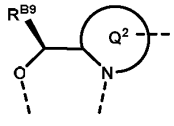
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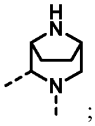
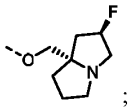
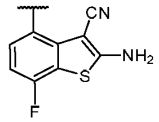
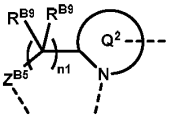
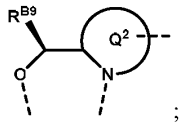
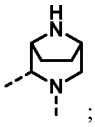
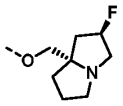
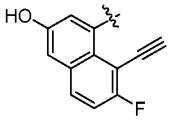
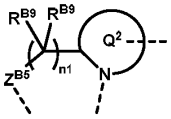
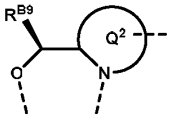
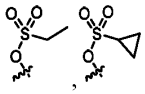
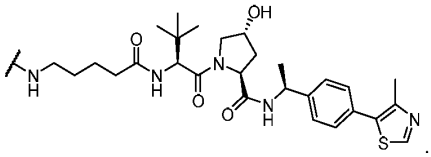

, and  ; R^{B8} is halogen; and 
is 
or

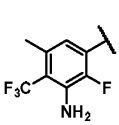
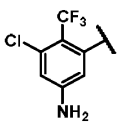
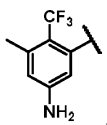
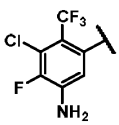
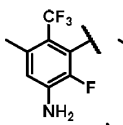
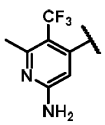
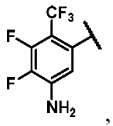
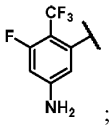
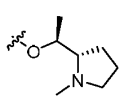
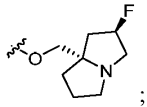
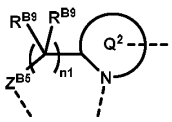
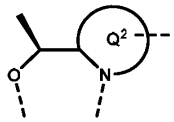
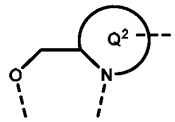
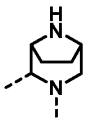
 . In some embodiments, R^{B2} is selected from 


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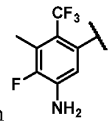
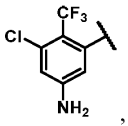
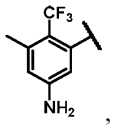
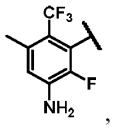
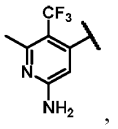
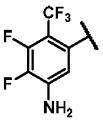
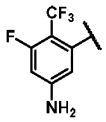
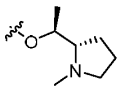
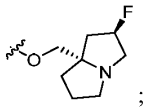
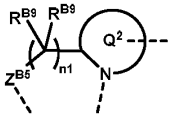
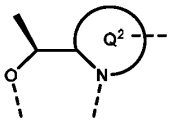
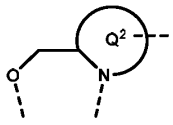
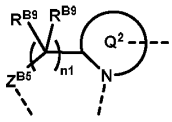
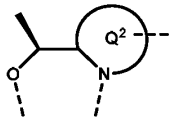
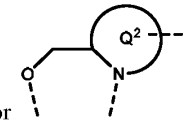
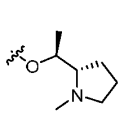
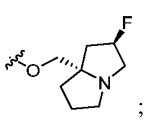
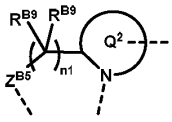
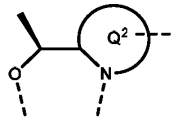
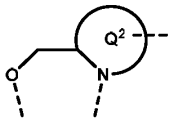
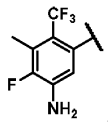
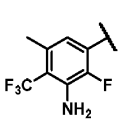
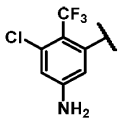
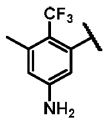
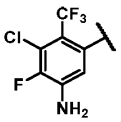
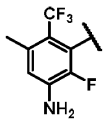
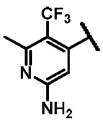
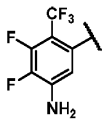
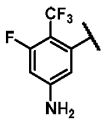
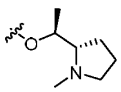
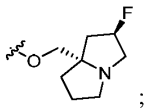
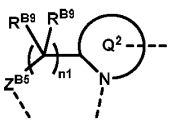
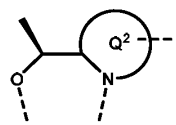
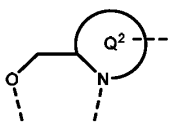
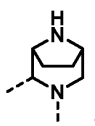



, and  ; R^{B6} is halogen or -CF_3; R^{B6b} is selected from C_{1-6}

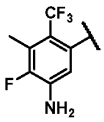
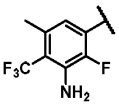
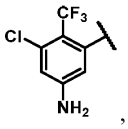
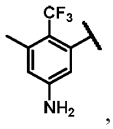
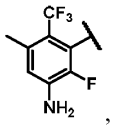
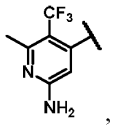
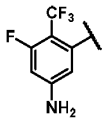
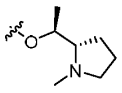
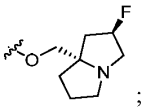
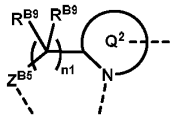
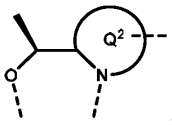
alkyl and -cyclopropyl; R^{B7} is selected from  ,  ,  , and  ; R^{B8} is halogen; and  is  or  .

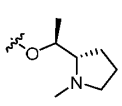
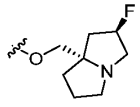
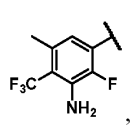
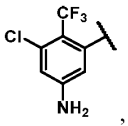
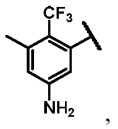
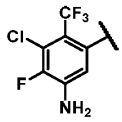
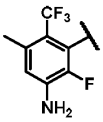
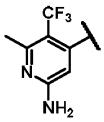
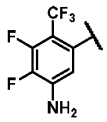
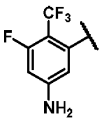
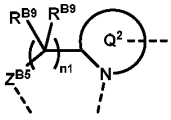
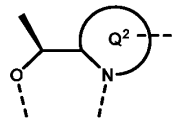
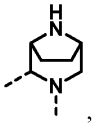
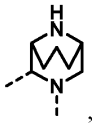
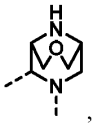
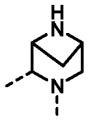
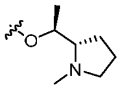
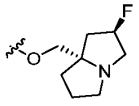
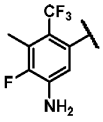
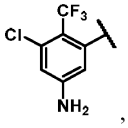
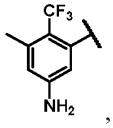
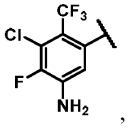
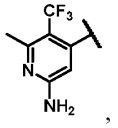
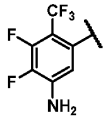
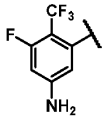
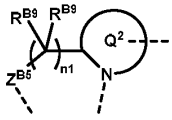
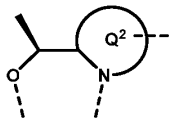
[238] In some embodiments of a compound of Formula (A0) or (a0), Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{1-4} alkylene optionally substituted with one, two, or three R^{B20}; Z^1 is N; Z^2 is $C(R^{B2})$; R^{B2} is selected from  ,  ,  ,  ,  ,  , and  , such as  ; Z^6 is selected from $C(R^{B6})$ and N; R^{B6} is selected from hydrogen, -Cl, and $-CF_3$; Z^7 is $C(R^{B7})$; R^{B7} is selected from  ,  ,  ,  , and  ; Z^8 is $C(R^{B8})$, R^{B8} is -F;  is  ; and R^{B9} is selected from hydrogen and C_{1-3} alkylene. In some embodiments of a compound of Formula (A0) or (a0), Q^2 is selected from  ,  ,  , and  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; Z^1 is N; Z^2 is $C(R^{B2})$; R^{B2} is selected from  and  ; Z^6 is selected from $C(R^{B6})$ and N; R^{B6} is selected from -Cl and $-CF_3$; Z^7 is $C(R^{B7})$; R^{B7} is selected from  ,  ,  ,  , and  ; Z^8 is $C(R^{B8})$, R^{B8} is -F;  is  ; and R^{B9} is selected from hydrogen and C_{1-2} alkylene. In some embodiments of a compound of

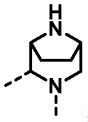
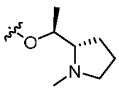
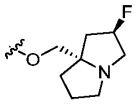
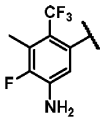
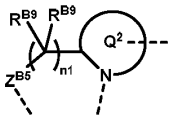
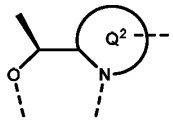
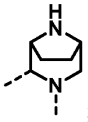
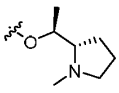
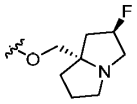
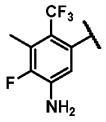
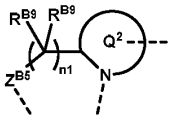
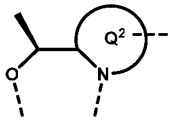
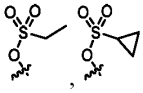
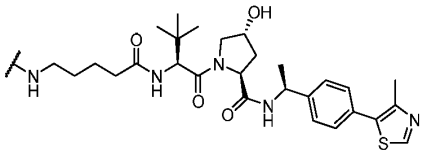
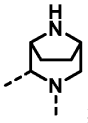
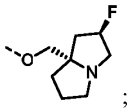
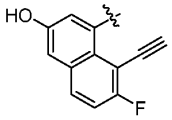
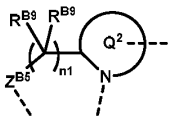
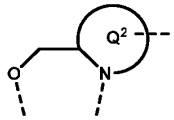
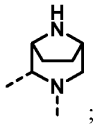
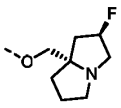
Formula (A0) or (a0), Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; Z^1 is N; Z^2 is $C(R^{B2})$; R^{B2} is  ; Z^6 is $C(R^{B6})$; R^{B6} is -Cl; Z^7 is $C(R^{B7})$; R^{B7} is  ; Z^8 is $C(R^{B8})$, R^{B8} is -F;  is  ; and R^{B9} is selected from hydrogen and unsubstituted methyl. In some embodiments of a compound of Formula (A0) or (a0), Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; Z^1 is N; Z^2 is $C(R^{B2})$; R^{B2} is  ; Z^6 is N; Z^7 is $C(R^{B7})$; R^{B7} is  ; Z^8 is $C(R^{B8})$, R^{B8} is -F;  is  ; and R^{B9} is selected from hydrogen and unsubstituted methyl. In some further embodiments of the embodiments of Compound (a0) above, LG is selected from  , and  . In some further embodiments of the embodiments of Compound (A0) above, DG is  .

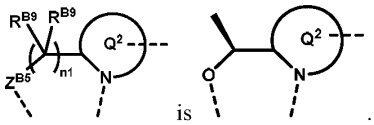
[239] In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; R^{B2} is selected from  and  ; and  is  or  . In some embodiments, Q^2 is  optionally substituted with one or

more R^{B20}; J^1 is -C(O)-; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; R^{B2} is selected from  and  ; Z^1 is N; and  is  or  . In some embodiments, Q^2 is 6- to 10-membered heterocycle that is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20};  and  is  or . In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms and is optionally substituted with one or more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}; R^{B2} is selected from  and  ; and  is  or  . In some embodiments, Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms and is optionally substituted with one or more R_{B20}; J^1 is a bond; J^2 is a bond; J3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-12} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; R^{B2} is selected from  and  ; and  is  or  . In some embodiments, Q^2 is  optionally substituted with one or

more R^{B20}; J^1 is a bond; J^2 is a bond; J^3 is selected from C_{1-6} alkylene and -C_{0-6} alkyl-(C_{3-6} carbocycle)-, each of which is optionally substituted with one, two, or three R^{B20}; R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; R^{B2} is selected from  and  ; Z^1 is N; and  is  .

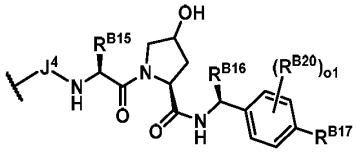
[240] In some embodiments of a compound of Formula (A0) or (a0), Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring nitrogen atoms; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{1-4} alkylene optionally substituted with one, two, or three R^{B20}; Z^1 is N; Z^2 is C(R^{B2}); R^{B2} is selected from  and  ; Z^6 is selected from C(R^{B6}) and N; R^{B6} is selected from hydrogen, -Cl, and -CF_3; Z^7 is C(R^{B7}); R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; Z^8 is C(R^{B8}), R^{B8} is -F; and  is  . In some embodiments of a compound of Formula (A0) or (a0), Q^2 is selected from  ,  ,  , and  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; Z^1 is N; Z^2 is C(R^{B2}); R^{B2} is selected from  and  ; Z^6 is selected from C(R^{B6}) and N; R^{B6} is selected from -Cl and -CF_3; Z^7 is C(R^{B7}); R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; Z^8 is C(R^{B8}), R^{B8} is -F; and  is  . In some embodiments of a compound of Formula (A0) or (a0), Q^2 is


; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; Z^1 is N; Z^2 is $C(R^{B2})$; R^{B2} is selected from  and  ; Z^6 is $C(R^{B6})$; R^{B6} is -Cl; Z^7 is $C(R^{B7})$; R^{B7} is  ; Z^8 is $C(R^{B8})$, R^{B8} is -F; and  is  . In some embodiments of a compound of Formula (A0) or (a0), Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; Z^1 is N; Z^2 is $C(R^{B2})$; R^{B2} is selected from  and  ; Z^6 is N; Z^7 is $C(R^{B7})$; R^{B7} is  ; Z^8 is $C(R^{B8})$, R^{B8} is -F; and  is  . In some further embodiments of the embodiments of Compound (a0) above, LG is selected from  , , and  . In some further embodiments of the embodiments of Compound (A0) above, DG is  . In some embodiments of a compound of Formula (A0) or (a0), Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; Z^1 is N; Z^2 is $C(R^{B2})$; R^{B2} is  ; Z^6 is N; Z^7 is $C(R^{B7})$; R^{B7} is  ; Z^8 is $C(R^{B8})$, R^{B8} is -F; and  is  . In some embodiments of a compound of Formula (A0) or (a0), Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; Z^1 is N; Z^2 is $C(R^{B2})$; R^{B2} is  ; Z^6 is N; Z^7 is $C(R^{B7})$; R^{B7} is  ; Z^8 is $C(R^{B8})$, R^{B8} is -F; and

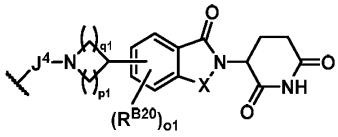


is .

[241] In some embodiments, the compound has a formula selected from (a-1) and (A-1); wherein R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen and halogen; R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl; R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OH, -NH_2, and C_{3-6} cycloalkyl; R^{B8} is halogen; n1 is 1 or 2; R^{B9} is independently selected from hydrogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms and is optionally substituted with one or more R^{B20}; J^1 is a bond or -C(O)-; J^2 is a bond; J^3 is C_{1-6} alkylene optionally substituted with one, two, or three R^{B20}; LG is selected from -OS(O)$_2R^{B4}$, -OS(O)(NH)R^{B4}, and -OS(O)(NCN)R^{B4}; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle; DG is selected from

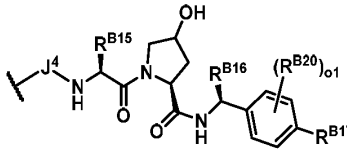


and



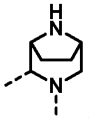
; J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, -OR^{B12}, -C(O)OR^{B12}, and -C(O)R^{B12}, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and -S(O)$_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O).

[242] In some embodiments, the compound has a formula selected from (a-1) and (A-1); wherein R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen and halogen; R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl; R^{B7} is selected from naphthyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OH, -NH_2, and C_{3-6} cycloalkyl; R^{B8} is halogen; n1 is 1 or 2; R^{B9} is independently selected from hydrogen and -CH_3; Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene optionally substituted with one, two, or three R^{B20}; LG is selected from -OS(O)$_2R^{B4}$; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3}

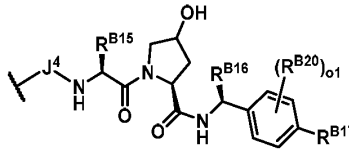


alkyl, and C_{3-4} carbocycle; DG is ; J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; and o1 is selected from 0, 1, and 2.

[243] In some embodiments, the compound has a formula selected from (a-1) and (A-1); wherein Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is N, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$; R^{B2} is $-O(C_{1-3}$ alkylene)(5- to 8-membered heterocycle), wherein 5- to 8-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen and C_{1-3} alkyl; R^{B7} is selected from naphthyl and phenyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkynyl, -OH,

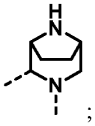


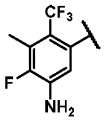
and $-NH_2$; R^{B8} is F; n1 is 1 or 2; R^{B9} is independently selected from hydrogen and $-CH_3$; Q^2 is ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene optionally substituted with one, two, or three R^{B20}; LG is selected from $-OS(O)_2R^{B4}$;

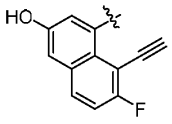
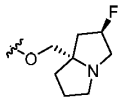
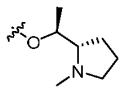
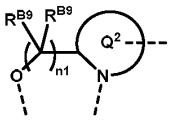
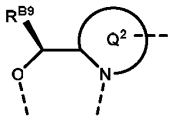
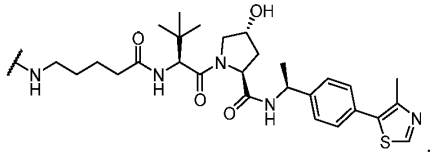


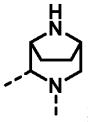
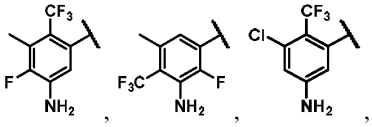
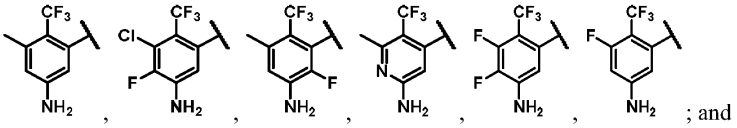
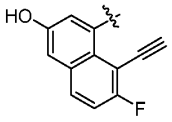
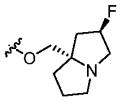
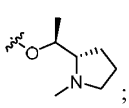
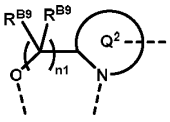
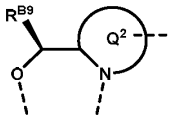
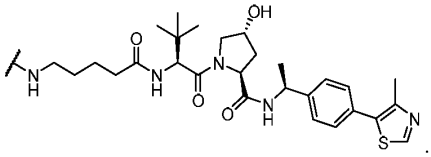
and R^{B4} is selected from C_{1-3} alkyl and C_{3-4} carbocycle; DG is ; J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; and o1 is selected from 0, 1, and 2.

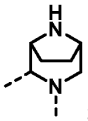
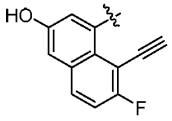
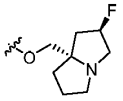
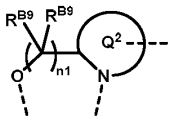
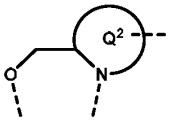
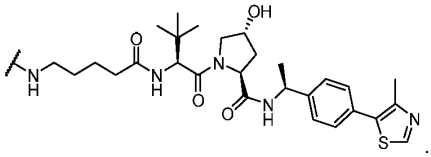
[244] In some embodiments, the compound has a formula selected from (a-1) and (A-1); wherein Z^6 is N; Q^2 is

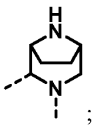
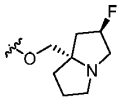
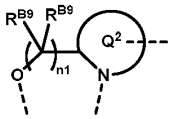
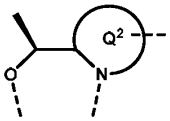
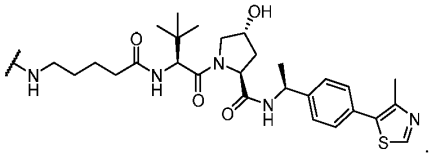


; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; R^{B7} is selected from  ,  , and


; R^{B2} is selected from  and  ; R^{B8} is F;  is  ; n1 is 1; R^{B9} is selected from hydrogen and unsubstituted methyl; LG is selected from  and  ; and DG is  .

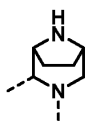
[245] In some embodiments, the compound has a formula selected from (a-1) and (A-1); wherein Z^6 is N; Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; R^{B7} is selected from   ; and  ; R^{B2} is selected from  and  ; R^{B8} is F;  is  ; n1 is 1;R^{B9} is selected from hydrogen and unsubstituted methyl; LG is selected from  and  ; and DG is  .

[246] In some embodiments, the compound has a formula selected from (a-1) and (A-1); wherein Z^6 is N; Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; R^{B7} is  ; R^{B2} is  ; R^{B8} is F;  is  ; n1 is 1; LG is selected from  and  ; and DG is  .

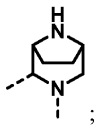
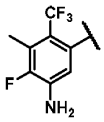
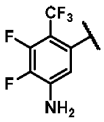
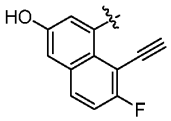
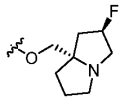
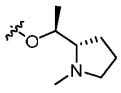
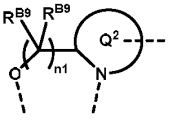
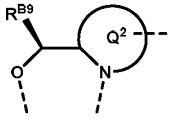
[247] In some embodiments, the compound has a formula selected from (a-1) and (A-1); wherein Z^6 is N; Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; R^{B7} is  ; R^{B2} is  ; R^{B8} is F;  is  ; n1 is 1; LG is selected from  and  ; and DG is  .

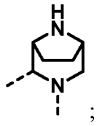
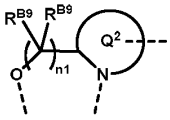
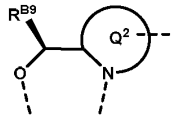
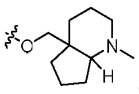
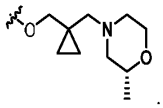
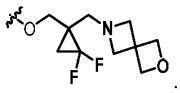
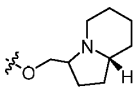
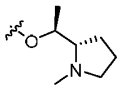
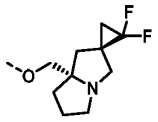
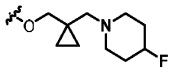
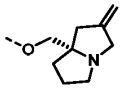
[248] In some embodiments, the compound has a formula (a-1); wherein R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen and halogen; R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl; R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OH, -NH_2, and C_{3-6} cycloalkyl; R^{B8} is halogen; n1 is 1 or 2; R^{B9} is independently selected from hydrogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms and is optionally substituted with one or more R^{B20}; J^1 is a bond or -C(O)-; J^2 is a bond; J^3 is C_{1-6} alkylene optionally substituted with one, two, or three R^{B20}; LG is selected from -OS(O)$_2R^{B4}$, -OS(O)(NH)R^{B4}, and -OS(O)(NCN)R^{B4}; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle.

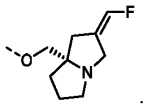
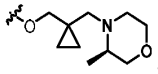
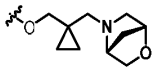
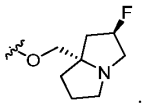
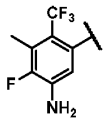
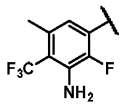
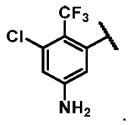
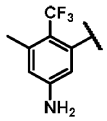
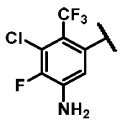
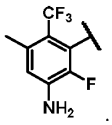
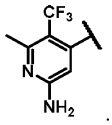
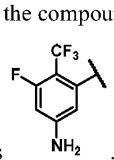
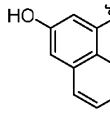
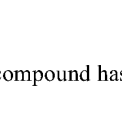
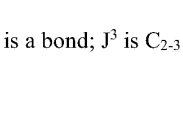
[249] In some embodiments, the compound has a formula (a-1); wherein R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen and halogen; R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl; R^{B7} is selected from naphthyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OH, -NH_2, and C_{3-6} cycloalkyl; R^{B8} is halogen; n1 is 1 or 2; R^{B9} is independently selected from hydrogen and -CH_3; Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene optionally substituted with one, two, or three R^{B20}; LG is selected from -OS(O)$_2R^{B4}$; and R^{B4} is selected from -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, C_{1-3} alkyl, and C_{3-4} carbocycle.

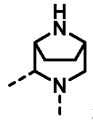
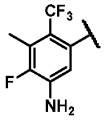
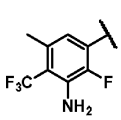
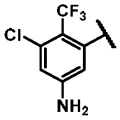
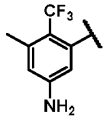
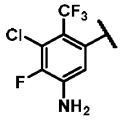
[250] In some embodiments, the compound has a formula (a-1); wherein Z^6 is N; R^{B2} is -O(C_{1-3} alkylene)(5- to 8-membered heterocycle), wherein 5- to 8-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen and C_{1-3} alkyl; R^{B7} is selected from naphthyl and phenyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkynyl, -OH, and -NH_2; R^{B8} is F; n1 is 1 or 2; R^{B9} is independently selected from hydrogen and -CH_3; Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene optionally substituted with one, two,

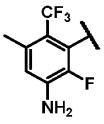
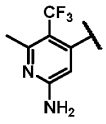
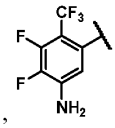
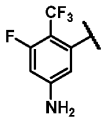
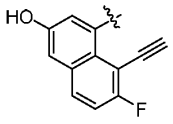
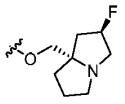
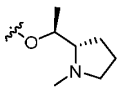
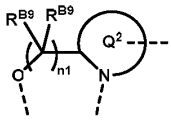
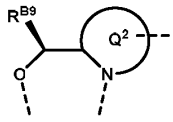
or three R^{B20}; LG is selected from $-OS(O)_2R^{B4}$; and R^{B4} is selected from C_{1-3} alkyl and C_{3-4} carbocycle.

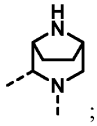
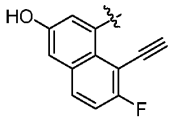
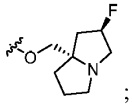
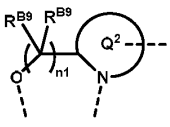
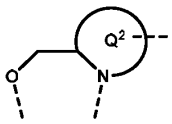
[251] In some embodiments, the compound has a formula (a-1); wherein Z^6 is N; Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; R^{B7} is selected from  ,  , and  ; R^{B2} is selected from  and  ; R^{B8} is F;  is  ; n1 is 1;R^{B9} is selected from hydrogen and unsubstituted methyl; and LG is selected from  and  .

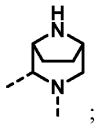
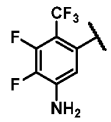
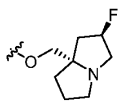
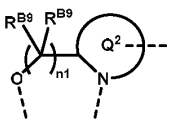
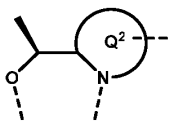
[252] In some embodiments, the compound has a formula (a-1); wherein Z^6 is N; Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; R^{B8} is F;  is  ; n1 is 1;R^{B9} is selected from hydrogen and unsubstituted methyl; and LG is selected from  and  . In some embodiments of the compound of formula (a-1), R^{B2} is  . In some embodiments of the compound of formula (a-1), R^{B2} is  . In some embodiments of the compound of formula (a-1), R^{B2} is  . In some embodiments of the compound of formula (a-1), R^{B2} is  . In some embodiments of the compound of formula (a-1), R^{B2} is  . In some embodiments of the compound of formula (a-1), R^{B2} is  . In some embodiments of the compound of formula (a-1), R^{B2} is  . In some embodiments of the compound of formula (a-1), R^{B2} is  . In some embodiments of the compound of formula (a-1), R^{B2} is


. In some embodiments of the compound of formula (a-1), R^{B2} is  . In some embodiments of the compound of formula (a-1), R^{B2} is  . In some embodiments of the compound of formula (a-1), R^{B2} is  . In some embodiments of the compound of formula (a-1), R^{B7} is  . In some embodiments of the compound of formula (a-1), R^{B7} is  . In some embodiments of the compound of formula (a-1), R^{B7} is  . In some embodiments of the compound of formula (a-1), R^{B7} is  . In some embodiments of the compound of formula (a-1), R^{B7} is  . In some embodiments of the compound of formula (a-1), R^{B7} is  . In some embodiments of the compound of formula (a-1), R^{B7} is  . In some embodiments of the compound of formula (a-1), R^{B7} is  . In some embodiments of the compound of formula (a-1), R^{B7} is  . In some embodiments of the compound of formula (a-1), R^{B7} is  . In some embodiments of the compound of formula (a-1), R^{B7} is . In some embodiments of the compound of formula (a-1), R^{B7} is  . In some embodiments of the compound of formula (a-1), R^{B7} is  .

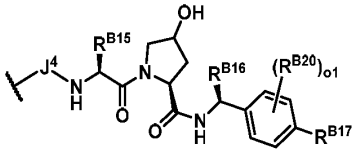
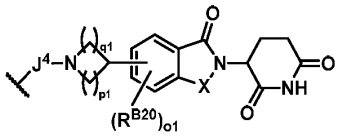
[253] In some embodiments, the compound has a formula (a-1); wherein Z^6 is N; Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; R^{B7} is selected from  ,  ,  ,  ,  ,





; and 
; R^{B2} is selected from  and 
; R^{B8} is F;  is 
; n1 is 1;R^{B9} is selected from hydrogen and unsubstituted methyl; and LG is selected from  and  .

[254] In some embodiments, the compound has a formula (a-1); wherein Z^6 is N; Q^2 is 
; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; R^{B7} is 
; R^{B2} is 
; R^{B8} is F;  is 
; n1 is 1; and LG is selected from  and  .

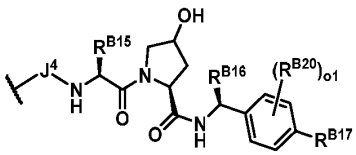
[255] In some embodiments, the compound has a formula (a-1); wherein Z^6 is N; Q^2 is 
; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; R^{B7} is 
; R^{B2} is 
; R^{B8} is F;  is 
; n1 is 1; and LG is selected from  and  .

[256] In some embodiments, the compound has a formula (A-1); wherein R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen and halogen; R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl; R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OH, -NH_2, and C_{3-6} cycloalkyl; R^{B8} is halogen; n1 is 1 or 2; R^{B9} is independently selected from hydrogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms and is optionally substituted with one or more R^{B20}; J^1 is a bond or -C(O)-; J^2 is a bond; J^3 is C_{1-6} alkylene optionally substituted with one, two, or three R^{B20}; DG is selected from

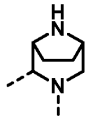
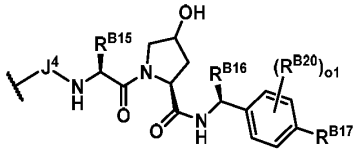
; J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; o1 is selected from 0, 1, and 2; p1 and q1 are independently selected from 1, 2, and 3; and X is selected from CH_2 and C(O).

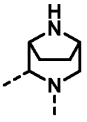
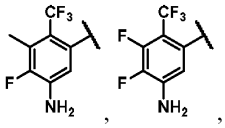
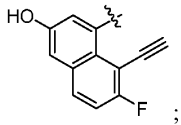
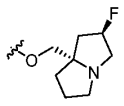
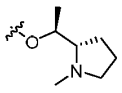
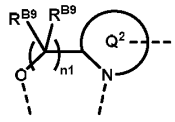
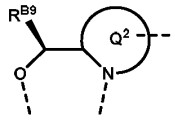
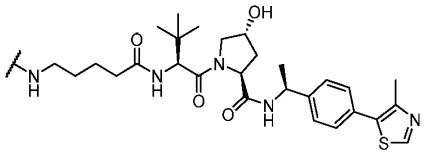
[257] In some embodiments, the compound has a formula (A-1); wherein R^{B2} is $-O(C_{1-3}$ alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, and $=C(R^{B21})_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen and halogen; R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl; R^{B7} is selected from naphthyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, -OH, $-NH_2$, and C_{3-6} cycloalkyl; R^{B8} is halogen; n1 is 1 or 2; R^{B9} is independently selected from hydrogen and $-CH_3$; Q^2 is 7- to 9-membered bridged bicyclic heterocycle that comprises at least two ring heteroatoms; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene optionally substituted with one, two, or three R^{B20}; DG is

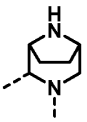
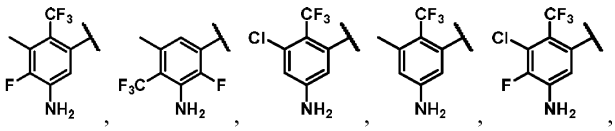
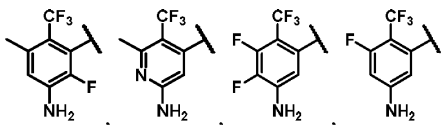
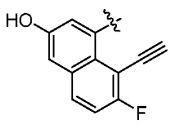
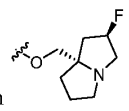


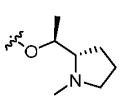
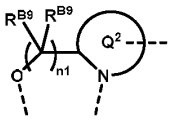
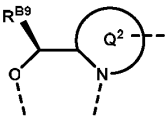
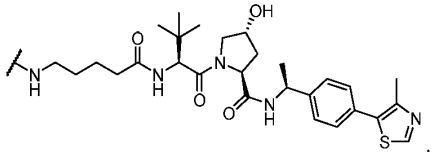
; J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; and o1 is selected from 0, 1, and 2.

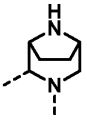
[258] In some embodiments, the compound has a formula (A-1); wherein Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is N, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$; R^{B2} is $-O(C_{1-3}$ alkylene)(5- to 8-membered heterocycle), wherein 5- to 8-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen and C_{1-3} alkyl; R^{B7} is selected from naphthyl and phenyl, each of which is optionally substituted with one, two, three, or four substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkynyl, -OH, and $-NH_2$; R^{B8} is

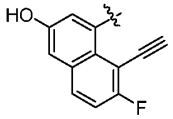
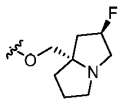
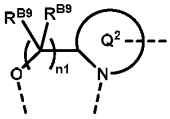
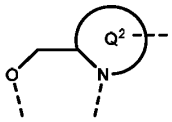
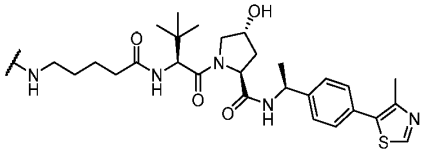
F; n1 is 1 or 2; R^{B9} is independently selected from hydrogen and -CH_3; Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene optionally substituted with one, two, or three R^{B20}; DG is  ; J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20}; R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20}; R^{B16} is selected from hydrogen, C_{1-6} alkyl, -OR^{B12}, -C(O)OR^{B12}, and -C(O)R^{B12}, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20}; R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and -$S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20}; and o1 is selected from 0, 1, and 2.

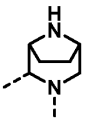
[259] In some embodiments, the compound has a formula (A-1); wherein Z^6 is N; Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; R^{B7} is selected from  , and  ; R^{B2} is selected from  and  ; R^{B8} is F;  is  ; n1 is 1;R^{B9} is selected from hydrogen and unsubstituted methyl; and DG is  .

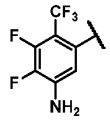
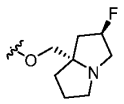
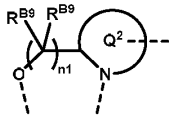
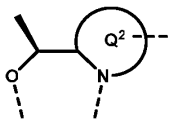
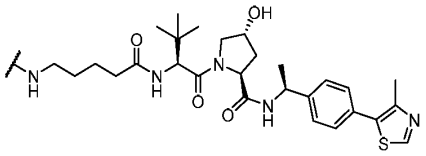
[260] In some embodiments, the compound has a formula (A-1); wherein Z^6 is N; Q^2 is  ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; R^{B7} is selected from  ,  ; and  ; R^{B2} is selected from  and


; R^{B8} is F;  is  ; n1 is 1;R^{B9} is selected from hydrogen and unsubstituted methyl; and DG is  .



[261] In some embodiments, the compound has a formula (A-1); wherein Z^6 is N; Q^2 is ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; R^{B7} is  ; R^{B2} is  ; R^{B8} is F;  is  ; n1 is 1; and DG is  .



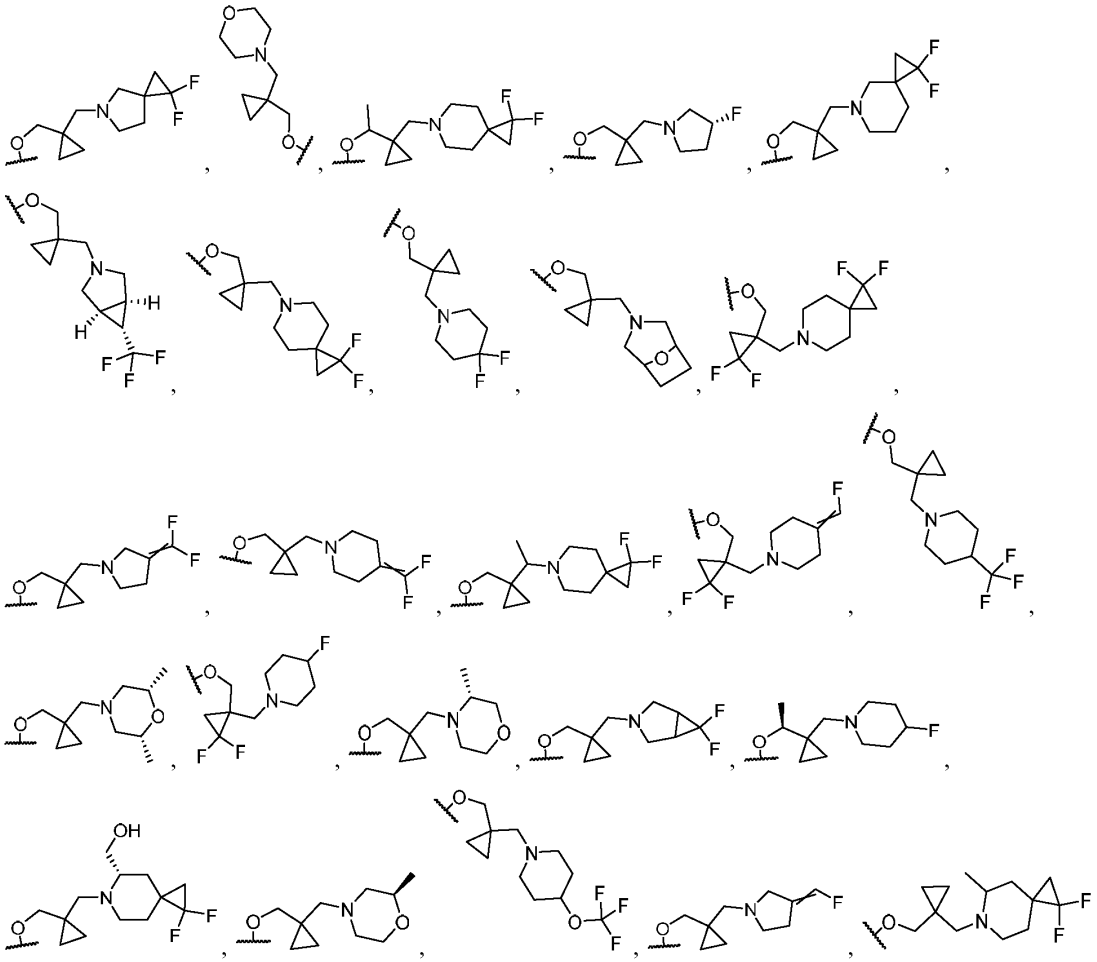
[262] In some embodiments, the compound has a formula (A-1); wherein Z^6 is N; Q^2 is ; J^1 is -C(O)-; J^2 is a bond; J^3 is C_{2-3} alkylene; R^{B7} is  ; R^{B2} is  ; R^{B8} is F;  is  ; n1 is 1; and DG is  .

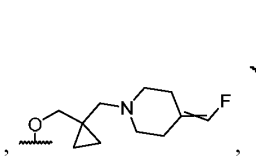
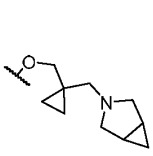
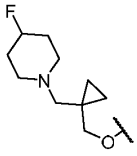
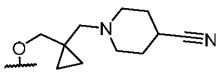
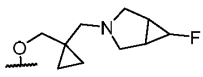
[263] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is -O-(C_{1-3} alkylene)-(C_{3-4} carbocycle)-(C_{1-3} alkylene)-(4- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}; and R^{B20}, R^{B21}, R^{B22}, and R^{B23} are as described in Formula (A0), (A0-1), (A0-2), (A0-3), (a0), (a0-1), (a0-2), (a0-3), (A), (A-1), (A-2), (A-3), (a), (a-1), (a-2), (a-3), or any embodiment thereof.

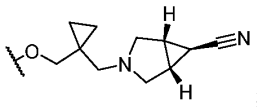
[264] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is -O-CH_2-

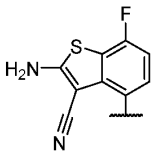
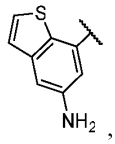
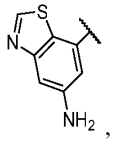
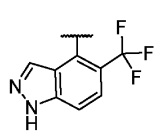
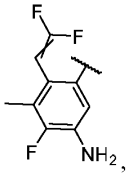
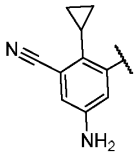
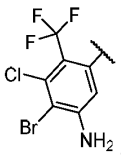
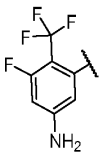
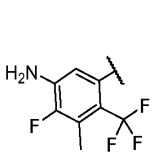
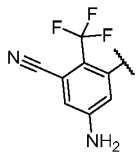
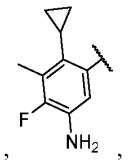
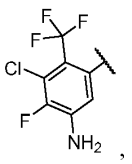
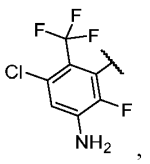
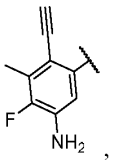
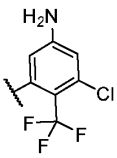
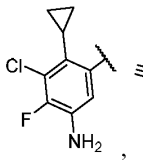
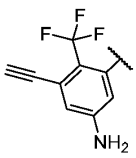
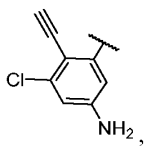
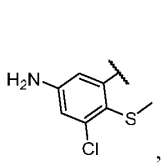
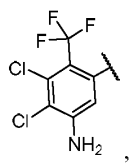
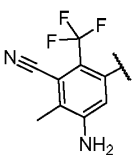
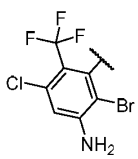
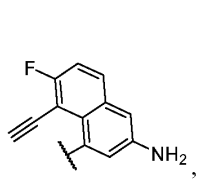
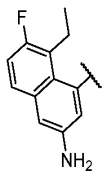
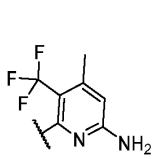
(cyclopropyl)-CH_2-(4- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, =C(R^{B21})$_2$, C_{1-3} alkoxy, C_{1-3} haloalkoxy, and C_{1-3} alkyl optionally substituted with one or more substituents selected from halogen, -OH, and -NH_2; R^{B21} is independently selected at each occurrence from hydrogen and halogen; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle),and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more substituents independently selected from halogen; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle.

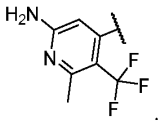
[265] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is selected from



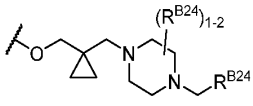





, and

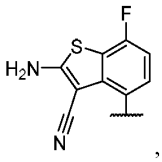
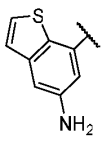

; R^{B6} is selected from -Cl and -CF_3; and R^{B7} is selected from

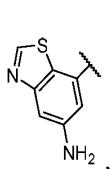
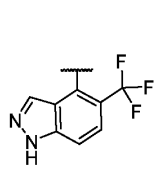
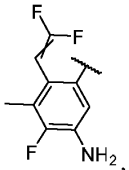
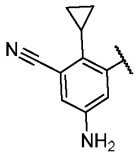
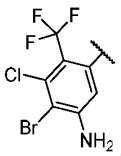
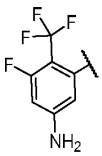
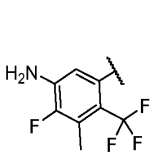
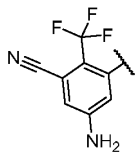

























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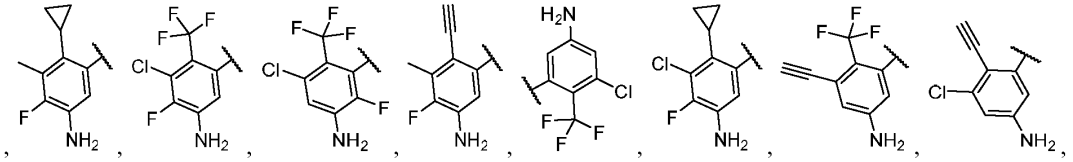

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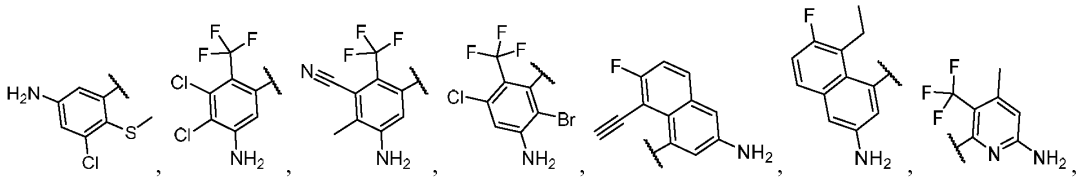
[266] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is

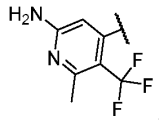

; R^{B24} is independently selected from hydrogen, halogen, -CN, -OH, -NH_2, C_{1-3} alkoxy, and C_{1-3} haloalkoxy; R^{B6} is selected from -Cl and -CF_3; and R^{B7} is selected from



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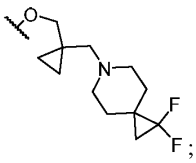











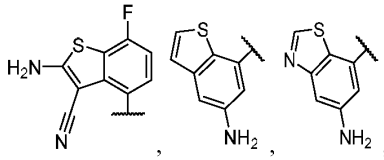




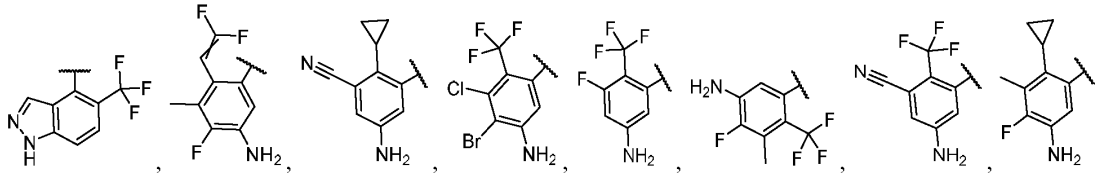
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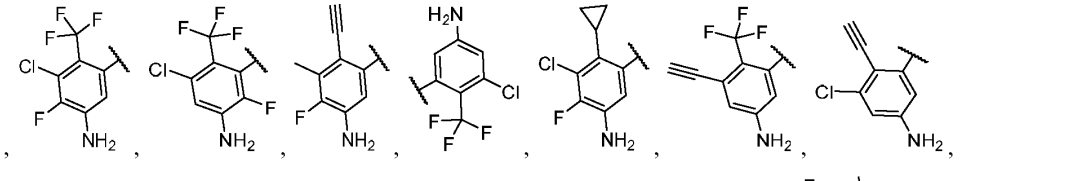


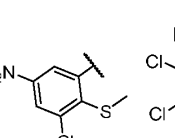
[267] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is ;



R^{B6} is selected from -Cl and $-CF_3$; and R^{B7} is selected from .





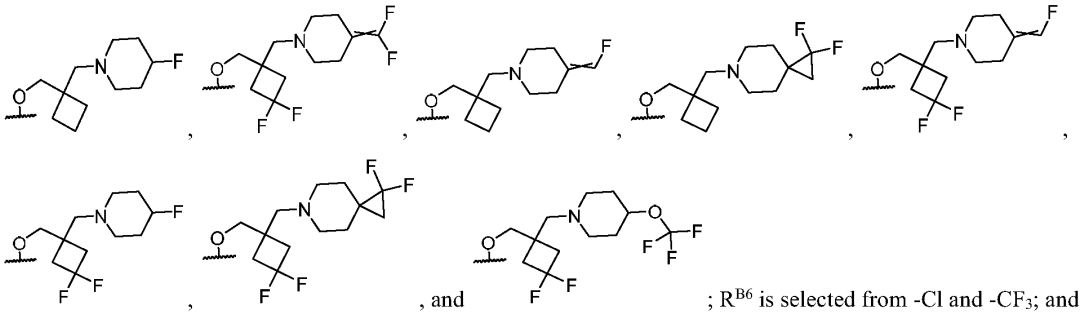


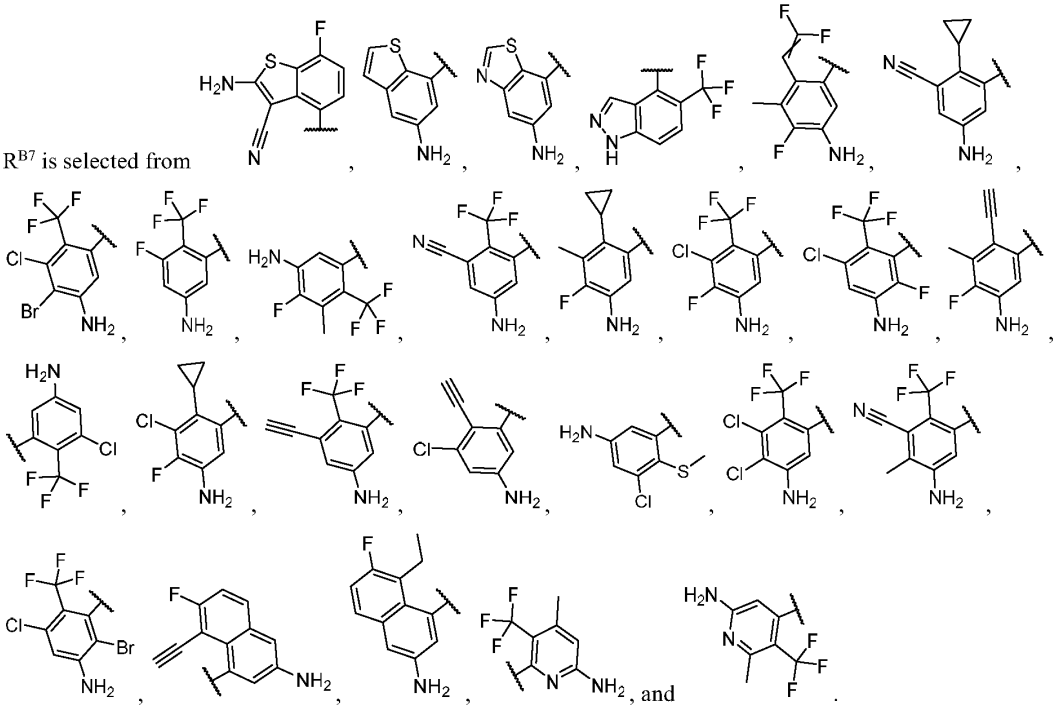
and .

[268] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is -O-CH_2-(cyclobutyl)-CH_2-(5- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, $=C(R^{B21})_2$, C_{1-3} alkoxy, C_{1-3} haloalkoxy, and C_{1-3} alkyl optionally

substituted with one or more substituents selected from halogen, -OH, and -NH_2; R^{B21} is independently selected at each occurrence from hydrogen and halogen; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle),and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more substituents independently selected from halogen; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle.

[269] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is selected from

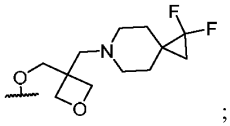
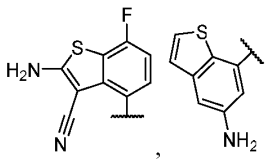
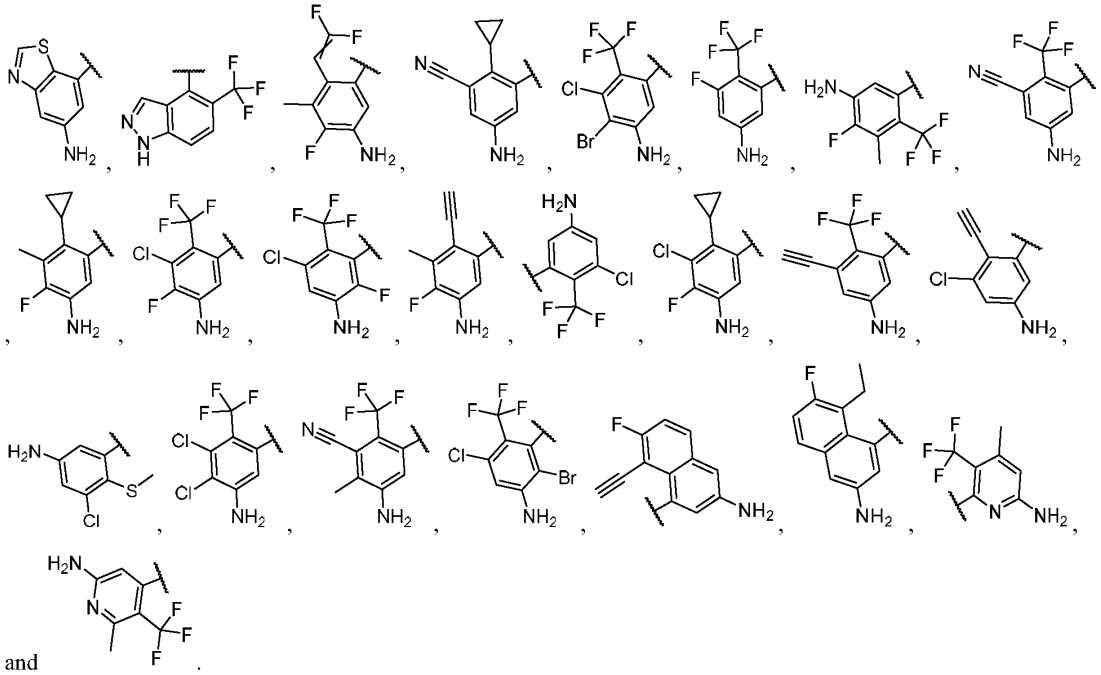

, and ; R^{B6} is selected from -Cl and -CF_3; and R^{B7} is selected from



[270] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is -O-CH_2-(3- to 4-membered heterocycle)-CH_2-(5- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, =$C(R^{B21})_2$, C_{1-3} alkoxy, C_{1-3} haloalkoxy, and C_{1-3} alkyl

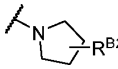
optionally substituted with one or more substituents selected from halogen, -OH, and -NH_2; R^{B21} is independently selected at each occurrence from hydrogen and halogen; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle),and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more substituents independently selected from halogen; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle.

[271] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is


; R^{B6} is selected from -Cl and -CF_3; and R^{B7} is selected from


and

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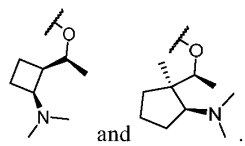
[272] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is -(4- to 7-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from R^{B20}; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}; and R^{B20} is as described in Formula (A0), (A0-1), (A0-2), (A0-3), (a0), (a0-1), (a0-2), (a0-3), (A), (A-1), (A-2), (A-3), (a), (a-1), (a-2), (a-3), or any embodiment thereof.

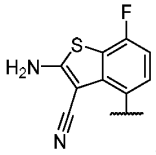
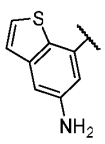
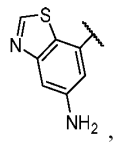
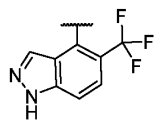
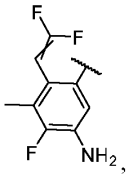
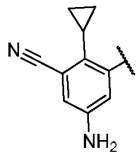
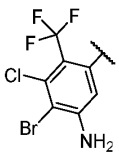
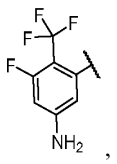
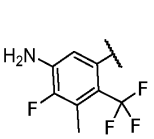
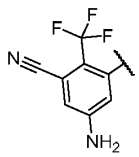
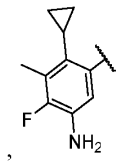
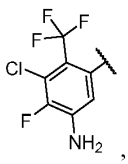
[273] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is

; R^{B24} is

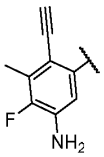
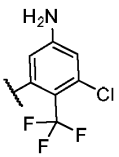
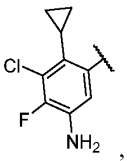
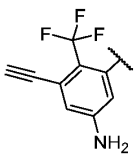
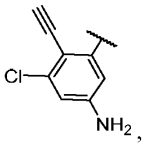
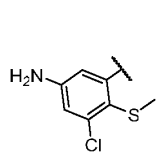
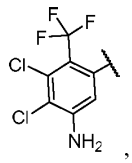
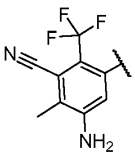
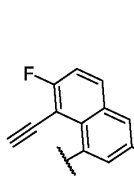
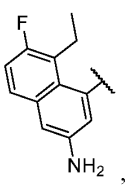
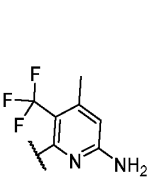
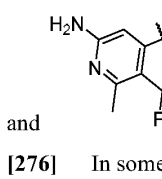
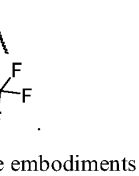
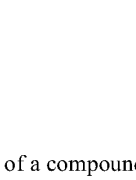
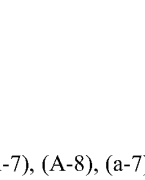
independently selected from hydrogen, halogen, -CN, -OH, $-NH_2$, C_{1-3} alkoxy, and C_{1-3} haloalkoxy; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle),and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more substituents independently selected from halogen; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle.

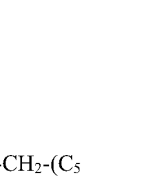
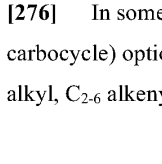
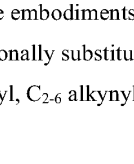
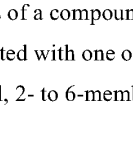
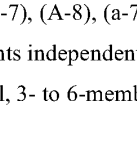
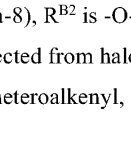
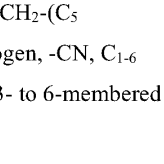
[274] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is -O-(C_{1-3} alkylene)-(C_{4-6} carbocycle) optionally substituted with one or more substituents independently selected from R^{B20}; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}; and R^{B20} is as described in Formula (A0), (A0-1), (A0-2), (A0-3), (a0), (a0-1), (a0-2), (a0-3), (A), (A-1), (A-2), (A-3), (a), (a-1), (a-2), (a-3), or any embodiment thereof.

[275] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is selected from


and

.; R^{B6} is selected from -Cl and -CF_3; and R^{B7} is selected from

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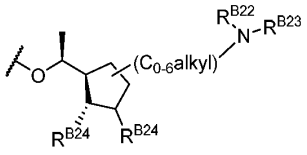
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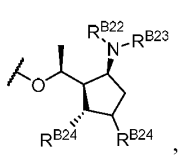
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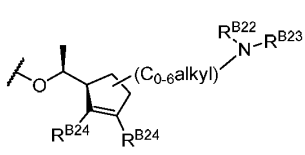
[276] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is -O-CH_2-(C_5 carbocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered

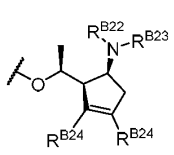
heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -OR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, and =$C(R^{B21})_2$; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, and -C_{0-6} alkyl-(C_{3-12} carbocycle) are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, and -$N(R^{B22})(R^{B23})$; R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle),and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more substituents independently selected from halogen; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle.

[277] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is selected from



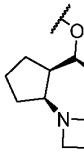
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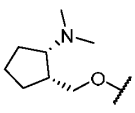
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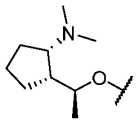
, and


; R^{B24} is independently selected from hydrogen, halogen, -CN, -OR^{B22}, -$N(R^{B22})(R^{B23})$, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy; R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle),and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more substituents independently selected from halogen; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle.

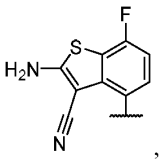
[278] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is selected from

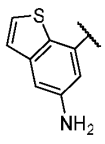


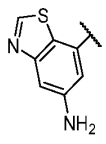
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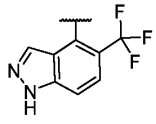
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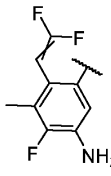
; R^{B6} is selected from -Cl and -CF_3; and R^{B7} is selected from

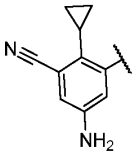


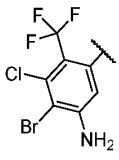
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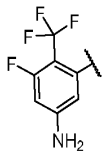
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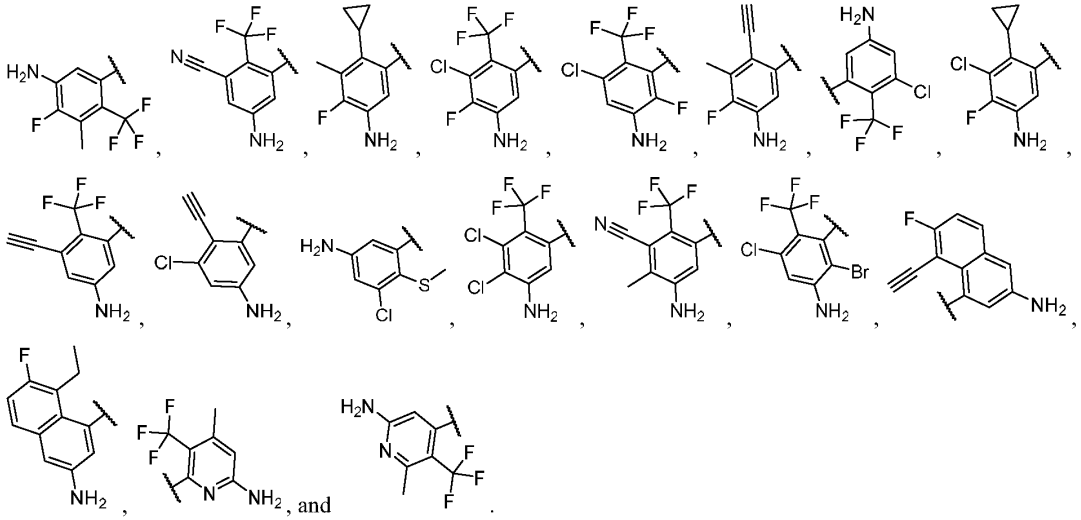
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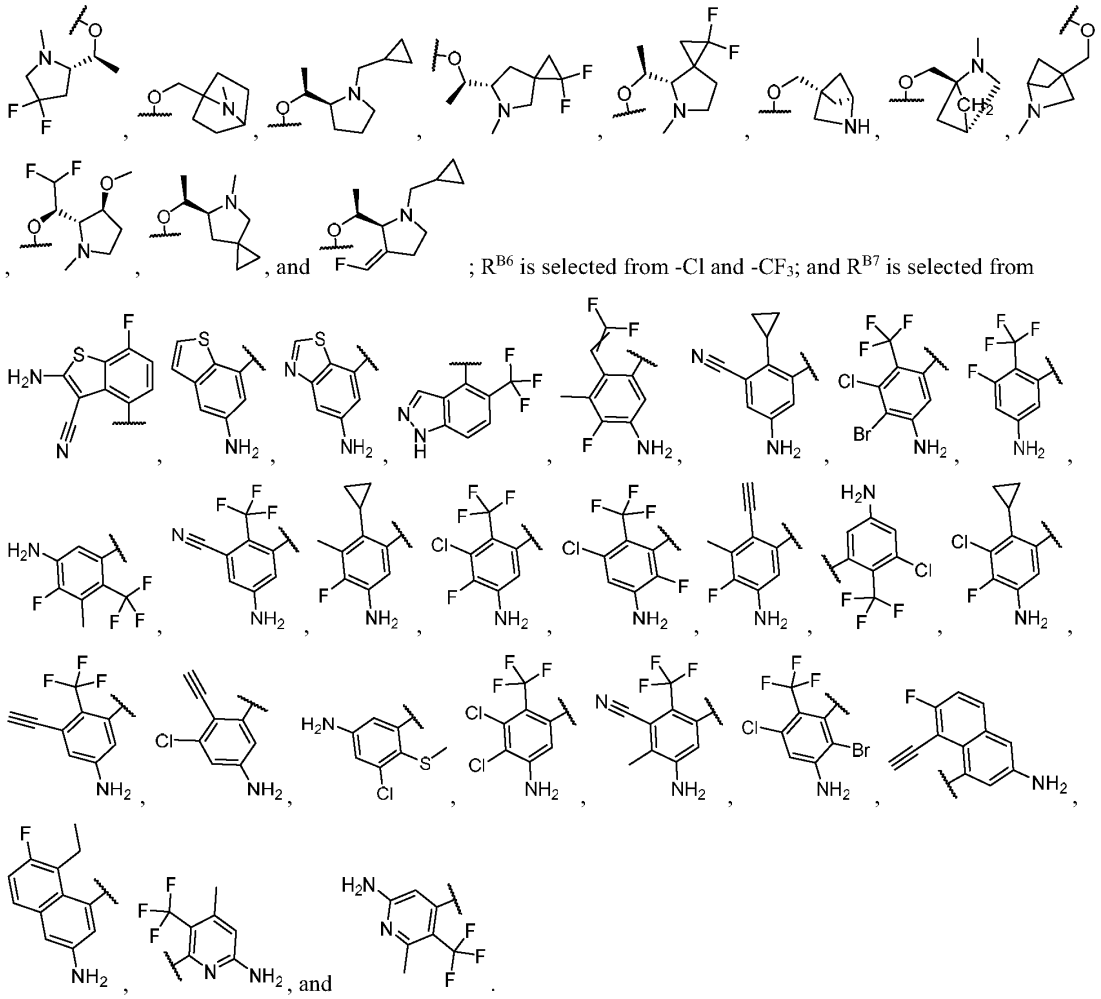
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[279] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is -O-(C_{1-3} alkylene)-(4- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from R^{B20}; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four R^{B20}; and R^{B20} is as described in Formula (A0), (A0-1), (A0-2), (A0-3), (a0), (a0-1), (a0-2), (a0-3), (A), (A-1), (A-2), (A-3), (a), (a-1), (a-2), (a-3), or any embodiment thereof.

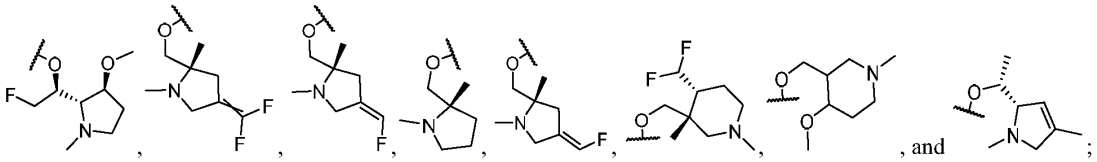
[280] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is -O-(C_{1-3} alkylene)-(4- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, , -C_{0-6} alkyl-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -OR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, and =$C(R^{B21})_2$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, and -$N(R^{B22})(R^{B23})$; R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle),and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more substituents independently selected from halogen; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle.

[281] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is selected from

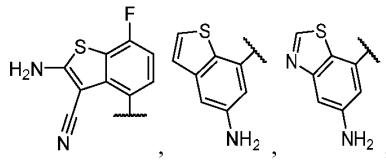


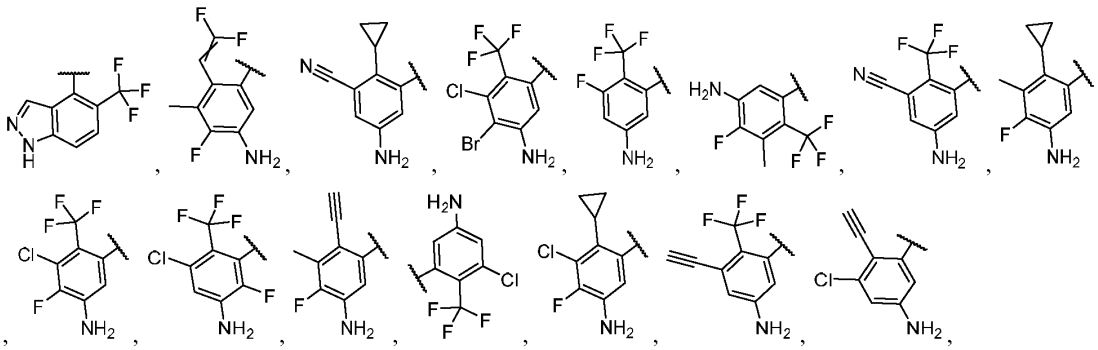
[282] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is -O-(C_{1-3} alkylene)-(4- to 8-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, =C(R^{B21})$_2$, -OR^{B22}, -N(R^{B22})(R^{B23}), phenyl, 5 membered heteroaryl, and C_{1-3} alkyl optionally substituted with one or more substituents selected from halogen, -OH, and -NH_2; R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle),and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more substituents independently selected from halogen; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle.

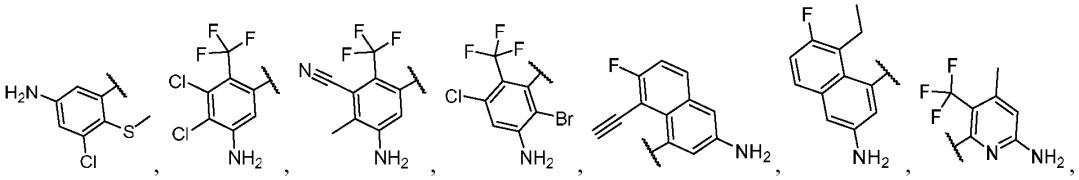
[283] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is selected from


, and ;

R^{B6} is selected from -Cl and -CF_3; and R^{B7} is selected from

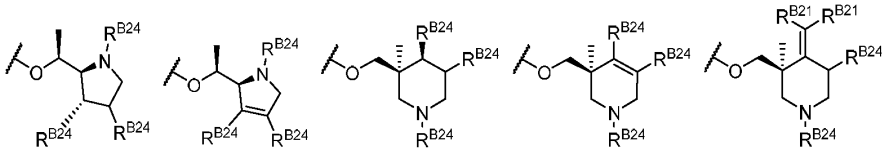


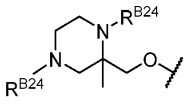




and .

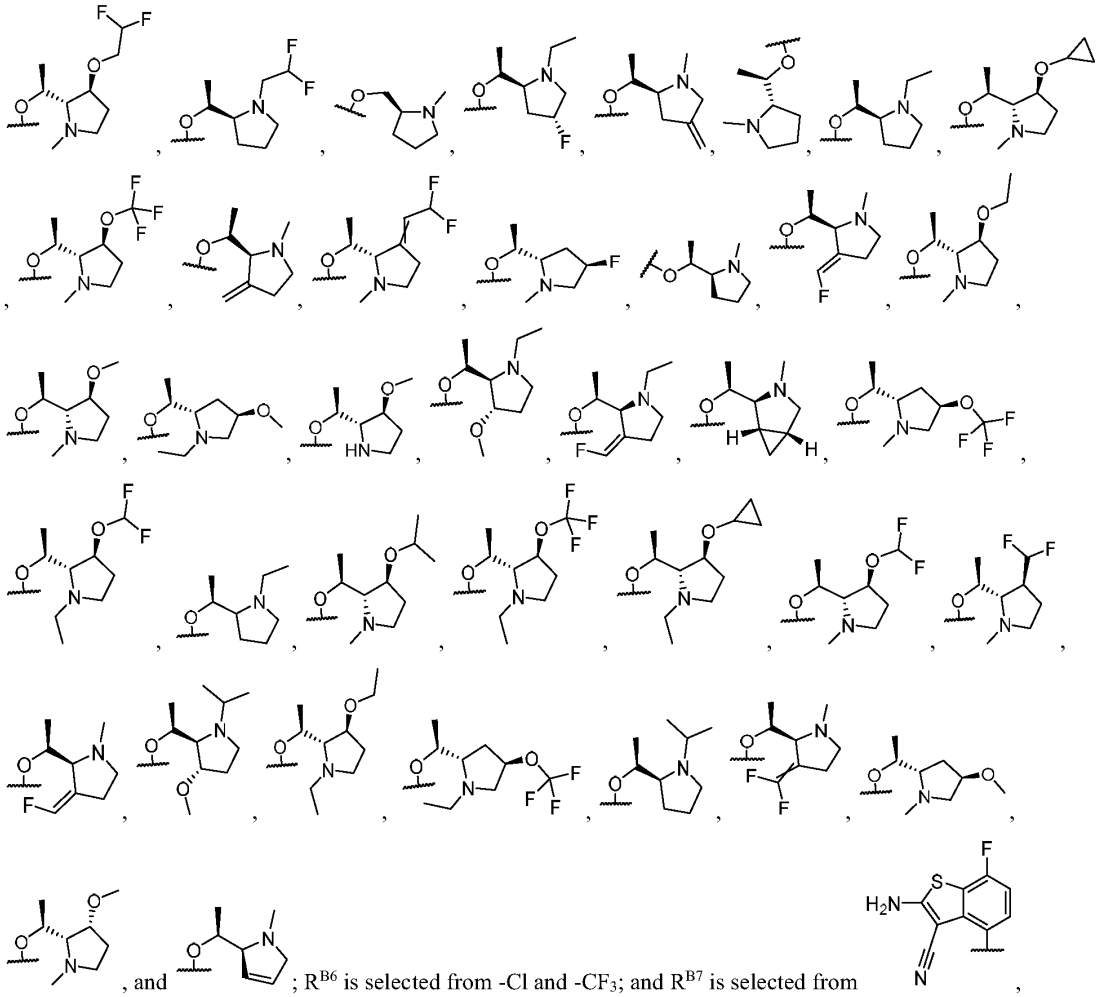
[284] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is selected from


, and

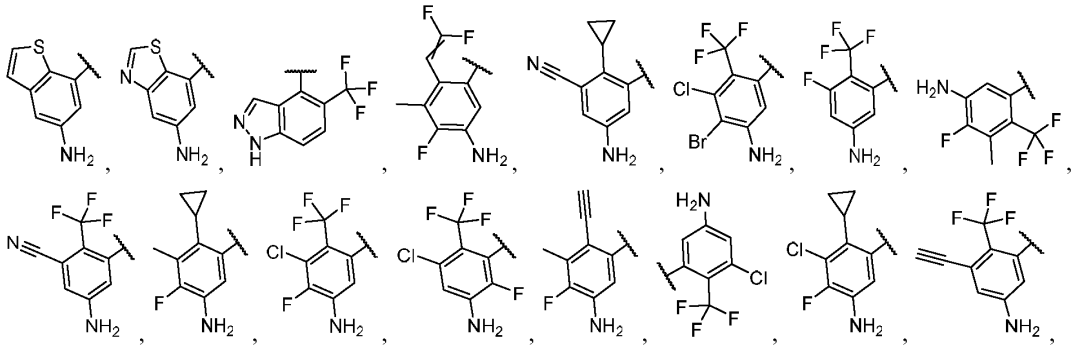

; R^{B24} is independently selected from hydrogen, halogen, -CN, -OR^{B22}, -$N(R^{B22})(R^{B23})$, =$C(R^{B21})_2$, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, phenyl, and 5 membered heteroaryl; or two R^{B24} are joined to form a C_{3-6} carbocycle or 3- to 5-membered heterocycle; R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle),and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more

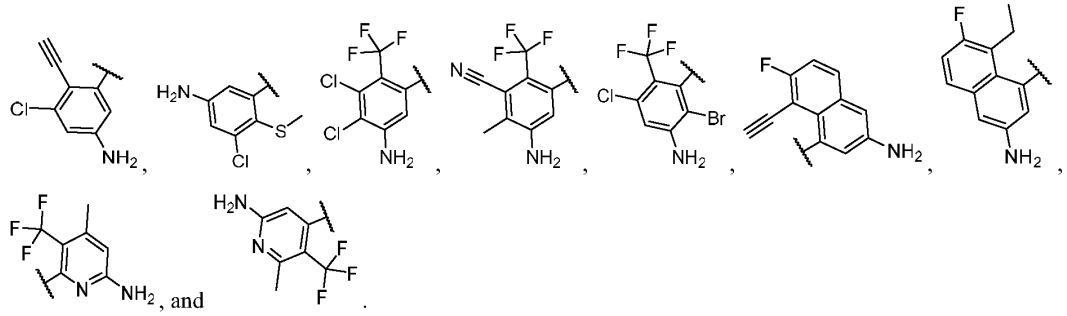
substituents independently selected from halogen; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle.

[285] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is selected from

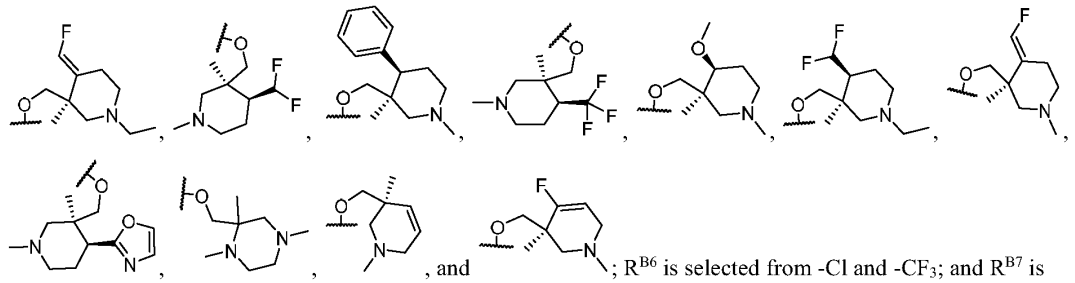


, and ; R^{B6} is selected from -Cl and -CF_3; and R^{B7} is selected from ,

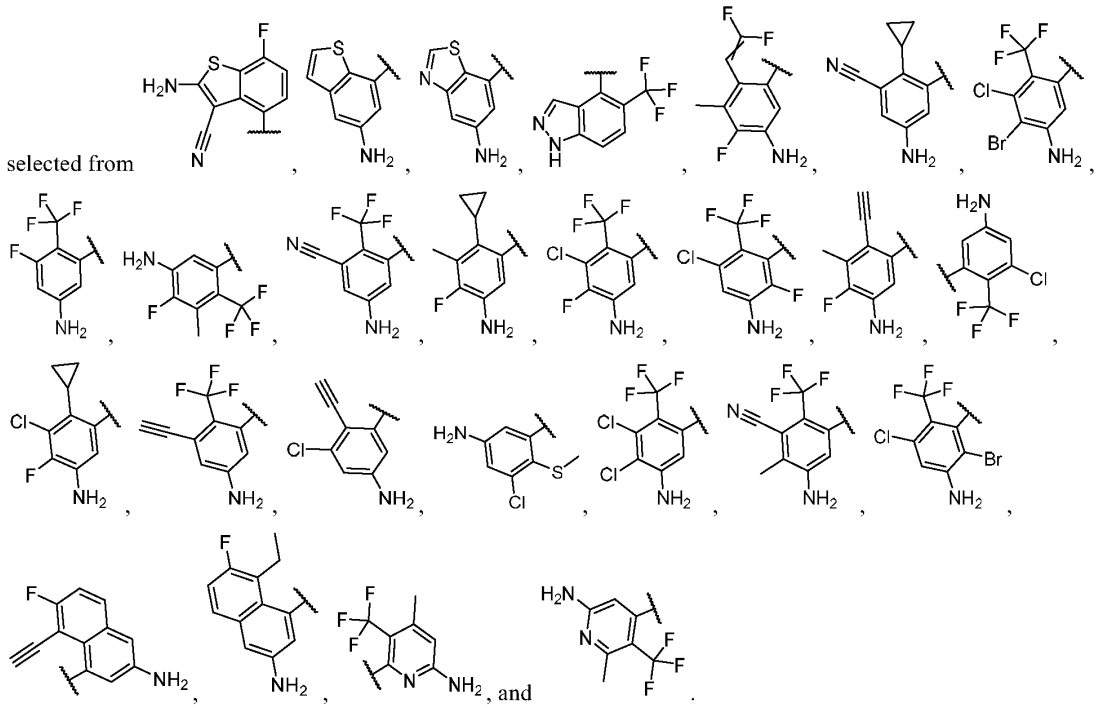




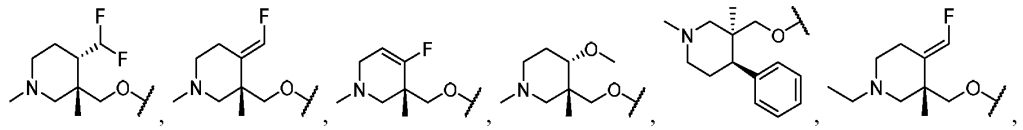
[286] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is selected from

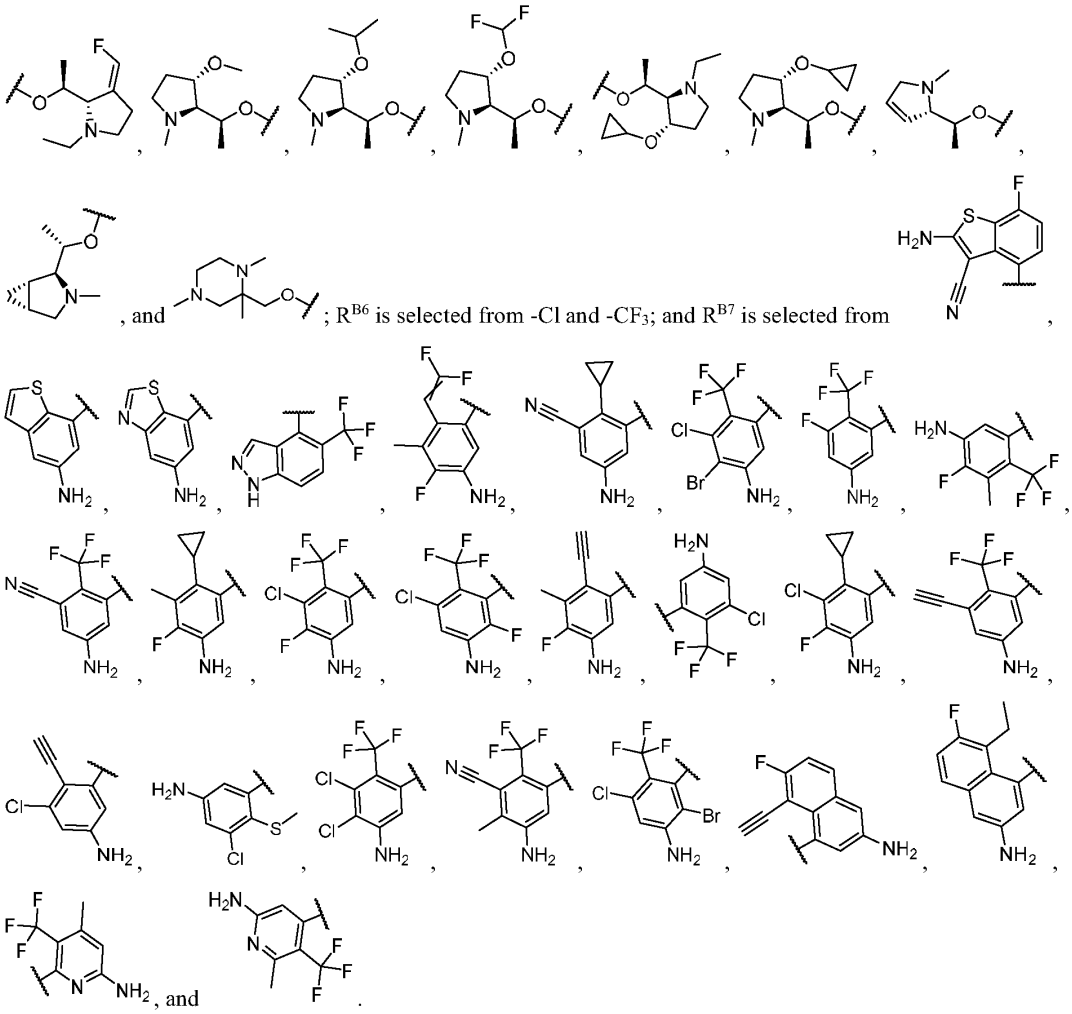


; R^{B6} is selected from -Cl and -CF_3; and R^{B7} is selected from



[287] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is selected from



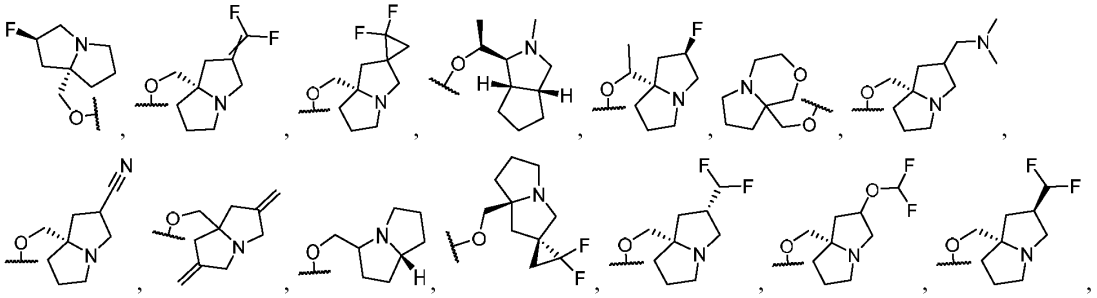


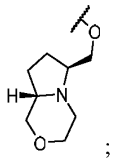
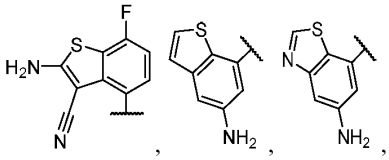
; R^{B6} is selected from -Cl and -CF_3; and R^{B7} is selected from

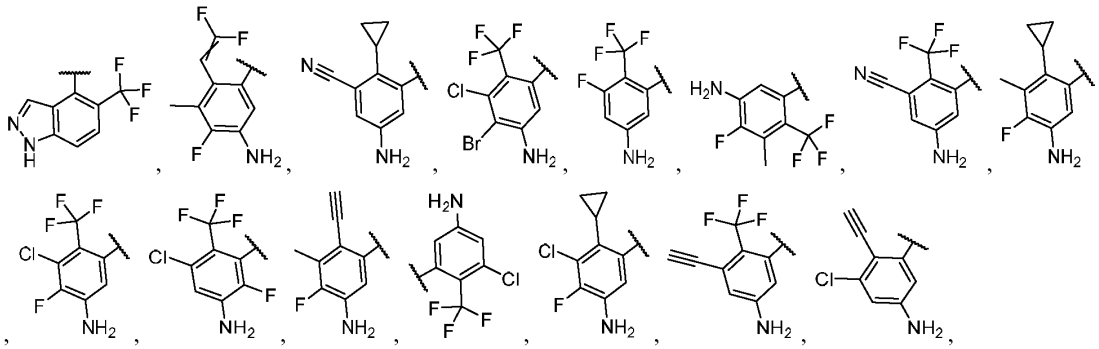
[288] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is -O-(C_{1-3} alkylene)-(8- to 10-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, -CN, =C(R^{B21})$_2$, -OR^{B22}, -N(R^{B22})(R^{B23}), phenyl, 5 membered heteroaryl, and C_{1-3} alkyl optionally substituted with one or more substituents selected from halogen, -OH, and -N(R^{B22})(R^{B23}); R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-3} alkyl, and C_{1-3} haloalkyl; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is selected from naphthyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle),and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more substituents independently selected from halogen; R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle); and R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle. In some embodiments of a compound of Formula (A-8) or (a-8), R^{B2} is -O-(C_{1-3} alkylene)-(8- to 10-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, =C(R^{B21})$_2$, and C_{1-3} alkyl

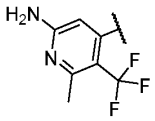
optionally substituted with one or more substituents selected from halogen; R^{B21} is independently selected at each occurrence from hydrogen and halogen; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is phenyl optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, C_1 alkyl, $-NH_2$, wherein C_1 alkyl is optionally substituted with one or more substituents independently selected from halogen. In some embodiments of a compound of Formula (A-7) or (a-7), R^{B2} is -O-(C_{1-3} alkylene)-(8- to 10-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen, $=C(R^{B21})_2$, and C_{1-3} alkyl optionally substituted with one or more substituents selected from halogen; R^{B21} is independently selected at each occurrence from hydrogen and halogen; R^{B7} is phenyl optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, C_1 alkyl, $-NH_2$, wherein C_1 alkyl is optionally substituted with one or more substituents independently selected from halogen. In some embodiments of a compound of Formula (A-8) or (a-8), R^{B2} is -O-(C_1 alkylene)-(8- to 10-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is phenyl optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, C_1 alkyl, $-NH_2$, wherein C_1 alkyl is optionally substituted with one or more substituents independently selected from halogen. In some embodiments of a compound of Formula (A-7) or (a-7), R^{B2} is -O-(C_1 alkylene)-(8- to 10-membered nitrogen containing heterocycle) optionally substituted with one or more substituents independently selected from halogen; R^{B7} is phenyl optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, C_1 alkyl, $-NH_2$, wherein C_1 alkyl is optionally substituted with one or more substituents independently selected from halogen. In some embodiments of a compound of Formula (A-8) or (a-8), R^{B2} is -O-(C_1 alkylene)-(8- to 10-membered nitrogen containing heterocycle) optionally substituted with one or more $=C(R^{B21})_2$; R^{B21} is independently selected at each occurrence from hydrogen and halogen; R^{B6} is selected from halogen and C_1 haloalkyl; R^{B7} is phenyl optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, C_1 alkyl, $-NH_2$, wherein C_1 alkyl is optionally substituted with one or more substituents independently selected from halogen. In some embodiments of a compound of Formula (A-7) or (a-7), R^{B2} is -O-(C_1 alkylene)-(8- to 10-membered nitrogen containing heterocycle) optionally substituted with one or more $=C(R^{B21})_2$; R^{B21} is independently selected at each occurrence from hydrogen and halogen; R^{B7} is phenyl optionally substituted with one, two, three, or four substituents independently selected at each occurrence from halogen, C_1 alkyl, $-NH_2$, wherein C_1 alkyl is optionally substituted with one or more substituents independently selected from halogen.

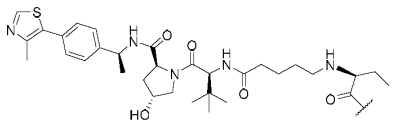
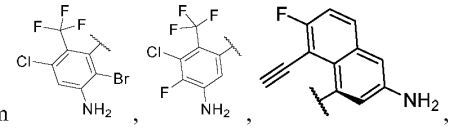
[289] In some embodiments of a compound of Formula (A-7), (A-8), (a-7), or (a-8), R^{B2} is selected from

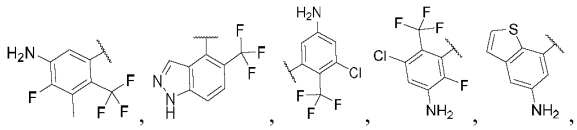
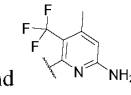


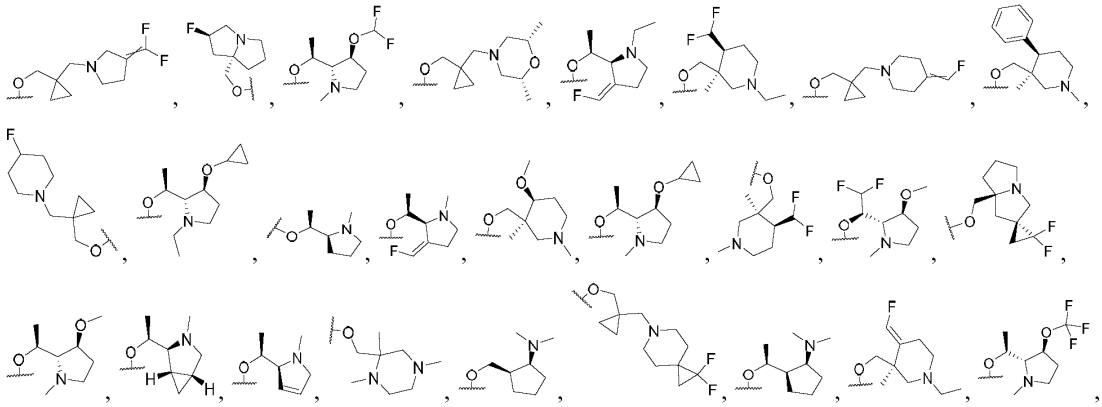
and  ; R^{B6} is selected from -Cl and -CF_3; and R^{B7} is selected from 

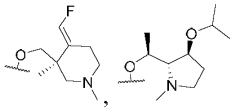
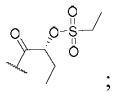
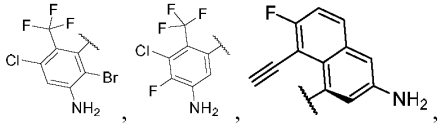
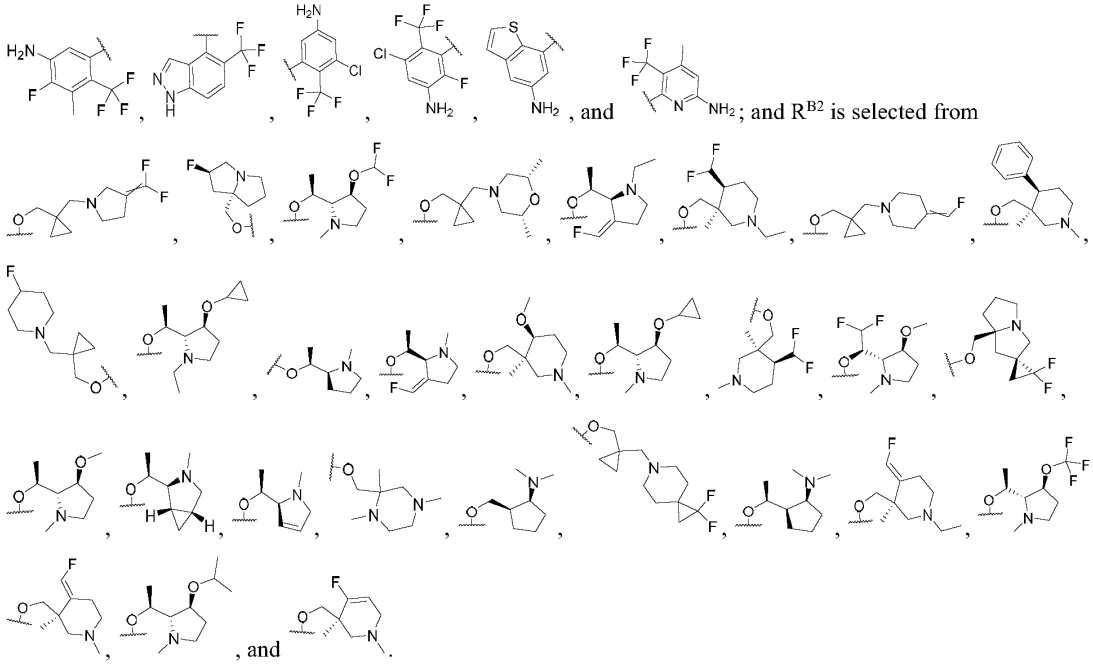


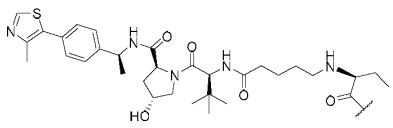
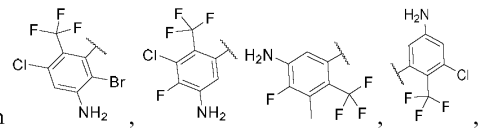
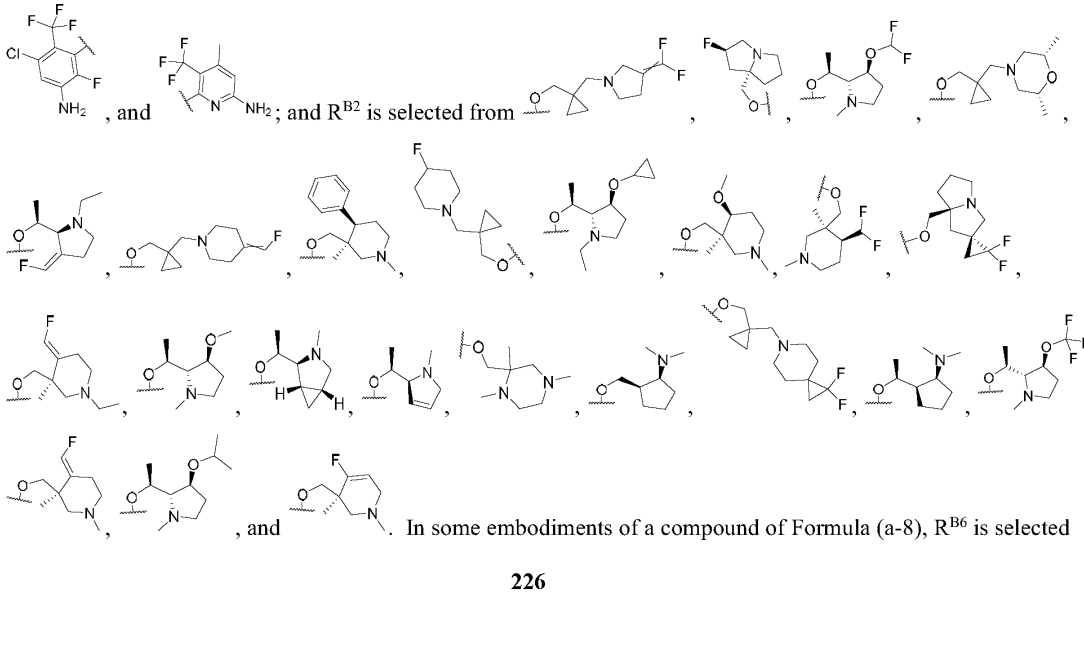
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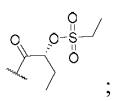
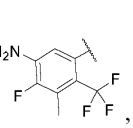
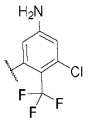
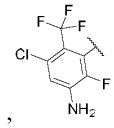
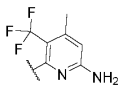
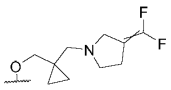
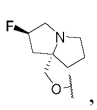
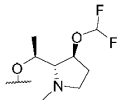
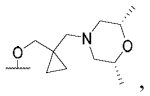
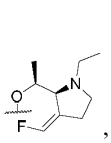
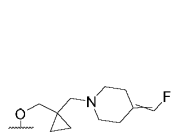
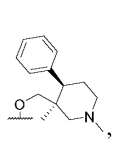
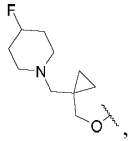
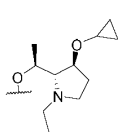
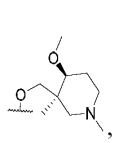
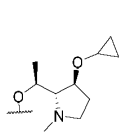
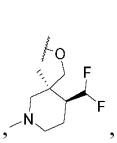
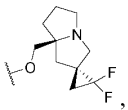
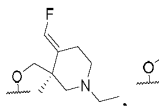
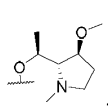
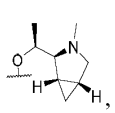
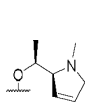
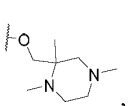
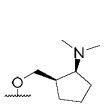
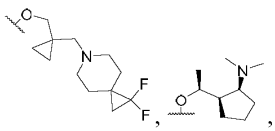
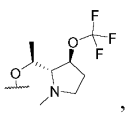
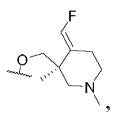
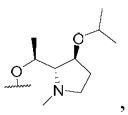
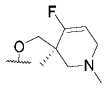
[290] In some embodiments of a compound of Formula (A-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-DG is  ; R^{B7} is selected from 

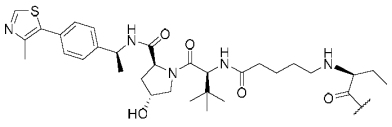
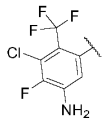
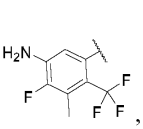
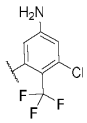
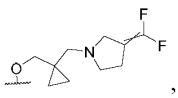
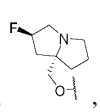
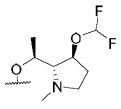
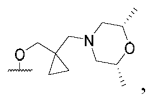
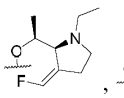
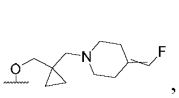
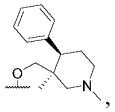
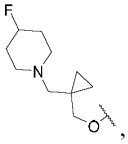
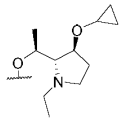
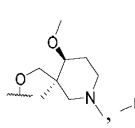
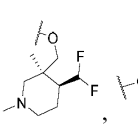
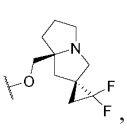
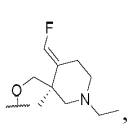
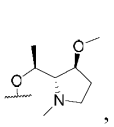
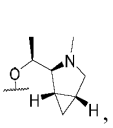
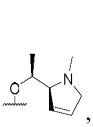
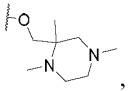
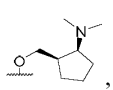
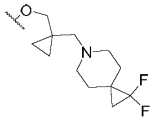
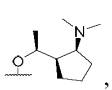
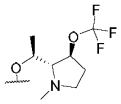
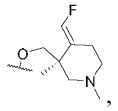
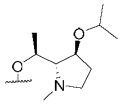
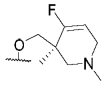
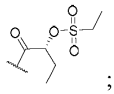
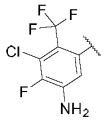
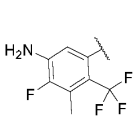
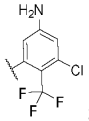
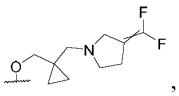
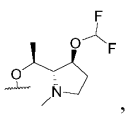
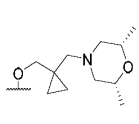
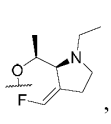
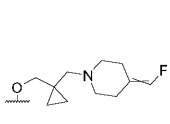
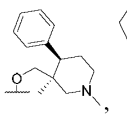
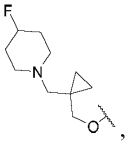
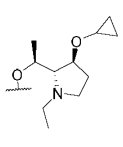
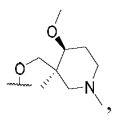
 and  ; and R^{B2} is selected from

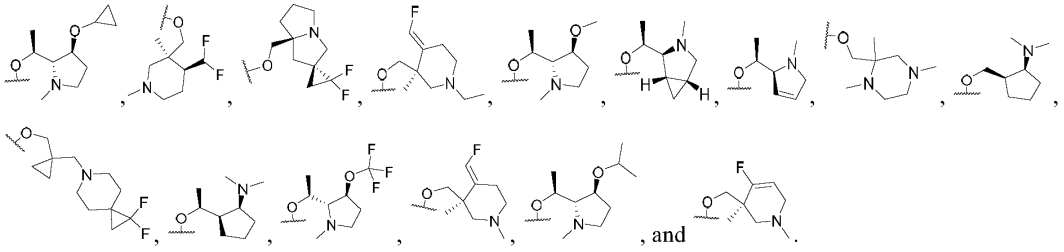


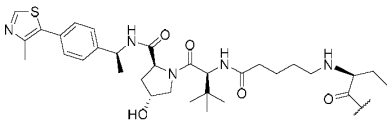
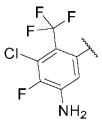
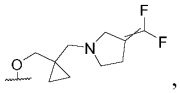
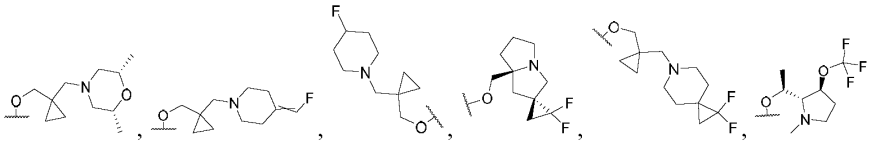
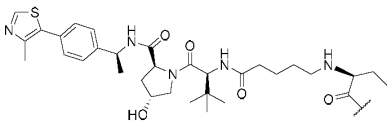
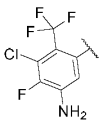
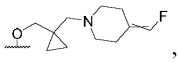
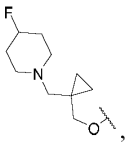
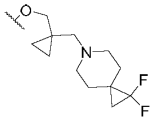
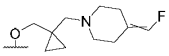
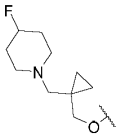
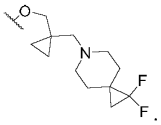
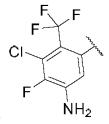
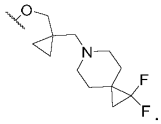
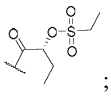
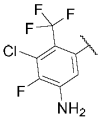
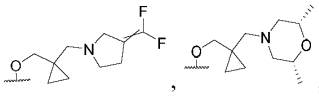
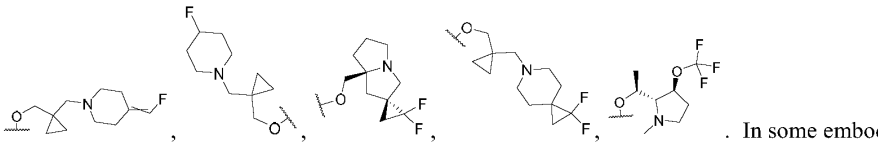
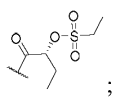
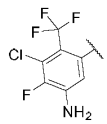

. In some embodiments of a compound of Formula (a-8), R^{B6} is selected from -Cl and $-CF_3$; $-J^1-J^2-J^3-LG$ is 
; R^{B7} is selected from 
; and R^{B2} is selected from 
.

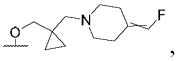
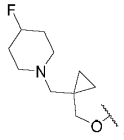
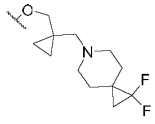
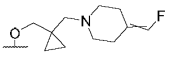
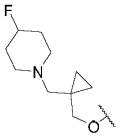
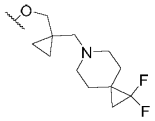
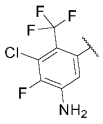
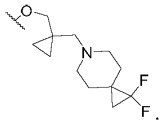
[291] In some embodiments of a compound of Formula (A-8), R^{B6} is selected from -Cl and $-CF_3$; $-J^1-J^2-J^3-DG$ is 
; R^{B7} is selected from 
; and R^{B2} is selected from 
. In some embodiments of a compound of Formula (a-8), R^{B6} is selected

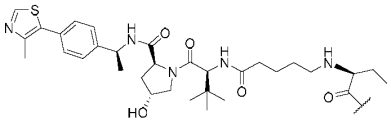
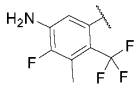
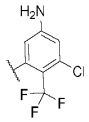
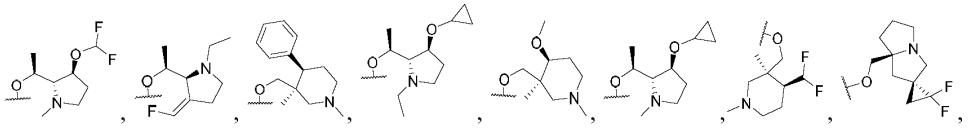
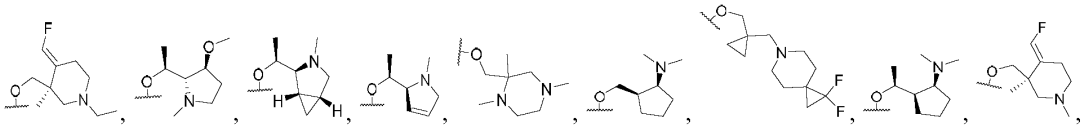
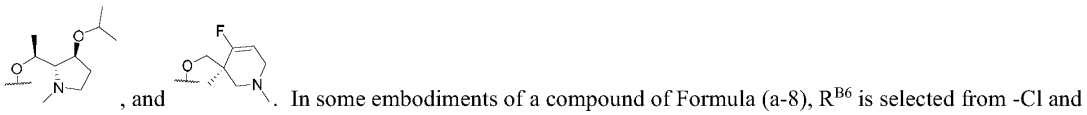
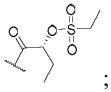
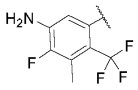
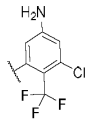
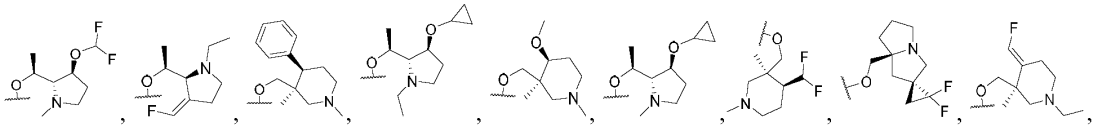
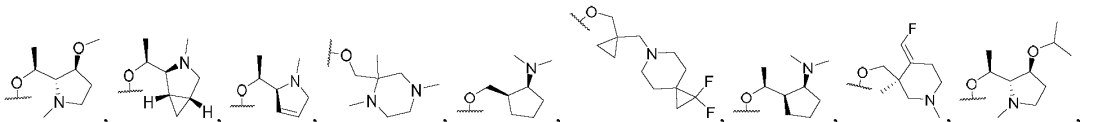
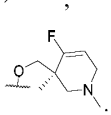
from -Cl and -CF_3; -J^1-J^2-J^3-LG is  ; R^{B7} is selected from      , and  ; and R^{B2} is selected from                        , and  .

[292] In some embodiments of a compound of Formula (A-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-DG is  ; R^{B7} is selected from   , and  ; and R^{B2} is selected from                        , and  . In some embodiments of a compound of Formula (a-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-LG is  ; R^{B7} is selected from  ,  , and  ; and R^{B2} is selected from          

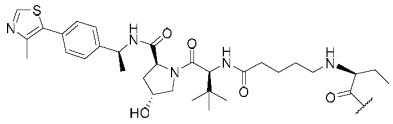
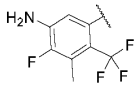
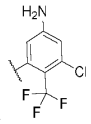
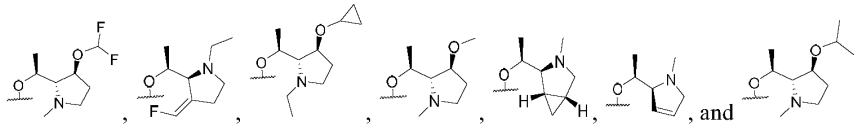
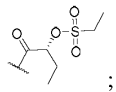
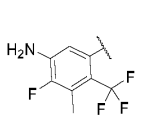
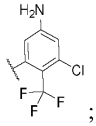
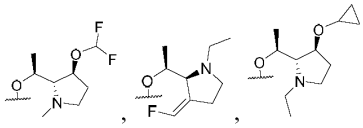


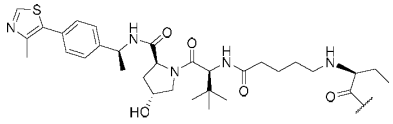
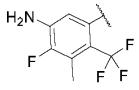
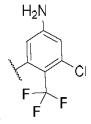
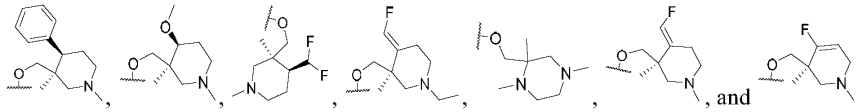
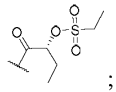
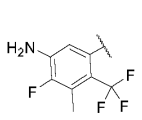
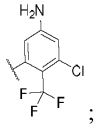
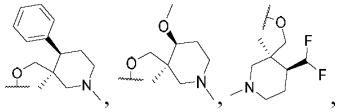
[293] In some embodiments of a compound of Formula (A-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-DG is  ; R^{B7} is  ; and R^{B2} is selected from  ,  . In some embodiments of a compound of Formula (A-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-DG is  ; R^{B7} is  ; and R^{B2} is selected from  ,  , and  . In some embodiments R^{B2} is  . In some embodiments R^{B2} is  . In some embodiments R^{B2} is  . In some embodiments R^{B6} is -CF_3; R^{B7} is  ; and R^{B2} is  . In some embodiments of a compound of Formula (a-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-LG is  ; R^{B7} is  ; and R^{B2} is selected from  ,  . In some embodiments of a compound of Formula (a-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-LG is  ; R^{B7} is  ; and R^{B2} is

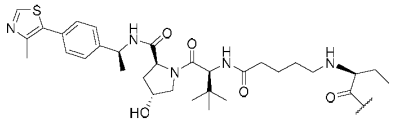
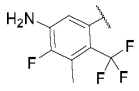
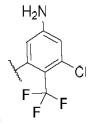
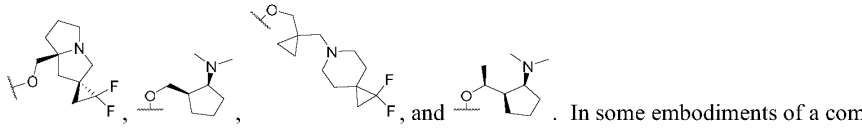
selected from  ,  , and  . In some embodiments R^{B2} is  . In some embodiments R^{B2} is  . In some embodiments R^{B2} is  . In some embodiments R^{B6} is $-CF_3$; R^{B7} is  ; and R^{B2} is  .

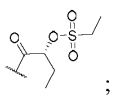
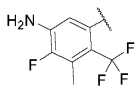
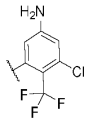
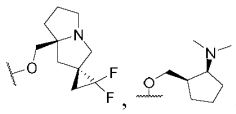
[294] In some embodiments of a compound of Formula (A-8), R^{B6} is selected from -Cl and $-CF_3$; $-J^1-J^2-J^3-DG$ is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  ,  ,  , and . In some embodiments of a compound of Formula (a-8), R^{B6} is selected from -Cl and -CF_3; $-J^1-J^2-J^3-LG$ is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  ,  , and  .

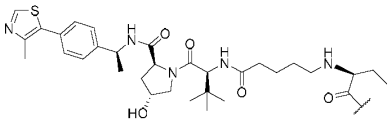
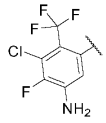
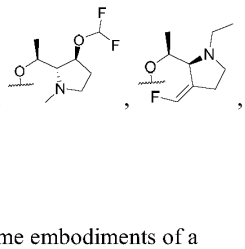
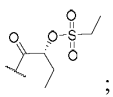
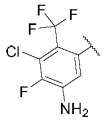
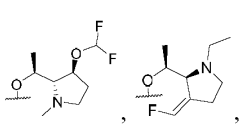
[295] In some embodiments of a compound of Formula (A-8), R^{B6} is selected from -Cl and $-CF_3$; $-J^1-J^2-J^3-DG$ is

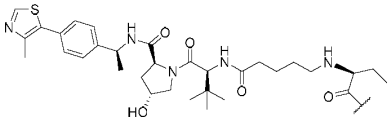
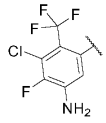
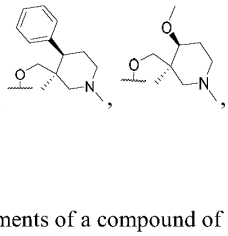
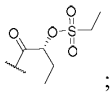
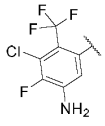
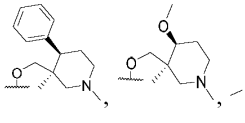

; R^{B7} is selected from  and  ; and R^{B2} is selected from  . In some embodiments of a compound of Formula (a-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-LG is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  .

[296] In some embodiments of a compound of Formula (A-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-DG is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  . In some embodiments of a compound of Formula (a-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-LG is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  .

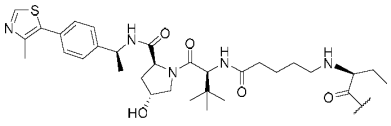
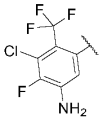
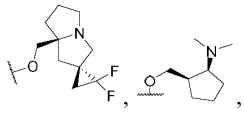
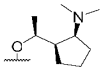
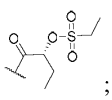
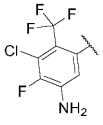
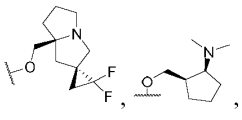
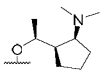
[297] In some embodiments of a compound of Formula (A-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-DG is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  . In some embodiments of a compound of Formula

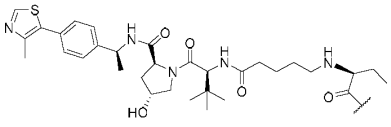
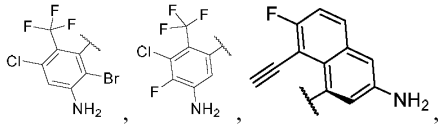
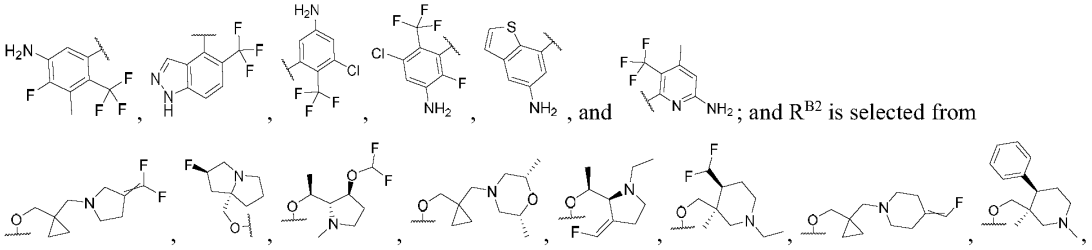
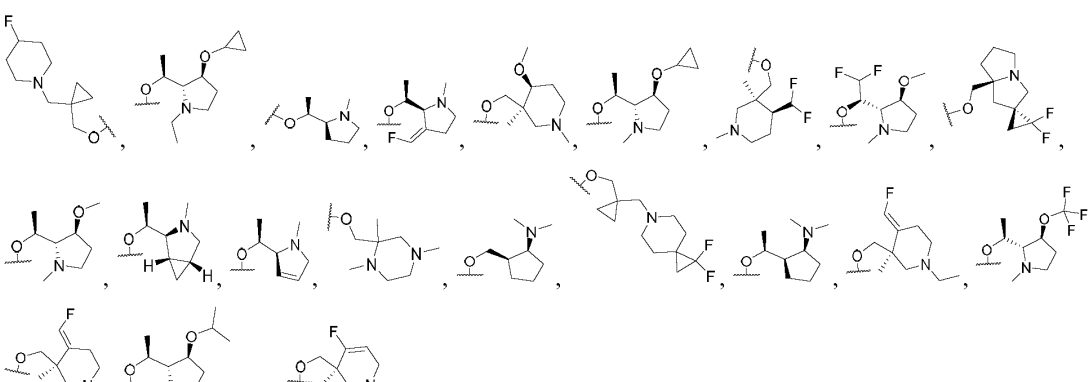
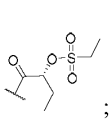
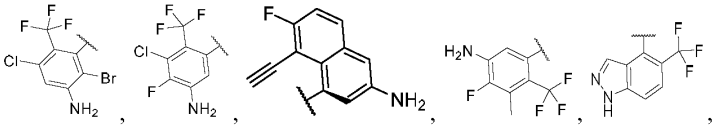
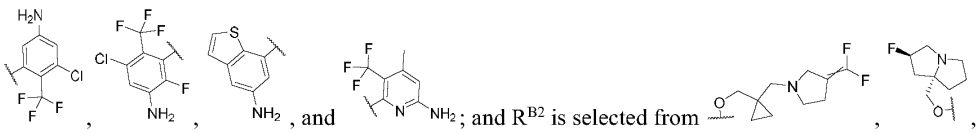
(a-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-LG is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  .

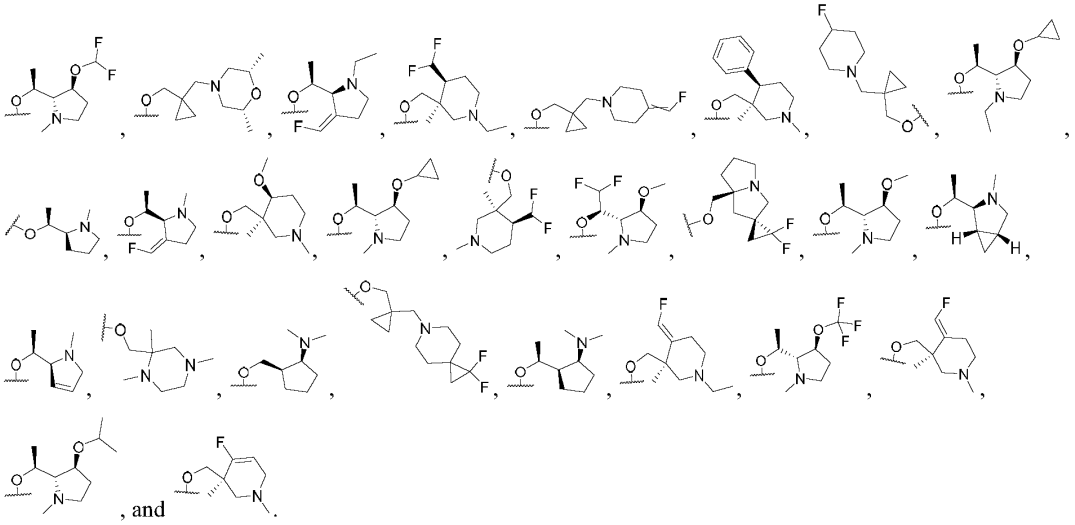
[298] In some embodiments of a compound of Formula (A-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-DG is  ; R^{B7} is  ; and R^{B2} is selected from  . In some embodiments of a compound of Formula (a-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-LG is  ; R^{B7} is  ; and R^{B2} is selected from  .

[299] In some embodiments of a compound of Formula (A-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-DG is  ; R^{B7} is  ; and R^{B2} is selected from  . In some embodiments of a compound of Formula (a-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-LG is  ; R^{B7} is  ; and R^{B2} is selected from  .

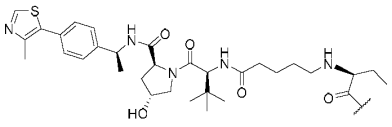
[300] In some embodiments of a compound of Formula (A-8), R^{B6} is selected from -Cl and -CF_3; -J^1-J^2-J^3-DG is


; R^{B7} is 
; and R^{B2} is selected from 
, and 
. In some embodiments of a compound of Formula (a-8), R^{B6} is selected from -Cl and $-CF_3$; $-J^1-J^2-J^3-LG$ is 
; R^{B7} is 
; and R^{B2} is selected from 
, and 
.

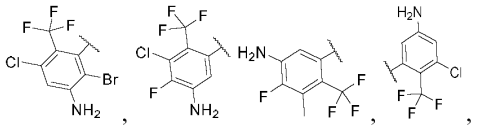
[301] In some embodiments of a compound of Formula (A-7), $-J^1-J^2-J^3-DG$ is 
; R^{B7} is selected from 
; and R^{B2} is selected from 
, and 
. In some embodiments of a compound of Formula (a-7), $-J^1-J^2-J^3-LG$ is 
; R^{B7} is selected from 
; and R^{B2} is selected from 
.

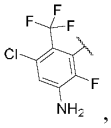


[302] In some embodiments of a compound of Formula (A-7), -J^1-J^2-J^3-DG is

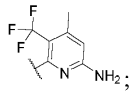


; R^{B7} is selected from

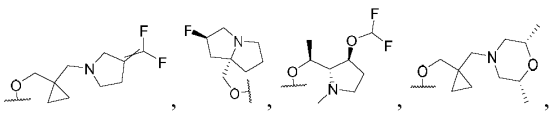


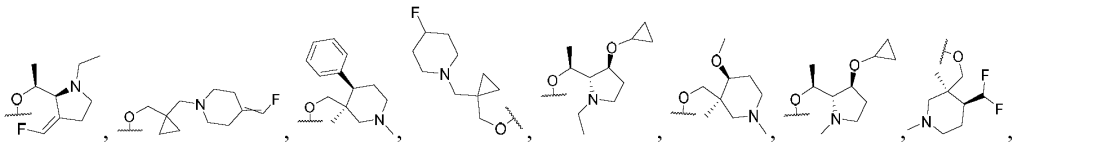


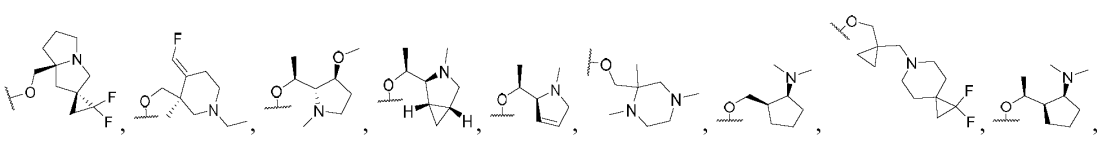
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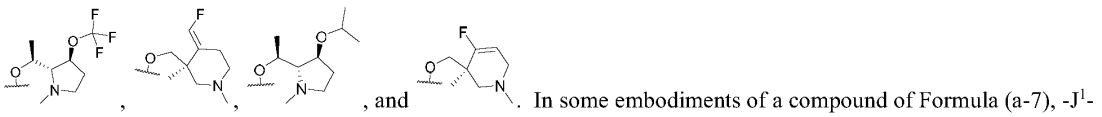


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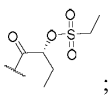




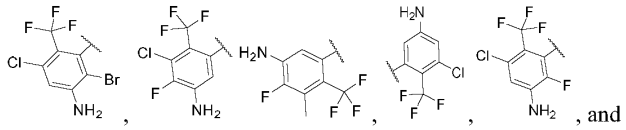


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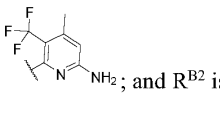
. In some embodiments of a compound of Formula (a-7), -J^1-J^2-J^3-LG is



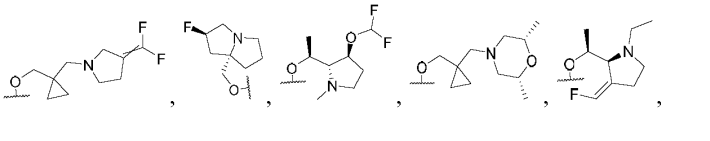
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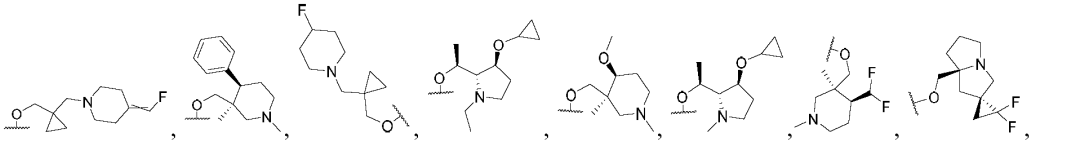


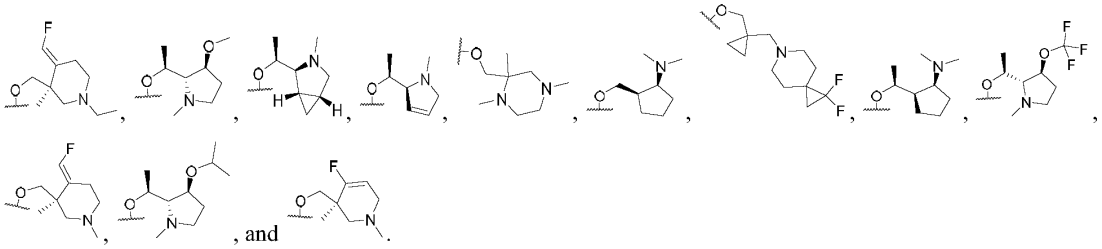
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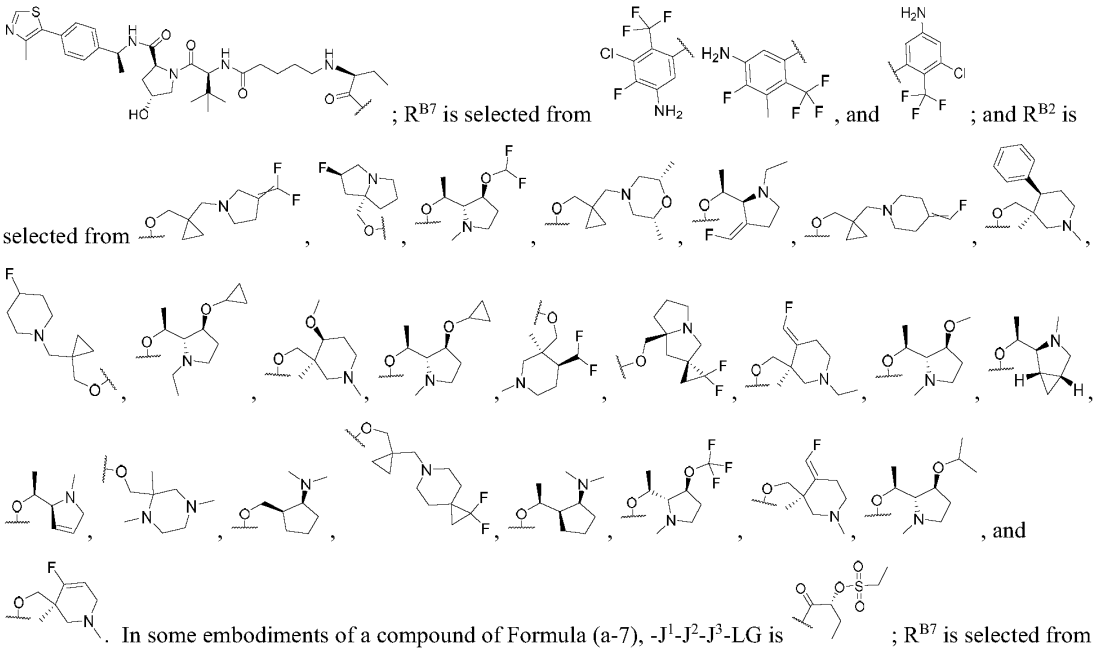
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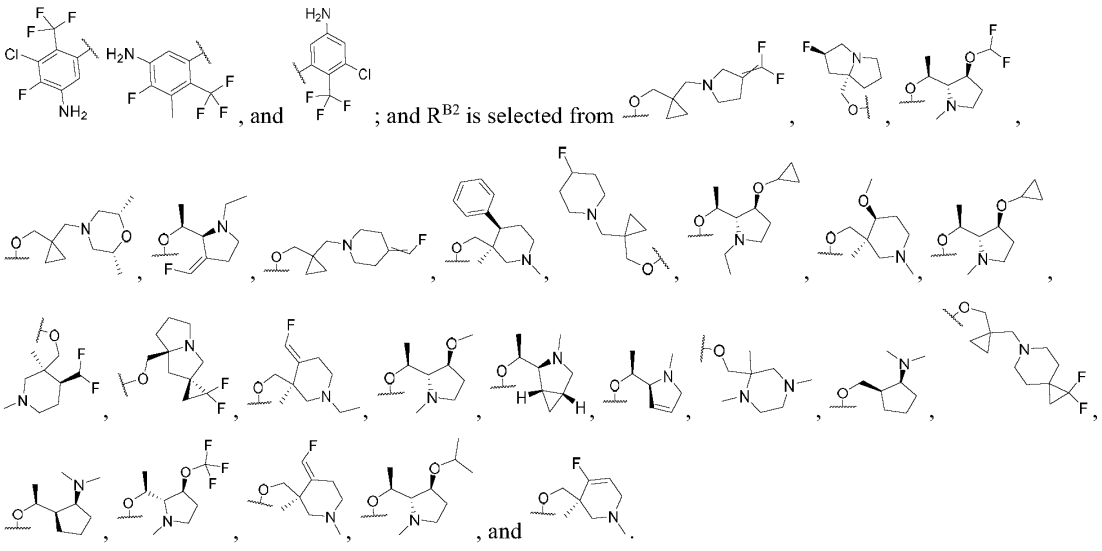


[303] In some embodiments of a compound of Formula (A-7), -J^1-J^2-J^3-DG is

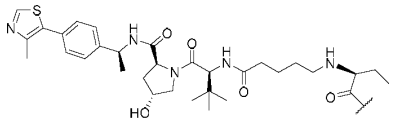
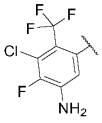
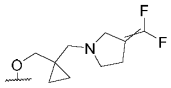
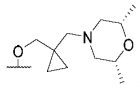
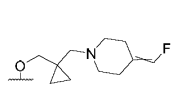
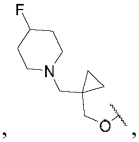
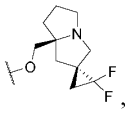
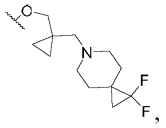
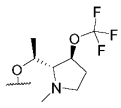
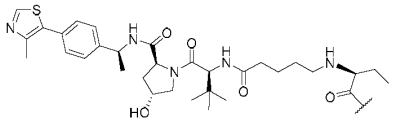
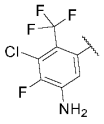
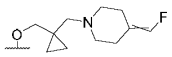
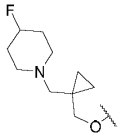
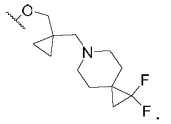
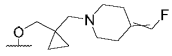
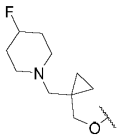
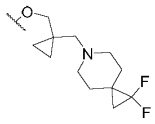
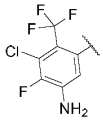
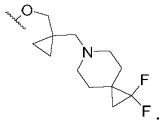
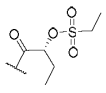
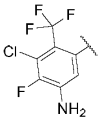
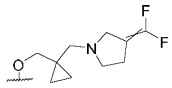
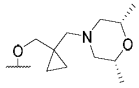
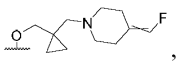
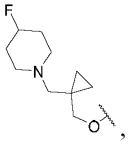
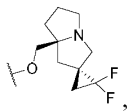
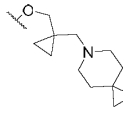
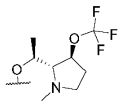
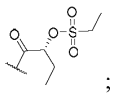
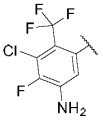
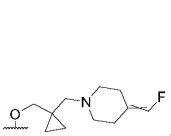
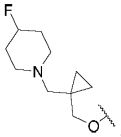
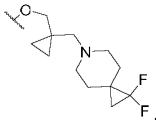
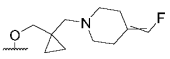
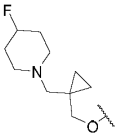
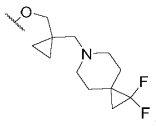


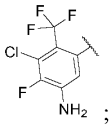
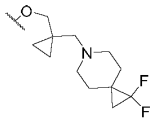
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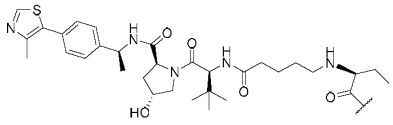
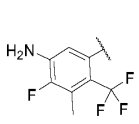
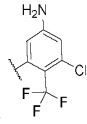
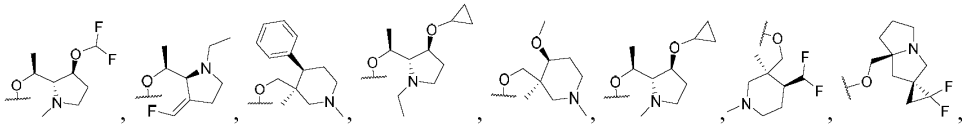
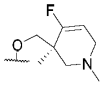
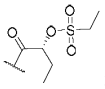
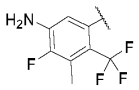
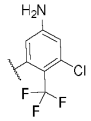
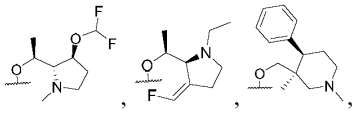
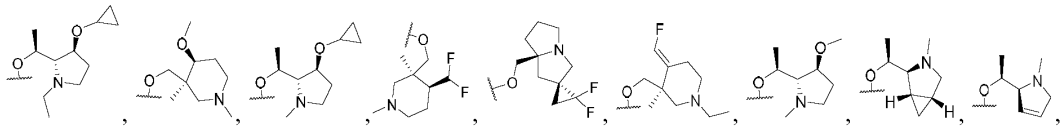
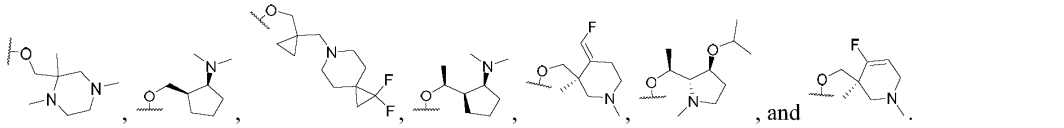
; R^{B7} is selected from

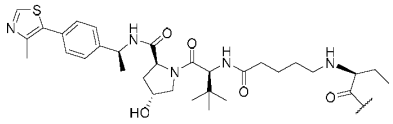
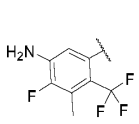
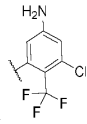
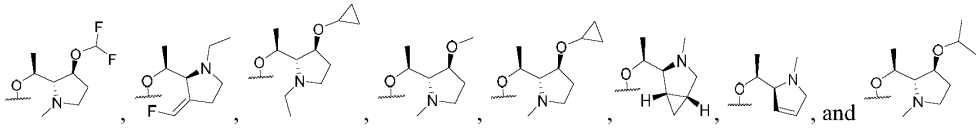
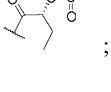
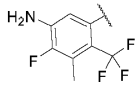


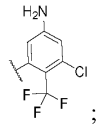
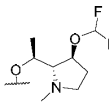
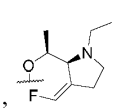
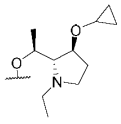
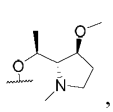
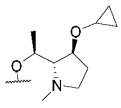
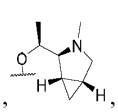
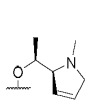
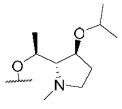
[304] In some embodiments of a compound of Formula (A-7), -J^1-J^2-J^3-DG is

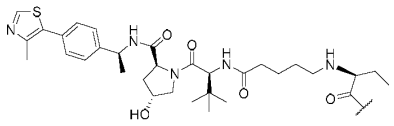
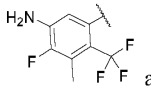
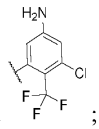
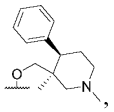
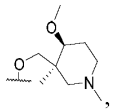
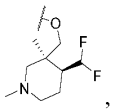
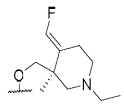
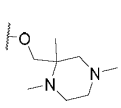
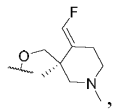
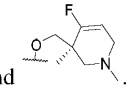
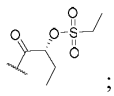
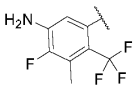
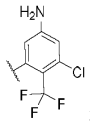
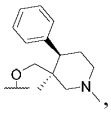
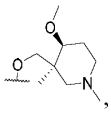
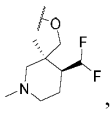
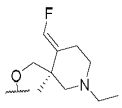
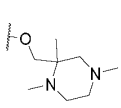
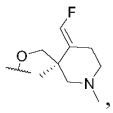
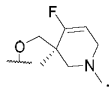

; R^{B7} is 
; and R^{B2} is selected from  ,
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 ,
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 ,
 ,
 . In some embodiments of a compound of Formula (A-7), -J^1-J^2-J^3-DG is 
; R^{B7} is 
; and R^{B2} is selected from  ,
 , and
 . In some embodiments R^{B2} is
 . In some embodiments R^{B2} is
 . In some embodiments R^{B2} is
 . In some embodiments R^{B6} is -CF_3; R^{B7} is

; and R^{B2} is
 . In some embodiments of a compound of Formula (a-7), -J^1-J^2-J^3-LG is

; R^{B7} is

; and R^{B2} is selected from
 ,
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 . In some embodiments of a compound of Formula (a-7), -J^1-J^2-J^3-LG is

; R^{B7} is

; and R^{B2} is selected from
 ,
 , and
 . In some embodiments R^{B2} is
 . In some embodiments R^{B2} is
 . In some embodiments R^{B2} is
 . In some embodiments

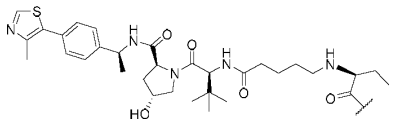
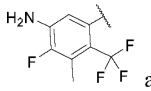
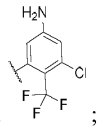
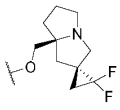
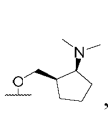
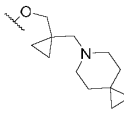
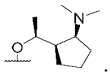
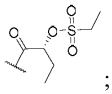
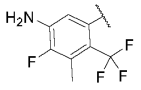
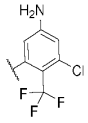
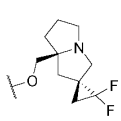
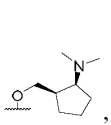
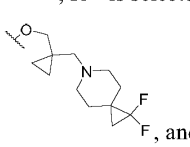
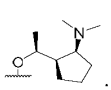
R^{B6} is $-CF_3$; R^{B7} is  ; and R^{B2} is  .

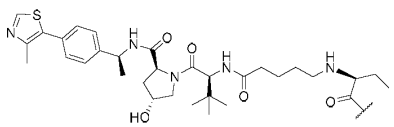
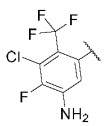
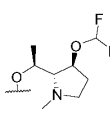
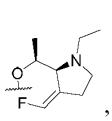
[305] In some embodiments of a compound of Formula (A-7), $-J^1-J^2-J^3$-DG is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  , and  . In some embodiments of a compound of Formula (a-7), $-J^1-J^2-J^3$-LG is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  ,  ,  , and .

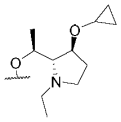
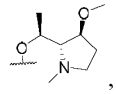
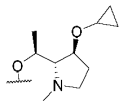
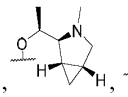
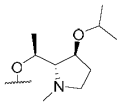
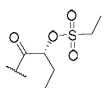
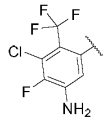
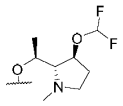
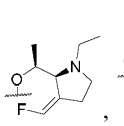
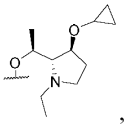
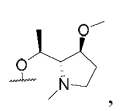
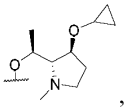
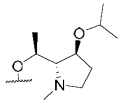
[306] In some embodiments of a compound of Formula (A-7), $-J^1-J^2-J^3$-DG is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  , and . In some embodiments of a compound of Formula (a-7), $-J^1-J^2-J^3$-LG is  ; R^{B7} is selected from 

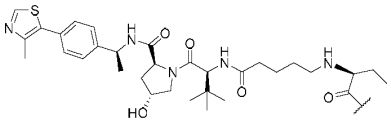
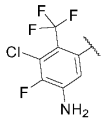
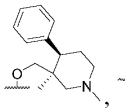
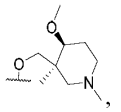
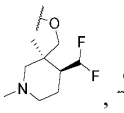
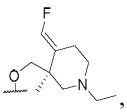
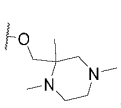
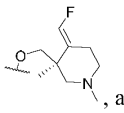
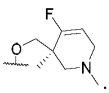
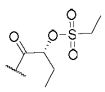
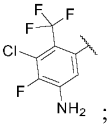
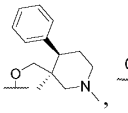
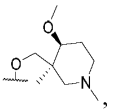
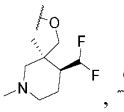
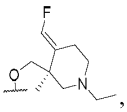
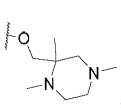
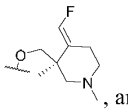
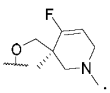
and  ; and R^{B2} is selected from  ,  ,  ,  ,  ,  ,  , and  .

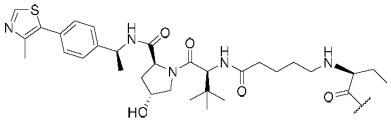
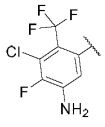
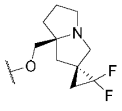
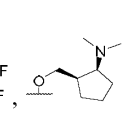
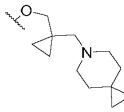
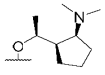
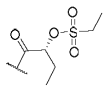
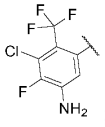
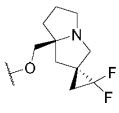
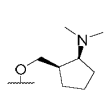
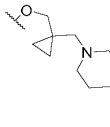
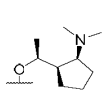
[307] In some embodiments of a compound of Formula (A-7), -J^1-J^2-J^3-DG is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  ,  ,  ,  ,  ,  , and  . In some embodiments of a compound of Formula (a-7), -J^1-J^2-J^3-LG is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  ,  ,  ,  ,  ,  , and  .

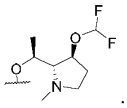
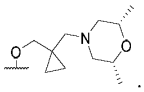
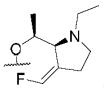
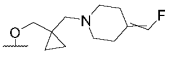
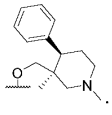
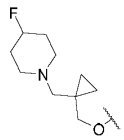
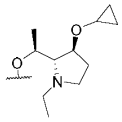
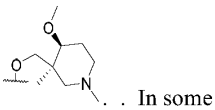
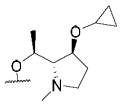
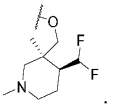
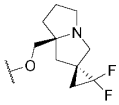
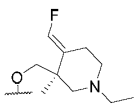
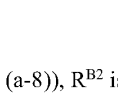
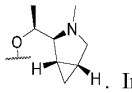
[308] In some embodiments of a compound of Formula (A-7), -J^1-J^2-J^3-DG is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  ,  ,  , and  . In some embodiments of a compound of Formula (a-7), -J^1-J^2-J^3-LG is  ; R^{B7} is selected from  and  ; and R^{B2} is selected from  ,  ,  , and  .

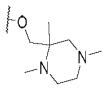
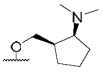
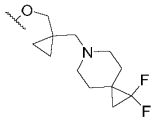
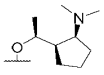
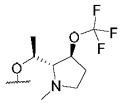
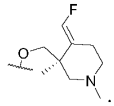
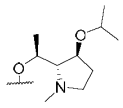
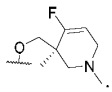
[309] In some embodiments of a compound of Formula (A-7), -J^1-J^2-J^3-DG is  ; R^{B7} is  ; and R^{B2} is selected from  ,  ,

 ,  ,  ,  ,  , and  . In some embodiments of a compound of Formula (a-7), -J^1-J^2-J^3-LG is  ; R^{B7} is  ; and R^{B2} is selected from  ,  ,  ,  ,  ,  , and  .

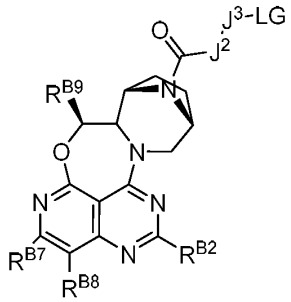
[310] In some embodiments of a compound of Formula (A-7), -J^1-J^2-J^3-DG is  ; R^{B7} is  ; and R^{B2} is selected from  ,  ,  ,  ,  ,  , and  . In some embodiments of a compound of Formula (a-7), -J^1-J^2-J^3-LG is  ; R^{B7} is  ; and R^{B2} is selected from  ,  ,  ,  ,  ,  , and  .

[311] In some embodiments of a compound of Formula (A-7), -J^1-J^2-J^3-DG is  ; R^{B7} is  ; and R^{B2} is selected from  ,  ,  , and  . In some embodiments of a compound of Formula (a-7), -J^1-J^2-J^3-LG is  ; R^{B7} is  ; and R^{B2} is selected from  ,  ,  , and  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is

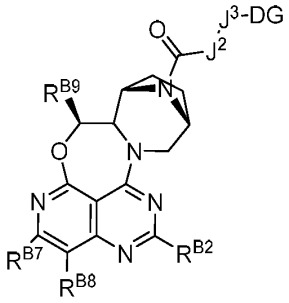
 . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected

from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  . In some embodiments (e.g., of a compound of one formula selected from (A-7), (a-7), (A-8), and (a-8)), R^{B2} is  .

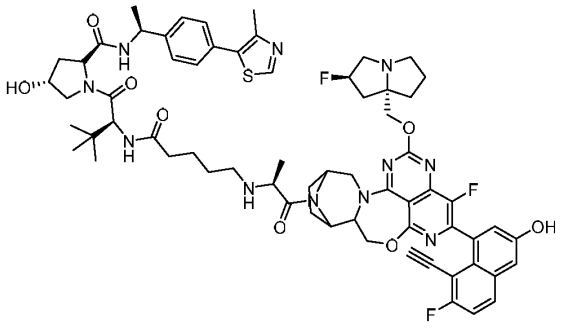
[312] In embodiments of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), the compound has the formula



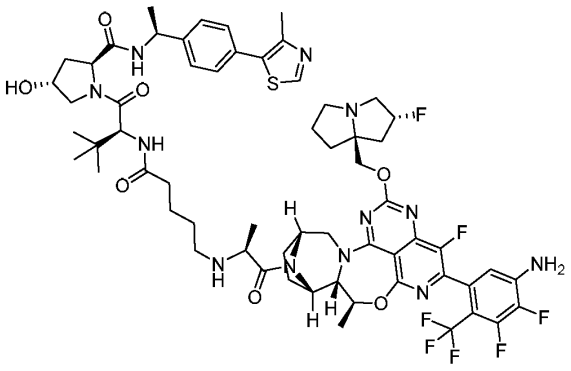
, wherein R^{B9} is independently unsubstituted methyl or hydrogen; and R^{B2}, R^{B7}, R^{B8}, J^2, J^3, and LG are as described herein, including in any aspect or embodiment of a formula recited above. In embodiments of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6), the compound has the formula



, wherein R^{B9} is independently unsubstituted methyl or hydrogen; and R^{B2}, R^{B7}, R^{B8}, J^2, J^3, and DG are as described herein, including in any aspect or embodiment of a formula recited above.

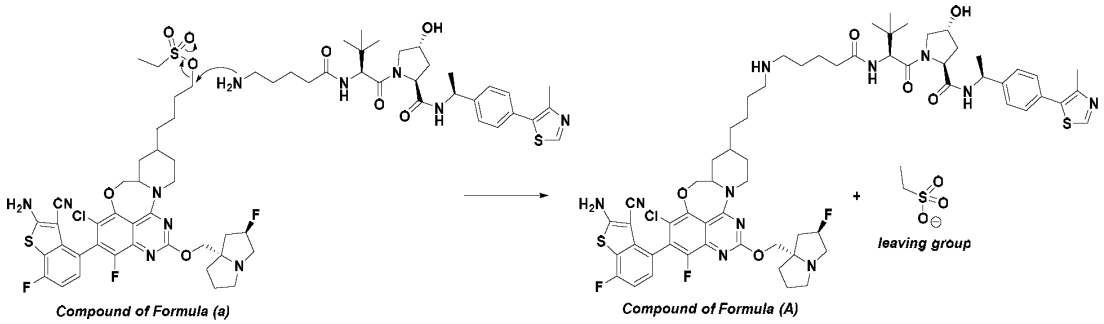


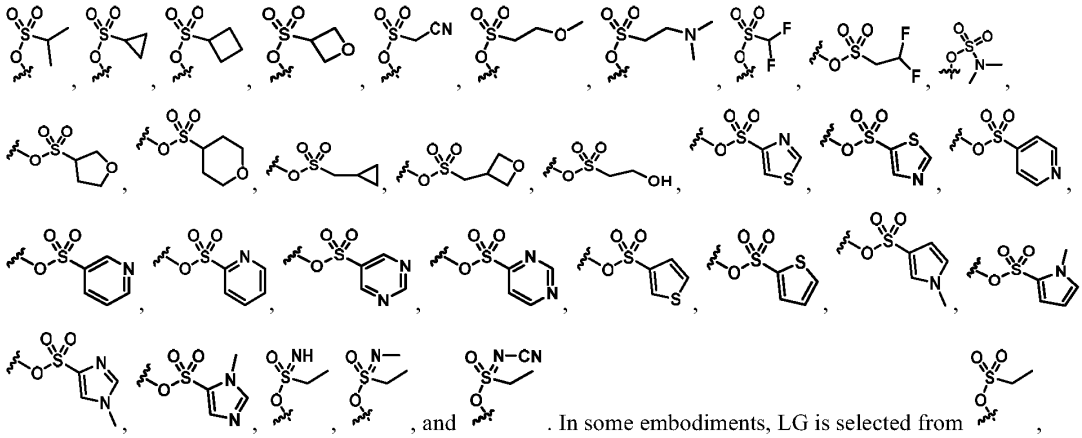
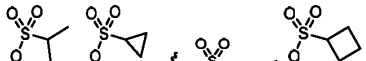
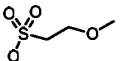
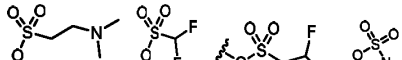
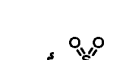
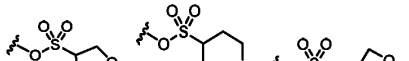
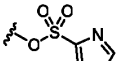
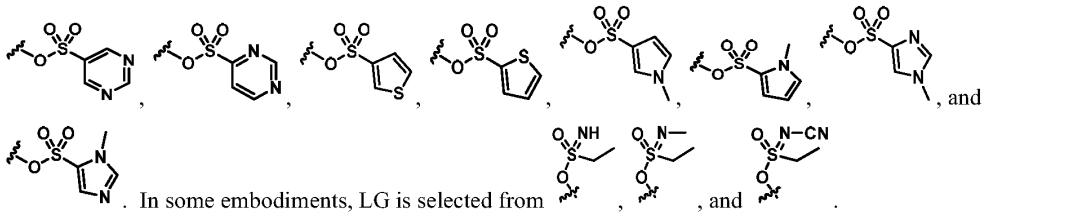
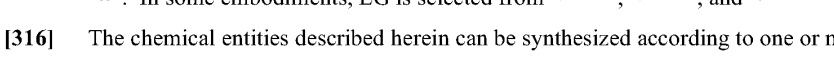
[313] In some embodiments, the compound is . In some embodiments, the compound is



.

[314] As used herein, the term "leaving group" refers to an atom or group that becomes detached from an atom in the residual or main part of the substrate in a specified reaction. The residual or main part of the substrate is also referred to herein as the "staying group". Not wishing to be bound by any particular theory, the mechanism below is provided as an example to illustrate a non-limiting types of leaving group that may be found in compounds of the present disclosure. In the example below, nucleophilic attack on a compound of Formula (a) by an amine group of a degradation enhancer reactant results in the cleavage of a C-O bond of the sulfonate ester of the compound of Formula (a), thereby forming the depicted compound of Formula (A) and the leaving group as two distinct molecules.



[315] In some embodiments, for a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), LG is selected from  ,  , and  . In some embodiments, LG is selected from  , and  . In some embodiments, LG is selected from  ,  , and  . In some embodiments, LG is selected from ,  , and  . In some embodiments, LG is selected from  , and  . In some embodiments, LG is selected from .

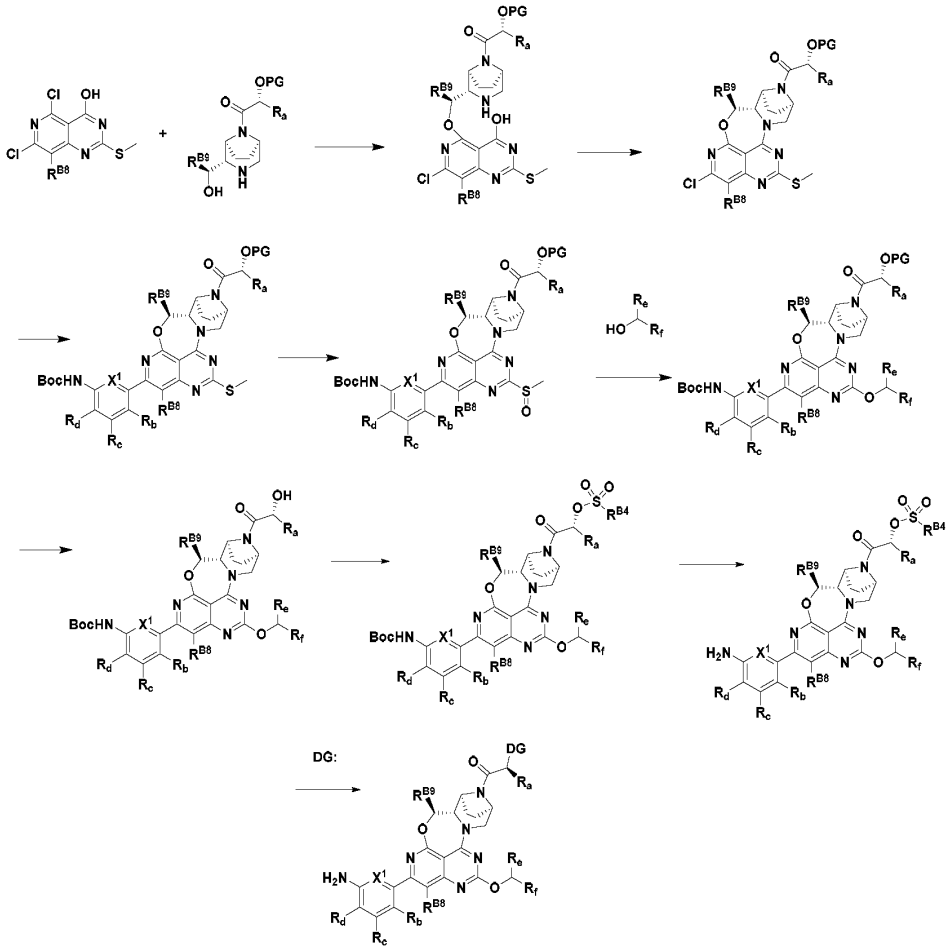
[316] The chemical entities described herein can be synthesized according to one or more illustrative schemes herein and/or techniques known in the art. Materials used herein are either commercially available or prepared by synthetic methods generally known in the art. These schemes are not limited to the compounds listed in the examples or by any particular substituents, which are employed for illustrative purposes. Although various steps are described and depicted in **Schemes 1-10**, the steps in some cases may be performed in a different order than the

order shown in **Schemes 1-10**. Various modifications to these synthetic reaction schemes may be made and will be suggested to one skilled in the art having referred to the present disclosure. Numberings or R groups in each scheme typically have the same meanings as those defined elsewhere herein unless otherwise indicated.

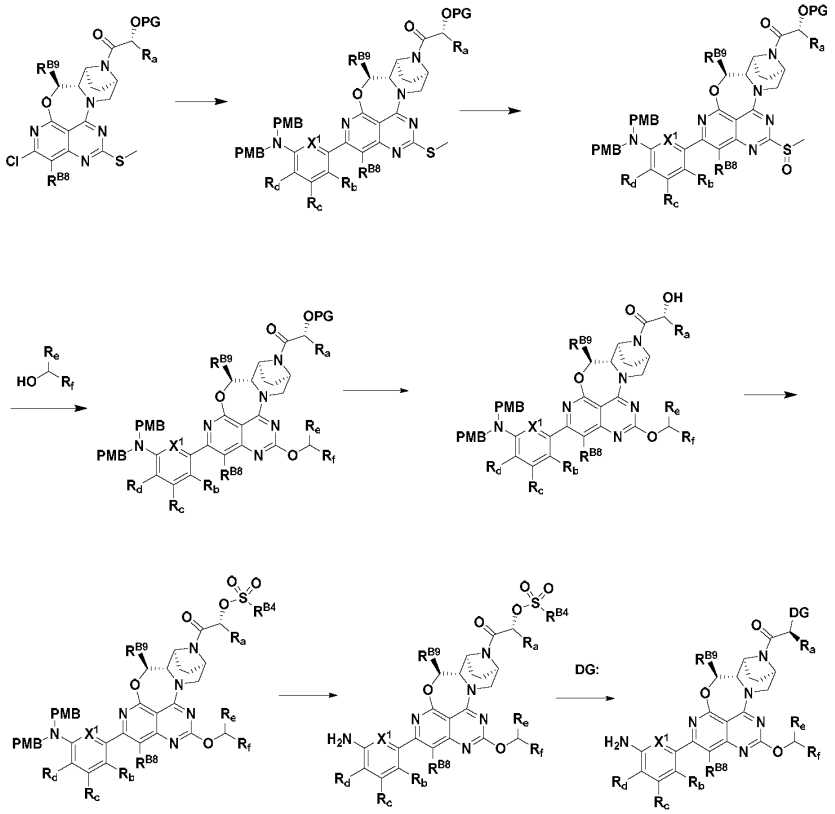
[317] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from -10 °C to 200 °C. Further, except as otherwise specified, reaction times and conditions are intended to be approximate, e.g., taking place at about atmospheric pressure within a temperature range of about -10 °C to about 110 °C over a period of about 1 to about 24 hours; reactions left to run overnight average a period of about 16 hours.

[318] In general, compounds of the disclosure may be prepared by the following reaction schemes:

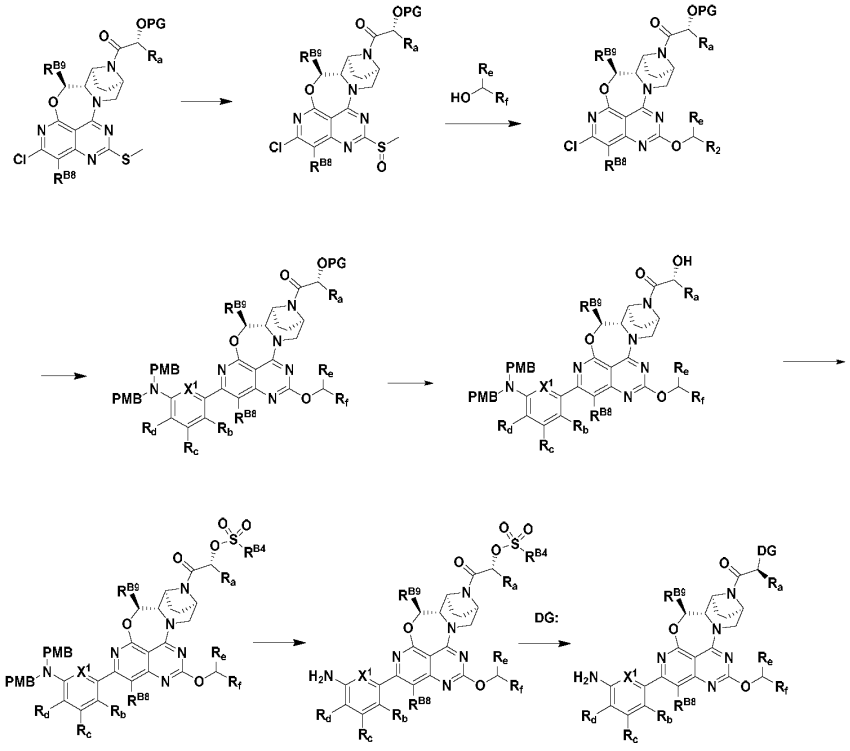
[319] **General Scheme 1**



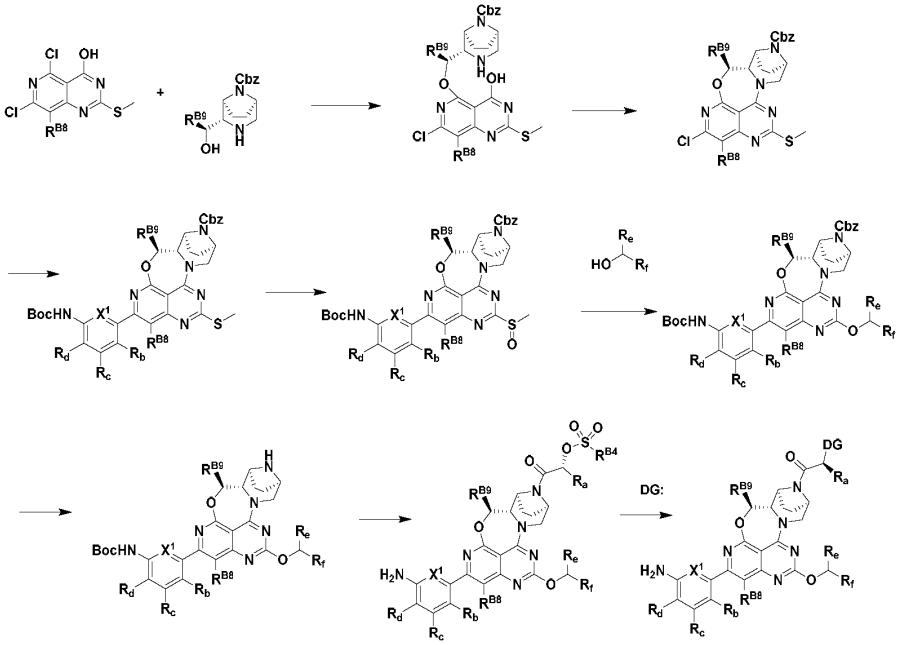
[320] **General Scheme 2**



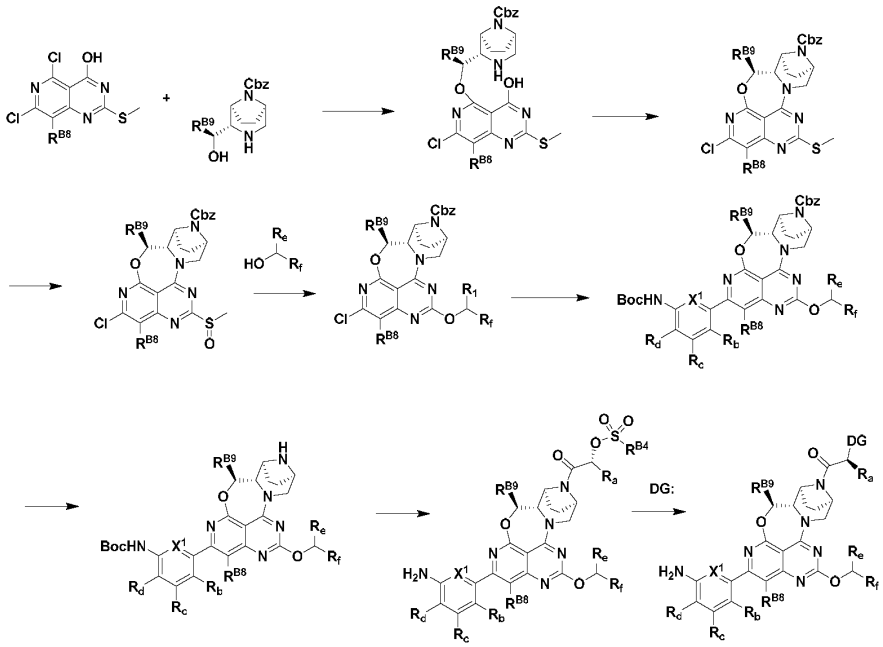
[321] General Scheme 3



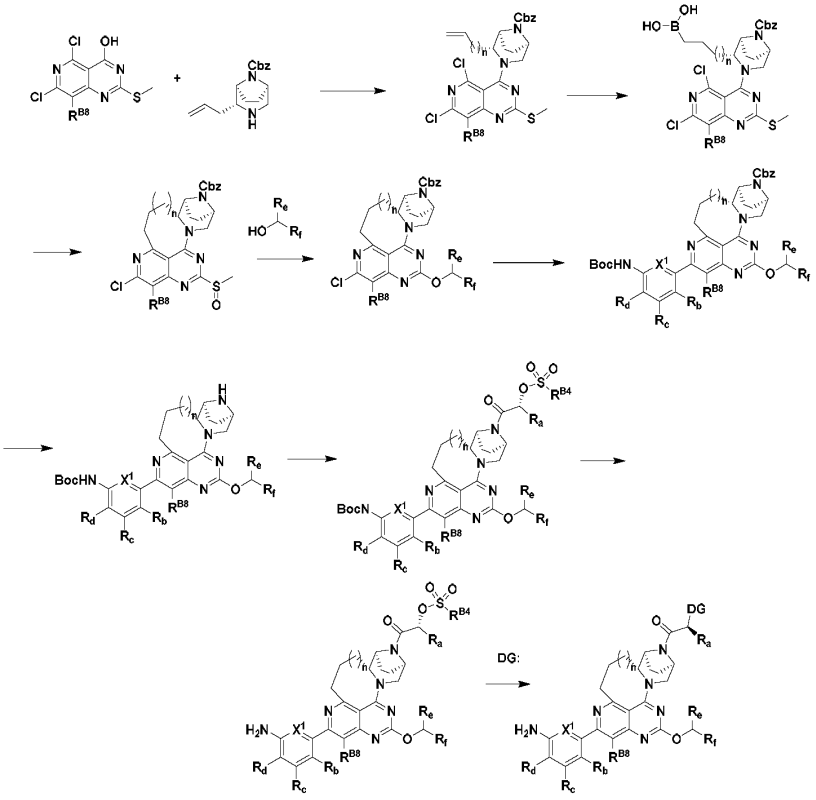
[322] General Scheme 4



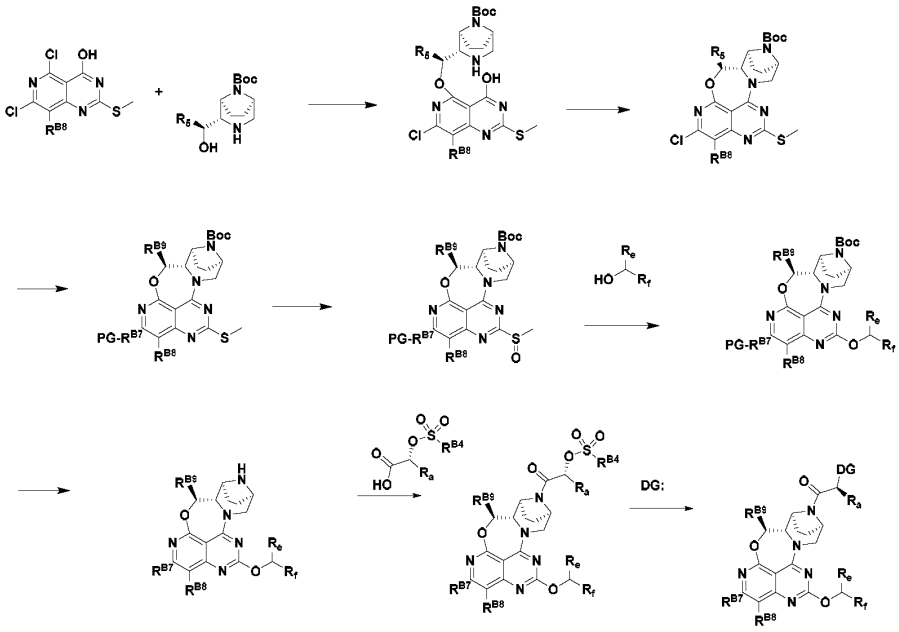
[323] General Scheme 5



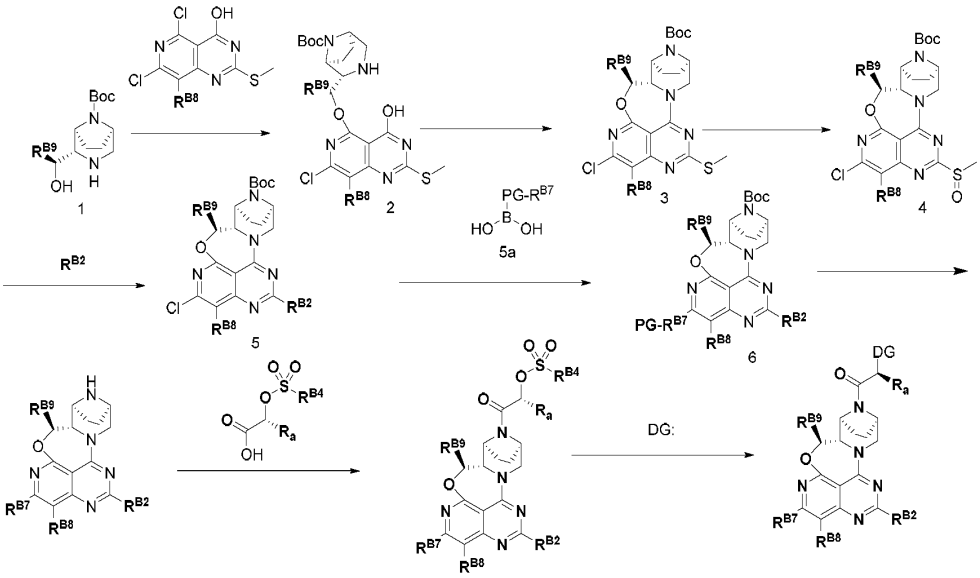
[324] General Scheme 6



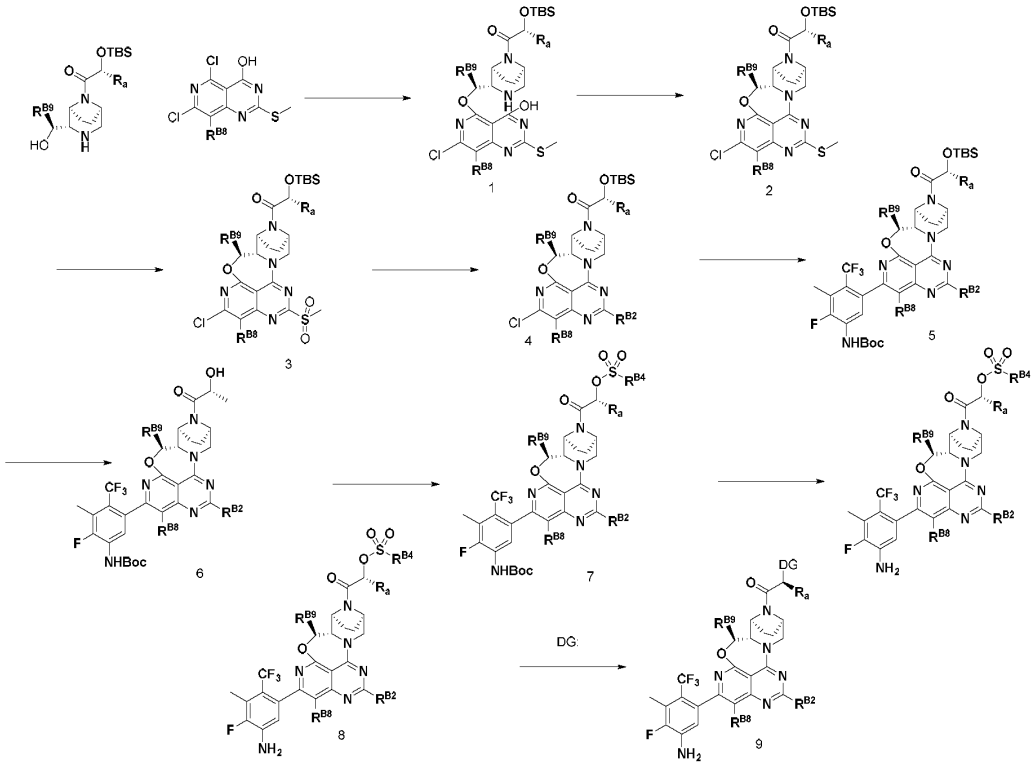
[325] General Scheme 7



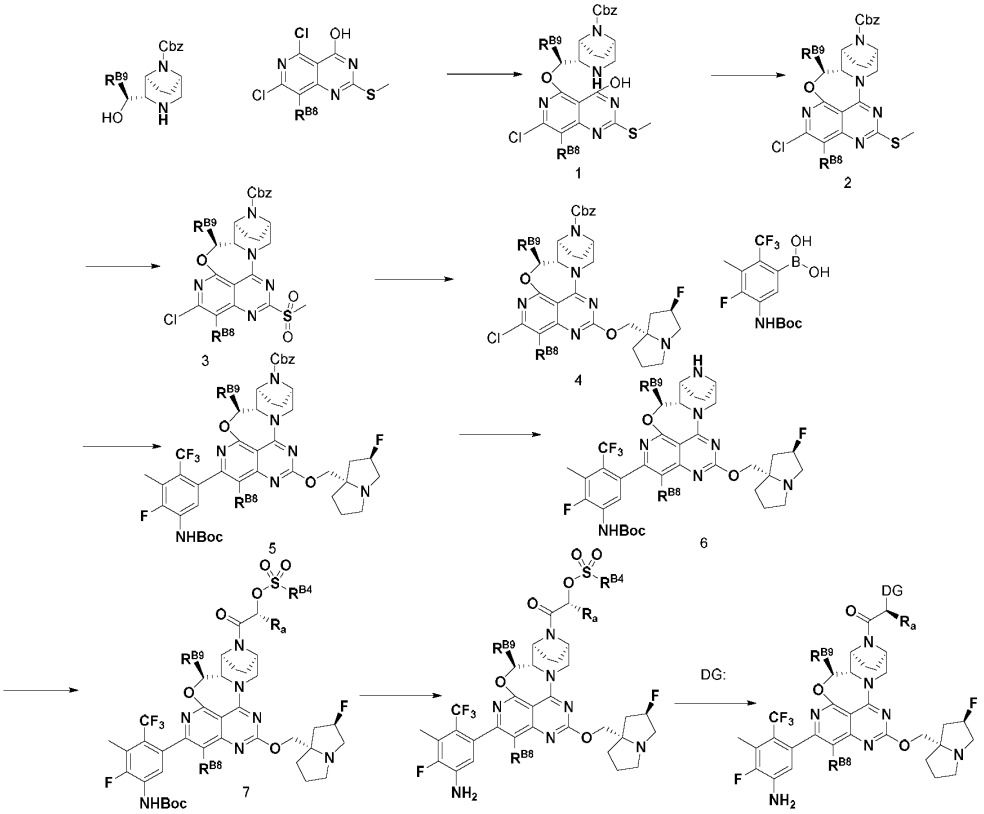
[326] General Scheme 8



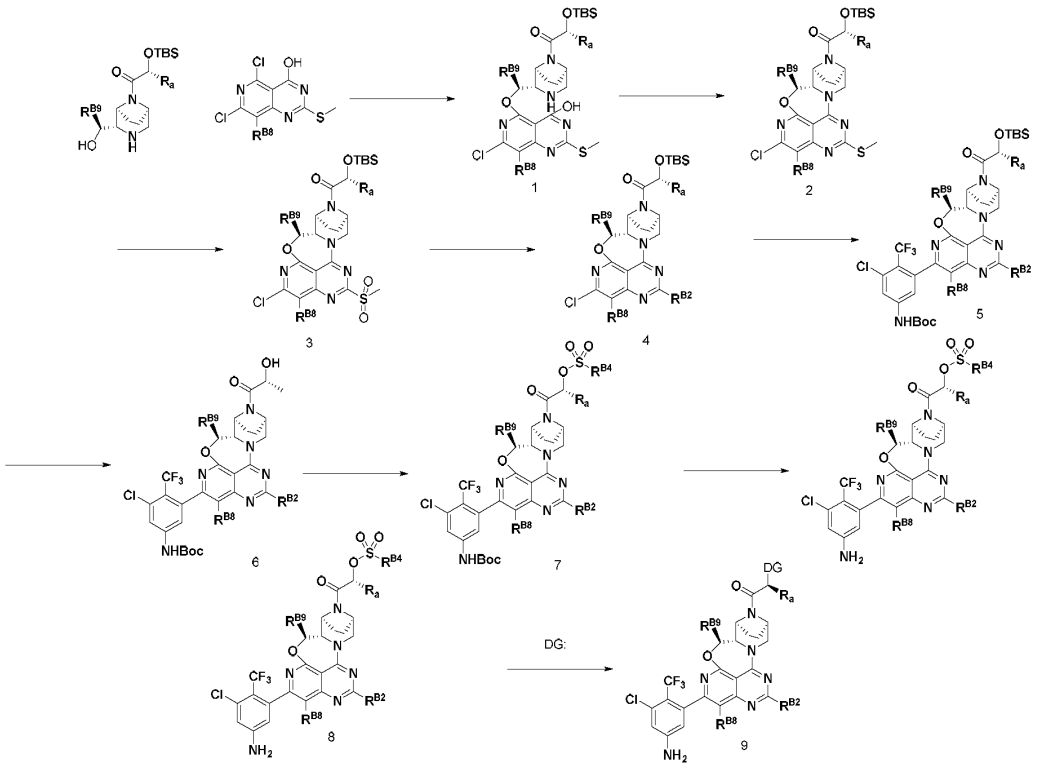
[327] General Scheme 9



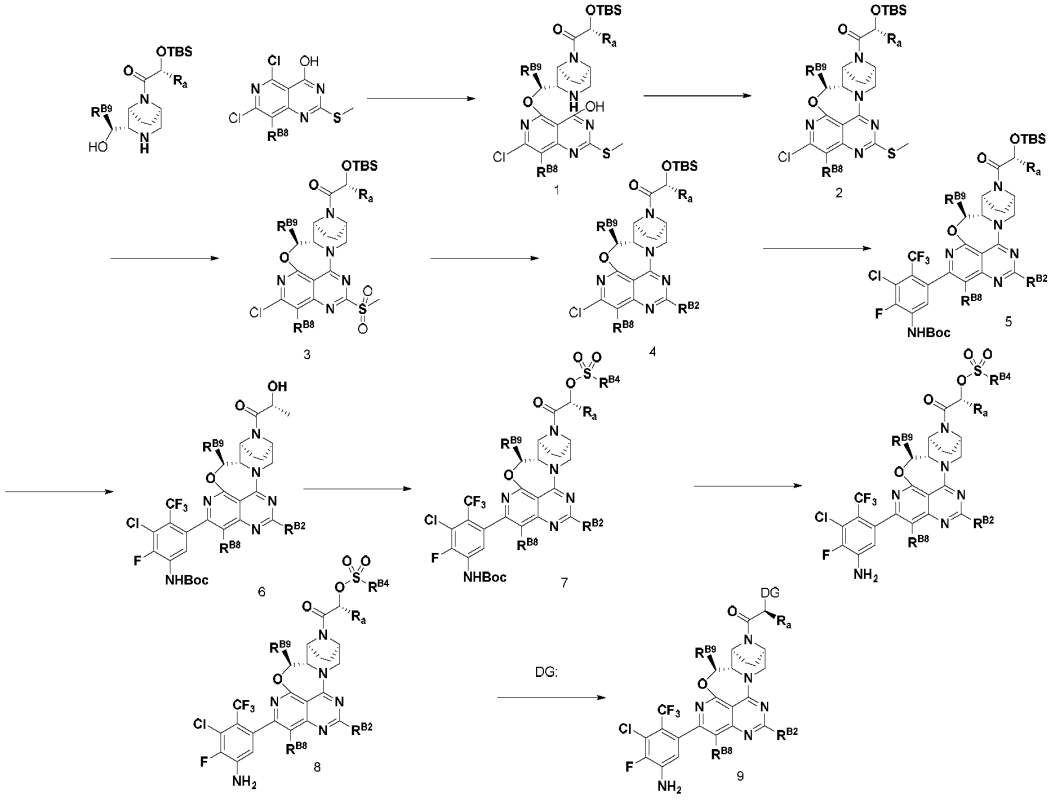
[328] General Scheme 10



[329] General Scheme 11



[330] General Scheme 12

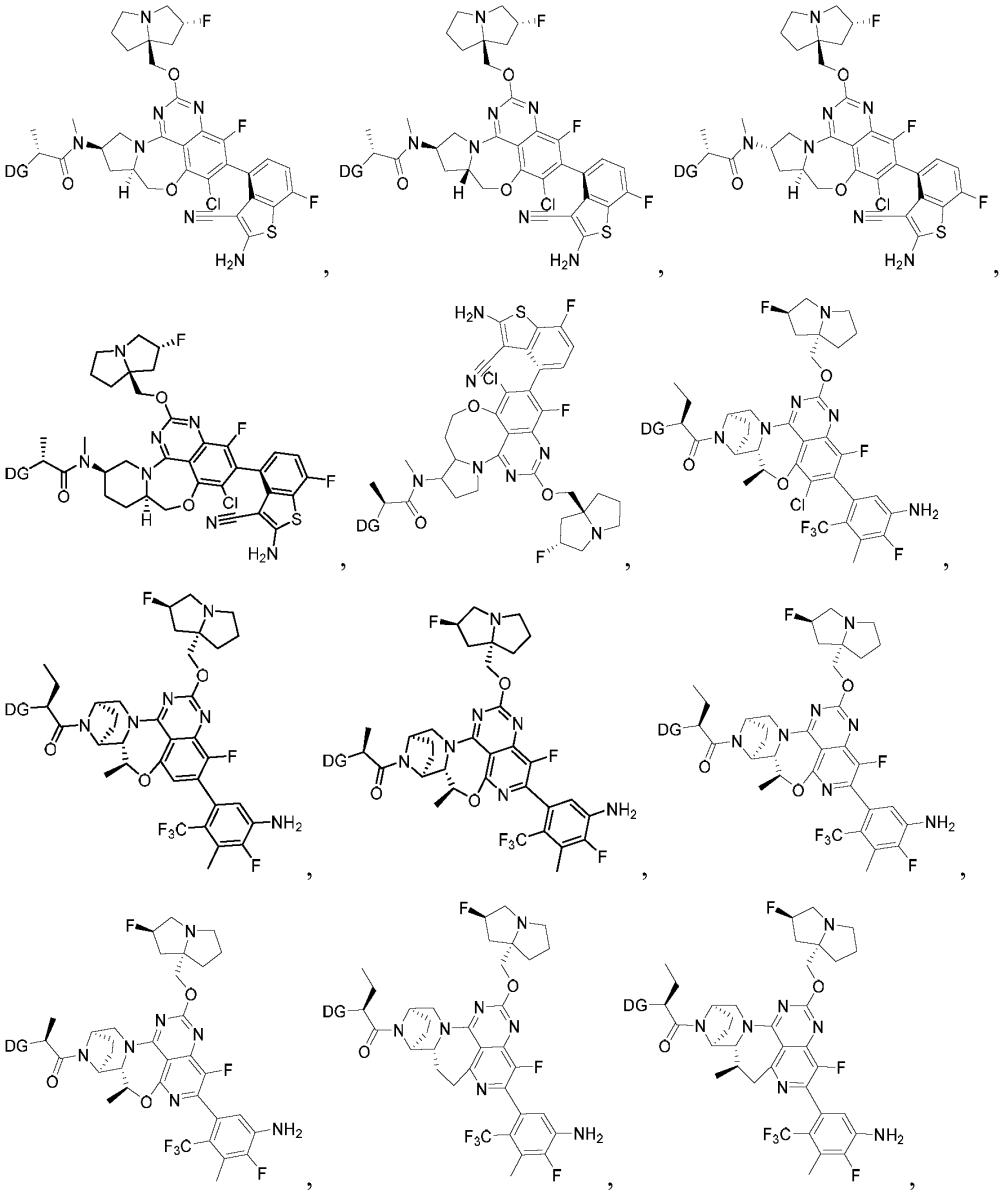


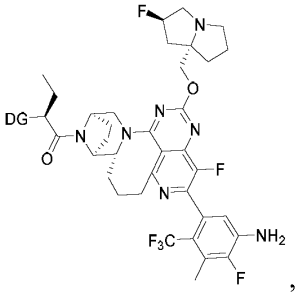
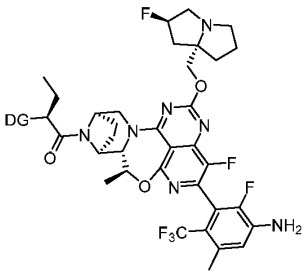
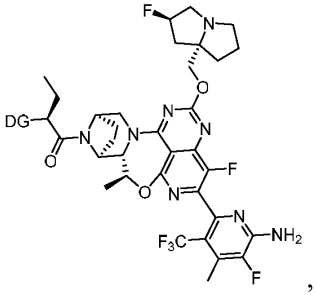
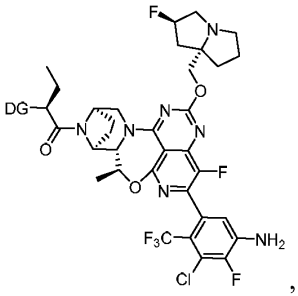
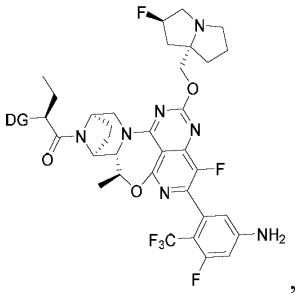
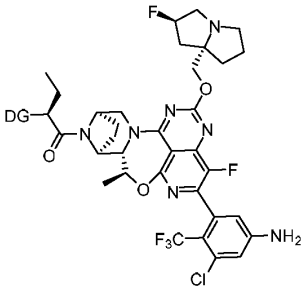
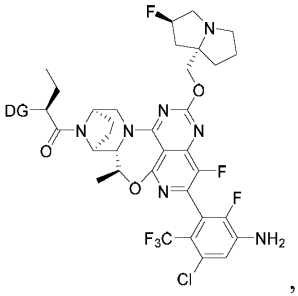
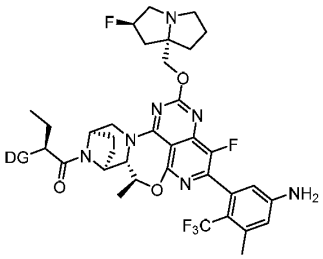
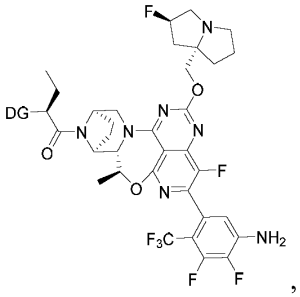
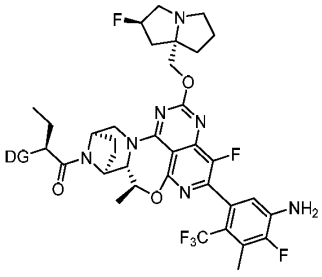
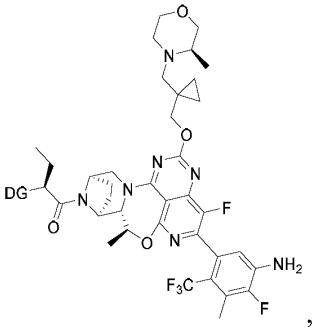
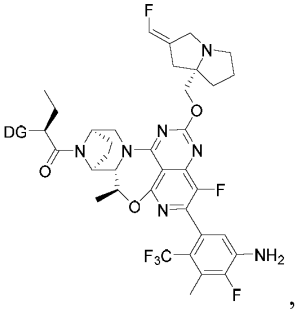
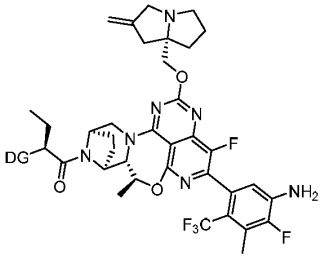
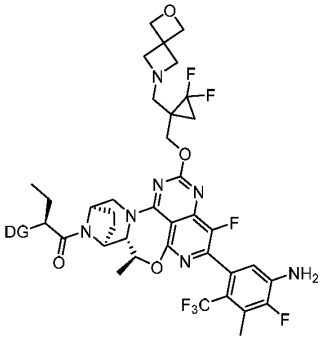
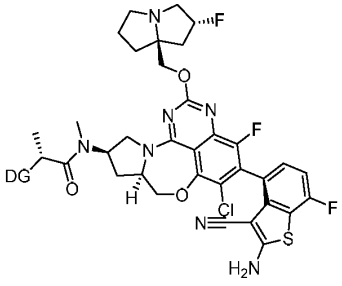
[331] In embodiments of the General Schemes 1-12, X^1 is selected from N and C(R_g); R_a, R_b, R_c, R_d, R_e, and R_f are independently selected from the values of the variables at the corresponding positions of the formulae in any aspect or embodiment described herein. All variables in General Schemes 1-12 that are recited in any aspect or embodiment herein are selected from the values of each corresponding variable in the formulae of the aspect or embodiment.

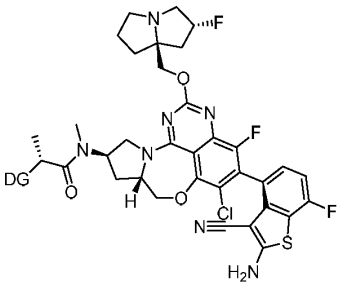
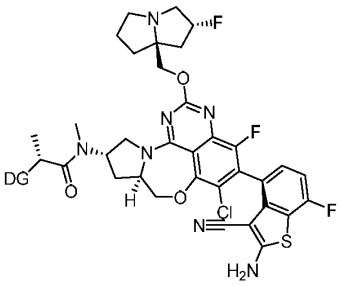
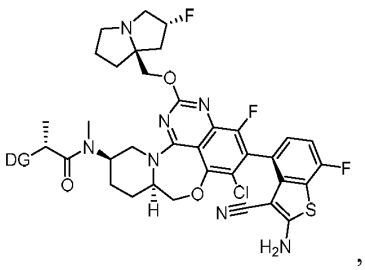
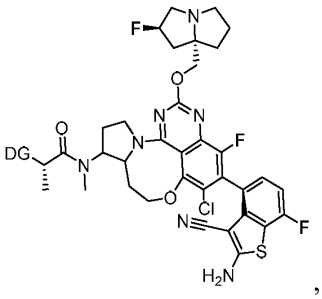
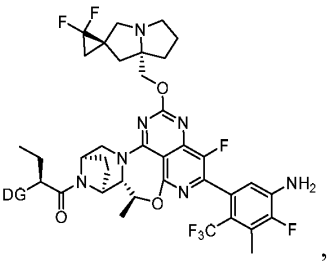
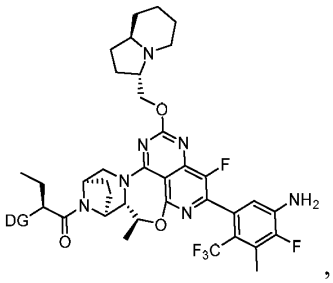
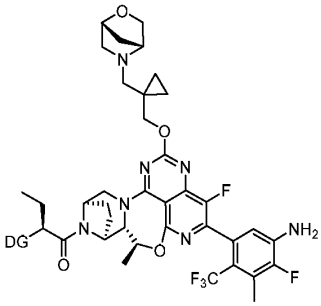
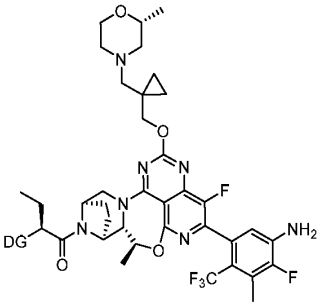
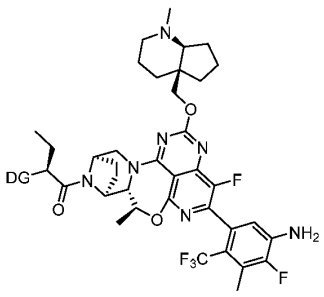
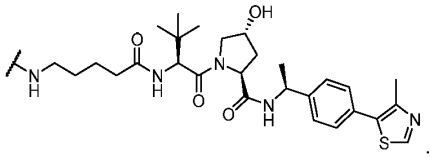
[332] In certain aspects, the present disclosure provides a compound selected from Table 1, or a pharmaceutically acceptable salt or solvate thereof. In certain aspects, the present disclosure provides a pharmaceutical composition comprising (i) a compound described herein (including compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a pharmaceutically acceptable salt or solvate thereof, and (ii) a pharmaceutically acceptable excipient. In embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), encompasses a compound of Table 1. In embodiments, a compound of Table 1 is a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6). In embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6), encompasses a compound of Table 1. In embodiments, a compound of Table 1 is a compound of Formula (A0),

(A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), or (A1-6). In embodiments, a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), encompasses a compound of Table 1. In embodiments, a compound of Table 1 is a compound of Formula (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6).

[333] In some embodiments, the present disclosure provides a degrader selected from:




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, or a pharmaceutically acceptable salt thereof, wherein DG is

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[334] In some embodiments, the present disclosure provides a compound selected from:

(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxopropan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl cyclopropanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxopropan-2-yl cyclopropanesulfonate;

(R)-1-((5aR,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5R,5aR,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((6aR,7S,10R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-15-yl)-1-oxobutan-2-yl ethanesulfonate;

(2R)-1-((5S,5aS,6S,9R)-2-(3-amino-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(6-amino-5-fluoro-4-methyl-3-(trifluoromethyl)pyridin-2-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]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-fluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(2R)-1-((5S,5aS,6S,9R)-2-(3-amino-5-chloro-2-fluoro-6-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3,4-difluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-(((R)-3-methylmorpholino)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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((S,Z)-2-(fluoromethylene)tetrahydro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((S)-2-methylenetetrahydro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(2R)-1-((5S,5aS,6S,9R)-12-((1-((2-oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-2,2-difluorocyclopropyl)methoxy)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((3S,8aR)-octahydroindolizin-3-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-12-((1-(((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-(((R)-2-methylmorpholino)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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((4aS,7aS)-1-methyloctahydro-4aH-cyclopenta[b]pyridin-4a-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-14-yl)-1-oxobutan-2-yl ethanesulfonate;

(2S)-1-(((2R,12aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,12,12a-tetrahydro-1H-pyrrolo[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-2-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate;

(2S)-1-(((2R,12aS)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,12,12a-tetrahydro-1H-pyrrolo[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-2-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate;

(2S)-1-(((2S,12aS)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,12,12a-tetrahydro-1H-pyrrolo[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-2-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate;

(2S)-1-(((2S,12aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,12,12a-tetrahydro-1H-pyrrolo[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-2-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate;

(S)-1-(((2R,5aR,8R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,8,9-hexahydropyrido[2',1':3,4][1,4]oxazepino[5,6,7-

de]quinazolin-8-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate;

(2R)-1-(((9S)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-1-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate;

(2S)-1-(((8aR,10R)-5-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,10,11-tetrahydro-8H-pyrrolo[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-10-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate;

(2S)-1-(((8aS,10R)-5-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,10,11-tetrahydro-8H-pyrrolo[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-10-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate;

(2S)-1-(((8aR,10S)-5-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,10,11-tetrahydro-8H-pyrrolo[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-10-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate;

(2S)-1-(((5aR,8R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,8,9-hexahydropyrido[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-8-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate; and

(2R)-1-((9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-1-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate;

or a pharmaceutically acceptable salt thereof. These compounds may be used in the preparation of the degraders in the preceding paragraph.

[335] It will be understood that when a compound is described as "inhibiting" a target (e.g., Ras, K-Ras, mutant Ras, mutant K-Ras such as K-Ras G12D) or a compound is described as an "inhibitor" of a target, the compound may reduce the inherent activity of the target (e.g., as measured by a biochemical, cell-based, or in vivo measurement assay) or the compound may reduce the level of expression of the target in an assay, cell, animal (e.g., rodent, monkey, dog), or human subject. For example, a compound may inhibit a target by reducing the level of the target protein in a cell or subject and thereby reducing the activity of the target in cell relative to the absence of the compound. In embodiments, a compound may inhibit a target by increasing the rate of degradation of the target protein compared to the rate of degradation of the target protein in the absence of the compound. In embodiments, a compound may inhibit a target by increasing the degradation of the target protein compared to the absence of the compound and thereby reducing the amount of the target protein present in a cell, subject, or assay.

[336] In some embodiments, a compound disclosed herein inhibits wildtype K-Ras or K-Ras G12D with an IC_{50} of less than 500 nM, such as less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, less than 90 nM, less than 80 nM, less than 70 nM, less than 60 nM, less than 50 nM, less than 40 nM, less than 30 nM, less than 20 nM, or less than 10 nM, as assessed by an in vitro assay described herein. In some embodiments, a compound described herein inhibits proliferation of a cell line that expresses K-Ras or K-Ras G12D with an IC_{50} of less than 5000 nM, such as less than 4000 nM, less than 3000 nM, less than 2000 nM, less than 1000 nM, less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, or less than 100 nM, as assessed by an in vitro cell proliferation assay.

[337] In some embodiments, a compound disclosed herein, exhibits selective and potent inhibition of K-Ras G12D relative to wildtype K-Ras or other K-Ras mutants (e.g., K-Ras G12V, K-Ras G12S, or K-Ras G12C).

[338] In some embodiments, a compound described herein, such as a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), is provided as a substantially pure stereoisomer. In some embodiments, the stereoisomer is provided in at least 80% enantiomeric excess, such as at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.9% enantiomeric excess.

[339] In some embodiments, the present disclosure provides an atropisomer of a compound described herein, such as a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6). In some embodiments, the atropisomer is provided in enantiomeric excess. In some embodiments, the atropisomer is provided in at least 80% enantiomeric excess, such as at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.9% enantiomeric excess. In some embodiments, a compound described herein is preferably used as a non-racemic mixture, wherein one atropisomer is present in excess of its corresponding enantiomer or epimer. Typically, such mixture contains a mixture of the two isomers in a ratio of at least 9:1, preferably at least 19:1. In some embodiments, the atropisomer is provided in at least 96% enantiomeric excess, meaning the compound has less than 2% of the corresponding enantiomer. In some embodiments, the atropisomer is provided in at least 96% diastereomeric excess, meaning the compound has less than 2% of the corresponding diastereomer.

[340] The term "atropisomers" refers to conformational stereoisomers which occur when rotation about a single bond in the molecule is prevented, restricted, or greatly slowed as a result of steric interactions with other parts of the molecule and wherein the substituents at both ends of the single bond are asymmetrical (i.e., optical activity arises without requiring an asymmetric carbon center or stereocenter). Where the rotational barrier about the single bond is high enough, and interconversion between conformations is slow enough, separation and isolation of the isomeric species may be permitted. Atropisomers are enantiomers (or epimers) without a single asymmetric atom. Atropisomers are typically considered stable if the barrier to interconversion is high enough to permit the atropisomers to undergo little or no interconversion at room temperature for a least a week, preferably at least a year. In some embodiments, an atropisomeric compound of the disclosure does not undergo more than about 5% interconversion to its opposite atropisomer at room temperature during one week when the atropisomeric compound is in substantially pure form, which is generally a solid state. In some embodiments, an atropisomeric compound of the disclosure does not undergo more than about 5% interconversion to its opposite atropisomer at room temperature (approximately 25 °C) during one year. The present chemical entities, pharmaceutical compositions, and methods are meant to include all such possible atropisomers, including racemic mixtures, diastereomeric mixtures, epimeric mixtures, optically pure forms of single atropisomers, and intermediate mixtures.

[341] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[342] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases or inorganic or organic acids to form a pharmaceutically acceptable salt. In some embodiments, such salts are prepared *in situ* during the final isolation and purification of the compounds described herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[343] In some embodiments, the compounds described herein exist as solvates. In some embodiments are methods of treating diseases by administering such solvates. Further described herein are methods of treating diseases by administering such solvates as pharmaceutical compositions.

[344] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein are conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein are conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran, or MeOH. In addition, the compounds provided herein exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[345] A "degradation enhancer" is a compound capable of binding a ubiquitin ligase protein (e.g., E3 ubiquitin ligase protein) or a compound capable of binding a protein that is capable of binding to a ubiquitin ligase protein to form a protein complex capable of conjugating a ubiquitin protein to a target protein. In some embodiments, the degradation enhancer is capable of binding to an E3 ubiquitin ligase protein or a protein complex comprising an E3 ubiquitin ligase protein. In some embodiments, the degradation enhancer is capable of binding to an E2 ubiquitin-conjugating enzyme. In some embodiments, the degradation enhancer is capable of binding to a protein complex comprising an E2 ubiquitin-conjugating enzyme and an E3 ubiquitin ligase protein.

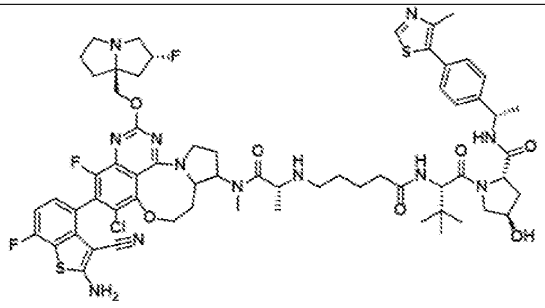
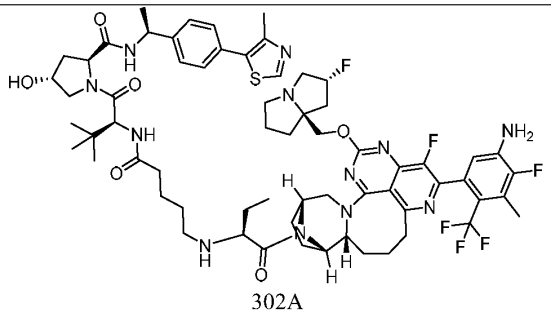
[346] In some embodiments, the degradation enhancer is capable of binding a protein selected from E3A, mdm2, APC, EDD1, SOCS/BC-box/eloBC/CUL5/RING, LNXp80, CBX4, CBLL1, HACE1, HECTD1, HECTD2, HECTD3, HECTD4, HECW1, HECW2, HERC1, HERC2, HERC3, HERC4, HER5, HERC6, HUWE1, ITCH, NEDD4, NEDD4L, PPIL2, PRPF19, PIAS1, PIAS2, PIAS3, PIAS4, RANBP2, RNF4, RBX1, SMURF1, SMURF2, STUB1, TOPORS, TRIP12, UBE3A, UBE3B, UBE3C, UBE3D, UBE4A, UBE4B, UBOX5, UBR5, VHL (von-Hippel-Lindau ubiquitin ligase), WWP1, WWP2, Parkin, MKRN1, CMA (chaperon-mediated autophage), SCFb-TRCP (Skip-Cullin-F box (Beta-TRCP) ubiquitin complex), b-TRCP (b-transducing repeat-containing protein), cIAP1 (cellular inhibitor of apoptosis protein 1), APC/C (anaphase-promoting complex/cyclosome), CRBN (cereblon), CUL4-RBX1-DDB1-CRBN ($CRL4^{CRBN}$) ubiquitin ligase, XIAP, IAP, KEAP1, DCAF15, RNF114, DCAF16, AhR, SOCS2, KLHL12, UBR2, SPOP, KLHL3, KLHL20, KLHDC2, SPSB1, SPSB2, SPSB4, SOCS6, FBXO4, FBXO31, BTRC, FBW7, CDC20, PML, TRIM21, TRIM24, TRIM33, GID4, avadomide, iberdomide, and CC-885. In some embodiments, the degradation enhancer is capable of binding a protein selected from UBE2A, UBE2B, UBE2C, UBE2D1, UBE2D2, UBE2D3, UBE2DR, UBE2E1, UBE2E2, UBE2E3, UBE2F, UBE2G1, UBE2G2, UBE2H, UBE2I, UBE2J1, UBE2J2, UBE2K, UBE2L3, UBE2L6, UBE2L1, UBE2L2, UBE2L4, UBE2M, UBE2N, UBE2O, UBE2Q1, UBE2Q2, UBE2R1, UBE2R2, UBE2S, UBE2T, UBE2U, UBE2V1, UBE2V2, UBE2W, UBE2Z, ATG3, BIRC6, and UFC1. In some embodiments, the degradation enhancer is a compound described in Ishida and Ciulli, SLAS Discovery 2021, Vol. 25(4) 484-502, which is incorporated by

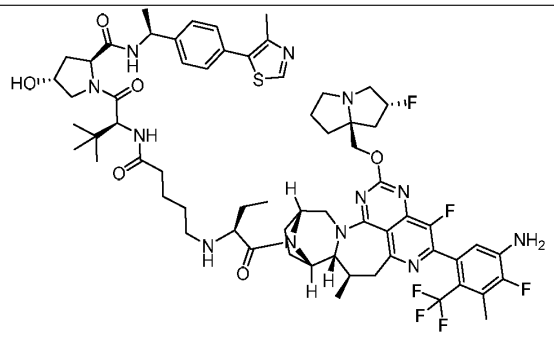
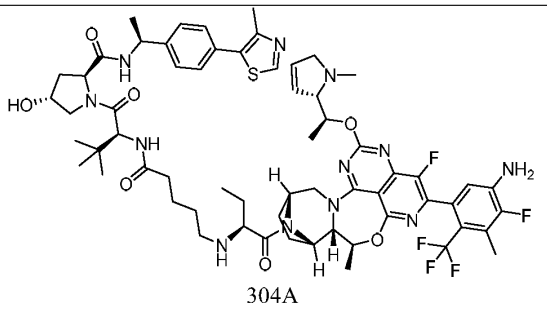
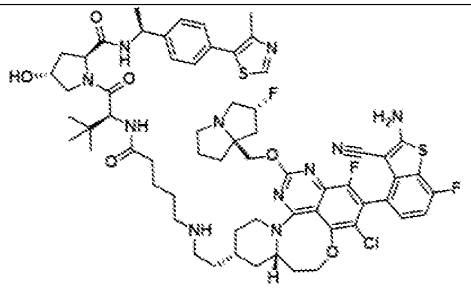
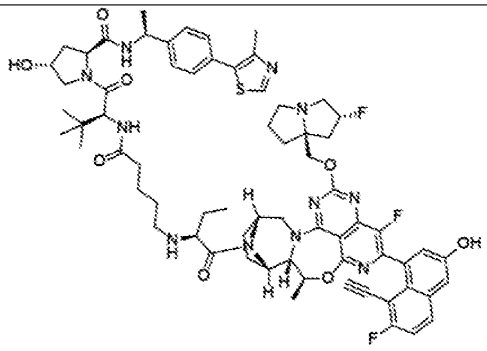
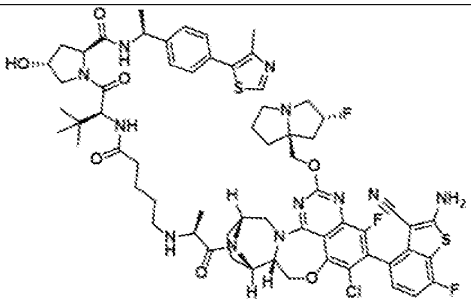
reference in its entirety for any purpose, for example VH032, VH101, VH298, thalidomide, bestatin, methyl bestatin, nutlin, idasanutlin, bardoxolone, bardoxolone methyl, indisulam (E7070), E7820, chloroquinoxaline sulfonamide (CQS), nimbolide, KB02, ASTX660, lenalidomide, or pomalidomide.

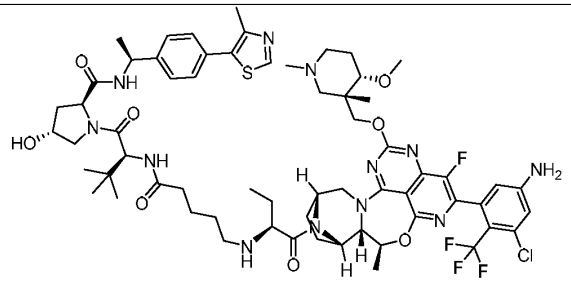
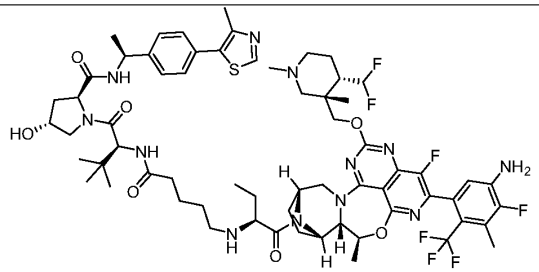
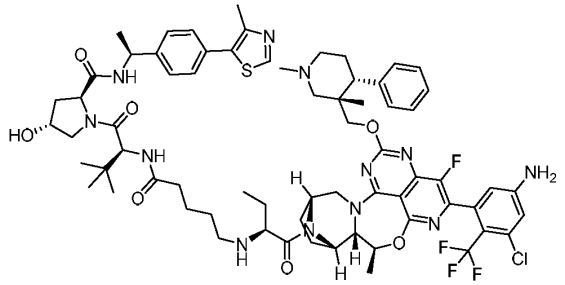
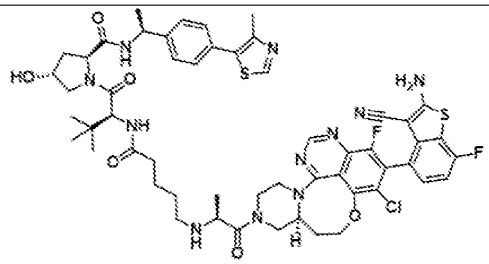
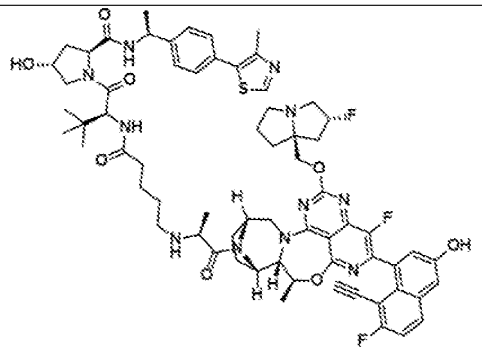
[347] In some embodiments, the degradation enhancer is a compound described in US20180050021, WO2016146985, WO2018189554, WO2018119441, WO2018140809, WO2018119448, WO2018119357, WO2018118598, WO2018102067, WO201898280, WO201889736, WO201881530, WO201871606, WO201864589, WO201852949, WO2017223452, WO2017204445, WO2017197055, WO2017197046, WO2017180417, WO2017176958, WO201711371, WO2018226542, WO2018223909, WO2018189554, WO2016169989, WO2016146985, CN105085620B, CN106543185B, US10040804, US9938302, US10144745, US10145848, US9938264, US9632089, US9821068, US9758522, US9500653, US9765019, US8507488, US8299057, US20180298027, US20180215731, US20170065719, US20170037004, US20160272639, US20150291562, or US20140356322, each of which is incorporated by reference in its entirety for any purpose.

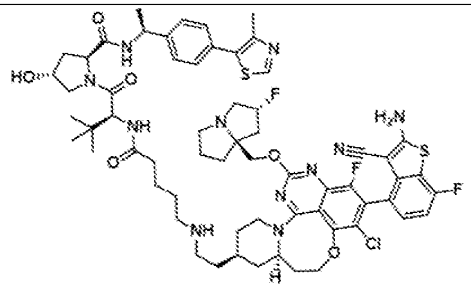
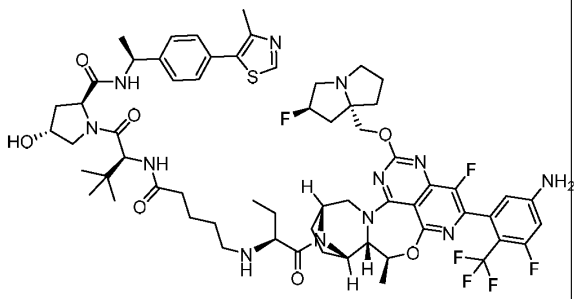
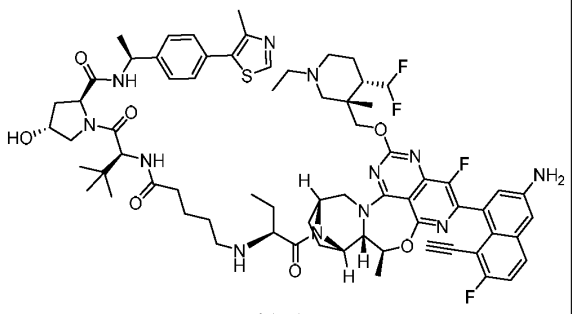
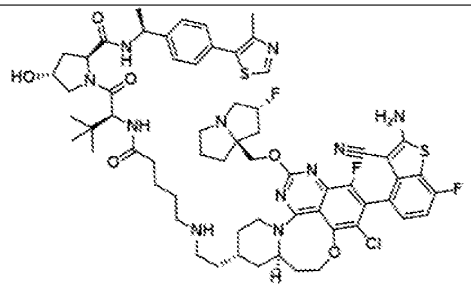
[348] In some embodiments, exemplary compounds may include, but are not limited to, a compound selected from **Table 1**, or a salt or solvate thereof. In the table below, "No." is the compound number of the Compound of Formula (a) for that cell.

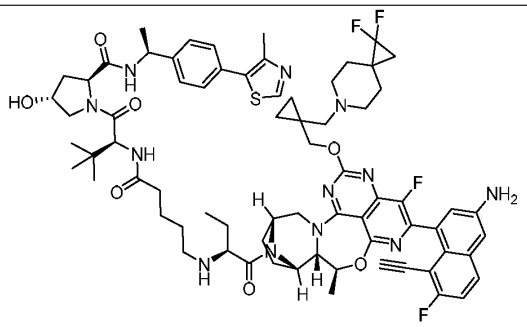
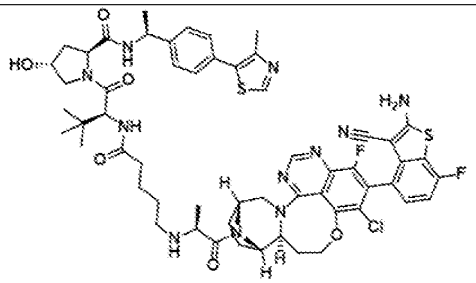
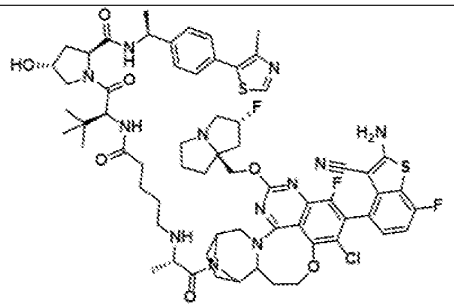
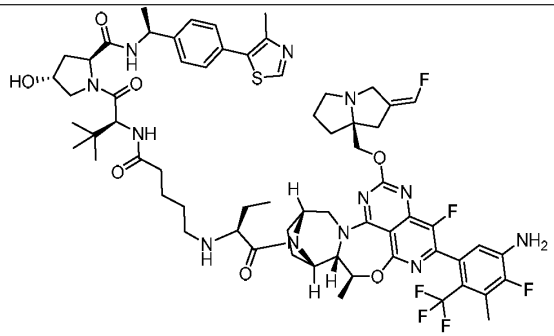
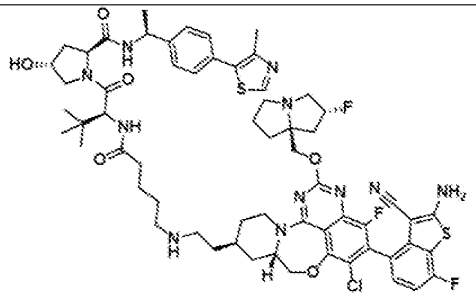
Table 1

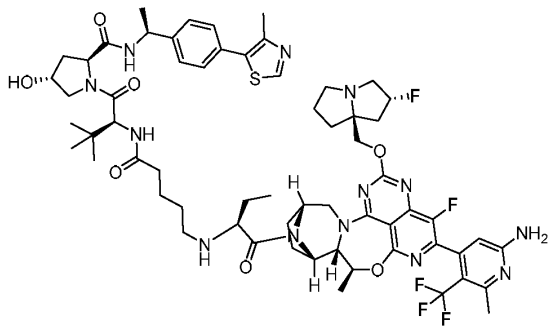
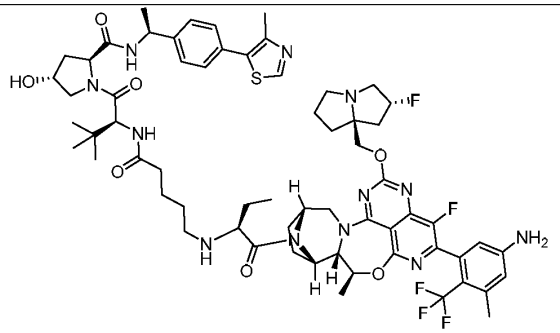
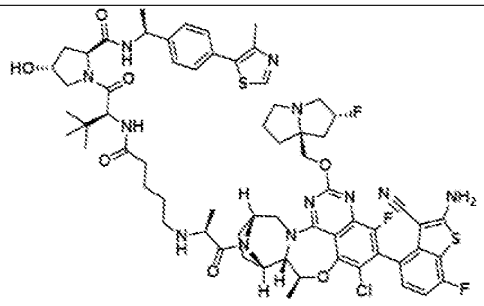
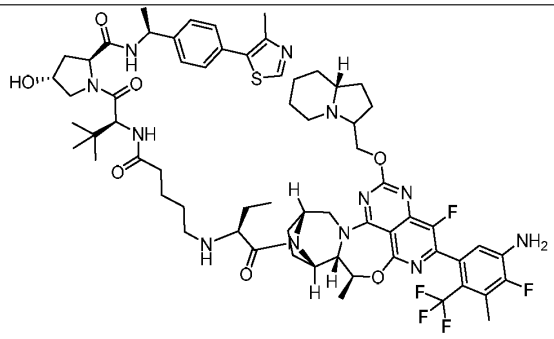
No.	Compound of Formula (a)	Compound of Formula (A)	Compound of Formula (A) MW (g/mol)
301[2]	(2S)-1-((9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-1-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 834.3)	 301A	1267.9
302[7]	(R)-1-((6aR,7S,10R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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]cyclooct a[1,2,3-de]naphthalen-15-yl)-1-oxobutan-2-yl cyclopropanesulfonate ([M+H]$^+$= 838.5)	 302A	1259.5

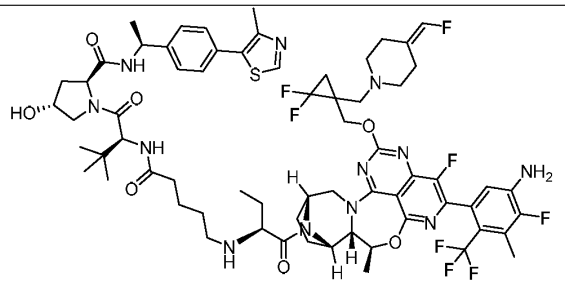
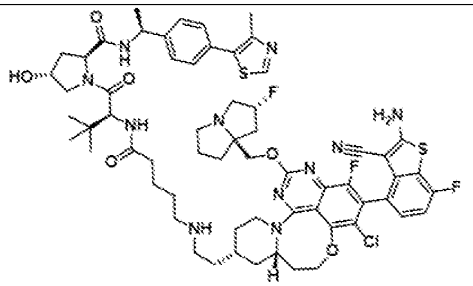
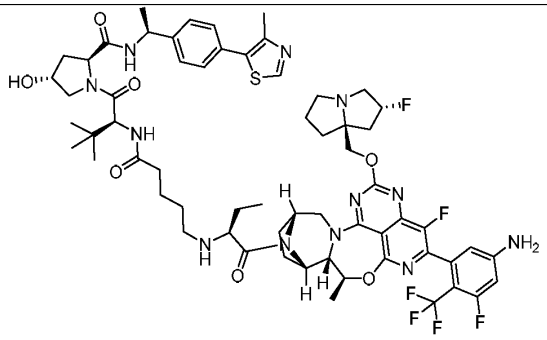
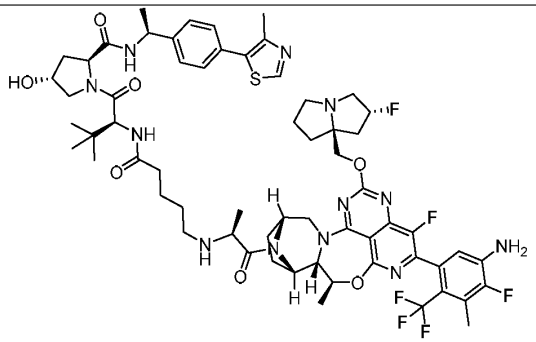
303[7]	(R)-1-((5R*,5aR,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 826.3)	 303A	1259.5
304[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methyl-2,5-dihydro-1H-pyrrol-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 796.5)	 304A	1229.4
305[2]	2-((6aS,8R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,6a,7,8,9,10-hexahydro-5H-pyrido[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-8-yl)ethyl ethanesulfonate ([M+H]$^+$= 790.9)	 305A	1224.9
306[7]	(R)-1-((5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-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]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 822)	 306A	1254.5
307[6]	(2R)-1-((5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl dimethylsulfamate		1265.9

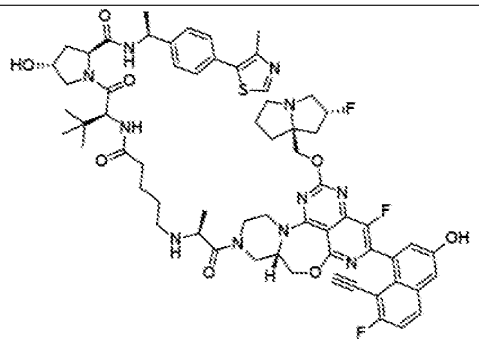
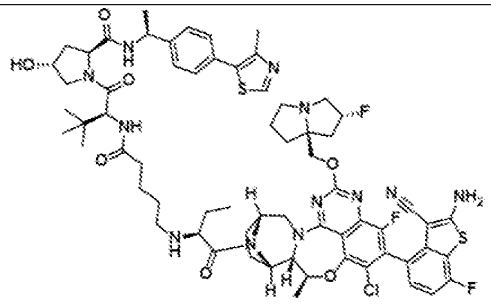
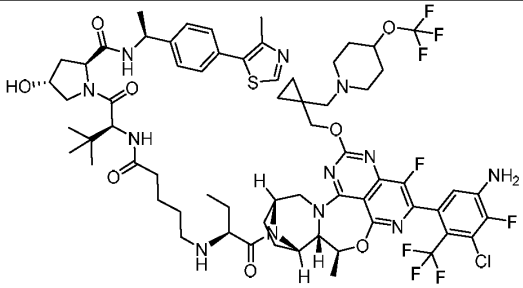
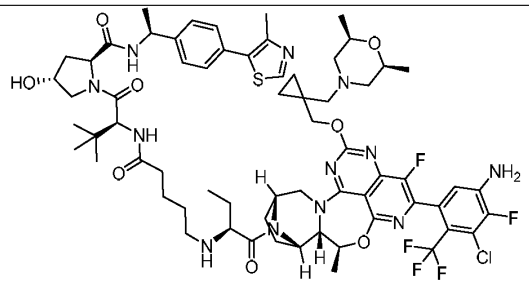
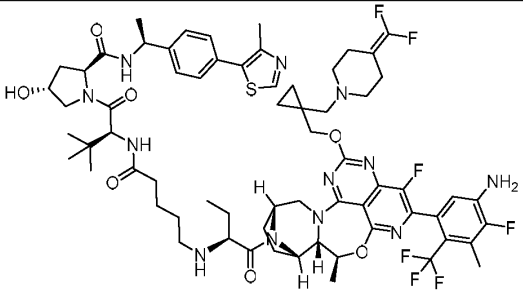
	([M+H]$^+$= 847.4)	307A	
308[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((3S,4S)-4-methoxy-1,3-dimethylpiperidin-3-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 845.6)	 308A	1277.9
309[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 862.6)	 309A	1295.5
310[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-12-(((3S,4R)-1,3-dimethyl-4-phenylpiperidin-3-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 890.6)	 310A	1324
311[2]	(2R)-1-((14aS)-10-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 663.2)	 311A	1096.7
312[7]	(R)-1-((5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-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]heptalen-14-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 807.4)		1240.5

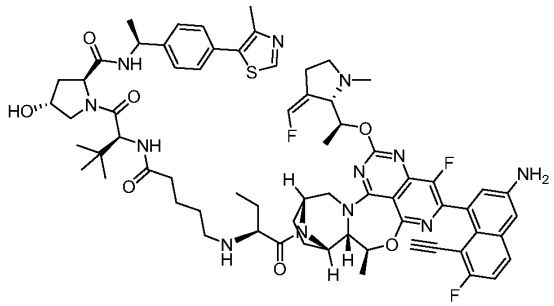
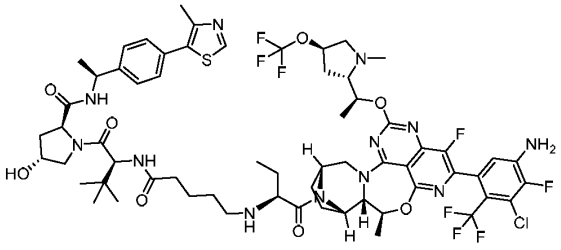
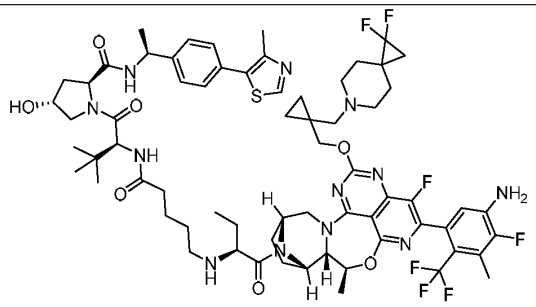
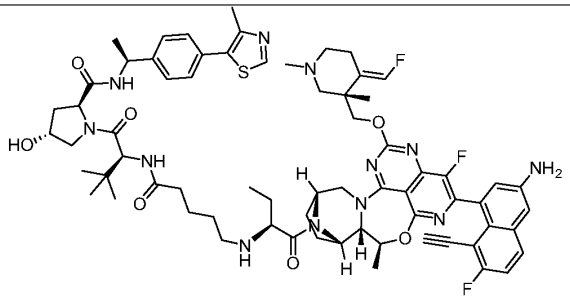
		312A	
313[2]	2-((6aR,8S)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,6a,7,8,9,10-hexahydro-5H-pyrido[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-8-yl)ethyl ethanesulfonate ([M+H]$^+$= 790.8)	 313A	1224.9
314[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-fluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl cyclopropanesulfonate ([M+H]$^+$= 826.6)	 314A	1261.4
315[7]	(R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-12-(((3S,4S)-4-(difluoromethyl)-1-ethyl-3-methylpiperidin-3-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 868.6)	 315A	1301.6
316[2]	2-((6aR,8R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,6a,7,8,9,10-hexahydro-5H-pyrido[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-8-yl)ethyl ethanesulfonate ([M+H]$^+$= 790.8)	 316A	1224.9

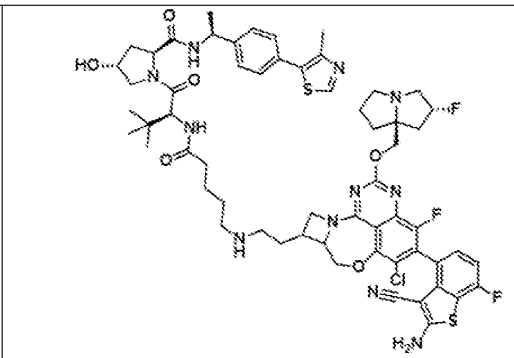
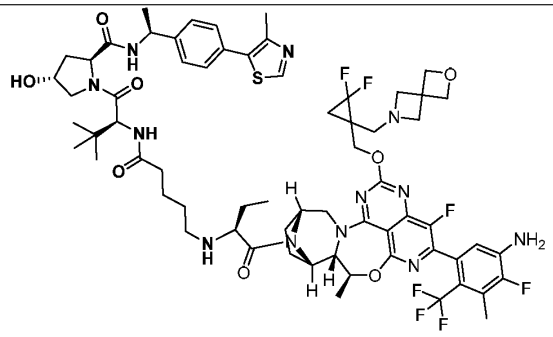
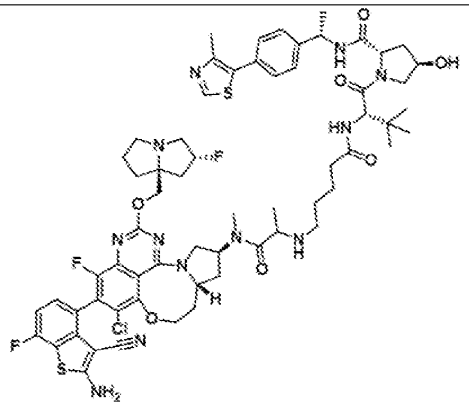
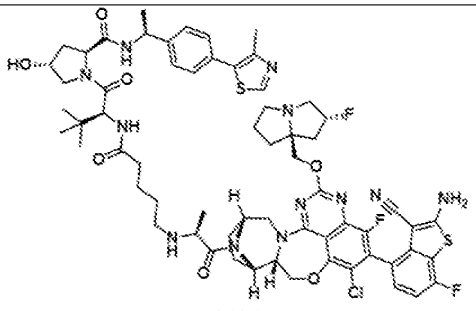
317[7]	(R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 892.6)	 317A	1325.6
318[2]	(2R)-1-((6aS,7S,10R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-7,10-epiminoazepino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-16-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 688.3)	 318A	1122.8
319[1]	(2R)-1-(2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-14-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-7,10-epiminoazepino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-16-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 846.3)	 319A	1279.9
320[1]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((S,Z)-2-(fluoromethylene)tetrahydro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 839.9)	 320A	1273.5
321[2]	2-((5aS,7S)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,8,9-hexahydropyrido[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-7-yl)ethyl ethanesulfonate ([M+H]$^+$= 776.7)	 321A	1210.9

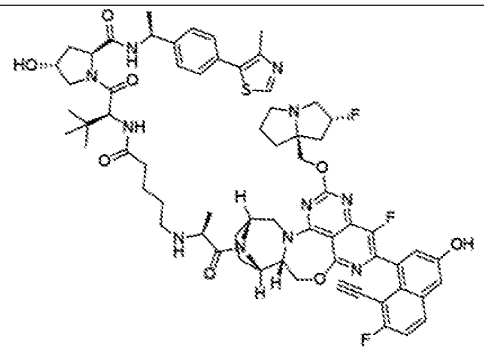
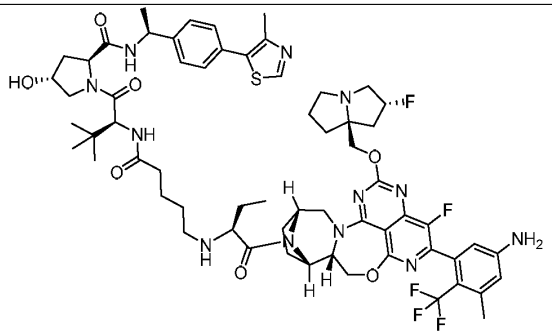
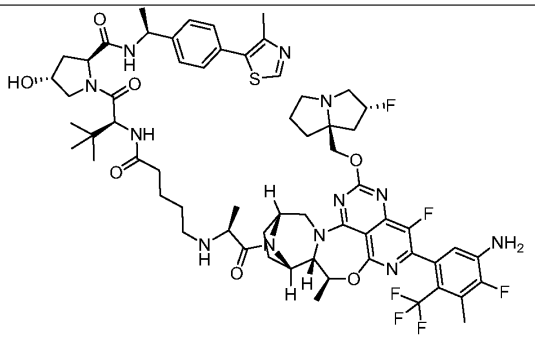
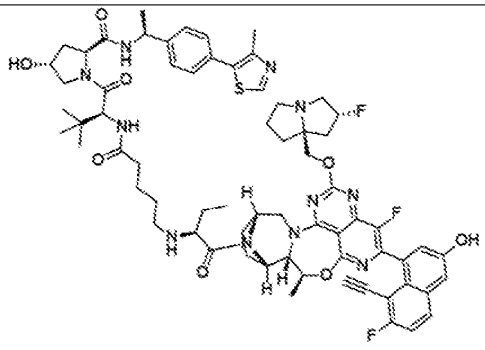
322[7]	(2R)-1-((5S,5aS,6S,9R)-2-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl cyclopropanesulfonate ([M+H]$^+$= 823.1)	 322A	1244.4
323[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl cyclopropanesulfonate ([M+H]$^+$= 822.2)	 323A	1243.5
324[5]	(2R)-1-((5S,5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)- 5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 846.4)	 324A	1279.9
325[6]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((8aR)-octahydroindolizin-3-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 824.6)	 325A	1257.5

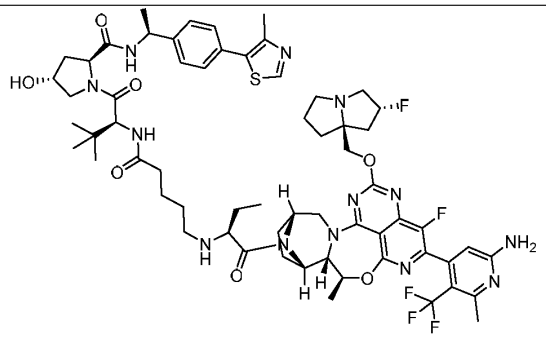
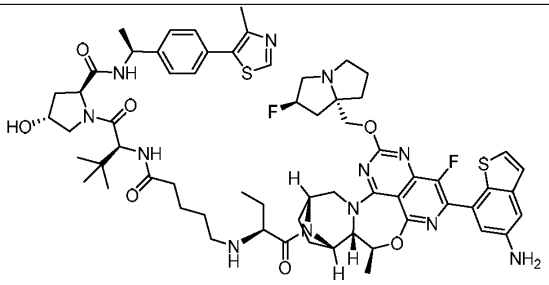
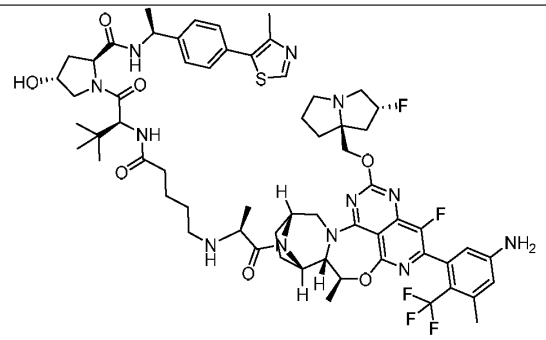
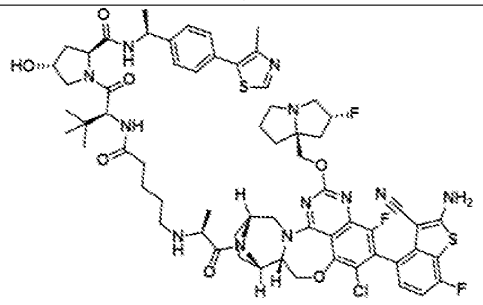
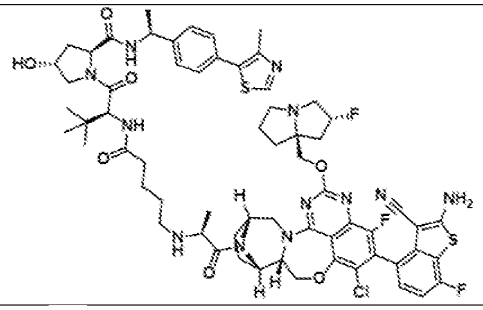
326[6]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((2,2-difluoro-1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 904.8)	 326A	1337.5
327[2]	2-((6aS,8R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,6a,7,8,9,10-hexahydro-5H-pyrido[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-8-yl)ethyl ethanesulfonate ([M+H]$^+$= 791.1)	 327A	1224.9
328[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-fluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 814.6)	 328A	1247.4
329[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 814.2)	 329A	1247.4

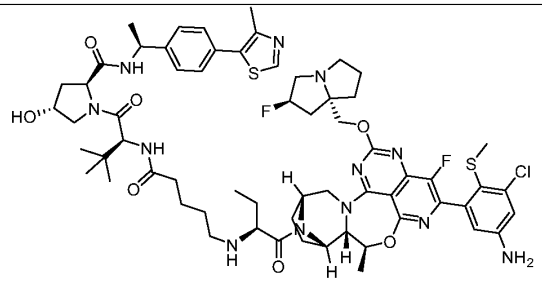
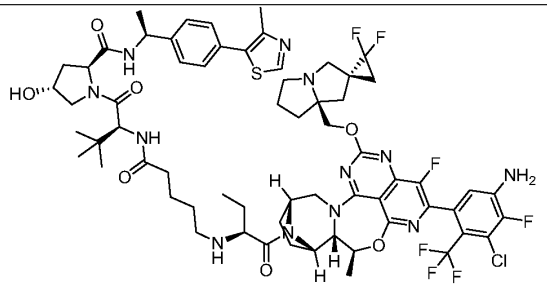
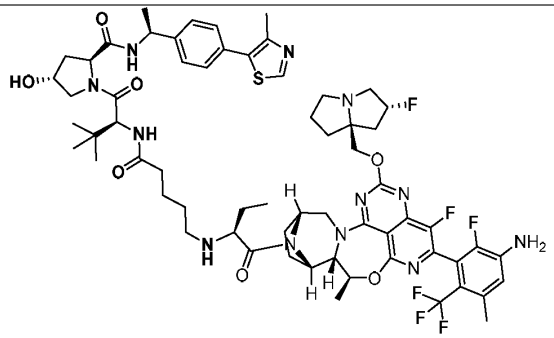
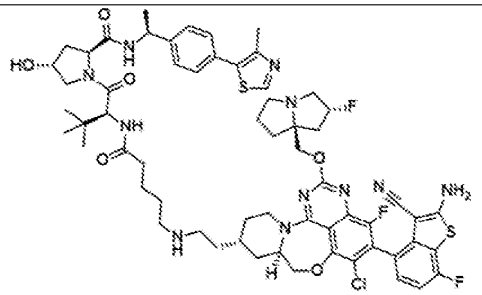
330[7]	(R)-1-((S)-5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8a,9,11,12-tetrahydro-7-oxa-1,3,6,10,12a-pentaazabenzo[4,5]cyclohepta[1,2,3-de]naphthalen-10(8H)-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 767.5)	 330A	1200.4
331[7]	(2R)-1-((5S,5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)- 5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxobutan-2-yl cyclopropanesulfonate ([M+H]$^+$= 872.3)	 331A	1294
332[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-((4-(trifluoromethoxy)piperidin-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 942.8)	 332A	1375.9
333[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-(((2S,6R)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 888.2)	 333A	1322
334[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((1-((4-(difluoromethylene)piperidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-		1319.5

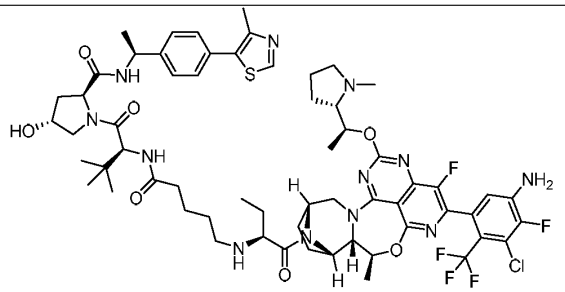
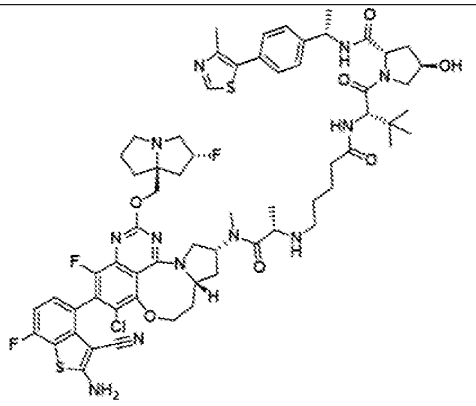
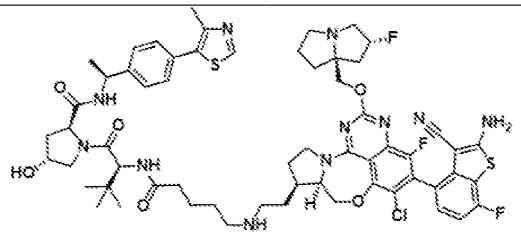
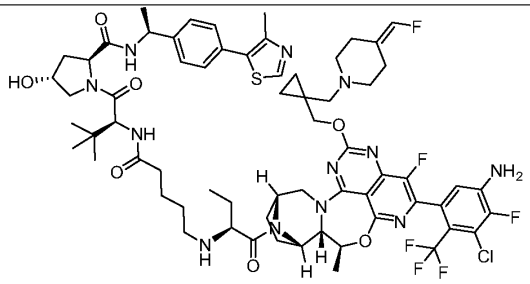
	2-yl ethanesulfonate ([M+H]$^+$= 886.6)	334A	
335[7]	(R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((S)-1-((S,Z)-3-(fluoromethylene)-1-methylpyrrolidin-2-yl)ethoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 820.6)	 335A	1253.5
336[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((2S,4R)-1-methyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 902.6)	 336A	1335.9
337[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 900.6)	 337A	1333.5
338[7]	(R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((S,E)-4-(fluoromethylene)-1,3-dimethylpiperidin-3-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 834.5)	 338A	1267.5

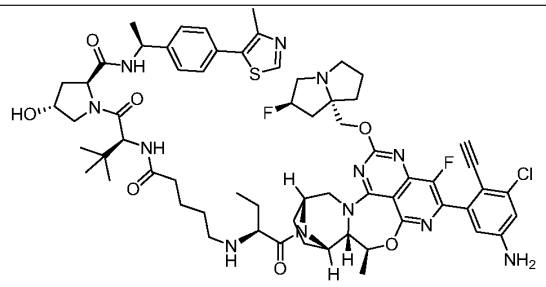
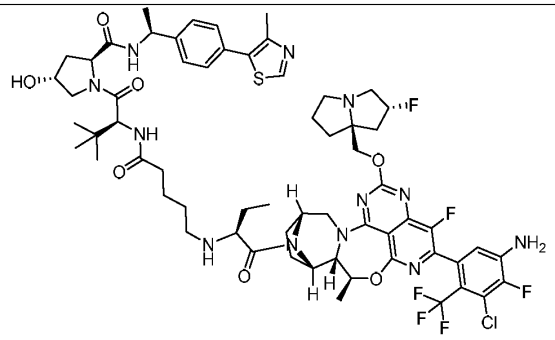
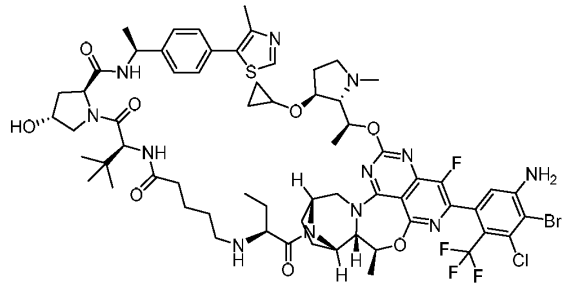
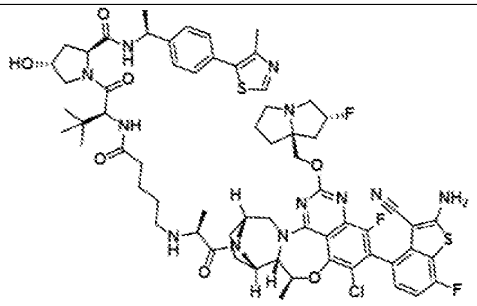
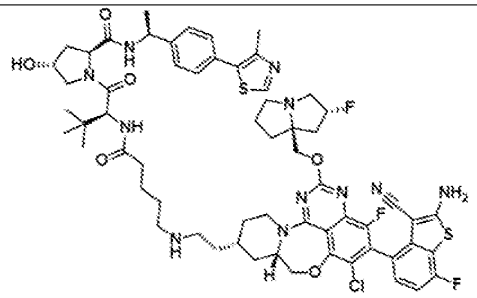
339[6]	2-(8-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-9-chloro-7-fluoro-5-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,11,11a-tetrahydroazeto[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-1-yl)ethyl ethanesulfonate ([M+H]$^+$= 748.8)	 339A	1182.8
340[1]	(2R)-1-((5S,5aS,6S,9R)-12-((1-((2-oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-2,2-difluorocyclopropyl)methoxy)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 888.2)	 340A	1321.4
341[1]	1-(((2S,13aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 834.1)	 341A	1267.9
342[7]	(2R)-1-((5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 832.4)	 342A	1265.9

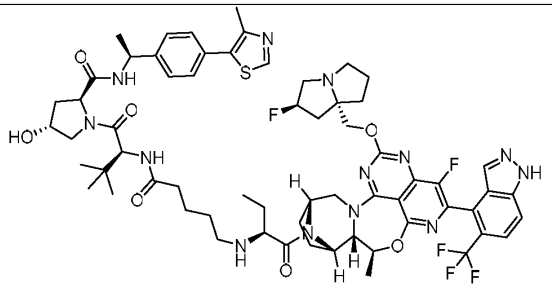
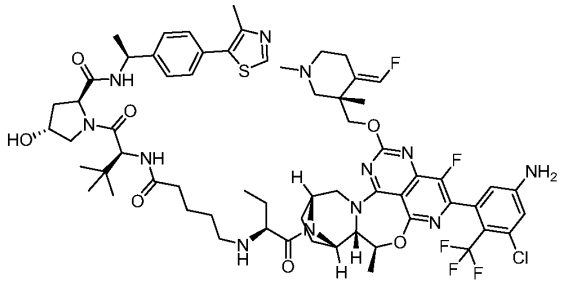
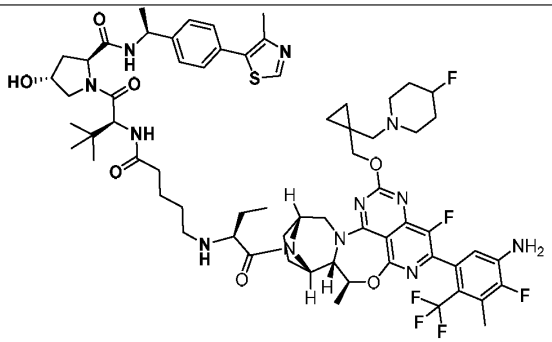
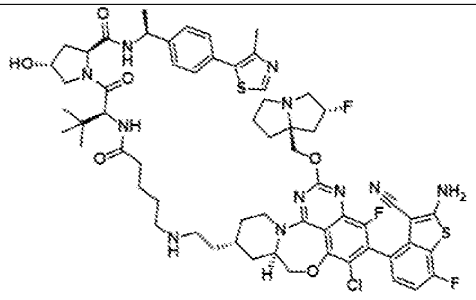
343[7]	(R)-1-((5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 793.4)	 343A	1226.4
344[7]	(R)-1-((5aS,6S,9R)-2-(5-amino-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 796.2)	 344A	1229.4
345[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxopropan-2-yl cyclopropanesulfonate ([M+H]$^+$= 826.3)	 345A	1247.4
346[7]	(R)-1-((5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-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]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 821.4)	 346A	1254.5

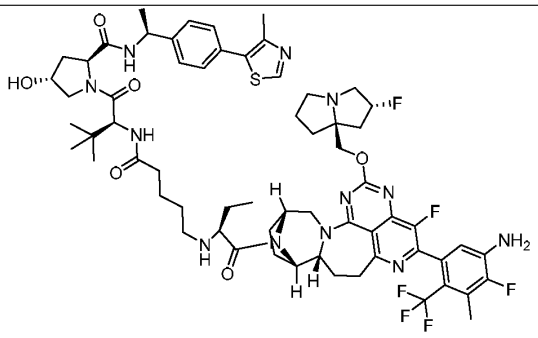
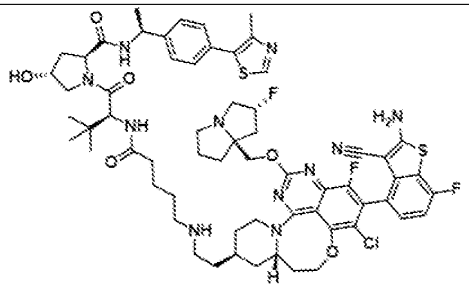
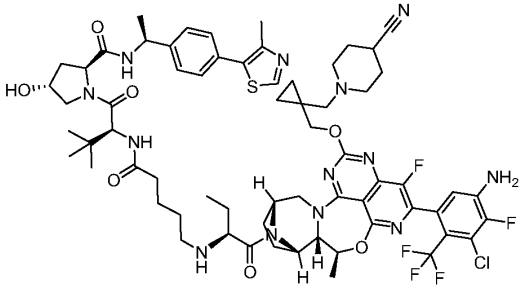
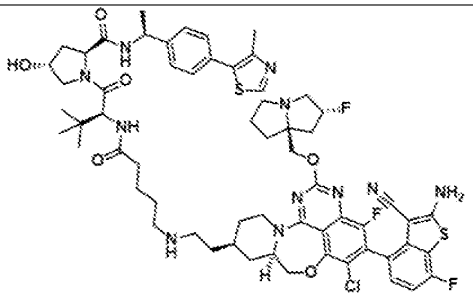
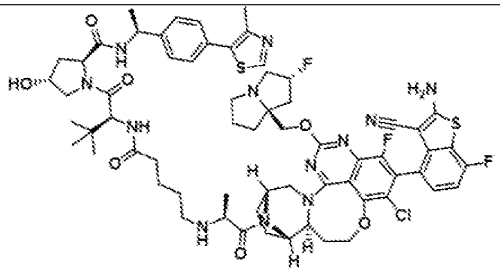
347[7]	(2R)-1-((5S,5aS,6S,9R)-2-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 811.3)	 347A	1244.4
348[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-aminobenzo[b]thiophen-7-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]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 784.4)	 348A	1217.5
349[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 796.3)	 349A	1229.4
350[5]	(2R)-1-((5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 832.4)	 350A	1265.9
351[2]	(2R)-1-((5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl ethanesulfonate		1265.9

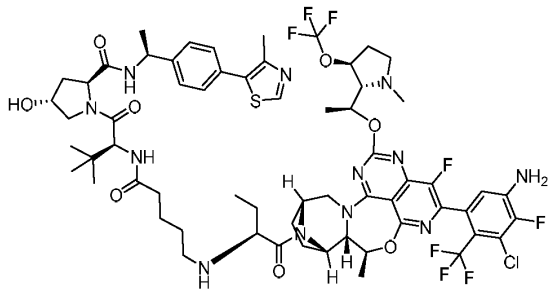
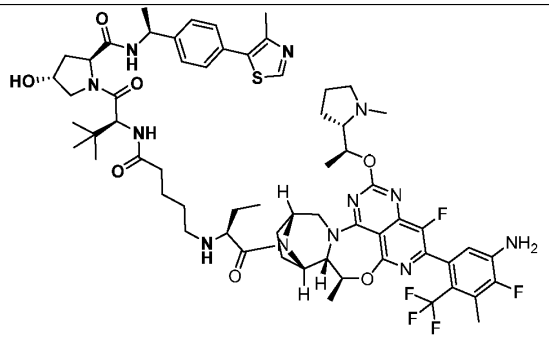
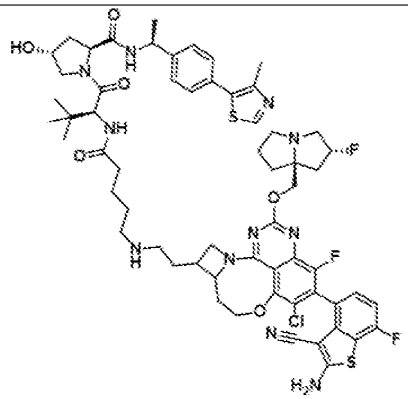
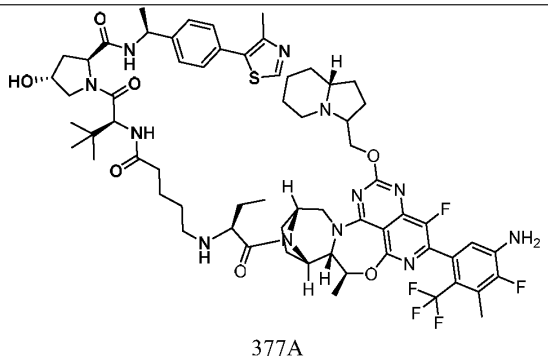
	([M+H]$^+$= 832.4)	351A	
352[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(methylthio)phenyl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 808.3)	 352A	1242
353[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl cyclopropanesulfonate ([M+H]$^+$= 904.6)	 353A	1325.9
354[1]	(2R)-1-((5S,5aS,6S,9R)-2-(3-amino-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 828.2)	 354A	1261.4
355[5]	2-((5aR,7R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,8,9-hexahydropyrido[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-7-yl)ethyl ethanesulfonate ([M+H]$^+$= 776.8)	 355A	1210.9
356[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-		1251.9

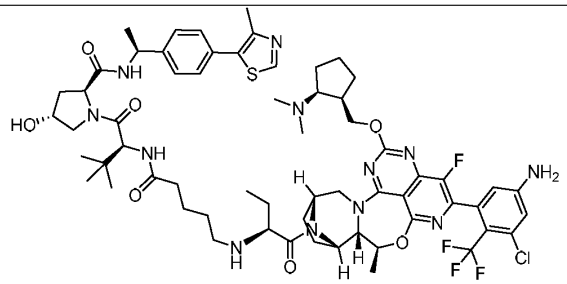
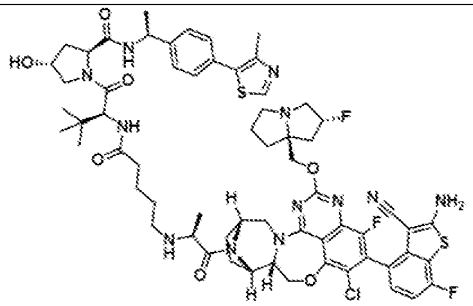
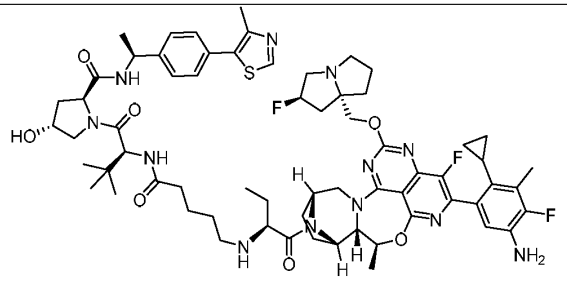
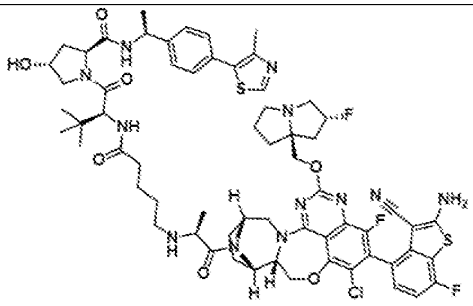
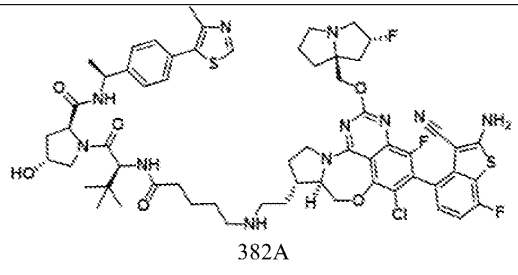
	2-yl ethanesulfonate ([M+H]$^+$= 818.4)	 356A	
357[7]	(2R)-1-(((2R,13aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 834.3)	 357A	1267.9
358[2]	2-((1R,12aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,12,12a-tetrahydro-1H-pyrrolo[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-1-yl)ethyl ethanesulfonate ([M+H]$^+$= 762.7)	 358A	1196.9
359[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)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-14-yl)-1-oxobutan-2-yl cyclopropanesulfonate ([M+H]$^+$= 900.9)	 359A	1321.9

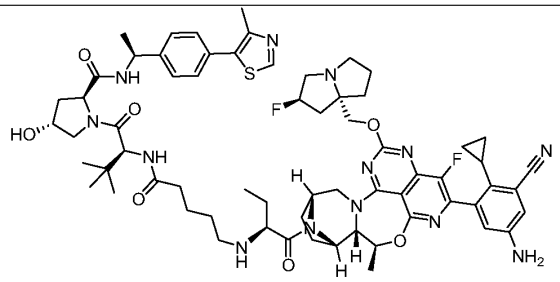
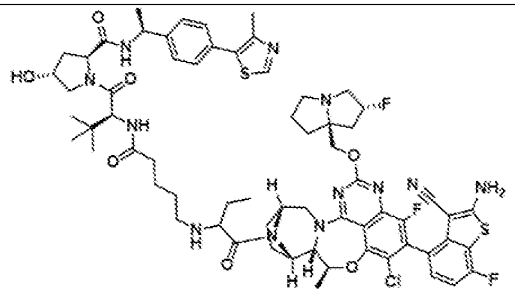
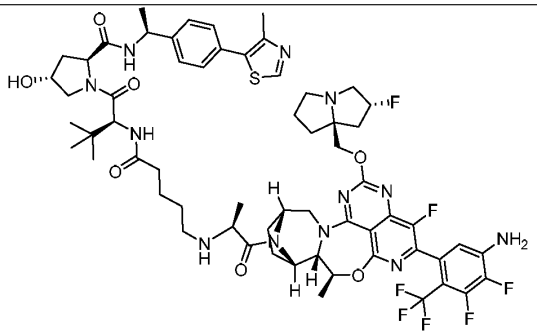
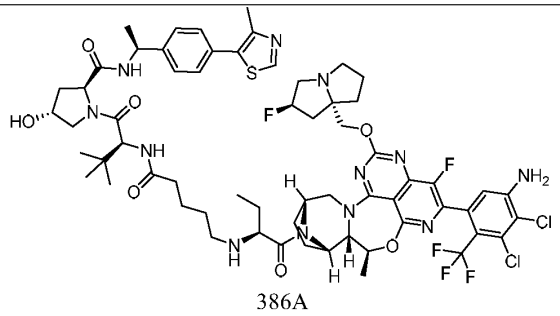
360[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-ethynylphenyl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 786.5)	 360A	1219.9
361[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 848.5)	 361A	1281.9
362[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-bromo-3-chloro-2-(trifluoromethyl)phenyl)-12-((S)-1-((2R,3S)-3-cyclopropoxy-1-methylpyrrolidin-2-yl)ethoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 936.2)	 362A	1368.8
363[2]	(2R)-1-((5S,5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)- 5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 846.4)	 363A	1279.9
364[2]	2-((5aS,7R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,8,9-hexahydropyrido[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-7-yl)ethyl ethanesulfonate ([M+H]$^+$= 788.5)		1210.9

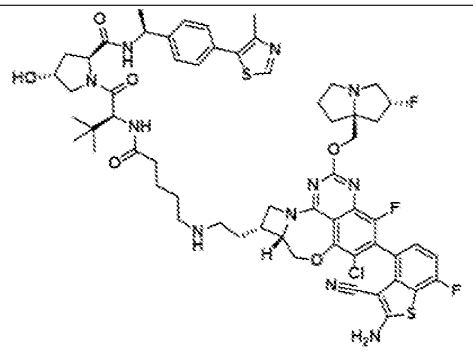
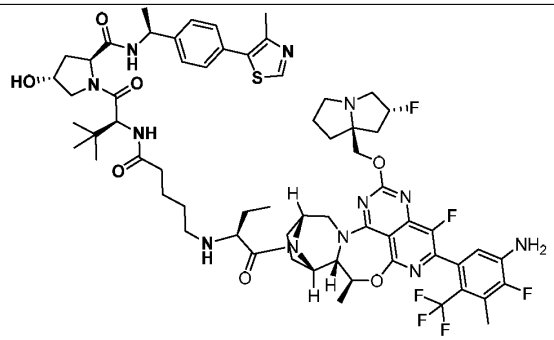
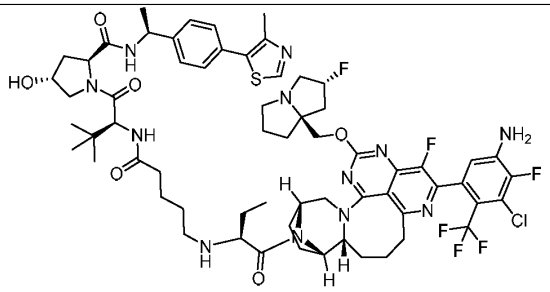
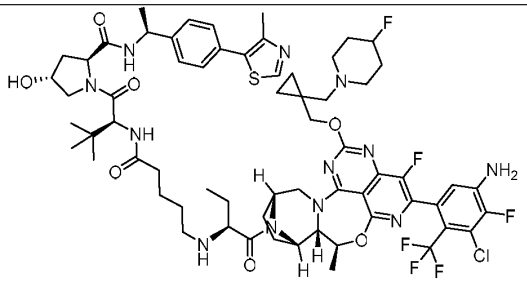
		364A	
365[7]	(2R)-1-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-2-(5-(trifluoromethyl)-1H-indazol-4-yl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 821.5)	 365A	1254.4
366[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((S,E)-4-(fluoromethylene)-1,3-dimethylpiperidin-3-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 844.3)	 366A	1277.9
367[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 856.2)	 367A	1289.5
368[2]	2-((5aR,7R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,8,9-hexahydropyrido[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-7-yl)ethyl ethanesulfonate ([M+H]$^+$= 776.8)	 368A	1210.9

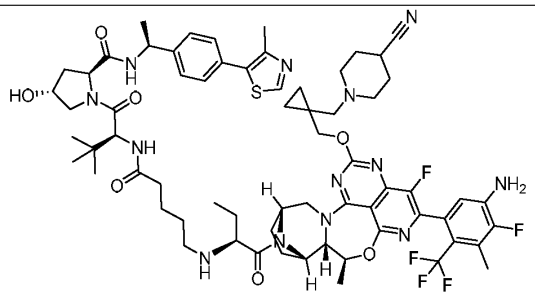
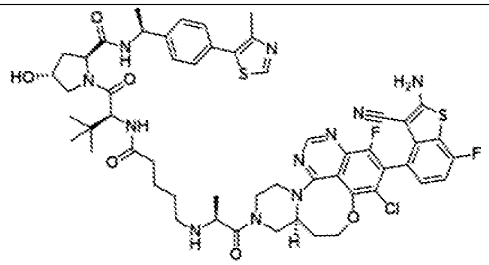
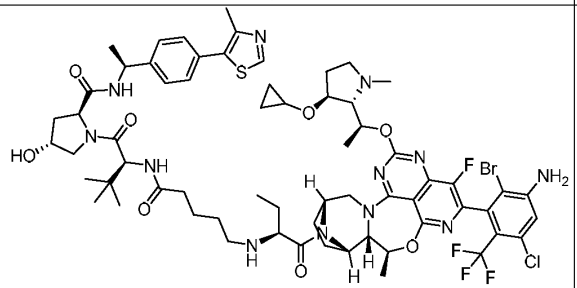
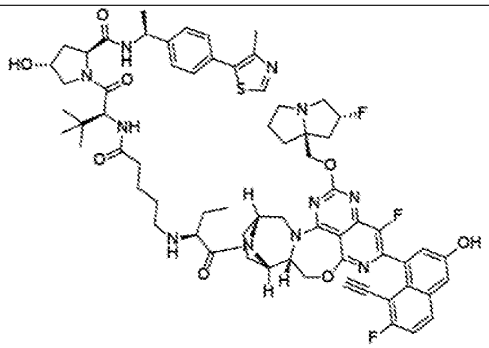
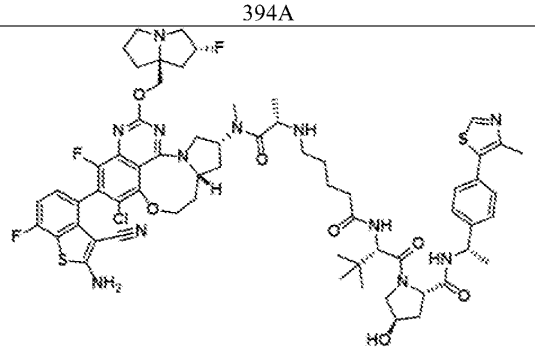
369[7]	(2R)-1-((5aR,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl cyclopropanesulfonate ([M+H]$^+$= 824.1)	 369A	1245.5
370[2]	2-((6aS,8S)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,6a,7,8,9,10-hexahydro-5H-pyrido[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-8-yl)ethyl ethanesulfonate ([M+H]$^+$= 791.1)	 370A	1224.9
371[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-((4-cyanopiperidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 883.4)	 371A	1316.9
372[2]	2-((5aR,7S)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,8,9-hexahydropyrido[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-7-yl)ethyl ethanesulfonate ([M+H]$^+$= 777)	 372A	1210.9
373[5]	(2R)-1-((6aS,7S,10R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-14-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-7,10-epiminoazepino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-16-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 856.4)	 373A	1279.9

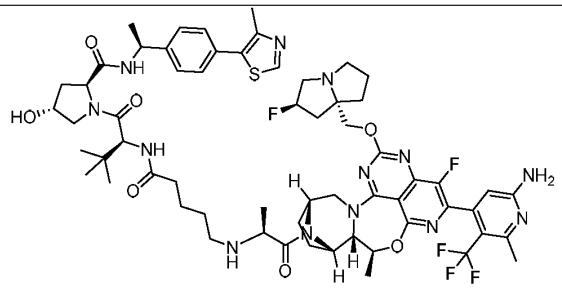
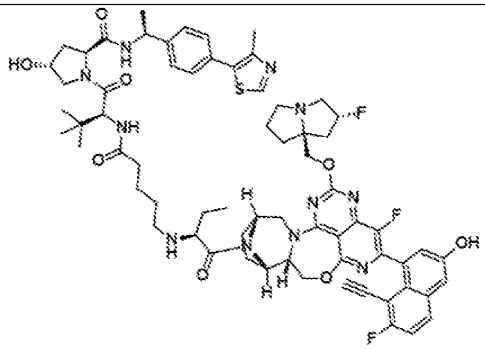
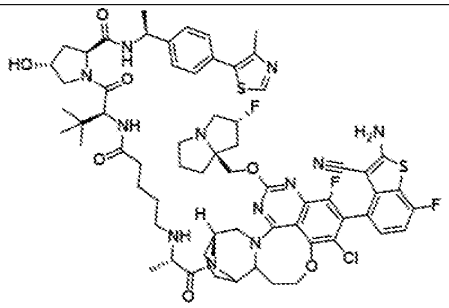
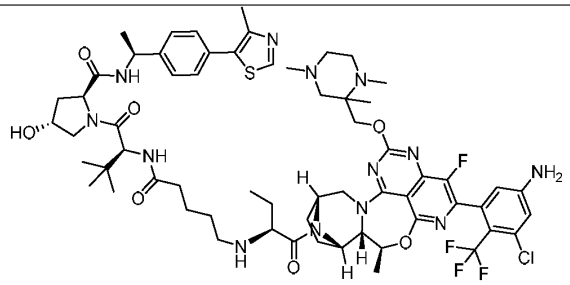
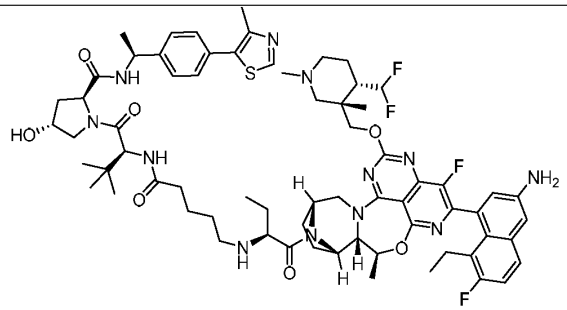
374[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((2R,3S)-1-methyl-3-(trifluoromethoxy)pyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 902.7)	 374A	1335.9
375[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 798.5)	 375A	1231.4
376[6]	2-(8-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-9-chloro-7-fluoro-5-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,11,12,12a-tetrahydro-2H-azeto[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-1-yl)ethyl ethanesulfonate ([M+H]$^+$= 762.9)	 376A	1196.9
377[6]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((8aR)-octahydroindolizin-3-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 824.4)	 377A	1257.5

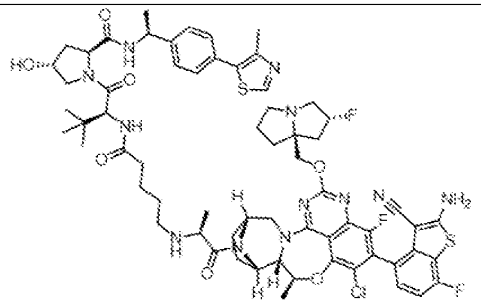
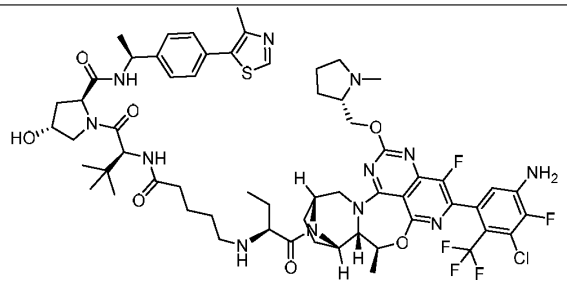
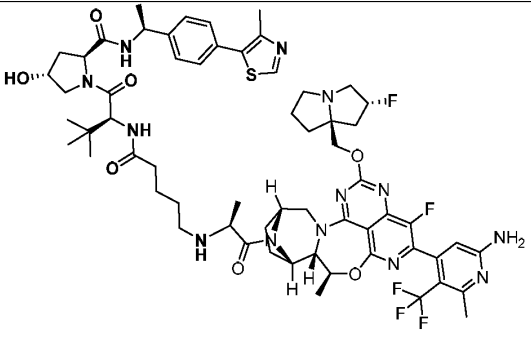
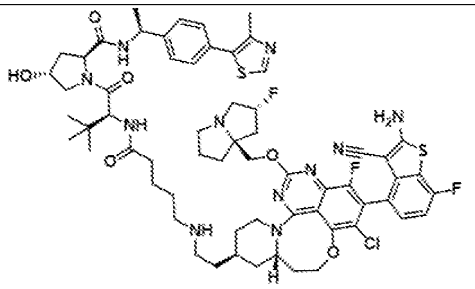
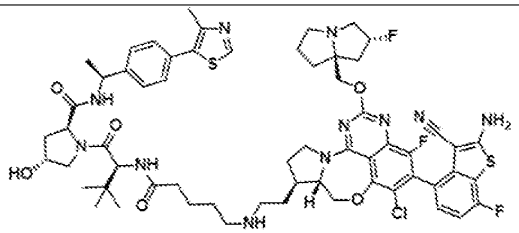
378[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-12-(((1R,2S)-2-(dimethylamino)cyclopentyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 814.6)	 378A	1247.9
379[5]	(2R)-1-((5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl methylsulfamate ([M+H]$^+$= 833.4)	 379A	1265.9
380[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-2-cyclopropyl-4-fluoro-3-methylphenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 800.5)	 380A	1233.5
381[7]	(2R)-1-((5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 832.4)	 381A	1265.9
382[2]	2-((1S,12aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,12,12a-tetrahydro-1H-pyrrolo[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-1-yl)ethyl ethanesulfonate ([M+H]$^+$= 762.9)	 382A	1196.9

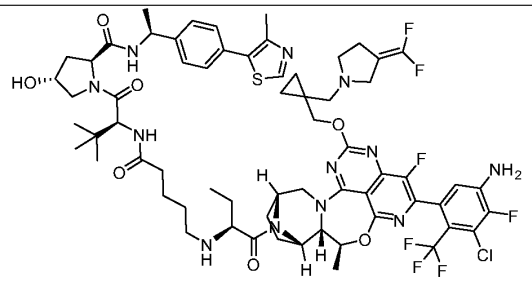
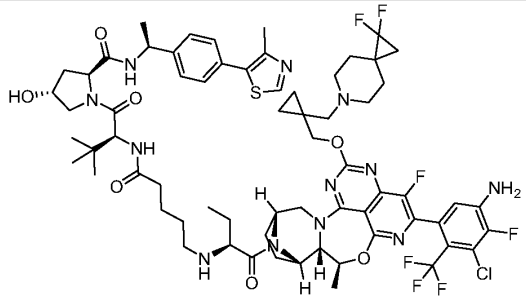
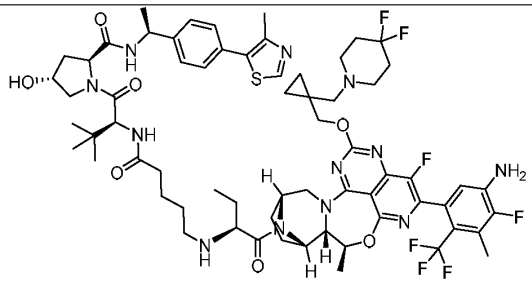
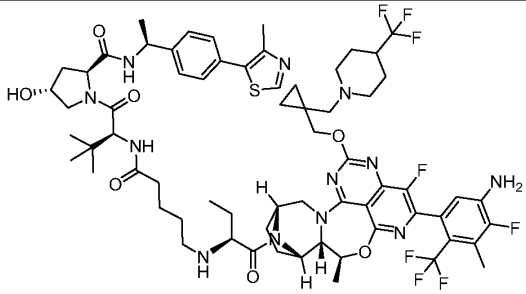
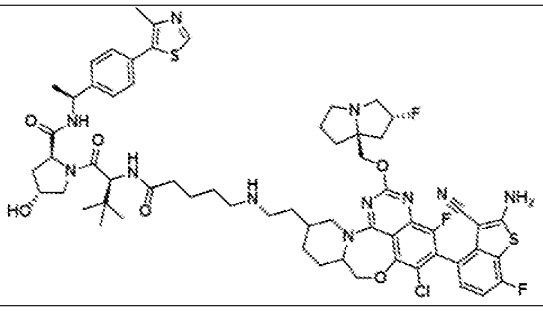
383[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-cyano-2-cyclopropylphenyl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 793.9)	 383A	1226.5
384[5]	1-((5S,5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxobutan-2-yl dimethylsulfamate ([M+H]$^+$= 875.3)	 384A	1294
385[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-3,4-difluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxopropan-2-yl cyclopropanesulfonate ([M+H]$^+$= 830.1)	 385A	1251.4
386[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3,4-dichloro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 864.6)	 386A	1298.3

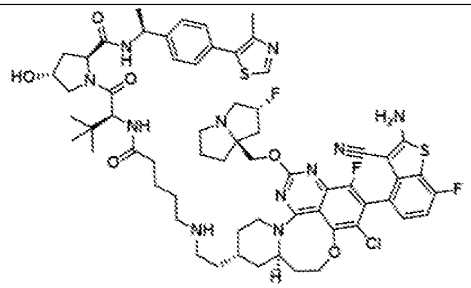
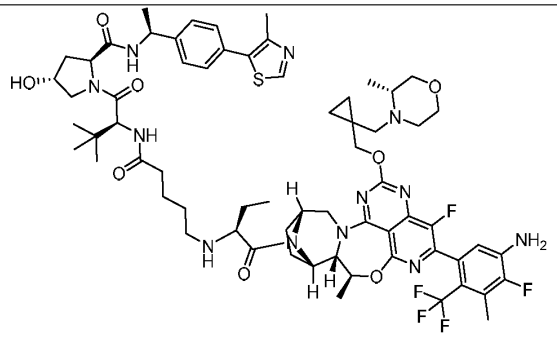
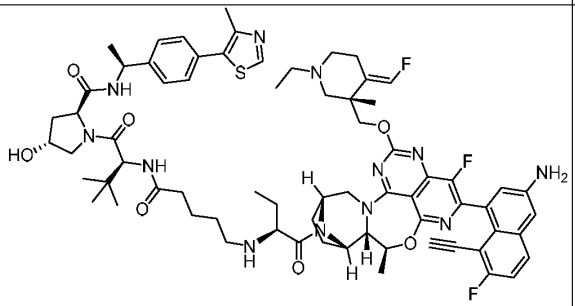
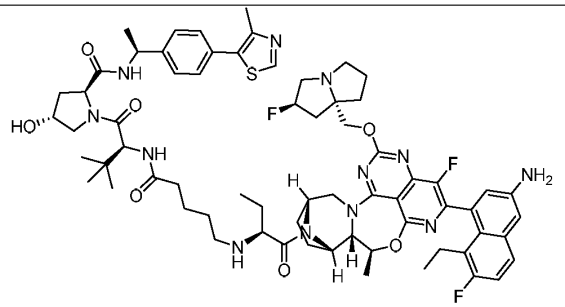
387[5]	2-((1R,11aS)-8-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-9-chloro-7-fluoro-5-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,11,11a-tetrahydroazeto[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-1-yl)ethyl ethanesulfonate ([M+H]$^+$= 748.9)	 387A	1182.8
388[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl cyclopropanesulfonate ([M+H]$^+$= 840.2)	 388A	1261.4
389[7]	(R)-1-((6aR,7S,10R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-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]cyclooct a[1,2,3-de]naphthalen-15-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 846.2)	 389A	1279.9
390[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 876.1)	 390A	1309.9

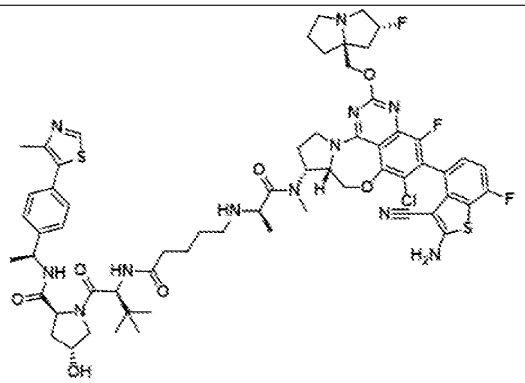
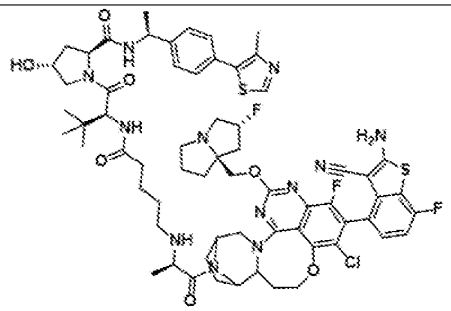
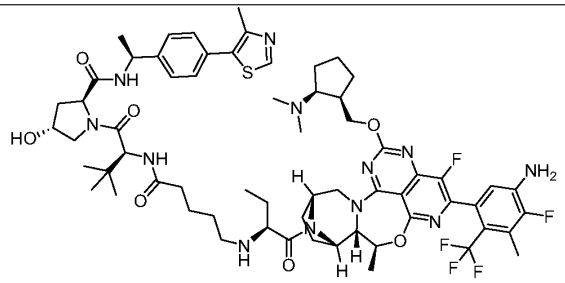
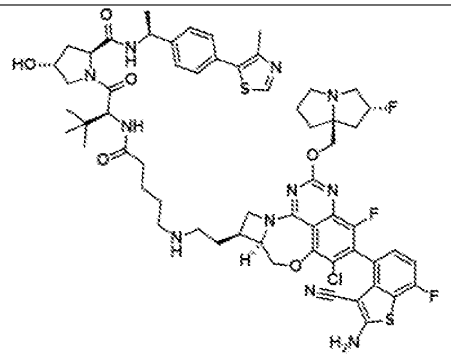
391[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((1-((4-cyanopiperidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 863.7)	 391A	1296.5
392[2]	(2R)-1-((14aS)-10-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 665.2)	 392A	1096.7
393[7]	(2R)-1-((5S,5aS,6S,9R)-2-(3-amino-2-bromo-5-chloro-6-(trifluoromethyl)phenyl)-12-((S)-1-((2R,3S)-3-cyclopropoxy-1-methylpyrrolidin-2-yl)ethoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 936.4)	 393A	1368.8
394[2]	(R)-1-((5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-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]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 807.3)	 394A	1240.5
395[6]	(2R)-1-(((2R,13aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 834.2)	 395A	1267.9

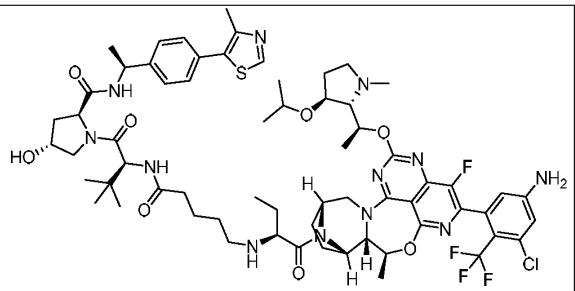
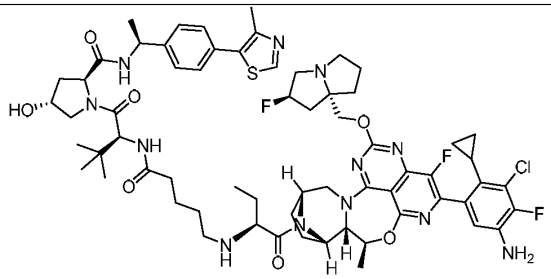
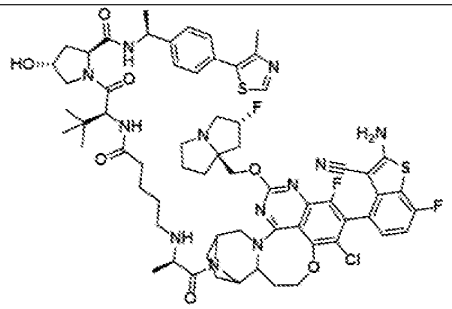
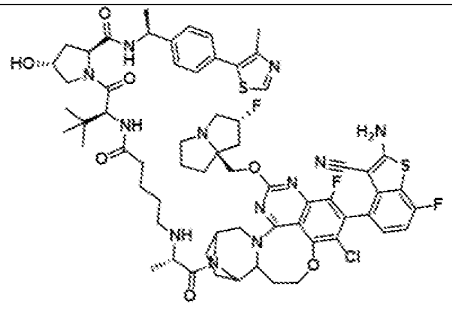
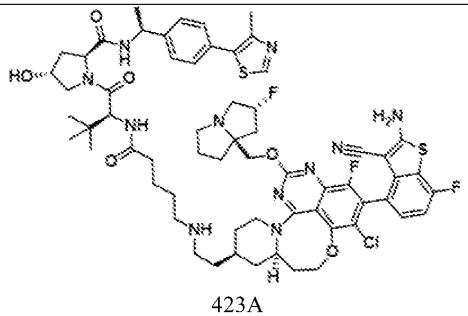
396[7]	(R)-1-((5S,5aS,6S,9R)-2-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)- 1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)- 5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 797)	 396A	1230.4
397[2]	(R)-1-((5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-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]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 807.3)	 397A	1240.5
398[2]	(2R)-1-(2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-14-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-7,10-epiminoazepino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-16-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 846.5)	 398A	1279.9
399[1]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1,2,4-trimethylpiperazin-2-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 829.5)	 399A	1262.9
400[7]	(R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethyl-7-fluoronaphthalen-1-yl)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate		1291.6

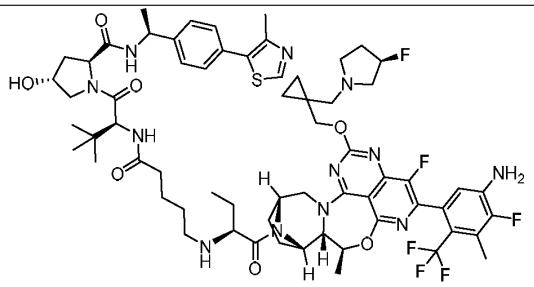
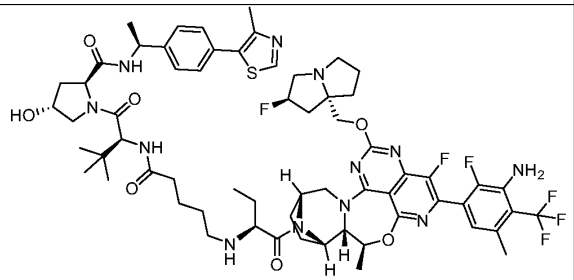
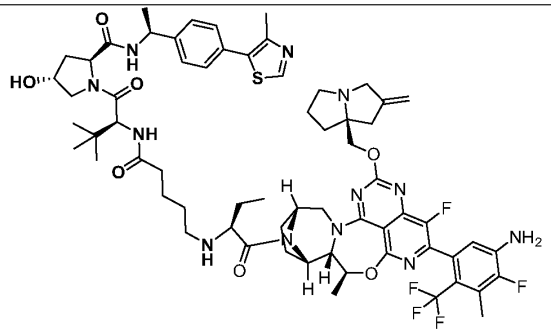
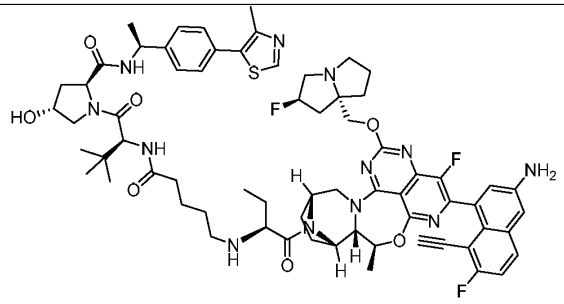
	([M+H]$^+$= 858.4)	400A	
401[7]	(2R)-1-((5S,5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 828.2)	 401A	1280
402[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((S)-1-methylpyrrolidin-2-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 804.4)	 402A	1237.8
403[7]	(2R)-1-((5S,5aS,6S,9R)-2-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-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]heptalen-14-yl)-1-oxopropan-2-yl cyclopropanesulfonate ([M+H]$^+$= 809)	 403A	1230.4
404[2]	2-((6aS,8S)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,6a,7,8,9,10-hexahydro-5H-pyrido[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-8-yl)ethyl ethanesulfonate ([M+H]$^+$= 793)	 404A	1224.9
405[5]	2-((1R,12aS)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,12,12a-tetrahydro-1H-pyrrolo[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-1-yl)ethyl ethanesulfonate ([M+H]$^+$= 762.7)	 405A	1196.9

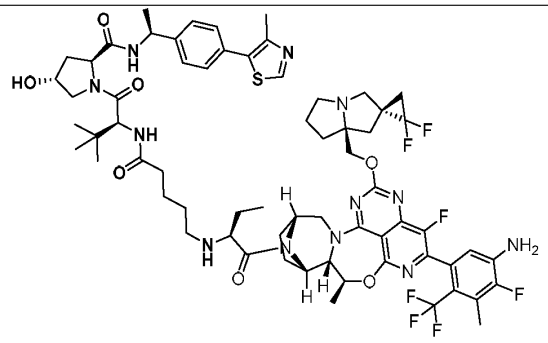
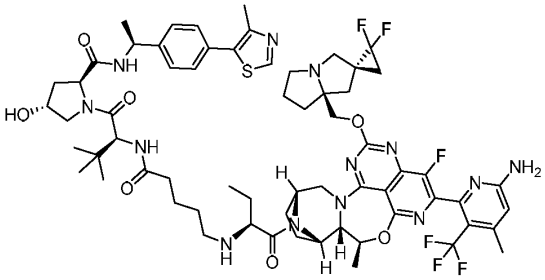
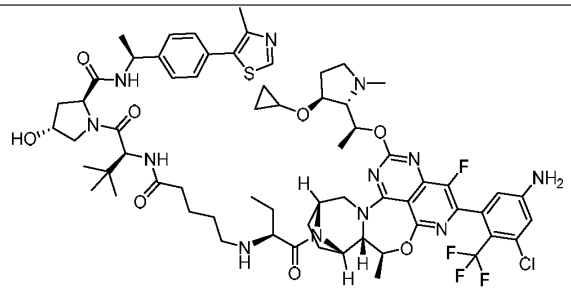
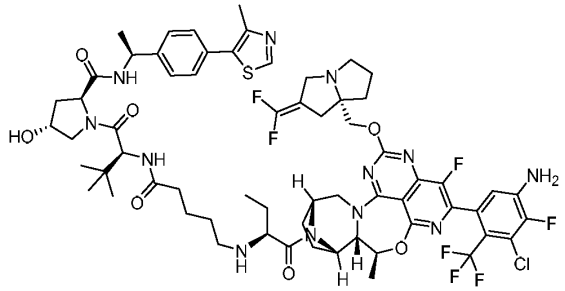
406[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-((3-(difluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 892.6)	 406A	1325.9
407[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 92.5)	 407A	1353.9
408[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((1-((4,4-difluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 874.3)	 408A	1307.5
409[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-((4-(trifluoromethyl)piperidin-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 906.8)	 409A	1339.5
410[1]	2-(2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,8,9-hexahydropyrido[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-8-yl)ethyl ethanesulfonate ([M+H]$^+$= 777)		1210.9

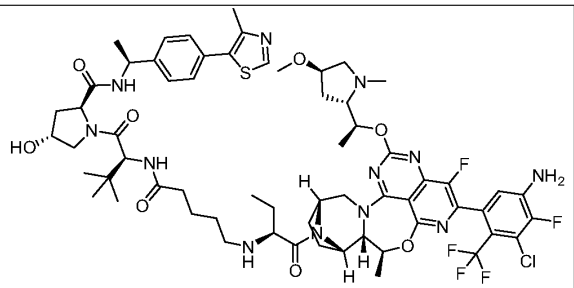
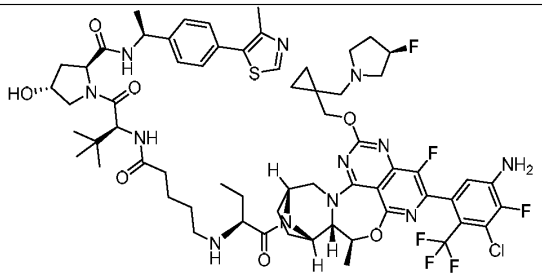
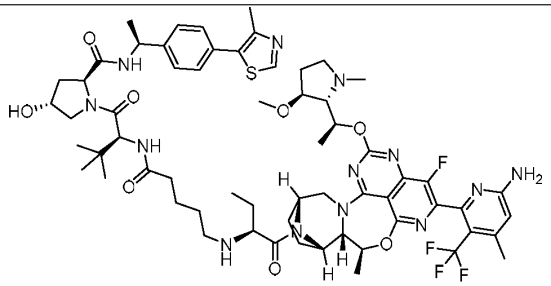
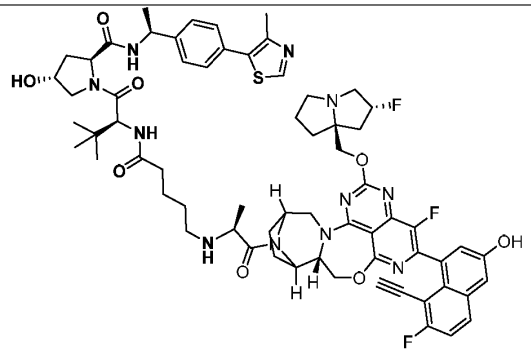
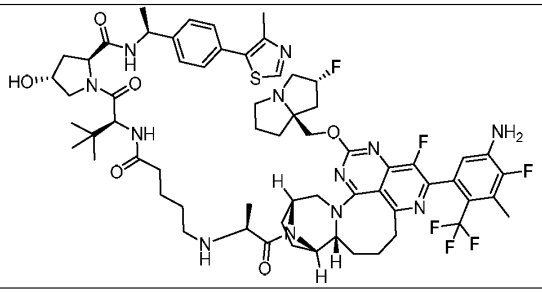
		410A	
411[2]	2-((6aR,8R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,6a,7,8,9,10-hexahydro-5H-pyrido[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-8-yl)ethyl ethanesulfonate ([M+H]$^+$= 790.8)	 411A	1224.9
412[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-(((R)-3-methylmorpholino)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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 854.6)	 412A	1287.5
413[7]	(R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-12-(((S,E)-1-ethyl-4-(fluoromethylene)-3-methylpiperidin-3-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 848.6)	 413A	1281.6
414[7]	(R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethyl-7-fluoronaphthalen-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]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 824.6)	 414A	1257.5

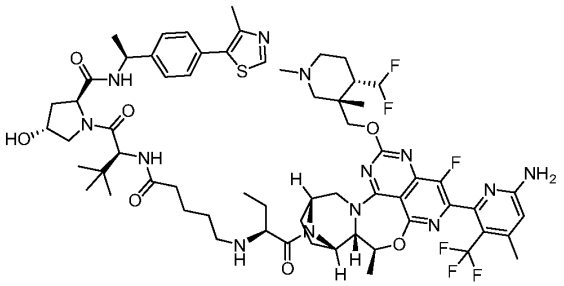
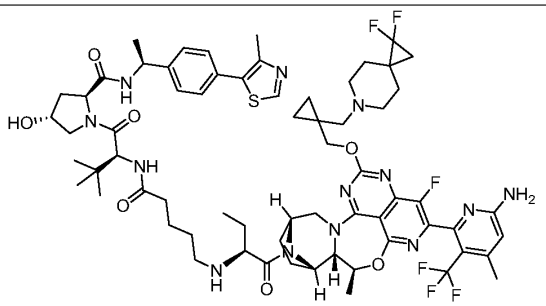
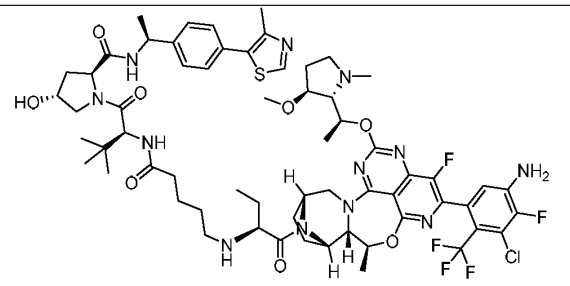
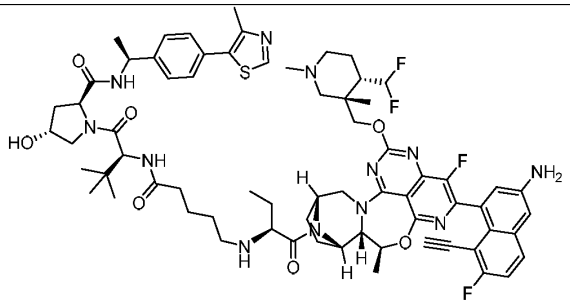
415[1]	(2S)-1-(((1R,12aS)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,12,12a-tetrahydro-1H-pyrrolo[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-1-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 820.4)	 415A	1253.9
416[1]	(2R)-1-(2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-14-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-7,10-epiminoazepino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-16-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 846.5)	 416A	1279.9
417[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-(((1R,2S)-2-(dimethylamino)cyclopentyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 812.7)	 417A	1245.5
418[2]	2-((1S,11aR)-8-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-9-chloro-7-fluoro-5-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,11,11a-tetrahydroazeto[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-1-yl)ethyl ethanesulfonate ([M+H]$^+$= 749)	 418A	1182.8

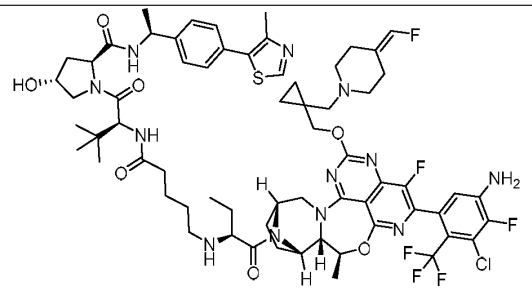
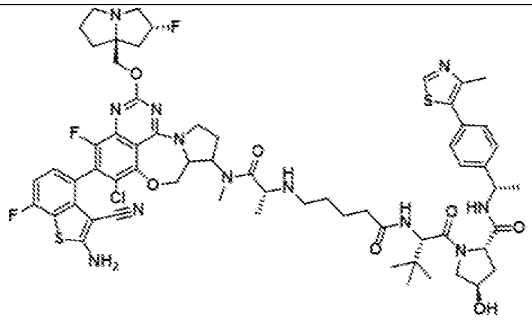
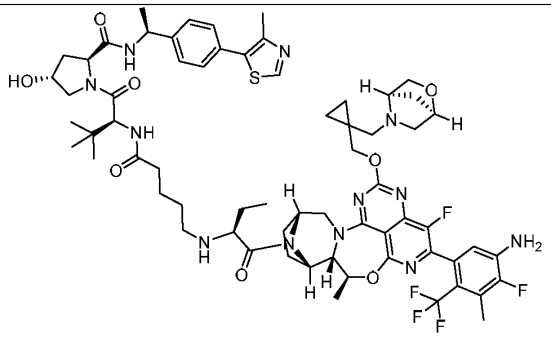
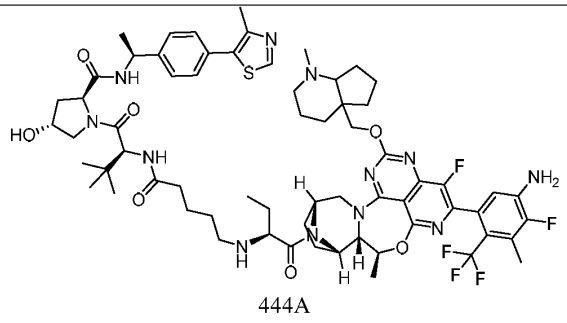
419[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((S)-1-((2R,3S)-3-isopropoxy-1-methylpyrrolidin-2-yl)ethoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 858.4)	 419A	1292
420[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-cyclopropyl-4-fluorophenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 820.6)	 420A	1253.9
421[1]	(2R)-1-(2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-14-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-7,10-epiminoazepino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-16-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 847.3)	 421A	1279.9
422[1]	(2R)-1-(2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-14-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-7,10-epiminoazepino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-16-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 846.2)	 422A	1279.9
423[2]	2-((6aR,8S)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-6,6a,7,8,9,10-hexahydro-5H-pyrido[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-8-yl)ethyl ethanesulfonate ([M+H]$^+$= 790.8)	 423A	1224.9

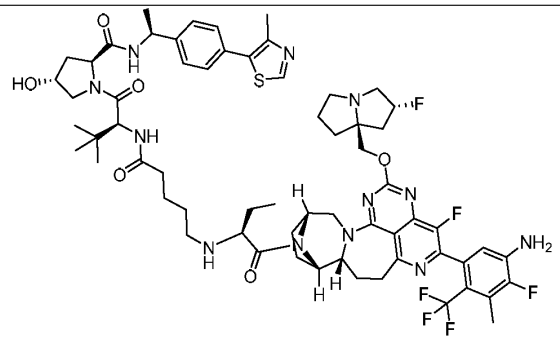
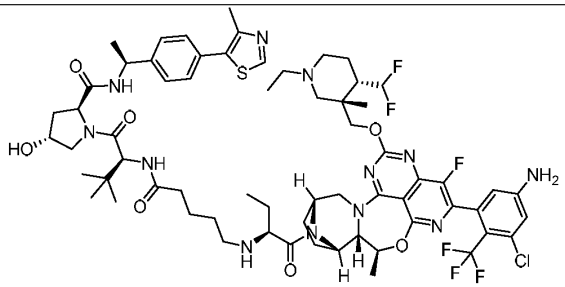
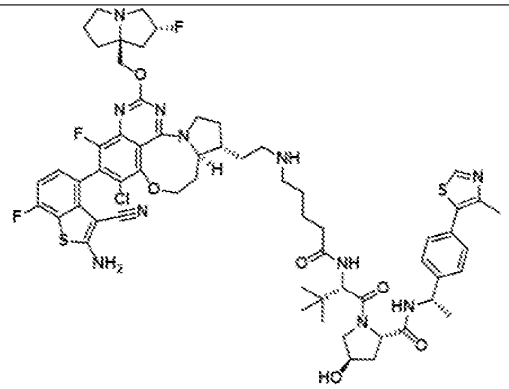
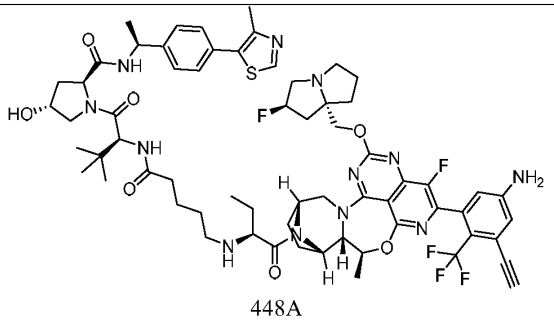
424[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-(((R)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl cyclopropanesulfonate ([M+H]$^+$= 854.3)	 424A	1275.5
425	(R)-1-((5S,5aS,6S,9R)-2-(3-amino-2-fluoro-5-methyl-4-(trifluoromethyl)phenyl)- 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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 828.5)	 425A	1261.4
426[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((S)-2-methylenetetrahydro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 822.9)	 426A	1255.5
427[7]	(R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-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]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 820.5)	 427A	1253.5

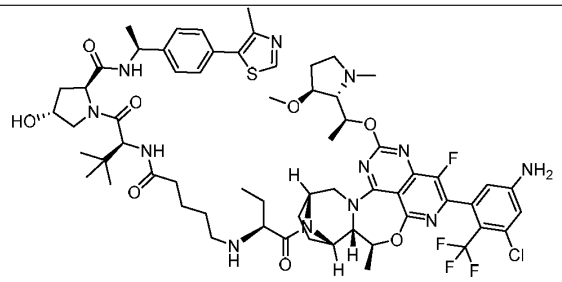
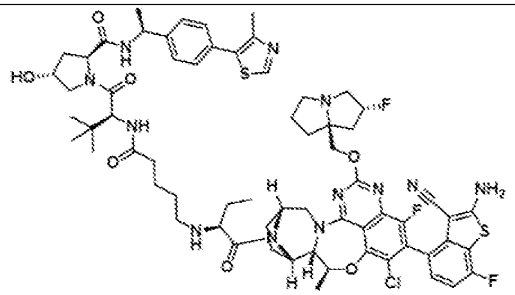
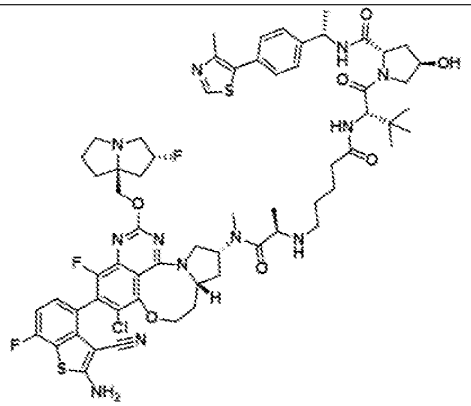
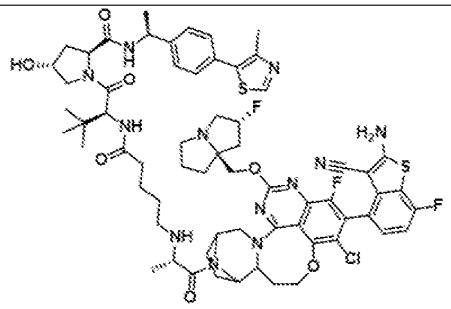
428[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-[6,9]methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 872.7)	 428A	1305.5
429[7]	(R)-1-((5S,5aS,6S,9R)-2-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 855.7)	 429A	1288.5
430[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-12-((S)-1-((2R,3S)-3-cyclopropoxy-1-methylpyrrolidin-2-yl)ethoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 857.6)	 430A	1289.9
431[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-(((S)-2-(difluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 878.5)	 431A	1311.9

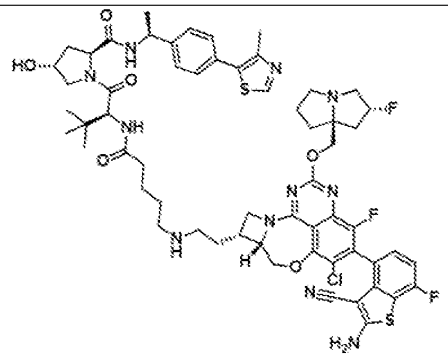
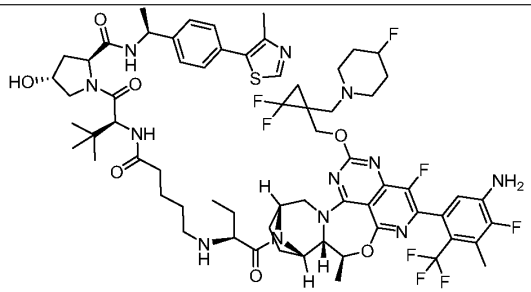
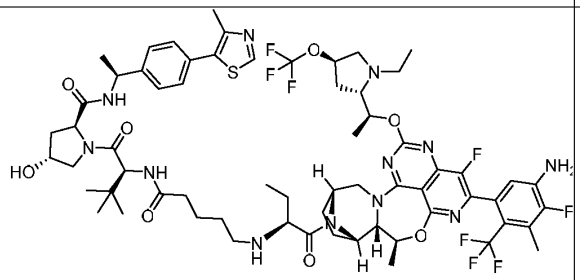
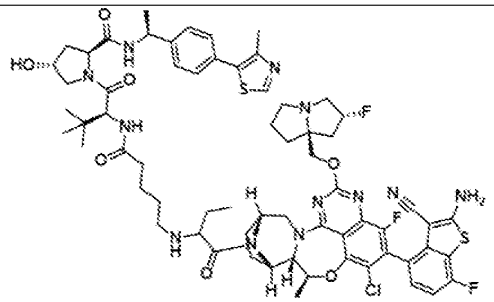
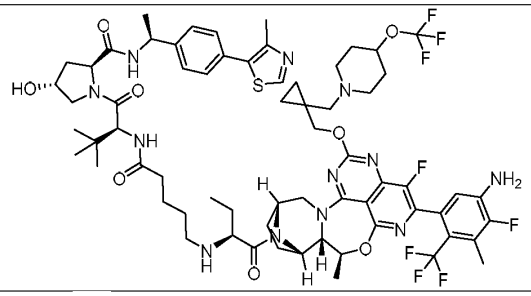
432[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((S)-1-((2S,4R)-4-methoxy-1-methylpyrrolidin-2-yl)ethoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 848.6)	 432A	1281.9
433[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-(((R)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 862.7)	 433A	1295.9
434[7]	(R)-1-((5S,5aS,6S,9R)-2-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-1-fluoro-12-((S)-1-((2R,3S)-3-methoxy-1-methylpyrrolidin-2-yl)ethoxy)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 811.6)	 434A	1244.5
435[7]	(2R)-1-((6R,9S)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-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]heptalen-14-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 793.4)	 435A	1226.4
436[7]	(R)-1-((6aR,7S,10R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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]cyclooct a[1,2,3-de]naphthalen-15-yl)-1-		1245.5

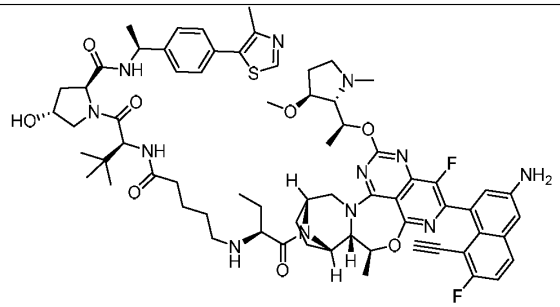
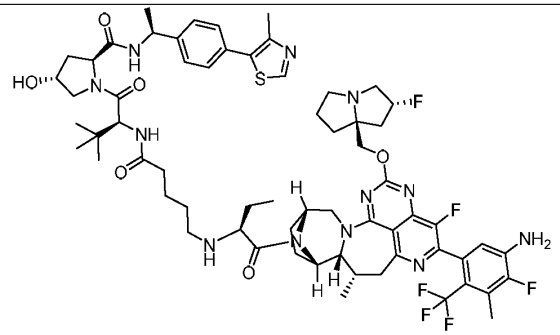
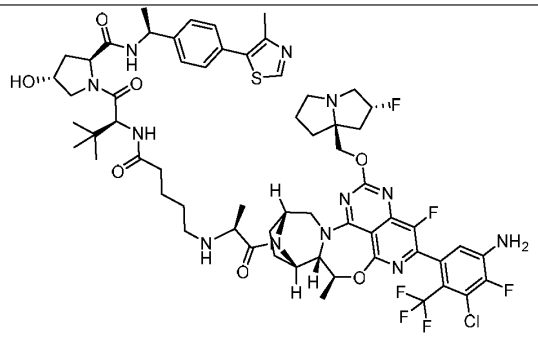
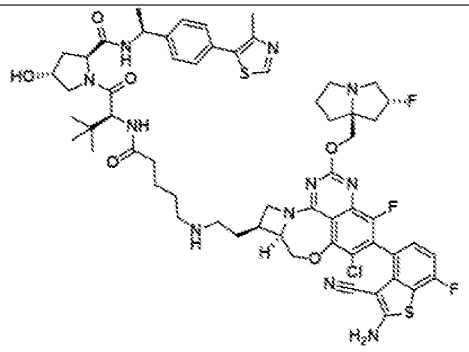
	oxopropan-2-yl cyclopropanesulfonate ([M+H]$^+$= 822.2)	436A	
437[7]	(R)-1-((5S,5aS,6S,9R)-2-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 845.6)	 437A	1278.5
438[7]	(R)-1-((5S,5aS,6S,9R)-2-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 883.7)	 438A	1316.5
439[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((S)-1-((2R,3S)-3-methoxy-1-methylpyrrolidin-2-yl)ethoxy)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 848.4)	 439A	1281.9
440[7]	(R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 854.6)	 440A	1287.5

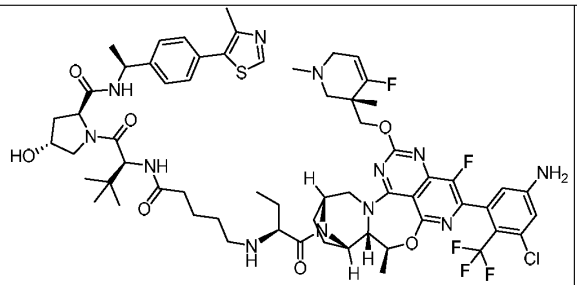
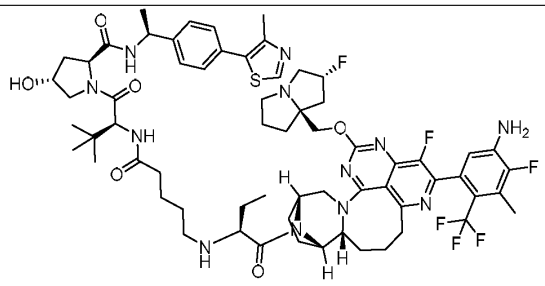
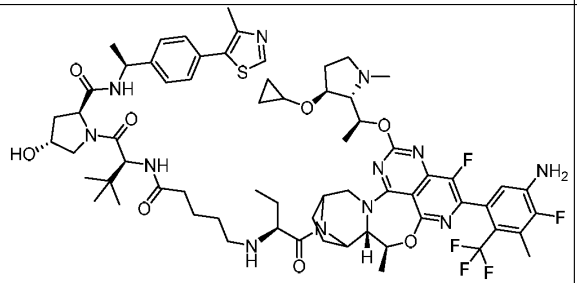
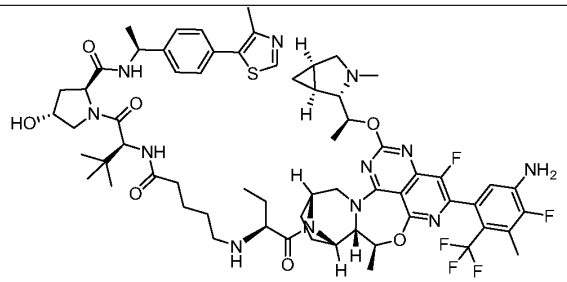
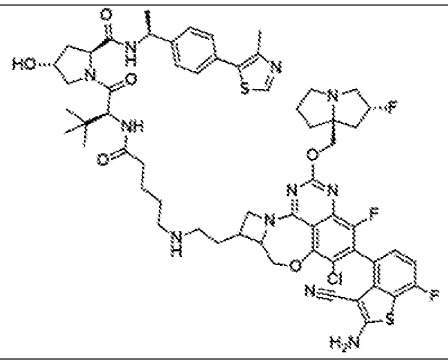
441[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 888.8)	 441A	1321.9
442[1]	(2S)-1-((9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,12,12a-tetrahydro-1H-pyrrolo[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-1-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 820.3)	 442A	1253.9
443[7]	(R)-1-((5S,5aS,6S,9R)-12-(((1-(((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 852.6)	 443A	1285.5
444	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-methyloctahydro-4aH-cyclopenta[b]pyridin-4a-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 838.3)	 444A	1271.5

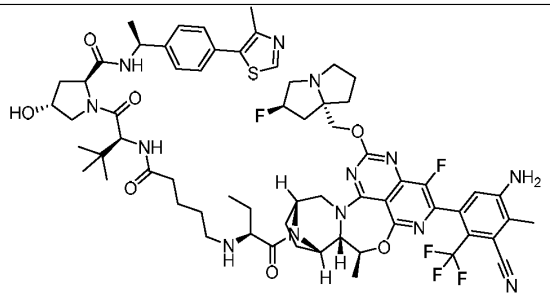
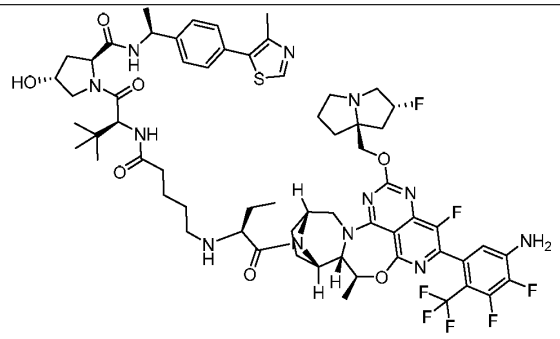
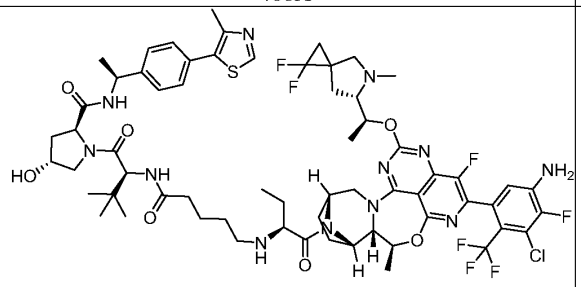
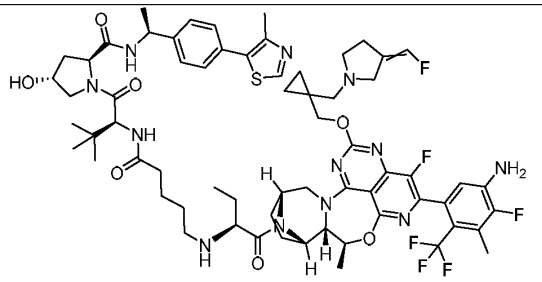
445[7]	(R)-1-((5aR,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4,5,5a,6,7,8,9,10-octahydro-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 812.3)	 445A	1245.5
446[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-12-(((3S,4S)-4-(difluoromethyl)-1-ethyl-3-methylpiperidin-3-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 699.4)	 446A	1311.9
447[2]	2-((1R,13aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-1-yl)ethyl ethanesulfonate ([M+H]$^+$= 776.8)	 447A	1210.9
448[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-ethynyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 820.5)	 448A	1253.5

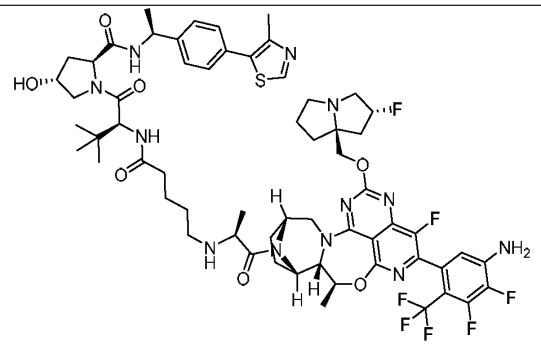
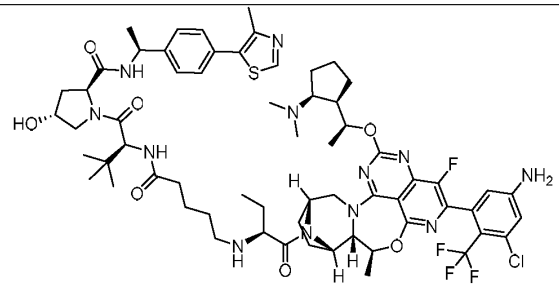
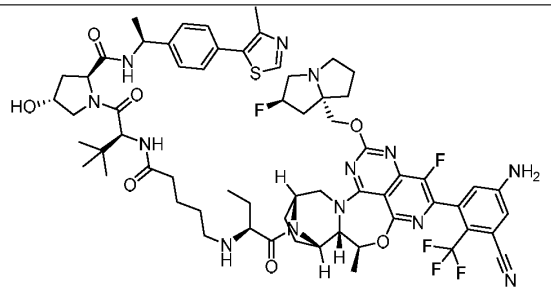
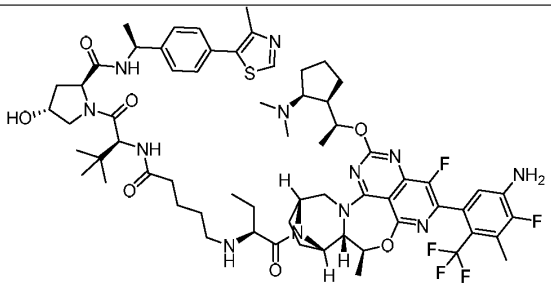
449[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((S)-1-((2R,3S)-3-methoxy-1-methylpyrrolidin-2-yl)ethoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 830.7)	 449A	1263.9
450[3]	(2R)-1-((5S,5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 860.3)	 450A	1294
451[2]	(2S)-1-(((2R,13aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 834.3)	 451A	1267.9
452[3]	(2R)-1-(2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-14-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-7,10-epiminoazepino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-16-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 846.5)	 452A	1279.9

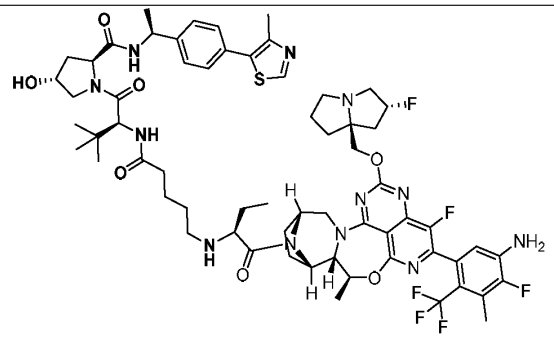
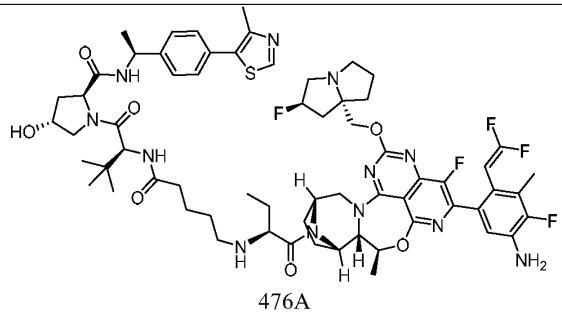
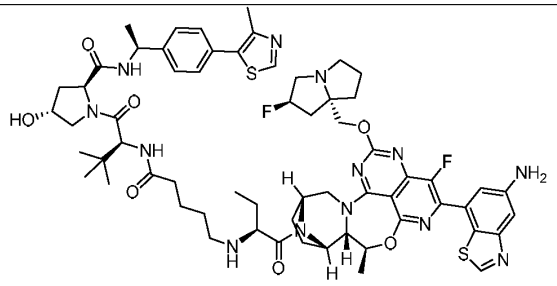
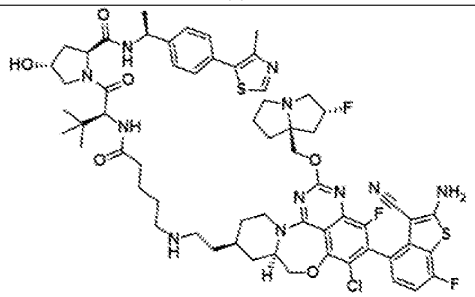
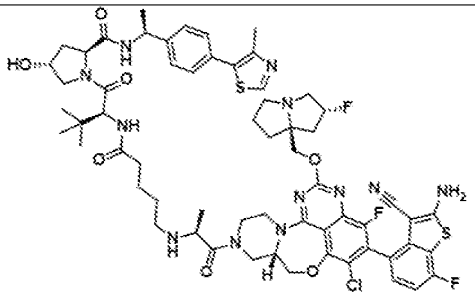
453[2]	2-((1R,11aS)-8-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-9-chloro-7-fluoro-5-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,11,11a-tetrahydroazeto[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-1-yl)ethyl ethanesulfonate ([M+H]$^+$= 748.9)	 453A	1182.8
454[6]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((2,2-difluoro-1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 892.6)	 454A	1325.5
455[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((S)-1-((2S,4R)-1-ethyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 896.6)	 455A	1329.5
456[1]	1-((5S,5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxobutan-2-yl dimethylsulfamate ([M+H]$^+$= 875.3)	 456A	1294
457[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-((4-(trifluoromethoxy)piperidin-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-14-yl)-1-oxobutan-		1355.5

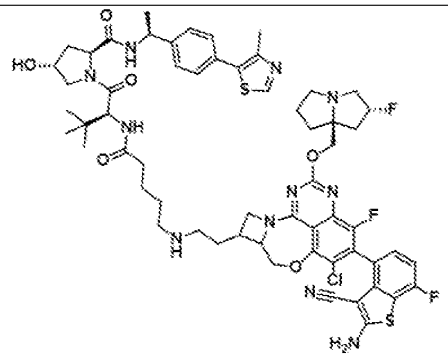
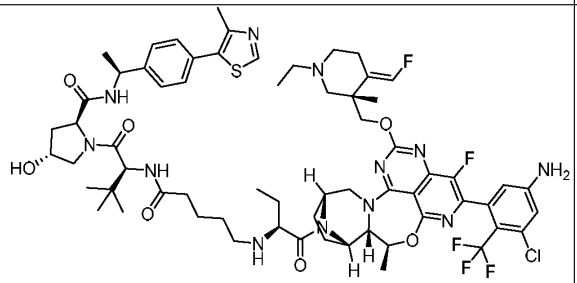
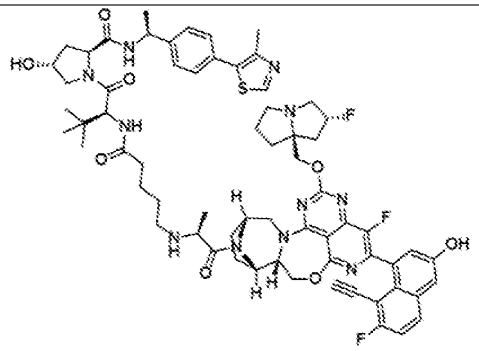
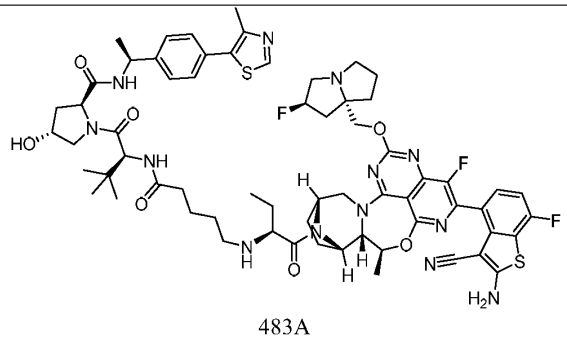
	2-yl cyclopropanesulfonate ([M+H]$^+$= 934.8)	457A	
458[7]	(R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-((S)-1-((2R,3S)-3-methoxy-1-methylpyrrolidin-2-yl)ethoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 820.6)	 458A	1253.5
459[7]	(R)-1-((5S*,5aR,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 826.3)	 459A	1259.5
460[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 835)	 460A	1267.8
461[6]	2-((1S,11aR)-8-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-9-chloro-7-fluoro-5-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,11,11a-tetrahydroazeto[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-1-yl)ethyl ethanesulfonate ([M+H]$^+$= 749)	 461A	1182.8
462[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((S)-4-fluoro-1,3-dimethyl-1,2,3,6-tetrahydropyridin-3-yl)methoxy)-5-methyl-		1263.9

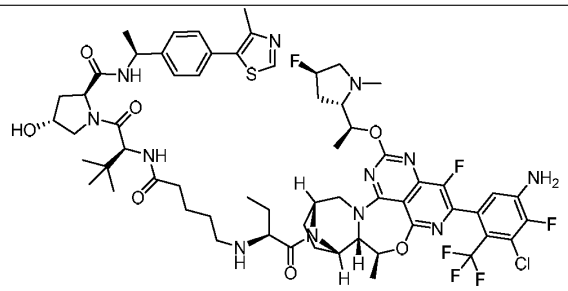
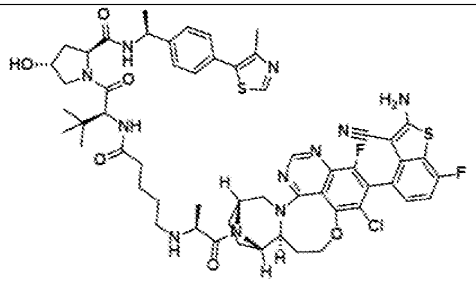
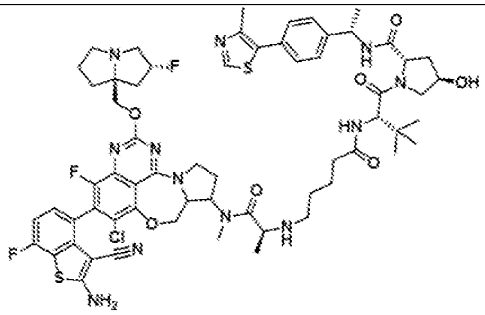
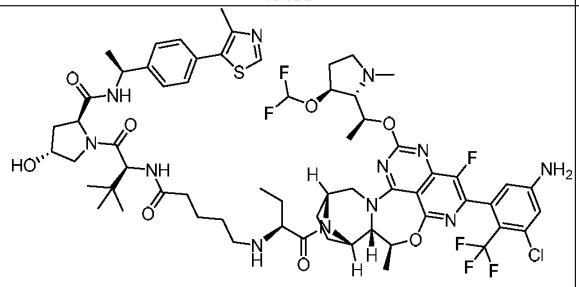
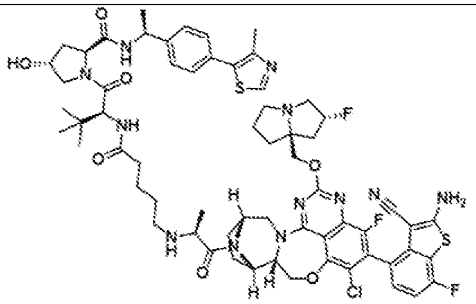
	5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 830.4)	 462A	
463[7]	(R)-1-((6aR,7S,10R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,6,6a,7,8,9,10,11-octahydro-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cyclooct a[1,2,3-de]naphthalen-15-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 826.2)	 463A	1259.5
464[7]	(2R)-1-((5S,5aS)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((S)-1-((2R,3S)-3-cyclopropoxy-1-methylpyrrolidin-2-yl)ethoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 854.5)	 464A	1287.5
465[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((1S,2S,5R)-3-methyl-3-azabicyclo[3.1.0]hexan-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 810.6)	 465A	1243.5
466[2]	2-(8-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-9-chloro-7-fluoro-5-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,11,11a-tetrahydroazeto[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-1-yl)ethyl ethanesulfonate ([M+H]$^+$= 748.9)		1182.8

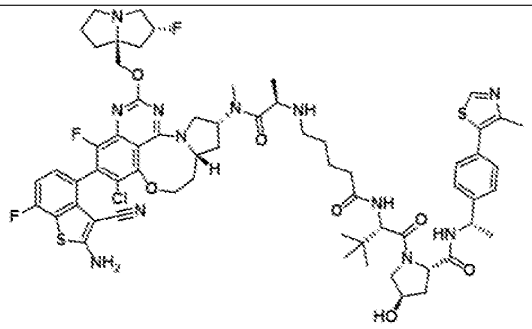
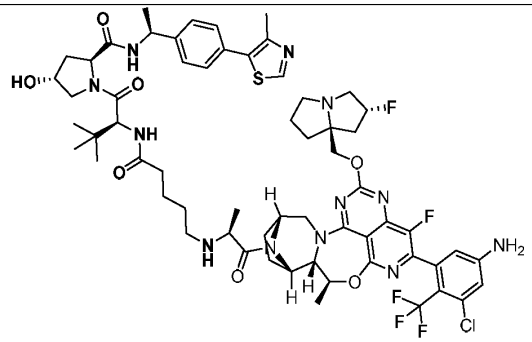
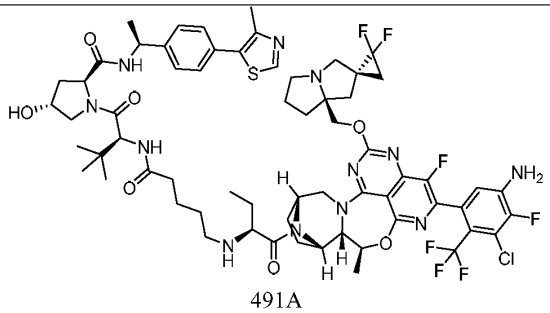
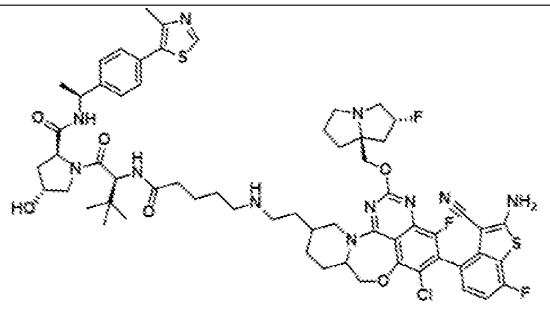
		466A	
467[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-cyano-4-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 835.5)	 467A	1268.5
468[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-3,4-difluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 832.5)	 468A	1265.4
469[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1S)-1-((6S)-1,1-difluoro-5-methyl-5-azaspiro[2.4]heptan-6-yl)ethoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 880.4)	 469A	1313.9
470[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((3-(fluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 854.6)	 470A	1287.5

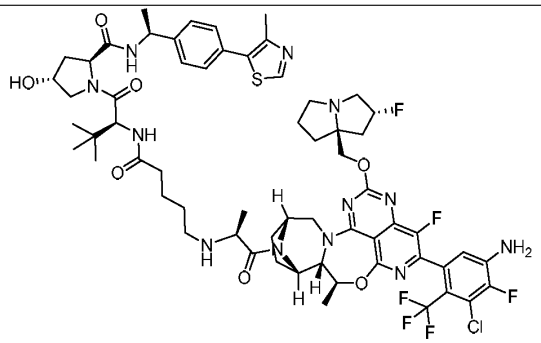
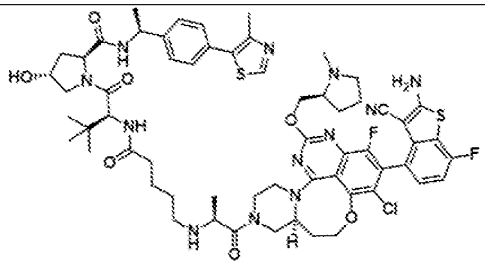
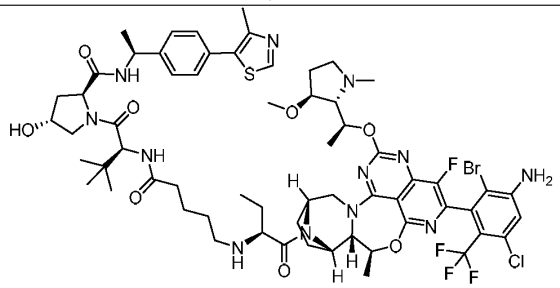
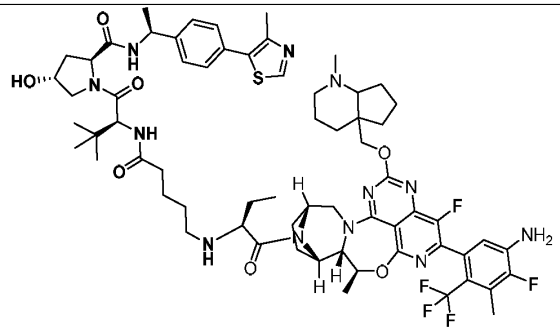
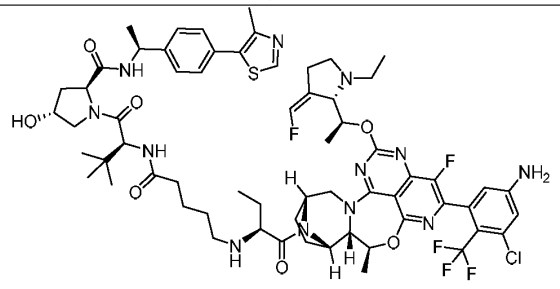
471[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-3,4-difluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 818.5)	 471A	1251.4
472[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-12-((S)-1-((1R,2S)-2-(dimethylamino)cyclopentyl)ethoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 828.3)	 472A	1261.9
473[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-cyano-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 821.5)	 473A	1254.4
474[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((S)-1-((1R,2S)-2-(dimethylamino)cyclopentyl)ethoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 826.3)	 474A	1259.5

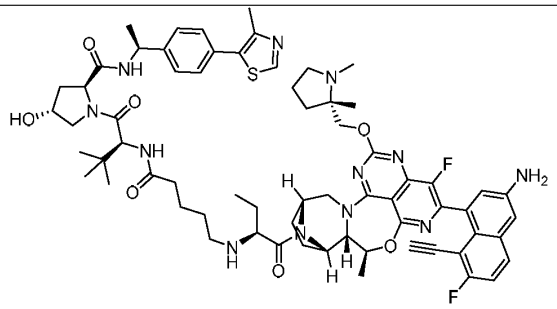
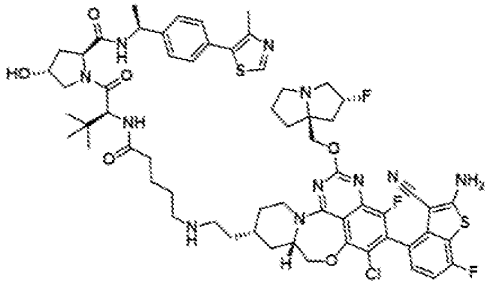
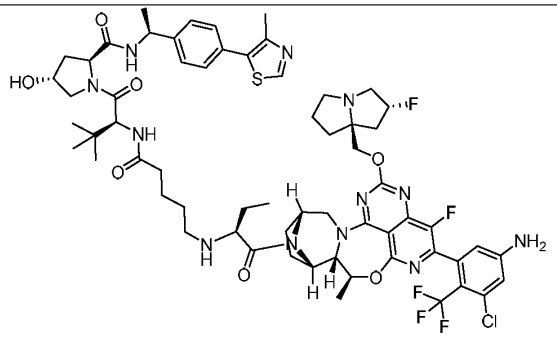
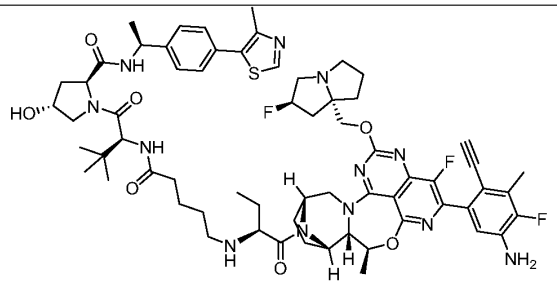
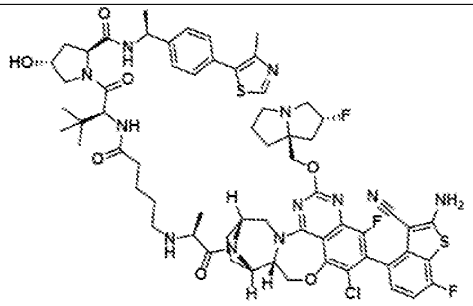
475[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 828.1)	 475A	1261.4
476[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-2-(2,2-difluorovinyl)-4-fluoro-3-methylphenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 713.6)	 476A	1255.5
477[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-aminobenzo[d]thiazol-7-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]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 785)	 477A	1218.5
478[2]	2-((5aR,7S)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,8,9-hexahydropyrido[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-7-yl)ethyl ethanesulfonate ([M+H]$^+$= 778.5)	 478A	1210.9
479[4]	(2R)-1-((13aS)-10-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-7-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3,4,13,13a-tetrahydropyrazino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-2(1H)-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 805.9)	 479A	1239.9

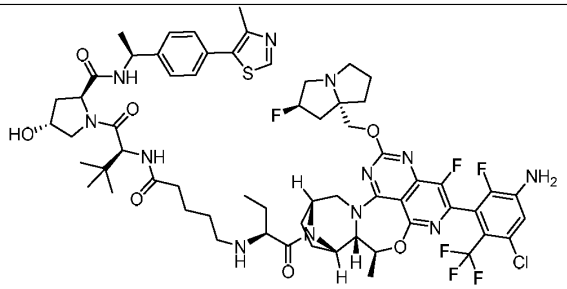
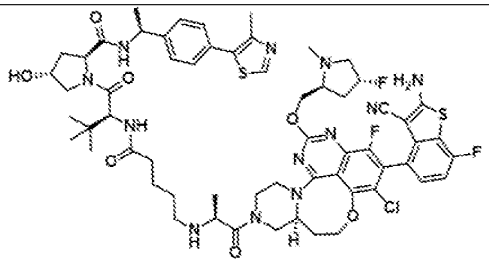
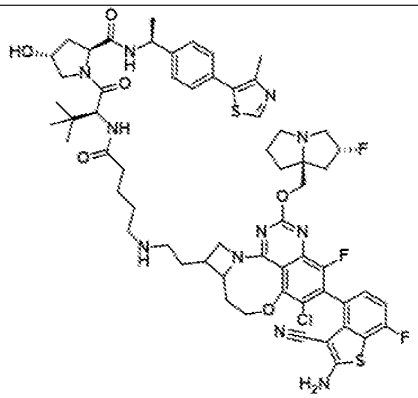
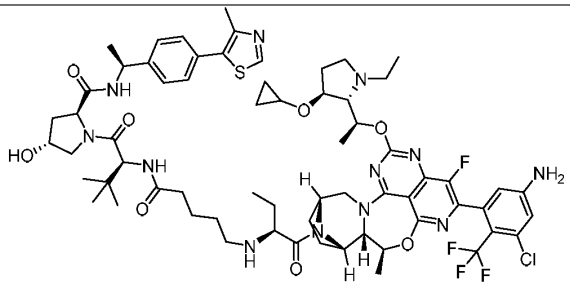
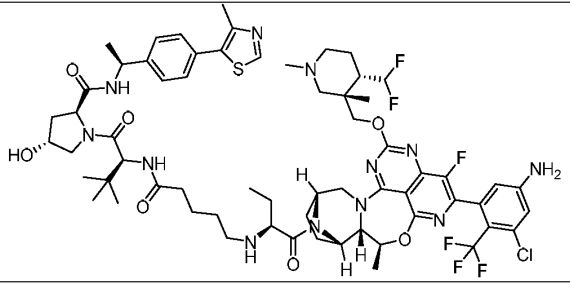
480[2]	2-(8-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-9-chloro-7-fluoro-5-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,11,11a-tetrahydroazeto[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-1-yl)ethyl ethanesulfonate ([M+H]$^+$= 748.9)	 480A	1182.8
481[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-12-(((S,E)-1-ethyl-4-(fluoromethylene)-3-methylpiperidin-3-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 858.6)	 481A	1291.9
482[7]	(R)-1-((5aS,6S,9R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-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]heptalen-14-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 793.4)	 482A	1226.4
483[7]	(R)-1-((5S,5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-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]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 884.1)	 483A	1260.5

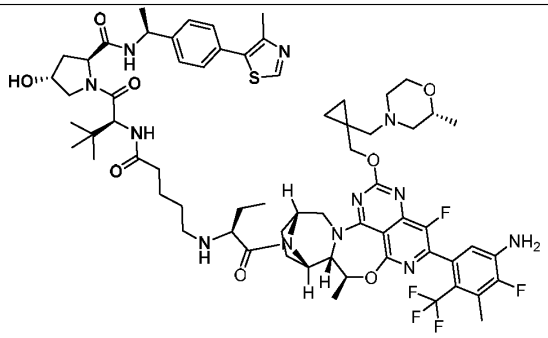
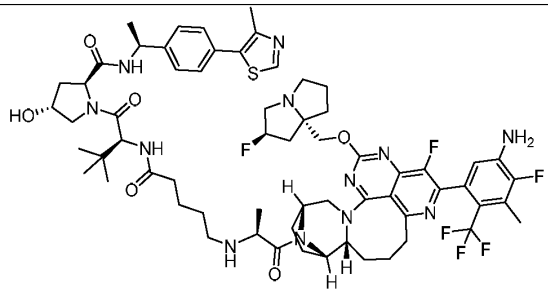
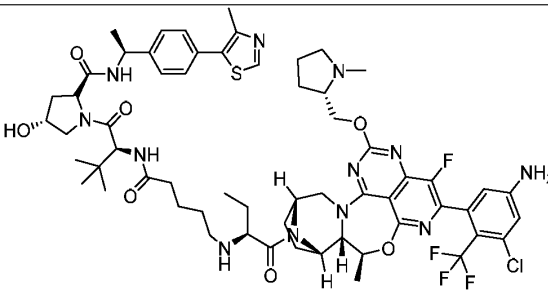
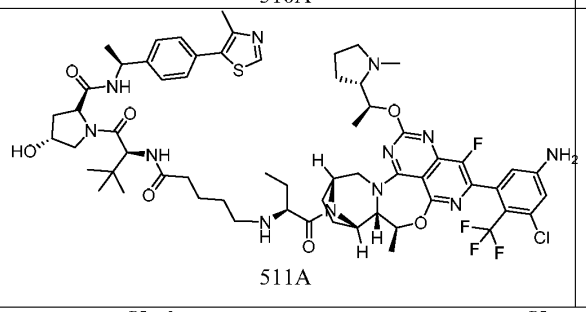
484[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((S)-1-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)ethoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 836.3)	 484A	1269.9
485[2]	(2R)-1-((6aS,7S,10R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-5,6,6a,7,8,9,10,11-octahydro-7,10-epiminoazepino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-16-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 689.3)	 485A	1122.8
486[1]	(2R)-1-((9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2,3,12,12a-tetrahydro-1H-pyrrolo[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-1-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 820.3)	 486A	1253.9
487[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-12-((S)-1-((2R,3S)-3-(difluoromethoxy)-1-methylpyrrolidin-2-yl)ethoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 866.4)	 487A	1299.9
488[7]	(2R)-1-((5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl methylsulfamate ([M+H]$^+$= 833.3)	 488A	1265.9

489[6]	(2S)-1-(((2R,13aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 834.3)	 489A	1267.9
490[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxopropan-2-yl cyclopropanesulfonate ([M+H]$^+$= 828.1)	 490A	1249.8
491[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 892.5)	 491A	1325.9
492[1]	2-(2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,8,9-hexahydropyrido[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-8-yl)ethyl ethanesulfonate ([M+H]$^+$= 777)	 492A	1210.9

493[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxopropan-2-yl cyclopropanesulfonate ([M+H]$^+$= 846.1)	 493A	1267.8
494[3]	(2R)-1-((14aS)-10-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-7-(((S)-1-methylpyrrolidin-2-yl)methoxy)-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 776.2)	 494A	1209.9
495[1]	(2R)-1-((5S,5aS,6S,9R)-2-(3-amino-2-bromo-5-chloro-6-(trifluoromethyl)phenyl)-1-fluoro-12-((S)-1-((2R,3S)-3-methoxy-1-methylpyrrolidin-2-yl)ethoxy)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 910.5)	 495A	1342.8
496[1]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-methyloctahydro-4aH-cyclopenta[b]pyridin-4a-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 838.3)	 496A	1271.5
497[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-12-((S)-1-((S,Z)-1-ethyl-3-(fluoromethylene)pyrrolidin-2-yl)ethoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 844.5)	 497A	1277.9

498[7]	(R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-12-(((S)-1,2-dimethylpyrrolidin-2-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 790.7)	 498A	1223.5
499[2]	2-((5aS,7R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5,5a,6,7,8,9-hexahydropyrido[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-7-yl)ethyl ethanesulfonate ([M+H]$^+$= 776.8)	 499A	1210.9
500[7]	(2R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 830.5)	 500A	1263.9
501[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-2-ethynyl-4-fluoro-3-methylphenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 784.5)	 501A	1217.5
502[5]	(2R)-1-((5aS,6S,9R)-2-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl dimethylsulfamate		1265.9

	([M+H]$^+$= 847.4)	502A	
503[7]	(2R)-1-((5S,5aS,6S,9R)-2-(3-amino-5-chloro-2-fluoro-6-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 848.5)	 503A	1281.9
504[3]	(2R)-1-((14aS)-10-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-7-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 794.3)	 504A	1227.9
505[2]	2-(8-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-9-chloro-7-fluoro-5-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,11,12,12a-tetrahydro-2H-azeto[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-1-yl)ethyl ethanesulfonate ([M+H]$^+$= 762.9)	 505A	1196.9
506[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-12-((S)-1-((2R,3S)-3-cyclopropoxy-1-ethylpyrrolidin-2-yl)ethoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 870.6)	 506A	1304
507[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-		1297.9

	2-yl ethanesulfonate ([M+H]$^+$= 864.5)	507A	
508[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-(((R)-2-methylmorpholino)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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 854.6)	 508A	1287.5
509	(R)-1-((6aR,7S,10R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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]cyclooct a[1,2,3-de]naphthalen-15-yl)-1-oxopropan-2-yl ethanesulfonate ([M+H]$^+$= 811.9)	 509A	1245.5
510[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((S)-1-methylpyrrolidin-2-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-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 786.3)	 510A	1287.5
511[7]	(R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate ([M+H]$^+$= 800.7)	 511A	1245.5

[1]Diastereomer mixture; [2]single unassigned atropisomer (R^{B7}); [3]tentatively assigned R atropisomer (R^{B7}); [4]atropisomer mixture (R^{B7}); [5]R atropisomer (R^{B7}); [6]single compound with undetermined stereochemistry; [7]single compound, absolute stereochemistry. Compounds of Table 1 are depicted with flat, wedged, and/or hashed wedged bonds. It is understood that compounds depicted in Table 1 encompass all possible stereoisomers, including atropisomers, of the compounds of Table 1. In some instances, the relative stereochemistry at one or more stereocenters of a compound has been determined; in some instances, the absolute stereochemistry has been determined. In some instances, a single compound number represents a mixture of stereoisomers, including atropisomers. In some instances, a single compound number represents a single stereoisomer, such as a single atropisomer. As such, it is understood that if two or more compound numbers in Table 1 are provided with the same depicted structure, then different stereoisomers or mixtures of stereoisomers of the depicted structure are represented by each compound number. Compounds of Formula (a), corresponding to the compound numbers provided in the

first column in Table 1, were synthesized and are used for preparing degrader compounds of Formula (A). Compound names were generated using ChemDraw Professional v. 20.0.0.41.

[349] In some embodiments, the compounds of the present disclosure exhibit one or more functional characteristics disclosed herein. For example, a subject compound binds to a Ras protein, a wildtype KRAS protein or a mutant form thereof. In some embodiments, a subject compound binds specifically and also inhibits a Ras protein, a wildtype KRAS protein or a mutant form thereof. In some embodiments, a subject compound selectively inhibits a KRAS protein (wildtype and/or mutant thereof) relative to other non-KRAS proteins. In some embodiments, a subject compound selectively inhibits a KRAS mutant in addition to a wildtype KRAS. In some embodiments, the IC50 of a subject compound for a KRAS mutant (e.g., including G12D) is less than about 5 μM, less than about 1 μM, less than about 500 nM, less than 250 nM, less than 100 nM, less than 50 nM, or even less, as measured in an in vitro assay known in the art or exemplified herein. In some embodiments, the IC50 of a subject compound for each of wildtype KRAS, KRAS G12D, KRAS G12C, KRAS G12V, and KRAS G12S is less than about 5 μM, less than about 1 μM, less than about 500 nM, less than 250 nM, less than 100 nM, less than 50 nM, or even less, as measured in an in vitro assay known in the art or exemplified herein. In some embodiments, a subject compound covalently binds to a KRAS mutant (e.g., KRAS G12D and/or KRAS G12C). In some embodiments, a subject compound covalently binds to wildtype KRAS.

[350] In some embodiments, a compound of the present disclosure is capable of reducing Ras signaling output. Such reduction may be evidenced by one or more of the following: (i) an increase in steady state level of GDP-bound modified protein; (ii) a reduction in steady state level of GTP-bound Ras protein; (iii) a reduction of phosphorylated AKTs473, (iv) a reduction of phosphorylated ERKT202/y204, (v) a reduction of phosphorylated S6S235/236, (vi) a reduction of cell growth of a tumor cell expressing a Ras mutant (e.g., G12S, G12C, G12D, G12V, G13C, and/or G13D) protein, (vii) a reduction in Ras interaction with a Ras-pathway signaling protein, and (viii) a reduction in expression level of Ras protein. In some cases, the reduction in Ras signaling output can be evidenced by two, three, four, five, six, seven or all of (i)-(viii) above.

[351] A compound of the present disclosure may exhibit advantageous solubility and DMPK properties. Fine-tuned pharmacological properties embodied in the subject compounds are of great significance for improving efficacy and safety of KRAS inhibitors for therapeutic clinical applications. Moreover, compounds disclosed herein may exhibit minimal cross reactivity to a wide spectrum of kinases, resulting in reduced undesired off-target side effects. In some embodiments, a compound of the present disclosure exhibits at least one, two, three, or multiple salient superior pharmacological and/or safety properties. Exemplary superior DMPK properties associated with a compound of the present disclosure may include, but are not limited to, improved metabolic stability, reduced hERG liability, decreased CYP inhibition, increased oral exposure, and decreased serum protein binding (hence increasing the free and available compound circulating in the blood of a subject following administration of the compound).

[352] It shall be understood that different aspects of the disclosure can be appreciated individually, collectively, or in combination with each other. Various aspects described herein may be applied to any of the particular applications disclosed herein. The compositions of matter, including compounds of any formulae disclosed in the compound section, of the present disclosure may be utilized in the method section, including methods of use and production disclosed herein, or vice versa.

Methods

[353] The compounds, salts, and solvates described herein are Ras inhibitors capable of inhibiting a Ras protein, such as wild-type Ras or a Ras mutant protein (e.g., G12S, G12C, G12D, G12V, G13C, and/or G13D) from K-Ras,

H-Ras or N-Ras. Compounds disclosed herein, including pharmaceutically acceptable salts or solvates thereof, have a wide range of applications in therapeutics, diagnostics, and other biomedical research.

[354] In certain aspects, the present disclosure provides a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein (e.g., a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a pharmaceutically acceptable salt or solvate thereof. In certain aspects, the present disclosure provides a method of preventing cancer from occurring, or preventing the reoccurrence of cancer, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the subject is pre-disposed to the cancer.

[355] In certain aspects, the present disclosure provides a method of treating a cancer comprising amplified wildtype Ras or a Ras mutant (e.g., G12S, G12C, G12D, G12V, G13C, and/or G13D) protein in a subject, comprising inhibiting amplified wildtype Ras or the Ras mutant protein of said subject by administering to said subject a compound, wherein the compound is characterized in that upon contacting the Ras protein, the Ras protein activity or function is inhibited (e.g., partially inhibited or completely inhibited), such that said inhibited Ras protein exhibits reduced Ras signaling output (e.g., compared to a corresponding Ras protein not contacted by the compound).

[356] In certain aspects, the present disclosure provides a method of treating a cancer comprising Ras G12D mutant protein in a subject, comprising inhibiting the Ras G12D protein of said subject by administering to said subject a compound, wherein the compound is characterized in that upon contacting the Ras protein, the Ras protein activity and/or expression is reduced (e.g., partially or completely reduced), such that said inhibited Ras protein exhibits reduced Ras signaling output (e.g., compared to a corresponding Ras protein not contacted by the compound).

[357] In certain aspects, the present disclosure provides a method of inhibiting activity and/or expression of a Ras protein (e.g., K-Ras, mutant K-Ras including but not limited to K-Ras G12C and K-Ras G12D), comprising contacting a Ras protein with an effective amount of a compound described herein (e.g., a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a pharmaceutically acceptable salt or solvate thereof, thereby inhibiting the activity and/or expression of the Ras protein.

[358] In certain aspects, the present disclosure provides a method of inhibiting cell growth, comprising administering an effective amount of a compound described herein (e.g., a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a pharmaceutically acceptable salt or solvate thereof, to a cell expressing a Ras (e.g., K-Ras) protein, thereby inhibiting growth of said cells. In some embodiments, the cells express a mutant K-Ras such as K-Ras G12D. In some embodiments, the subject method comprises administering an additional agent to said cell.

[359] In certain aspects, the present disclosure provides a method of treating a disease mediated at least in part by a Ras protein, such as K-Ras or a mutant thereof, in a subject in need thereof, comprising administering to the

subject an effective amount of a compound disclosed herein (e.g., a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the Ras protein is K-Ras G12D. In some embodiments, the disease is cancer, such as a solid tumor or a hematological cancer. In some embodiments, the method further comprises administering an additional agent to the subject, such as a SHP2 inhibitor, a SOS inhibitor, an EGFR inhibitor, a MEK inhibitor, an ERK inhibitor, a CDK4/6 inhibitor, a BRAF inhibitor, or a combination thereof.

[360] In certain aspects, the present disclosure provides a method of inhibiting activity and/or expression of a Ras protein, such as K-Ras or a mutant thereof, comprising contacting the Ras protein with a compound disclosed herein (e.g., a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound (e.g., a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6))exhibits an IC50 against the Ras protein of less than 10 μM, such as less than 5 μM, 1 μM, 500 nM, 100 nM, 50 nM, 10 nM, 5 nM, 1 nM, 500 pM, 50 pM, 10 pM or less. In some embodiments, the Ras protein is K-Ras G12D.

[361] In certain aspects, the present disclosure provides a method of treating a Ras-mediated cancer in a subject in need thereof, comprising administering to the subject a SHP2 inhibitor, a SOS inhibitor, an EGFR inhibitor, a MEK inhibitor, an ERK inhibitor, a CDK4/6 inhibitor, or a BRAF inhibitor and an effective amount of a compound disclosed herein, such as a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is a hematological cancer.

[362] In practicing any of the methods disclosed herein, the Ras target to which a subject compound binds, either covalently or reversibly, can be a Ras mutant (e.g., K-Ras G12C or K-Ras G12D). In some embodiments, the methods of treating cancer can be applied to treat a solid tumor or a hematological cancer. In some embodiments, the cancer being treated can be, without limitation, prostate cancer, brain cancer, colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, various lung cancers including non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally

induced cancers, combinations of said cancers, and metastatic lesions of said cancers. In some embodiments is a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a hematological cancer. In some embodiments is a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, wherein the cancer is a hematological cancer selected from one or more of chronic lymphocytic leukemia (CLL), acute leukemias, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and pre-leukemia. In some embodiments is a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, wherein the cancer is one or more cancers selected from the group consisting of chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), T-cell acute lymphoblastic leukemia (T-ALL), B cell acute lymphoblastic leukemia (B-ALL), and/or acute lymphoblastic leukemia (ALL).

[363] Any of the treatment methods disclosed herein can be administered alone or in combination or in conjunction with another therapy or another agent. By "combination" it is meant to include (a) formulating a subject composition containing a subject compound together with another agent, or (b) using the subject composition separate from the another agent as an overall treatment regimen. By "conjunction" it is meant that the another therapy or agent is administered either simultaneously, concurrently or sequentially with a subject composition comprising a compound disclosed herein, with no specific time limits, wherein such conjunctive administration provides a therapeutic effect.

[364] In some embodiments, a subject treatment method is combined with surgery, cellular therapy, chemotherapy, radiation, and/or immunosuppressive agents. Additionally, compositions of the present disclosure can be combined with other therapeutic agents, such as other anti-cancer agents, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, immunostimulants, and combinations thereof. In one embodiment, a subject treatment method is combined with a chemotherapeutic agent.

[365] Exemplary chemotherapeutic agents include an anthracycline (e.g., doxorubicin (e.g., liposomal doxorubicin)), a vinca alkaloid (e.g., vinblastine, vincristine, vindesine, vinorelbine), an alkylating agent (e.g., cyclophosphamide, decarbazine, melphalan, ifosfamide, temozolomide), an immune cell antibody, an antimetabolite (including, e.g., folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors (e.g., fludarabine)), a TNFR glucocorticoid induced TNFR related protein (GITR) agonist, a proteasome inhibitor, an immunomodulator such as thalidomide or a thalidomide derivative. Additional chemotherapeutic agents contemplated for use in combination include busulfan (Myleran®), busulfan injection (Busulfex®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), daunorubicin hydrochloride (Cerubidine®), daunorubicin citrate liposome injection (DaunoXome®), dexamethasone, doxorubicin hydrochloride (Adriamycin®, Rubex®), etoposide

(Vepesid®), fludarabine phosphate (Fludara®), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), mitoxantrone (Novantrone®), Gemtuzumab Ozogamicin (Mylotarg®), anastrozole (Arimidex®), bicalutamide (Casodex®), bleomycin sulfate (Blenoxane®), busulfan injection (Busulfex®), capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), carmustine (BiCNU®), chlorambucil (Leukeran®), cisplatin (Platinol®), dacarbazine (DTIC-Dome®), dactinomycin (Actinomycin D, Cosmegan), dexamethasone, docetaxel (Taxotere®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitibine, Gemcitabine (difluorodeoxycitidine), ifosfamide (IFEX®), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone (Novantrone®), mylotarg, paclitaxel (Taxol®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-thioguanine, thiotepa, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®).

[366] Anti-cancer agents of particular interest for combinations with a compound of the present disclosure include: anthracyclines; alkylating agents; antimetabolites; drugs that inhibit either the calcium dependent phosphatase calcineurin or the p70S6 kinase FK506 or inhibit the p70S6 kinase; mTOR inhibitors; immunomodulators; anthracyclines; vinca alkaloids; proteosome inhibitors; GITR agonists; protein tyrosine phosphatase inhibitors; a CDK4 kinase inhibitor; a BTK inhibitor; a MKN kinase inhibitor; a DGK kinase inhibitor; or an oncolytic virus.

[367] Exemplary antimetabolites include, without limitation, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors: methotrexate (Rheumatrex®, Trexall®), 5-fluorouracil (Adrucil®, Efudex®, Fluoroplex®), floxuridine (FUDF®), cytarabine (Cytosar-U®, Tarabine PFS), 6-mercaptopurine (Puri-Nethol®)), 6-thioguanine (Thioguanine Tabloid®), fludarabine phosphate (Fludara®), pentostatin (Nipent®), pemetrexed (Alimta®), raltitrexed (Tomudex®), cladribine (Leustatin®), clofarabine (Clofarex®, Clolar®), azacitidine (Vidaza®), decitabine and gemcitabine (Gemzar®). Preferred antimetabolites include, cytarabine, clofarabine and fludarabine.

[368] Exemplary alkylating agents include, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes: uracil mustard (Aminouracil Mustard®, Chlorethaminacil®, Demethyldopan®, Desmethyldopan®, Haemanthamine®, Nordopan®, Uracil nitrogen Mustard®, Uracillost®, Uracilmostaza®, Uramustin®, Uramustine®), chlormethine (Mustargen®), cyclophosphamide (Cytoxan®, Neosar®, Clafen®, Endoxan®, Procytox®, Revimmune™), ifosfamide (Mitoxana®), melphalan (Alkeran®), Chlorambucil (Leukeran®), pipobroman (Amedel®, Vercyte®), triethylenemelamine (Hemel®, Hexalen®, Hexastat®), triethylenethiophosphoramine, Temozolomide (Temodar®), thiotepa (Thioplex®), busulfan (Busilvex®, Myleran®), carmustine (BiCNU®), lomustine (CeeNU®), streptozocin (Zanosar®), and Dacarbazine (DTIC-Dome®). Additional exemplary alkylating agents include, without limitation, Oxaliplatin (Eloxatin®); Temozolomide (Temodar® and Temodal®); Dactinomycin (also known as actinomycin-D, Cosmegen®); Melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, Alkeran®); Altretamine (also known as hexamethylmelamine (HMM), Hexalen®); Carmustine (BiCNU®); Bendamustine (Treanda®); Busulfan (Busulfex® and Myleran®); Carboplatin (Paraplatin®); Lomustine (also known as CCNU, CeeNU®); Cisplatin (also known as CDDP, Platinol® and Platinol®-AQ); Chlorambucil (Leukeran®); Cyclophosphamide (Cytoxan® and Neosar®); Dacarbazine (also known as DTIC, DIC and imidazole carboxamide, DTIC-Dome®); Altretamine (also known as hexamethylmelamine (HMM), Hexalen®); Ifosfamide (Ifex®); Prednumustine; Procarbazine (Matulane®); Mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride,

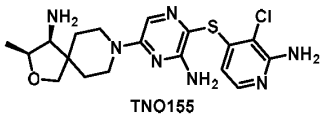
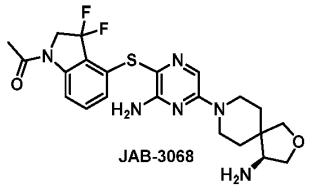
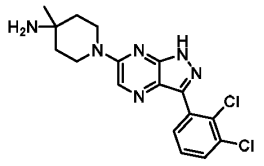
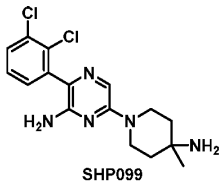
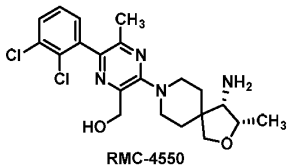
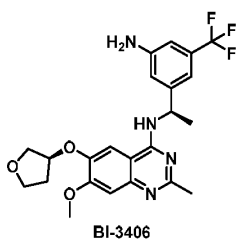
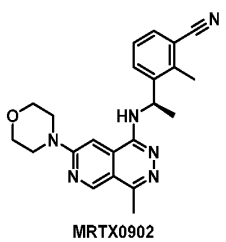
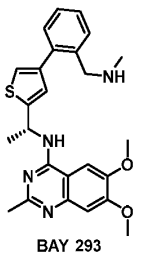
Mustargen®); Streptozocin (Zanosar®); Thiotepa (also known as thiophosphoamide, TESPA and TSPA, Thioplex®); Cyclophosphamide (Endoxan®, Cytoxan®, Neosar®, Procytox®, Revimmune®); and Bendamustine HCl (Treanda®).

[369] In certain aspects, compositions provided herein can be administered in combination with radiotherapy, such as radiation. Whole body radiation may be administered at 12 Gy. A radiation dose may comprise a cumulative dose of 12 Gy to the whole body, including healthy tissues. A radiation dose may comprise from 5 Gy to 20 Gy. A radiation dose may be 5 Gy, 6 Gy, 7 Gy, 8 Gy, 9 Gy, 10 Gy, 11 Gy, 12, Gy, 13 Gy, 14 Gy, 15 Gy, 16 Gy, 17 Gy, 18 Gy, 19 Gy, or up to 20 Gy. Radiation may be whole body radiation or partial body radiation. In the case that radiation is whole body radiation it may be uniform or not uniform. For example, when radiation may not be uniform, narrower regions of a body such as the neck may receive a higher dose than broader regions such as the hips.

[370] Where desirable, an immunosuppressive agent can be used in conjunction with a subject treatment method. Exemplary immunosuppressive agents include but are not limited to cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies or other antibody therapies, cytoxin, fludarabine, cyclosporin, FK506, rapamycin, mycophenolic acid, steroids, FR901228, cytokines, and irradiation, peptide vaccine, and any combination thereof. In accordance with the presently disclosed subject matter, the above-described various methods can comprise administering at least one immunomodulatory agent. In certain embodiments, the at least one immunomodulatory agent is selected from the group consisting of immunostimulatory agents, checkpoint immune blockade agents (e.g., blockade agents or inhibitors of immune checkpoint genes, such as, for example, PD-1, PD-L1, CTLA-4, IDO, TIM3, LAG3, TIGIT, BTLA, VISTA, ICOS, KIRs and CD39), radiation therapy agents, chemotherapy agents, and combinations thereof. In some embodiments, the immunostimulatory agents are selected from the group consisting of IL-12, an agonist costimulatory monoclonal antibody, and combinations thereof. In one embodiment, the immunostimulatory agent is IL-12. In some embodiments, the agonist costimulatory monoclonal antibody is selected from the group consisting of an anti-4-lBB antibody, an anti-OX40 antibody, an anti-ICOS antibody, and combinations thereof. In one embodiment, the agonist costimulatory monoclonal antibody is an anti-4-l BB antibody. In some embodiments, the checkpoint immune blockade agents are selected from the group consisting of anti-PD-L1 antibodies, anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-LAG3 antibodies, anti-B7-H3 antibodies, anti-TIM3 antibodies, and combinations thereof. In one embodiment, the checkpoint immune blockade agent is an anti-PD-Ll antibody. In some cases, a compound of the present disclosure can be administered to a subject in conjunction with (e.g., before, simultaneously or following) bone marrow transplantation, T cell ablative therapy using either chemotherapy agents such as, fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, or antibodies such as OKT3 or CAMPATH. In some cases, expanded cells can be administered before or following surgery. Alternatively, compositions comprising a compound described herein can be administered with immunostimulants. Immunostimulants can be vaccines, colony stimulating agents, interferons, interleukins, viruses, antigens, co-stimulatory agents, immunogenicity agents, immunomodulators, or immunotherapeutic agents. An immunostimulant can be a cytokine such as an interleukin. One or more cytokines can be introduced with modified cells provided herein. Cytokines can be utilized to boost function of modified T lymphocytes (including adoptively transferred tumor-specific cytotoxic T lymphocytes) to expand within a tumor microenvironment. In some cases, IL-2 can be used to facilitate expansion of the modified cells described herein. Cytokines such as IL-15 can also be employed. Other relevant cytokines in the field of immunotherapy can also be utilized, such as IL-2, IL-7, IL-12, IL-15, IL-21,

or any combination thereof. An interleukin can be IL-2, or aldesleukin. Aldesleukin can be administered in low dose or high dose. A high dose aldesleukin regimen can involve administering aldesleukin intravenously every 8 hours, as tolerated, for up to about 14 doses at about 0.037 mg/kg (600,000 IU/kg). An immunostimulant (e.g., aldesleukin) can be administered within 24 hours after a cellular administration. An immunostimulant (e.g., aldesleukin) can be administered in as an infusion over about 15 minutes about every 8 hours for up to about 4 days after a cellular infusion. An immunostimulant (e.g., aldesleukin) can be administered at a dose from about 100,000 IU/kg, 200,000 IU/kg, 300,000 IU/kg, 400,000 IU/kg, 500,000 IU/kg, 600,000 IU/kg, 700,000 IU/kg, 800,000 IU/kg, 900,000 IU/kg, or up to about 1,000,000 IU/kg. In some cases, aldesleukin can be administered at a dose from about 100,000 IU/kg to 300,000 IU/kg, from 300,000 IU/kg to 500,000 IU/kg, from 500,000 IU/kg to 700,000 IU/kg, from 700,000 IU/kg to about 1,000,000 IU/kg.

[371] In some embodiments, a compound described herein, such as a compound, salt, or solvate of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), is administered in combination or in conjunction with one or more pharmacologically active agents selected from (1) an inhibitor of MEK (e.g., MEK1, MEK2) or of mutants thereof; (2) an inhibitor of epidermal growth factor receptor (EGFR) and/or of mutants thereof; (3) an immunotherapeutic agent (e.g., checkpoint immune blockade agents, as disclosed herein); (4) a taxane (e.g., paclitaxel, docetaxel); (5) an anti-metabolite (e.g. antifolates such as methotrexate, raltitrexed, pyrimidine analogues such as 5-fluorouracil (5-FU), ribonucleoside and deoxyribonucleoside analogues, capecitabine and gemcitabine, purine and adenosine analogues such as mercaptopurine, thioguanine, cladribine and pentostatin, cytarabine (ara C), fludarabine); (6) an inhibitor of FGFR1 and/or FGFR2 and/or FGFR3 and/or FGFR4 and/or of mutants thereof; (7) a mitotic kinase inhibitor (e.g., a CDK4/6 inhibitor); (8) an anti-angiogenic drug (e.g., an anti-VEGF antibody); (9) a topoisomerase inhibitor; (10) a platinum-containing compound (e.g. cisplatin, oxaliplatin, carboplatin); (11) an inhibitor of ALK and/or of mutants thereof; (12) an inhibitor of c-MET and/or of mutants thereof; (13) an inhibitor of BCR-ABL and/or of mutants thereof; (14) an inhibitor of ErbB2 (Her2) and/or of mutants thereof; (15) an inhibitor of AXL and/or of mutants thereof; (16) an inhibitor of NTRK1 and/or of mutants thereof; (17) an inhibitor of RET and/or of mutants thereof; (18) an inhibitor of A-Raf and/or B-Raf and/or C-Raf and/or of mutants thereof; (19) an inhibitor of ERK and/or of mutants thereof; (20) an MDM2 inhibitor; (21) an inhibitor of mTOR; (22) an inhibitor of BET; (23) an inhibitor of IGF1/2 and/or of IGF1-R; (24) an inhibitor of CDK9; (25) an inhibitor of farnesyl transferase; (26) an inhibitor of SHIP pathway including SHIP2 inhibitor, as well as SHIP1 inhibitors; (27) an inhibitor of SRC; (28) an inhibitor of JAK; (29) a PARP inhibitor, (30) a BTK inhibitor, (31) a ROS1 inhibitor, (32) an inhibitor of Src, FLT3, HDAC, VEGFR, PDGFR, LCK, Bcr-Abl or AKT, (33) an inhibitor of KRAS G12C mutant (e.g., including but not limited to AMG510, MRTX849, and any covalent inhibitors binding to the cysteine residue 12 of KRAS, the structures of which are publicly known) (e.g., an inhibitor of Ras G12C as described in US20180334454, US20190144444, US20150239900, US10246424, US20180086753, WO2018143315, WO2018206539, WO201911075 19, WO2019141250, WO2019150305, US9862701, US20170197945, US20180086753, US10144724, US20190055211, US20190092767, US20180127396, US20180273523, US10280172, US20180319775, US20180273515, US20180282307, US20180282308, WO2019051291, WO2019213526, WO2019213516, WO2019217691, WO2019241157, WO2019217307, WO2020047192, WO2017087528, WO2018218070, WO2018218069, WO2018218071, WO2020027083, WO2020027084, WO2019215203, WO2019155399, WO2020035031, WO2014160200, WO2018195349,

WO2018112240, WO2019204442, WO2019204449, WO2019104505, WO2016179558, WO2016176338, or related patents and applications, each of which is incorporated by reference in its entirety), (34) an SHC inhibitor, (35) a GAB inhibitor, (36) a GRB inhibitor, (37) a PI-3 kinase inhibitor, (38) a MARPK inhibitor, (39) a CDK4/6 inhibitor, (40) a MAPK inhibitor, or (41) a SHP pathway inhibitor, such as a SHP2 inhibitor (e.g., RMC-4630, ERAS-601, 
TNO155
, 
JAB-3068
, 
IACS-13909/BBP-398
, 
SHP099
, and 
RMC-4550
) or a SHP1 inhibitor. In some embodiments, a Ras inhibitor described herein, such as a compound, salt, or solvate of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), is administered in combination or in conjunction with one or more checkpoint immune blockade agents (e.g., anti-PD-1 and/or anti-PD-L1 antibody, anti-CLTA-4 antibody). In some embodiments, a Ras inhibitor described herein, such as a compound, salt, or solvate of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), is administered in combination or in conjunction with one or more pharmacologically active agents comprising an inhibitor against one or more targets selected from: MEK, epidermal growth factor receptor (EGFR), FGFR1, FGFR2, FGFR3, mitotic kinase, topoisomerase, ALK, ALK5, c-MET, ErbB2, AXL, NTRK1, RET, A-Raf, B-Raf, C-Raf, ERK, MDM2, mTOR, BET, IGF1/2, IGF1-R, CDK9, SHIP1, SHIP2, SHP2, SRC, JAK, PARP, BTK, FLT3, HDAC, VEGFR, PDGFR, LCK, Bcr-Abl, AKT, KRAS G12C mutant, and ROS1. In some embodiments, a Ras inhibitor described herein, such as a compound, salt, or solvate of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), is administered in combination or in conjunction with one or more additional pharmacologically active agents comprising an inhibitor of SOS (e.g., SOS1, SOS2) or of mutants thereof, such as 
BI-3406
, 
MRTX0902
, 
BAY 293
, RMC-5845, or BI-1701963. In some embodiments, a Ras inhibitor described herein, such as a compound, salt, or solvate of Formula (A), (A-1), (A-2),

(A-3), (A-4), (A-5), (A-6), (a), (a-1), (a-2), (a-3), (a-4), (a-5), or (a-6), is administered in combination or in conjunction with an inhibitor of SOS described in WO2021092115, WO2018172250, WO2019201848, WO2019122129, WO2018115380, WO2021127429, WO2020180768, or WO2020180770, each of which is herein incorporated by reference in its entirety for all purposes.

[372] In some embodiments, a Ras inhibitor described herein, such as a compound, salt, or solvate of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), is administered in combination or in conjunction with one or more checkpoint immune blockade agents (e.g., anti-PD-1 and/or anti-PD-L1 antibody, anti-CLTA-4 antibody).

[373] In some embodiments, a compound described herein, such as a compound, salt, or solvate of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), and one or more pharmacologically active agents are administered either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two or more compounds in the body of the patient.

[374] In some embodiments, a compound described herein, such as a compound, salt, or solvate of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), and one or more pharmacologically active agents are administered sequentially in any order by a suitable route, such as infusion or orally. The dosing regimen may vary depending upon the stage of the disease, physical fitness of the patient, safety profiles of the individual drugs, and tolerance of the individual drugs, as well as other criteria known to the attending physician and medical practitioner(s) administering the combination. The compound of the present disclosure and other pharmacologically active agent(s) may be administered within minutes of each other, hours, days, or even weeks apart depending upon the particular cycle being used for treatment. In addition, the cycle could include administration of one drug more often than the other during the treatment cycle and at different doses per administration of the drug.

[375] In some cases, a treatment regime may be dosed according to a body weight of a subject. In subjects who are determined obese (BMI > 35) a practical weight may need to be utilized. BMI is calculated by: BMI = weight (kg)/[height (m)]^2. Body weight may be calculated for men as 50 kg + 2.3*(number of inches over 60 inches) or for women 45.5 kg + 2.3*(number of inches over 60 inches). An adjusted body weight may be calculated for subjects who are more than 20% of their ideal body weight. An adjusted body weight may be the sum of an ideal body weight + (0.4*(Actual body weight – ideal body weight)). In some cases, a body surface area may be utilized to calculate a dosage. A body surface area (BSA) may be calculated by: BSA (m^2) = $\sqrt{}$Height (cm) ∗Weight (kg)/3600.

[376] In certain aspects, the present disclosure provides a method of modulating activity (including expression) of a Ras (e.g., K-Ras) protein, comprising contacting a Ras protein with an effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, thereby modulating the activity of the Ras (e.g., K-Ras) protein. In some embodiments, the subject method comprises administering an additional agent or therapy.

[377] In certain aspects, the present disclosure provides a method of inhibiting activity (including expression) of

a Ras protein (wildtype or mutant thereof), comprising contacting a Ras protein with an effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof. Ras protein whose activity and/or expression can be inhibited includes but is not limited to mutants such as G12S, G12C, G12D, G12V, G13C, and/or G13D proteins of K-Ras, H-Ras, and N-Ras.

[378] In certain aspects, the present disclosure provides a method of reducing Ras signaling output in a cell by contacting the cell with a compound described herein (e.g., a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)). A reduction in Ras signaling can be evidenced by one or more of the following: (i) an increase in steady state level of GDP-bound modified protein; (ii) a reduction in steady state level of GTP-bound Ras protein; (iii) a reduction of phosphorylated AKTs473, (iv) a reduction of phosphorylated ERKT202/y204, (v) a reduction of phosphorylated S6S235/236, (vi) a reduction of cell growth of a tumor cell expressing a Ras mutant (e.g., G12S, G12C, G12D, G12V, G13C, and/or G13D) protein, (vii) a reduction in Ras interaction with a Ras-pathway signaling protein, and (viii) a reduction in expression level of Ras protein. Non-limiting examples of Ras-pathway signaling proteins include SOS (including SOS1 and SOS2), RAF, SHC, SHP (including SHP1 and SHP2), MEK, MAPK, ERK, GRB, RASA1, and GNAQ. In some embodiments, the reduction in Ras signaling output can be evidenced by two, three, four, five, six, seven, or all of (i)-(viii) above. In some embodiments, the reduction of any one or more of (i)-(viii) can be 0.1-fold, 0.2-fold, 0.3-fold, 0.4-fold, 0.5-fold, 0.6-fold, 0.7-fold, 0.8-fold, 0.9-fold, 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold, 2000-fold, 3000-fold, 4000-fold, 5000-fold, or more as compared to a control not treated with a subject compound. A reduction in cell growth can be demonstrated with the use of tumor cells or cell lines. A tumor cell line can be derived from a tumor in one or more tissues, e.g., pancreas, lung, ovary, biliary tract, intestine (e.g., small intestine, large intestine, colon), endometrium, stomach, hematopoietic tissue (e.g., lymphoid tissue), etc. Examples of tumor cell lines comprising a K-Ras mutation include, but are not limited to, A549 (e.g., K-Ras G12S), AGS (e.g., K-Ras G12D), ASPC1 (e.g., K-Ras G12D), Calu-6 (e.g., K-Ras Q61K), CFPAC-1 (e.g., K-Ras G12V), CL40 (e.g., K-Ras G12D), COLO678 (e.g., K-Ras G12D), COR-L23 (e.g., K-Ras G12V), DAN-G (e.g., K-Ras G12V), GP2D (e.g., K-Ras G12D), GSU (e.g., K-Ras G12F), HCT116 (e.g., K-Ras G13D), HEC1A (e.g., K-Ras G12D), HEC1B (e.g., K-Ras G12F), HEC50B (e.g., K-Ras G12F), HEYA8 (e.g., K-Ras G12D or G13D), HPAC (e.g., K-Ras G12D), HPAFII (e.g., K-Ras G12D), HUCCT1 (e.g., K-Ras G12D), KARPAS620 (e.g., K-Ras G13D), KOPN8 (e.g., K-Ras G13D), KP-3 (e.g., K-Ras G12V), KP-4 (e.g., K-Ras G12D), L3.3 (e.g., K-Ras G12D), LoVo (e.g., K-Ras G13D), LS180 (e.g., K-Ras G12D), LS513 (e.g., K-Ras G12D), MCAS (e.g., K-Ras G12D), NB4 (e.g., K-Ras A18D), NCI-H1355 (e.g., K-Ras G13C), NCI-H1573 (e.g., K-Ras G12A), NCI-H1944 (e.g., K-Ras G13D), NCI-H2009 (e.g., K-Ras G12A), NCI-H441 (e.g., K-Ras G12V), NCI-H747 (e.g., K-Ras G13D), NOMO-1 (e.g., K-Ras G12D), OV7 (e.g., K-Ras G12D), PANC0203 (e.g., K-Ras G12D), PANC0403 (e.g., K-Ras G12D), PANC0504 (e.g., K-Ras G12D), PANC0813 (e.g., K-Ras G12D), PANC1 (e.g., K-Ras G12D), Panc-10.05 (e.g., K-Ras G12D), PaTu-8902 (e.g., K-Ras G12V), PK1 (e.g., K-Ras G12D), PK45H (e.g., K-Ras G12D), PK59 (e.g., K-Ras G12D), SK-CO-1 (e.g., K-Ras G12V), SKLU1 (e.g., K-Ras G12D), SKM-1 (e.g., K-Ras K117N), SNU1 (e.g., K-Ras G12D), SNU1033 (e.g., K-Ras G12D), SNU1197 (e.g., K-Ras G12D), SNU407 (e.g., K-Ras G12D), SNU410 (e.g., K-Ras G12D), SNU601 (e.g., K-Ras G12D), SNU61 (e.g., K-Ras G12D), SNU8 (e.g., K-Ras G12D), SNU869 (e.g., K-Ras G12D), SNU-C2A (e.g., K-Ras G12D), SU.86.86

(e.g., K-Ras G12D), SUIT2 (e.g., K-Ras G12D), SW1990 (e.g., K-Ras G12D), SW403 (e.g., K-Ras G12V), SW480 (e.g., K-Ras G12V), SW620 (e.g., K-Ras G12V), SW948 (e.g., K-Ras Q61L), T3M10 (e.g., K-Ras G12D), TCC-PAN2 (e.g., K-Ras G12R), TGBC11TKB (e.g., K-Ras G12D), and MIA Pa-Ca (e.g., MIA Pa-Ca 2 (e.g., K-Ras G12C)).

[379] A reduction of signaling output can be ascertained by a wide variety of methods known in the art. For example, phosphorylation of a substrate or a specific amino acid residue thereof can be detected and/or quantified using one or more techniques, such as kinase activity assays, phospho-specific antibodies, Western blot, enzyme-linked immunosorbent assays (ELISA), cell-based ELISA, intracellular flow cytometry, mass spectrometry, and multi-analyte profiling. A host of readout can evidence a reduction of Ras signaling output, including without limitation: (i) an increase in steady state level of GDP-bound modified protein; (ii) a reduction in steady state level of GTP-bound Ras protein; (iii) a reduction of phosphorylated AKTs473, (iv) a reduction of phosphorylated ERKT202/y204, (v) a reduction of phosphorylated S6S235/236, (vi) a reduction of cell growth of a tumor cell expressing a Ras mutant (e.g., G12S, G12C, G12D, G12V, G13C, and/or G13D) protein, (vii) a reduction in Ras interaction with a Ras-pathway signaling protein, and (viii) a reduction in expression level of Ras protein. In some embodiments, a reduction is evidenced by 2, 3, 4 or more of items (i)-(viii). In some embodiments, the reduction in Ras signaling output can be evidenced by any one of (i)-(viii) as compared to control corresponding Ras protein in the absence of a compound disclosed herein. For example, a control Ras protein, as described herein, can be a Ras protein (e.g., wildtype or mutated) that is not bound to any subject compound of the present disclosure. The increase in item (i) or reduction in items (ii) through (vi) can be at least about 0.1-fold, 0.2-fold, 0.3-fold, 0.4-fold, 0.5-fold, 0.6-fold, 0.7-fold, 0.8-fold, 0.9-fold, 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold, 2000-fold, 3000-fold, 4000-fold, 5000-fold, or more as compared to the control Ras protein. In some embodiments, a reduction in Ras interaction with a Ras-pathway signaling protein is established by a reduced interaction with SOS (including SOS1 and SOS2), RAF, SHC, SHP (including SHP1 and SHP2), MEK, MAPK, ERK, GRB, RASA1, or GNAQ.

[380] Signaling output measured in terms of IC50 values can be obtained and a ratio of IC50 against one mutant relative to another mutant can be calculated. For instance, a selective reduction of K-Ras G12D signaling output can be evidenced by a ratio greater than one. In particular, a selective reduction of K-Ras G12D signaling relative to K-Ras G12V signaling or wildtype K-Ras signaling is evidenced if the ratio of IC50 (against K-Ras G12V or wildtype) to IC50 (against K-Ras G12D) is greater than 1.

[381] It will be understood that when a compound described herein (e.g., a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)) selectively binds to a K-Ras G12D protein compared to another K-Ras protein(s) (e.g., WT, G12S, or G12V), the compound binds to the K-Ras G12D protein with greater speed or to a greater degree or by any other quantifiable measurement compared to the other K-Ras protein (e.g., WT, G12S, G12V), under similar or identical reaction conditions for the proteins being compared. In some embodiments, the greater binding of K-Ras G12D can be 0.1-fold, 0.2-fold, 0.3-fold, 0.4-fold, 0.5-fold, 0.6-fold, 0.7-fold, 0.8-fold, 0.9-fold, 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold, 2000-fold, 3000-fold, 4000-fold, 5000-fold, or more as compared to

another K-Ras protein (e.g., WT, G12S, or G12V).

[382] In an aspect is provided a method of inhibiting activity of a Ras protein (e.g., K-Ras, mutant K-Ras, K-Ras G12D), comprising contacting a Ras protein with an effective amount of a compound described herein (e.g., a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a pharmaceutically acceptable salt or solvate thereof, thereby inhibiting the activity of the Ras protein.

[383] In practicing any of the methods disclosed herein, the Ras target to which a subject compound binds can be a wildtype Ras (e.g., KRAS, NRAS, or HRAS) or a Ras mutant (e.g., KRAS G12D, KRAS G12C, KRAS G12S, KRAS G12V, KRAS G13D, KRAS G13C, NRAS G12D, NRAS G12C, NRAS G12S, NRAS G13D, NRAS G13C, HRAS G12D, HRAS G12C, HRAS G12S, HRAS G13D, or HRAS G13C).

[384] In some embodiments, compounds of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6), exhibit at least one, two, three or multiple salient superior pharmacological and/or safety properties. In some embodiments, one or more Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibit at least one, two, three or multiple salient superior pharmacological and/or safety properties compared to a compound having the same core but substantially incapable of forming a covalent bond with the aspartic residue and/or cysteine at the position corresponding to the 12th position of human Kras protein. In embodiments, the superior pharmacological and/or safety properties associated with the subject compound are DMPK properties. In embodiments, the superior DMPK properties associated with the subject compounds include but are not limited to improved metabolic stability, reduced hERG liability, decreased CYP inhibition, increased oral exposure, and decreased serum protein binding (hence increasing the free and available compound circulating in a subject's blood upon administration of the compounds).

[385] In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits improved metabolic stability as compared to a compound having the same core but substantially incapable of forming a covalent bond with an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein. In embodiments, the improved metabolic stability is measured using the method described in Example 17 or similar method. In embodiments, the half-life of the subject compound is greater than the half-life of the comparator compound described above (e.g., as measured using the methods and equations of Example 17). In embodiments, the half-life of the subject compound is greater than the half-life of the comparator compound described above by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the half-life of the subject compound is greater than the half-life of the comparator compound described above by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 50, 600, 700, 800, 900, 1000-fold, or more. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A),

(A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits improved metabolic stability as compared to other known inhibitors of human Kras protein. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits metabolic stability measured in half-life of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 20000, 30000, 40000, 50000, 60000, 70000, 80000, 90000, or 100000 minutes. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits metabolic stability measured as the calculated hepatic extraction ratio of less than 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95%. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits metabolic stability measured as the predicted hepatic clearance of less than 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95% of the blood flow rate.

[386] In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits reduced hERG liability (i.e., reduced hERG inhibition) as compared to a compound having the same core but substantially incapable of forming a covalent bond with an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein. In embodiments, the hERG liability is measured using the method described in Example 21 or similar method. In embodiments, the hERG inhibition of the subject compound is less than the hERG inhibition of the comparator compound described above (e.g., as measured using the methods of Example 21). In embodiments, the hERG inhibition of the subject compound is less than the hERG inhibition of the comparator compound described above by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90%, or more. In embodiments, the hERG inhibition of the subject compound is less than the hERG inhibition of the comparator compound described above by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90%, or more. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits decreased hERG inhibition as compared to other known inhibitors of human Kras protein. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits hERG inhibition measured as IC50 of hERG of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000,

4000, 5000, 6000, 7000, 8000, 9000, 10000, 20000, 30000, 40000, 50000, 60000, 70000, 80000, 90000, or 100000 nmol/L. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits hERG inhibition measured as % of reduced hERG activity of less than 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, or 30% at highest tolerated dose. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits hERG inhibition measured as IC50 of hERG of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 micromolar.

[387] In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits decreased CYP inhibition as compared to a compound having the same core but substantially incapable of forming a covalent bond with an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein. In embodiments, the CYP inhibition is measured using the method described in Example 18 or similar method. In embodiments, the CYP inhibition of the subject compound is less than the CYP inhibition of the comparator compound described above (e.g., as measured using the methods of Example 18). In embodiments, the CYP inhibition of the subject compound is less than the CYP inhibition of the comparator compound described above by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90%, or more. In embodiments, the CYP inhibition of the subject compound is less than the CYP inhibition of the comparator compound described above by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90%, or more. In embodiments, the measured CYP inhibition is inhibition of CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits decreased CYP inhibition as compared to other known inhibitors of human Kras protein. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits CYP inhibition measured as IC50 of CYP of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 20000, 30000, 40000, 50000, 60000, 70000, 80000, 90000, or 100000 nM.

[388] In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits increased oral exposure as compared to a compound having the same core but substantially incapable of forming a covalent bond with an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein. In embodiments, the increased oral exposure is measured

using the method described in Example 11, 12, 13, or 14, or a similar method. In embodiments, the oral exposure of the subject compound is greater than the oral exposure of the comparator compound described above (e.g., as measured using the methods and equations of Example 11, 12, 13, or 14). In embodiments, the oral exposure of the subject compound is greater than the oral exposure of the comparator compound described above by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 50, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the oral exposure of the subject compound is greater than the oral exposure of the comparator compound described above by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the oral exposure measured is the oral exposure in a mouse model. In embodiments, the oral exposure measured is the oral exposure in a rat model. In embodiments, the oral exposure measured is the oral exposure in a dog model. In embodiments, the oral exposure measured is the oral exposure in a monkey model. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits increased oral exposure as compared to other known inhibitors of human Kras protein. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits oral exposure measured as the percentage of administered compound that reaches circulation of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95%, or more. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits oral exposure measured as the oral bioavailability of greater than 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95%, or more.

[389] In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits decreased serum protein binding as compared to a compound having the same core but substantially incapable of forming a covalent bond with an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein. In embodiments, the serum protein binding is measured using the method described in Example 19 or similar method. In embodiments, the serum protein binding of the subject compound is less than the serum protein binding of the comparator compound described above (e.g., as measured using the methods of Example 19). In embodiments, the serum protein binding of the subject compound is less than the serum protein binding of the comparator compound described above by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90%, or more. In embodiments, the serum protein binding of the subject compound is less than the serum protein binding of the comparator compound described above by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90%, or more. In embodiments, the measured serum protein binding is human serum protein binding. In embodiments, the measured serum protein binding is mouse serum protein binding. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-

5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits decreased serum protein binding as compared to other known inhibitors of human Kras protein. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits serum protein binding measured as the percentage of administered compound bound of less than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95%.

[390] In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits an increase in unbound/free compound present in plasma as compared to a compound having the same core but substantially incapable of forming a covalent bond with an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein. In embodiments, the increase in unbound/free compound present in plasma is measured using the method described in Example 19, or a similar method. In embodiments, the unbound/free compound present in plasma of the subject compound is greater than the unbound/free compound present in plasma of the comparator compound described above (e.g., as measured using the methods of Example 19). In embodiments, the unbound/free compound present in plasma of the subject compound is greater than the unbound/free compound present in plasma of the comparator compound described above by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the unbound/free compound present in plasma of the subject compound is greater than the unbound/free compound present in plasma of the comparator compound described above by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the unbound/free compound present in plasma measured is the unbound/free compound present in plasma in a mouse model. In embodiments, the unbound/free compound present in plasma measured is the unbound/free compound present in plasma in a rat model. In embodiments, the unbound/free compound present in plasma measured is the unbound/free compound present in plasma in a dog model. In embodiments, the unbound/free compound present in plasma measured is the unbound/free compound present in plasma in a monkey model. In embodiments, the unbound/free compound present in plasma measured is the unbound/free compound present in human. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits increased unbound/free compound present in plasma as compared to other known inhibitors of human Kras protein. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits unbound/free compound present in plasma measured as the percentage of administered compound free in plasma of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95%.

[391] In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0),

(a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits an increase in tumor exposure as compared to a compound having the same core but substantially incapable of forming a covalent bond with an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein. In embodiments, the increase in tumor exposure is measured using the method described in Example 20, or a similar method. In embodiments, the tumor exposure of the subject compound is greater than the tumor exposure of the comparator compound described above (e.g., as measured using the methods of Example 20). In embodiments, the tumor exposure of the subject compound is greater than the tumor exposure of the comparator compound described above by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the tumor exposure of the subject compound is greater than the tumor exposure of the comparator compound described above by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the tumor exposure measured is the tumor exposure in a mouse model. In embodiments, the tumor exposure measured is the tumor exposure in a rat model. In embodiments, the tumor exposure measured is the tumor exposure in a dog model. In embodiments, the tumor exposure measured is the tumor exposure in a monkey model. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits increased tumor exposure as compared to other known inhibitors of human Kras protein. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits tumor exposure measured as concentration of compound (ng)/tumor (mg) of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 20000, 30000, 40000, 50000, 60000, 70000, 80000, 90000, or 100000.

[392] In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits an increase in covalent engagement to an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein as compared to a compound having the same core but a different covalent moiety. In embodiments, the increase in covalent engagement to an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein is measured using the method described in Example 8, or a similar method. In embodiments, the covalent engagement to an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein of the subject compound is greater than the covalent engagement to an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein of the comparator compound described above by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 50000, 100000-fold, or more. In embodiments, the covalent engagement to an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras

protein of the subject compound is greater than the covalent engagement to an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein of the comparator compound described above by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 50000, 100000-fold, or more. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits increase in covalent engagement as compared to other known inhibitors of human Kras protein. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits covalent engagement measured as the percentage of covalently modified human Kras protein following incubation with fixed concentration of compound (e.g., 1, 2, 3, 4,5, 6, 7, 8, 9, 10, 25, 50, 100 micromolar) of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95%.

[393] In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits decreased plasma clearance as compared to a compound having the same core but substantially incapable of forming a covalent bond with an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein. In embodiments, the rate of plasma clearance of the subject compound is less than the rate of plasma clearance of the comparator compound described above. In embodiments, the rate of plasma clearance of the subject compound is less than the rate of plasma clearance of the comparator compound described above by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the rate of plasma clearance of the subject compound is less than the rate of plasma clearance of the comparator compound described above by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the rate of plasma clearance measured is the rate of plasma clearance in a mouse model. In embodiments, the rate of plasma clearance measured is the rate of plasma clearance in a rat model. In embodiments, the rate of plasma clearance measured is the rate of plasma clearance in a dog model. In embodiments, the rate of plasma clearance measured is the rate of plasma clearance in a monkey model. In embodiments, the rate of plasma clearance measured is the rate of plasma clearance in a human. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits decreased plasma clearance as compared to other known inhibitors of human Kras protein. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits plasma clearance measured in half-life of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800,

900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 20000, 30000, 40000, 50000, 60000, 70000, 80000, 90000, or 100000 minutes. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits plasma clearance measured as ml/min/kg of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, or 10000. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits plasma clearance measured in half-life of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 20000, 30000, 40000, 50000, 60000, 70000, 80000, 90000, or 100000 minutes. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits plasma clearance of less than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, or 70% of blood flow rate.

[394] In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits improved plasma PK (e.g., increased AUC) as compared to a compound having the same core but substantially incapable of forming a covalent bond with an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein. In embodiments, the improved plasma PK (e.g., increased AUC) is measured using the method described in Example 19, or a similar method. In embodiments, the plasma PK (e.g., AUC) of the subject compound is greater than the plasma PK (e.g., AUC) of the comparator compound described above (e.g., as measured using the methods of Example 19). In embodiments, the plasma PK (e.g., AUC) of the subject compound is greater than the plasma PK (e.g., AUC) of the comparator compound described above by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 50, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the plasma PK (e.g., AUC) of the subject compound is greater than the plasma PK (e.g., AUC) of the comparator compound described above by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the plasma PK (e.g., AUC) measured is the plasma PK (e.g., AUC) in a mouse model. In embodiments, the plasma PK (e.g., AUC) measured is the plasma PK (e.g., AUC) in a rat model. In embodiments, the plasma PK (e.g., AUC) measured is the plasma PK (e.g., AUC) in a dog model. In embodiments, the plasma PK (e.g., AUC) measured is the plasma PK (e.g., AUC) in a monkey model. In embodiments, the plasma PK (e.g., AUC) measured is the plasma PK (e.g., AUC) in a human. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits increased AUC as compared to other known inhibitors of human Kras protein. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6),

(a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits AUC measured in h*ng/mL of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 20000, 30000, 40000, 50000, 60000, 70000, 80000, 90000, or 100000 following administration of 1, 3, 5, 10, 30, or 100 mg/kg compound.

[395] In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits increased plasma stability as compared to a compound having the same core but substantially incapable of forming a covalent bond with an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein. In embodiments, the increased plasma stability is measured using the method described in Example 19, or a similar method. In embodiments, the plasma stability of the subject compound is greater than the plasma stability of the comparator compound described above (e.g., as measured using the methods of Example 19). In embodiments, the plasma stability of the subject compound is greater than the plasma stability of the comparator compound described above by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the plasma stability of the subject compound is greater than the plasma stability of the comparator compound described above by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the plasma stability measured is the plasma stability in a mouse model. In embodiments, the plasma stability measured is the plasma stability in a rat model. In embodiments, the plasma stability measured is the plasma stability in a dog model. In embodiments, the plasma stability measured is the plasma stability in a monkey model. In embodiments, the plasma stability measured is the plasma stability in a human. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits increased plasma stability as compared to other known inhibitors of human Kras protein. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits plasma stability measured in half-life of greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 20000, 30000, 40000, 50000, 60000, 70000, 80000, 90000, or 100000 minutes.

[396] In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits different in vivo activity against G12D or G12C cell lines as compared to a compound having the same core but substantially incapable of forming a covalent bond with an aspartic or cysteine residue at the position corresponding to the 12th position of human Kras protein. In embodiments, the different in vivo activity between G12D or G12C cell lines is measured using the method described in Example 9, or a similar

method. In embodiments, the in vivo activity against G12D or G12C cell lines of the subject compound is superior to that of the comparator compound described above by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 50, 600, 700, 800, 900, 1000-fold, or more. In embodiments, the in vivo activity against G12D or G12C cell lines of the subject compound is superior to that of the comparator compound described above by at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000-fold, or more. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits different in vivo activity against G12D or G12C cell lines as compared to other known inhibitors of human Kras protein. In some embodiments, a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6) exhibits in vivo activity against G12D or G12C cell lines that is superior to that of a known inhibitor of human Kras protein by greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000-fold or more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, or 90%. In embodiments, the in vivo activity against G12D or G12C cell lines of the compound differs from another inhibitor of human Kras protein as measured in 1, 2, 3, 4, 5, 6, 7, 8, 9, or10 cell lines selected from AGS (e.g., K-Ras G12D), ASPC1 (e.g., K-Ras G12D), CL40 (e.g., K-Ras G12D), COLO678 (e.g., K-Ras G12D), GP2D (e.g., K-Ras G12D), HEC1A (e.g., K-Ras G12D), HEYA8 (e.g., K-Ras G12D or G13D), HPAC (e.g., K-Ras G12D), HPAFII (e.g., K-Ras G12D), HUCCT1 (e.g., K-Ras G12D), KP-4 (e.g., K-Ras G12D), L3.3 (e.g., K-Ras G12D), LS180 (e.g., K-Ras G12D), LS513 (e.g., K-Ras G12D), MCAS (e.g., K-Ras G12D), NOMO-1 (e.g., K-Ras G12D), OV7 (e.g., K-Ras G12D), PANC0203 (e.g., K-Ras G12D), PANC0403 (e.g., K-Ras G12D), PANC0504 (e.g., K-Ras G12D), PANC0813 (e.g., K-Ras G12D), PANC1 (e.g., K-Ras G12D), Panc-10.05 (e.g., K-Ras G12D), PK1 (e.g., K-Ras G12D), PK45H (e.g., K-Ras G12D), PK59 (e.g., K-Ras G12D), SKLU1 (e.g., K-Ras G12D), SNU1 (e.g., K-Ras G12D), SNU1033 (e.g., K-Ras G12D), SNU1197 (e.g., K-Ras G12D), SNU407 (e.g., K-Ras G12D), SNU410 (e.g., K-Ras G12D), SNU601 (e.g., K-Ras G12D), SNU61 (e.g., K-Ras G12D), SNU8 (e.g., K-Ras G12D), SNU869 (e.g., K-Ras G12D), SNU-C2A (e.g., K-Ras G12D), SU.86.86 (e.g., K-Ras G12D), SUIT2 (e.g., K-Ras G12D), SW1990 (e.g., K-Ras G12D), T3M10 (e.g., K-Ras G12D), and TGBC11TKB (e.g., K-Ras G12D).

Pharmaceutical compositions and methods of administration

[397] In an aspect is provided a pharmaceutical composition comprising (i) a compound described herein (e.g., a compound of Formula (A0), (A0-1), (A0-2), (A0-3), (A0-4), (A0-5), (A0-6), (a0), (a0-1), (a0-2), (a0-3), (a0-4), (a0-5), (a0-6), (A), (A-1), (A-2), (A-3), (A-4), (A-5), (A-6), (A-7), (A-8), (a), (a-1), (a-2), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (A1), (A1-1), (A1-2), (A1-3), (A1-4), (A1-5), (A1-6), (a1), (a1-1), (a1-2), (a1-3), (a1-4), (a1-5), or (a1-6)), or a pharmaceutically acceptable salt or solvate thereof, and (ii) a pharmaceutically acceptable excipient.

[398] In some embodiments, a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, is administered to a subject in a biologically compatible form suitable for administration to treat or prevent diseases, disorders, or conditions. Administration of a compound described herein can be in any pharmacological form including a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, alone or in combination with a pharmaceutically acceptable carrier.

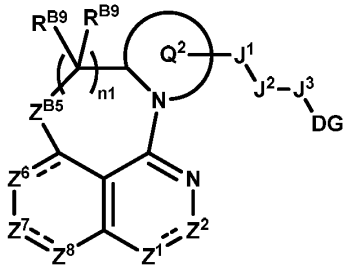
[399] In some embodiments, a compound described herein is administered as a pure chemical. In some embodiments, the compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[400] Accordingly, provided herein is a pharmaceutical composition comprising at least one compound described herein, or a pharmaceutically acceptable salt, together with one or more pharmaceutically acceptable excipients. The excipient(s) (or carrier(s)) is acceptable or suitable if the excipient is compatible with the other ingredients of the composition and not deleterious to the recipient (i.e., the subject) of the composition.

[401] In some embodiments of the methods described herein, a compound described herein is administered either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition. Administration of a compound or composition described herein can be affected by any method that enables delivery of the compound to the site of action. These methods include, though are not limited to delivery via enteral routes (including oral, gastric or duodenal feeding tube, rectal suppository and rectal enema), parenteral routes (injection or infusion, including intraarterial, intracardiac, intradermal, intraduodenal, intramedullary, intramuscular, intraosseous, intraperitoneal, intrathecal, intravascular, intravenous, intravitreal, epidural and subcutaneous), inhalational, transdermal, transmucosal, sublingual, buccal and topical (including epicutaneous, dermal, enema, eye drops, ear drops, intranasal, vaginal) administration, although the most suitable route may depend upon for example the condition and disorder of the recipient. By way of example only, a compound described herein can be administered locally to the area in need of treatment, by, for example, local infusion during surgery, topical application such as creams or ointments, injection, catheter, or implant. The administration can also be by direct injection at the site of a diseased tissue or organ. In some embodiments, a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, is administered orally.

[402] Additional Embodiments

1. A compound of Formula (A0):



(A0),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^{B5} is selected from $C(R^{B9})_2$ and O;

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -N(R^{B12})-, -C(O)-, -N(R^{B12})C(O)-, -C(O)N(R^{B12})-, -S-, -S(O)$_2$-, -S(O)-, -P(O)R^{B12}-, -N(R^{B12})S(O)$_2$-, -N(R^{B12})S(O)-, -N(R^{B12})P(O)R^{B12}-, -S(O)$_2$N(R^{B12})-, -S(O)N(R^{B12})-, -P(O)R^{B12}N(R^{B12})-, -OS(O)$_2$-, -OS(O)-, -OP(O)R^{B12}-, -S(O)$_2$O-, -S(O)O-, and -P(O)R^{B12}O-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -C(O)OR^{B12}, -C(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -S(O)$_2$$R^{B12}$, -S(O)($NR^{B12}$)$R^{B12}$, -S(O)$_2$N($R^{B12}$)($R^{B13}$), and -S(=O)(=$NR^{B12}$)N($R^{B12}$)($R^{B13}$), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -N(R^{B12})(R^{B13}), -C(O)OR^{B12}, -OC(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)OR^{B12}, -N(R^{B12})S(O)$_2$$R^{B12}$, -C(O)$R^{B12}$, -S(O)$R^{B12}$, -OC(O)$R^{B12}$, -C(O)N($R^{B12}$)($R^{B13}$), -C(O)C(O)N($R^{B12}$)($R^{B13}$), -N($R^{B12}$)C(O)$R^{B12}$, -S(O)$_2$$R^{B12}$, -S(O)($NR^{B12}$)$R^{B12}$, -S(O)$_2$N($R^{B12}$)($R^{B13}$), and -S(=O)(=$NR^{B12}$)N($R^{B12}$)($R^{B13}$), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}

alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

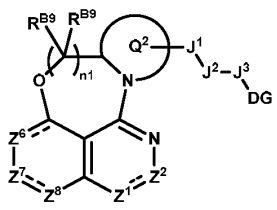
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

2. A compound of Formula (A):



(A),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})-$, -C(O)-, $-N(R^{B12})C(O)-$, $-C(O)N(R^{B12})-$, -S-, $-S(O)_2-$, -S(O)-, $-P(O)R^{B12}-$, $-N(R^{B12})S(O)_2-$, $-N(R^{B12})S(O)-$, $-N(R^{B12})P(O)R^{B12}-$, $-S(O)_2N(R^{B12})-$, $-S(O)N(R^{B12})-$, $-P(O)R^{B12}N(R^{B12})-$, $-OS(O)_2-$, -OS(O)-, $-OP(O)R^{B12}-$, $-S(O)_2O-$, -S(O)O-, and $-P(O)R^{B12}O-$, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-OR^{B12}$, $-SR^{B12}$, $-N(R^{B12})(R^{B13})$, $-C(O)OR^{B12}$, $-OC(O)N(R^{B12})(R^{B13})$, $-N(R^{B12})C(O)N(R^{B12})(R^{B13})$, $-N(R^{B12})C(O)OR^{B12}$, $-N(R^{B12})S(O)_2R^{B12}$, $-C(O)R^{B12}$, $-S(O)R^{B12}$, $-OC(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-N(R^{B12})C(O)R^{B12}$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are

optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

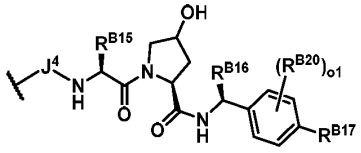
------ indicates a single or double bond such that all valences are satisfied.

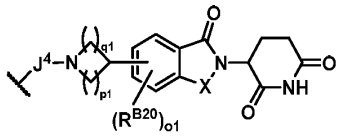
3. The compound, salt, or solvate of any one of embodiments 1 to 2, wherein the degradation enhancer is capable of binding a protein selected from E3A, mdm2, APC, EDD1, SOCS/BC-box/eloBC/CUL5/RING, LNXp80, CBX4, CBLL1, HACE1, HECTD1, HECTD2, HECTD3, HECTD4, HECW1, HECW2, HERC1, HERC2, HERC3, HERC4, HER5, HERC6, HUWE1, ITCH, NEDD4, NEDD4L, PPIL2, PRPF19, PIAS1, PIAS2, PIAS3, PIAS4, RANBP2, RNF4, RBX1, SMURF1, SMURF2, STUB1, TOPORS, TRIP12, UBE3A, UBE3B, UBE3C, UBE3D,

UBE4A, UBE4B, UBOX5, UBR5, VHL (von-Hippel-Lindau ubiquitin ligase), WWP1, WWP2, Parkin, MKRN1, CMA (chaperon-mediated autophage), SCFb-TRCP (Skip-Cullin-F box (Beta-TRCP) ubiquitin complex), b-TRCP (b-transducing repeat-containing protein), cIAP1 (cellular inhibitor of apoptosis protein 1), APC/C (anaphase-promoting complex/cyclosome), CRBN (cereblon), CUL4-RBX1-DDB1-CRBN ($CRL4^{CRBN}$) ubiquitin ligase, XIAP, IAP, KEAP1, DCAF15, RNF114, DCAF16, AhR, SOCS2, KLHL12, UBR2, SPOP, KLHL3, KLHL20, KLHDC2, SPSB1, SPSB2, SPSB4, SOCS6, FBXO4, FBXO31, BTRC, FBW7, CDC20, PML, TRIM21, TRIM24, TRIM33, GID4, avadomide, iberdomide, and CC-885.

4. The compound, salt, or solvate of any one of embodiments 1 to 2, wherein the degradation enhancer is capable of binding a protein selected from UBE2A, UBE2B, UBE2C, UBE2D1, UBE2D2, UBE2D3, UBE2DR, UBE2E1, UBE2E2, UBE2E3, UBE2F, UBE2G1, UBE2G2, UBE2H, UBE2I, UBE2J1, UBE2J2, UBE2K, UBE2L3, UBE2L6, UBE2L1, UBE2L2, UBE2L4, UBE2M, UBE2N, UBE2O, UBE2Q1, UBE2Q2, UBE2R1, UBE2R2, UBE2S, UBE2T, UBE2U, UBE2V1, UBE2V2, UBE2W, UBE2Z, ATG3, BIRC6, and UFC1.

5. The compound, salt, or solvate of any one of the preceding embodiments, wherein DG is selected from:



and


,

wherein:

J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20};

R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20};

R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20};

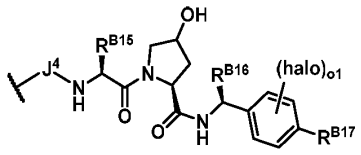
R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20};

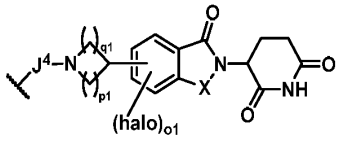
o1 is selected from 0, 1, and 2;

p1 and q1 are independently selected from 1, 2, and 3; and

X is selected from CH_2 and C(O).

6. The compound, salt, or solvate of any one of the preceding embodiments, wherein DG is selected from:



and


,

wherein:

J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20};

R^{B15} is selected from $-CH(CH_3)_2$ and $-C(CH_3)_3$;

R^{B16} is selected from hydrogen, $-CH_3$, and $-CH_2OH$;

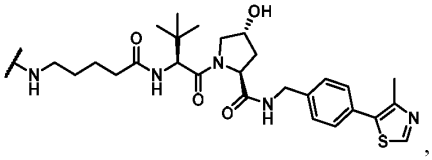
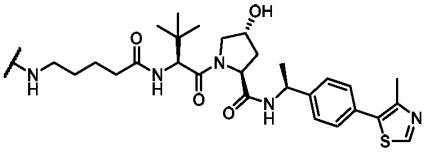
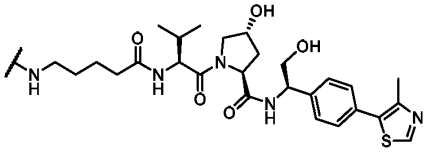
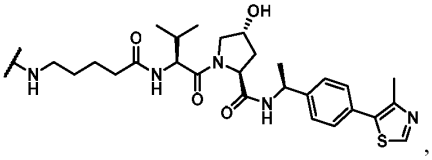
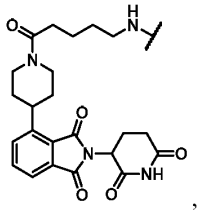
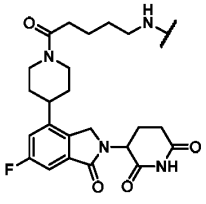
R^{B17} is selected from methylthiazole and methylpyrazole;

o1 is selected from 0 and 1;

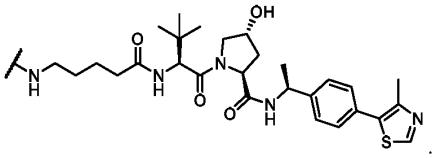
p1 and q1 are independently selected from 1 and 2; and

X is selected from CH_2 and C(O).

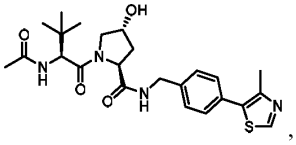
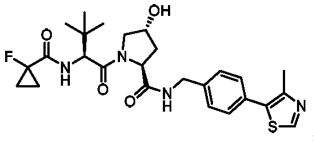
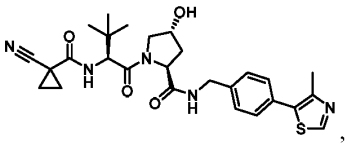
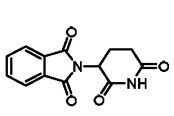
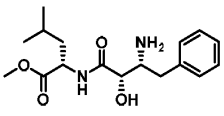
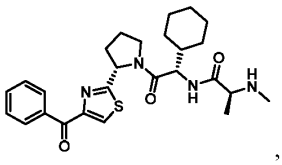
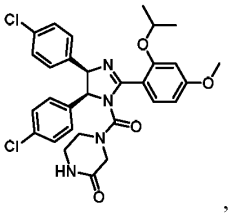
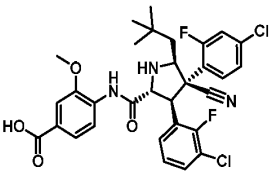
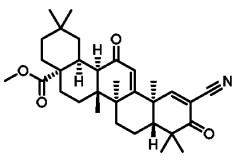
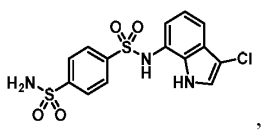
7. The compound, salt, or solvate of any one of the preceding embodiments, wherein DG is selected from:

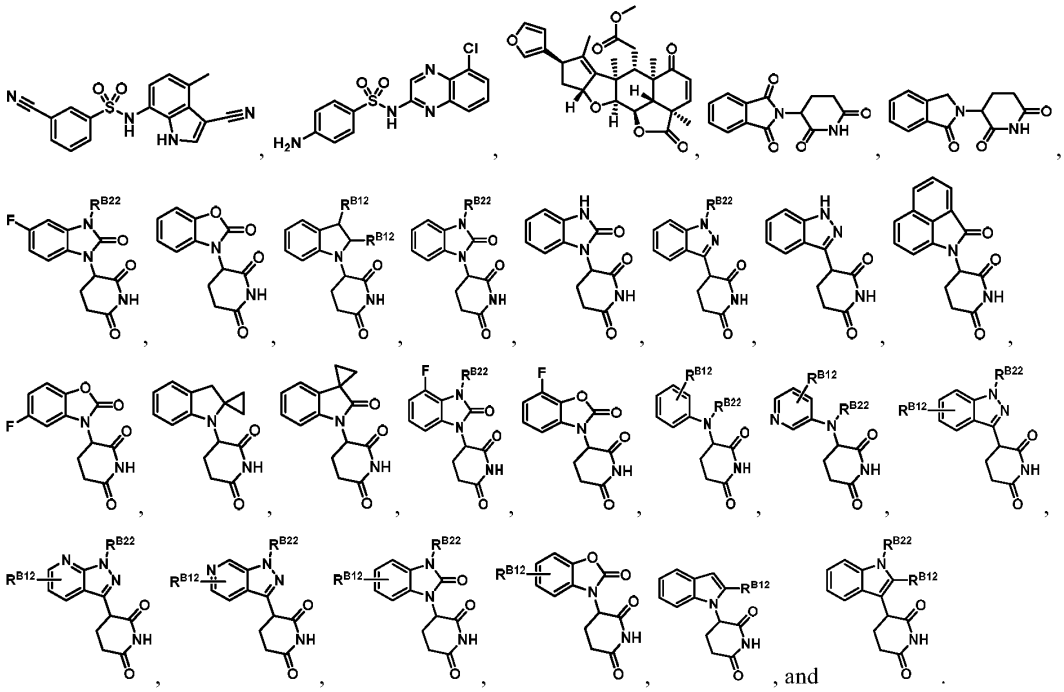

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and .

8. The compound, salt, or solvate of any one of the preceding embodiments, wherein DG is

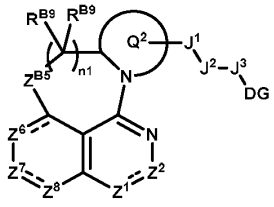

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9. The compound, salt, or solvate of any one of embodiments 1 to 4, wherein DG comprises a monovalent form of a compound selected from


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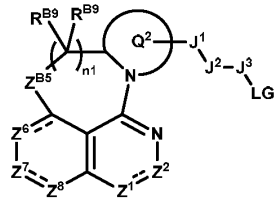
10. A method of preparing a compound of Formula (A0):



(A0),

the method comprising:

(a) reacting a compound of Formula (a0):



(a0),

with a degradation enhancer under conditions to effect release of LG and production of the compound of Formula (A0), wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^{B5} is selected from $C(R^{B9})_2$ and O;

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered

heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -N(R^{B12})-, -C(O)-, -N(R^{B12})C(O)-, -C(O)N(R^{B12})-, -S-, -S(O)$_2$-, -S(O)-, -P(O)R^{B12}-, -N(R^{B12})S(O)$_2$-, -N(R^{B12})S(O)-, -N(R^{B12})P(O)R^{B12}-, -S(O)$_2$N(R^{B12})-, -S(O)N(R^{B12})-, -P(O)R^{B12}N(R^{B12})-, -OS(O)$_2$-, -OS(O)-, -OP(O)R^{B12}-, -S(O)$_2$O-, -S(O)O-, and -P(O)R^{B12}O-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

LG is a leaving group;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -C(O)OR^{B12}, -C(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -S(O)$_2$$R^{B12}$, -S(O)($NR^{B12}$)$R^{B12}$, -S(O)$_2$N($R^{B12}$)($R^{B13}$), and -S(=O)(=$NR^{B12}$)N($R^{B12}$)($R^{B13}$), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -N(R^{B12})(R^{B13}), -C(O)OR^{B12}, -OC(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)OR^{B12}, -N(R^{B12})S(O)$_2$$R^{B12}$, -C(O)$R^{B12}$, -S(O)$R^{B12}$, -OC(O)$R^{B12}$, -C(O)N($R^{B12}$)($R^{B13}$), -C(O)C(O)N($R^{B12}$)($R^{B13}$), -N($R^{B12}$)C(O)$R^{B12}$, -S(O)$_2$$R^{B12}$, -S(O)($NR^{B12}$)$R^{B12}$, -S(O)$_2$N($R^{B12}$)($R^{B13}$), and -S(=O)(=$NR^{B12}$)N($R^{B12}$)($R^{B13}$), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}

alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

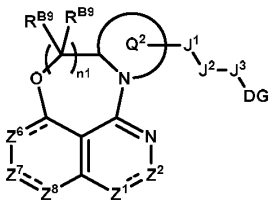
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

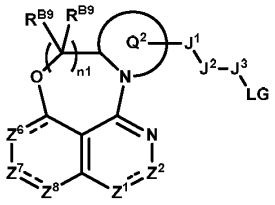
11. A method of preparing a compound of Formula (A):



(A),

the method comprising:

(a) reacting a compound of Formula (a):



(a),

with a degradation enhancer under conditions to effect release of LG and production of the compound of Formula (A), wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

LG is a leaving group;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

12. The method of any one of embodiments 10 to 11, wherein the reaction mixture comprises a base.

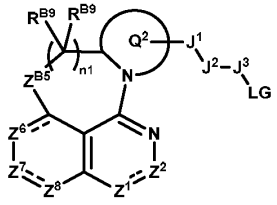
13. The method of embodiment 12, wherein the reaction mixture comprises 5- to 12-equivalents of the base relative to the amount of degradation enhancer.

14. The method of any one of embodiments 10 to 13, wherein the base is *N*,*N*-diisopropylethylamine.

15. The method of any one of embodiments 10 to 14, wherein the compound of Formula (a) or (a0) and the degradation enhancer are heated to 40 to 100 °C for 2 to 48 hours.

16. The method of any one of embodiments 10 to 15, further comprising (b) purifying the compound of Formula (A) or (A0).

17. A compound of Formula (a0):



(a0),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and N(R^{B1b});

Z^2 is selected from C(R^{B2}) and C(O);

Z^{B5} is selected from C(R^{B9})$_2$ and O;

Z^6 is selected from C(R^{B6}), C(R^{B6})$_2$, N, and N(R^{B6b});

Z^7 is selected from C(R^{B7}) and N(R^{B7b});

Z^8 is selected from C(R^{B8}), C(R^{B8})$_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -N(R^{B12})-, -C(O)-, -N(R^{B12})C(O)-, -C(O)N(R^{B12})-, -S-, -S(O)$_2$-, -S(O)-, -P(O)R^{B12}-, -N(R^{B12})S(O)$_2$-, -N(R^{B12})S(O)-, -N(R^{B12})P(O)R^{B12}-, -S(O)$_2$N(R^{B12})-, -S(O)N(R^{B12})-, -P(O)R^{B12}N(R^{B12})-, -OS(O)$_2$-, -OS(O)-, -OP(O)R^{B12}-, -S(O)$_2$O-, -S(O)O-, and -P(O)R^{B12}O-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-

membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

LG is selected from -$OS(O)_2R^{B4}$ and -$OS(O)(NR^{B4b})R^{B4}$;

n1 is selected from 1, 2, and 3;

R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and -$N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B1b}, R^{B4b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -$C(O)OR^{B12}$, -$C(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered

heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$-, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

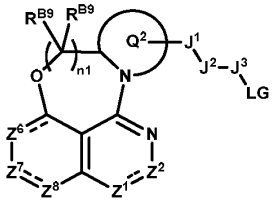
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

18. A compound of Formula (a):



(a),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and -

$P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

LG is selected from -$OS(O)_2R^{B4}$ and -$OS(O)(NR^{B4b})R^{B4}$;

n1 is selected from 1, 2, and 3;

R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and -$N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B1b}, R^{B4b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -$C(O)OR^{B12}$, -$C(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

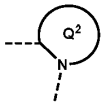
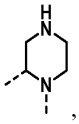
------ indicates a single or double bond such that all valences are satisfied.

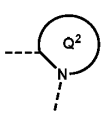
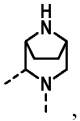
19. The compound, salt, solvate, or method of any one of embodiments 1 to 18, wherein Z^{B5} is $C(R^{B9})_2$.

20. The compound, salt, solvate, or method of any one of embodiments 1 to 19, wherein n1 is 1.

21. The compound, salt, solvate, or method of any one of embodiments 1 to 20, wherein Q^2 is 4- to 6-membered monocyclic heterocycloalkyl optionally substituted with one or more R^{B20}.

22. The compound, salt, solvate, or method of any one of embodiments 1 to 20, wherein Q^2 is 7- to 9-membered bridged bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}.

23. The compound, salt, solvate, or method of embodiment 21, wherein  is selected from  ,  ,  , and  , each of which is optionally substituted with one or more R^{B20}.

24. The compound, salt, solvate, or method of embodiment 22, wherein  is  , which is optionally substituted with one or more R^{B20}.

25. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein:

Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$;

Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is N, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$;

Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})_2$, Z^7 is $N(R^{B7b})$, and Z^8 is $C(R^{B8})_2$; or

Z^1 is $N(R^{B1b})$, Z^2 is C(O), Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is N.

26. The compound, salt, solvate, or method of embodiment 25, wherein Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$.

27. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein J^1 is selected from a bond, C_{1-6} alkylene, 2- to 6-membered heteroalkylene, and -C(O)-, wherein C_{1-6} alkylene and 2- to 6-membered heteroalkylene are optionally substituted with one or more R^{B20}.

28. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein J^1 is -C(O)-.

29. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, and -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)- and -C_{0-6} alkyl-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20}.

30. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein J^2 is a bond.

31. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein J^3 is selected from C_{1-6} alkylene, 2- to 6-membered heteroalkylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20}.

32. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein J^3 is selected from C_{1-6} alkylene and 2- to 6-membered heteroalkylene, each of which is optionally substituted with one or more R^{B20}.

33. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein J^3 is selected from -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20}.

34. The compound, salt, solvate, or method of any one of embodiments 1 to 26, wherein:

J^1 is -C(O)-;

J^2 is a bond; and

J^3 is C_{1-6} alkylene.

35. The compound, salt, solvate, or method of any one of embodiments 1 to 26, wherein:

J^1 is a bond;

J^2 is a bond; and

J^3 is selected from C_{1-6} alkylene and 2- to 6-membered heteroalkylene, each of which is optionally substituted with one or more R^{B20}.

36. The compound, salt, solvate, or method of any one of embodiments 1 to 26, wherein:

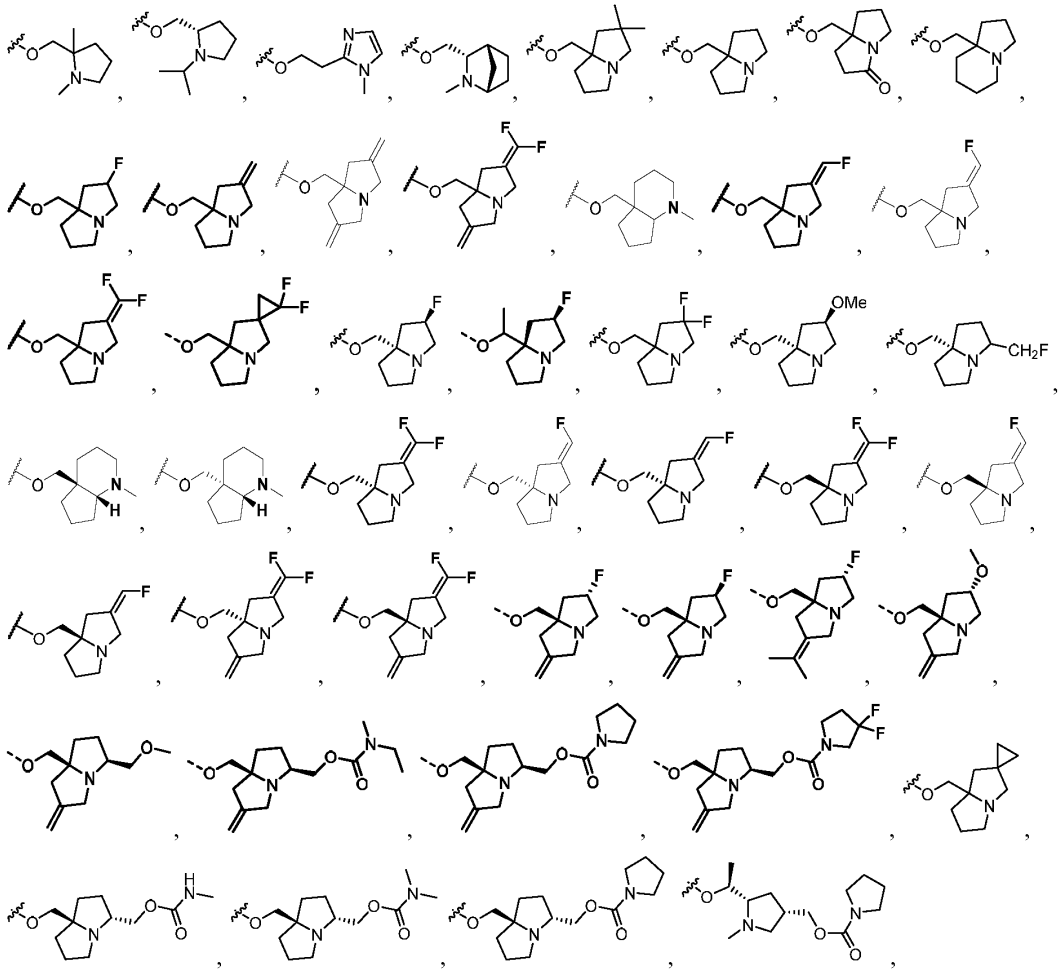
J^1 is -C(O)-;

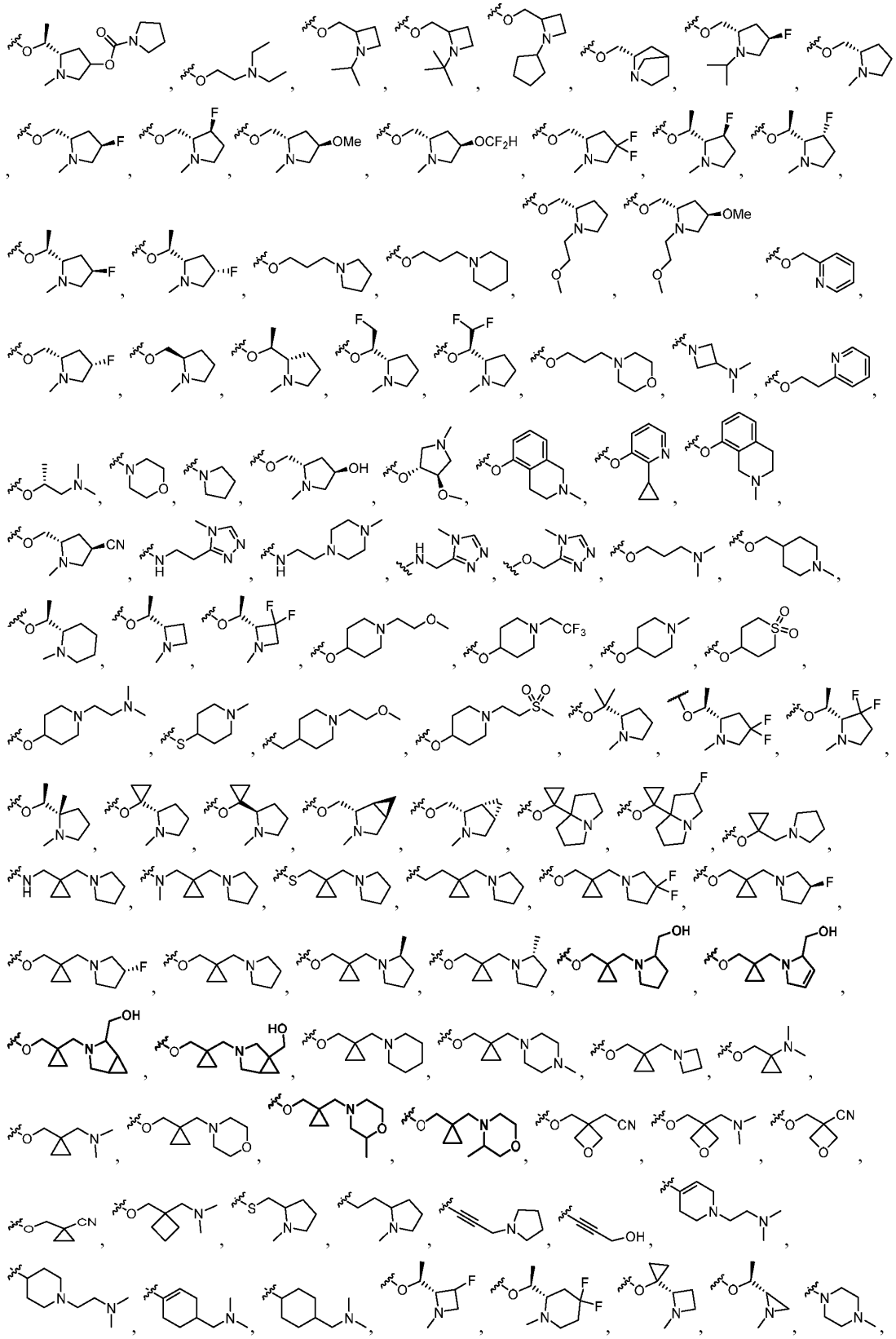
J^2 is 3- to 12-membered heterocycle optionally substituted with one or more R^{B20}; and

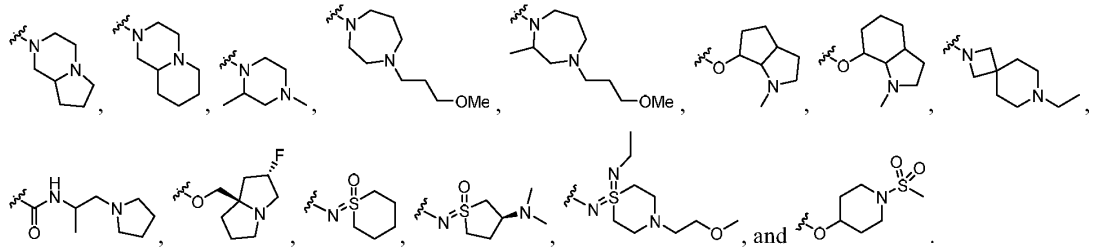
J^3 is C_{1-6} alkylene.

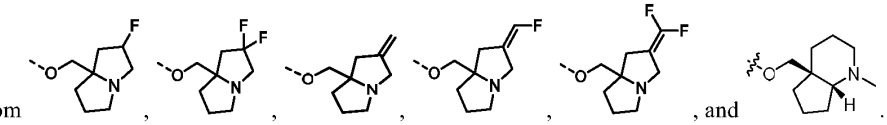
37. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl.

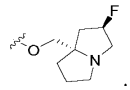
38. The compound, salt, solvate, or method of any one of embodiments 1 to 36, wherein R^{B2} is selected from

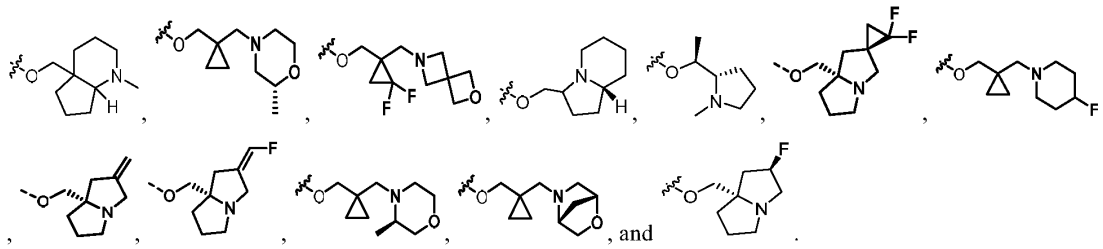


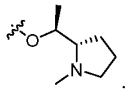




39. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein R^{B2} is selected from  .

40. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein R^{B2} is  .

41. The compound, salt, solvate, or method of any one of embodiments 1 to 36, wherein R^{B2} is selected from  .

42. The compound, salt, solvate, or method of any one of embodiments 1 to 36, wherein R^{B2} is  .

43. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein R^{B6} is selected from hydrogen, halogen, and C_{1-3} haloalkyl.

44. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein R^{B6} is halogen or C_{1-3} haloalkyl.

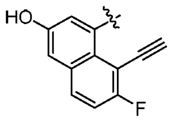
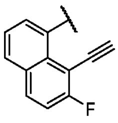
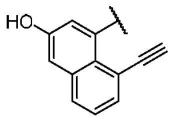
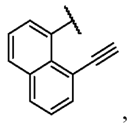
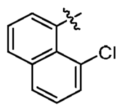
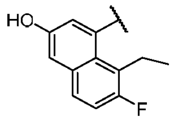
45. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one or more R^{B20}.

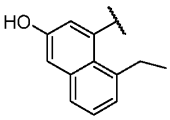
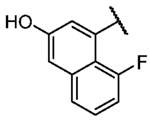
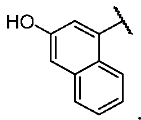
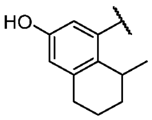
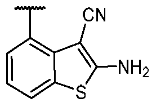
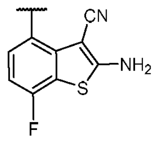
46. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}.

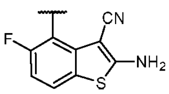
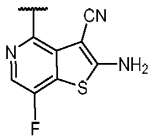
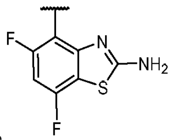
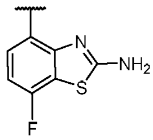
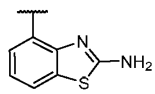
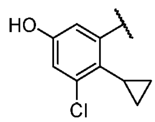
47. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, $-OR^{B22}$, $-N(R^{B22})(R^{B23})$, and C_{3-6} cycloalkyl.

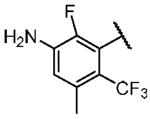
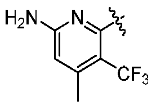
48. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, $-CH_3$, $-CH_2CH_3$, $-CH{=}CH_2$, $-CF_3$, $-C{\equiv}CH$, -OH, $-NH_2$, and -cyclopropyl.

49. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein R^{B7} is selected

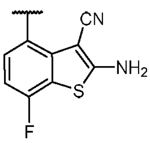
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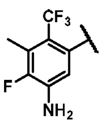
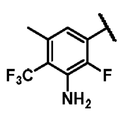
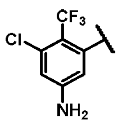
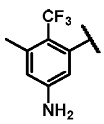
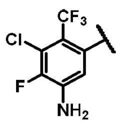
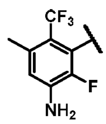
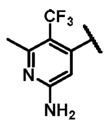
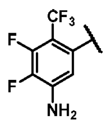
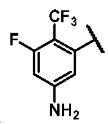
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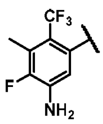
50. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein R^{B7} is

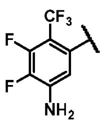
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51. The compound, salt, solvate, or method of any one of embodiments 1 to 44, wherein R^{B7} is selected from

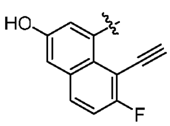
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52. The compound, salt, solvate, or method of any one of embodiments 1 to 44, wherein R^{B7} is  .

53. The compound, salt, solvate, or method of any one of embodiments 1 to 44, wherein R^{B7} is  .

54. The compound, salt, solvate, or method of any one of embodiments 1 to 44, wherein R^{B7} is

 .

55. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein each R^{B8} is independently selected from hydrogen and halogen.

56. The compound, salt, solvate, or method of any one of the preceding embodiments, wherein R^{B8} is halogen.

57. The compound, salt, solvate, or method of any one of embodiments 1 to 40, wherein:

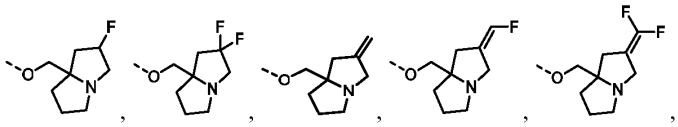
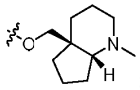
R^{B6} is halogen;

R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and

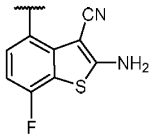
pyridinyl, each of which is optionally substituted with one or more R^{B20}; and

R^{B8} is halogen.

58. The compound, salt, solvate, or method of any one of embodiments 1 to 36, wherein:

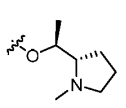
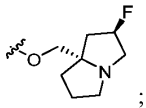
R^{B2} is selected from  , and  ;

R^{B6} is halogen;

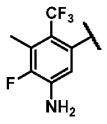
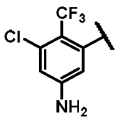
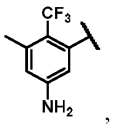
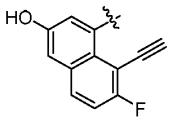
R^{B7} is  ; and

R^{B8} is halogen.

59. The compound, salt, solvate, or method of any one of embodiments 1 to 36, wherein:

R^{B2} is selected from  and  ;

R^{B6} is halogen;

R^{B7} is selected from  ,  ,  ,  , and  ; and

R^{B8} is halogen.

60. A pharmaceutical composition comprising a compound of any one of embodiments 1 to 9 or 17 to 59, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

61. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 1 to 9 or 17 to 59, or a pharmaceutically acceptable salt or solvate thereof.

62. A method of treating cancer in a subject comprising a Ras mutant protein, the method comprising: inhibiting the Ras mutant protein of said subject by administering to said subject a compound of any one of embodiments 1 to 9 or 17 to 59, wherein the compound is characterized in that upon contacting the Ras mutant protein, said Ras mutant protein exhibits reduced Ras signaling output.

63. The method of embodiment 61 or 62, wherein the cancer is a solid tumor or a hematological cancer.

64. A method of reducing signaling output of a Ras protein, comprising contacting a Ras protein with an effective amount of a compound of any one of embodiments 1 to 9 or 17 to 59, or a pharmaceutically acceptable salt or solvate thereof, thereby reducing the signaling output of the Ras protein.

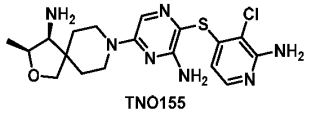
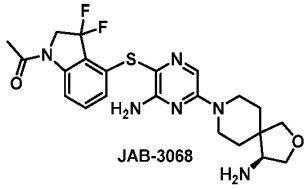
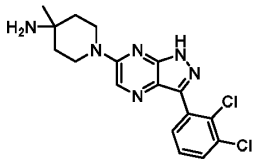
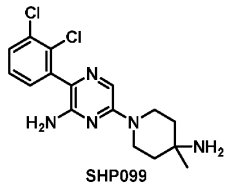
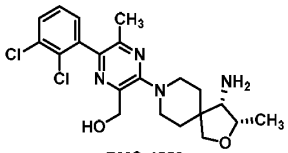
65. The method of embodiment 64, wherein the compound binds covalently or non-covalently to the Ras protein, thereby reducing the signaling output of the Ras protein.

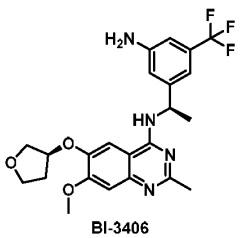
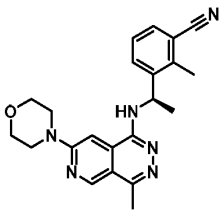
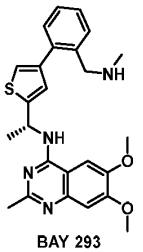
66. A method of inhibiting cell growth, comprising administering an effective amount of a compound of any one of embodiments 1 to 9 or 17 to 59, or a pharmaceutically acceptable salt or solvate thereof, to a cell expressing a

Ras protein, thereby inhibiting growth of said cells.

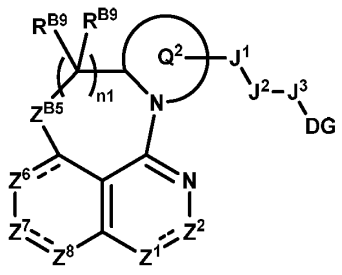
67. The method of any one of embodiments 61 to 66, comprising administering an additional agent.

68. The method of embodiment 67, wherein the additional agent comprises (1) an inhibitor of MEK; (2) an inhibitor of epidermal growth factor receptor (EGFR) and/or mutants thereof; (3) an immunotherapeutic agent; (4) a taxane; (5) an anti-metabolite; (6) an inhibitor of FGFR1 and/or FGFR2 and/or FGFR3 and/or mutants thereof; (7) a mitotic kinase inhibitor; (8) an anti-angiogenic drug; (9) a topoisomerase inhibitor; (10) a platinum-containing compound; (11) an inhibitor of c-MET and/or mutants thereof; (12) an inhibitor of BCR-ABL and/or mutants thereof; (13) an inhibitor of ErbB2 (Her2) and/or mutants thereof; (14) an inhibitor of AXL and/or mutants thereof; (15) an inhibitor of NTRK1 and/or mutants thereof; (16) an inhibitor of RET and/or mutants thereof; (17) an inhibitor of A-Raf and/or B-Raf and/or C-Raf and/or mutants thereof; (18) an inhibitor of ERK and/or mutants thereof; (19) an MDM2 inhibitor; (20) an inhibitor of mTOR; (21) an inhibitor of IGF1/2 and/or IGF1-R; (22) an inhibitor of CDK9; (23) an inhibitor of farnesyl transferase; (24) an inhibitor of SHIP pathway; (25) an inhibitor of SRC; (26) an inhibitor of JAK; (27) a PARP inhibitor, (28) a ROS1 inhibitor; (29) an inhibitor of SHP pathway; (30) an inhibitor of Src, FLT3, HDAC, VEGFR, PDGFR, LCK, Bcr-Abl or AKT; (31) an inhibitor of KRAS G12C; (32) an SHC inhibitor; (33) a GAB inhibitor; (34) a PI-3 kinase inhibitor; (35) a MARPK inhibitor; (36) a CDK4/6 inhibitor; (37) a MAPK inhibitor; (38) a SHP2 inhibitor; (39) a checkpoint immune blockade agent; (40) a SOS1 inhibitor; or (41) a SOS2 inhibitor.

69. The method of embodiment 67, wherein the additional agent comprises an inhibitor of SHP2 selected from RMC-4630, ERAS-601, 
TNO155
, 
JAB-3068
, 
IACS-13909/BBP-398
, 
SHP099
, and 
RMC-4550
.

70. The method of embodiment 67, wherein the additional agent comprises an inhibitor of SOS selected from RMC-5845, BI-1701963, 
BI-3406
, 
MRTX0902
, and 
BAY 293
.

71. A compound of Formula (A0):



(A0),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^{B5} is selected from $C(R^{B9})_2$ and O;

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})-$, -C(O)-, $-N(R^{B12})C(O)-$, $-C(O)N(R^{B12})-$, -S-, $-S(O)_2-$, -S(O)-, $-P(O)R^{B12}-$, $-N(R^{B12})S(O)_2-$, $-N(R^{B12})S(O)-$, $-N(R^{B12})P(O)R^{B12}-$, $-S(O)_2N(R^{B12})-$, $-S(O)N(R^{B12})-$, $-P(O)R^{B12}N(R^{B12})-$, $-OS(O)_2-$, -OS(O)-, $-OP(O)R^{B12}-$, $-S(O)_2O-$, -S(O)O-, and $-P(O)R^{B12}O-$, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are

optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl,

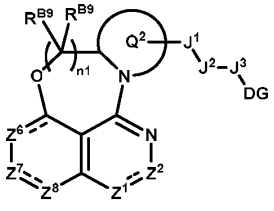
and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

72. A compound of Formula (A):



(A),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and N(R^{B1b});

Z^2 is selected from C(R^{B2}) and C(O);

Z^6 is selected from C(R^{B6}), C(R^{B6})$_2$, N, and N(R^{B6b});

Z^7 is selected from C(R^{B7}) and N(R^{B7b});

Z^8 is selected from C(R^{B8}), C(R^{B8})$_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -N(R^{B12})-, -C(O)-, -N(R^{B12})C(O)-, -C(O)N(R^{B12})-, -S-, -S(O)$_2$-, -S(O)-, -P(O)R^{B12}-, -N(R^{B12})S(O)$_2$-, -N(R^{B12})S(O)-, -N(R^{B12})P(O)R^{B12}-, -S(O)$_2$N(R^{B12})-, -S(O)N(R^{B12})-, -P(O)R^{B12}N(R^{B12})-, -OS(O)$_2$-, -OS(O)-, -OP(O)R^{B12}-, -S(O)$_2$O-, -S(O)O-, and -P(O)R^{B12}O-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to

6-membered heteroalkyl)-(3- to 12-membered heterocycle), -C(O)OR^{B12}, -C(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -S(O)$_2$R^{B12}, -S(O)(NR^{B12})R^{B12}, -S(O)$_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C$_{0-6}$ alkyl-(C$_{3-12}$ carbocycle), -(2- to 6-membered heteroalkyl)-(C$_{3-12}$ carbocycle), -C$_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C$_{0-6}$ alkyl-(C$_{3-12}$ carbocycle), -(2- to 6-membered heteroalkyl)-(C$_{3-12}$ carbocycle), -C$_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -N(R^{B12})(R^{B13}), -C(O)OR^{B12}, -OC(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)OR^{B12}, -N(R^{B12})S(O)$_2$R^{B12}, -C(O)R^{B12}, -S(O)R^{B12}, -OC(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)R^{B12}, -S(O)$_2$R^{B12}, -S(O)(NR^{B12})R^{B12}, -S(O)$_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C$_{0-6}$ alkyl-(C$_{3-12}$ carbocycle), -(2- to 6-membered heteroalkyl)-(C$_{3-12}$ carbocycle), -C$_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, -C$_{0-6}$ alkyl-(C$_{3-12}$ carbocycle), and -C$_{0-6}$ alkyl-(3- to 12-membered heterocycle), wherein C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, -C$_{0-6}$ alkyl-(C$_{3-12}$ carbocycle), and -C$_{0-6}$ alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C$_{1-6}$ alkyl, and C$_{1-6}$ haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C$_{0-6}$ alkyl-(C$_{3-12}$ carbocycle), -(2- to 6-membered heteroalkyl)-(C$_{3-12}$ carbocycle), -C$_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), =NR^{B22}, =C(R^{B21})$_2$, -C(O)OR^{B22}, -OC(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)OR^{B22}, -N(R^{B22})S(O)$_2$R^{B22}, -C(O)R^{B22}, -S(O)R^{B22}, -OC(O)R^{B22}, -C(O)N(R^{B22})(R^{B23}), -C(O)C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)R^{B22}, -S(O)$_2$R^{B22}, -S(O)(NR^{B22})R^{B22}, -S(O)$_2$N(R^{B22})(R^{B23})-, and -S(=O)(=NR^{B22})N(R^{B22})(R^{B23}); wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C$_{3-12}$ carbocycle or 3- to 12-membered heterocycle; wherein C$_{1-6}$ alkyl, C$_{2-6}$ alkenyl, C$_{2-6}$ alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C$_{0-6}$ alkyl-(C$_{3-12}$ carbocycle), -(2- to 6-membered heteroalkyl)-(C$_{3-12}$ carbocycle), -C$_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C$_{3-12}$ carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C$_{1-6}$ alkyl, C$_{1-6}$ haloalkyl, C$_{1-6}$ hydroxyalkyl, C$_{1-6}$ alkoxy, C$_{1-6}$ haloalkoxy, -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), =NR^{B22}, =C(R^{B21})$_2$, -C(O)OR^{B22}, -OC(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)OR^{B22}, -N(R^{B22})S(O)$_2$R^{B22}, -C(O)R^{B22}, -S(O)R^{B22}, -OC(O)R^{B22}, -C(O)N(R^{B22})(R^{B23}), -C(O)C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)R^{B22}, -S(O)$_2$R^{B22}, -S(O)(NR^{B22})R^{B22}, -

$S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle);

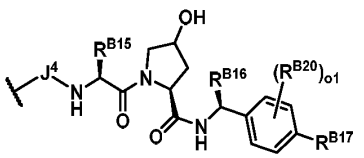
R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

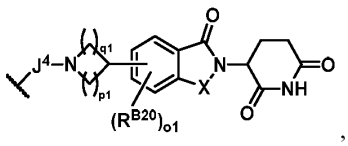
------ indicates a single or double bond such that all valences are satisfied.

73. The compound, salt, or solvate of any one of embodiments 71 to 72, wherein the degradation enhancer is capable of binding a protein selected from E3A, mdm2, APC, EDD1, SOCS/BC-box/eloBC/CUL5/RING, LNXp80, CBX4, CBLL1, HACE1, HECTD1, HECTD2, HECTD3, HECTD4, HECW1, HECW2, HERC1, HERC2, HERC3, HERC4, HER5, HERC6, HUWE1, ITCH, NEDD4, NEDD4L, PPIL2, PRPF19, PIAS1, PIAS2, PIAS3, PIAS4, RANBP2, RNF4, RBX1, SMURF1, SMURF2, STUB1, TOPORS, TRIP12, UBE3A, UBE3B, UBE3C, UBE3D, UBE4A, UBE4B, UBOX5, UBR5, VHL (von-Hippel-Lindau ubiquitin ligase), WWP1, WWP2, Parkin, MKRN1, CMA (chaperon-mediated autophage), SCFb-TRCP (Skip-Cullin-F box (Beta-TRCP) ubiquitin complex), b-TRCP (b-transducing repeat-containing protein), cIAP1 (cellular inhibitor of apoptosis protein 1), APC/C (anaphase-promoting complex/cyclosome), CRBN (cereblon), CUL4-RBX1-DDB1-CRBN ($CRL4^{CRBN}$) ubiquitin ligase, XIAP, IAP, KEAP1, DCAF15, RNF114, DCAF16, AhR, SOCS2, KLHL12, UBR2, SPOP, KLHL3, KLHL20, KLHDC2, SPSB1, SPSB2, SPSB4, SOCS6, FBXO4, FBXO31, BTRC, FBW7, CDC20, PML, TRIM21, TRIM24, TRIM33, GID4, avadomide, iberdomide, and CC-885.

74. The compound, salt, or solvate of any one of embodiments 71 to 72, wherein the degradation enhancer is capable of binding a protein selected from UBE2A, UBE2B, UBE2C, UBE2D1, UBE2D2, UBE2D3, UBE2DR, UBE2E1, UBE2E2, UBE2E3, UBE2F, UBE2G1, UBE2G2, UBE2H, UBE2I, UBE2J1, UBE2J2, UBE2K, UBE2L3, UBE2L6, UBE2L1, UBE2L2, UBE2L4, UBE2M, UBE2N, UBE2O, UBE2Q1, UBE2Q2, UBE2R1, UBE2R2, UBE2S, UBE2T, UBE2U, UBE2V1, UBE2V2, UBE2W, UBE2Z, ATG3, BIRC6, and UFC1.

75. The compound, salt, or solvate of any one of embodiments 71 to 74, wherein DG is selected from:



and


,

wherein:

J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20};

R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20};

R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20};

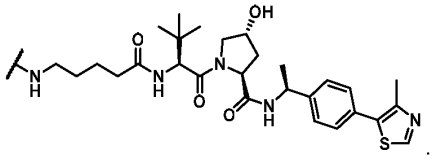
R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20};

o1 is selected from 0, 1, and 2;

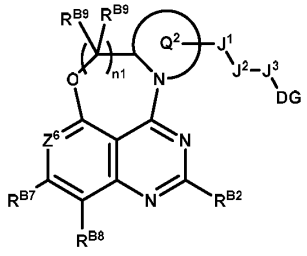
p1 and q1 are independently selected from 1, 2, and 3; and

X is selected from CH_2 and C(O).

76. The compound, salt, or solvate of any one of embodiments 71 to 75, wherein DG is



77. The compound, salt, or solvate of embodiment 71, wherein the compound is a compound of Formula (A-1):



(A-1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

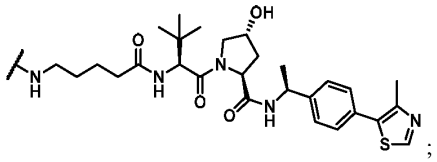
Z^6 is selected from $C(R^{B6})$ and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, and $-C(O)N(R^{B12})$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, , wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)- and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, each of which is optionally substituted with one or more R^{B20};

DG is  ;

n1 is 1;

R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), -O(C_{1-3} alkylene)-(4- to 5-membered heterocycle)-(C_{1-3} alkylene)-(4- to 10-membered heterocycle), or -O(C_{1-3} alkylene)-(C_{3-4} cycloalkyl)-(C_{1-3} alkylene)-(4- to 10-membered heterocycle), wherein C_{1-3} alkylene, C_{3-4} cycloalkyl, 4- to 5-membered heterocycle, and 4- to 10-membered heterocycle are each optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, -O-(C_{3-4} cycloalkyl), $-NH_2$, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and =C(R^{B21})$_2$;

R^{B6} is halogen or C_{1-3} haloalkyl;

R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one or more R^{B20};

R^{B8} is halogen;

R^{B9} is independently selected at each occurrence from hydrogen and methyl;

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), =NR^{B22}, =C(R^{B21})$_2$, -C(O)OR^{B22}, -OC(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)OR^{B22}, -N(R^{B22})S(O)$_2R^{B22}$, -C(O)R^{B22}, -S(O)R^{B22}, -OC(O)R^{B22}, -C(O)N(R^{B22})(R^{B23}), -C(O)C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)R^{B22}, -S(O)$_2R^{B22}$, -S(O)(NR^{B22})R^{B22}, -S(O)$_2$N(R^{B22})(R^{B23})-, and -S(=O)(=NR^{B22})N(R^{B22})(R^{B23}); wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), =NR^{B22}, =C(R^{B21})$_2$, -C(O)OR^{B22}, -OC(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)OR^{B22}, -N(R^{B22})S(O)$_2R^{B22}$, -C(O)R^{B22}, -S(O)R^{B22}, -OC(O)R^{B22}, -C(O)N(R^{B22})(R^{B23}), -C(O)C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)R^{B22}, -S(O)$_2R^{B22}$, -S(O)(NR^{B22})R^{B22}, -S(O)$_2$N(R^{B22})(R^{B23}), and -S(=O)(=NR^{B22})N(R^{B22})(R^{B23});

R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl;

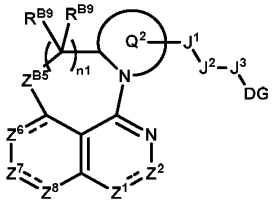
R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached

to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

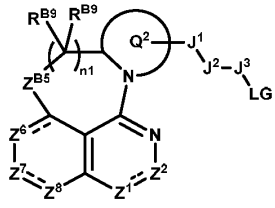
78. A method of preparing a compound of Formula (A0):



(A0),

the method comprising:

(a) reacting a compound of Formula (a0):



(a0),

with a degradation enhancer under conditions to effect release of LG and production of the compound of Formula (A0), wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^{B5} is selected from $C(R^{B9})_2$ and O;

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered

heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

LG is a leaving group;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -C(O)OR^{B12}, -C(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -S(O)$_2R^{B12}$, -S(O)(NR^{B12})R^{B12}, -S(O)$_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -N(R^{B12})(R^{B13}), -C(O)OR^{B12}, -OC(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)OR^{B12}, -N(R^{B12})S(O)$_2R^{B12}$, -C(O)R^{B12}, -S(O)R^{B12}, -OC(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)R^{B12}, -S(O)$_2R^{B12}$, -S(O)(NR^{B12})R^{B12}, -S(O)$_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), =NR^{B22}, =C(R^{B21})$_2$, -C(O)OR^{B22}, -OC(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)OR^{B22}, -N(R^{B22})S(O)$_2R^{B22}$, -C(O)R^{B22}, -S(O)R^{B22}, -OC(O)R^{B22}, -C(O)N(R^{B22})(R^{B23}), -C(O)C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)R^{B22}, -S(O)$_2R^{B22}$, -S(O)(NR^{B22})R^{B22}, -S(O)$_2$N(R^{B22})(R^{B23})-, and -S(=O)(=NR^{B22})N(R^{B22})(R^{B23}); wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered

heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

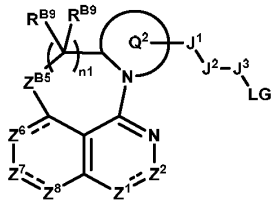
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

79. A compound of Formula (a0):



(a0),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^{B5} is selected from $C(R^{B9})_2$ and O;

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -$N(R^{B12})$-, -C(O)-, -$N(R^{B12})C(O)$-, -$C(O)N(R^{B12})$-, -S-, -$S(O)_2$-, -S(O)-, -$P(O)R^{B12}$-, -$N(R^{B12})S(O)_2$-, -$N(R^{B12})S(O)$-, -$N(R^{B12})P(O)R^{B12}$-, -$S(O)_2N(R^{B12})$-, -$S(O)N(R^{B12})$-, -$P(O)R^{B12}N(R^{B12})$-, -$OS(O)_2$-, -OS(O)-, -$OP(O)R^{B12}$-, -$S(O)_2O$-, -S(O)O-, and -$P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12}

carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

LG is selected from -$OS(O)_2R^{B4}$ and -$OS(O)(NR^{B4b})R^{B4}$;

n1 is selected from 1, 2, and 3;

R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and -$N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B1b}, R^{B4b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -$C(O)OR^{B12}$, -$C(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

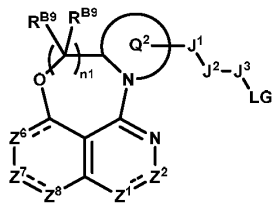
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

80. A compound of Formula (a):



(a),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

LG is selected from $-OS(O)_2R^{B4}$ and $-OS(O)(NR^{B4b})R^{B4}$;

n1 is selected from 1, 2, and 3;

R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and $-N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B1b}, R^{B4b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-OR^{B12}$, $-SR^{B12}$, $-N(R^{B12})(R^{B13})$, $-C(O)OR^{B12}$, $-OC(O)N(R^{B12})(R^{B13})$, $-N(R^{B12})C(O)N(R^{B12})(R^{B13})$, $-N(R^{B12})C(O)OR^{B12}$, -

$N(R^{B12})S(O)_2R^{B12}$, $-C(O)R^{B12}$, $-S(O)R^{B12}$, $-OC(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-N(R^{B12})C(O)R^{B12}$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$-, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle);

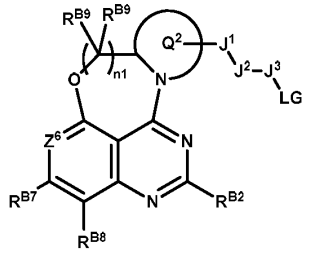
R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

81. The compound, salt, solvate, or method of any one of embodiments 71 or 73 to 79, wherein Z^{B5} is $C(R^{B9})_2$.

82. The compound, salt, solvate, or method of any one of embodiments 71 to 81, wherein n1 is 1.

83. The compound, salt, or solvate of any one of embodiments 79 or 80, wherein the compound is a compound of Formula (a-1):



(a-1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^6 is selected from $C(R^{B6})$ and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})-$, -C(O)-, $-N(R^{B12})C(O)-$, and $-C(O)N(R^{B12})-$, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, , wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)- and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, each of which is optionally substituted with one or more R^{B20};

LG is selected from $-OS(O)_2R^{B4}$;

R^{B4} is selected from C_{2-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and $-N(R^{B12})(R^{B13})$, wherein C_{2-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

n1 is 1;

R^{B2} is $-O(C_{1-3}$ alkylene)(4- to 10-membered heterocycle), $-O(C_{1-3}$ alkylene)-(4- to 5-membered heterocycle)-(C_{1-3} alkylene)-(4- to 10-membered heterocycle), or $-O(C_{1-3}$ alkylene)-(C_{3-4} cycloalkyl)-(C_{1-3} alkylene)-(4- to 10-membered heterocycle), wherein C_{1-3} alkylene, C_{3-4} cycloalkyl, 4- to 5-membered heterocycle, and 4- to 10-membered heterocycle are each optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, -O-(C_{3-4} cycloalkyl), $-NH_2$, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl)$_2$, and $=C(R^{B21})_2$;

R^{B6} is halogen or C_{1-3} haloalkyl;

R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one or more R^{B20};

R^{B8} is halogen;

R^{B9} is independently selected at each occurrence from hydrogen and methyl;

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

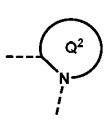
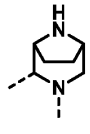
R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

84. The compound, salt, solvate, or method of any one of embodiments 71 to 83, wherein Q^2 is 7- to 9-membered bridged bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}.

85. The compound, salt, solvate, or method of embodiment 84, wherein  is  , which is

optionally substituted with one or more R^{B20}.

86. The compound, salt, solvate, or method of any one of embodiments 71 to 85, wherein:
Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$;
Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is N, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$;
Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})_2$, Z^7 is $N(R^{B7b})$, and Z^8 is $C(R^{B8})_2$; or
Z^1 is $N(R^{B1b})$, Z^2 is C(O), Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is N.

87. The compound, salt, solvate, or method of embodiment 86, wherein Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$.

88. The compound, salt, solvate, or method of embodiment 86, wherein Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is N, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$.

89. The compound, salt, solvate, or method of any one embodiments 71 to 88, wherein J^1 is selected from a bond, C_{1-6} alkylene, 2- to 6-membered heteroalkylene, and -C(O)-, wherein C_{1-6} alkylene and 2- to 6-membered heteroalkylene are optionally substituted with one or more R^{B20}.

90. The compound, salt, solvate, or method of any one of embodiments 71 to 89, wherein J^1 is -C(O)-.

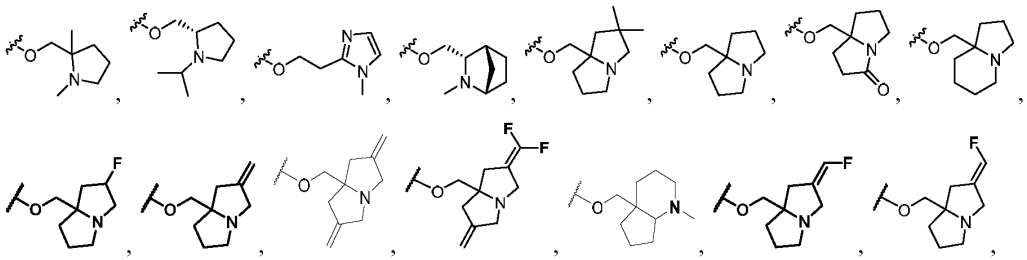
91. The compound, salt, solvate, or method of any one of embodiments 71 to 90, wherein J^2 is a bond.

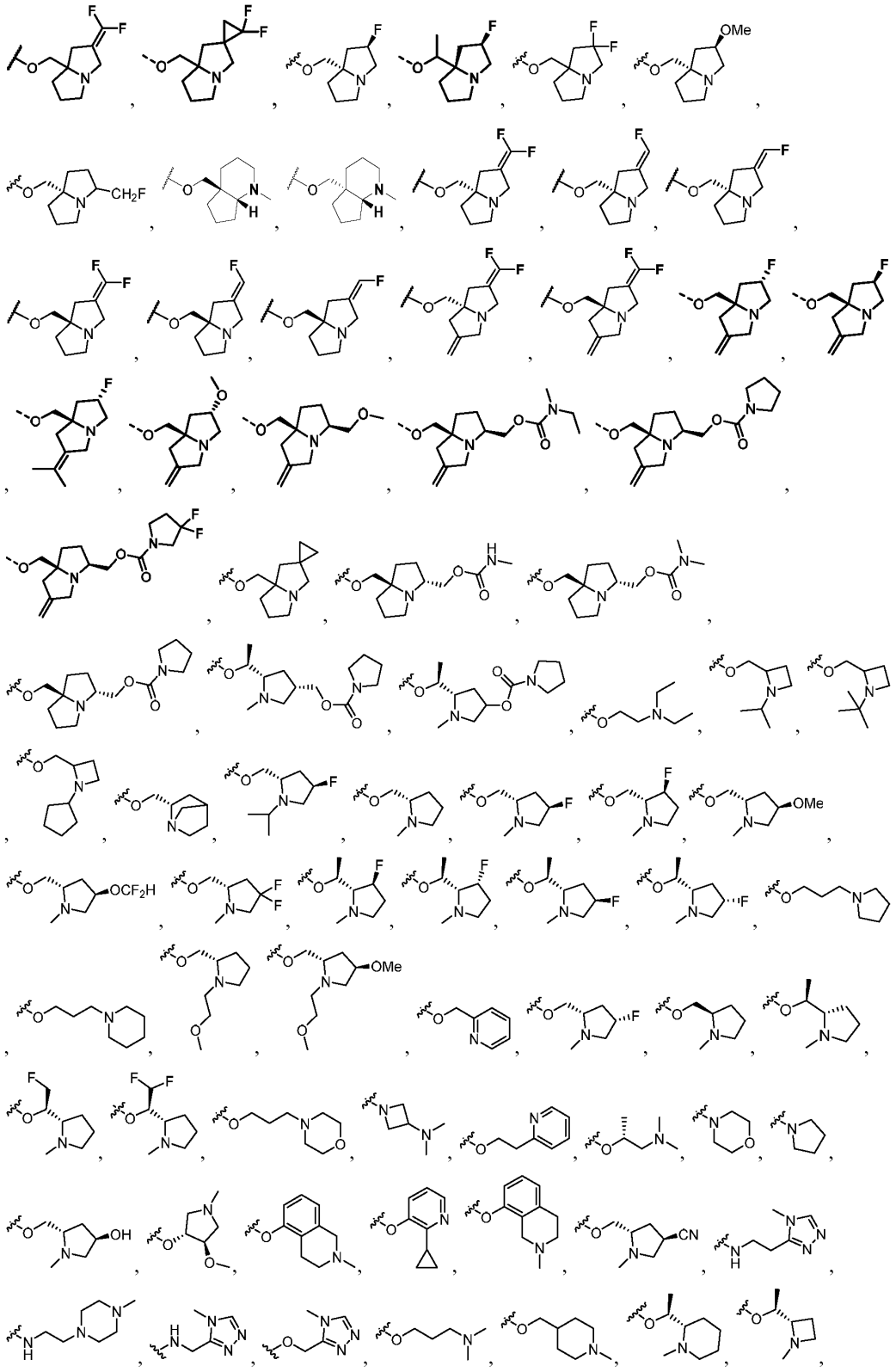
92. The compound, salt, solvate, or method of any one of embodiments 71 to 91, wherein J^3 is selected from C_{1-6} alkylene and 2- to 6-membered heteroalkylene, each of which is optionally substituted with one or more R^{B20}.

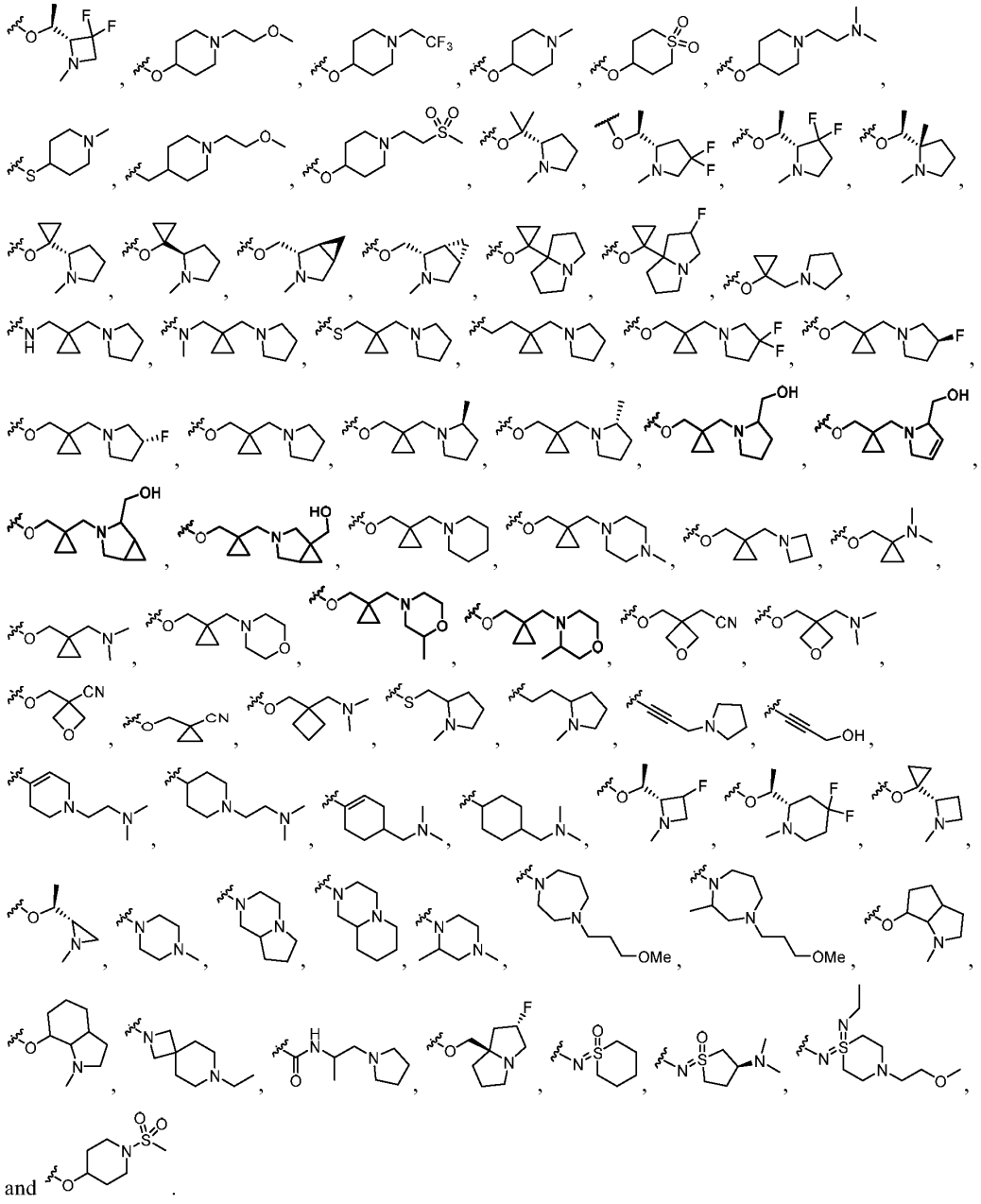
93. The compound, salt, solvate, or method of any one of embodiments 71 to 88, wherein:
J^1 is -C(O)-;
J^2 is a bond; and
J^3 is C_{1-6} alkylene.

94. The compound, salt, solvate, or method of any one of embodiments 71 to 93, wherein R^{B2} is $-O(C_{1-3}$ alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and $=C(R^{B21})_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl.

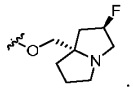
95. The compound, salt, solvate, or method of any one of embodiments 71 to 93, wherein R^{B2} is selected from



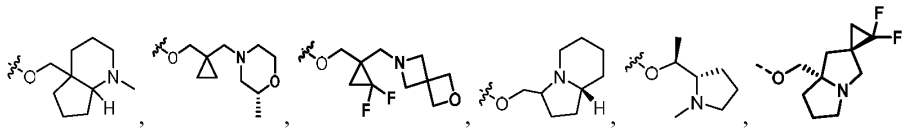


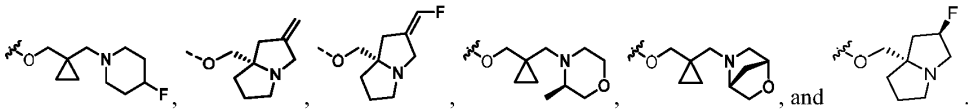


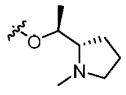
and .

96. The compound, salt, solvate, or method of any one of embodiments 71 to 93, wherein R^{B2} is  .

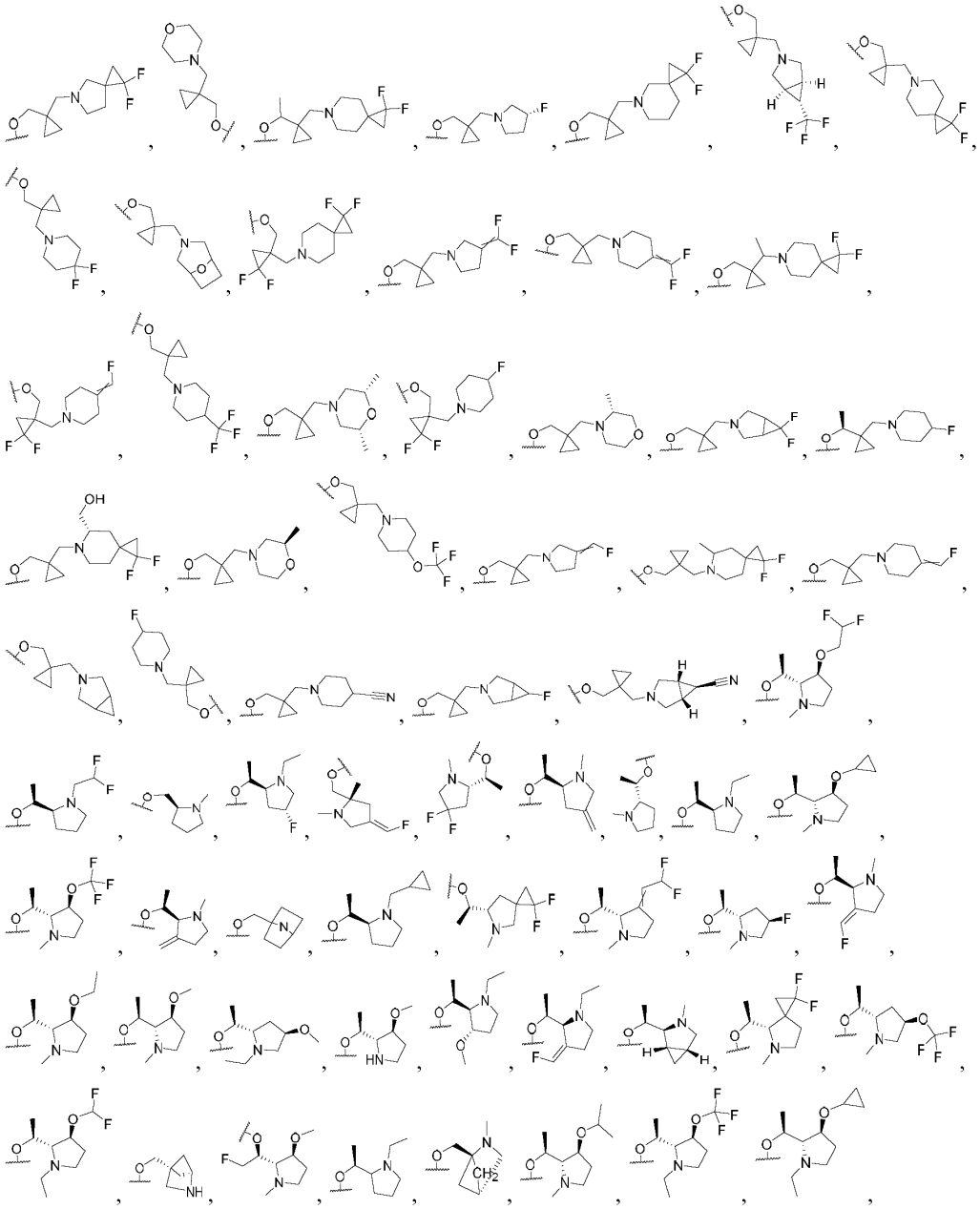
97. The compound, salt, solvate, or method of any one of embodiments 71 to 93, wherein R^{B2} is selected from

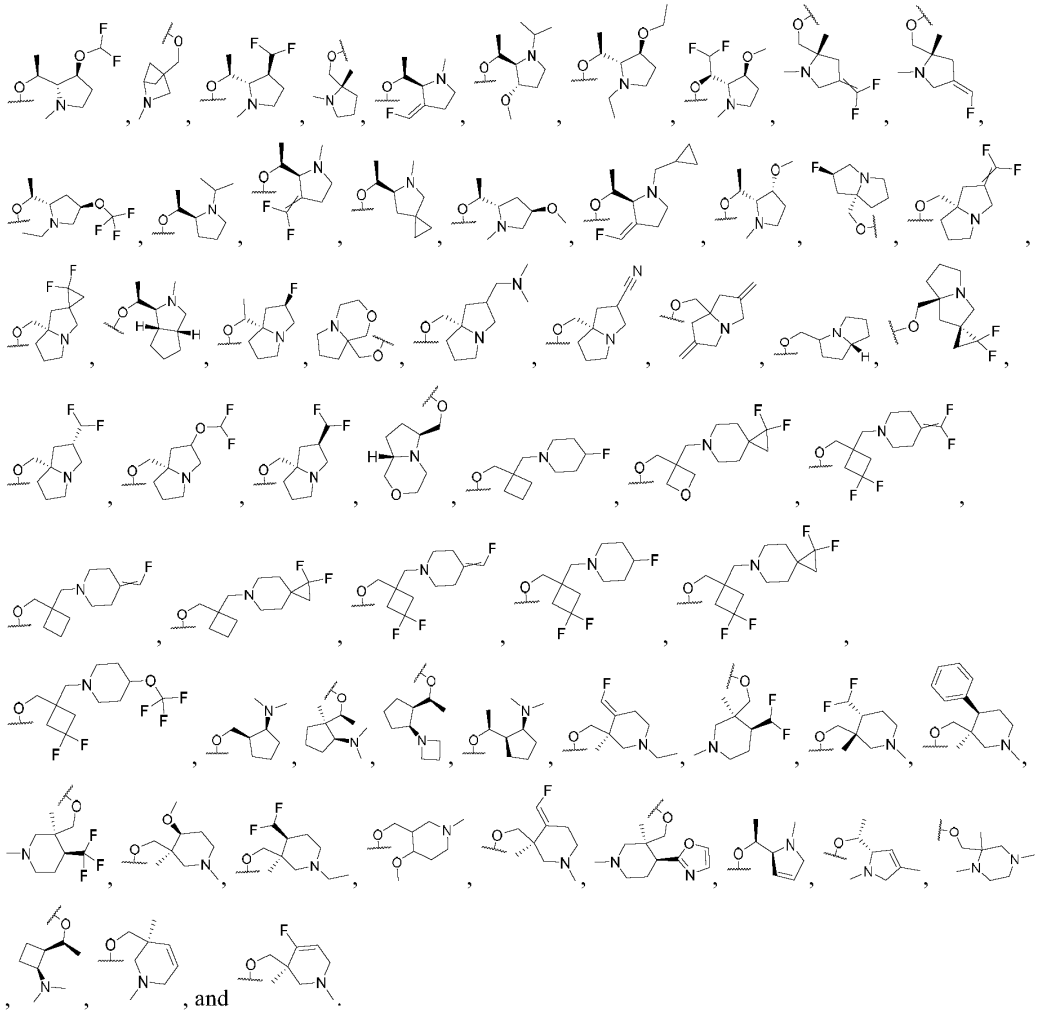




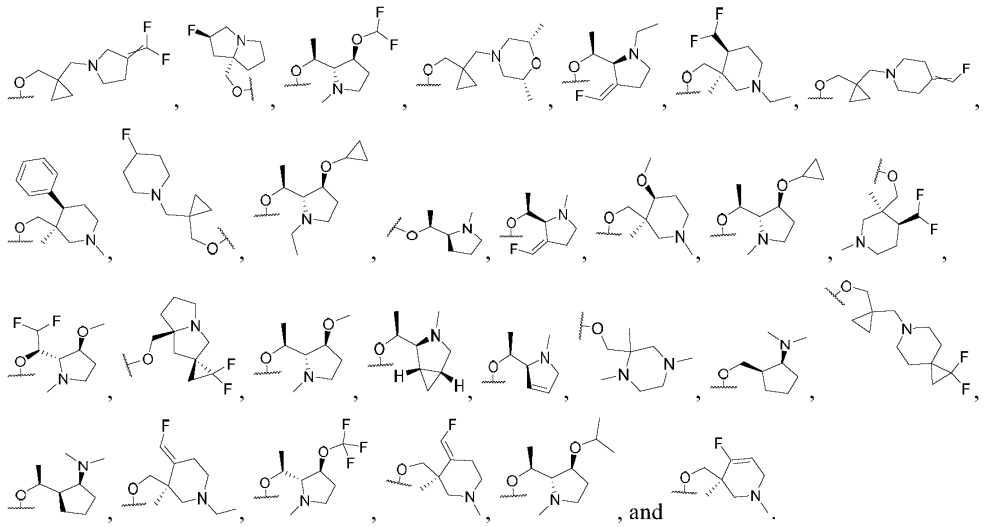
98. The compound, salt, solvate, or method of any one of embodiments 71 to 93, wherein R^{B2} is  .

99. The compound, salt, solvate, or method of any one of embodiments 71 to 93, wherein R^{B2} is selected from

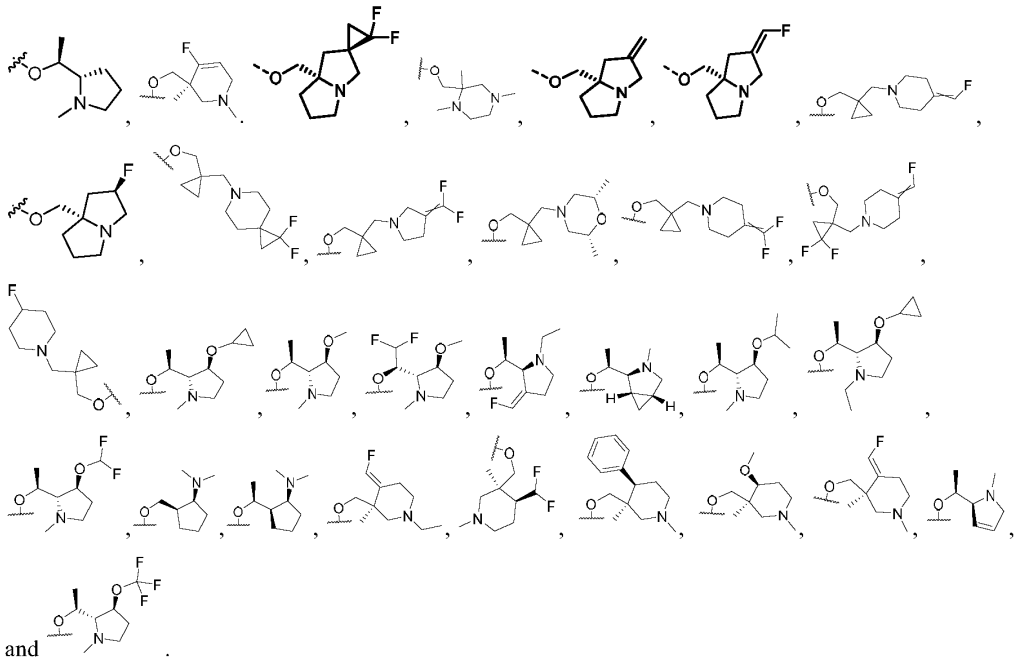




100. The compound, salt, solvate, or method of any one of embodiments 71 to 93, wherein R^{B2} is selected from



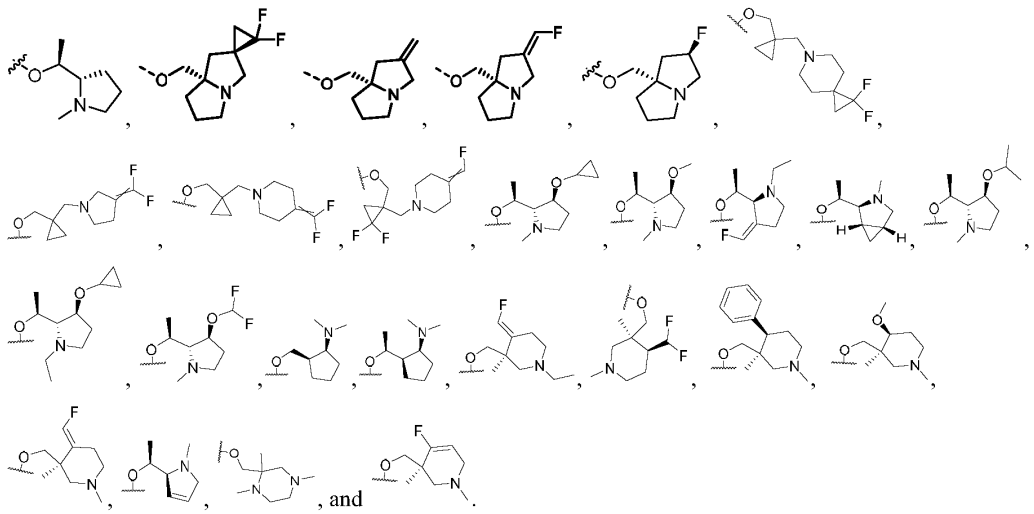
101. The compound, salt, solvate, or method of any one of embodiments 71 to 93, wherein R^{B2} is selected from



and

.

102. The compound, salt, solvate, or method of any one of embodiments 71 to 93, wherein R^{B2} is selected from



, and

.

103. The compound, salt, solvate, or method of any one of embodiments 71 to 102, wherein R^{B6} is halogen or C_{1-3} haloalkyl.

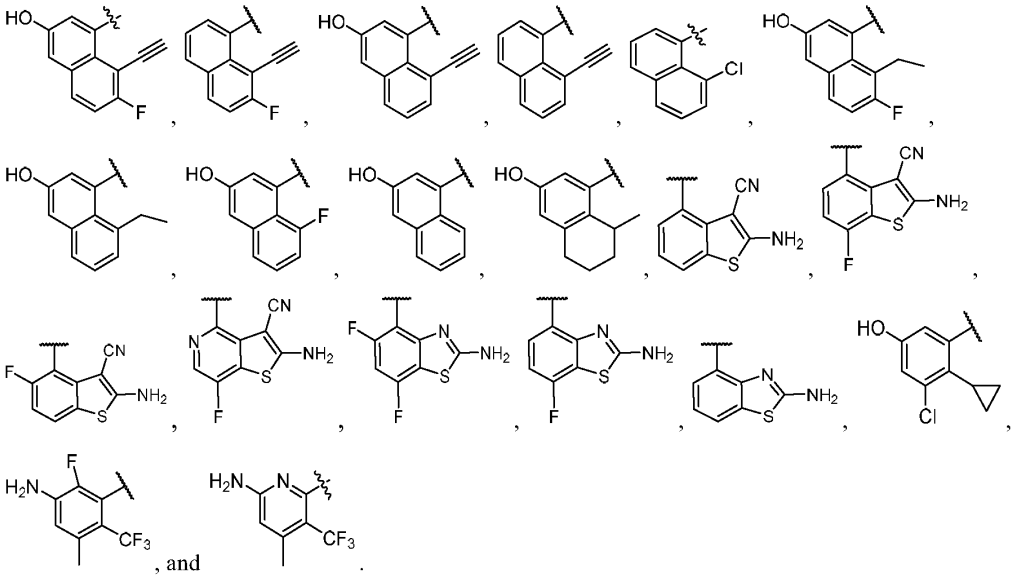
104. The compound, salt, solvate, or method of any one of embodiments 71 to 103, wherein R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one or more R^{B20}.

105. The compound, salt, solvate, or method of any one of embodiments 71 to 104, wherein R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}.

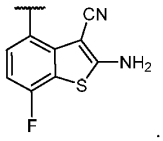
106. The compound, salt, solvate, or method of any one of embodiments 71 to 105, wherein R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, $-OR^{B22}$, $-N(R^{B22})(R^{B23})$, and C_{3-6} cycloalkyl.

107. The compound, salt, solvate, or method of any one of embodiments 71 to 106, wherein R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, $-CH_3$, $-CH_2CH_3$, $-CH{=}CH_2$, $-CF_3$, -C≡CH, -OH, $-NH_2$, and -cyclopropyl.

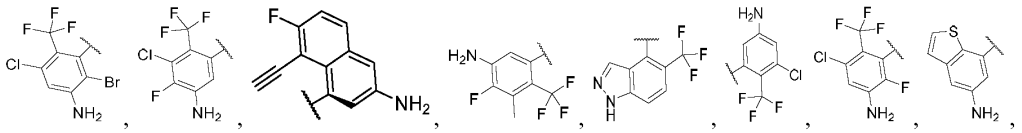
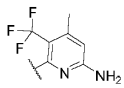
108. The compound, salt, solvate, or method of any one of embodiments 71 to 107, wherein R^{B7} is selected from


, and .

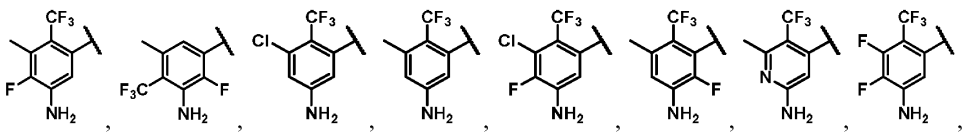
109. The compound, salt, solvate, or method of any one of embodiments 71 to 108, wherein R^{B7} is

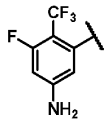

.

110. The compound, salt, solvate, or method of any one of embodiments 71 to 103, wherein R^{B7} is selected from


and  .

111. The compound, salt, solvate, or method of any one of embodiments 71 to 103, wherein R^{B7} is selected from

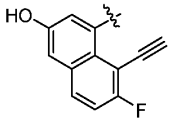

, and

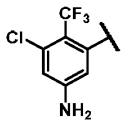


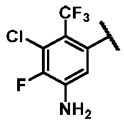
112. The compound, salt, solvate, or method of any one of embodiments 71 to 103, wherein R^{B7} is  .

113. The compound, salt, solvate, or method of any one of embodiments 71 to 103, wherein R^{B7} is  .

114. The compound, salt, solvate, or method of any one of embodiments 71 to 103, wherein R^{B7} is

 .

115. The compound, salt, solvate, or method of any one of embodiments 71 to 103, wherein R^{B7} is  .

116. The compound, salt, solvate, or method of any one of embodiments 71 to 103, wherein R^{B7} is  .

117. The compound, salt, solvate, or method of any one of embodiments 71 to 116, wherein R^{B8} is halogen.

118. The compound, salt, solvate, or method of any one of embodiments 71 to 116, wherein R^{B8} is fluoro.

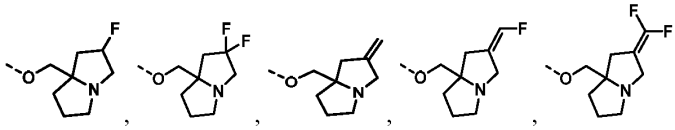
119. The compound, salt, solvate, or method of any one of embodiments 71 to 103, wherein:

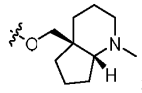
R^{B6} is halogen;

R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and

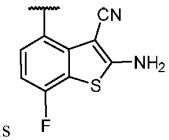
R^{B8} is halogen.

120. The compound, salt, solvate, or method of any one of embodiments 71 to 103, wherein:

R^{B2} is selected from  , and

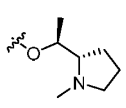
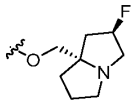

;

R^{B6} is halogen;

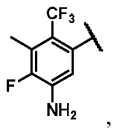
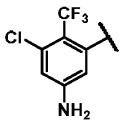
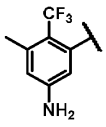
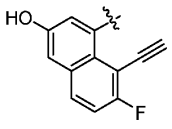

R^{B7} is ; and

R^{B8} is halogen.

121. The compound, salt, solvate, or method of any one of embodiments 71 to 93, wherein:

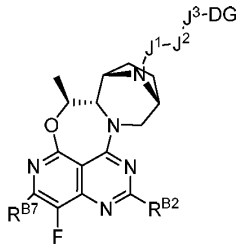
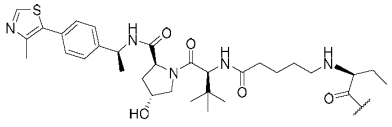
R^{B2} is selected from  and  ;

R^{B6} is halogen;

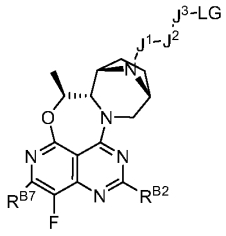
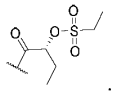
R^{B7} is selected from  ,  ,  ,  , and  ; and

R^{B8} is halogen.

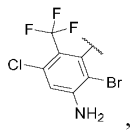
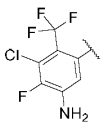
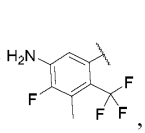
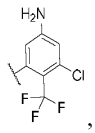
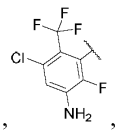
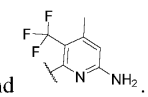
122. The compound, salt, solvate, or method of any one of embodiments 71 to 78, 81, 82, 84 to 86, or 88 to 121, wherein the compound of Formula (A0) or (A), has the formula:

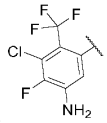
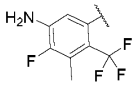
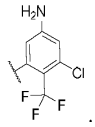

(A-7), wherein:-J^1-J^2-J^3-DG is  .

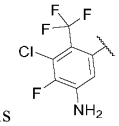
123. The compound, salt, solvate, or method of any one of embodiments 78 to 86, or 88 to 121, wherein the compound of Formula (a0) or (a), has the formula:

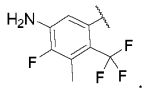

(a-7), wherein -J^1-J^2-J^3-LG is  .

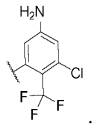
124. The compound, salt, solvate, or method of embodiment 122 or 123, wherein R^{B7} is selected from

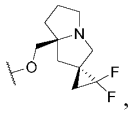
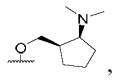
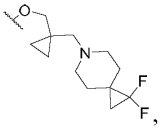
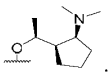
 ,  ,  ,  ,  , and  .

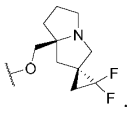
125. The compound, salt, solvate, or method of embodiment 122 or 123, wherein R^{B7} is selected from  ,  , and  .

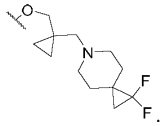
126. The compound, salt, solvate, or method of embodiment 122 or 123, wherein R^{B7} is  .

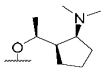
127. The compound, salt, solvate, or method of embodiment 122 or 123, wherein R^{B7} is  .

128. The compound, salt, solvate, or method of embodiment 122 or 123, wherein R^{B7} is  .

129. The compound, salt, solvate, or method of any one of embodiments 122 to 128, wherein R^{B2} is selected from  ,  ,  , and  .

130. The compound, salt, solvate, or method of any one of embodiments 122 to 128, wherein R^{B2} is  .

131. The compound, salt, solvate, or method of any one of embodiments 122 to 128, wherein R^{B2} is  .

132. The compound, salt, solvate, or method of any one of embodiments 122 to 128, wherein R^{B2} is  .

133. The compound, salt, solvate, or method of any one of embodiments 71, 78, and 79, wherein the compound is selected from a compound of Table 1.

134. A pharmaceutical composition comprising a compound of any one of embodiments 71 to 77 or 79 to 133, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

135. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 71 to 77 or 79 to 133, or a pharmaceutically acceptable salt or solvate thereof.

136. A method of treating cancer in a subject comprising a Ras mutant protein, the method comprising: inhibiting the Ras mutant protein of said subject by administering to said subject a compound of any one of embodiments 71 to 77 or 79 to 133, wherein the compound is characterized in that upon contacting the Ras mutant protein, said Ras mutant protein exhibits reduced Ras signaling output.

137. The method of embodiment 135 or 136, wherein the cancer is a solid tumor or a hematological cancer.

138. A method of reducing signaling output of a Ras protein, comprising contacting a Ras protein with an effective amount of a compound of any one of embodiments 71 to 77 or 79 to 133, or a pharmaceutically acceptable salt or solvate thereof, thereby reducing the signaling output of the Ras protein.

139. The method of embodiment 138, wherein the compound binds covalently or non-covalently to the Ras protein, thereby reducing the signaling output of the Ras protein.

140. A method of inhibiting cell growth, comprising administering an effective amount of a compound of any one of embodiments 71 to 77 or 79 to 133, or a pharmaceutically acceptable salt or solvate thereof, to a cell expressing a Ras protein, thereby inhibiting growth of said cells.

141. The method of any one of embodiments 135 to 140, comprising administering an additional agent.

EXAMPLES

[403] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein. Unless noted otherwise, all materials, such as reagents, starting materials and solvents, were purchased from commercial suppliers, such as Sigma-Aldrich, VWR, and the like, and were used without further purification. Reactions were run under nitrogen atmosphere, unless noted otherwise. The progress of reactions was monitored by thin layer chromatography (TLC), analytical high performance liquid chromatography (anal. HPLC), and mass spectrometry, the details of which may be provided in specific examples.

[404] Reactions were worked up as described specifically in each preparation; commonly, reaction mixtures were purified by extraction and other purification methods such as temperature- and solvent-dependent crystallization, and precipitation. In addition, reaction mixtures were routinely purified by preparative HPLC, for example, using Microsorb C18 or Microsorb BDS column packings and conventional eluents. Progress of reactions was typically monitored by liquid chromatography mass spectrometry (LCMS). Characterization of isomers was typically done by Nuclear Overhauser effect spectroscopy (NOE). Characterization of reaction products was routinely carried out by mass spectrometry and/or ^{1}H-NMR spectroscopy. For NMR measurement, samples were dissolved in deuterated solvent (CD_3OD, $CDCl_3$, or DMSO-d_6).

[405] **Example 1**: Compound Syntheses

[406] **Example 1a:** Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(317A)**

[407] Step 1: To a solution of tert-butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-1-fluoro-5-methyl-12-(methylsulfonyl)-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 (200 mg, 0.24 mmol) and (1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methanol (90 mg, 0.37 mmol) in toluene (2 mL) was added t-BuONa (60 mg, 0.6 mmol) at 0 °C. The mixture was stirred at 25 °C for 1.5 hours, quenched with saturated aqueous solution of NH_4Cl (10 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase column to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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 as a yellow solid. MS m/z (ESI): 1070.8 $[M+H]^+$.

[408] Step 2: A solution of tert-butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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 (65 mg, 0.06 mmol) and CsF (91 mg, 0.6 mmol) in DMF (1 mL) was stirred at 30°C for 2 hours under nitrogen. The mixture was diluted with brine (20 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were separated, dried over sodium sulfate, concentrated to give a residue. The residue was purified by prep-TLC (DCM:MeOH=10:1) to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-8-ethynyl-7-fluoronaphthalen-1-yl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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 as a yellow solid. MS m/z (ESI): 914.4 $[M+H]^+$.

[409] Step 3: A solution of tert-butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-8-ethynyl-7-fluoronaphthalen-1-yl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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 (50 mg, 0.05 mmol) in TFA (2 mL) was stirred at 30°C for 1 hour under nitrogen and concentrated to give a residue. The residue was adjusted to pH~8 by saturated sodium bicarbonate aqueous solution (20 mL) and extracted with DCM: MeOH=10:1 (50 mL x 3). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-TLC (DCM:NH_3.MeOH=10:1) to give the desired product 4-((5S,5aS,6S,9R)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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)-5-ethynyl-6-fluoronaphthalen-2-amine as a yellow solid. MS m/z (ESI): 714.3 $[M+H]^+$.

[410] Step 4: A solution of 4-((5S,5aS,6S,9R)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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)-5-ethynyl-6-fluoronaphthalen-2-amine (25 mg, 0.04 mmol) and (R)-2-((ethylsulfonyl)oxy)butanoic acid (7 mg, 0.04 mmol) in NMP (1 mL) was stirred at 0 °C for 5 minutes.

Then DMTMM (12 mg, 0.06 mmol) was added at 0 °C and the mixture was stirred at room temperature for 10 minutes. The mixture was diluted with saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired product ((R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate) (317) as a white solid. MS m/z (ESI): 892.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.83 – 7.71 (m, 1H), 7.43 – 7.26 (m, 1H), 7.15 – 6.85 (m, 2H), 5.65 – 5.61 (d, J = 16 Hz, 2H), 5.40 – 5.27 (m, 2H), 4.88 – 4.74 (m, 1H), 4.68 – 4.52 (m, 2H), 4.36 – 4.22 (m, 2H), 4.18 – 4.07 (m, 1H), 3.96 – 3.83 (m, 2H), 2.48 – 2.26 (m, 6H), 2.10 – 1.69 (m, 7H), 1.61 – 1.44 (m, 7H), 1.34 – 1.15 (m, 6H), 1.05 – 0.95 (m, 3H), 0.66 (s, 2H), 0.44 (s, 2H).

[411] Step 5: To (R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**317A**).

[412] **Example 1b**: Synthesis of (2S,4R)-1-((2S)-2-(5-(((2S)-1-((8S,8aS,9S,12R)-5-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8-methyl-8a,9,10,11,12,13-hexahydro-8H-9,12-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**324A**).

[413] Step 1: To a solution of tert-butyl (1S,2S,5R)-2-((S)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (556.31 mg, 2.17 mmol) in DMF (10 mL) was added NaH (1.74 g, 43.33 mmol) at 0 °C under nitrogen atmosphere, and the mixture was stirred at 0 °C for 15 minutes. Tert-butyl (R)-(4-(6-chloro-5,8-difluoro-4-hydroxy-2-(methylthio)quinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.2 g, 2.17 mmol) in DMF (15 mL) was added to the above mixture at 0 °C, and the resulting mixture was stirred at 60 °C for 1 hour. The mixture was cooled to room temperature, quenched with water (50 mL) and extracted with ethyl acetate (50 mL x 4). The extracts were combined, washed with brine (100 mL) and dried over Na_2SO_4. The resulting product was filtered and the filtrate was concentrated in vacuo to give a residue which was purified by flash column ($MeOH/CH_2Cl_2$ = 0~14%, 50 mL/min) to give tert-butyl (1S,2S,5R)-2-((S)-1-((7-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-4-hydroxy-2-(methylthio)quinazolin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate as a yellow solid. MS m/z (ESI): 789.4 $[M+H]^+$.

[414] Step 2: A solution of compound tert-butyl (1S,2S,5R)-2-((S)-1-((7-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-4-hydroxy-2-(methylthio)quinazolin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.5 g, 1.90 mmol) in DCM (15 mL) were added PyBOP (750 mg, 2.95 mmol) and DIEA (510 mg, 3.95 mmol) at room temperature and the resulting mixture was stirred at 25 °C for 15

hours. The mixture was quenched with water (60 mL) and extracted with ethyl acetate (50 mL x 3). The extracts were combined, washed with brine and dried over Na_2SO_4. The resulting product was filtered and the filtrated was concentrated in vacuo to give a residue which was purified by flash column (EtOAc/petroleum ether = 0~20%) to give tert-butyl (5S,5aS,6S,9R)-2-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-5-methyl-13-(methylthio)-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazoline-15-carboxylate as a light-yellow solid. MS m/z (ESI): 771.0 $[M+H]^+$.

[415] Step 3: To a solution of tert-butyl (5S,5aS,6S,9R)-2-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-5-methyl-13-(methylthio)-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazoline-15-carboxylate (1.0 g, 1.30 mmol) in DCM (15 mL) was added m-CPBA (335.61 mg, 1.94 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 hour and quenched with saturated Na_2SO_3 solution (50 mL). The mixture was extracted with DCM (30 mL x 3) and extracts were dried over Na_2SO_4. The resulting product was filtered and the filtrated was concentrated in vacuo to give tert-butyl (5S,5aS,6S,9R)-2-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-5-methyl-13-(methylsulfinyl)-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazoline-15-carboxylate. MS m/z (ESI): 787.0 $[M+H]^+$.

[416] Step 4: To a solution of [(2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl]methanol (404.43 mg, 2.54 mmol) in toluene (5 mL) was added t-BuOK (712.63 mg, 6.35 mmol) at 0 °C under nitrogen atmosphere and the mixture was stirred for 0.5 hour. Tert-butyl (5S,5aS,6S,9R)-2-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-5-methyl-13-(methylsulfinyl)-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazoline-15-carboxylate (1.0 g, 1.27 mmol) in toluene was added at 0 °C and the mixture was warmed to room temperature and stirred for 1 hour. The mixture was quenched with water (60 mL) and extracted with ethyl acetate (40 mL x 3). The extracts were combined, washed with brine (50 mL) and dried over Na_2SO_4. It filtered and the filtrate was concentrated in vacuo to give a residue which was purified by flash column (ethyl acetate/petroleum ether = 0~65%) to give tert-butyl (5S,5aS,6S,9R)-2-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazoline-15-carboxylate as a light-yellow solid. MS m/z (ESI): 882.4 $[M+H]^+$.

[417] Step 5: A solution of tert-butyl (5S,5aS,6S,9R)-2-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazoline-15-carboxylate (600 mg, 0.679 mmol) in CH_2Cl_2 (8 mL) was added TFA (1.6 mL) and the resulting mixture was stirred at room temperature for 2 hours. The mixture was concentrated in vacuo to give a residue which was purified by C18 column chromatography (MeCN/H_2O = 65%, NH_4HCO_3) to give (R)-2-amino-4-((5S,5aS,6S,9R)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-2-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile as a white solid. MS m/z (ESI): 682.2 $[M+H]^+$.

[418] Step 6: A solution of (R)-2-amino-4-((5S,5aS,6S,9R)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-2-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (400

mg, 0.586 mmol) and (R)-2-((ethylsulfonyl)oxy)propanoic acid (138.88 mg, 0.762 mmol) in NMP (8 mL) was degassed and purged with nitrogen 3 times. The mixture was stirred at 0 °C for 10 minutes, then DMTMM (243.39 mg, 0.880 mmol) was added and the mixture was warmed to room temperature and stirred for 10 minutes. The mixture was added dropwise to saturated $NaHCO_3$ (40 mL) at 0 °C, and the resulting mixture was extracted with ethyl acetate (30 mL x 3). The extracts were combined, washed with brine and dried over sodium sulfate. It was filtered and the filtrate was concentrated in vacuo to give a residue which was purified by prep-HPLC (NH_4HCO_3) to give ((R)-1-((5S,5aS,6S,9R)-2-((R)-2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl ethanesulfonate) (324) as a white solid. MS m/z (ESI): 847.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d6) δ 8.09 (s, 2H), 7.23 – 7.10 (m, 2H), 5.57 – 5.44 (m, 1H), 5.39 – 5.19 (m, 2H), 4.84 – 4.72 (m, 1H), 4.60 – 4.46 (m, 2H), 4.26 – 3.94 (m, 3H), 3.48 – 3.36 (m, 2H), 3.27 – 2.97 (m, 4H), 2.88 – 2.78 (m, 1H), 2.22 – 1.70 (m, 10H), 1.61 – 1.44 (m, 6H), 1.35 – 1.25 (m, 3H).

[419] Step 7: To a solution of (R)-1-((5S,5aS,6S,9R)-2-((R)-2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-3-chloro-1-fluoro-13-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl ethanesulfonate (112) is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide and DIEA in THF with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((2S)-2-(5-(((2S)-1-((8S,8aS,9S,12R)-5-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8-methyl-8a,9,10,11,12,13-hexahydro-8H-9,12-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-15-yl)-1-oxopropan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(324A)**.

[420] **Example 1c:** Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-(((2S,6R)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**333A**)

[421] Step 1: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-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 (2 g, 3.9 mmol) and (1-(((2S,6R)-2,6-dimethylmorpholino)methyl)cyclopropyl)methanol (1.55 g, 7.8 mmol) in toluene (20 mL) was added t-BuONa (936 mg, 9.7 mmol) at 0 °C. The mixture was stirred at 25 °C for 1.5 hours. The reaction was quenched by saturated aqueous solution of NH_4Cl (30 mL). The solution was extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure to give a residue. The residue was purified by reverse phase column to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-12-((1-(((2S,6R)-2,6-dimethylmorpholino)methyl)-cyclopropyl)methoxy)-1-fluoro-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 as a yellow solid. MS m/z (ESI): 633.1 $[M+H]^+$.

[422] Step 2: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-12-((1-(((2S,6R)-2,6-dimethylmorpholino)methyl)-cyclopropyl)methoxy)-1-fluoro-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-carboxylat (1 g, 1.58 mmol) in dry THF (10 mL)

and H_2O (2 mL) was added (5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)boronic acid (787 mg, 1.58 mmol), K_3PO_4 (1.68 g, 7.9 mmol) at 25 °C under argon. Then Catacxium A Pd G3 (243 mg, 0.32 mmol) was added, the mixture was sparged with argon at 25 °C for 3 times. The mixture was stirred at 70 °C for 1 hour under argon. The mixture was cooled to room temperature and diluted with brine (20 mL). The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were separated, dried over sodium sulfate, concentrated to give a residue. The residue was purified by reverse phase column (1% NH_4HCO_3) to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-(((2S,6R)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-1-fluoro-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 as a yellow solid. MS m/z (ESI):1050.6 $[M+H]^+$.

[423] Step 3: A solution of tert-butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-(((2S,6R)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-1-fluoro-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 (800 mg, 0.76 mmol) in TFA (8 mL) was stirred at 30 °C for 1 hour under nitrogen. The reaction was concentrated to give a residue. The residue was adjusted to pH~8 by saturated sodium bicarbonate aqueous solution (20 mL). The solution was extracted with DCM: MeOH=10:1 (50 mL x 3). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by Prep-TLC (DCM:NH_3:MeOH=10:1) to give the desired product 3-Chloro-5-((5S,5aS,6S,9R)-12-((1-(((2S,6R)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-1-fluoro-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)-2-fluoro-4-(trifluoromethyl)aniline as a yellow solid. MS m/z (ESI): 709.8 $[M+H]^+$.

[424] Step 4: A solution of 3-chloro-5-((5S,5aS,6S,9R)-12-((1-(((2S,6R)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-1-fluoro-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)-2-fluoro-4-(trifluoromethyl)aniline (150 mg, 0.21 mmol) and (R)-2-((ethylsulfonyl)oxy)butanoic acid (54 mg, 0.28 mmol) in NMP (2 mL) was stirred at 0 °C for 10 minutes. DMTMM (88 mg, 0.32mmol) was added to the mixture at 0 °C. The mixture was stirred at room temperature for 10 minutes. The reaction mixture was diluted with saturated aqueous solution of $NaHCO_3$ (20 mL). The mixture was extracted with ethyl acetate (30 mL x 3). The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired product (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-(((2S,6R)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate (333) as a white solid. MS m/z (ESI): 888.2$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.80 – 6.37 (m, 3H), 5.40 – 5.12 (m, 2H), 4.86 – 4.47 (m, 3H), 4.39 – 4.19 (m, 2H), 4.16 – 3.87 (m, 1H), 3.55 – 3.36 (m, 4H), 3.24 – 2.99 (m, 1H), 2.86 – 2.72 (m, 2H), 2.36 – 2.22 (m, 2H), 2.05 – 1.68 (m, 6H), 1.62 – 1.46 (m, 5H), 1.35 – 1.26 (m, 3H), 1.08 – 0.92 (m, 9H), 0.65 (s, 2H), 0.43 (s, 2H).

[425] Step 5: To (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-(((2S,6R)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to

provide the degrader (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-(((2S,6R)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**333A**).

[426] **Example 1d:** Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((2S,4R)-1-methyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(336A)**

[427] Step 1: To a solution of 1-(tert-butyl) 2-methyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (20 g, 81.63 mmol, 1 eq) in ethyl acetate (450 ml) and AgOTf (60 g, 244.9 mmol, 3 eq), KF(18.4 g, 326.52 mmol, 4 eq), selectfluor (42 g, 122.45 mmol, 1.5 eq), 2-fluoropyridine(20 ml, 244.9 mmol, 3 eq) , $TMSCF_3$(35.2 ml, 244.9 mmol, 33 eq) was added at 0°C. The reaction mixture stirred at 50 °C for 48 hours and cooled to room temperature. The mixture was filtered and the filtrate was washed by ethyl acetate. Organic phase was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (petroleum:ethyl acetate from 0% to 15%) to afford the desired product 1-(tert-Butyl) 2-methyl (2S,4R)-4-(trifluoromethoxy)pyrrolidine-1,2-dicarboxylate as yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.8 (1 H, brs); 4.47 (1 H, m), 3.76 (5 H, m), 2.5 (1 H, m), 2.25 (1 H, m), 1.45 (9 H, s)

[428] Step 2: To a solution of 1-(tert-butyl) 2-methyl (2S,4R)-4-(trifluoromethoxy)pyrrolidine-1,2-dicarboxylate (10 g, 31.9 mmol) in MeOH/H_2O (100 mL/50 mL) was added LiOH (6.7 g, 159.7 mmol). After stirring for 1 h at 60°C, the mixture was cooled to room temperature and extracted with ethyl acetate (300 mL). The aqueous layer was adjusted to pH ~ 2 with 2M HCl and extracted with ethyl acetate (200 mL×3). The organic phase was combined, washed with brine (200 mL) and dried by sodium sulfate. The mixture was filtered, the filtrate was concentrated under reduced pressure to give the desired product (2S,4R)-1-(tert-butoxycarbonyl)-4-(trifluoromethoxy)pyrrolidine-2-carboxylic acid which was used directly in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.5 (1 H, brs); 5.05 (1 H, s), 4.15 (1 H, m), 3.55 (2 H, m), 2.55 (2 H, m), 2.2 (1 H, m), 1.35 (9H, s)

[429] Step 3: To a solution of N,O-dimethylhydroxylamine hydrochloride (10 g, 33.4 mmol) in DCM (100 ml) was added CDI (8.1 g, 50.2 mmol) at 0°C. The reaction mixture was stirred at rt for 2 h, followed by the addition of (2S,4R)-1-(tert-butoxycarbonyl)-4-(trifluoromethoxy)pyrrolidine-2-carboxylic acid (4.9 g, 50.2 mmol). The reaction mixture was stirred at room temperature for 16 hour and extracted with DCM (200 mL×3). The organic phase was combined, washed with brine (100 mL) and dried over sodium sulfate. The mixture was filtered, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography on silica gel column (petroleum: ethyl acetate= 1:1) to give desired product tert-Butyl (2S,4R)-2-(methoxy(methyl)carbamoyl)-4-(trifluoromethoxy)pyrrolidine-1-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.05 (1 H, s), 4.75 (1 H, m), 3.75 (3 H, m), 3.65 (2 H, m), 3.15 (3H, s), 2.5 (1H, m), 2.1 (1 H, m), 1.45 (9H, s)

[430] Step 4: To a solution of tert-butyl (2S,4R)-2-(methoxy(methyl)carbamoyl)-4-(trifluoromethoxy)pyrrolidine-1-carboxylate (2 g, 5.83 mmol) in THF (20 ml) was added MeMgBr (2.5 mL, 7.58 mmol, 3 M) at -10°C. The reaction mixture was stirred at -10°C for 1 hour, quenched with brine and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous

sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography on silica gel column (petroleum: ethyl acetate = 2:1) to give the desired product tert-Butyl (2S,4R)-2-acetyl-4-(trifluoromethoxy)pyrrolidine-1-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.0 (1 H, s), 4.3 (1 H, m), 3.55 (2 H, m), 2.45 (1H, m), 2.05 (4 H, m), 1.35 (9H, s)

[431] Step 5: To a solution of (*R*)-2-Methyl-CBS-oxazaborolidine (242 mg, 0.875 mmol) in THF (15 ml) was added borane-methyl sulfide complex (3.1 mL, 6.13 mmol, 2 M) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, followed by the addition of tert-butyl (2S,4R)-2-acetyl-4-(trifluoromethoxy)pyrrolidine-1-carboxylate (1.3 g, 4.38 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 hour and quenched with MeOH. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography on silica gel column (petroleum: ethyl acetate= 1:1) to give the desired product tert-Butyl (2S,4R)-2-((S)-1-hydroxyethyl)-4-(trifluoromethoxy)pyrrolidine-1-carboxylate.

[432] Step 6: To a solution of tert-butyl (2S,4R)-2-((S)-1-hydroxyethyl)-4-(trifluoromethoxy)pyrrolidine-1-carboxylate (500 mg, 1.67 mmol) in THF (5 ml) was added $LiAlH_4$ (2.7 mL, 6.69 mmol, 2.5 M) at 0°C. The reaction mixture was stirred at 60°C for 1 hour and cooled down to room temperature. The mixture was quenched with $Na_2SO_4 \cdot 10H_2O$ and filtered. The filtrate was concentrated under reduced pressure to give the desired product (S)-1-((2S,4R)-1-methyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethan-1-ol which was used directly in the next step without further purification.

[433] Step 7: To a solution of S)-1-((2S,4R)-1-methyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethan-1-ol (248 mg, 1.17 mmol) in toluene (8 mL) was added tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-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 (400 mg, 1.56 mmol) and t-BuONa (149 mg, 1.56 mmol) at 0°C. The reaction mixture was stirred at room temperature for 30 minutes and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (DCM: MeOH= 10:1) to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-((S)-1-((2S,4R)-1-methyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethoxy)-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 as a yellow solid. MS m/z (ESI): 648.2 $[M+H]^+$.

[434] Step 8: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-((S)-1-((2S,4R)-1-methyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethoxy)-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 (200 mg, 0.31 mmol) in dioxane (20 mL) and H_2O (4 mL) was added (5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)boronic acid (231 mg, 0.46 mmol), Cs_2CO_3 (303 mg, 0.93 mmol) and $Pd(PPh_3)_4$ (72 mg, 0.06 mmol). The mixture was stirred at 100 °C under nitrogen for 3 hours and cooled to room temperature. The mixture was diluted with brine (30 mL), extracted with ethyl acetate (100 mL x 3). The combined organic layers were separated, dried over sodium sulfate, concentrated to give a residue. The residue was purified by flash column chromatography on silica gel (petroleum:ethyl acetate = 2:1) to afford the desired product tert-Butyl (5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((2S,4R)-1-methyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethoxy)-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 as a yellow solid. MS m/z (ESI): 1064.8 $[M+H]^+$.

[435] Step 9: A solution of tert-butyl (5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((2S,4R)-1-methyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethoxy)-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 (250 mg, 0.24 mmol) in TFA (3 mL) was stirred at room temperature for 1 hour under nitrogen. The mixture was concentrated to give a residue. The residue was adjusted to pH~8 by saturated sodium bicarbonate aqueous solution (30 mL). The solution was extracted with DCM (30 ml x 2). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-TLC (DCM:NH_3.MeOH=10:1) to give the desired product 3-Chloro-2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-5-methyl-12-((S)-1-((2S,4R)-1-methyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethoxy)-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)-4-(trifluoromethyl)aniline as a yellow solid. MS m/z (ESI): 724.2 $[M+H]^+$.

[436] Step 10: A solution of 3-chloro-2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-5-methyl-12-((S)-1-((2S,4R)-1-methyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethoxy)-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)-4-(trifluoromethyl)aniline (90 mg, 0.12 mmol) and (R)-2-((ethylsulfonyl)oxy)butanoic acid (32 mg, 0.16 mmol) in NMP (1 mL) was stirred at 0 °C for 10 minutes. Then DMTMM (52 mg, 0.19 mmol) was added at 0 °C. The mixture was stirred at room temperature for 10 minutes. The reaction mixture was diluted with saturated aqueous solution of $NaHCO_3$ (20 mL). The mixture was extracted with ethyl acetate (30 mL x 3). The organic layer was combined, dried over anhydrous sodium sulfate. It was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired product ((R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((2S,4R)-1-methyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate) (336) as a white solid. MS m/z (ESI): 902.7 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.71 (s, 1H), 6.30 (s, 2H), 5.42 – 5.11 (m, 3H), 4.91 – 4.50 (m, 4H), 4.22-3.82 (m, 1H), 3.46 – 3.32 (m, 3H), 3.28 – 3.17 (m, 1H), 3.01 – 2.89 (m, 1H), 2.48 – 2.37 (m, 4H), 2.21 – 2.09 (m, 1H), 2.07 – 1.64 (m, 7H), 1.59 – 1.44 (m, 3H), 1.35 – 1.24 (m, 6H), 1.05 – 0.90 (m, 3H).

[437] Step 11: To (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((2S,4R)-1-methyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((2S,4R)-1-methyl-4-(trifluoromethoxy)pyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**336A**).

[438] **Example 1e:** Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((S,E)-4-(fluoromethylene)-1,3-dimethylpiperidin-3-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(338A)**

[439] Step 1: To a solution of (fluoromethyl)triphenyl-l4-phosphane tetrafluoroborate (21.1 g, 55.4 mmol) in THF (100 mL) was added t-BuOK (55.4 mL, 55.4 mmol) at -70 °C and the mixture was stirred at -70 °C under nitrogen for 1 hour. 1-(tert-butyl) 3-methyl (R)-3-methyl-4-oxopiperidine-1,3-dicarboxylate (10 g, 36.9 mmol) in

THF (10 mL) was added at -70 °C and the mixture was warmed up to room temperature and stirred under nitrogen for 2 hours. The mixture was poured into water (200 mL) and extracted with ethyl acetate (3 x 200 mL). The extracts were combined, washed with brine and dried over sodium sulfate. The product was filtered, and the filtrate was concentrated under reduced pressure to give a crude which was purified by silica del column chromatography (EtOAc : petroleum = 10:90) to get the desired product 1-(tert-Butyl) 3-methyl (S,E)-4-(fluoromethylene)-3-methylpiperidine-1,3-dicarboxylate as a yellow oil as peak 1 as a yellow oil.

[440] Step 2: To a solution of 1-(tert-butyl) 3-methyl (S,E)-4-(fluoromethylene)-3-methylpiperidine-1,3-dicarboxylate (4.6 g, 16.0 mmol) in dioxane was added HCl dioxane (25 mL) at room temperature and the mixture was stirred at room temperature for 2 hours. The mixture was neutralized and extracted with DCM. The extracts were combined, washed with brine and dried over sodium sulfate. The product was filtered and concentrated to give the desired product methyl (S,E)-4-(fluoromethylene)-3-methylpiperidine-3-carboxylate as a white solid. MS m/z (ESI): 188.0 $[M+H]^+$

[441] Step 3: To a solution of methyl (S,E)-4-(fluoromethylene)-3-methylpiperidine-3-carboxylate (3.0 g, 16 mmol) and HCHO (2.6 g, 32.1 mmol) in MeOH (30 mL) stirred at room temperature for 2 hours. STAB (6.8 g, 32.1 mmol) was added at room temperature and the resulting mixture was stirred for 2 hours and quenched with a.q $NaHCO_3$ (60 mL). The mixture was extracted with ethyl acetate (3 x 80 mL). The extracts were combined, washed with brine and dried over sodium sulfate. The mixture was filtered, and the filtrated was concentrated under reduced pressure to give the crude which was purified by silica gel column chromatography (DCM : NH_3·MeOH = 90:10) to give the desired product methyl (S,E)-4-(fluoromethylene)-1,3-dimethylpiperidine-3-carboxylate as a yellow oil.

[442] Step 4: To a stirred solution of methyl (S,E)-4-(fluoromethylene)-1,3-dimethylpiperidine-3-carboxylate (2.76 g, 13.7 mmol) in THF (28 mL) was added $LiAlH_4$ (7.1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour and quenched with $Na_2SO_4 \cdot 10H_2O$. Then the reaction mixture was filtered, and the filtrate was concentrated under vacuum to give the desired product (S,E)-(4-(fluoromethylene)-1,3-dimethylpiperidin-3-yl)methanol as a yellow oil. MS m/z (ESI):174.2 $[M+H]^+$.

[443] Step 5: To a solution of tert-butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-1-fluoro-5-methyl-12-(methylthio)-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 (200 mg, 0.23 mmol) in DCM (4 mL) was added m-CPBA (215 mg, 0.69 mmol) at 0°C. The mixture was stirred at room temperature for 1.5 hours and quenched with aqueous solution of $NaHCO_3$ (50 mL). The mixture was extracted with DCM (2 x 100 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-1-fluoro-5-methyl-12-(methylsulfonyl)-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 which was used directly in the next step without further purification. MS m/z (ESI): 919.6 $[M+H]^+$.

[444] Step 6: To a solution of tert-butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-1-fluoro-5-methyl-12-(methylsulfonyl)-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 (200 mg, 0.22 mmol) and (S,E)-(4-(fluoromethylene)-1,3-dimethylpiperidin-3-yl)methanol (76 mg, 0.44 mmol) in toluene (2 mL) was added t-BuONa (52 mg, 0.54 mmol) at 25 °C. The mixture was stirred at 25°C for 1 hour, quenched by saturated aqueous solution of NH_4Cl (100 mL) and extracted with ethyl acetate (50 mL x 3). The extracts were combined, and

combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase column to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-1-fluoro-12-(((S,E)-4-(fluoromethylene)-1,3-dimethylpiperidin-3-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 as a yellow solid. MS m/z (ESI): 1012.6 $[M+H]^+$.

[445] Step 7: A solution of tert-butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-1-fluoro-12-(((S,E)-4-(fluoromethylene)-1,3-dimethylpiperidin-3-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 (80 mg, 0.08 mmol) and CsF (120 mg, 0.79 mmol) in DMF (1.5 mL) was stirred at 25 °C for 1 hour under nitrogen and quenched by water (100 mL). The solution was extracted with ethyl acetate (50 mL x 3). The extracts were combined, washed with water and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((S,E)-4-(fluoromethylene)-1,3-dimethylpiperidin-3-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 which was directly without further purification. MS m/z (ESI): 856.4 $[M+H]^+$.

[446] Step 8: A solution of tert-butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((S,E)-4-(fluoromethylene)-1,3-dimethylpiperidin-3-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 (80 mg, 0.09 mmol) in DCM (2 mL) was added TFA (1 mL) at 25 °C for 1 hour under nitrogen and concentrated to give a residue. The residue was adjusted to pH~8 by saturated sodium bicarbonate aqueous solution (100 mL) and extracted with DCM (50 mL x 2). The extracts were combined, washed with brine and dried over Na_2SO_4. The mixture was filtered and concentrated to give a residue. The residue was purified by prep-TLC (DCM:NH_3.MeOH=10:1) to give the desired product 5-Ethynyl-6-fluoro-4-((5S,5aS,6S,9R)-1-fluoro-12-(((S,E)-4-(fluoromethylene)-1,3-dimethylpiperidin-3-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-amine as a yellow solid. MS m/z (ESI): 656.4 $[M+H]^+$.

[447] Step 9: A solution of 5-ethynyl-6-fluoro-4-((5S,5aS,6S,9R)-1-fluoro-12-(((S,E)-4-(fluoromethylene)-1,3-dimethylpiperidin-3-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-amine (35 mg, 0.05 mmol) and (R)-2-((ethylsulfonyl)oxy)butanoic acid (5 mg, 0.03 mmol) in NMP (1 mL) was stirred at 0 °C for 5 minute. Then DMTMM (21 mg, 0.08 mmol) was added at 0°C and the mixture was stirred at room temperature for 10 minutes. It was diluted with saturated aqueous solution of $NaHCO_3$ (100 mL) and extracted with ethyl acetate (40 mL x 3). The organic layer was combined, washed with brine and dried over anhydrous sodium sulfate. It was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired product ((R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((S,E)-4-(fluoromethylene)-1,3-dimethylpiperidin-3-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-14-yl)-1-oxobutan-2-yl ethanesulfonate) (338) as a white solid. MS m/z (ESI): 834.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.84 - 7.69 (m, 1H), 7.40 - 7.27 (m, 1H), 7.10 - 6.92 (m, 2H), 6.86 - 6.60 (m, 1H), 5.74 - 5.52 (m, 2H), 5.41 - 5.23 (m, 2H), 4.90 - 4.75 (m, 1H), 4.70

- 4.50 (m, 3H), 4.35 - 4.26 (m, 1H), 4.17 - 3.83 (m, 2H), 3.53 - 3.42 (m, 3H), 3.26 - 3.04 (m, 1H), 2.76 - 2.66 (m, 2H), 2.26 - 2.10 (m, 4H), 2.08 - 1.73 (m, 8H), 1.59 - 1.46 (m, 3H), 1.35 - 1.24 (m, 3H), 1.15 - 1.07 (m, 3H), 1.07 - 0.93 (m, 3H).

[448] Step 10: To (R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((S,E)-4-(fluoromethylene)-1,3-dimethylpiperidin-3-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-14-yl)-1-oxobutan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-12-(((S,E)-4-(fluoromethylene)-1,3-dimethylpiperidin-3-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**338A**).

[449] **Example 1f:** Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-aminobenzo[b]thiophen-7-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]heptalen-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(348A)**

[450] Step 1: To a solution of 7-bromo-5-nitrobenzo[b]thiophene-2-carboxylic acid (1.7 g, 5.6 mmol) in DMSO (20 mL) and acetic acid (0.017 g) was added Ag_2CO_3 (1.5 g, 5.6 mmol) at room temperature and the resulting mixture was stirred at 120 °C for 2 hours and cooled to room temperature. The mixture was extracted with ethyl acetate (10 mL x 3), washed by brine (10 mL x 2) and dried over Na_2SO_4. The mixture was filtered and concentrated in vacuo, purified by column chromatography on silica gel, eluting with 0-30 % ethyl acetate in petroleum to give the desired product 7-Bromo-5-nitrobenzo[b]thiophene as yellow oil.

[451] Step 2: To a solution of 7-bromo-5-nitrobenzo[b]thiophene (0.7 g, 2.7 mmol) in EtOH (10 mL) and water (10 mL) was added iron (0.76 g ,13.5 mmol), NH_4Cl (0.43 g ,8.1 mmol) at room temperature, then the resulting mixture was stirred at 60 °C for 3 hours. A solution of $NaHCO_3$ a.q (10 mL) was added and the mixture was extracted with ethyl acetate (10 mL x 3). The extracts were combined, washed with brine (10 mL x 2) and dried over Na_2SO_4. The mixture was filtered and concentrated in vacuo to give a crude which was purified by column chromatography on silica gel, eluting with 0-10 % MeOH in DCM to give the desired product 7-Bromobenzo[b]thiophen-5-amine as yellow oil. MS m/z (ESI): $(M+H)^+$ 227.9

[452] Step 3: To a solution of 7-bromobenzo[b]thiophen-5-amine (0.65 g ,2.8 mmol) in 1,4-dioxane (15 mL) was added Pin_2B_2 (1.1 g,4.2 mmol), $Pd(dppf)Cl_2$ (0.2 g ,0.28 mmol), KOAc (0.55 g,5.6 mmol) at room temperature under nitrogen, then the mixture was stirred at 100 °C for 3 hours and cooled down to room temperature. The mixture was concentrated in vacuo to give a crude which was purified by column chromatography on silica gel, eluting with 0-10 % MeOH in DCM to give the desired product 7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-5-amine as yellow oil. MS m/z (ESI): $(M+H)^+$ 276.1

[453] Step 4: To a solution of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-5-amine (140 mg , 0.5 mmol) in 1,4-dioxane (10 mL) and in water (1 mL) was added tert-butyl (5S,5aS,6S,9R)-2-chloro-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 (150 mg ,0.25 mmol), $Pd(PPh_3)_4$ (29

mg ,0.025 mmol), Cs_2CO_3 (163 mg,0.75 mmol) at room temperature under nitrogen atmosphere, then the resulting mixture was stirred at 100 °C for 3 hours and cooled down to room temperature. The mixture was concentrated in vacuo to give a crude which was purified by column chromatography on silica gel, eluting with 0-100 % ethyl acetate in petroleum to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(5-aminobenzo[b]thiophen-7-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 as yellow oil. MS m/z (ESI): $(M+H)^+$ 706.1,

[454] Step 5: To a solution of tert-butyl (5S,5aS,6S,9R)-2-(5-aminobenzo[b]thiophen-7-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 (0.15 g, 0.21 mmol) in DCM (3 mL) was added TFA (3 mL) at room temperature, then the resulting mixture was stirred at room temperature for 0.5 hours. The mixture was adjusted pH~ 9 with 7M NH_3 in CH_3OH. The mixture was then concentrated in vacuo to give a crude which was purified by pre-TLC to give the desired product 7-((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)benzo[b]thiophen-5-amine as yellow solid.

[455] Step 6: (R)-1-((5S,5aS,6S,9R)-2-(5-aminobenzo[b]thiophen-7-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]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate To a solution of 7-((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)benzo[b]thiophen-5-amine (50 mg, 0.08 mmol) in NMP (4 mL) was added (R)-2-((ethylsulfonyl)oxy)butanoic acid (24 mg, 0.12 mmol) and DMTMM (33 mg, 0.13 mmol) at 0 °C, then the resulting mixture was stirred at room temperature for 15 minutes, quenched with a.q. $NaHCO_3$, and extracted with ethyl acetate (10 mL x 3). The extracts were combined, washed with brine and dried over Na_2SO_4. It was filtered and the filtrate was concentrated in vacuo to give a crude which was purified by pre-HPLC to give the desired product ((R)-1-((5S,5aS,6S,9R)-2-(5-aminobenzo[b]thiophen-7-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]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate) (348) as white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, J = 8 Hz, 1H), 7.36 (s, 1H), 7.23 (d, J = 8 Hz, 1H), 7.12 (d, J = 4 Hz, 1H), 5.41 – 5.16 (m, 5H), 4.90 – 4.50 (m, 3H), 4.22 – 3.89 (m, 3H), 3.46 – 3.39 (m, 2H), 3.30 (s, 1H), 3.23 (d, J = 13.6 Hz, 1H), 3.14 – 3.06 (m, 2H), 3.03 (s, 1H), 2.85 (d, J = 6.4 Hz, 1H), 2.21 – 2.14 (m, 1H), 2.05 (m, 3H), 1.84 (m, 7H), 1.58 (m, 3H), 1.30 (m, 3H), 1.07 – 0.92 (m, 3H).

[456] Step 7: To (R)-1-((5S,5aS,6S,9R)-2-(5-aminobenzo[b]thiophen-7-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]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-aminobenzo[b]thiophen-7-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]heptalen-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(348A)**.

Example 1g: Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(375A)**

Step 1: To a solution of tert-butyl (1R,2S,5S)-2-((S)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (3.0 g, 11.7 mmol) in THF (60 mL) was added NaH (1.2 g, 29.3 mmol, 60% in mineral oil) at 0°C. The resulting solution was stirred at 25 °C for 2 hours under nitrogen. A solution of 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-ol (3.3 g, 11.7 mmol) in THF (100 mL) was then added at 0 °C, and the mixture was stirred at 25°C for 4 hours under nitrogen. The reaction was quenched by saturated aqueous solution of NH_4Cl (200 mL). The organic layer (THF) was separated, concentrated to 40 mL and filtered to give the desired product tert-Butyl (1S,2S,5R)-2-((S)-1-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate as a white solid which was used for next step without further purification. LCMS: (ES, m/z): 499.8 $[M+H]^+$.

Step 2: To a solution of tert-Butyl (1S,2S,5R)-2-((S)-1-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (5.3 g, 10.6 mmol) in DCM (80 mL) was added DIEA (21.9 g, 169.9 mmol) and BOPCl (10.8 g, 42.7 mmol) at 25°C. The mixture was stirred at 25 °C for 16 hours under nitrogen. The mixture was filtered and water (200 mL) was added. The mixture was extracted with DCM (200 mL x 2). The combined organic layers were washed with brine (100 mL), dried with Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by flash column chromatography on silica gel (petroleum:ethyl acetate = 3:1) to afford the desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-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 as a yellow solid. LCMS: (ES, m/z): 482.0 $[M+H]^+$

Step 3: To a solution of tert-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-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 (5 g, 10.37 mmol) in DCM (80 mL) was added m-CPBA (5.37 g, 31.12 mmol) at 0°C. The mixture was stirred at room temperature for 1.5 hours. Saturated aqueous solution of $NaHCO_3$ (50 mL) was added and the mixture was extracted with DCM (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-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, which was used in the next step without purification. MS m/z (ESI): 513.8 $[M+H]^+$.

Step 4: To a solution of tert-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-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 (5.33 g, 10.37 mmol) and (S)-1-((S)-1-methylpyrrolidin-2-yl)ethan-1-ol (2.68 g, 20.74 mmol) in toluene (80 mL) was added t-BuONa (2.49 g, 25.93 mmol) at 0 °C. The mixture was stirred at 25 °C for 1.5 hours. The reaction was quenched by saturated aqueous solution of water (150 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase column to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-

2-yl)ethoxy)-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 as a yellow solid. MS m/z (ESI): 564.2 $[M+H]^+$.

Step 5: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-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 (3.1 g, 5.518 mmol) in THF (30 mL) and water (10 mL) were added (5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (4.03 g, 8.277 mmol), cataCxium A Pd G3 (1.2 g, 1.6554 mmol), and K_3PO4 (4.65 g, 22.01 mmol) under nitrogen. The mixture was stirred at 70 °C for 2 hours and cooled down to room temperature. The mixture was diluted with brine (60 mL) and extracted with ethyl acetate (60 mL x 3). The combined organic layers were separated, dried over sodium sulfate and concentrated to give a residue. The residue was purified by flash column chromatography on silica gel (DCM: MeOH=10:1) to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-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 as a yellow solid. MS m/z (ESI): 960.3 $[M+H]^+$.

Step 6: A solution of tert-butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-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 (500 mg, 0.52 mmol) in TFA(7.5 mL) was stirred at 25 °C for 1 hour under nitrogen. The reaction was concentrated to give a residue. The residue was adjusted to pH~8 by treating with saturated sodium bicarbonate aqueous solution (15 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4. The mixture was filtered and concentrated to give a residue. The residue was purified by flash column chromatography on silica gel (DCM:NH_3.MeOH=12:1) to give the desired product 2-Fluoro-5-((5S,5aS,6S,9R)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-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)-3-methyl-4-(trifluoromethyl)aniline as a yellow solid. MS m/z (ESI): 620.4 $[M+H]^+$.

Step 7: A solution of 2-Fluoro-5-((5S,5aS,6S,9R)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-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)-3-methyl-4-(trifluoromethyl)aniline (100 mg, 0.16 mmol) and (R)-2-((ethylsulfonyl)oxy)butanoic acid (50 mg, 0.242 mmol) in NMP (1 mL) was stirred at 0 °C for 10 minutes. DMTMM (60 mg, 0.208 mmol) was added at 0 °C. The mixture was stirred at room temperature for 10 minutes, diluted with saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with ethyl acetate (15 mL x 3). The organic layer was combined, dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired product ((R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate) (375) as a white solid. MS m/z (ESI): 798.8 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6, 333K) δ 6.58 (s, 1H), 5.84 (s, 2H),5.34 – 5.18 (m, 3H), 4.85 – 4.50 (m, 3H), 4.10 – 3.82 (m, 1H), 3.41 – 3.33 (m, 2H), 3.29 – 3.16 (m, 1H), 3.00 – 2.93 (m, 1H), 2.67 – 2.57 (m, 1H), 2.38 (s, 3H), 2.35 – 2.30 (m, 3H), 2.25 – 2.16 (m, 1H), 2.04 – 1.65 (m, 10H), 1.56 – 1.46 (s, 3H), 1.34 – 1.25 (m, 6H), 0.99 (t, J = 6.8 Hz, 3H).

Step 8: To a solution of (R)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate (200 mg, 0.25 mmol) and

(2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (136 mg, 0.25 mmol) in MeCN (4 mL) was added DIEA (645 mg, 5 mmol) at 25 °C. The mixture was stirred at 80 °C for 16 hours and cooled down to room temperature. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (10 mL x 3). The organic layer was combined and dried over anhydrous sodium sulfate. It was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC to give the desired product ((2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide) **(375A)** as white solid. MS m/z (ESI):1231.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.47 – 8.42 (m, 0.48H), 8.39 – 8.32 (m, 1H), 7.78 (d, J = 9.4 Hz, 1H), 7.45 – 7.35 (m, 4H), 6.68 – 6.36 (m, 1H), 6.14 – 5.91 (m, 2H), 5.31 – 5.03 (m, 3H), 4.96 – 4.60 (m, 4H), 4.56 – 4.25 (m, 3H), 4.01 – 3.85 (m, 1H), 3.67 – 3.55 (m, 2H), 3.11 – 3.03 (m, 1H), 2.97 – 2.92 (m, 1H), 2.64 – 2.56 (m, 1H), 2.45 (s, 3H), 2.37 (s, 3H), 2.34 – 2.29 (m, 4H), 2.26 – 1.60 (m, 16H), 1.56 – 1.32 (m, 13H), 1.28 – 1.23 (m, 3H), 0.94 – 0.88 (m, 11H).

[457] **Example 1h:** Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**390A**)

[458] Step 1: To a solution of tert-butyl (1S,2S,5R)-2-((S)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (3.0 g, 11.7 mmol) in THF (60 mL) was added NaH (1.2 g, 29.3 mmol, 60% in mineral oil) at 0°C. The resulting solution was stirred at 25°C for 1 hour under nitrogen. Then a solution of 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-ol (3.3 g, 11.7 mmol) in THF (100 mL) was added at 0 °C, and the mixture was stirred at 25°C for 4 hours under nitrogen. The reaction was quenched by saturated aqueous solution of NH_4Cl (200 mL). The organic layer (THF) was separated, concentrated to 40 mL and filtered to give the desired product tert-Butyl (1S,2S,5R)-2-((S)-1-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate as a white solid which was used for next step without further purification. LCMS: (ES, m/z): 499.8 $[M+H]^+$.

[459] Step 2: To a solution of tert-butyl (1S,2S,5R)-2-((S)-1-((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (5.3 g, 10.6 mmol) in DCM (80 mL) were added DIEA (21.9 g, 169.9 mmol) and BOPCl (10.8 g, 42.7 mmol) at 25°C. The mixture was stirred at 25 °C for 16 hours under nitrogen. The mixture was filtered. Then H_2O (200 mL) was added, and the mixture was extracted with DCM (200 ml x 2). The combined organic layers were washed with brine (100 mL), dried with Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by flash column chromatography on silica gel (petroleum: ethyl acetate = 3:1) to afford the desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-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 as a yellow solid. LCMS: (ES, m/z): 482.0 $[M+H]^+$

[460] Step 3: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-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 (5 g, 10.37 mmol) in DCM (80 mL) was added m-CPBA (5.37 g, 31.12 mmol) at 0°C. The mixture was stirred at room temperature for 1.5 hours and saturated aqueous solution of $NaHCO_3$ (50 mL) was added. The mixture was extracted with DCM (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to dryness under reduced pressure to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-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 which was used in the next step without purification. MS m/z (ESI): 513.8 [M+H]+.

[461] Step 4: To a solution of compound tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-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 (3 g, 5.85 mmol) and (1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)methanol (1.64 g, 8.77 mmol) in toluene (60 mL) was added t-BuONa (1.4 g, 14.6 mmol) at 0 °C. The mixture was stirred at 25 °C for 1.5 hours. The reaction was quenched by saturated aqueous solution of NH_4Cl (60 mL) and extracted with ethyl acetate (60 mL x 3). The combined organic layers were washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase column to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)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 as a yellow solid. MS m/z (ESI): 620.9 $[M+H]^+$.

[462] Step 5: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)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 (1.5 g, 2.42 mmol) in THF (20 ml) and H_2O (4 mL) were added (5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)boronic acid (1.2 g, 2.42 mmol), cataCxium A Pd G3 (372 mg, 0.48 mmol), and K_3PO_4 (2.57 g, 12.1 mmol) under nitrogen. The mixture was stirred at 70 °C for 1 hour and cooled to room temperature. The solution was diluted with brine (20 mL), extracted with ethyl acetate (100 mL x 3). The combined organic layers were separated, dried over sodium sulfate, concentrated to dryness to give a residue. The residue was purified by reverse phase column (1% FA) to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)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 as a yellow solid. MS m/z (ESI): 1038.0 $[M+H]^+$.

[463] Step 6: A solution of tert-butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)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 (450 mg, 0.43 mmol) in TFA (5 mL) was stirred at 50 °C for 1 hour under nitrogen. The reaction was concentrated to give a residue. The residue was adjusted to pH~8 by saturated sodium bicarbonate aqueous solution (20 mL). The solution was extracted with DCM (50 ml x 2). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by prep-TLC (DCM:NH_3.MeOH=10:1) to give the desired product 3-Chloro-2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)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)-4-(trifluoromethyl)aniline as a yellow solid. MS m/z (ESI): 698.3 $[M+H]^+$.

[464] Step 7: A solution of 3-chloro-2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)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)-4-(trifluoromethyl)aniline (120 mg, 0.17 mmol) and (R)-2-((ethylsulfonyl)oxy)butanoic acid (43.9 mg, 0.22 mmol) in NMP (2 mL) was stirred at 0 °C for 10 minutes. DMTMM (70.6 mg, 0.26 mmol) was added to the mixture at 0 °C. The mixture was stirred at room temperature for 10 minutes. The reaction mixture was diluted with saturated aqueous solution of $NaHCO_3$ (10 mL). The mixture was extracted with ethyl acetate (30 mL x 3). The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired product ((R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)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-14-yl)-1-oxobutan-2-yl ethanesulfonate) (390) as a white solid. MS m/z (ESI): 876.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.79 – 6.40 (m, 3H), 5.37 – 5.15 (m, 2H), 4.88 – 4.48 (m, 4H), 4.39 – 4.20 (m, 2H), 4.15 – 3.88 (m, 1H), 3.46 – 3.36 (m, 2H), 3.25 – 2.99 (m, 1H), 2.59 – 2.54 (m, 1H), 2.38 – 2.21 (m, 4H), 2.12 – 1.41 (m, 14H), 1.33 – 1.25 (m, 3H), 1.05 – 0.93 (m, 3H), 0.65 (s, 2H), 0.43 (s, 2H).

[465] Step 8: To (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)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-14-yl)-1-oxobutan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-fluoropiperidin-1-yl)methyl)cyclopropyl)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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**390A**).

[466] **Example 1i:** Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-((3-(difluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(406A)**

[467] Step 1: To a solution of 1-(methoxycarbonyl)cyclopropane-1-carboxylic acid (1.11 g, 7.74 mmol) in DCM (15 mL) was added oxalyl chloride (3.28 g, 25.8 mmol), DMF (0.05 ml) at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The mixture was warmed to room temperature and stirred for an additional 1 hour. The reaction mixture was concentrated to give a residue. The residue was dissolved with DCM (15 mL). Then DIEA (4.16 g, 32.2 mmol) and 3-(difluoromethylene)pyrrolidine (1 g, 6.45 mmol) was added at 0 °C. The resulting mixture was stirred at 25 °C for 2.5 hours. The reaction was quenched with water (50 mL), extracted with DCM (30 mL x 2). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column to give the desired product methyl 1-(3-(difluoromethylene)pyrrolidine-1-carbonyl)cyclopropane-1-

carboxylate as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.05 (d, J = 40 Hz, 2H), 3.66 (s, 3H), 3.60 – 3.50 (m, 2H), 2.68 – 2.52 (m, 2H), 1.40 – 1.23 (m, 4H).

[468] Step 2: To a solution of compound methyl 1-(3-(difluoromethylene)pyrrolidine-1-carbonyl)cyclopropane-1-carboxylate (2.0 g, 8.16 mmol) in THF (20 mL) were added $LiAlH_4$ (16.33 mL, 16.33 mmol) at 0°C. The mixture solution was stirred at 25°C for 1 hour under nitrogen and quenched by 1.35 eq sodium sulfate decahydrate. The mixture was filtered and the filtrate was concentrated under reduced pressure to afford the desired product (1-((3-(Difluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)methanol as a yellow liquid. LCMS: (ES, m/z): 203.8 $[M+H]^+$.

[469] Step 3: To a solution of (1-((3-(difluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)methanol (792 mg, 3.9 mmol) and compound tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-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 (1.0 g, 1.95 mmol) in toluene (20 mL) was added t-BuONa (468 mg, 4.88 mmol) at 0 °C. The mixture was stirred at 25 °C for 1.5 hours and quenched by saturated aqueous solution of NH_4Cl (50 mL). The mixture was extracted with ethyl acetate (80 mL x 3). The combined organic layers were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase column to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-12-((1-((3-(difluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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 as a yellow solid. MS m/z (ESI): 637.3 $[M+H]^+$.

[470] Step 4: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-12-((1-((3-(difluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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 (200 mg, 0.31 mmol) in 1,4-dioxane (20 mL) and water (4 mL) were added (5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)boronic acid (234.7 mg, 0.47 mmol), Pd(PPh3)4 (71.61 mg, 0.062 mmol), and Cs_2CO_3 (303.2 mg, 0.93 mmol) under nitrogen. The mixture was stirred at 100 °C for 1 hour and cooled to room temperature. The mixture was diluted with brine (10 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were separated, dried over sodium sulfate, concentrated to give a residue. The residue was purified by reverse phase column (1% FA) to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-((3-(difluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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 as a yellow solid. MS m/z (ESI): 1054.7 $[M+H]^+$.

[471] Step 5: A solution of tert-butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-((3-(difluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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 (200 mg, 0.19 mmol) in TFA (5 mL) was stirred at 25 °C for 1 hour under nitrogen. The reaction was concentrated to give a residue. The residue was adjusted to pH~8 by saturated sodium bicarbonate aqueous solution (30 mL). The solution was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by prep-TLC (DCM:NH_3:MeOH=10:1) to give the desired product 3-Chloro-5-((5S,5aS,6S,9R)-12-((1-((3-(difluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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)-2-fluoro-4-(trifluoromethyl)aniline as a yellow solid. MS m/z (ESI): 714.3 $[M+H]^+$.

[472] Step 6: A solution of 3-chloro-5-((5S,5aS,6S,9R)-12-((1-((3-(difluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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)-2-fluoro-4-(trifluoromethyl)aniline (110 mg, 0.15 mmol) and (R)-2-((ethylsulfonyl)oxy)butanoic acid (39 mg, 0.2 mmol) in NMP (1 mL) was stirred at 0 °C for 10 minutes. DMTMM (63 mg, 0.23 mmol) was then added at 0 °C. The mixture was stirred at room temperature for 10 minutes. The reaction mixture was diluted with saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired product ((R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-((3-(difluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate) (406) as a white solid. MS m/z (ESI): 893.6 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.80 – 6.56 (m, 1H), 6.54 – 6.40 (m, 2H), 5.36 – 5.13 (m, 2H), 4.97 – 4.69 (m, 1H), 4.68-4.48 (m, 2H) ,4.47 - 4.23 (m, 2H), 4.17 – 3.38 (m, 1H), 3.58 – 3.29 (m, 2H), 3.27-3.01 (m, 3H), 2.81 – 2.57 (m, 2H), 2.55-2.48 (m, 1H), 2.49-2.42 (m, 1H), 2.39-2.27 (m, 2H) , 2.06-1.71 (m, 6H), 1.69-1.44 (m, 3H) , 1.38-1.25 (m, 3H), 1.08-0.92 (m, 3H), 0.73 – 0.58 (m, 2H), 0.57 – 0.43 (m, 2H),.

[473] Step 7: To (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-((3-(difluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-((3-(difluoromethylene)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(406A)**.

[474] **Example 1j:** Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**407A**)

[475] Step 1: To a solution of 1-(methoxycarbonyl)cyclopropane-1-carboxylic acid (10 g, 69.4 mmol) in DCM (100 ml) was added $(COCl)_2$ (35.2 g, 277.6 mmol) at 0°C, then added DMF (0.5 mL). The mixture solution was stirred at 0°C for 20 minutes and continued to stir at room temperature for 1 hour. The reaction was concentrated and the residue was dissolved in DCM (100 mL) followed by the addition of DIEA (26 g, 208.2 mmol) and 1,1-difluoro-6-azaspiro[2.5]octane (12.2 g, 833 mmol) under nitrogen. The mixture was stirred at 25°C for 1 hour, diluted with water (20 mL) and extracted with DCM (40 mL x 3). The combined organic layers were separated, dried over sodium sulfate, concentrated to give a residue. The residue was purified by flash column chromatography

on silica gel (DCM:MeOH=10:1) to afford the desired product Methyl 1-(1,1-difluoro-6-azaspiro[2.5]octane-6-carbonyl)cyclopropane-1-carboxylate as yellow oil.

[476] Step 2: To a solution of methyl 1-(1,1-difluoro-6-azaspiro[2.5]octane-6-carbonyl)cyclopropane-1-carboxylate (10 g, 36.6 mmol) in THF (100 mL) was added LiAlH (30 mL, 2.5M in THF) at 0°C. The mixture was stirred at 25 °C for 1 hour under nitrogen and quenched by sodium sulfate decahydrate (15 g, 5.0 mmol). The mixture was diluted with THF (50 mL), filtered and concentrated to give the desired product (1-((1,1-Difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methanol as a yellow oil which was used for next step without further purification.

[477] Step 3: To a solution of (1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methanol (450.3 mg, 1.95 mmol, 2.0 eq) in toluene (100 mL) were added compound tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-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 (500 mg, 0.97 mmol, 1.0 eq) and t-BuONa (233.9 mg, 2.44 mmol, 2.5 eq) at 0°C. The mixture was stirred at 25°C for 0.5 hours. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (15 mL x 2). The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to dryness under reduced pressure to give the crude which was purified by reverse phase column (H2O:MeCN=0~100%) to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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 as a white solid. MS m/z (ESI):665.16 $[M+H]^+$.

[478] Step 4: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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 (240 mg, 0.47 mmol, 1.0 eq) in dioxane (10 mL) and H_2O (2 mL) was added (5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)boronic acid (538.9 mg, 1.40 mmol, 3.0 eq), Pd(PPh3)4 (83.6 mg, 0.07 mmol, 0.2 eq) and Cs_2CO_3 (353.5 mg, 1.08 mmol, 3.0 eq) at 25°C. The mixture was stirred at 100°C for 4 hours. The mixture was cooled to room temperature, diluted with water (10 mL) and extracted with ethyl acetate (20 mL x 2). The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to under reduced pressure to give the crude which was purified by flash column chromatography on silica gel (petroleum : ethyl acetate = 0~60%) to get the desired product tert-Butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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 as a white solid.

[479] Step 5: A solution of tert-butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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 (240 mg, 0.22 mmol, 1.0 eq) in TFA (3 mL) was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure to give a residue and the residue was treated with DCM (5 mL), NH_3.MeOH. The mixture was then concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (DCM/NH_3.MeOH (10:1) to afford the desired product 3-Chloro-5-((5S,5aS,6S,9R)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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)-2-fluoro-4-(trifluoromethyl)aniline as a white solid. MS m/z (ESI): 742.14 $[M+H]^+$.

[480] Step 6: To a solution of compound (R)-2-((ethylsulfonyl)oxy)butanoic acid (51.6 mg, 0.26 mmol, 1.3 eq) in NMP (2 mL) was added 3-chloro-5-((5S,5aS,6S,9R)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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)-2-fluoro-4-(trifluoromethyl)aniline (150 mg, 0.20 mmol, 1.0 eq) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 10 minutes. Then to this mixture was added DMTMM (84.0 mg, 0.30 mmol, 1.5 eq) and (R)-2-((ethylsulfonyl)oxy)butanoic acid at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C for 15 minutes, extracted with ethyl acetate (5 mL x 3). The organic layer was combined, dried with anhydrous Na_2SO_4 and concentrated under vacuum to give a crude. The crude was purified by prep-HPLC $NaHCO_3$ to give the desired product ((R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro -2-(trifluoromethyl)phenyl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate) (407) as a white solid. MS m/z (ESI): 920.34 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.88 – 6.33 (m, 3H), 5.39 – 5.14 (m, 2H), 4.91 – 4.65 (m, 2H), 4.62 – 4.48 (m, 1H), 4.42 - 4.22 (m, 2H), 4.16 - 3.84 (m, 1H), 3.46 – 3.33 (m, 3H), 3.29 – 2.95 (m, 1H), 2.46 - 2.35 (m, 4H), 2.33 - 2.22 (m, 1H), 2.07 – 1.65 (m, 6H), 1.64 – 1.40 (m, 7H), 1.37 - 1.25 (m, 3H), 1.22 - 1.12 (m, 2H), 1.07 - 0.91 (m, 3H), 0.75 - 0.57 (s, 2H), 0.49 - 0.35 (s, 2H).

[481] Step 7: To (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro -2-(trifluoromethyl)phenyl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-((1-((1,1-difluoro-6-azaspiro[2.5]octan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(407A)**.

[482] **Example 1k:** Synthesis of (2S,4R)-1-((2S)-2-(5-(((2S)-1-(2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-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]heptalen-14-yl)-1-oxopropan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(435A)**

[483] Step 1: To a solution of tert-butyl (1R,5S)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (260 mg, 1.08 mmol) in THF (5 mL) was added NaH (110 mg, 2.69 mmol, 60% purity) at 0 °C. The mixture was stirred at 25 °C for 30 minutes. 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-ol (300 mg, 1.10 mmol) in THF (5 mL) was then added at 0 °C. The mixture was stirred at 50 °C for 1 hour under nitrogen atmosphere and quenched with ice sat. NH_4Cl (20 mL). The organic layers were washed with brine (3 x 20 mL) and the aqueous was extracted with EtOAc (2 x 30 mL). The combined organic layers were combined and dried over anhydrous sodium sulfate. The product was filtered and concentrated in vacuo to give a crude. The crude product was purified by silica gel column chromatography (petroleum ether : ethyl acetate=5:1) to give the desired product (tert-butyl 2-(((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate) as a yellow solid. MS m/z (ESI): 486.1 [M+H].

[484] Step 2: To a solution of tert-butyl 2-(((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (480 mg, 0.99 mmol) in DCM (10 mL) was added DIEA (1.92 g, 14.8 mmol) and BOPCl (1.0 g, 3.96 mmol). The mixture was stirred at 25 °C for 16 hours under nitrogen atmosphere. The mixture was poured into water (30 mL), and was extracted with DCM (20 mL x 3). The organic layers were combined, washed with brine (50 mL) and dried over anhydrous sodium sulfate. The product was filtered and the filtrate was concentrated to dryness under reduced pressure to give a crude. The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate =5:1) to give the desired product (tert-butyl (6S,9R)-2-chloro-1-fluoro-12-(methylthio)-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) as a yellow solid. MS m/z (ESI):468.1 [M+H].

[485] Step 3: To a solution of tert-butyl (6S,9R)-2-chloro-1-fluoro-12-(methylthio)-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 (420 mg, 0.90 mmol), K_3PO_4 (380 mg, 1.80 mmol), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (600 mg, 1.17 mmol) in dioxane/water (10/2 mL) was added Cataxium Pd G3(70 mg, 0.09 mmol). The mixture was stirred at 90 °C for 2 hours under nitrogen. The mixture was poured into water (20 mL), and the solution was extracted with ethyl acetate (20 mL x 3). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness under reduced pressure. The crude product was purified by reverse column (NH_4HCO_3) to give the desired product (tert-butyl (6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(methylthio)-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) as a brown solid. MS m/z (ESI): 818.3 [M+H].

[486] Step 4: To a solution of tert-butyl (6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(methylthio)-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 (650 mg, 0.79 mmol) in DCM (13 mL) was added m-CPBA (178 mg, 0.87 mmol) at 0 °C. The mixture was stirred at 25 °C for 30 minutes under nitrogen. The reaction mixture was diluted with aq. $NaHCO_3$ (10 mL) and the mixture was extracted with DCM (3 x 20 mL). The organic layers were combined and washed with brine (20 mL). The combined organic layers were dried over anhydrous sodium sulfate. The product was filtered, and the filtrate was concentrated in vacuo to give the desired product (tert-butyl (6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(methylsulfinyl)-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) as a yellow solid which was used in the next step without purification. MS m/z (ESI): 834.2 [M+H].

[487] Step 5: To a solution of ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (270 mg, 1.44 mmol) in toluene (10 mL) was added t-BuOK (0.19 g, 1.44 mmol). The mixture was stirred at 0 °C for 20 minutes. Tert-butyl (6S,9R)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(methylsulfinyl)-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 (600 mg, 0.72 mmol) was then added. The mixture was stirred at 25 °C for 4 hours under nitrogen. The mixture was poured into water (20 mL), and the solution was extracted with ethyl acetate (20 mL x 3). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate. The product was filtered and the filtrate was concentrated to dryness under reduced pressure to give a residue. The residue was purified by reverse column (NH_4HCO_3) to give the desired product (tert-butyl (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)-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) as a yellow solid. MS m/z (ESI): 929.3 [M+H].

[488] Step 6: To a solution of tert-butyl (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)-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 (530 mg, 0.57 mmol) in DMF (8 mL) was added CsF (1.02 g, 5.7 mmol) at 25 °C. The mixture was stirred at 60 °C for 1 hour under nitrogen. The mixture was poured into water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate. The product was filtered and the filtrate was concentrated in vacuo to give a residue. The residue was purified by reverse column (NH_4HCO_3) to give the desired product (tert-butyl (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)-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) as a yellow oil. MS m/z (ESI): 773.2 [M+H].

[489] Step 7: A solution of tert-butyl (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)-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 (300 mg, 0.389mmol) in 4M HCl/dioxane (5 mL) was stirred at 25°C for 1 hour. The solvent was removed under reduced pressure and the residue was diluted with aq. $NaHCO_3$ (10 mL) and DCM (20 mL). The organic layer was separated, washed with brine and dried over sodium sulfate. The product was filtered, and the filtrate was concentrated in vacuo to give a crude. The crude product was purified by reverse phase column (NH_4HCO_3) to give the desired product (5-ethynyl-6-fluoro-4-((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) as a yellow solid. MS m/z (ESI): 629.2 [M+H].

[490] Step 8: To a solution of 5-ethynyl-6-fluoro-4-((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 (100 mg, 0.159 mmol) in NMP (2 mL) was added (R)-2-((ethylsulfonyl)oxy)propanoic acid (34 mg, 0.159 mmol). The mixture was stirred at 0 °C for 15 minutes. DMTMM (110 mg, 0.318 mmol) was then added, and the resulting mixture was stirred at 0 °C for 10 minutes under nitrogen. The product was poured into water (10 mL), and the mixture was extracted with ethyl acetate (10 mL x 3). The organic layers were combined, washed with aq. $NaHCO_3$ (10 mL), dried over anhydrous sodium sulfate. The product was filtered and the filtrate was concentrated to dryness under reduced pressure to give a crude. The crude product was purified by Prep-HPLC to give the desired product ((2R)-1-((6S,9R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-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]heptalen-14-yl)-1-oxopropan-2-yl ethanesulfonate) (435) as a yellow solid. MS m/z (ESI): 793.4 [M+H]. ^{1}H NMR (400 MHz, DMSO) δ 10.19 (s, 1H), 8.03 - 7.89 (m, 1H), 7.52 – 7.42 (m, 1H), 7.38 (s, 1H), 7.23 - 7.06 (m, 1H), 5.61 - 5.48 (m, 1H), 5.36 (d, J = 53.6 Hz, 1H), 5.07 - 4.45 (m, 5H), 4.20 - 4.08 (m, 2H), 4.05 - 3.95 (m, 2H), 3.64 - 3.50 (m, 2H), 3.23 - 3.05 (m, 3H), 3.03 (s, 1H), 2.90 - 2.77 (m, 1H), 2.14 (s, 1H), 2.10-1.91(m, 4H), 1.90 - 1.70 (m, 5H), 1.56 – 1.43 (m, 3H), 1.34 - 1.22 (m, 3H).

[491] Step 9: To (2R)-1-((6S,9R)-2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-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]heptalen-14-yl)-1-oxopropan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((2S)-2-(5-(((2S)-1-(2-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-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]heptalen-14-yl)-1-oxopropan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(435A)**.

[492] **Example 1l:** Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(440A)**

[493] Step 1: To a solution of 1-(tert-butyl) 3-methyl (R)-3-methyl-4-oxopiperidine-1,3-dicarboxylate (1.1 g, 4.06 mmol) in DMF (10 mL) was added 2-((difluoromethyl)sulfonyl)pyridine (1.57 g, 8.12 mmol) and t-BuOK (12.2 mL, 12.18 mmol, 1 M) at -68°C. The reaction mixture was stirred at -68°C for 4 hours, diluted with DCM:MeOH=10:1 (100 mL) and washed with LiCl (50 mL × 4). The organic layer was separated, concentrated in vacuo to give a residue. The residue was purified by silica gel column (petroleum/ethyl acetate = 10/1) to give the desired product 1-(tert-Butyl) 3-methyl (S)-4-(difluoromethylene)-3-methylpiperidine-1,3-dicarboxylate.

[494] Step 2: To a solution of 1-(tert-butyl) 3-methyl (S)-4-(difluoromethylene)-3-methylpiperidine-1,3-dicarboxylate (3.5 g, 11.5 mmol) and Pd/C (1.75 g) in MeOH (105 mL) at 30 °C under hydrogen atmosphere. The mixture was stirred at 30 °C for 4 hours. The mixture was filtered and the filtrate was concentrated to give the desired product 1-(tert-Butyl) 3-methyl (3S,4S)-4-(difluoromethyl)-3-methylpiperidine-1,3-dicarboxylate as oil which was used directly in the next step without further purification.

[495] Step 3: To a suspension of 1-(tert-butyl) 3-methyl (3S,4S)-4-(difluoromethyl)-3-methylpiperidine-1,3-dicarboxylate in dioxane was added (5 g, 16.3 mmol, 1 eq) in HCl/dioxane (40 mL). The resulting reaction mixture was stirred for 1 hour at room temperature. The mixture was concentrated under reduced pressure to give the desired product Methyl (3S,4S)-4-(difluoromethyl)-3-methylpiperidine-3-carboxylate. MS m/z (ESI): 208.1 [M+H]+.

[496] Step 4: To a solution of methyl (3S,4S)-4-(difluoromethyl)-3-methylpiperidine-3-carboxylate (4.0 g, 19.3 mmol) in MeOH (40 mL) was added formaldehyde (3.14 g, 38.6 mmol) at 25 °C. The resulting solution was stirred at 25 °C for 1 hour under nitrogen. STAB (8.2 g, 38.6 mmol) was added and the mixture was stirred for an additional hour under nitrogen. The mixture was quenched by saturated aqueous solution of $NaHCO_3$ (100 mL) and extracted with ethyl acetate (200 mL x 2). The combined organic layers were washed with brine (100 mL), dried with Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by flash column chromatography on silica gel to afford the desired product Methyl (3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidine-3-carboxylate as a yellow oil. MS m/z (ESI): 222.1 $[M+H]^+$

[497] Step 5: To a solution of Methyl (3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidine-3-carboxylate (2.2 g, 9.95 mmol) in THF (25 mL) was added LiAlH4 (2.5 M in THF) (5.2 mL, 12.9 mmol) at 0°C. The mixture was stirred at 0 °C for 1 hour under nitrogen followed by the addition of $Na_2SO_4 \cdot 10H_2O$. The mixture was stirred and filtered. The filtrate was concentrated under vacuum to give the desired product ((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methanol as a yellow oil which was used directly in the next step without further purification.

[498] Step 6: To a solution of ((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methanol (84 mg, 0.44 mmol) in THF (2 mL) was added LiHMDS (0.66 mL, 0.66 mmol) and the mixture was stirred at 0°C for 15 minutes. tert-butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-1-fluoro-5-methyl-12-(methylsulfonyl)-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 (200 mg, 0.22 mmol) was added and the mixture was stirred at room temperature for 30 minutes. The ,mixture was quenched by saturated aqueous solution of NH_4Cl (100 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were combined, washed with brine (100 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column (DCM/MeOH= 20/1) to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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. MS m/z (ESI): 1032.6 $[M+H]^+$.

[499] Step 7: A solution of compound tert-butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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 (95 mg, 0.09 mmol) and CsF (140 mg, 0.92 mmol) in DMF (2 mL) was stirred at 25 °C for 1 hour under nitrogen and quenched by saturated aqueous solution of water (100 mL). The mixture was extracted with ethyl acetate (50 mL x 3). The extracts were combined, washed with brine and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-8-ethynyl-7-fluoronaphthalen-1-yl)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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 which was used directly in the next step without further purification. MS m/z (ESI): 876.4 $[M+H]^+$.

[500] Step 8: To a solution of compound tert-butyl (5S,5aS,6S,9R)-2-(3-((tert-butoxycarbonyl)amino)-8-ethynyl-7-fluoronaphthalen-1-yl)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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 (90 mg, 0.10 mmol) in DCM (2 mL) was added TFA (1 mL) at 25 °C for 1 hour under nitrogen and concentrated to give a residue. The residue was adjusted to pH~8 by saturated sodium bicarbonate aqueous solution (100 mL) and extracted with DCM (50 mL x 2). The extracts were combined, dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by prep-TLC (DCM:NH_3.MeOH=10:1) to give the desired product 4-((5S,5aS,6S,9R)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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)-5-ethynyl-6-fluoronaphthalen-2-amine as a yellow solid. MS m/z (ESI): 676.8 $[M+H]^+$.

[501] Step 9: A solution of 4-((5S,5aS,6S,9R)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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)-5-ethynyl-6-fluoronaphthalen-2-amine (62 mg, 0.09 mmol) and (R)-2-((ethylsulfonyl)oxy)butanoic acid (18 mg, 0.09 mmol) in NMP (1 mL) was stirred at 0 °C for 5 minutes. Then DMTMM (38 mg, 0.13 mmol) was added, and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was diluted with saturated aqueous solution of $NaHCO_3$ (100 mL) and extracted with ethyl acetate (40 mL x 3). The organic layer was combined, dried over anhydrous sodium sulfate. It was filtered and the filtrate

was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired product ((R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate) (440) as a white solid. MS m/z (ESI): 854.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.80 – 7.72 (m, 1H), 7.37 – 7.29 (m, 1H), 7.08 – 6.91 (m, 2H), 6.49 – 6.15 (m, 1H), 5.69 – 5.58 (m, 2H), 5.46 – 5.23 (m, 2H), 4.87 – 4.76 (m, 1H), 4.74 – 4.35 (m, 4H), 4.18 – 3.86 (m, 2H), 3.49 – 3.38 (m, 2H), 3.28 – 3.20 (m, 1H), 2.91 – 2.79 (m, 2H), 2.15 – 1.49 (m, 17H), 1.33 – 1.24 (m, 3H), 1.13 (s, 3H), 1.05 – 0.94 (m, 3H).

[502] Step 10: To (R)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(3-amino-8-ethynyl-7-fluoronaphthalen-1-yl)-12-(((3S,4S)-4-(difluoromethyl)-1,3-dimethylpiperidin-3-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(440A)**.

[503] **Example 1m:** Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(441A)**

[504] Step 1: To a solution of 1-(methoxycarbonyl) cyclopropane-1-carboxylic acid (4 g, 27.8 mmol) in DCM (20 mL) were added oxalyl chloride (14.1 g, 111.0 mmol) and DMF (24 mg, 0.33 mmol) at 0 °C. The mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and the resulting residue was dissolved in DCM (40 mL) followed by the addition of DIEA (11.76 g, 83.3 mmol) and 4-(difluoromethylene)piperidine (4.42 g, 33.3 mmol) under nitrogen. The mixture was stirred at 25°C for 3 hours and quenched by water (100 mL). The mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The mixture was purified by flash column chromatography on silica gel to give the desired product Methyl 1-(4-(difluoromethylene)piperidine-1-carbonyl)cyclopropane-1-carboxylate as a white oil. LCMS m/z (ESI): 259.8 $[M+H]^+$.

[505] Step 2: To a solution of methyl 1-(4-(difluoromethylene)piperidine-1-carbonyl)cyclopropane-1-carboxylate (3 g, 11.58 mol)) in THF (30 mL) was added sodium bis (2-methoxyethoxy) aluminum hydride (32.4 mL, 78.76 mmol, 3.5 M, 70% toluene) at 0 °C. The mixture was stirred at 60 °C for 24 hours and cooled down to room temperature, quenched by NaOH (15%, 2.4 mL) and filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash column chromatography on silica gel to give the desired product (1-((4-(Fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)methanol as a yellow oil. LCMS m/z (ESI): 200.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 6.65 (d, J = 87.6 Hz, 1H), 4.48 (s, 1H), 3.37 – 3.33 (m, 2H), 2.42 – 2.36 (m, 4H), 2.33 – 2.18 (m, 4H), 2.05 – 1.97 (m, 2H), 0.43 – 0.38 (m, 2H), 0.24 – 0.16 (m, 2H).

[506] Step 3: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-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 (1 g, 1.95 mmol) and (1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)methanol (0.77 g, 3.9 mmol) in toluene (20 mL) was added t-BuONa (468 mg, 4.85 mmol) at 0 °C. The mixture was stirred at 25 °C for 1.5 hours. The reaction mixture was treated with saturated aqueous solution of NH_4Cl (30 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase column to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-12-((1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)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 as a yellow solid. MS m/z (ESI): 633.1 $[M+H]^+$.

[507] Step 4: To a stirred solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-12-((1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)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 (350 mg, 0.56 mmol) and (5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)boronic acid (420 mg, 0.84 mmol) in dioxane/H_2O (70/14 mL) was added Cs_2CO_3 (548 mg, 1.68 mmol) and $Pd(PPh_3)_4$ (140 mg, 0.11 mmol) under nitrogen. The reaction mixture was heated to 100°C for 3 hours and cooled down to room temperature. The solution was diluted with brine (20 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were separated, dried over sodium sulfate, and concentrated to give a residue. The residue was purified by reverse phase column (0.1% NH_4HCO_3) to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)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 as a yellow solid. MS m/z (ESI): 1050.7 $[M+H]^+$.

[508] Step 5: A solution of tert-butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)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 (300 mg, 0.29 mmol) in TFA (5 ml) was stirred at 25°C for 1 hour under nitrogen. The reaction was concentrated to dryness to give a residue. The residue was adjusted to pH~8 by saturated sodium bicarbonate aqueous solution (10 ml). The mixture was extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by prep-TLC (DCM:NH_3.MeOH=10:1) to give the desired product 3-Chloro-2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-((1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)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)-4-(trifluoromethyl)aniline as a yellow solid. MS m/z (ESI): 710.6 $[M+H]^+$.

[509] Step 6: A solution of 3-chloro-2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-((1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)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)-4-(trifluoromethyl)aniline (90 mg, 0.12 mmol) and (R)-2-((ethylsulfonyl)oxy)butanoic acid (32 mg, 0.16 mmol) in NMP (2 mL) was stirred at 0 °C for 10 minutes. DMTMM (50 mg, 0.18mmol) was added at 0°C. The mixture was stirred at room temperature for 10 minutes. The reaction mixture was diluted with saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with ethyl acetate (10 mL x 3). The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under

reduced pressure to give a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired product ((R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)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-14-yl)-1-oxobutan-2-yl ethanesulfonate) (441) as a white solid. MS m/z (ESI): 888.8 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.74 (s, 1H), 6.52 – 6.48 (m, 3H), 5.40 – 5.14 (m, 2H), 4.86 – 4.48 (m, 3H), 4.30 – 4.24 (m, 2H), 3.92 (s, 1H), 3.42 – 3.18 (m, 2H), 2.45 – 2.25 (m, 7H), 2.18 (s, 2H), 1.98 – 1.84 (m, 8H), 1.60 – 1.46 (m, 3H), 1.32 – 1.24 (m, 3H), 1.02 – 0.96 (m, 3H), 0.66 (s, 2H), 0.43 (s, 2H).

[510] Step 7: To (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)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-14-yl)-1-oxobutan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-((4-(fluoromethylene)piperidin-1-yl)methyl)cyclopropyl)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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**441A**).

[511] **Example 1n**: Synthesis of (2S,4R)-1-((2S)-2-(5-(((2R)-1-(((2R,13aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)(methyl)amino)-1-oxopropan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**451A**).

[512] Step 1: To a solution of 1-benzyl 2-methyl (2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (15 g, 50 mmol) in DMF (150 mL) was added imidazole (7.3 g, 100 mmol) and TBSCl (10.0 g, 60 mmol) and the resulting mixture was stirred for 16 hours at room temperature. The mixture was quenched with water (300 mL) and the aqueous layer was extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The resulting product was filtered and the filtrate was concentrated to give a crude. The crude mixture was purified by flash chromatography to afford 1-benzyl 2-methyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate as a colorless oil. MS m/z (ESI): 394.6 $[M+H]^+$.

[513] Step 2: To a solution of 1-benzyl 2-methyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (10 g, 25 mmol) in THF (100 mL) was added $LiBH_4$ (0.8 g, 38 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 3 hours. It was quenched with aq. citric acid solution (1M/50 mL) and the mixture was extracted with ethyl acetate (50 mL x 3). The organic layer was combined, washed with brine (50 mL) and dried over anhydrous sodium sulfate. The resulting product was filtered and the filtrate was concentrated to dryness under reduced pressure to give a residue. The residue was purified by prep-TLC (petroleum ether/ethyl acetate = 3/1) to give benzyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate as a white solid.

[514] Step 3: To a solution of benzyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (8.0 g, 22 mmol) in DCM (60 mL) was added DMP (14.0 g, 32 mmol) at 0 °C. The mixture was stirred for 16h at rt. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL). The

aqueous layer was extracted with EA (2 x 60 mL). The combined organic extracts were dried over Na_2SO_4, then filtered and the filtrate was concentrated to dryness under reduced pressure. The crude mixture was purified by flash chromatography to afford benzyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)-2-formylpyrrolidine-1-carboxylate as a yellow oil.

[515] Step 4: Potassium t-butoxide (0.561 g, 5 mmol) was dissolved in anhydrous tetrahydrofuran (50 mL) and the mixture was cooled to 0 °C under nitrogen. $MeBrP(Ph)_3$ (1.786 g, 5 mmol) was added and the mixture was stirred for 2 hours at 0 °C. A solution of benzyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)-2-formylpyrrolidine-1-carboxylate (1.82 g, 5 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise to the reaction mixture with stirring. After 2 hours the reaction mixture was allowed to warm to room temperature and was stirred overnight. It was then treated with saturated ammonium chloride solution (30 mL) and extracted with diethyl ether (3 x 50 mL). The combined extracts were washed with saturated sodium chloride, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give crude product. The crude product was purified by column chromatography on silica gel with gradient elution 20% to 100% ethyl acetate/hexanes to afford benzyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)-2-vinylpyrrolidine-1-carboxylate. MS m/z (ESI): 362.6 $[M+H]^+$.

[516] Step 5: To a solution of benzyl (2R,4R)-4-((tert-butyldimethylsilyl)oxy)-2-vinylpyrrolidine-1-carboxylate (1.80 g, 4.97 mmol) in anhydrous tetrahydrofuran (80 mL) was added 9-BBN (0.5 M THF, 20 mL, 10 mmol) and the resulting mixture was stirred at room temperature overnight. The mixture was cooled to 0 °C and water (30 mL) was added followed by the addition of sodium hydroxide solution (3M, 10 mL). Hydrogen peroxide solution (30%, 11 mL) was added slowly, and the mixture was stirred at room temperature for 4 hours. The resulting product was extracted with diethyl ether (3 x 50 mL). The combined extracts were washed with saturated sodium chloride and dried over anhydrous sodium sulfate. The resulting product was filtered and solvent was removed under reduce pressure to give crude product. The crude was purified by column chromatography on silica gel eluting with gradient of ethyl acetate/hexanes to (0%-100%) to give benzyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-2-(2-hydroxyethyl)pyrrolidine-1-carboxylate. MS m/z (ESI): 380.6 $[M+H]^+$. ^1H NMR (DMSO-d): 8 ppm 5.32 (m SH), 5.05 (m 2H); 4.38 (m 2H); 3.89 (m 1H); 3.58 (m 1H); 3.36 (m 3H); 3.13 (m 1H); 2.08 (m 2H); 1.66 (m 2H); 0.84 (s 9H); 0.04 (s 6H).

[517] Step 6: To a solution of benzyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-2-(2-hydroxyethyl)pyrrolidine-1-carboxylate (6.0 g, 18 mmol) in DCM (60 mL) was added DHP (3.0 g, 36 mmol) and PPTS (1000 mg, 5 mmol) at room temperature and the mixture was stirred for 5 hours. The reaction mixture was quenched with water (80 mL) and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The resulting product was filtered and the filtrate was concentrated to give a crude. The crude was purified by flash chromatography to afford benzyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyrrolidine-1-carboxylate as a yellow oil. MS m/z (ESI): 464.3 $[M+H]^+$.

[518] Step 7: To a solution of benzyl (2S,4R)-4-((tert-butyldimethylsilyl)oxy)-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyrrolidine-1-carboxylate (2.0g, 50 mmol) in MeOH (40 mL) was added TBAF (11 ml) at 0 °C. The mixture was stirred for 4 hours at room temperature. The mixture was quenched with water (50 mL) and the aqueous layer was extracted with ethyl acetate (2 x 60 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The resulting product was filtered and the filtrate was concentrated to give a crude. The crude mixture was purified by flash chromatography to afford benzyl (2S,4R)-4-hydroxy-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyrrolidine-1-carboxylate as a yellow oil. MS m/z (ESI): 372.0 $[M+Na]^+$.

[519] Step 8: To a solution of benzyl (2S,4R)-4-hydroxy-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyrrolidine-1-carboxylate (1.7 g, 5 mmol) in DCM (30 mL) was added DMP (2.7 g, 7 mmol) at 0 °C and the mixture was stirred for 16 hours at room temperature. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL) and extracted with ethyl acetate (2 x 60 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The resulting product was filtered and the filtrate was concentrated to give a crude. The crude was purified by flash chromatography to afford benzyl (2S)-4-oxo-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyrrolidine-1-carboxylate as a yellow oil. MS m/z (ESI): 370.1 $[M+Na]^+$.

[520] Step 9: To a solution of benzyl (2S)-4-oxo-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyrrolidine-1-carboxylate (1.4 g, 0.408 mmol) in THF (10 mL) was added methylamine (2M, 14 mL). The mixture was stirred for 16 hours at room temperature. $NaBH_4$ (993 mg, 9.834 mmol) was added and the resulting mixture was stirred at 0 °C for 20 minutes. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The resulting product was filtered and the filtrate was concentrated to give a crude. The crude was purified by flash chromatography to afford benzyl (2R,4R)-4-(methylamino)-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyrrolidine-1-carboxylate as a yellow oil. MS m/z (ESI): 363.3 $[M+H]^+$.

[521] Step 10: To a solution of benzyl (2R,4R)-4-(methylamino)-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyrrolidine-1-carboxylate (1.1 g, 3 mmol) in DCM (15 mL) was added triethylamine (920 mg, 9 mmol) and $(Boc)_2O$ (2 mL) at 0 °C and the mixture was stirred for 16 hours at room temperature. The mixture was quenched with water (20 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The resulting product was filtered and the filtrate was concentrated to give a crude. The crude was purified by flash chromatography to afford benzyl (2R,4R)-4-((tert-butoxycarbonyl)(methyl)amino)-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyrrolidine-1-carboxylate (800 mg, 70%) as a yellow oil. MS m/z (ESI): 485.4 $[M+Na]^+$.

[522] Step 11: To a solution of benzyl (2R,4R)-4-((tert-butoxycarbonyl)(methyl)amino)-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyrrolidine-1-carboxylate (800 mg, 0.023 mmol) in ethyl acetate (10 mL) was added Pd/C (140 mg). The mixture was stirred for 2 hours at room temperature under hydrogen atmosphere. The mixture was filtered and the filtrate was concentrated to afford tert-butyl methyl((3R,5R)-5-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyrrolidin-3-yl)carbamate as a yellow oil. MS m/z (ESI): 329.2 $[M+H]^+$.

[523] Step 12: To a solution of tert-butyl methyl((3R,5R)-5-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyrrolidin-3-yl)carbamate (400 mg, 1.22 mmol) in MeOH (5 mL) was added TsOH (100 mg) and the mixture was stirred for 3 hours at room temperature. The mixture was then quenched with water (5 mL) and extracted with MeOH:DCM = 1:10 (2 x 10 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The resulting product was filtered and the filtrate was concentrated in vacuo to give a crude. The crude mixture was purified by flash chromatography to afford tert-butyl ((3R,5R)-5-(2-hydroxyethyl)pyrrolidin-3-yl)(methyl)carbamate as a yellow oil. MS m/z (ESI): 245.2 $[M+H]^+$.

[524] Step 13: To a solution of tert-butyl ((3R,5R)-5-(2-hydroxyethyl)pyrrolidin-3-yl)(methyl)carbamate (200 mg, 0.820 mmol) in DMF (5 ml) was added NaH (197 mg, 4.918 mmol) at 0 °C and the resulting mixture was stirred for 30 minutes under nitrogen followed by addition of a solution of 7-bromo-6-chloro-5,8-difluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)quinazolin-4-ol (370 mg, 0.820 mmol) dropwise. The resulting reaction mixture was stirred at 60 °C for 2 hours, then cooled to room temperature. The mixture was quenched with aq. NH_4Cl, poured into ice water (100 mL) and extracted with ethyl acetate (100 mL x 3). The

extracts were combined, washed with brine (100 mL) and dried over anhydrous sodium sulfate. The resulting product was filtered and the filtrate was concentrated to give a residue. The residue was purified by HPLC (DCM/MeOH = 10/1) to give tert-butyl ((3R,5R)-5-(2-((7-bromo-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxyquinazolin-5-yl)oxy)ethyl)pyrrolidin-3-yl)(methyl)carbamate as a white solid. MS m/z (ESI): 679.2 $[M+H]^+$

[525] Step 14: To a solution of tert-butyl ((3R,5R)-5-(2-((7-bromo-6-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxyquinazolin-5-yl)oxy)ethyl)pyrrolidin-3-yl)(methyl)carbamate (200 mg, 0.296 mmol) and PyBOP (754.40 mg, 2.963 mmol) in dry DCM (5 mL) was added DIEA (383 mg, 2.963 mmol) at room temperature and the mixture was stirred for 16 hours. It was quenched with aq. $NaHCO_3$, poured into ice water (100 mL) and extracted with ethyl acetate (100 mL x 3). The extracts were combined, washed with brine (100 mL) and dried over anhydrous sodium sulfate. The resulting product was filtered and the filtrate was concentrated to give a crude. The crude was purified by column chromatography (DCM/ DCM/MeOH·NH_3 = 10/1) to give tert-butyl ((2R,13aR)-9-bromo-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)(methyl)carbamate as colorless oil. MS m/z (ESI): 674.1 $[M+H]^+$.

[526] Step 15: To a mixture of tert-butyl ((2R,13aR)-9-bromo-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)(methyl)carbamate (150 mg, 0.228 mmol), tert-butyl (3-cyano-4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate (184 mg, 0.457 mmol), and Cs_2CO_3 (223 mg, 0.685 mmol) in toluene (5 mL) was added Pd(DPEPhos)Cl_2 (33 mg, 0.046 mmol). The mixture was stirred at 110 °C under nitrogen for 3 hours, then cooled to room temperature and diluted with ethyl acetate (100 mL) and water (100 ml). The organic layers were separated, washed with brine (50 mL) and dried over Na_2SO_4. The resulting product was filtered and the filtrate was concentrated to give a residue. The residue was purified by silica gel column (petroleum ether/ethyl acetate = 1/1) to give tert-butyl ((2R,13aR)-9-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)(methyl)carbamate as a yellow solid. MS m/z (ESI): 870.2 $[M+H]^+$.

[527] Step 16: To a solution of tert-butyl ((2R,13aR)-9-(2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)(methyl)carbamate (40 mg, 0.046 mmol) in DCM (0.5 mL) was added TFA (0.5 mL) at 0 °C. The mixture was stirred at room temperature for 1 hour and quenched with aq. $NaHCO_3$. It was poured into ice water (50 mL) and extracted with ethyl acetate (50 mL x 3). The organic layer was combined, washed with brine (50 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by column chromatography (DCM/MeOH·NH_3 = 10/1) to give 2-amino-4-((2R,13aR)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(methylamino)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-9-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile as a yellow solid. MS m/z (ESI): 670.1 $[M+H]^+$.

[528] Step 17: To a solution of 2-amino-4-((2R,13aR)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2-(methylamino)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-9-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (20 mg, 0.03 mmol) in NMP (0.5 mL) was added (S)-2-((ethylsulfonyl)oxy)propanoic acid (20 mg, 0.03 mmol) in NMP (0.5 mL) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 0.15 hours followed by the addition of DMTMM (16.5 mg, 0.006 mmol). The mixture was stirred at 0 °C for 6 minutes, then quenched with ice water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC to give the desired product ((2S)-1-(((2R,13aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate) (451) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.10 (s, 2H), 7.29 – 7.21 (m, 1H), 7.20 – 7.11 (m, 1H), 5.71 – 5.49 (m, 1H), 5.26 (d, J = 53.6 Hz, 1H), 4.89 -4.75 (m, 1H), 4.61 – 4.50 (m, 1H), 4.40 – 4.30 (m, 3H), 4.20 – 4.00 (m, 5H), 3.15 - 3.00-(m, 3H), 2.95 – 2.81 (m, 4H), 2.18 – 1.75 (m, 10H), 1.54 – 1.27 (m, 6H).

[529] Step 18: To (2S)-1-(((2R,13aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)(methyl)amino)-1-oxopropan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((2S)-2-(5-(((2R)-1-(((2R,13aR)-9-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-10-chloro-8-fluoro-6-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1,2,3,12,13,13a-hexahydropyrrolo[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)(methyl)amino)-1-oxopropan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(451A)**.

[530] **Example 1o**: Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3,4-difluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxopropan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(471A)**

[531] Step 1: To a solution of 5-bromo-2,3-difluoro-N,N-bis(4-methoxybenzyl)-4-(trifluoromethyl)-aniline (2.8 g, 5.44 mmol, 1.0 eq) in THF (130 ml) cooled to -78°C was added n-BuLi (2.9 mL, 5.98 mmol, 1.1 eq, 2.0M) under N_2. The mixture was stirred at -78°C for 1 hour. Trimethyl borate (0.735 g, 7.06 mmol, 1.5 eq) was then added and the mixture was stirred at -78°C C for 3 hours. The reaction mixture was then quenched with NH_4Cl (200 mL) and extracted with ethyl acetate (200 mL x 3). The organic layers were combined and dried over anhydrous sodium sulfate. The product was filtered and the filtrate was concentrated under vacuum to give a residue. The residue was purified by reverse column to the desired product ((5-(bis(4-methoxybenzyl)amino)-3,4-difluoro-2-(trifluoromethyl)phenyl)boronic acid) as a yellow oil. MS m/z (ESI):482.0 $[M+H]^+$.

[532] Step 2: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-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 (1.0 g, 1.69 mmol, 1.0 eq) in THF (20 mL) and H_2O (2 mL) were added Cataxium Pd G3 (0.37 g, 0.51 mmol, 0.3 eq), (5-(bis(4-methoxybenzyl)amino)-3,4-difluoro-2-

(trifluoromethyl)phenyl)boronic acid (1.63 g, 3.38 mmol, 2.0 eq) and K_3PO_4 (1.79 g, 8.45 mmol, 5.0 eq) at room temperature. The mixture was stirred at 70 °C for 3 hours and cooled to room temperature. The reaction mixture was then diluted with ethyl acetate (100 mL) and water (50 mL). The organic layer was separated and dried over anhydrous sodium sulfate. The product was filtered and the filtrate was concentrated to dryness under reduced pressure to give a residue. The residue was purified by Prep-TLC to give the desired product (tert-butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3,4-difluoro-2-(trifluoromethyl)-phenyl)-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) as a gray solid. MS m/z (ESI):994.02 $[M+H]^+$.

[533] Step 3: A mixture of tert-butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3,4-difluoro-2-(trifluoromethyl)-phenyl)-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 (200 mg, 0.20 mmol, 1.0 eq) and TFA (3 mL) was stirred at room temperature for 2 hours and the solvent was removed under reduced pressure. DCM (5 mL) and NH_3·MeOH (7M) were then added to adjust the pH > 7. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC (DCM/NH_3·MeOH (10:1) to afford the desired product (2,3-difluoro-5-((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)-4-(trifluoromethyl)aniline) as a white solid. MS m/z (ESI): 653.6 [M+H].

[534] Step 4: To a solution of (R)-2-((ethylsulfonyl)oxy)propanoic acid (40 mg, 0.22 mmol, 1.3 eq) in NMP (2 mL) was added tert-butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3,4-difluoro-2-(trifluoromethyl)-phenyl)-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 (110 mg, 0.17 mmol, 1.0 eq) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 10 minutes. DMTMM (60 mg, 0.22 mmol, 1.5 eq) was then added at 0 °C. The mixture was stirred at 0 °C for 15 minutes and diluted by sat.a.q.$NaHCO_3$ (20 ml) and EtOAc (100 mL).The organic layer was separated and dried with anhydrous Na_2SO_4. The product was filtered and the filtrate was concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC to give the desired product ((R)-1-((5S,5aS,6S,9R)-2-(5-amino-3,4-difluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxopropan-2-yl ethanesulfonate) as a white solid. MS m/z (ESI): 817.8 [M+H]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.62 (d, J = 8.0 Hz, 1H), 6.30 (s, 2H), 5.52 – 5.41 (m, 1H), 5.38 – 5.18 (m, 2H), 4.86 – 4.49 (m, 3H), 4.23 – 3.88 (m, 3H), 3.42 - 3.20 (m, 2H), 3.26 – 3.16 (m, 1H), 3.13 - 2.96 (m, 3H), 2.89 – 2.79 (m, 1H), 2.20 – 2.04 (m, 2H), 2.04 – 1.97 (m, 2H), 1.97 - 1.86 (m, 2H), 1.86 – 1.71 (m, 4H), 1.51 (s, 6H), 1.33 – 1.44 (m, 3H).

[535] Step 5: To (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3,4-difluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxopropan-2-yl ethanesulfonate (471) is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3,4-difluoro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxopropan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(471A)**.

[536] **Example 1p:** Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**491A**)

[537] Step 1: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-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 (3 g, 5.85 mmol) and ((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol (1.64 g, 8.77 mmol) in toluene (60 mL) was added t-BuONa (1.4 g, 14.6 mmol) at 0 °C. The mixture was stirred at 25 °C for 1.5 hours. The reaction was quenched by saturated aqueous solution of NH_4Cl (60 mL) and extracted with ethyl acetate (60 mL x 3). The combined organic layers were washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase column to give desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-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 as a yellow solid. MS m/z (ESI): 620.9 $[M+H]^+$.

[538] Step 2: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-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 (200 mg, 0.3 mmol) in dioxane (20 mL) and H_2O (4 mL) was added (5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)boronic acid (229 mg, 0.46 mmol), Cs_2CO_3 (300 mg, 0.92 mmol) and $Pd(PPh_3)_4$ (71 mg, 0.06 mmol). The mixture was stirred at 100 °C under nitrogen for 3 hours and cooled to room temperature. The mixture was diluted with brine (30 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were separated, dried over sodium sulfate, concentrated to give a residue. The residue was purified by flash column chromatography on silica gel (DCM:MeOH=10:1) to afford the desired product tert-Butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-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 as a yellow solid. MS m/z (ESI): 1054.7 $[M+H]^+$.

[539] Step 3: A solution of tert-butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-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-carboxyl (200 mg, 0.19 mmol) in TFA (2 mL) was stirred at room temperature for 1 hour under nitrogen. The reaction was concentrated to give a residue. The residue was adjusted to pH~8 by saturated sodium bicarbonate aqueous solution (30 mL). The solution was extracted with DCM (30 ml x 2). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by prep-TLC (DCM:NH_3:MeOH=10:1) to give the desired product 3-Chloro-5-((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)-1-fluoro-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)-2-fluoro-4-(trifluoromethyl)aniline as a yellow solid. MS m/z (ESI): 714.2 $[M+H]^+$.

[540] Step 4: A solution of 3-chloro-5-((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)-1-fluoro-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)-2-fluoro-4-(trifluoromethyl)aniline (110 mg, 0.15 mmol) and (R)-2-((ethylsulfonyl)oxy)butanoic acid (39 mg, 0.2 mmol) in NMP (1.5 mL) was stirred at 0 °C for 10 minutes. DMTMM (64 mg, 0.23 mmol) was then added at 0 °C. The mixture was stirred at room temperature for 10 minutes, diluted with saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was combined, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired product ((R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate) (491) as a white solid. MS m/z (ESI): 892.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.71 (s, 1H), 6.31 (s, 2H), 5.35 – 5.17 (m, 2H), 4.89 – 4.47 (m, 3H), 4.23 (s, 2H), 4.13 – 3.83 (m, 1H), 3.45 – 3.30(m, 2H), 3.14 – 2.99 (m, 3H), 2.79 – 2.72(m, 1H), 2.60 – 2.52(m, 1H), 2.11 – 1.71(m, 11H), 1.68 – 1.62 (m, 1H), 1.57 – 1.40 (m, 5H), 1.34 – 1.27 (m, 3H), 1.06 – 0.91 (m, 3H).

[541] Step 5: To (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-12-(((1S,7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(491A)**.

Example 1q: Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(500A)**

Step 1: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-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 (5.32 g, 10.35 mmol) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (3.3 g, 20.7 mmol) in toluene (80 mL) was added t-BuONa (2.5 g, 25.88 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 hour, quenched by saturated aqueous solution of water (80 mL) and extracted with ethyl acetate (60 mL x 3). The combined organic layers were washed with brine (80 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase column to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-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 as a yellow solid. MS m/z (ESI): 593.1 $[M+H]^+$.

Step 2: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-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 (308 mg, 0.51 mmol) in 1,4-dioxane (30 ml) and water (6 mL) were added 3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline (250 mg, 0.78 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05mmol), and Cs_2CO_3 (500 mg, 1.53 mmol) under nitrogen. The mixture was stirred at 100°C for 1 hour and cooled to room temperature. The mixture was diluted with brine (100 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were separated, dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by reverse phase column (1% FA) to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-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 as a yellow solid. MS m/z (ESI):752.1 $[M+H]^+$.

Step 3: A solution of tert-Butyl (5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-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 (225 mg, 0.29 mmol) in TFA (2 ml) was stirred at 30°C for 1 hour under nitrogen. The mixture was concentrated and the residue was adjusted to pH~8 by saturated sodium bicarbonate aqueous solution (80 mL). The mixture was extracted with DCM: MeOH=10:1 (150 mL x 3). The combined organic layers were washed with brine (40 mL) and dried over Na_2SO_4. The mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by prep-TLC (DCM:NH_3.MeOH=10:1) to give the desired product 3-Chloro-5-((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)-4-(trifluoromethyl)aniline as a yellow solid. MS m/z (ESI): 651.8 $[M+H]^+$.

Step 4: A solution of 3-Chloro-5-((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)-4-(trifluoromethyl)aniline (150 mg, 0.23 mmol) and (R)-2-((ethylsulfonyl)oxy)butanoic acid (54 mg, 0.28 mmol) in NMP (2 mL) was stirred at 0 °C for 10 minutes. DMTMM (95 mg, 0.35 mmol) was added at 0 °C and the mixture was stirred at room temperature for 10 minutes. The mixture was diluted with saturated aqueous solution of $NaHCO_3$ (15 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was combined and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired product (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate (500) as a white solid. MS m/z (ESI): 830.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 6.86 (s, 1H), 6.60 – 6.22 (m, 3H), 5.39 – 5.14 (m, 3H), 4.88 – 4.64 (m, 2H), 4.61 – 4.50 (m, 1H), 4.20 – 3.86 (m, 3H), 3.48 – 3.34 (m, 3H), 3.25 – 3.16 (m, 1H), 3.12 – 2.99 (m, 3H), 2.89 – 2.77 (m, 1H), 2.16 – 1.97 (m, 4H), 1.92 – 1.67 (m, 7H), 1.62 – 1.44 (m, 3H), 1.38 – 1.25 (m, 3H), 1.05 – 0.90 (m, 3H),

Step 5: To a solution of (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl ethanesulfonate (210 mg, 0.25 mmol) and (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (136 mg, 0.25 mmol) in MeCN (4 mL) was added DIEA (645 mg, 5 mmol) at 25 °C. The mixture was stirred at 80 °C for 16 hours and cooled down to room temperature. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (10 mL x 3). The organic layer was combined and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC to give the desired product ((2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide) **(500A)** as white solid. MS m/z (ESI):1263.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.42 – 8.33 (m, 1H), 7.78 (d, J = 9.2 Hz, 1H), 7.46 – 7.35 (m, 4H), 6.87 – 6.84 (m, 1H), 6.56 – 6.25 (m, 3H), 5.38 – 5.00 (m, 3H), 4.96 – 4.66 (m, 4H), 4.54 – 3.91 (m, 7H), 3.64 – 3.57 (m, 2H), 3.10 – 3.00 (m, 4H), 2.88 – 2.79 (m, 1H), 2.45 (s, 3H), 2.35 – 1.78 (m, 15H), 1.69 – 1.29 (m, 14H), 0.95 – 0.85 (m, 12H).

[542] **Example 1r**: Synthesis of (2S,4R)-1-((2S)-2-(5-(((2S)-1-((14aS)-10-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-7-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)-1-oxopropan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(504A)**.

[543] Step 1: To a solution of tert-butyl (S)-3-(2-hydroxyethyl)piperazine-1-carboxylate (582mg, 2.54 mmol) in DMF (20 mL) was added NaH (2.2 g, 50.8 mmol) at 0 °C and the mixture stirred at the same temperature for 10 minutes followed by the addition of tert-butyl (R)-(4-(6-chloro-5,8-difluoro-4-hydroxy-2-(methylthio)quinazolin-7-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate (1.4 g, 2.54 mmol). The resulting mixture was stirred at 60 °C for 2 hours and cooled to room temperature. The mixture was diluted with ethyl acetate (100 mL) and washed with water (30 mL). The organics were washed with brine and dried over sodium sulfate. The resulting product was filtered and the filtrate was concentrated in vacuo to give a crude. The crude was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 1:1) to give tert-butyl (S)-3-(2-((7-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-4-hydroxy-2-(methylthio)quinazolin-5-yl)oxy)ethyl)piperazine-1-carboxylate as a yellow solid. MS m/z (ESI): 763.2 $[M+H]^+$.

[544] Step 2: To a solution of tert-butyl (S)-3-(2-((7-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-6-chloro-8-fluoro-4-hydroxy-2-(methylthio)quinazolin-5-yl)oxy)ethyl)piperazine-1-carboxylate (500 mg, 0.65 mmol) in DCM (15 mL) were added diisopropylethylamine (252 mg, 1.96 mmol) and BopCl (248.6 mg, 0.975 mmol) and the resulting mixture was stirred at room temperature for 16 hours. The mixture was then diluted with DCM (150 mL) and washed with water (30 mL). The organic layer was separated and dried over sodium sulfate. The resulting product was filtered and the filtrate was concentrated in vacuo to give a crude. The crude was purified by silica gel chromatography (petroleum ether:ethyl acetate = 3:1) to afford tert-butyl (S)-10-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-7-(methylthio)-

1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazoline-2-carboxylate as white solid. MS m/z (ESI): 744.9 $[M+H]^+$.

[545] Step 3: To a solution of tert-butyl (S)-10-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-7-(methylthio)-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazoline-2-carboxylate (50 mg, 0.067 mmol) in DCM (5 mL) was added m-CPBA (18 mg, 0.1005 mmol) and the resulting mixture was stirred at 0 °C for 1 hour. The mixture was diluted with ethyl acetate (60 mL) and washed with aq. Na_2SO_3 (10 mL). The organic layer was separated and dried over sodium sulfate. The resulting product was filtered and the filtrate was concentrated in vacuo to give the desired product tert-butyl (14aS)-10-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-7-(methylsulfinyl)-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazoline-2-carboxylate as a yellow solid. MS m/z (ESI): 760.8 $[M+H]^+$.

[546] Step 4: To a solution of ((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methanol (18 mg, 0.132 mmol) in toluene (5 mL) was added t-BuOK (37 mg, 0.33 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 0.5 hours, then tert-butyl (14aS)-10-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-7-(methylsulfinyl)-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazoline-2-carboxylate (50 mg, 0.066 mmol) was added and the mixture stirred an additional 1 hour. The mixture was then diluted with ethyl acetate (80 mL) and washed with water (10 mL). The organics was separated and dried over sodium sulfate. The resulting product was filtered and the filtrate was concentrated in vacuo to give a residue. The residue was purified by silica gel chromatography (DCM:MeOH = 10:1) to afford tert-butyl (S)-10-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-7-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazoline-2-carboxylate as a white solid. MS m/z (ESI): 831.6 $[M+H]^+$.

[547] Step 5: To a solution of tert-butyl (S)-10-((R)-2-((tert-butoxycarbonyl)amino)-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-7-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazoline-2-carboxylate (40 mg, 0.05 mmol) in DCM (3 mL) was added TFA (1 mL) and the mixture was stirred at room temperature for 1 hour. It was then concentrated to give a residue which was purified by prep-HPLC (NH_4HCO_3) to give 2-amino-4-((10S,14aS)-11-chloro-9-fluoro-7-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-10-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile as a white solid. MS m/z (ESI): 630.3 $[M+H]^+$.

[548] Step 6: To a solution of 2-amino-4-((10S,14aS)-11-chloro-9-fluoro-7-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-10-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (10 mg, 0.016 mmol) NMP (2 mL) was added (R)-2-((ethylsulfonyl)oxy)propanoic acid (2.9 mg, 0.016 mmol) and the mixture was stirred at 0 °C for 10 minutes. DMTMM (8.8 mg, 0.032 mmol) was added at 0 °C and reaction mixture was stirred at room temperature for 15 minutes. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (20 mL x 3). The extracts were combined and dried over anhydrous sodium sulfate. The resulting product was filtered and the filtrate was concentrated to give a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired compound ((R)-1-((S)-10-((R)-2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-7-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-

de]quinazolin-2-yl)-1-oxopropan-2-yl ethanesulfonate) (504) as a white solid. MS m/z (ESI): 794.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.09 (s, 1H), 7.25 – 7.10 (m, 2H)5.60 – 5.50 (m, 1H), 5.19 (d, J = 55.2 Hz, 1H), 4.46 – 4.05 (m, 5H), 4.00 – 3.72 (m, 4H), 3.66 – 3.37 (m, 4H), 3.30 – 3.18 (m, 2H), 2.98 – 2.88 (m, 1H), 2.41 (s, 3H), 1.98 – 1.85 (m, 4H), 1.46 – 1.38 (m, 3H), 1.28 – 1.16 (m, 3H).

[549] Step 7: To (R)-1-((S)-10-((R)-2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-7-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)-1-oxopropan-2-yl ethanesulfonate (104) is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((2S)-2-(5-(((2S)-1-((14aS)-10-(2-amino-3-cyano-7-fluorobenzo[b]thiophen-4-yl)-11-chloro-9-fluoro-7-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-1,3,4,13,14,14a-hexahydro-2H-pyrazino[1',2':5,6][1,5]oxazocino[4,3,2-de]quinazolin-2-yl)-1-oxopropan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(504A)**.

[550] **Example 1s:** Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((6aR,7S,10R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-15-yl)-1-oxopropan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(509A)**

[551] Step 1: To a mixture of tert-butyl (1S,2S,5R)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (10 g, 1 eq, 41.3 mmol) and Na_2CO_3 (8.76 g, 2 eq, 82.6 mmol) in THF/H_2O (150 mL/38 mL) was added FmocCl (11.8 g, 1.1 eq, 45.4 mmol) and the resulting mixture was stirred for 2 hours. After the reaction, the mixture was quenched with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by com-flash chromatography on a silica gel column (ethyl acetate in petroleum ether 0~25%) to give the desired product 3-((9H-fluoren-9-yl)methyl) 8-(tert-butyl) (1S,2S,5R)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate as an off-white solid. ESI-MS m/z: 487 $[M+Na]^+$.

[552] Step 2: To a mixture of 3-((9H-fluoren-9-yl)methyl) 8-(tert-butyl) (1S,2S,5R)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (16.5 g, 1 eq, 35.5 mmol) in DCM was added Dess-Martin (18 g, 1.2 eq, 42.6 mmol). The mixture was stirred for 2 hours. The mixture was quenched with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by com-flash chromatography on a silica gel column (ethyl acetate in petroleum ether 0~25%) to give the desired product 3-((9H-fluoren-9-yl)methyl) 8-(tert-butyl) (1S,2S,5R)-2-formyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate as an off-white solid. ESI-MS m/z: 463 $[M+H]^+$.

[553] Step 3: To a mixture of 3-((9H-fluoren-9-yl)methyl) 8-(tert-butyl) (1R,2S,5S)-2-formyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (14.6 g, 1 eq, 31.6 mmol) in THF(150 mL) was added vinylmagnesium bromide (80 mL, 3 eq, 94.8 mmol) at -78°C. The mixture was stirred for 2 hours, quenched with water (80 mL) and extracted with ethyl acetate (3 x 80 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by com-flash chromatography on a silica gel column (ethyl acetate in petroleum ether 0~30%) to give the desired product 3-((9H-fluoren-9-yl)methyl)

8-(tert-butyl) (1R,2S,5S)-2-((R)-1-hydroxyallyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate as a colorless oil. ESI-MS m/z: 513 $[M+Na]^+$.

[554] Step 4: To a mixture of 3-((9H-fluoren-9-yl)methyl) 8-(tert-butyl) (1S,2S,5R)-2-((R)-1-hydroxyallyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (14.2 g, 1 eq, 29.6 mmol), DMAP (4.3 g, 1 eq, 29.6 mmol) and pyridine (11.6 g, 5 eq, 148 mmol) in DCM (200 mL) was added acetic anhydride (9.1 g, 3 eq, 88.7 mmol) at room temperature. The mixture was stirred for 2 hours and concentrated to give a residue. The residue was purified by com-flash chromatography on a silica gel column (ethyl acetate in petroleum ether 0~20%) to give the desired product 3-((9H-fluoren-9-yl)methyl) 8-(tert-butyl) (1S,2S,5R)-2-((R)-1-acetoxyallyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate as a colorless oil. ESI-MS m/z: 555 $[M+Na]^+$

[555] Step 5: A mixture of 3-((9H-fluoren-9-yl)methyl) 8-(tert-butyl) (1S,2S,5R)-2-((R)-1-acetoxyallyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (9.6 g, 1 eq, 18 mmol), $Pd(PPh_3)_4$ (5.2 g, 0.25 eq, 4.5 mmol) and $HCOONH_4$ (34 g, 30 eq, 540 mmol) in toluene (120 mL) was stirred at 100 °C for 2 hours. The mixture was cooled to room temperature and concentrated to provide a residue. The residue was dissolved with water (80 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to provide a residue The residue was purified by com-flash chromatography on a silica gel column (ethyl acetate in petroleum ether 0~20%) to give the desired product 3-((9H-fluoren-9-yl)methyl) 8-(tert-butyl) (1S,2S,5R)-2-allyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate as a colorless oil. ESI-MS m/z: 475 $[M+1]^+$

[556] Step 6: A mixture of 3-((9H-fluoren-9-yl)methyl) 8-(tert-butyl) (1S,2S,5R)-2-allyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (6.2 g, 13 mmol) in Dimethylamine in THF (60 mL) was stirred at room temperature for 3 hours. The mixture was quenched with water (60 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by com-flash chromatography on a silica gel column (MeOH in DCM0~10%) to give the desired product tert-Butyl (1S,2S,5R)-2-allyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate as a light-yellow oil. ESI-MS m/z: 253 $[M+1]^+$

[557] Step 7: To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (78 g, 1 eq, 310.7 mmol) in 2-methyltetrahydrofuran (585 mL) was added MeONa (58.5 mL, 1.1 eq, 341.8 mmol) at -40 °C.. The mixture was stirred for 2 hours, quenched with solution of NH_4Cl (200 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was concentrated to give the desired product 2,7-Dichloro-8-fluoro-4-methoxypyrido[4,3-d]pyrimidine as a light-yellow solid which was used directly in the next step without further purification. ESI-MS m/z: 248 $[M+1]^+$

[558] Step 8: To a solution of 2,7-dichloro-8-fluoro-4-methoxypyrido[4,3-d]pyrimidine (30.7 g, 1 eq, 124 mmol) in 2-methyltetrahydrofuran (400 mL) was added EtSNa (11 g, 1 eq, 124 mmol) room temperature. The mixture was stirred for 2 hours at 50 °C. The mixture was cooled to room temperature, quenched with water (60 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by com-flash chromatography on a silica gel column (ethyl acetate in petroleum ether 0~8%) to give the desired product 7-Chloro-2-(ethylthio)-8-fluoro-4-methoxypyrido[4,3-d]pyrimidine as a white solid. ESI-MS m/z: 274 $[M+1]^+$

[559] Step 9: To a solution of 7-chloro-2-(ethylthio)-8-fluoro-4-methoxypyrido[4,3-d]pyrimidine (16.7 g, 1 eq, 61.2 mmol) in THF (50 mL) was added 2,2,6,6-Tetramethylpiperidinylmagnesium chloride lithium chloride complex (244 mL, 4 eq, 244 mmol) at 0 °C. The mixture was stirred for 1 hour followed by the addition of 1,2-

dibromotetrachloroethane (75.9 g, 4 eq, 244 mmol) in THF. The mixture was stirred for 3 hours, quenched with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by com-flash chromatography on a silica gel column (ethyl acetate in petroleum ether 0~4%) to give the desired product 5-Bromo-7-chloro-2-(ethylthio)-8-fluoro-4-methoxypyrido[4,3-d]pyrimidine as a white solid. ESI-MS m/z: 352 $[M+1]^+$

[560] Step 10: To a solution of 5-bromo-7-chloro-2-(ethylthio)-8-fluoro-4-methoxypyrido[4,3-d]pyrimidine (9.1 g, 25.9 mmol) in AcOH (120 mL) was added NaI (15.5 g, 5 eq, 103.7 mmol). The mixture was stirred at 100 °C for 2 hours. The mixture was cooled to room temperature, quenched with water (200 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the desired product 5-Bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-ol as a white solid which was used directly in the next step without further purification. ESI-MS m/z: 338 $[M+1]^+$

[561] Step 11: To a solution of 5-bromo-7-chloro-2-(ethylthio)-8-fluoropyrido[4,3-d]pyrimidin-4-ol (5 g, 1 eq, 14.8 mmol) in $POCl_3$ was added DIEA(5.3 mL). The mixture was stirred at 70 °C for 0.5 hours. The mixture was cooled to room temperature and concentrated to give a residue. The residue was dissolved in DCM and DIEA and tert-butyl (1S,2S,5R)-2-allyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (4.4 g, 1.2 eq, 17.7 mmol) was added. The mixture was stirred for 1 hour, quenched with water (40 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column flash chromatography on a silica gel column (ethyl acetate in petroleum ether 0~25%) to give the desired product 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 as a light yellow solid. ESI-MS m/z: 572 $[M+1]^+$

[562] Step 12: To a solution of 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 (3 g, 1 eq, 5.25 mmol) in dioxane (75 mL) was added 9-BBN (42 mL, 4 eq). The mixture was stirred at 70 °C for 0.5 hours. It was cooled to room temperature and $Pd(dppf)Cl_2$ (383 mg, 0.1 eq, 0.525 mmol) and K_3PO_4 (3.3 g, 3 eq, 15.7 mmol) in water (15 mL) was added. The residue was stirred at 90 °C for 2 hours and cooled to room temperature. The mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by com-flash chromatography on a silica gel column (ethyl acetate in petroleum ether 0~25%) to give the desired product tert-Butyl (6aR,7S,10R)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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 as a light yellow solid. ESI-MS m/z: 572 $[M+1]^+$

[563] Step 13: A mixture of tert-butyl (6aR,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 (1.7 g, 1 eq, 3.4 mmol) and (5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (2.96 g, 1.8 eq, 6.2 mmol), CatacxiumAPdG3 (750 mg, 0.3 eq, 1.02 mmol) and K_3PO_4 (2.92 g, 3 eq, 10.2 mmol) in THF/H_2O (20 mL/2 mL) was stirred at 60 °C for 2 hours under nitrogen atmosphere. The mixture was cooled to room temperature and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by

com-flash chromatography on a silica gel column (ethyl acetate in petroleum ether 0~30%) to give the desired product tert-Butyl (6aR,7S,10R)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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 as a light yellow solid. ESI-MS m/z: 891 $[M+1]^+$

[564] Step 14: To a mixture of tert-butyl (6aR,7S,10R)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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 (1.46 g, 1.64 mmol) in DCM (20 mL) was added m-CPBA (709 mg, 2.5 eq, 4.1 mmol). The mixture was stirred at room temperature for 2 hours, quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give desired product tert-Butyl (6aR,7S,10R)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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 as a light-yellow solid which was used directly in the next step without further purification. ESI-MS m/z: 923 $[M+1]^+$

[565] Step 15: To a mixture of ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (157 mg, 1.5 eq, 0.99 mmol) in toluene(6 mL) was added t-BuOK(111 mg,1.5 eq, 0.99 mmol) at 0 °C. The mixture was stirred for 20 minutes. Then, tert-butyl (6aR,7S,10R)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-13-(ethylsulfinyl)-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 (600 mg, 1 eq, 0.66 mmol) was added. The mixture was stirred for 1 hour, quenched with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column flash chromatography on a silica gel column (ethyl acetate in petroleum ether 0~100%) to give the desired product tert-Butyl (6aR,7S,10R)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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 as an off-white solid. ESI-MS m/z: 988 $[M+H]^+$.

[566] Step 16: A mixture of tert-butyl (6aR,7S,10R)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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 (400 mg, 1 eq, 35.5 mmol) in TFA (2 mL) was stirred at room temperature for 1 hour. The mixture was concentrated and re-dissolved in ethyl acetate. The mixture was adjusted pH value to ~ 8 using $NaHCO_3$ solution. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by com-flash chromatography on a silica gel column (DCM in MeOH 0~10%) to give the desired product 2-Fluoro-5-((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-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline as a light yellow solid. ESI-MS m/z: 648 $[M+1]^+$.

[567] Step 17: To a mixture of 2-fluoro-5-((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-4H-3,11a,12,14,15-pentaaza-7,10-methanocyclohepta[4,5]cycloocta[1,2,3-de]naphthalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (100 mg, 1 eq,

0.15 mmol) and (R)-2-((ethylsulfonyl)oxy)propanoic acid (33 mg, 1.2 eq, 0.18 mmol) in NMP (2 mL) was added DMTMM (62 mg, 1.5 eq, 0.23 mmol) at room temperature. The mixture was stirred for 10 minutes, quenched with $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by prep-HPLC (10 mmol NH_4HCO_3 in water/ acetonitrile) to the desired compound ((R)-1-((6aR,7S,10R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-15-yl)-1-oxopropan-2-yl ethanesulfonate) (509) as a light white solid. ESI-MS m/z: 812 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.60 (s, 1H), 6.00 (s, 2H), 5.56-5.45 (m, 1H), 5.29 (d, J = 55.6 Hz, 1H), 5.12 (d, J = 12.4 Hz, 1H), 4.84-4.66 (m, 1H), 4.52-4.34 (m, 1H), 4.20-4.03 (m, 2H), 3.89-3.69 (m, 1H), 3.46-3.40 (m, 1H), 3.27-3.19 (m, 1H), 3.09 (s, 2H), 3.01 (s, 1H), 2.93-2.79 (m, 2H), 2.78-2.65 (m, 2H), 2.33 (s, 3H), 2.20-1.95 (m, 4H), 1.90-1.75(m, 4H), 1.71-1.41 (m, 8H), 1.35-1.25 (m, 4H).

[568] Step 18: To (R)-1-((6aR,7S,10R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-15-yl)-1-oxopropan-2-yl ethanesulfonate is added (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide, DIEA, and THF, with reflux. The resulting product is purified to provide the degrader (2S,4R)-1-((S)-2-(5-(((S)-1-((6aR,7S,10R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-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-15-yl)-1-oxopropan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(509A)**.

Example 1t: Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((S)-1-methylpyrrolidin-2-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (**510A**)

Step 1: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-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 (5.32 g, 10.35 mmol) and (S)-(1-methylpyrrolidin-2-yl)methanol (2.38 g, 20.7 mmol) in Toluene (80 mL) was added t-BuONa (2.5 g, 25.88 mmol) at 0°C. The mixture was stirred at 25°C for 1 hour, quenched by saturated aqueous solution of NH_4Cl (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse phase column to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(((S)-1-methylpyrrolidin-2-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 as a yellow solid. MS m/z (ESI): 549.3 $[M+H]^+$.

Step 2: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-(((S)-1-methylpyrrolidin-2-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 (1 g, 1.82 mmol) in THF (30 mL) and water (6 mL) were added 3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline (0.6 g, 1.82 mmol), cataCxium A Pd G3 (266 mg, 0.37 mmol), and

K_3PO_4 (1.93 g, 9.1 mmol) under nitrogen. The mixture was stirred at 80 °C for 3 hours and cooled to room temperature. The solution was diluted with brine (20 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were separated and dried over sodium sulfate. The mixture was concentrated to give a residue. The residue was purified by reverse phase column (0.1% FA) to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((S)-1-methylpyrrolidin-2-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 as a yellow solid. MS m/z (ESI): 708.4 $[M+H]^+$.

Step 3: A solution of tert-butyl (5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((S)-1-methylpyrrolidin-2-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 (650 mg, 0.9 mmol) in TFA (7 mL) was stirred at 25 °C for 1 hour under nitrogen. The reaction was concentrated to give a residue. The residue was adjusted to pH~8 by saturated sodium bicarbonate aqueous solution (15 mL) and extracted with DCM (30 mL x 2). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. The mixture was filtered and concentrated to give a residue. The residue was purified by column on silica gel (DCM:NH_3.MeOH=10:1) to give the desired product 3-Chloro-5-((5S,5aS,6S,9R)-1-fluoro-5-methyl-12-(((S)-1-methylpyrrolidin-2-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)-4-(trifluoromethyl)aniline as a yellow solid. MS m/z (ESI): 608.3 $[M+H]^+$.

Step 4: A solution of 3-chloro-5-((5S,5aS,6S,9R)-1-fluoro-5-methyl-12-(((S)-1-methylpyrrolidin-2-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)-4-(trifluoromethyl)aniline (200 mg, 0.33 mmol) and (R)-2-((ethylsulfonyl)oxy)butanoic acid (84 mg, 0.43 mmol) in NMP (5 mL) was stirred at 0°C for 10 minute. DMTMM (136 mg, 0.5mmol) was added and the mixture was stirred at room temperature for 10 minutes. The mixture was diluted with saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with ethyl acetate (20 mL x 3). The organic layer was dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired product (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((S)-1-methylpyrrolidin-2-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-14-yl)-1-oxobutan-2-yl ethanesulfonate (510) as a white solid. MS m/z (ESI): 786.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 6.86 (s, 1H), 6.52 – 6.00 (m, 3H), 5.38 – 5.16 (m, 2H), 4.76 – 4.70 (m, 2H), 4.68 – 4.62 (m, 1H), 4.40 – 4.36 (m, 1H), 4.20 – 4.08 (m, 1H), 3.92 (s, 1H), 3.45 – 3.38 (m, 2H), 3.24 – 3.20 (m, 1H), 2.99 – 2.93 (m, 1H), 2.62 – 2.58 (m, 1H), 2.37 (s, 3H), 2.24 – 2.16 (m, 1H), 2.02 – 1.63 (m, 10H), 1.58 – 1.54 (m, 1H), 1.52 – 1.48 (m, 2H), 1.33 – 1.26 (m, 3H), 1.04 – 0.96 (m, 3H).

Step 5: To a solution of (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((S)-1-methylpyrrolidin-2-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-14-yl)-1-oxobutan-2-yl ethanesulfonate (210 mg, 0.27 mmol) and (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (147 mg, 0.27 mmol) in MeCN (4 mL) was added DIEA (697 mg, 5.4 mmol) at 25 °C. The mixture was stirred at 80 °C for 16 hours and cooled down to room temperature. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (10 mL x 3). The organic layer was combined and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC to give the desired product ((2S,4R)-1-

((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((S)-1-methylpyrrolidin-2-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-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide) **(510A)** as a white solid. MS m/z (ESI):1220.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.40 – 8.30 (m, 1.42H), 7.78 (d, J = 8.8 Hz, 1H), 7.45 – 7.34 (m, 4H), 6.88 – 6.83 (m, 1H), 6.53 – 6.24 (m, 3H), 5.30 – 4.98 (m, 2H), 4.97 – 4.63 (m, 4H), 4.59 – 4.15 (m, 6H), 4.07 – 3.89 (m, 1H), 3.63 – 3.57 (m, 1H), 3.10 – 3.03 (m, 1H), 2.98 – 2.92 (m, 1H), 2.63 – 2.56 (m, 4H), 2.47 – 2.35 (m, 7H), 2.33 – 1.74 (m, 11H), 1.71 – 1.46 (m, 11H), 1.43 – 1.29 (m, 5H), 0.96 – 0.85 (m, 12H).

Example 1u: Synthesis of (2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide **(511A)**

Step 1: To a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-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 (4.3 g, 7.65 mmol) in 1,4-dioxane (450 mL) and water (90 mL) were added 3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline (3.7 g, 11.5 mmol), $Pd(PPh_3)_4$ (884 mg, 0.765mmol), and Cs_2CO_3 (7.4 g, 22.8 mmol) under nitrogen. The mixture was stirred at 100°C for 1 hour and cooled to room temperature. The mixture was diluted with brine (500 mL) and extracted with ethyl acetate (500 mL x 3). The combined organic layers were washed with brine and dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by reverse phase column (1% FA) to give the desired product tert-Butyl (5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-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 as a yellow solid. MS m/z (ESI):722.7 [M+H]+.

Step 2: A solution of tert-Butyl (5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-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 (4.1 g, 5.7 mmol) in TFA (20 ml) was stirred at 30°C for 1 hour under nitrogen. The mixture was concentrated and the residue was adjusted to pH~8 by saturated sodium bicarbonate aqueous solution (80 mL). The solution was extracted with DCM: MeOH=10:1 (150 mL x 3). The combined organic layers were washed with brine (40 mL) and dried over Na_2SO_4. The mixture was filtered and concentrated to give a residue. The residue was purified by column on silica gel (DCM:NH_3.MeOH=10:1) to give the desired product 3-Chloro-5-((5S,5aS,6S,9R)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-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)-4-(trifluoromethyl)aniline as a yellow solid. MS m/z (ESI): 764.7 $[M+H]^+$.

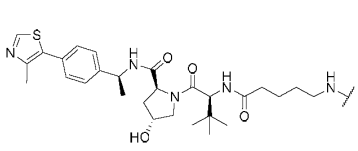
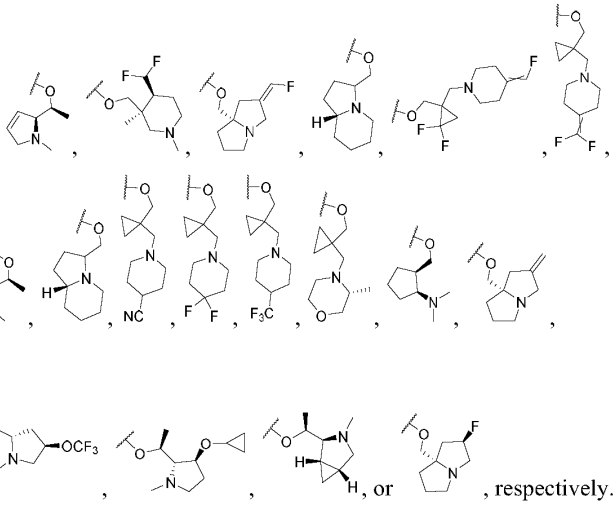
Step 3: A solution of 3-chloro-5-((5S,5aS,6S,9R)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline (2.3 g, 3.7 mmol) and (R)-2-((ethylsulfonyl)oxy)butanoic acid (1.1 g, 5.5 mmol) in NMP (25 mL) was stirred at 0 °C for 10 minutes. DMTMM (1.5 g, 5.5 mmol) was added at 0 °C and the mixture was stirred at room temperature for 10 minutes. The mixture was diluted with Saturated aqueous solution of $NaHCO_3$ (150 mL) and extracted with ethyl acetate (300 mL x 3). The organic layer was combined, washed and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give

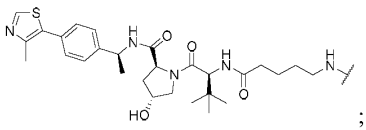
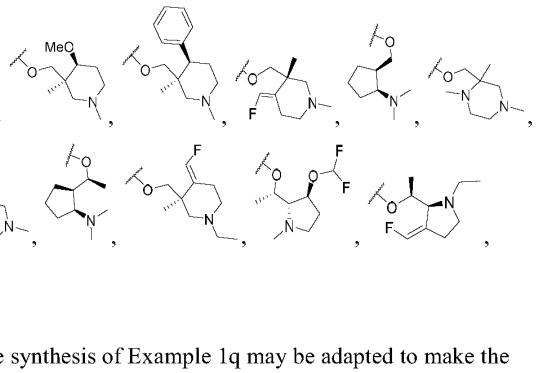
a residue. The residue was purified by pre-HPLC (NH_4HCO_3) to give the desired product ((R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate) (511) as a white solid. MS m/z (ESI): 800.7 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 6.86 (s, 1H), 6.57 – 6.24 (m, 3H), 5.43 – 5.14 (m, 3H), 4.87 – 4.64 (m, 2H), 4.61– 4.45 (m, 1H), 4.15– 3.80 (m, 1H), 3.46– 3.35 (m, 2H), 3.28– 3.15 (m, 1H), 3.02 – 2.90 (m, 1H), 2.66– 2.56 (m, 1H), 2.37 (s, 3H), 2.24– 2.15 (m, 1H), 2.04 – 1.61 (m, 10H), 1.59 – 1.44 (m, 3H), 1.36 – 1.19 (m, 6H), 1.06 – 0.90 (m, 3H),

Step 4: To a solution of 5-((tert-butoxycarbonyl)amino)pentanoic acid (2.9 g, 13.3 mmol) in DMF (2 mL) was added HATU (5 g, 13.3 mmol), DIEA (6.2 mL, 33.7 mmol) and stirred 15 minutes followed by the addition of (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (5 g, 11.2 mmol) at room temperature. The mixture was stirred for 16 hours, diluted with ethyl acetate and washed with brine. The organic layer was separated and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column to give the desired product tert-Butyl (5-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-oxopentyl)carbamate as a white solid. MS m/z (ESI): 644.3$[M+H]^+$

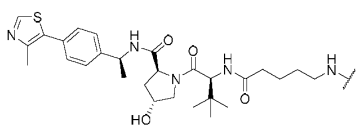
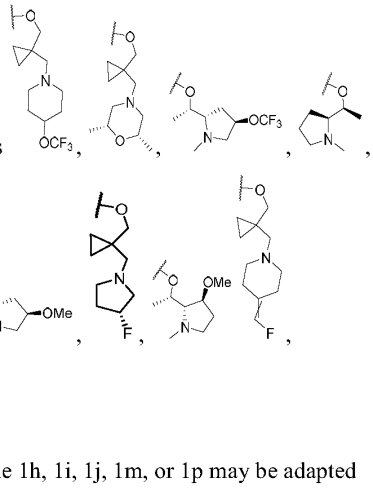
Step 5: To a solution of tert-butyl (5-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-oxopentyl)carbamate (4 g, 6.2 mmol) in DCM (20 mL) was added TFA (10 mL) at room temperature. The mixture was stirred at room temperature for 3 hours and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (NH_4HCO_3) to give the desired product (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide as a white solid. MS m/z (ESI): 544.5 $[M+H]^+$.

Step 6: To a solution of (R)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl ethanesulfonate (200 mg, 0.25 mmol) and (2S,4R)-1-((S)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (136 mg, 0.25 mmol) in MeCN (4 mL) was added DIEA (645 mg, 5 mmol) at 25 °C. The mixture was stirred at 80 °C for 16 hours and cooled down to room temperature. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (10 mL x 3). The organic layer was combined and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (FA) to give the desired product ((2S,4R)-1-((S)-2-(5-(((S)-1-((5S,5aS,6S,9R)-2-(5-amino-3-chloro-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((S)-1-((S)-1-methylpyrrolidin-2-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-14-yl)-1-oxobutan-2-yl)amino)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide) **(511A)** as white solid. MS m/z (ESI):1233.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.33 – 8.19 (m, 0.45H), 8.14 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 9.4 Hz, 1H), 7.44 – 7.35 (m, 4H), 6.92 – 6.83 (m, 1H), 6.48 (s, 1H), 6.15 (s, 2H), 5.31 – 5.28 (m, 2H), 4.99 – 4.59 (m, 5H), 4.53 – 4.27 (m, 3H), 4.04 – 3.89 (m, 1H), 3.64 – 3.57 (m, 2H), 3.41 – 3.35 (m, 2H), 2.98 – 2.93 (m, 1H), 2.64 – 2.59 (m, 1H), 2.46 – 2.36 (m, 7H), 2.32 – 1.61 (m, 15H), 1.55 – 1.25 (m, 15H), 0.96 – 0.88 (m, 12H).

[569] General Scheme 9, as described herein, may be used to make compounds described herein. For example, compound 9 of General Scheme 9 described herein represents compounds 304A, 309A, 320A, 325A, 326A, 334A, 337A, 340A, 367A, 375A, 377A, 391A, 408A, 409A, 412A, 417A, 426A, 428A, 443A, 444A, 454A, 455A, 464A, 465A, and 475A of Table 1, and intermediate compound 8 of General Scheme 9 corresponds to compounds 304, 309, 320, 325, 326, 334, 337, 340, 367, 375, 377, 391, 408, 409, 412, 417, 426, 428, 443, 444, 454, 455, 464, 465, and 475 of Table 1; wherein R_a and R^{B4} are each ethyl, R^{B9} is methyl, R^{B8} is fluoro, DG is  ; and R^{B2} is  , respectively. The synthesis of Example 1g may be adapted to make the compounds described above.

[570] General Scheme 11, as described herein, may be used to make compounds described herein. For example, compound 9 of General Scheme 11 described herein represents compounds 308A, 310A, 366A, 378A, 399A, 419A, 430A, 446A, 449A, 462A, 472A, 481A, 487A, 497A, 500A, 506A, and 507A of Table 1, and intermediate compound 8 of General Scheme 12 corresponds to compounds 308, 310, 366, 378, 399, 419, 430, 446, 449, 462, 472, 481, 487, 497, 500, 506, and 507 of Table 1; wherein R_a and R^{B4} are each ethyl, R^{B9} is methyl, R^{B8} is fluoro, DG is  ; and R^{B2} is  , respectively. The synthesis of Example 1q may be adapted to make the compounds described above.

[571] General Scheme 12, as described herein, may be used to make compounds described herein. For example, compound 9 of General Scheme 12 described herein represents compounds 332A, 333A, 336A, 356A, 361A, 371A, 374A, 390A, 402A, 406A, 407A, 431A, 432A, 433A, 439A, 441A, 469A, 484A, and 491 of Table 1, and intermediate compound 8 of General Scheme 12 corresponds to compounds 332, 333, 336, 356, 361, 371, 374, 390, 402, 406, 407, 431, 432, 433, 439, 441, 469, 484, and 491 of Table 1; wherein R_a and R^{B4} are each ethyl, R^{B9} is

methyl, R^{B8} is fluoro, DG is  ; and R^{B2} is  , respectively. The synthesis of Example 1h, 1i, 1j, 1m, or 1p may be adapted to make the compounds described above.

[572] For example, the selected compounds below were made using at least one of the General Schemes 1-12 described herein above or a scheme adapted from the schemes of Example 1, or a related scheme. The NMR spectra for each compound described below follows the compound number of the compound of Formula (a) from Table 1: (Compound of Formula (a) No. 304) ^{1}H NMR (400 MHz, DMSO-d_6, 333K) δ 6.59 (s, 1H), 5.97 – 5.69 (m, 4H), 5.38 – 5.11 (m, 3H), 4.85 – 4.48 (m, 3H), 3.95 (s, 1H), 3.82 – 3.62 (m, 2H), 3.43 – 3.32 (m, 2H), 3.32 – 3.20 (m, 2H), 3.14 – 3.01 (m, 1H), 2.53 – 2.49 (m, 2H), 2.33 (s, 3H), 2.05 – 1.68 (m, 6H), 1.52 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.25 (d, J = 6.4 Hz, 3H), 1.07 – 0.93 (m, 3H). (Compound of Formula (a) No. 308) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.86 (s, 1H), 6.55-6.24 (m, 3H), 5.41 – 5.18 (m, 2H), 4.86 – 4.64 (m, 2H), 4.60 – 4.31 (m, 3H), 4.12 – 3.87 (m, 1H), 3.45-3.37 (m, 2H), 3.36-3.33 (m, 1H), 3.29 – 3.20 (m, 4H), 3.08 – 3.03 (m, 1H), 2.19 – 1.46 (m, 17H), 1.32 – 1.25 (m, 3H), 1.08 (s, 3H), 1.03 – 0.93 (m, 3H). (Compound of Formula (a) No. 309) ^{1}H NMR (400 MHz, DMSO-d_6, 333K) δ 6.74 – 6.46 (m, 1H), 6.44 – 6.10 (m, 1H), 5.85 (s, 2H), 5.41 – 5.17 (m, 2H), 4.85 – 4.43 (m, 5H), 4.16 – 3.84 (m, 1H), 3.43 – 3.34 (m, 2H), 3.29 – 3.19 (m, 1H), 2.92 – 2.76 (m, 2H), 2.35 – 2.32 (m, 3H), 2.13 (s, 3H), 2.03 – 1.62 (m, 11H), 1.57 – 1.47 (m, 3H), 1.36 – 1.28 (m, 3H), 1.13 (s, 3H), 1.04 – 0.94 (m, 3H). (Compound of Formula (a) No. 310) ^{1}H NMR (400 MHz, DMSO) δ 7.46-7.17 (m, 5H), 6.86 (s, 1H), 6.56-6.18 (m, 3H), 5.51-5.12 (m, 2H), 4.93-4.41 (m, 4H), 4.13-3.83 (m, 2H), 3.50-3.38 (m, 3H), 3.30-3.17 (m, 2H), 3.08-2.93 (m, 2H), 2.69-2.54 (m, 2H), 2.43-2.32 (m, 1H), 2.04-1.82 (m, 4H), 1.79-1.44 (m, 8H), 1.36-1.26 (m, 3H), 1.04 (t, J = 7.2 Hz, 3H), 0.85 (s, 3H). (Compound of Formula (a) No. 315) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 – 7.65 (m, 1H), 7.40 – 7.25 (m, 1H), 7.08 – 6.89 (m, 2H), 6.48 – 6.12 (m, 1H), 5.68 – 5.55 (m, 2H), 5.44 – 5.19 (m, 2H), 4.88 – 4.31 (m, 5H), 4.19 – 3.81 (m, 2H), 3.47 – 3.38 (m, 2H), 3.30 – 3.23 (m, 1H), 3.12 – 2.90 (m, 2H), 2.36 – 2.21 (m, 2H), 2.13 – 1.48 (m, 14H), 1.34 – 1.26 (m, 3H), 1.14 (s, 3H), 1.04 – 0.89 (m, 6H). (Compound of Formula (a) No. 335) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 – 7.72 (m, 1H), 7.38 – 7.28 (m, 1H), 7.10 – 6.70 (m, 3H), 5.63 (d, J = 9.6 Hz, 2H), 5.41 – 5.18 (m, 3H), 4.88 – 4.50 (m, 3H), 4.20 – 3.82 (m, 2H), 3.63 – 3.48 (m, 1H), 3.48 – 3.38 (m, 2H), 3.28 – 3.17 (m, 1H), 3.10 – 2.99 (m, 1H), 2.47 (d, J = 4.0 Hz, 3H), 2.29 (s, 2H), 2.19 – 1.48 (m, 10H), 1.35 – 1.22 (m, 6H), 1.06 – 0.94 (m, 3H). (Compound of Formula (a) No. 337) 1H NMR (400 MHz, DMSO-d_6) δ 6.79 – 6.36 (m, 1H), 6.02 (s, 2H), 5.36 – 5.16 (m, 2H), 4.85 – 4.50 (m, 3H), 4.38 – 4.22 (m, 2H), 4.17 – 3.82 (m, 1H), 3.44 – 3.37 (m, 2H), 3.28 – 2.95 (m, 1H), 2.48 – 2.23 (m, 9H), 2.07 – 1.68 (m, 6H), 1.60 – 1.42 (m, 7H), 1.32 – 1.26 (m, 3H), 1.22 – 1.13 (m, 2H), 1.03 – 0.93 (m, 3H), 0.70 – 0.61 (m, 2H), 0.47 – 0.39 (m, 2H). (Compound of Formula (a) No. 340) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.61 - 6.45 (m, 1H), 6.03 (s, 2H), 5.44 – 5.11 (m, 2H), 4.80 – 4.60 (m, 2H), 4.59 – 4.45 (m,

6H), 4.40 – 4.25 (m, 1H), 4.21 – 3.83 (m, 1H), 3.28 – 2.93 (m, 4H), 2.60 (s, 2H), 2.32 (s, 3H), 2.05 - 1.47 (m, 11H), 1.45 – 1.15 (m, 3H), 1.10 – 0.80 (m, 3H). (Compound of Formula (a) No. 354) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.84 (d, J=8.8, 1H), 5.82 (d, J=14.8, 2H), 5.37 - 5.19 (m, 3H), 4.86 - 4.52 (m, 3H), 4.20 - 3.90 (m, 3H), 3.41 - 3.20 (m, 3H), 3.12 – 2.96 (m, 3H), 2.88 - 2.79 (m, 1H), 2.37 - 2.31 (m, 3H), 2.24 - 1.96 (m, 4H), 1.93 - 1.71 (m, 7H), 1.55 - 1.45 (m, 3H), 1.34 -1.22 (m, 4H), 1.04 - 0.94 (m, 3H). (Compound of Formula (a) No. 365) ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.67 (d, J = 2.4 Hz, 1H), 7.92 – 7.77 (m, 3H), 5.37-5.24 (m, 3H), 4.80-4.59 (m, 3H), 4.14-3.96 (m, 3H), 3.43-3.41 (m, 2H), 3.28 (s, 2H), 3.10-3.03 (m, 3H), 2.85 (s, 1H), 2.19 – 2.00 (m, 4H), 1.95 – 1.70(m, 7H), 1.56-1.49 (m, 3H), 1.32-1.27 (m, 3H), 1.02-0.96 (m,3H). (Compound of Formula (a) No. 366) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.89 – 6.58 (m, 2H), 6.55 – 6.24 (m, 3H), 5.38 – 5.17 (m, 2H), 4.87 – 4.50 (m, 4H),4.36 – 4.22 (m, 1H), 4.16 – 3.84 (m, 1H), 3.47 – 3.36 (m, 2H), 3.25 – 3.01 (m, 1H), 2.74 – 2.64 (m, 2H), 2.58 – 2.51 (m, 1H), 2.34 – 2.20 (m, 1H), 2.15 (s, 3H), 2.05 – 1.70 (m, 8H), 1.57 – 1.46 (m, 3H), 1.33 – 1.25 (m, 3H), 1.11 (s, 3H), 1.05 – 0.92 (m, 3H). (Compound of Formula (a) No. 367) ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 6.59 (s, 1H), 5.85 (s, 2H), 5.36 – 5.21 (m, 2H), 4.86 – 4.53 (m, 4H), 4.44 – 4.28 (m, 2H), 4.12 – 3.87 (m, 1H), 3.45 – 3.34 (m, 2H), 2.64 – 2.54 (m, 2H), 2.43 – 2.28 (m, 7H), 2.12 – 1.43 (m, 13H), 1.34 – 1.24 (m, 3H), 1.01 – 0.95 (m, 3H), 0.67 (s, 2H), 0.45 (s, 2H). (Compound of Formula (a) No. 375) ^{1}H NMR (400 MHz, DMSO--d_6) δ 6.57 (s, 1H), 5.84 (s, 2H), 5.33 – 5.19 (m, 3H), 4.80 – 4.54 (m, 3H), 4.10 – 3.84 (m, 1H), 3.40 – 3.3 (m, 2H), 3.27 – 3.15 (m, 1H), 2.98 – 2.93 (m, 1H), 2.65 – 2.57 (m, 1H), 2.37 (s, 3H), 2.33 (s, 3H), 2.25 – 2.16 (m, 1H), 2.05 – 1.72 (m, 8H), 1.70 – 1.64 (m, 2H), 1.55 – 1.47 (m, 3H), 1.32 – 1.26 (m, 6H), 1.02 – 0.94 (m, 3H). (Compound of Formula (a) No. 377) ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 6.70 -6.40 (m, 1H), 6.02 (s, 2H), 5.50 – 5.00 (m, 3H), 4.80 - 4.49 (m, 3H), 4.13 – 3.85 (m, 1H), 3.50 – 3.30 (m, 2H), 3.27 – 2.99 (m, 2H), 2.71 (d, J = 10.0 Hz, 1H), 2.32 (s, 3H), 2.13 (s, 1H), 2.06 – 1.63 (m, 11H), 1.49 – 1.07 (m, 13H), 1.06 – 0.91 (m, 3H). (Compound of Formula (a) No. 378) ^{1}H NMR (400 MHz, DMSO-d_6, 333K) δ 6.88 – 6.85(m, 1H), 6.48 (s, 1H), 6.17 (s, 2H) 5.38 – 5.11 (m, 2H), 4.83 –4.54 (m, 4H), 4.15 – 3.91 (m, 2H), 3.44 – 3.24 (m, 2H), 3.26 – 3.17 (m, 1H), 2.40 – 2.30 (m, 1H), 2.23 (s, 6H), 2.05 – 1.44 (m, 16H), 1.32 (t, J = 7.2 Hz, 3H), 1.05 – 0.92 (m, 3H). (Compound of Formula (a) No. 388) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.59 (s, 1H), 5.85 (s, 2H), 5.40 – 5.17 (m, 3H), 4.87 – 4.52 (m, 3H), 4.21 – 3.89 (m, 3H), 3.15 – 2.79 (m, 6H), 2.36 – 2.30 (m, 3H), 2.23 – 2.00 (m, 4H), 1.96 – 1.69 (m, 8H), 1.57 – 1.46 (m, 3H), 1.18 – 0.97 (m, 7H). (Compound of Formula (a) No. 393) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.14 – 7.13 (d, J = 4Hz, 1H), 6.58 – 6.55 (m, 2H), 5.42 – 5.08 (m, 3H), 4.90 – 4.48 (m, 3H), 4.15 – 3.89 (m, 2H), 3.47 – 3.36 (m, 2H), 3.29 – 3.18 (m, 2H), 2.93 – 2.85 (m, 1H), 2.68 – 2.60 (m, 2H), 2.45 – 2.33 (m, 4H), 2.05 – 1.64 (m, 8H), 1.60 – 1.46 (m, 3H), 1.39 – 1.24 (m, 6H), 1.06 – 0.93 (m, 6H), 0.52 – 0.58 (m, 4H). (Compound of Formula (a) No. 399) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.86 (s, 1H), 6.58 – 6.26 (m, 3H), 5.44 – 5.15 (m, 2H), 4.87 – 4.35 (m, 5H), 4.15 – 3.88 (m, 1H), 3.47 – 3.36 (m, 2H), 3.26 – 3.02 (m, 1H), 2.69 – 2.53 (m, 2H), 2.40 – 2.23 (m, 6H), 2.22 – 2.15 (m, 1H), 2.12 (s, 3H), 2.04 – 1.71 (m, 6H), 1.58 – 1.46 (m, 3H), 1.34 – 1.26 (m, 3H), 1.10 (s, 3H), 1.05 – 0.93 (m, 3H). (Compound of Formula (a) No. 403) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.65 (s, 2H), 6.25 (s, 1H), 5.50 – 5.42 (m, 1H), 5.37 – 5.18 (m, 2H), 4.83 – 4.52 (m, 3H), 4.20 – 3.90 (m, 3H), 3.14 – 3.01 (m, 4H), 2.95 – 2.80 (m, 2H), 2.46 (d, J = 2.0 Hz, 3H), 2.21 – 1.73 (m, 10H), 1.62 – 1.44 (m, 6H), 1.20 – 1.04 (m, 4H). (Compound of Formula (a) No. 413) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 – 7.70 (m, 1H), 7.41 – 7.27 (m, 1H), 7.14 – 6.90 (m, 2H), 6.87 – 6.58 (m, 1H), 5.63 (d, J = 13.2 Hz, 2H), 5.44 – 5.21 (m, 2H), 4.91 – 4.74 (m, 1H), 4.73 – 4.48 (m, 3H), 4.40 – 4.24 (m, 1H), 4.19 – 3.80 (m, 2H), 3.51 – 3.38 (m, 2H), 3.28 – 3.01 (m, 1H), 2.89 – 2.74 (m, 2H), 2.61 – 2.53 (m, 1H), 2.27 – 2.38 (m, 2H), 2.26 – 2.11 (m, 1H), 2.10 – 1.67 (m, 8H), 1.60 – 1.44 (m, 3H), 1.25 – 1.38 (m, 3H), 1.13 (d, J = 2.8 Hz, 3H), 1.08 – 0.93 (m, 6H). (Compound of Formula (a) No. 417) ^{1}H NMR (400 MHz, DMSO-d_6, 333K) δ 6.58 (s, 1H), 5.83 (s, 2H), 5.36 – 5.16 (m, 2H), 4.80 – 4.55 (m, 4H), 4.06 –

3.91 (m, 2H), 3.43 – 3.32 (m, 2H), 3.25 – 3.18(m, 1H), 2.34 – 2.30 (m, 4H), 2.21 (s, 6H), 1.99 – 1.43 (m, 16H), 1.30 (t, J = 8.0 Hz, 3H), 1.04 – 0.94 (m, 3H).(Compound of Formula (a) No. 419) ^{1}H NMR (400 MHz, DMSO-d_6, 333K) δ 6.89 (s, 1H), 6.50 (s, 1H), 6.16 (s, 2H), 5.37 – 5.14 (m, 3H), 4.86 – 4.51 (m, 3H), 4.09 – 3.86 (m, 2H), 3.69 – 3.53 (m, 1H), 3.44 – 3.30 (m, 4H), 2.89 (t, J = 7.2 Hz, 1H), 2.64 – 2.56 (m, 1H), 2.41 (s, 3H), 2.05 – 1.64 (m, 8H), 1.53 (s, 3H), 1.37 – 1.27 (m, 6H), 1.09 – 0.95 (m, 9H). (Compound of Formula (a) No. 426) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.58 (s, 1H), 5.84 (s, 2H), 5.32 – 5.18 (m, 2H), 4.91 – 4.52 (m, 5H), 4.14 – 3.90 (m, 3H), 3.59 (d, J = 14.4 Hz, 1H), 3.40 – 3.32 (m, 2H), 3.27 – 3.16 (m, 2H), 3.11 – 2.93 (m, 2H), 2.64 – 2.55 (m, 2H), 2.43 – 2.23 (m, 5H), 2.03 – 1.95 (m, 2H), 1.92 – 1.85 (m, 2H), 1.83 – 1.79 (m, 2H), 1.77 – 1.67 (m, 2H), 1.55 – 1.46 (m, 3H), 1.33 – 1.26 (m, 3H), 1.04 – 0.94 (m, 3H). (Compound of Formula (a) No. 428) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.59 (s, 1H), 5.85 (s, 2H), 5.35 – 5.20 (m, 2H), 4.90 – 4.50 (m, 3H), 4.24 (s, 2H), 4.15 – 3.85 (m, 1H), 3.45 – 3.35 (m, 2H), 3.30 – 3.17 (m, 1H), 3.12 – 3.00 (m, 2H), 2.78 (d, J = 11.6 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.35 – 2.32 (m, 3H), 2.11 – 1.92 (m, 4H), 1.88 – 1.64 (m, 7H), 1.57 – 1.43 (m, 5H), 1.31 (t, J = 7.2 Hz, 3H), 1.03 – 0.97 (m, 3H). (Compound of Formula (a) No. 429) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.80 (s, 2H), 6.48 (s, 1H), 5.36 – 5.11 (m, 2H), 4.87 – 4.53 (m, 3H), 4.25 – 4.14 (m, 2H), 3.99 – 3.88 (m, 1H), 3.42 – 3.41 (m, 1H), 3.25 – 3.18 (m, 1H), 3.13 – 3.01 (m, 2H), 2.76 – 2.70 (m, 1H), 2.57 – 2.53 (m, 1H), 2.35 (s, 3H), 2.11 – 1.46 (m, 18H), 1.35 – 1.24 (m, 3H), 1.08 – 0.90 (m, 3H). (Compound of Formula (a) No. 430) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.86 (s, 1H), 6.63 – 6.18 (m, 3H), 5.43 – 5.06 (m, 3H), 4.93 – 4.38 (m, 3H), 4.19 – 3.85 (m, 2H), 3.48 – 3.36 (m, 2H), 3.27 – 2.96 (m, 2H), 2.94 – 2.83 (m, 1H), 2.70 – 2.61 (m, 1H), 2.45 – 2.32 (m, 4H), 2.05 – 1.64 (m, 8H), 1.60 – 1.46 (m, 3H), 1.39 – 1.18 (m, 6H), 1.09 – 0.83 (m, 3H), 0.53 – 0.23 (m, 4H). (Compound of Formula (a) No. 434) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.79 (s, 2H), 6.48 (s, 1H), 5.40 – 5.14 (m, 3H), 4.89 – 4.45 (m, 3H), 4.15 – 3.88 (m, 1H), 3.86 – 3.77 (m, 1H), 3.46 – 3.36 (m, 2H), 3.26 – 3.00 (m, 4H), 2.95 – 2.84 (m, 1H), 2.65 – 2.58 (m, 1H), 2.24 – 2.29 (m, 7H), 2.06 – 1.61 (m, 8H), 1.58 – 1.44 (m, 3H), 1.38 – 1.21 (m, 6H), 1.07 –0.89 (m, 3H). (Compound of Formula (a) No. 435) ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.03 - 7.89 (m, 1H), 7.52 – 7.42 (m, 1H), 7.38 (s, 1H), 7.23 - 7.06 (m, 1H), 5.61 - 5.48 (m, 1H), 5.36 (d, J = 53.6 Hz, 1H), 5.07 - 4.45 (m, 5H), 4.20 - 4.08 (m, 2H), 4.05 - 3.95 (m, 2H), 3.64 - 3.50 (m, 2H), 3.23 - 3.05 (m, 3H), 3.03 (s, 1H), 2.90 - 2.77 (m, 1H), 2.14 (s, 1H), 2.10-1.91(m, 4H), 1.90 - 1.70 (m, 5H), 1.56 – 1.43 (m, 3H), 1.34 - 1.22 (m, 3H). (Compound of Formula (a) No. 436) ^{1}H-NMR (400 MHz, DMSO-d_6) δ 6.61 (s, 1H), 6.00 (s, 2H), 5.56-5.47 (m, 1H), 5.29 (d, J = 52.8 Hz, 1H), 5.13 (d, J = 13.2 Hz, 1H), 4.74 (s, 1H), 4.52-4.37 (m, 1H), 4.17-4.05 (m, 2H), 3.85 – 3.72 (m, 1H), 3.37-3.33 (m, 1H), 3.27-3.17 (m, 1H), 3.15-2.96 (m, 4H), 2.94-2.80 (m, 2H), 2.77-2.66 (m, 1H), 2.33 (s, 3H), 2.21-1.99 (m, 4H), 1.91-1.76 (m, 4H), 1.71-1.53 (m, 5H), 1.49 (d, J = 6.8 Hz, 2H), 1.21-0.97 (m, 5H). (Compound of Formula (a) No. 437) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.80 (s, 2H), 6.54 – 6.09 (m, 2H), 5.46 – 5.16 (m, 2H), 4.86 – 4.32 (m, 5H), 4.16 – 3.86 (m, 1H), 3.49 – 3.38 (m, 2H), 3.25 – 3.06 (m, 1H), 2.91 – 2.79 (m, 2H), 2.35 (s, 3H), 2.14 – 1.62 (m, 14H), 1.57 – 1.46 (m, 3H), 1.34 – 1.25 (m, 3H), 1.13 (s, 3H), 1.03 – 0.92 (m, 3H). (Compound of Formula (a) No. 438) ^{1}H NMR (400 MHz, DMSO-d6) δ 6.80 (s, 2H), 6.49 (s, 1H), 5.43 – 5.14 (m, 2H), 4.86 – 4.48 (m, 3H), 4.38 – 4.22 (m, 2H), 4.14 – 3.86 (m, 1H), 3.30 – 2.98 (m, 2H), 2.48 – 2.26 (m, 9H), 2.13 – 1.64 (m, 7H), 1.60 – 1.41 (m, 7H), 1.34 – 1.29 (m, 3H), 1.24 – 1.13 (m, 2H), 1.07 – 0.92 (m, 3H), 0.66 (s, 2H), 0.44 (s, 2H). (Compound of Formula (a) No. 449) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.86 (s, 1H), 6.52-6.25 (m, 3H), 5.36 – 5.17 (m, 3H), 4.85 – 4.50 (m, 3H), 4.11-3.82 (m, 2H), 3.43-3.37 (m, 2H), 3.20-3.16 (m, 3H), 2.89 (s, 1H), 2.68-2.59 (m, 1H), 2.45 -2.33 (m, 4H), 1.99 – 1.71 (m, 9H), 1.56 – 1.48 (m, 3H),1.31-1.27 (m, 6H), 1.08 – 0.91 (m, 3H). (Compound of Formula (a) No. 458) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7. 84 - 7.71(m, 1H), 7. 39 - 7.26(m, lH), 7. 71- 6.91(m, 2H), 5.63 (d, J = 11.2 Hz, 2H), 5.40 – 5.18 (m, 3H), 4.85 - 4.52 (m, 3H), 4.23 - 4.07 (m, 1H), 3.94 l– 3.29 (m, 2H), 3.47 - 3.43 (m, 1H), 3.28 – 3.19 (m, 1H), 3.18 –

3.11 (m, 3H) 2.93 - 2.85 (m, 1H), 2.65 - 2.60 (m, 1H), 2.45 – 2.31 (m, 4H), 2.10 – 1.64 (m, 9H), 1.59 – 1.45 (m, 3H), 1.36 - 1.24 (m, 6H), 1.07 - 0.94 (m, 3H). (Compound of Formula (a) No. 462) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.87 (s, 1H), 6.58 – 6.26 (m, 3H), 5.46 – 5.17 (m, 3H), 4.90 – 4.31 (m, 5H), 4.15 – 3.85 (m, 1H), 3.47 – 3.39 (m, 2H), 3.30 – 3.18 (m, 1H), 3.10 – 2.65 (m, 3H), 2.35 – 2.24 (m, 4H), 2.06 – 1.69 (m, 6H), 1.59 – 1.46 (m, 3H), 1.33 – 1.26 (m, 3H), 1.20 (s, 3H), 1.05 – 0.93 (m, 3H). (Compound of Formula (a) No. 464) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.61 -6.45 (m, 1H), 6.01 (s, 2H), 5.90 – 5.13 (m, 3H), 4.84 – 4.65 (m, 2H), 4.60 – 4.47 (m, 1H), 4.12 – 3.86 (m, 2H), 3.44 – 3.40 (m, 1H), 3.25 – 3.16 (m, 2H), 3.10 – 2.81 (m, 2H), 2.65 (s, 1H), 2.45 – 2.25 (m, 7H), 2.02 – 1.69 (m, 8H), 1.58 – 1.45 (m, 3H), 1.35 – 1.25 (m, 6H), 1.06 – 0.92 (m, 3H), 0.49 – 0.28 (m, 4H). (Compound of Formula (a) No. 465) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.73 – 6.33 (m, 1H), 6.02 (s, 2H), 5.41 – 5.13 (m, 3H), 4.89 – 4.45 (m, 3H), 4.17 – 3.80 (m, 1H), 3.27 – 2.95 (m, 4H), 2.61 – 2.53 (m, 1H), 2.40 (s, 3H), 2.32 (s, 3H), 2.07 – 1.41 (m, 12H), 1.37 – 1.25 (m, 6H), 1.06 – 0.91 (m, 3H), 0.73 – 0.60 (m, 1H), 0.20 – 0.07 (m, 1H). (Compound of Formula (a) No. 471) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.62 (d, J = 8.0 Hz, 1H), 6.30 (s, 2H), 5.52 – 5.41 (m, 1H), 5.38 – 5.18 (m, 2H), 4.86 – 4.49 (m, 3H), 4.23 – 3.88 (m, 3H), 3.42 - 3.20 (m, 2H), 3.26 – 3.16 (m, 1H), 3.13 - 2.96 (m, 3H), 2.89 – 2.79 (m, 1H), 2.20 – 2.04 (m, 2H), 2.04 – 1.97 (m, 2H), 1.97 - 1.86 (m, 2H), 1.86 – 1.71 (m, 4H), 1.51 (s, 6H), 1.33 – 1.44 (m, 3H). (Compound of Formula (a) No. 472) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.86 (s, 1H), 6.57 – 6.21 (m, 3H), 6.61 – 6.54 (m, 1H), 5.42 – 5.12 (m, 2H), 4.86 – 4.45 (m, 3H), 4.16 – 3.81(m, 1H), 3.48 – 3.36 (m, 2H), 3.31 – 2.99 (m, 2H), 2.25 – 2.12 (m, 6H), 2.07 – 1.48 (m, 16H), 1.33 – 1.23 (m, 6H), 1.04 – 0.91 (m, 3H). (Compound of Formula (a) No. 474) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.69 – 6.38 (m, 1H), 6.02 (s, 2H), 5.65 – 5.62 (m, 1H), 5.38 – 5.27 (m, 1H), 5.23 – 5.13 (m, 1H), 4.85 – 4.63 (m, 3H), 4.14 – 3.82 (m, 1H), 3.47 – 3.37 (m, 2H), 3.25 – 3.11(m, 1H), 2.32 (s, 3H), 2.26 – 2.18 (m, 6H), 2.02 – 1.68 (m, 10H), 1.58- 1.47 (m, 4H), 1.32 – 1.23 (m, 9H), 1.02 – 0.93 (m, 3H).(Compound of Formula (a) No. 475) ^{1}H NMR (400 MHz, DMSO- d_6) δ 6.59 (s, 1H), 5.85 (s, 2H), 5.38 – 5.19 (m, 3H), 4.85 – 4.55 (m, 3H), 4.20 – 3.94 (m, 3H), 3.41 – 3.34 (m, 2H), 3.28 – 3.17 (m, 1H), 3.13 – 2.97 (m, 3H), 2.89 – 2.81 (m, 1H), 2.33 (s, 3H), 2.24 – 1.95 (m, 5H), 1.93 – 1.77 (m, 7H), 1.56 – 1.48 (m, 3H), 1.31 (t, J = 7.6 Hz, 3H), 1.03 – 0.97 (m, 3H). (Compound of Formula (a) No. 481) ^{1}H NMR (400 MHz, DMSO-d_6, 333K) δ 6.87 (s, 1H), 6.82 – 6.34 (m, 2H), 6.16 (s, 2H), 5.40 – 5.16 (m, 2H), 4.91 – 4.48 (m, 4H), 4.36 (d, J = 10.4 Hz, 1H), 4.20 – 3.85 (m, 1H), 3.44 – 3.32 (m, 2H), 3.27 – 3.18 (m, 1H), 2.82 – 2.69 (m, 2H), 2.59 – 2.51 (m, 1H), 2.38 – 2.17 (m, 3H), 2.13 – 1.67 (m, 8H), 1.58 – 1.43 (m, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.13 (s, 3H), 1.06 – 0.91 (m, 6H). (Compound of Formula (a) No. 487) ^{1}H NMR (400 MHz, DMSO-d_6, 333K) δ 6.92 – 6.84 (m, 1H), 6.83 – 6.38 (m, 2H), 6.15 (d, 2H), 5.40 – 5.14 (m, 3H), 4.88 – 4.47 (m, 4H), 4.16 – 3.85 (m, 1H), 3.43 – 3.32 (m, 2H), 3.29 – 3.18 (m, 1H), 3.02 – 2.92 (m, 1H), 2.83 – 2.74 (m, 1H), 2.48 – 2.40 (m, 4H), 2.12 – 1.67 (m, 8H), 1.62 – 1.45 (m, 3H), 1.40 – 1.27 (m, 6H), 1.06 – 0.90 (m, 3H). (Compound of Formula (a) No. 490) ^{1}H NMR (DMSO- d_6, 400 MHz) δ 6.87 (d, J = 1.2 Hz, 1H), 6.56 – 6.40 (m, 1H), 6.16 (s, 2H), 5.50 – 5.42 (m, 1H), 5.37 – 5.19 (m, 2H), 4.81 – 4.53 (m, 3H), 4.19 – 3.91 (m, 3H), 3.10 – 2.81 (m, 6H), 2.23 – 1.73 (m, 10H), 1.52 (s, 6H), 1.18 – 1.04 (m, 4H). (Compound of Formula (a) No. 496) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.59 (s, 1H), 5.85 (s, 2H), 5.36 – 5.20 (m, 2H), 4.85 – 4.37 (m, 4H), 4.24 – 4.17 (m, 1H), 4.11 – 3.90 (m, 1H), 3.40 – 3.34 (m, 2H), 3.21 – 3.18 (m, 2H), 3.12 – 3.10 (m, 1H), 2.68 – 2.62 (m, 1H), 2.33 (s, 3H), 2.25 – 2.18 (m, 4H), 2.08 – 1.77 (m, 8H), 1.63 – 1.49 (m, 10H), 1.31 (t, J = 7.2 Hz, 3H), 1.02 – 0.95 (m, 3H). (Compound of Formula (a) No. 497) ^{1}H NMR (400 MHz, DMSO-d_6, 333K) δ 6.96 – 6.63 (m, 2H), 6.49 (s, 1H), 6.16 (s, 2H), 5.39 – 5.14 (m, 3H), 4.87 – 4.47 (m, 3H), 4.19 – 3.84 (m, 1H), 3.71 (s, 1H), 3.42 – 3.32 (m, 2H), 3.24 – 3.17 (m, 1H), 3.13 – 3.09 (m, 1H), 3.04 – 2.90 (m, 1H), 2.48 – 2.43 (m, 1H), 2.38 – 2.14 (m, 3H), 2.08 – 1.66 (m, 6H), 1.65 – 1.43 (m, 3H), 1.36– 1.27 (m, 6H), 1.09 – 0.94 (m, 6H). (Compound of Formula (a) No. 503) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.10 – 7.08 (d, J = 8 Hz, 1H), 6.61 –

6.36 (d, J = 16 Hz, 2H), 5.42 – 5.08 (m, 3H), 4.87 – 4.50 (m, 3H), 4.19 – 3.85 (m, 3H), 3.48 – 3.40 (m, 2H), 3.26 – 3.01 (m, 4H), 2.89 – 2.78 (m, 1H), 2.17 – 1.70 (m, 12H), 1.60 – 1.46 (m, 3H), 1.38 – 1.25 (m,3H), 1.07 – 0.91 (m, 3H). (Compound of Formula (a) No. 506) ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.87 – 6.86 (d, J = 4Hz, 1H), 6.63 – 6.18 (m, 3H), 5.43 – 5.06 (m, 3H), 4.90 – 4.43 (m, 3H), 4.14 – 3.85 (m, 2H), 3.48 – 3.36 (m, 2H), 3.27 – 3.06 (m, 2H), 3.03 – 2.83 (m, 3H), 2.45 – 2.28 (m,2H), 2.05 – 1.64 (m, 8H), 1.60 – 1.46 (m, 3H), 1.39 – 1.24 (m, 6H), 1.06 – 0.96 (m, 6H), 0.48 – 0.23 (m, 4H). (Compound of Formula (a) No. 507) ^{1}H NMR (400 MHz, DMSO-d_6, 333K) δ 6.94 – 6.77 (m, 1H), 6.59 – 6.10 (m, 4H), 5.39 – 5.20 (m, 2H), 4.87 – 4.43 (m, 5H), 4.12 – 3.88 (m, 1H), 3.44 – 3.33 (m, 2H), 3.31 – 3.19 (m, 1H), 2.92 – 2.75 (m, 2H), 2.18 – 1.63 (m, 14H), 1.58 – 1.45 (m, 3H), 1.35 – 1.28 (m, 3H), 1.13 (s, 3H), 1.05 – 0.93 (m, 3H). (Compound of Formula (a) No. 508) ^{1}H-NMR (400 MHz, DMSO-d_6, 60°C) δ 6.58 (s, 1H), 5.84 (s, 2H), 5.28 – 5.21 (m, 2H), 4.76 (s, 1H), 4.66 – 4.57 (m, 2H), 4.34 (s, 2H), 3.94 (s, 1H), 3.68 (d, J = 10 Hz, 1H), 3.45 – 3.31 (m, 4H), 3.18 (s, 1H), 2.76 (dd, J_1 = 10.8 Hz, J_2 = 11.2 Hz, 2H), 2.32 (s, 5H), 2.02 – 1.66 (m, 8H), 1.52 (s, 3H), 1.31 (t, J = 7.6 Hz, 3H), 1.02-0.99 (m, 6H), 0.65 (s, 2H), 0.43 (s, 2H).

[573] **Example 2**: Ras sequences

[574] Human K-Ras Wildtype sequence (SEQ ID NO. 1)

1 MTEYKLVVVG AGGVGKSALT IQLIQNHFVD EYDPTIEDSY RKQVVIDGET
51 CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC VFAINNTKSF EDIHHYREQI
101 KRVKDSEDVP MVLVGNKCDL PSRTVDTKQA QDLARSYGIP FIETSAKTRQ
151 GVDDAFYTLV REIRKHKEKM SKDGKKKKKK SKTKCVIM

[575] Human K-Ras G12D (SEQ ID NO. 2)

1 MTEYKLVVVG ADGVGKSALT IQLIQNHFVD EYDPTIEDSY RKQVVIDGET
51 CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC VFAINNTKSF EDIHHYREQI
101 KRVKDSEDVP MVLVGNKCDL PSRTVDTKQA QDLARSYGIP FIETSAKTRQ
151 GVDDAFYTLV REIRKHKEKM SKDGKKKKKK SKTKCVIM

[576] Human K-Ras G12V (SEQ ID NO. 3)

1 MTEYKLVVVG AVGVGKSALT IQLIQNHFVD EYDPTIEDSY RKQVVIDGET
51 CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC VFAINNTKSF EDIHHYREQI
101 KRVKDSEDVP MVLVGNKCDL PSRTVDTKQA QDLARSYGIP FIETSAKTRQ
151 GVDDAFYTLV REIRKHKEKM SKDGKKKKKK SKTKCVIM

[577] Human K-Ras G12S (SEQ ID NO. 4):

1 MTEYKLVVVG ASGVGKSALT IQLIQNHFVD EYDPTIEDSY RKQVVIDGET
51 CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC VFAINNTKSF EDIHHYREQI
101 KRVKDSEDVP MVLVGNKCDL PSRTVDTKQA QDLARSYGIP FIETSAKTRQ
151 GVDDAFYTLV REIRKHKEKM SKDGKKKKKK SKTKCVIM

[578] Human N-Ras wildtype (SEQ ID NO. 5)

1 MTEYKLVVVG AGGVGKSALT IQLIQNHFVD EYDPTIEDSY RKQVVIDGET
51 CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC VFAINNSKSF ADINLYREQI
101 KRVKDSDDVP MVLVGNKCDL PTRTVDTKQA HELAKSYGIP FIETSAKTRQ
151 GVEDAFYTLV REIRQYRMKK LNSSDDGTQG CMGLPCVVM

[579] H-Ras G12D (SEQ ID NO. 6)

1 MTEYKLVVVG ADGVGKSALT IQLIQNHFVD EYDPTIEDSY RKQVVIDGET
51 CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC VFAINNTKSF EDIHQYREQI

101 KRVKDSDDVP MVLVGNKCDL AARTVESRQA QDLARSYGIP YIETSAKTRQ

151 GVEDAFYTLV REIRQHKLRK LNPPDESGPG CMSCKCVLS

[580] H-Ras wildtype (SEQ ID NO. 7)

1 MTEYKLVVVG AGGVGKSALT IQLIQNHFVD EYDPTIEDSY RKQVVIDGET

51 CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC VFAINNTKSF EDIHQYREQI

101 KRVKDSDDVP MVLVGNKCDL AARTVESRQA QDLARSYGIP YIETSAKTRQ

151 GVEDAFYTLV REIRQHKLRK LNPPDESGPG CMSCKCVLS

[581] Human N-Ras G12D (SEQ ID NO. 8)

1 MTEYKLVVVG ADGVGKSALT IQLIQNHFVD EYDPTIEDSY RKQVVIDGET

51 CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC VFAINNSKSF ADINLYREQI

101 KRVKDSDDVP MVLVGNKCDL PTRTVDTKQA HELAKSYGIP FIETSAKTRQ

151 GVEDAFYTLV REIRQYRMKK LNSSDDGTQG CMGLPCVVM

[582] Human K-Ras G12C (SEQ ID NO. 9)

1 MTEYKLVVVG ACGVGKSALT IQLIQNHFVD EYDPTIEDSY RKQVVIDGET

51 CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC VFAINNTKSF EDIHHYREQI

101 KRVKDSEDVP MVLVGNKCDL PSRTVDTKQA QDLARSYGIP FIETSAKTRQ

151 GVDDAFYTLV REIRKHKEKM SKDGKKKKKK SKTKCVIM

[583] **Example 3**: Protein expression

[584] DNA expression constructs encoding one or more protein sequences of interest (e.g., KRAS fragments thereof, mutant variants thereof, etc.) and its corresponding DNA sequences are optimized for expression in E. coli and synthesized by, for example, the GeneArt Technology at Life Technologies. In some cases, the protein sequences of interest are fused with a tag (e.g., glutathione S-transferase (GST), histidine (His), or any other affinity tags) to facilitate recombinant expression and purification of the protein of interest. Such tag can be cleaved subsequent to purification. Alternatively, such tag may remain intact to the protein of interest and may not interfere with activities (e.g., target binding and/or phosphorylation) of the protein of interest

[585] A resulting expression construct is additionally encoded with (i) att-site sequences at the 5' and 3' ends for subcloning into various destination vectors using, for example, the Gateway Technology, as well as (ii) a Tobacco Etch Virus (TEV) protease site for proteolytic cleavage of one or more tag sequences. The applied destination vectors can be a pET vector series from Novagen (e.g., with ampicillin resistance gene), which provides an N-terminal fusion of a GST-tag to the integrated gene of interest and/or a pET vector series (e.g., with ampicillin resistance gene), which provides an N-terminal fusion of a HIS-tag to the integrated gene. To generate the final expression vectors, the expression construct of the protein of interest is cloned into any of the applied destination vectors. The expression vectors are transformed into an E. coli strain, e.g., BL21 (DE3). Cultivation of the transformed strains for expression is performed in a 10 L or 1 L fermenter. The cultures are grown, for example, in Terrific Broth media (MP Biomedicals, Kat. #1 13045032) with 200 μg/mL ampicillin at a temperature of 37 °C to a density of 0.6 (OD600), shifted to a temperature of ~27 °C (for K-Ras expression vectors) induced for expression with 100 mM IPTG, and further cultivated for 24 hours. After cultivation, the transformed E. coli cells are harvested by centrifugation and the resulting pellet is suspended in a lysis buffer, as provided below, and lysed by passing three-times through a high-pressure device. The lysate is centrifuged (49000g, 45 min, 4 °C) and the supernatant is used for further purification.

[586] **Example 4**: Ras protein purification

[587] A Ras (e.g., K-Ras wildtype or a mutant such as K-Ras G12S, K-Ras G12D, K-Ras G12V or K-Ras G12C) construct or a variant thereof is tagged with GST. E. coli culture from a 10L fermenter is lysed in lysis buffer (50 mM Tris HCl 7.5, 500 mM NaCl, 1 mM DTT, 0.5% CHAPS, Complete Protease Inhibitor Cocktail-(Roche)). As a first chromatography step, the centrifuged lysate is incubated with 50 mL Glutathione Agarose 4B (Macherey-Nagel; 745500.100) in a spinner flask (16 h, 10 °C). The Glutathione Agarose 4B loaded with protein is transferred to a chromatography column connected to a chromatography system, e.g., an Akta chromatography system. The column is washed with wash buffer (50 mM Tris HCl 7.5, 500 mM NaCl, 1 mM DTT) and the bound protein is eluted with elution buffer (50 mM Tris HCl 7.5, 500 mM NaCl, 1 mM DTT, 15 mM glutathione). The main fractions of the elution peak (monitored by OD280) are pooled. For further purification by size-exclusion chromatography, the above eluate volume is applied to a column Superdex 200 HR prep grade (GE Healthcare) and the resulting peak fractions of the eluted fusion protein is collected. Native mass spectrometry analyses of the final purified protein construct can be performed to assess its homogeneous load with GDP.

[588] **Example 5**: HTRF (homogenous time-resolved fluorescence) resonance energy transfer assay

[589] The ability of a compound of the present disclosure to reduce Ras signaling output can be demonstrated by an HTRF assay. This assay can be also used to assess a selective inhibition or reduction of signaling output of a mutant Ras protein relative to a wildtype, or relative to a different mutant Ras protein. For example, the equilibrium interaction of wildtype KRAS or K-Ras mutant (e.g., wildtype or a mutant thereof) with SOS1 (e.g., hSOS1) can be assessed as a proxy or an indication for the ability of a subject compound to bind and inhibit Ras protein. The HTRF assay detects from (i) a fluorescence resonance energy transfer (FRET) donor (e.g., antiGST-Europium) that is bound to GST-tagged K-Ras mutant to (ii) a FRET acceptor (e.g., anti-6His-XL665) bound to a His-tagged hSOS1.

[590] The assay buffer can contain ~5 mM HEPES pH 7.4, ~150 mM NaCl, ~ 1 mM DTT, 0.05% BSA and 0.0025% (v/v) Igepal. A Ras working solution is prepared in an assay buffer containing typically a suitable amount of the protein construct (e.g., GST-tagged K-Ras mutant) and the FRET donor (e.g., antiGST-Eu(K) from Cisbio, France). A SOS1 working solution is prepared in an assay buffer containing suitable amount of the protein construct (e.g., His-hSOS1) and the FRET acceptor (e.g., anti-6His-XL665 from Cisbio, France). A suitable amount of the protein construct will depend on the range of activity or range of IC50 values being detected or under investigation. For detecting an IC50 within a range of 500 nM, the protein constructs of the same range of molarity can be utilized. An inhibitor control solution is prepared in an assay buffer containing a comparable amount of the FRET acceptor without the SOS1 protein.

[591] A fixed volume of DMSO with or without test compound is transferred into a 384-well plate. Ras working solution is added to all wells of the test plate. SOS1 working solution is added to all wells except for those that are subsequently filled with inhibitor control solution. Upon incubation for about 10 minutes or longer, the fluorescence is measured with a M1000Pro plate reader (Tecan) using HTRF detection (excitation 337 nm, emission 1: 620 nm, emission 2: 665 nm). Compounds are tested in duplicate at different concentrations (for example, 10 μM, 2.5 μM, 0.63 μM, 0.16 μM, 0.04 μM, 0.01 μM test compound). The ratiometric data (i.e., emission 2 divided by emission 1) is used to calculate IC50 values against Ras using GraphPad Prism (GraphPad software). Signaling output measured in terms of IC50 values can be obtained and a ratio of IC50 against one mutant relative to another mutant can be calculated. For instance, a selective reduction of K-Ras G12D signaling output can be evidenced by a ratio greater than one. In particular, a selective reduction of K-Ras G12D signaling relative to K-Ras WT signaling is evidenced if the ratio of IC50 (against K-Ras WT) to IC50 (against K-Ras G12D) is greater than 1. In some embodiments, one or more subject compounds disclosed herein are expected to exhibit selective inhibition of a Ras mutant (e.g.,

G12D) over WT by at least 1-fold, and in some instances greater than 2-, 3-, 4- or 5-fold. In some embodiments, subject compounds are expected to exhibit an IC50 against KRas mutants (e.g., G12D) less than 500 nM, such as less than 100 nM, 50 nM, or even less.

[592] The ability of one or more compounds exemplified in Table 1 to inhibit wildtype KRAS or a KRAS mutant is demonstrated utilizing the procedures described above. Described below are the resulting IC50 values of exemplary compounds against KRAS G12S, KRAS G12D, and wildtype KRAS using the HTRF assay described herein. Compound numbers correspond to the numbers and structures provided in **Table 1** and **Example 1**.

[593] The following compounds inhibit KRas G12S with an IC50 value of less than 1000 nM: 301, 302, 304, 305, 306, 307, 308, 309, 310, 311, 312, 314, 315, 317, 318, 319, 320, 322, 323, 324, 325, 326, 328, 329, 330, 331, 332, 333, 334, 335, 336, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 366, 367, 369, 370, 371, 372, 373, 374, 375, 375A, 376, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 393, 395, 396, 397, 398, 399, 400, 401, 402, 403, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 417, 418, 419, 420, 421, 422, 423, 424, 426, 427, 428, 429, 430, 431, 432, 433, 434, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 454, 455, 456, 457, 458, 459, 460, 462, 463, 464, 465, 466, 468, 469, 470, 471, 472, 473, 474, 475, 476, 479, 481, 483, 484, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 500A, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 510A, 511, and 511A. The following compounds inhibit KRas G12S with an IC50 value greater than or equal to 1000 nM and less than 5 micromolar: 303, 321, 348, 365, 368, 377, 416, 452, 453, 461, 467, 477, 478, and 480. The following compounds inhibit KRas G12D with an IC50 value of less than 1000 nM: 302, 304, 305, 306, 307, 308, 309, 310, 312, 314, 315, 317, 318, 319, 320, 322, 323, 324, 325, 326, 328, 329, 330, 331, 332, 333, 334, 335, 336, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 365, 366, 367, 369, 370, 371, 372, 373, 374, 375, 375A, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 393, 395, 396, 397, 398, 399, 400, 401, 402, 403, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 417, 418, 419, 420, 421, 422, 423, 424, 426, 427, 428, 429, 430, 431, 432, 433, 434, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 454, 455, 456, 457, 458, 459, 460, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 479, 481, 483, 484, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 500A, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 510A, 511, and 511A. The following compounds inhibit KRas G12D with an IC50 value greater than or equal to 1000 nM and less than 5 micromolar: 301, 303, 311, 321, 368, 452, 453, 461, 478, and 480. The following compounds inhibit KRas WT protein with an IC50 value of less than 1000 nM: 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 314, 315, 317, 318, 319, 320, 322, 323, 324, 325, 326, 328, 329, 330, 331, 332, 333, 334, 335, 336, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 375A, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 393, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 416, 417, 418, 419, 420, 421, 422, 423, 424, 426, 427, 428, 429, 430, 431, 432, 433, 434, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 479, 480, 481, 483, 484, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 500A, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 510A, 511, and 511A. The following compounds inhibit KRas WT protein with an IC50 value greater than or equal to 1000 nM and less than 5 micromolar: 321, 392, and 478.

[594] **Example 6**: GTPase activity assay

[595] The ability of a compound of the present disclosure to inhibit Ras protein signaling can be demonstrated by a reduced GTPase activity. This assay can also be used to assess selective inhibition of a mutant Ras protein relative to a wildtype or different mutant Ras protein. For instance, the assay can be used to establish a subject compound's ability to selectively inhibit KRAS G12D relative to wildtype, KRAS G12D relative to KRAS G12V, KRAS G12D relative to KRAS G12S, KRAS G12C relative to KRAS G12S, or KRAS G12C relative to KRAS G12V or wildtype. In particular, intrinsic and GTPase-activating protein (GAP)-stimulated GTPase activity for a K-Ras construct or a mutant thereof can be measured using EnzCheck phosphate assay system (Life Technologies). For example, K-Ras WT, K-Ras D154Q mutant, K-Ras G12D mutant, K-Ras G12S mutant, and K-Ras G12D/D154Q mutant proteins (2.5 mg/mL) in buffer (20 mmol/L Tris, pH 8.0, 50 mM NaCl) are loaded with GTP at room temperature for 2 hours by exposing to exchange buffer containing EDTA. Proteins are buffer exchanged to assay buffer (30 mM Tris, pH 7.5, 1 mM DTT) and the concentration is adjusted to 2 mg/mL. GTP loading is verified by back extraction of nucleotide using 6M urea and evaluation of nucleotide peaks by HPLC using an ion-exchange column. The assay is performed in a clear 384-well plate (Costar) by combining GTP-loaded K-Ras proteins (50 mM final) with 2-amino-6-mercapto-7-methylpurine ribonucleoside (MESG) (200 mM final), and purine nucleotide phosphorylase (5 U/mL final). GTP hydrolysis is initiated by the addition of $MgCl_2$ at a working concentration of 40 mM. For GAP stimulation, Ras p21 protein activator 1 (P120GAP) can be included at 50 mM. Absorbance at 360 nm can be measured every 8 to 15 s for 1,000 s at 20 °C. Samples are tested with or without a subject compound disclosed herein to assess the ability of each compound to inhibit signaling of a given Ras protein (e.g., a given mutant KRAS) of interest.

[596] **Example 7**: Nucleotide exchange assay

[597] The ability of a compound of the present disclosure to inhibit Ras protein signaling can be demonstrated by reduced nucleotide exchange activity. This assay can be also used to assess selective inhibition of a mutant Ras protein relative to a wildtype or different mutant Ras protein. For example, 250 nM or 500 nM GDP-loaded K-Ras protein (e.g., wildtype or a mutant thereof, including those mentioned in Example 4) is incubated with different concentrations of compounds (for example ~60 μM, ~20 μM, ~6.7 μM, ~2.2 μM, ~0.7 μM, or ~0.2 μM subject compound). A control reaction without subject compound is also included. SOS1 (catalytic domain) protein is added to the K-Ras protein solution. The nucleotide exchange reaction is initiated by adding fluorescent labelled GDP (guanosine 5'-diphosphate, BODIPY™ FL 2'-(or-3')-O-(N-(2-aminoethyl)urethane) to a final concentration of 0.36 μM. Fluorescence is measured every 30 s for 70 minutes at 490nm/515nm (excitation/emission) in a M1000Pro plate reader (Tecan). Data is exported and analyzed to calculate an IC50 using GraphPad Prism (GraphPad Software). Sample(s) can be tested with or without a subject compound disclosed herein to assess the ability of the compound to inhibit K-Ras signaling or its IC50 against a given Ras protein (e.g., a given mutant K-Ras) of interest.

[598] **Example 8**: Testing for modification of Ras protein via covalent binding

[599] Test compounds are prepared as 10 mM stock solutions in DMSO (Fisher cat#BP231-100). KRAS protein (His-tagged GDP-loaded wildtype 1-169, His-tagged GDP-loaded G12S 1-169 or His-tagged GDP-loaded G12D 1-169) is diluted to ~2 μM in appropriate buffer (e.g., a Hepes buffer at physiological conditions). For testing KRAS modification, compounds are diluted to 50X final test concentration in DMSO in 96-well storage plates. 2 μL of the diluted 50X compounds are added to appropriate wells in the PCR plate (Fisher cat#AB-0800). ~49 μL of the stock protein solution is added to each well of the 96-well PCR plate. Reactions are mixed carefully. The plate is sealed well with aluminum plate seal and stored in a drawer at room temperature for 24 hrs. 5 μL of 2% formic acid (Fisher cat#A117-50) in MilliQ H_2O is then added to each well followed by mixing with a pipette. The plate is then resealed

with aluminum seal and stored until mass spectrometry analysis.

[600] The extent of covalent modification of KRAS proteins can be determined by liquid chromatography electrospray mass spectrometry analysis of the intact proteins on a Thermo Q-Exactive Plus mass spectrometer. 20 μL of sample is injected onto a bioZen 3.6 μm Intact C4 column (Phenomenex cat#00B-4767-AN) placed in a column oven set to 40 °C and separated using a suitable LC gradient from ~20% to ~60% solvent B. Solvent A is 0.1% formic acid and solvent B is 0.1% formic acid in acetonitrile. HESI source settings are set to 40, 5 and 1 for the sheath, auxiliary and sweep gas flow, respectively. The spray voltage is 4 kV, and the capillary temperature is 320 °C. S-lens RF level is 50 and auxiliary gas heater temperature is set to 200 °C. The mass spectrometry is acquired using a scan range from 650 to 1750 m/z using positive polarity at a mass resolution of 70,000, AGC target of 1e6 ions and maximum injection time of 250 ms. The recorded protein mass spectrum is deconvoluted from the raw data file using Protein Deconvolution v4.0 (Thermo). The protein mass and adduct masses are exported with their peak intensities. The peak intensities for the unmodified and modified protein are used to calculate the percent covalent modification of the KRAS protein based on the following equation: %KRAS protein modification = ((KRAS-compound) / (KRAS) + (KRAS-Compound)) *100.

[601] **Example 9**: Ras cellular assay

[602] The ability of a compound of the present disclosure to inhibit Ras protein signaling can be demonstrated by inhibiting growth of a given KRAS mutant cell line. For example, this assay can be also used to assess selective growth inhibition of a mutant Ras protein relative to a wildtype or different mutant Ras protein.

a. Growth of cells with K-Ras G12C mutation

[603] MIA PaCa-2 (ATCC CRL-1420) and NCI-H1792 (ATCC CRL-5895) cell lines comprise a G12C mutation and can be used to assess Ras cellular signaling in vitro, e.g., in response to an inhibitor compound of the present disclosure. This cellular assay can also be used to discern selective inhibition of a subject compound against certain types of KRAS mutants, e.g., more potent inhibition against KRAS G12C relative to KRAS G12D mutant, by comparing inhibition of MIA PaCa-2 (G12C driven tumor cell line) to inhibition of GP2d (G12D driven tumor cell line). MIA PaCa-2 culture medium is prepared with DMEM/Ham's F12 (e.g., with stable glutamine, 10% FCS, and 2.5% horse serum. NCI-H1792 culture medium is prepared with RPMI 1640 (e.g., with stable glutamine) and 10% FCS.

[604] On a first day (e.g., Day 1), Softagar (Select Agar, Invitrogen, 3% in ddH_2O autoclaved) is boiled and tempered at 48 ºC. Appropriate culture medium (i.e., medium) is tempered to 37 ºC. Agar (3%) is diluted 1:5 in medium (=0.6%) and plated into 96 well plates (Corning, #3904), then incubated at room temperature for agar solidification. A 3% agar is diluted to 0.25% in medium (1:12 dilution) and tempered at 42 ºC. Cells are trypsinized, counted, and tempered at 37 ºC. The cells (e.g., MIA PaCa-2 at about 125-150 cells, NCI-H1792 at about 1000 cells) are resuspended in 100 mL 0.25% Agar and plated, followed by incubation at room temperature for agar solidification. The wells are overlaid with 50 mL of the medium. Sister wells in a separate plate are plated for time zero determination. All plates are incubated overnight at 37 ºC and 5% CO_2.

[605] On a second day (e.g., Day 2), time zero values are measured. A 40 mL volume of Cell Titer 96 Aqueous Solution (Promega) is added to each well and incubated in the dark at 37 ºC and 5% CO_2. Absorption can be measured at 490 nm and reference wavelength 660 nm. DMSO-prediluted test compounds are added to wells of interest, e.g., with HP Dispenser, to one or more desired concentrations (e.g., a final DMSO concentration of 0.3%).

[606] On a tenth day (e.g., Day 10), absorption by wells treated with the test compounds and control wells are measured with, for example, Cell Titer 96 AQueous and analyzed in comparison to the time zero measurements. The

IC50 values are determined using the four parameter fit. The resulting IC50 value is a measurement of the ability of the test compound to reduce cell growth of Ras-driven cells (e.g., tumor cell lines) in vitro and/or in vivo. One or more compounds disclosed herein is expected to exhibit an IC50 value less than 5 μM, 1 μM, 100 nM, or even less, against one or more KRAS G12C cell line (including MIA PaCa-2 and NCI-H1792).

b. Growth of cells with K-Ras G12D mutation

[607] ASPC-1 (ATCC CRL-1682), Panc-10.05 (ATCC CRL-2547), A427, and GP2d cell lines, or any other cell lines comprising a G12D mutation, can be used to assess Ras cellular signaling in vitro, e.g., in response to a compound described herein. For example, ASPC-1 culture medium is prepared with RPMI-1640 and 10% heat-inactivated FBS. Panc-10.05 culture medium is prepared with RPMI-1640, 10 units/mL human recombinant insulin, and 10% FBS. A427 cell culture is prepared with RPMI-1640 and 10% heat-inactivated FBS. A CellTiter-Glo (CTG) luminescent based assay (Promega) is used to assess growth of the cells, as a measurement of the ability of the compounds herein to inhibit Ras signaling in the cells. The cells (e.g., 800 per well) are seeded in their respective culture medium in standard tissue culture-treated 384-well format plates (Falcon #08-772-116) or ultra-low attachment surface 384-well format plates (S-Bio # MS-9384UZ). The day after plating, cells are treated with a dilution series (e.g., a 9 point, 3-fold dilution series) of the compounds herein (e.g., approximately 40 μL final volume per well). Cell viability can be monitored (e.g., approximately 5 days later) according to the manufacturer's recommended instructions, where CellTiter-Glo reagent is added (e.g., approximately 10 μL), vigorously mixed, covered, and placed on a plate shaker (e.g., approximately for 20 min) to ensure sufficient cell lysis prior to assessment of luminescent signal. The IC50 values are determined using the four-parameter fit. The resulting IC50 value is a measurement of the ability of the test compound to reduce cell growth of Ras-driven cells (e.g., tumor cell lines) in vitro and/or in vivo. One or more compounds disclosed herein is expected to exhibit an IC50 value less than 5 μM, 1 μM, 100 nM, or even less, against one or more KRAS G12D cell line (including AsPC-1, Panc-10.05, 1427, and GP2d).

c. Growth of cells with K-Ras G12S mutation

[608] A549 (ATCC CRL-185) and LS123 (ATCC CRL-255) cell lines comprise a G12S mutation and can be used to assess Ras cellular signaling in vitro, e.g., in response to treatment with a compound described herein. A549 culture medium is prepared with RPMI-1640 and 10% heat-inactivated FBS. LS123 culture medium is prepared with RPMI-1640 and 10% heat-inactivated FBS. A CellTiter-Glo (CTG) luminescent based assay (Promega) is used to assess growth of the cells, as a measurement of the ability of the compounds herein to inhibit Ras signaling in the cells. The cells (e.g., 800 per well) are seeded in their respective culture medium in standard tissue culture-treated 384-well format plates (Falcon #08-772-116) or ultra-low attachment surface 384-well format plates (S-Bio # MS-9384WZ). The day after plating, cells are treated with a dilution series (e.g., a 10 point, 3-fold dilution series) of the compounds herein (e.g., approximately 40 μL final volume per well). Cell viability can be monitored (e.g., approximately 6 days later) according to the manufacturer's recommended instructions, where CellTiter-Glo reagent is added (e.g., approximately 10 μL), vigorously mixed, covered, and placed on a plate shaker (e.g., approximately for 20 min) to ensure sufficient cell lysis prior to assessment of luminescent signal. The IC50 values are determined using the four parameter fit. The resulting IC50 value is a measurement of the ability of the test compound to reduce cell growth of Ras-driven cells (e.g., tumor cell lines) in vitro and/or in vivo. One or more compounds disclosed herein is expected to exhibit an IC50 value less than 5 μM, 1 μM, 100 nM, or even less, against one or more KRAS G12S cell line (including A549 and LS123).

[609] Below are the resulting IC50 values of exemplary compounds against GP2D cells using the cell

proliferation assays described herein. Compound numbers correspond to the numbers and structures provided in **Table 1** and **Example 1**. The following compounds inhibit GP2d cell growth with an IC50 value of less than 1000 nM: 302, 304, 306, 308, 309, 310, 312, 314, 315, 317, 320, 322, 323, 324, 326, 328, 329, 331, 332, 333, 334, 335, 337, 338, 340, 342, 343, 345, 346, 347, 348, 349, 350, 352, 353, 354, 356, 359, 360, 361, 362, 366, 367, 369, 371, 373, 374, 375, 375A, 378, 379, 380, 381, 383, 385, 386, 387, 388, 389, 390, 391, 393, 396, 398, 399, 400, 401, 402, 403, 405, 406, 407, 408, 409, 412, 413, 414, 417, 419, 420, 422, 424, 426, 427, 428, 429, 430, 431, 432, 433, 434, 436, 437, 438, 439, 440, 441, 443, 444, 445, 446, 448, 449, 450, 451, 454, 455, 456, 457, 458, 459, 460, 462, 463, 464, 465, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 481, 483, 484, 487, 490, 491, 493, 495, 496, 497, 498, 499, 500, 500A, 501, 502, 503, 506, 507, 508, 509, 510, 510A, 511, and 511A. The following compounds inhibit GP2d cell growth with an IC50 value greater than or equal to 1000 nM and less than 5 micromolar: 330, 339, 341, 355, 365, 372, 376, 418, 423, 447, and 479.

[610] **Example 10**: In vivo Ras inhibition

[611] The in vivo reduction in Ras signaling output by a compound of the present disclosure is determined in a mouse tumor xenograft model, particularly by using a mutant K-Ras model including without limitation a K-Ras G12S model, a K-Ras G12C model, a K-Ras G12D model, a K-Ras G13D model, and a K-Ras G13C model. These models can be generated by the methods and procedures described below. In particular, the methods disclosed below involving the use of a K-Ras G12D mutant cell line for generating a K-Ras G12D xenograft model can be applied to other K-Ras mutant animal models using the respective K-Ras mutant cell lines described above.

Xenograft with K-Ras G12D, G12C, or G12S mutation

[612] Tumor xenografts are established by administration of tumor cells with a K-Ras G12D mutation (e.g., ASPC-1 cells), a K-Ras G12C mutation (e.g., MIA PaCa-2 cells), or a K-Ras G12S mutation (e.g., A549 or LS123 cells) into mice. Female 6- to 8-week-old athymic BALB/c nude (NCr) nu/nu mice are used for xenografts. The tumor cells (e.g., approximately $5x10^6$) are harvested on the day of use and injected in growth-factor-reduced Matrigel/PBS (e.g., 50% final concentration in 100 μL). One flank is inoculated subcutaneously per mouse. Mice are monitored daily, weighed twice weekly, and caliper measurements begin when tumors become visible. For efficacy studies, animals are randomly assigned to treatment groups by an algorithm that assigns animals to groups to achieve best case distributions of mean tumor size with lowest possible standard deviation. Tumor volume can be calculated by measuring two perpendicular diameters using the following formula: $(L \times w^2) / 2$, in which L and w refer to the length and width of the tumor, respectively. Percent tumor volume change can be calculated using the following formula: $(V_{final} - V_{initial})/V_{initial} \times 100$. Percent of tumor growth inhibition (%TGI) can be calculated using the following formula: %TGI = 100 x (1 – (average $V_{final} - V_{initial}$ of treatment group) / (average $V_{final} - V_{initial}$ of control group). When tumors reach a threshold average size (e.g., approximately 200-400 mm^3), mice are randomized into 3-10 mice per group and are treated with vehicle (e.g., 100% Labrasol®) or a compound disclosed herein, using, for example, a daily schedule by oral gavage. Results can be expressed as mean and standard deviation of the mean.

[613] **Example 11**: Rat Oral Exposure (F)

[614] A pharmacokinetic profile for a test compound is measured by single dosing in jugular vein cannulated male Sprague-Dawley rats. Animal weights are typically over 200 grams, and animals are allowed to acclimate to their new environment for at least 3 days prior to the initiation of any studies. One set of animals is dosed intravenously (IV) with test compound (2 mg/kg in 20% HP-beta-CD or 20% Captisol, pH adjusted to above 4 by citric acid). The IV dosing solution concentration is 0.4 mg/mL test compound. Blood is sampled at 5 minutes, 15

minutes, 30 minutes, 90 minutes, 360 minutes, and 24 hours following IV dosing. Another set of animals is dosed oral (PO) with test compound (10 mg/kg in 20% HP-beta-CD or 20% Captisol, pH adjusted to ~4 by citric acid). The oral dosing solution concentration is 1 mg/mL test compound. Blood is sampled at 15 minutes, 30 minutes, 90 minutes, 180 minutes, 360 minutes and 24 hours following PO dosing. Blood samples (~0.2 mL/ sample) is collected via the jugular vein, placed in tubes containing EDTA-K2 and stored on ice until centrifuged. The blood samples are centrifuged at approximately 6800g for 6 minutes at 2-8 °C and the resulting plasma is separated and stored frozen at approximately -80 °C.

[615] The plasma samples are analyzed using an Agilent Technologies 6430 Triple Quad LC/MS system, following the manufacturer's instructions. The analytes are detected with positive-mode electrospray ionization (ESI). A standard curve for each test compound is generated and used to measure test compound concentrations in the rat plasma samples. Based on the time course sampling, an area under the curve is calculated for the oral dose group and the intravenous dose group. Percentage rat bioavailability is calculated based on equation 1.

Equation 1

$F\ (rat\ ) = 100\ X \frac{AUC_{po} * Dose_{IV}}{AUC_{IV}\ * Dose_{po}}$, where F is bioavailability, AUC_{po} is area under curve of oral drug, AUC_{IV} is area under curve of intravenous drug, $Dose_{IV}$ is the intravenous dose and $Dose_{po}$ is the oral dose.

[616] **Example 12**: Mouse Oral Exposure (F)

[617] A pharmacokinetic profile for a test compound is assessed by single dosing in female CD-1 mice. Animal weights are typically between 20-50 grams, and animals are allowed to acclimate to their new environment for at least 3 days prior to the initiation of any studies. One set of animals is dosed intravenous (IV) with test compound, 2 mg/kg in 20% HP-beta-CD or 20% Captisol, pH adjusted to above 4 by citric acid at 10 mL/kg. Time of blood sampling is 5 minutes, 15 minutes, 30 minutes, 90 minutes, 360 minutes, and 24 hours following IV dosing. Another set of animals is dosed oral (PO) with test compound, 10 mg/kg in 20% HP-beta-CD or 20% Captisol, pH adjusted to ~3-4 by citric acid at 10 mg/mL. Oral dosing solution concentration is 1 mg/mL test compound and 10 mL/kg. Time of blood sampling is 15 minutes, 30 minutes, 90 minutes, 180 minutes, 360 minutes and 24 hours following PO dosing. Blood samples (~0.1 mL/sample) are collected via submandibular facial vein and placed in tubes containing EDTA-K2 and stored on ice until centrifuged. The blood samples are centrifuged at approximately 6800g for 6 minutes at 2-8 °C and the resulting plasma is separated and stored frozen at approximately -80 °C.

[618] Plasma samples are analyzed using an Agilent Technologies 6430 Triple Quad LC/MS system, following the manufacturer instructions. All the analytes are detected with positive-mode electrospray ionization (ESI). A standard curve for each test compound is generated and used to measure test compound concentrations in the mouse plasma samples. Based on the time course sampling, an area under the curve is calculated for the oral dose group and the intravenous dose group. Percentage mouse bioavailability is calculated based on equation 2.

Equation 2

$F\ (mouse\ ) = 100\ X \frac{AUC_{po} * Dose_{IV}}{AUC_{IV}\ * Dose_{po}}$, where F is bioavailability, AUC_{po} is area under curve of oral drug, AUC_{IV} is area under curve of intravenous drug, $Dose_{IV}$ is the intravenous dose and $Dose_{po}$ is the oral dose.

[619] **Example 13**: Dog Oral Exposure (F)

[620] A pharmacokinetic profile for a test compound is measured by single dosing in male Beagle dogs. Animal weights are typically between 8-12 kilograms, and animals are allowed to acclimate to their new environment for at least 3 days prior to the initiation of any studies. One set of animals is dosed intravenously (IV) with test compound (1 mg/kg in 20% HP-beta-CD or 20% Captisol, pH adjusted to above 4 by citric acid). The IV dosing solution concentration is 0.5 mg/mL test compound. Blood is sampled at 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours,

4 hours, 8 hours, and 24 hours following IV dosing. Another set of animals is dosed oral (PO) with test compound (5 mg/kg in 20% HP-beta-CD or 20% Captisol, pH adjusted to ~4 by citric acid). The oral dosing solution concentration is 1 mg/mL test compound. Blood is sampled at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours and 24 hours following PO dosing. Blood samples (~1 mL/ sample) is collected via the jugular vein or other suitable vein, placed in tubes containing EDTA-K2 and stored on ice until centrifuged. The blood samples are centrifuged at approximately 6800g for 6 minutes at 2-8 °C and the resulting plasma is separated and stored frozen at approximately -80 °C.

[621] The plasma samples are analyzed using an Agilent Technologies 6430 Triple Quad LC/MS system, following the manufacturer's instructions. The analytes are detected with positive-mode electrospray ionization (ESI). A standard curve for each test compound is generated and used to measure test compound concentrations in the dog plasma samples. Based on the time course sampling, an area under the curve is calculated for the oral dose group and the intravenous dose group. Percentage dog bioavailability is calculated based on equation 3.

Equation 3

$F\ (dog\ ) = 100\ X \frac{AUC_{po} * Dose_{IV}}{AUC_{IV} * Dose_{po}}$, where F is bioavailability, AUC_{po} is area under curve of oral drug, AUC_{IV} is area under curve of intravenous drug, $Dose_{IV}$ is the intravenous dose and $Dose_{po}$ is the oral dose.

[622] **Example 14**: Monkey Oral Exposure (F)

[623] A pharmacokinetic profile for a test compound is assessed by single dosing in male Cynomolgus monkeys. Animal weights are typically between 2-5 kilograms, and animals are allowed to acclimate to their new environment for at least 3 days prior to the initiation of any studies. One set of animals is dosed intravenously (IV) with test compound (1 mg/kg in 20% HP-beta-CD or 20% Captisol, pH adjusted to above 4 by citric acid). The IV dosing solution concentration is 0.5 mg/mL test compound. Blood is sampled at 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, and 24 hours following IV dosing. Another set of animals is dosed oral (PO) with test compound (5 mg/kg in 20% HP-beta-CD or 20% Captisol, pH adjusted to ~4 by citric acid). The oral dosing solution concentration is 1 mg/mL test compound. Blood is sampled at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours and 24 hours following PO dosing. Blood samples (~1 mL/sample) are collected via femoral vein or other suitable vein and placed in tubes containing EDTA-K2 and stored on ice until centrifuged. The blood samples are centrifuged at approximately 6800g for 6 minutes at 2-8 °C and the resulting plasma is separated and stored frozen at approximately -80 °C.

[624] Plasma samples are analyzed using an Agilent Technologies 6430 Triple Quad LC/MS system, following the manufacturer instructions. All the analytes are detected with positive-mode electrospray ionization (ESI). A standard curve for each test compound is generated and used to measure test compound concentrations in the monkey plasma samples. Based on the time course sampling, an area under the curve is calculated for the oral dose group and the intravenous dose group. Percentage monkey bioavailability is calculated based on equation 4.

[625] Equation 4

$F\ (monkey\ ) = 100\ X \frac{AUC_{po} * Dose_{IV}}{AUC_{IV} * Dose_{po}}$, where F is bioavailability, AUC_{po} is area under curve of oral drug, AUC_{IV} is area under curve of intravenous drug, $Dose_{IV}$ is the intravenous dose and $Dose_{po}$ is the oral dose.

[626] **Example 15**: Cell-based Degradation Assays

[627] SW620, GP2D, SW1990, MIA PaCa-2, ASPC-1, A549, LS123, and other cell lines expressing mutant KRas proteins are cultured in appropriate media conditions for each cell line. DPBS (ThermoFisher; cat. no. 14190250) is used to wash cells and 0.25% Trypsin-EDTA (ThermoFisher; cat. no. 252000-056) is used to detach cells for passaging. Compounds were synthesized according to methods described herein. Between 2.5 x 10^5 and 6.0

x 10^5 cells are seeded into 6-well plates. The next day, media is removed and cells are treated with varying amounts of Compounds of Formula (A) for 1, 2, 4, 8, 12, or 24 hours. For longer time course experiments and time courses in which cells are treated with compounds of Formula (A), cells are concurrently treated with a single compound, then lysed by scraping in RIPA buffer at the indicated time points. Between 2.5 x 10^5 and 5.0 x 10^5 cells are seeded into 6-well plates. The next day cells are pretreated with a compound of Formula (A) or control for 1 hour. Media is then removed and cells are treated with DMSO or a compound of Formula (A). Cells are lysed by scraping in RIPA buffer supplemented as appropriate for each cell line. Cell lysates are clarified at 21000 x g for 15 mins at 4° C. Protein levels are quantified using a 50:1 mixture of bicinchoninic acid solution and 4% (w/v) copper(II) sulfate solution incubated at 37° C for 30 mins. Absorbance values at 560 nm are read on an EnVision 2101 Multilabel Reader (PerkinElmer). Proteins are separated using 26 well Criterion TGX precast 4-15% or 8-16% gradient midi gels. After separation, proteins are transferred to nitrocellulose or PVDF membranes at 76 V for 2 hours at 4° C. Blots are then blocked in 5% milk in tris-buffered saline with Tween-20 (TBST; 20 mM Tris, 150 mM NaCl, 0.02 % Tween-20). After blocking, blots are incubated in primary antibody overnight (12-18 hours) at 4° C or for 2 hours at room temperature with mild agitation at the manufacturer's indicated dilution in either 5% milk or 5% BSA in TBST. Blots are then washed thrice with TBST for 5 mins at room temperature. After washing, blots are incubated with 1:5,000-1:10,000 of donkey anti-rabbit or sheep anti-mouse secondary antibody diluted in 5% milk for 1 hour at room temperature with mild agitation. Blots are again washed thrice with TBST for 5 mins. Chemiluminescent signal is generated using Amersham ECL Prime Western Blotting Detection Reagant (GE Life Sciences; cat. no. RPN2232) or SuperSignal West Femto Maximum Sensitivity Substrate (ThermoFisher; cat. no. 34095). Images are obtained using a Bio-Rad ChemiDoc Imager. Band intensities are quantified using BioRad's Image Lab Software. KRAS levels are examined by quantifying levels of both conjugated KRAS and unbound KRAS. Data are analyzed by computing one-way ANOVAs or two-way ANOVAs (for grouped data) using multiple comparisons in which the mean of DMSO is compared to all treatment means using GraphPad Prism 7. For time courses, protein levels are compared to DMSO for each time point. DC50 and D(max) are quantified by fitting data to an inhibitor vs. dose response non-linear regression using GraphPad Prism 7.

[628] **Example 16**: Hi Bit Degradation assay

[629] A HiBit protein detection tag is introduced immediately downstream of the initiating Methionine codon of the endogenous KRAS locus of GP5d cells (ECACC Cat. No.95090715) or GP2d cells (ECACC Cat. No. 95090714) by CRISPR-based genome engineering using a KRAS G12D mutant donor construct encoding the HiBit tag, resulting in the heterozygous introduction of an N- terminal HiBit tagged version of KRAS G12D into the KRAS WT allele. Modification of the KRAS locus is assessed by PCR-based genotyping and Sanger sequencing of the PCR products. The resulting cell line is referred to as HiBit-KRAS(G12D).

[630] To assess PROTAC-mediated degradation of KRAS G12D, HiBit- KRAS (G12D) cells are seeded at 25000 cells per well in 100 µL Dulbecco's Modified Eagle medium (Sigma cat. no. D6429) supplemented with 10 % fetal calf serum into white bottom opaque 96 well plates (Perkin Elmer cat no. 5680). Plates are incubated at 37 °C, 5% CO_2 in a humidified incubator over night to allow the cells to adhere. Test compounds ,from 10 mM stock in DMSO, are added at logarithmic dose series using the HP Digital Dispenser D300 (Tecan), normalizing for added DMSO. Plates are further incubated at 37°C for 18 hours. Following incubation, 100 µL per well Promega Nano-Gio HiBit lytic detection reagent mix (Promega Nano-Gio HiBit Lytic Detection System #N3050), prepared according to the manufacturer's instructions in the kit, are added. To allow for adequate cell lysis, plates are incubated on an orbital shaker for 15 min and further incubated 30 min at room temperature. Luminescence is

measured using an Envision plate reader with the Ultrasensitive Luminescence Protocol for 96 well plates. Luminescence levels are normalized by the values obtained with DMSO-treated samples and plotted as percent of DMSO control. DC50 values are computed using a four parametric logistic model. Dmax values represent the maximal extent of degradation observed and are stated as a percent of control (%Ctrl.).

[631] The therapeutically relevant mutant KRAS constructs (WT, G12C, G12D, G12V, G13D) are obtained by site directed mutagenesis using a KRAS4B WT cDNA construct as a template. GP5d cells (ECACC Cat. No. 95090715) or GP2d cells (ECACC Cat. No. 95090714) are transduced with lentiviral vectors expressing mutant KRAS4B cDNA under control of a CMV promoter. Stably transduced cells are selected using a neomycin selectable marker.

[632] To assess PROTAC-mediated degradation of various KRAS mutants, GP5d or GP2d cells stably transduced with KRAS4B constructs as described above are seeded at 25000 cells per well in 100 µL Dulbecco's Modified Eagle medium (Sigma cat. no. D6429) supplemented with 10% fetal calf serum into white bottom opaque 96 well plates (Perkin Elmer cat no.5680). Plates are incubated at 37°C, 5% CO_2 in a humidified incubator over night to allow the cells to adhere. Test compounds, from 10 mM stock in DMSO, are added at logarithmic dose series using the HP Digital Dispenser D300 (Tecan), normalizing for added DMSO. Plates are further incubated at 37°C for 18 hours. Following incubation, 100 µL per well Promega Nano-Gio HiBit lytic detection reagent mix (Promega Nano-Gio HiBit Lytic Detection System #N3050), prepared according to the manufacturer's instructions in the kit, are added. Plates are then incubated on an orbital shaker for 15 min and further incubated 30 min at room temperature. Luminescence is measured using an Envision plate reader using the Ultrasensitive Luminescence Protocol for 96 well plates. Luminescence levels are normalized by the values obtained with DMSO-treated control samples and plotted as percent of DMSO control. DC50 values are computed using a four parametric logistic model. Dmax values represent the maximal extent of degradation observed and are stated as a percent of control (%Ctrl.).

[633] **Example 17:** Metabolic (Microsomal) Stability Assay

[634] The metabolic stability of a test compound is assayed at 37 °C using pooled liver microsomes (mouse or human liver microsomes). An aliquot of 10 µL of 50 µM test compound is mixed with 490 µL of 0.611 mg/mL liver microsomes, then 50 µL of the mixtures are dispensed to the 96 well tubes and warmed at 37 °C for 10 minutes. The reactions are initiated by adding 50 µL of the pre-warmed NADPH regeneration system solution (add 1.2 µL solution, 240 µl solution B, mix with 10.56 ml KPBS) and then incubated at 37 °C. The final incubation solution contains 100 mM potassium phosphate (pH 7.4), 1.3 mM NADP+, 3.3 mM glucose 6-phosphate, 0.4 Unit/mL of glucose 6-phosphate dehydrogenase, 3.3 mM magnesium chloride, 0.3 mg/mL liver microsomes and 0.5 µM test article. After 0, 15, 30 and 60 minutes in a shaking incubator, the reactions are terminated by adding 100 µL of acetonitrile containing 200 nM buspirone as an internal standard. All incubations are conducted in duplicate. Plates are vortexed vigorously by using Fisher Scientific microplate vortex mixer (Henry Troemner, US). Samples are then centrifuged at 3500 rpm for 10 minutes (4 °C) using Sorvall Legend XRT Centrifuge (Thermo Scientific, GE). Supernatants (40 µL) are transferred into clean 96-deep well plates. Each well is added with 160 µL of ultrapure water (Milli-Q, Millipore Corporation) with 0.1% (v/v) formic acid (Fisher Chemical), mixed thoroughly and subjected to LC/MS/MS analysis in MRM positive ionization mode.

[635] All the samples are measured using a mass spectrometer (QTrap 5500 quadrupole/ion trap) coupled with a Shimadzu HPLC system. The HPLC system consisted of a Shimadzu series degasser, binary quaternary gradient pumps, column heater coupled to an autosampler, and a Phenomenex Gemini-NX, C18, 3.0 µm or Phenomenex Lunar, C8, 5.0 µM HPLC column (Phenomenex, Torrance, CA), and eluted with a mobile phase gradient consisting

of Solution A (0.1% formic acid water) and Solution B (0.1% formic acid acetonitrile). The column temperature is maintained at 40 °C. All the analytes are detected with positive-mode electrospray ionization (ES+).

[636] The half-life for the metabolic degradation of the test compound is calculated by plotting the time-course disappearance of the test compound during the incubation with liver microsomes. Each plot is fitted to a first-order equation for the elimination of the test compound (% remaining compound) versus time using non-linear regression (Equation 5).

Equation 5:

$$\frac{C_t}{C_0} = e^{-kt}$$

[637] where C_t is the mean relative substrate concentration at time t and C_0 is the initial concentration (0.5 μM) at time 0. Note that the area ratio of the substrate peak to an internal standard peak is proportional to the analyte concentration and is used for regression analysis to derive a value of k.

[638] The half-life $t_{1/2}$ for metabolic (microsome) stability is derived from the test compound elimination constant k using Equation 6 below.

Equation 6:

$$t_{1/2} = \frac{0.693}{k}$$

[639] **Example 18:** CYP2C19 Inhibition Assay

[640] Some xenobiotics can inhibit cytochrome P450 (CYP) enzyme function, which alters their ability to metabolize drugs. Administration of a CYP inhibitor with a drug whose clearance is dependent on CYP metabolism can result in increased plasma concentrations of this concomitant drug, leading to potential toxicity. The inhibition of CYP2C19 by a test compound is assayed in human liver microsomes using S-Mephenytoin as a CYP2C19 substrate. The stock solution of the test compound or known CYP2C19 inhibitor as a positive control (10 mM) is diluted with KPBS to 40 μM. In a similar way, the stock solutions of the human liver microsomes and S-Mephenytoin are diluted with KPBS buffer. The pre-incubations are started by incubating a plate containing 25 μL human liver microsomes (final concentration of 0.2 mg/mL), 25 μL NADPH-generating system, and a 25 μL test compound (final concentration 10 μM) or the positive control for 30 min at 37±1 °C. After the pre-incubation, 25 μL S-Mephenytoin (final concentration 200 μM) is added and incubated another 12 minutes at 37±1 °C for substrate metabolism. The reactions are terminated by addition of 100 μL of ice-cold acetonitrile containing an internal standard (buspirone). Precipitated proteins are removed by centrifugation at 3500rpm for 10 minutes at 4 °C (Allegra 25R, Beckman Co. Fullerton, CA) and then aliquot of the supernatant is transferred to an assay plate.

[641] All the samples are assessed using a mass spectrometer (QTrap 5500 quadrupole/ion trap) coupled with a Shimadzu HPLC system, following the manufacturer's instructions. The metabolism of S-Mephenytoin in human liver microsomes is monitored by LC/MS/MS as representative of CYP2C19 inhibitory activity. The amount of metabolite formed is assessed by the peak area ratio (metabolite/IS) and % inhibition at 10 μM is expressed as a percentage of the metabolite signal reduced compared to the control (i.e. an incubation that contained no inhibitor and represented 100% enzyme activity): % inhibition = (1-A/B) × 100%, where A is the metabolite peak area ratio formed in the presence of test compound or inhibitor at 10 μM and B is the metabolite peak area ratio formed without test compound or inhibitor in the incubation.

[642] **Example 19:** Mouse and Human Protein Binding Assay to Assess Free Drug Concentration

[643] This assay can be used to determine the plasma protein binding of the test compound in the plasma of human and animal species using a Rapid Equilibrium Dialysis (RED) device for equilibrium dialysis and LC-

MS/MS for sample analysis. Test compound is spiked in. The stock solution of the test compound is prepared at 5 mM concentration. One μL of 5 mM working solution is added into 1000 μL plasma to achieve a final concentration of 5 μM. The spiked plasma is placed on a rocker, and gently agitated for approximately 20 minutes. A volume of 300 μL of the plasma sample containing 5 μM test compound from each species is added to designate RED device donor chambers followed by addition of 500 μL of potassium phosphate buffer to the corresponding receiver chambers in duplicate. The RED device is then sealed with sealing tape and shaken at 150 RPM for 4 hours at 37 °C. Post-dialysis donor and receiver compartment samples are prepared for LC-MS/MS analysis, including spiking samples with an internal standard for the bioanalytical analysis. Warfarin and propranolol are purchased from Sigma-Aldrich (St. Louis, MO), and used as positive controls for low and high plasma protein binding, respectively.

[644] All the samples are analyzed using an Agilent Technologies 6430 Triple Quad LC/MS system. The HPLC system consists of an Agilent 1290 Infinity Liquid Chromatograph coupled to an autosampler (Agilent 1290 Infinity LC Injector HTC), and a Phenomenex Gemini-NX, C18, 3.0 μm or Phenomenex Lunar, C8, 5.0 μM HPLC column (Phenomenex, Torrance, CA), eluting with a mobile phase gradient consisting of Solution A (0.1% formic acid water) and Solution B (0.1% formic acid acetonitrile). The column temperature is maintained at 40 °C. All the analytes are detected with positive-mode electrospray ionization (ES+). The percentage of the test compound bound to plasma is calculated following Equation 7 and 8.

Equation 7

$$\%\ Free\ test\ compound = \frac{Peak\ ratio\ (\frac{test\ compound}{Internal\ standard}), receiver\ compartment}{Peak\ ratio(\frac{test\ compound}{Internal\ standard}), donor\ compartment} * 100$$

Equation 8

$$\%\ Plasma\ protein\ bound\ test\ compound = 100 - \%\ Free\ test\ compound$$

[645] **Example 20:** Compound Tumor Exposure

[646] This assay can be used to determine the exposure of a test compound in a tumor of an animal species. For a test compound tumor exposure study, the test compound is administered to tumor-bearing mice for a certain period. The tumor is harvested at the end of the in-vivo study (e.g., 1 hour to multiple weeks depending on the study) and subjected to bioanalysis to quantify the amount of test compound in the tumor. To quantify the amount of test compound distributed into the tumor, a certain amount of tumor is weighed and combined with 5-fold of deionized water (weight by weight) and homogenized into tissue homogenate by a Bead Mill Homogenizer (Omni International) into tissue suspension in de-ionized water. An aliquot of 40 μL from each individual homogenized tissue sample is combined with 10 μL blank DMSO and 20 μL of internal standard solution (e.g., verapamil 150 nM in water acidified by 0.1% formic acid) and crushed with 200 μL acetonitrile containing 0.1% formic acid, followed by vortex-mixing for 1 minute. Calibration standard and QC samples are made by adding 10 μL stock solution of different amounts of test compound in DMSO into 40 μL blank tumor homogenate solution suspension to make calibration standard samples at a series of nominal concentrations of test compound in blank tumor homogenate. Similarly, 20 μL of internal standard solution (e.g., verapamil 150 nM in water acidified by 0.1% formic acid) and 200 μL acetonitrile containing 0.1% formic acid are added to each of the calibration standard and QC samples, followed by vortex-mixing for 1 minute. The mixed samples are centrifuged at 4000 rpm for 6 min to obtain supernatant. A volume of 10 μL supernatant from each sample is combined with 190 μL of dilution solution (20% acetonitrile in water containing 0.1% formic acid) and transferred into a well in a 96-well analytical plate prior to a 2-5 μL injection into LC-MS/MS instrument system composed of Sciex Qtrap 6500$^+$ and Shimadzu HPLC for analysis. The concentration of test compound in tumor homogenate determined is corrected by a dilution factor of 6

to obtain the test compound concentration in tumor is expressed in ng/mg of tumor.

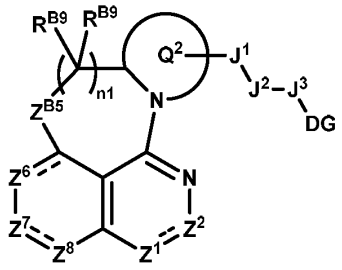
[647] **Example 21:** hERG (automated patch-clamp) Assay

[648] The human ether-a-go-go related gene (hERG) encodes the voltage gated potassium channel in the heart (IKr) which is involved in cardiac repolarization. Inhibition of the hERG causes QT interval prolongation and can lead to potential fatal events in humans. It is thus important to assess hERG inhibition early in drug discovery. A hERG automated patch-clamp assay is done using a hERG CHO-K1 cell line using an incubation time of 5 min. The degree of hERG inhibition (%) is obtained by measuring the tail current amplitude, which is induced by a one second test pulse to - 40 mV after a two second pulse to + 20 mV, before and after drug incubation (the difference current is normalized to control and multiplied by 100 to obtain the percent of inhibition). The percent hERG inhibition is measured in the presence of 10 μM test compound.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (A0):



(A0),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^{B5} is selected from $C(R^{B9})_2$ and O;

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$,

wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6}

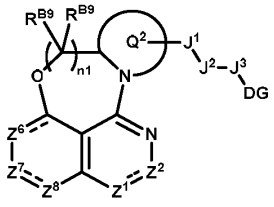
alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

2. A compound of Formula (A):



(A),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and N(R^{B1b});

Z^2 is selected from C(R^{B2}) and C(O);

Z^6 is selected from C(R^{B6}), C(R^{B6})$_2$, N, and N(R^{B6b});

Z^7 is selected from C(R^{B7}) and N(R^{B7b});

Z^8 is selected from C(R^{B8}), C(R^{B8})$_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -N(R^{B12})-, -C(O)-, -N(R^{B12})C(O)-, -C(O)N(R^{B12})-, -S-, -S(O)$_2$-, -S(O)-, -P(O)R^{B12}-, -N(R^{B12})S(O)$_2$-, -N(R^{B12})S(O)-, -N(R^{B12})P(O)R^{B12}-, -S(O)$_2$N(R^{B12})-, -S(O)N(R^{B12})-, -P(O)R^{B12}N(R^{B12})-, -OS(O)$_2$-, -OS(O)-, -OP(O)R^{B12}-, -S(O)$_2$O-, -S(O)O-, and -P(O)R^{B12}O-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -C(O)OR^{B12}, -C(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -S(O)$_2R^{B12}$, -S(O)(NR^{B12})R^{B12}, -S(O)$_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -N(R^{B12})(R^{B13}), -C(O)OR^{B12}, -OC(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)OR^{B12}, -N(R^{B12})S(O)$_2R^{B12}$, -C(O)R^{B12}, -S(O)R^{B12}, -OC(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)R^{B12}, -S(O)$_2R^{B12}$, -S(O)(NR^{B12})R^{B12}, -S(O)$_2$N(R^{B12})(R^{B13}), and -S(=O)(=NR^{B12})N(R^{B12})(R^{B13}), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -N(R^{B22})(R^{B23}), =NR^{B22}, =C(R^{B21})$_2$, -C(O)OR^{B22}, -OC(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)OR^{B22}, -N(R^{B22})S(O)$_2R^{B22}$, -C(O)R^{B22}, -S(O)R^{B22}, -OC(O)R^{B22}, -C(O)N(R^{B22})(R^{B23}), -C(O)C(O)N(R^{B22})(R^{B23}), -N(R^{B22})C(O)R^{B22}, -S(O)$_2R^{B22}$, -S(O)(NR^{B22})R^{B22}, -S(O)$_2$N(R^{B22})(R^{B23})-, and -S(=O)(=NR^{B22})N(R^{B22})(R^{B23}); wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6}

alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle);

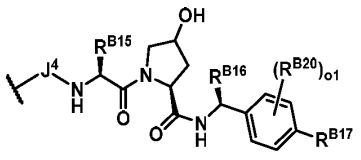
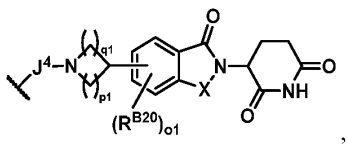
R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

3. The compound, salt, or solvate of any one of claims 1 to 2, wherein the degradation enhancer is capable of binding a protein selected from E3A, mdm2, APC, EDD1, SOCS/BC-box/eloBC/CUL5/RING, LNXp80, CBX4, CBLL1, HACE1, HECTD1, HECTD2, HECTD3, HECTD4, HECW1, HECW2, HERC1, HERC2, HERC3, HERC4, HER5, HERC6, HUWE1, ITCH, NEDD4, NEDD4L, PPIL2, PRPF19, PIAS1, PIAS2, PIAS3, PIAS4, RANBP2, RNF4, RBX1, SMURF1, SMURF2, STUB1, TOPORS, TRIP12, UBE3A, UBE3B, UBE3C, UBE3D, UBE4A, UBE4B, UBOX5, UBR5, VHL (von-Hippel-Lindau ubiquitin ligase), WWP1, WWP2, Parkin, MKRN1, CMA (chaperon-mediated autophage), SCFb-TRCP (Skip-Cullin-F box (Beta-TRCP) ubiquitin complex), b-TRCP (b-transducing repeat-containing protein), cIAP1 (cellular inhibitor of apoptosis protein 1), APC/C (anaphase-promoting complex/cyclosome), CRBN (cereblon), CUL4-RBX1-DDB1-CRBN ($CRL4^{CRBN}$) ubiquitin ligase, XIAP, IAP, KEAP1, DCAF15, RNF114, DCAF16, AhR, SOCS2, KLHL12, UBR2, SPOP, KLHL3, KLHL20, KLHDC2, SPSB1, SPSB2, SPSB4, SOCS6, FBXO4, FBXO31, BTRC, FBW7, CDC20, PML, TRIM21, TRIM24, TRIM33, GID4, avadomide, iberdomide, and CC-885.

4. The compound, salt, or solvate of any one of claims 1 to 2, wherein the degradation enhancer is capable of binding a protein selected from UBE2A, UBE2B, UBE2C, UBE2D1, UBE2D2, UBE2D3, UBE2DR, UBE2E1, UBE2E2, UBE2E3, UBE2F, UBE2G1, UBE2G2, UBE2H, UBE2I, UBE2J1, UBE2J2, UBE2K, UBE2L3, UBE2L6, UBE2L1, UBE2L2, UBE2L4, UBE2M, UBE2N, UBE2O, UBE2Q1, UBE2Q2, UBE2R1, UBE2R2, UBE2S, UBE2T, UBE2U, UBE2V1, UBE2V2, UBE2W, UBE2Z, ATG3, BIRC6, and UFC1.

5. The compound, salt, or solvate of any one of the preceding claims, wherein DG is selected from:


and

,

wherein:

J^4 is selected from a bond, 2- to 10-membered heteroalkylene, 3- to 10-membered heteroalkenylene, and 3- to 10-membered heteroalkynylene, wherein 2- to 10-membered heteroalkylene, 3- to 10-membered

heteroalkenylene, and 3- to 10-membered heteroalkynylene are optionally substituted with one or more R^{B20};

R^{B15} is selected from hydrogen, C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle, wherein C_{1-6} alkyl, C_{3-8} carbocycle, and 3- to 8-membered heterocycle are optionally substituted with one or more R^{B20};

R^{B16} is selected from hydrogen, C_{1-6} alkyl, $-OR^{B12}$, $-C(O)OR^{B12}$, and $-C(O)R^{B12}$, wherein C_{1-6} alkyl is optionally substituted with one or more R^{B20};

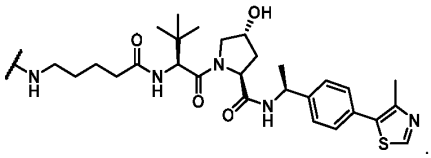
R^{B17} is selected from halogen, -CN, C_{1-3} alkyl, C_{3-6} carbocycle, 4- to 6-membered heterocycle, and $-S(O)_2CH_3$, wherein C_{1-3} alkyl, C_{3-6} carbocycle, and 4- to 6-membered heterocycle are optionally substituted with one or more R^{B20};

o1 is selected from 0, 1, and 2;

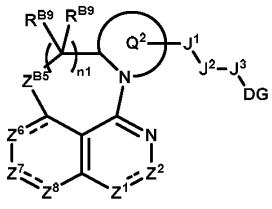
p1 and q1 are independently selected from 1, 2, and 3; and

X is selected from CH_2 and C(O).

6. The compound, salt, or solvate of any one of the preceding claims, wherein DG is



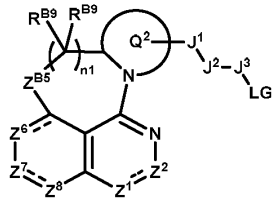
7. A method of preparing a compound of Formula (A0):



(A0),

the method comprising:

(a) reacting a compound of Formula (a0):



(a0),

with a degradation enhancer under conditions to effect release of LG and production of the compound of Formula (A0), wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^{B5} is selected from $C(R^{B9})_2$ and O;

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered

heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, -N(R^{B12})-, -C(O)-, -N(R^{B12})C(O)-, -C(O)N(R^{B12})-, -S-, -S(O)$_2$-, -S(O)-, -P(O)R^{B12}-, -N(R^{B12})S(O)$_2$-, -N(R^{B12})S(O)-, -N(R^{B12})P(O)R^{B12}-, -S(O)$_2$N(R^{B12})-, -S(O)N(R^{B12})-, -P(O)R^{B12}N(R^{B12})-, -OS(O)$_2$-, -OS(O)-, -OP(O)R^{B12}-, -S(O)$_2$O-, -S(O)O-, and -P(O)R^{B12}O-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

DG is a degradation enhancer;

LG is a leaving group;

n1 is selected from 1, 2, and 3;

R^{B1b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -C(O)OR^{B12}, -C(O)R^{B12}, -C(O)N(R^{B12})(R^{B13}), -C(O)C(O)N(R^{B12})(R^{B13}), -S(O)$_2$$R^{B12}$, -S(O)($NR^{B12}$)$R^{B12}$, -S(O)$_2$N($R^{B12}$)($R^{B13}$), and -S(=O)(=$NR^{B12}$)N($R^{B12}$)($R^{B13}$), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -N(R^{B12})(R^{B13}), -C(O)OR^{B12}, -OC(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)N(R^{B12})(R^{B13}), -N(R^{B12})C(O)OR^{B12}, -N(R^{B12})S(O)$_2$$R^{B12}$, -C(O)$R^{B12}$, -S(O)$R^{B12}$, -OC(O)$R^{B12}$, -C(O)N($R^{B12}$)($R^{B13}$), -C(O)C(O)N($R^{B12}$)($R^{B13}$), -N($R^{B12}$)C(O)$R^{B12}$, -S(O)$_2$$R^{B12}$, -S(O)($NR^{B12}$)$R^{B12}$, -S(O)$_2$N($R^{B12}$)($R^{B13}$), and -S(=O)(=$NR^{B12}$)N($R^{B12}$)($R^{B13}$), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}

alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, =NR^{B22}, =$C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

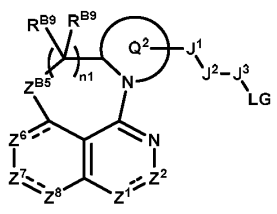
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

8. A compound of Formula (a0):



(a0),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^{B5} is selected from $C(R^{B9})_2$ and O;

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

LG is selected from $-OS(O)_2R^{B4}$ and $-OS(O)(NR^{B4b})R^{B4}$;

n1 is selected from 1, 2, and 3;

R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and $-N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B1b}, R^{B4b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), $-C(O)OR^{B12}$, $-C(O)R^{B12}$, $-C(O)N(R^{B12})(R^{B13})$, $-C(O)C(O)N(R^{B12})(R^{B13})$, $-S(O)_2R^{B12}$, $-S(O)(NR^{B12})R^{B12}$, $-S(O)_2N(R^{B12})(R^{B13})$, and $-S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered

heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

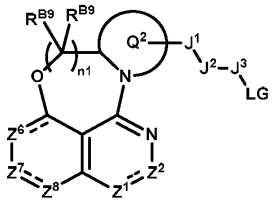
R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle);

R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

9. A compound of Formula (a):



(a),

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^1 is selected from N and $N(R^{B1b})$;

Z^2 is selected from $C(R^{B2})$ and C(O);

Z^6 is selected from $C(R^{B6})$, $C(R^{B6})_2$, N, and $N(R^{B6b})$;

Z^7 is selected from $C(R^{B7})$ and $N(R^{B7b})$;

Z^8 is selected from $C(R^{B8})$, $C(R^{B8})_2$, and N;

Q^2 is 4- to 12-membered heterocycle optionally substituted with one or more R^{B20};

J^1 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -O-, $-N(R^{B12})$-, -C(O)-, $-N(R^{B12})C(O)$-, $-C(O)N(R^{B12})$-, -S-, $-S(O)_2$-, -S(O)-, $-P(O)R^{B12}$-, $-N(R^{B12})S(O)_2$-, $-N(R^{B12})S(O)$-, $-N(R^{B12})P(O)R^{B12}$-, $-S(O)_2N(R^{B12})$-, $-S(O)N(R^{B12})$-, $-P(O)R^{B12}N(R^{B12})$-, $-OS(O)_2$-, -OS(O)-, $-OP(O)R^{B12}$-, $-S(O)_2O$-, -S(O)O-, and $-P(O)R^{B12}O$-, wherein C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, and 3- to 6-membered heteroalkynylene are optionally substituted with one or more R^{B20};

J^2 is selected from a bond, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, wherein -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)- are optionally substituted with one or more R^{B20};

J^3 is selected from C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, 2- to 6-membered heteroalkylene, 3- to 6-membered heteroalkenylene, 3- to 6-membered heteroalkynylene, -C_{0-6} alkyl-(C_{3-12} carbocycle)-, -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle)-, -C_{0-6} alkyl-(3- to 12-membered heterocycle)-, and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle)-, each of which is optionally substituted with one or more R^{B20};

LG is selected from $-OS(O)_2R^{B4}$ and $-OS(O)(NR^{B4b})R^{B4}$;

n1 is selected from 1, 2, and 3;

R^{B4} is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), and $-N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B1b}, R^{B4b}, R^{B6b}, and R^{B7b} are independently selected from hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -$C(O)OR^{B12}$, -$C(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one, two, or three R^{B20};

R^{B2}, R^{B6}, R^{B7}, and R^{B8} are independently selected at each occurrence from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B12}, -SR^{B12}, -$N(R^{B12})(R^{B13})$, -$C(O)OR^{B12}$, -$OC(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)OR^{B12}$, -$N(R^{B12})S(O)_2R^{B12}$, -$C(O)R^{B12}$, -$S(O)R^{B12}$, -$OC(O)R^{B12}$, -$C(O)N(R^{B12})(R^{B13})$, -$C(O)C(O)N(R^{B12})(R^{B13})$, -$N(R^{B12})C(O)R^{B12}$, -$S(O)_2R^{B12}$, -$S(O)(NR^{B12})R^{B12}$, -$S(O)_2N(R^{B12})(R^{B13})$, and -$S(=O)(=NR^{B12})N(R^{B12})(R^{B13})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), and -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B9} is independently selected at each occurrence from hydrogen and R^{B20};

R^{B12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle), wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), and -C_{0-6} alkyl-(3- to 12-membered heterocycle) are optionally substituted with one or more R^{B20};

R^{B13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{B12} and R^{B13} attached to the same nitrogen atom form 3- to 10-membered heterocycle optionally substituted with one or more R^{B20};

R^{B20} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), -OR^{B22}, -SR^{B22}, -$N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, -$C(O)OR^{B22}$, -$OC(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)OR^{B22}$, -$N(R^{B22})S(O)_2R^{B22}$, -$C(O)R^{B22}$, -$S(O)R^{B22}$, -$OC(O)R^{B22}$, -$C(O)N(R^{B22})(R^{B23})$, -$C(O)C(O)N(R^{B22})(R^{B23})$, -$N(R^{B22})C(O)R^{B22}$, -$S(O)_2R^{B22}$, -$S(O)(NR^{B22})R^{B22}$, -$S(O)_2N(R^{B22})(R^{B23})$-, and -$S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$; wherein two R^{B20} attached to the same or adjacent atoms optionally join to form C_{3-12} carbocycle or 3- to 12-membered heterocycle; wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 2- to 6-membered heteroalkyl, 3- to 6-membered heteroalkenyl, 3- to 6-membered heteroalkynyl, -C_{0-6} alkyl-(C_{3-12} carbocycle), -(2- to 6-membered heteroalkyl)-(C_{3-12} carbocycle), -C_{0-6} alkyl-(3- to 12-membered heterocycle), -(2- to 6-membered heteroalkyl)-(3- to 12-membered heterocycle), C_{3-12} carbocycle, and 3- to 12-membered heterocycle are optionally substituted with one or more substituents independently selected from halogen, oxo, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6}

alkoxy, C_{1-6} haloalkoxy, $-OR^{B22}$, $-SR^{B22}$, $-N(R^{B22})(R^{B23})$, $=NR^{B22}$, $=C(R^{B21})_2$, $-C(O)OR^{B22}$, $-OC(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)OR^{B22}$, $-N(R^{B22})S(O)_2R^{B22}$, $-C(O)R^{B22}$, $-S(O)R^{B22}$, $-OC(O)R^{B22}$, $-C(O)N(R^{B22})(R^{B23})$, $-C(O)C(O)N(R^{B22})(R^{B23})$, $-N(R^{B22})C(O)R^{B22}$, $-S(O)_2R^{B22}$, $-S(O)(NR^{B22})R^{B22}$, $-S(O)_2N(R^{B22})(R^{B23})$, and $-S(=O)(=NR^{B22})N(R^{B22})(R^{B23})$;

R^{B21} is independently selected at each occurrence from hydrogen, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle), or two R^{B21} are taken together with the carbon atom to which they are attached to form C_{3-12} carbocycle or 3- to 12-membered heterocycle, each of which is optionally substituted with one or more substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and -OH;

R^{B22} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-C_{0-6}$ alkyl-(C_{3-12} carbocycle), and $-C_{0-6}$ alkyl-(3- to 12-membered heterocycle);

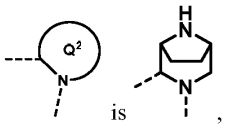
R^{B23} is independently selected at each occurrence from hydrogen and C_{1-6} alkyl; or R^{B22} and R^{B23} attached to the same nitrogen atom form 3- to 10 membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

10. The compound, salt, solvate, or method of any one of claims 1 or 3 to 8, wherein Z^{B5} is $C(R^{B9})_2$.

11. The compound, salt, solvate, or method of any one of claims 1 to 10, wherein n1 is 1.

12. The compound, salt, solvate, or method of any one of claims 1 to 11, wherein Q^2 is 7- to 9-membered bridged bicyclic heterocycloalkyl optionally substituted with one or more R^{B20}.

13. The compound, salt, solvate, or method of claim 12, wherein  is , which is optionally substituted with one or more R^{B20}.

14. The compound, salt, solvate, or method of any one of the preceding claims, wherein:

Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$;

Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is N, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$;

Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})_2$, Z^7 is $N(R^{B7b})$, and Z^8 is $C(R^{B8})_2$; or

Z^1 is $N(R^{B1b})$, Z^2 is C(O), Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is N.

15. The compound, salt, solvate, or method of claim 14, wherein Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is $C(R^{B6})$, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$.

16. The compound, salt, solvate, or method of claim 14, wherein Z^1 is N, Z^2 is $C(R^{B2})$, Z^6 is N, Z^7 is $C(R^{B7})$, and Z^8 is $C(R^{B8})$.

17. The compound, salt, solvate, or method of any one of the preceding claims, wherein J^1 is selected from a bond, C_{1-6} alkylene, 2- to 6-membered heteroalkylene, and -C(O)-, wherein C_{1-6} alkylene and 2- to 6-membered heteroalkylene are optionally substituted with one or more R^{B20}.

18. The compound, salt, solvate, or method of any one of the preceding claims, wherein J^1 is -C(O)-.

19. The compound, salt, solvate, or method of any one of the preceding claims, wherein J^2 is a bond.

20. The compound, salt, solvate, or method of any one of the preceding claims, wherein J^3 is selected from C_{1-6} alkylene and 2- to 6-membered heteroalkylene, each of which is optionally substituted with one or more R^{B20}.

21. The compound, salt, solvate, or method of any one of claims 1 to 16, wherein:

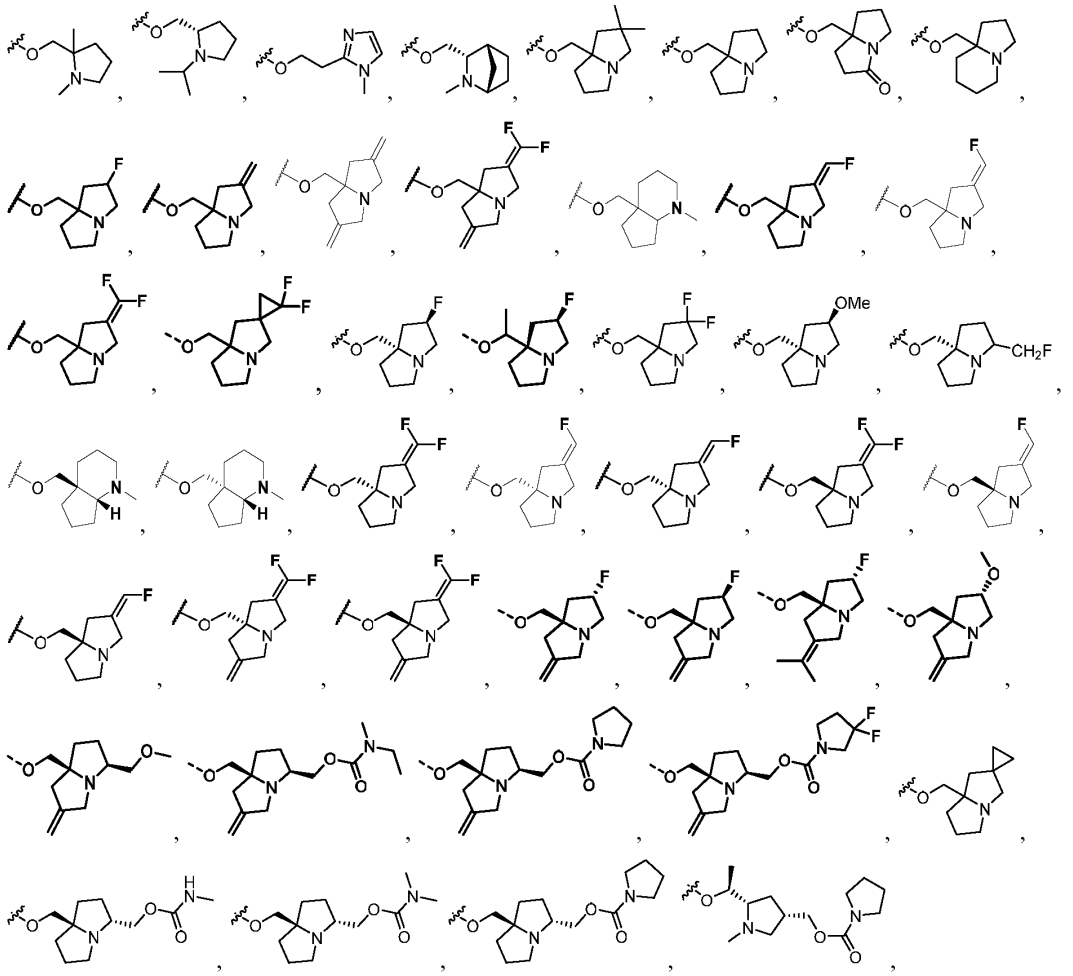
J^1 is -C(O)-;

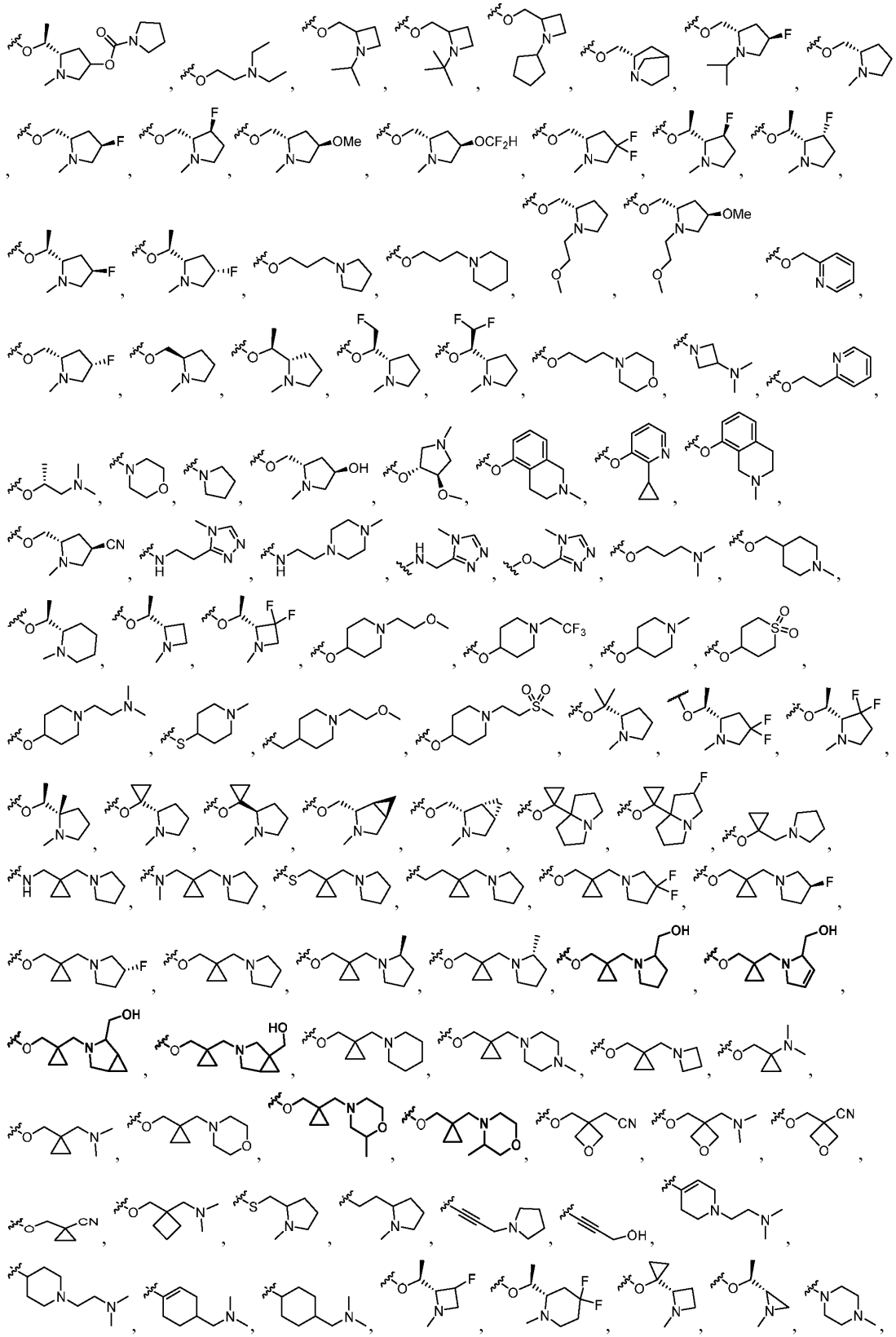
J^2 is a bond; and

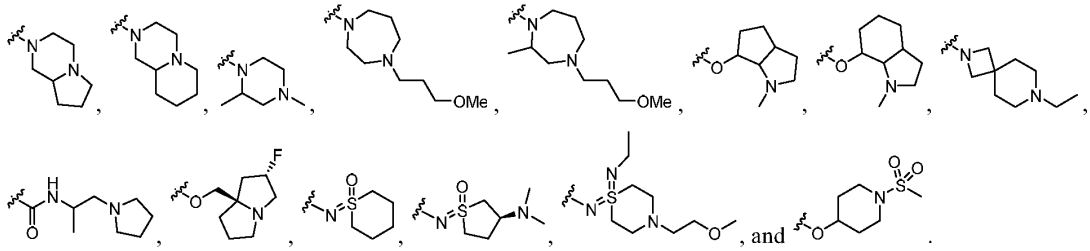
J^3 is C_{1-6} alkylene.

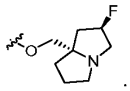
22. The compound, salt, solvate, or method of any one of the preceding claims, wherein R^{B2} is -O(C_{1-3} alkylene)(4- to 10-membered heterocycle), wherein 4- to 10-membered heterocycle is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-3} alkyl, C_{1-3} haloalkyl, and =C(R^{B21})$_2$, and wherein R^{B21} is independently selected at each occurrence from hydrogen, halogen, and C_{1-3} alkyl.

23. The compound, salt, solvate, or method of any one of claims 1 to 21, wherein R^{B2} is selected from

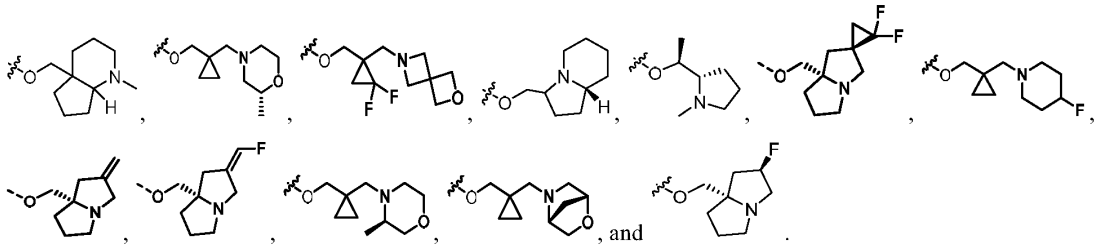


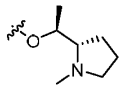




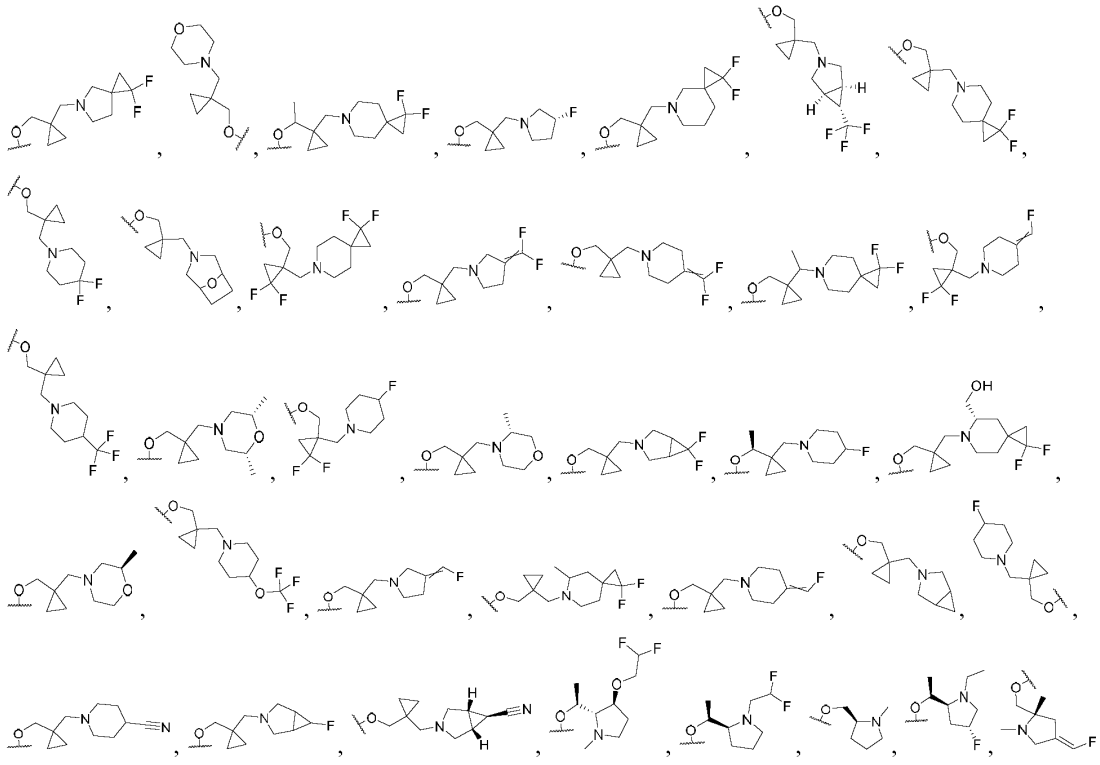
24. The compound, salt, solvate, or method of any one of the preceding claims, wherein R^{B2} is  .

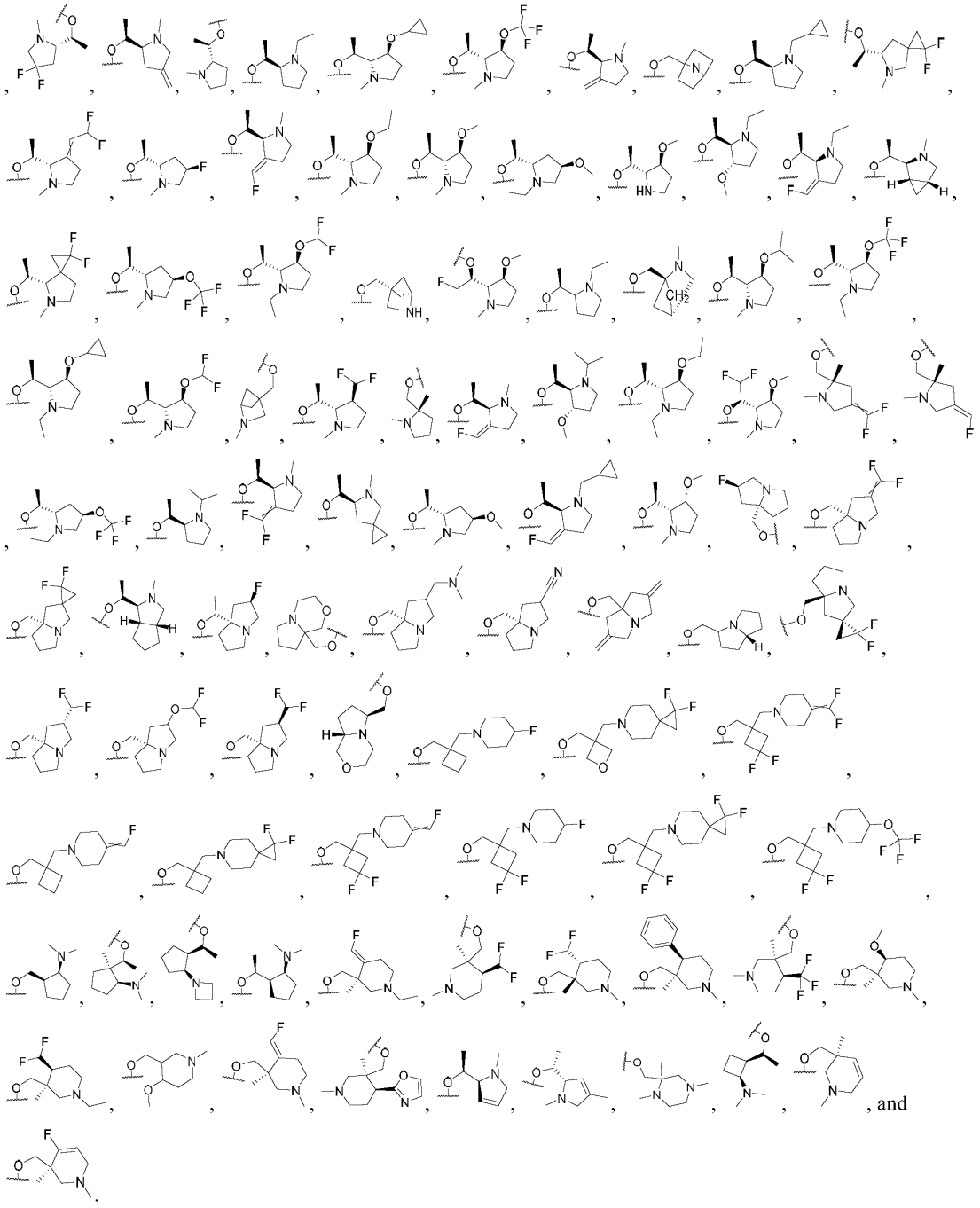
25. The compound, salt, solvate, or method of any one of claims 1 to 21, wherein R^{B2} is selected from



26. The compound, salt, solvate, or method of any one of claims 1 to 21, wherein R^{B2} is  .

27. The compound, salt, solvate, or method of any one of claims 1 to 21, wherein R^{B2} is selected from





28. The compound, salt, solvate, or method of any one of the preceding claims, wherein R^{B6} is halogen or C_{1-3} haloalkyl.

29. The compound, salt, solvate, or method of any one of the preceding claims, wherein R^{B7} is selected from C_{6-12} aryl and 5- to 12-membered heteroaryl, each of which is optionally substituted with one or more R^{B20}.

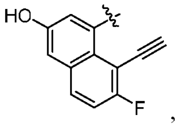
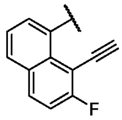
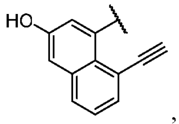
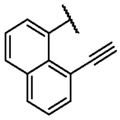
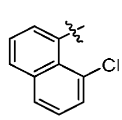
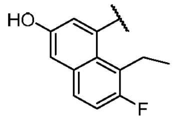
30. The compound, salt, solvate, or method of any one of the preceding claims, wherein R^{B7} is selected from

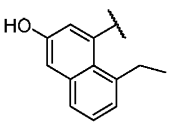
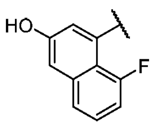
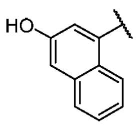
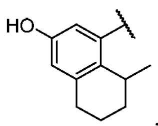
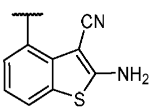
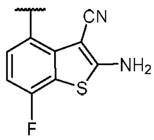
naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}.

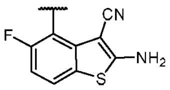
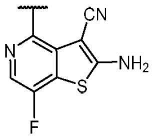
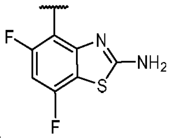
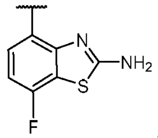
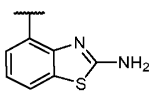
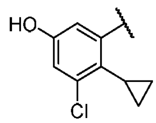
31. The compound, salt, solvate, or method of any one of the preceding claims, wherein R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, $-OR^{B22}$, $-N(R^{B22})(R^{B23})$, and C_{3-6} cycloalkyl.

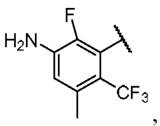
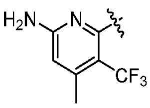
32. The compound, salt, solvate, or method of any one of the preceding claims, wherein R^{B7} is substituted with one, two, three, or four substituents independently selected from halogen, -CN, $-CH_3$, $-CH_2CH_3$, $-CH=CH_2$, $-CF_3$, -C≡CH, -OH, $-NH_2$, and -cyclopropyl.

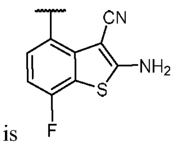
33. The compound, salt, solvate, or method of any one of the preceding claims, wherein R^{B7} is selected from

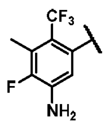
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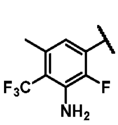
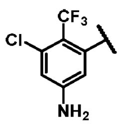
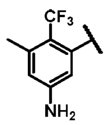
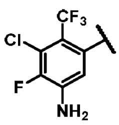
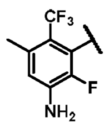
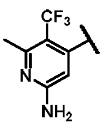
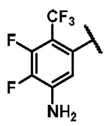
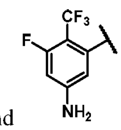
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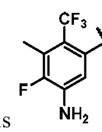
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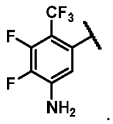
 , and  .

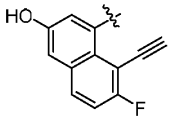
34. The compound, salt, solvate, or method of any one of the preceding claims, wherein R^{B7} is  .

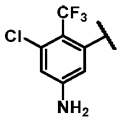
35. The compound, salt, solvate, or method of any one of claims 1 to 28, wherein R^{B7} is selected from  ,

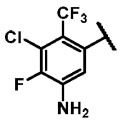
 ,  ,  ,  ,  ,  ,  , and  .

36. The compound, salt, solvate, or method of any one of claims 1 to 28, wherein R^{B7} is  .

37. The compound, salt, solvate, or method of any one of claims 1 to 28, wherein R^{B7} is  .

38. The compound, salt, solvate, or method of any one of claims 1 to 28, wherein R^{B7} is  .

39. The compound, salt, solvate, or method of any one of claims 1 to 28, wherein R^{B7} is  .

40. The compound, salt, solvate, or method of any one of claims 1 to 28, wherein R^{B7} is  .

41. The compound, salt, solvate, or method of any one of the preceding claims, wherein R^{B8} is halogen.

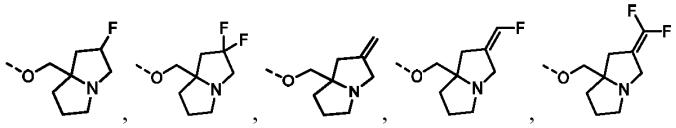
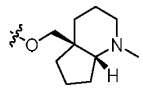
42. The compound, salt, solvate, or method of any one of claims 1 to 28, wherein:

R^{B6} is halogen;

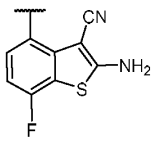
R^{B7} is selected from naphthyl, isoquinolinyl, indazolyl, benzothiazolyl, benzothiophenyl, phenyl, and pyridinyl, each of which is optionally substituted with one or more R^{B20}; and

R^{B8} is halogen.

43. The compound, salt, solvate, or method of any one of claims 1 to 21, wherein:

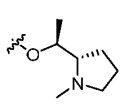
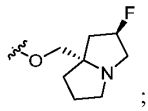
R^{B2} is selected from  , and  ;

R^{B6} is halogen;

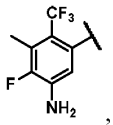
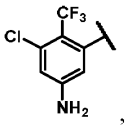
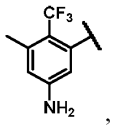
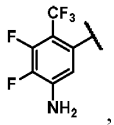
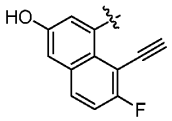
R^{B7} is  ; and

R^{B8} is halogen.

44. The compound, salt, solvate, or method of any one of claims 1 to 21, wherein:

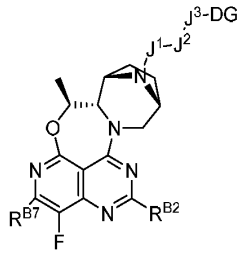
R^{B2} is selected from  and  ;

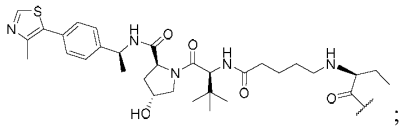
R^{B6} is halogen;

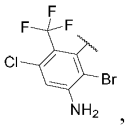
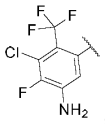
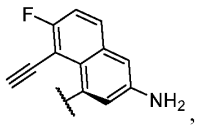
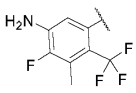
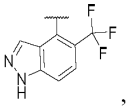
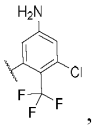
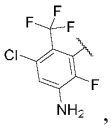
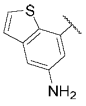
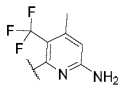
R^{B7} is selected from  ,  ,  ,  , and  ; and

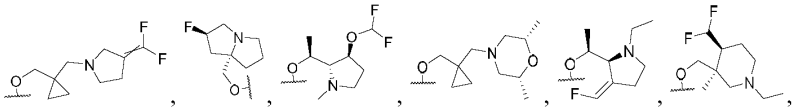
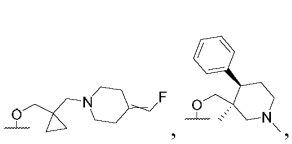
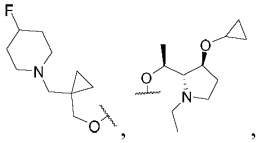
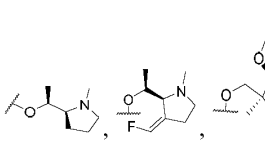
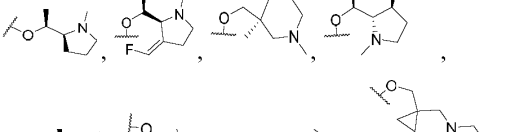
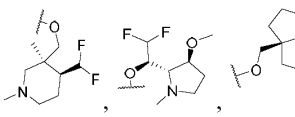
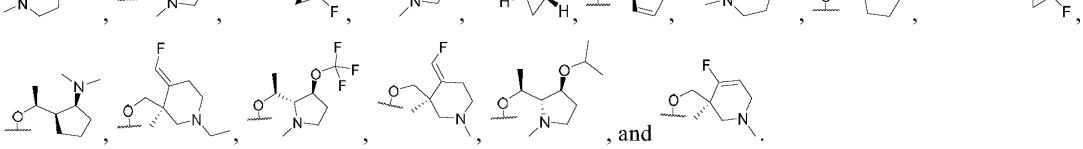
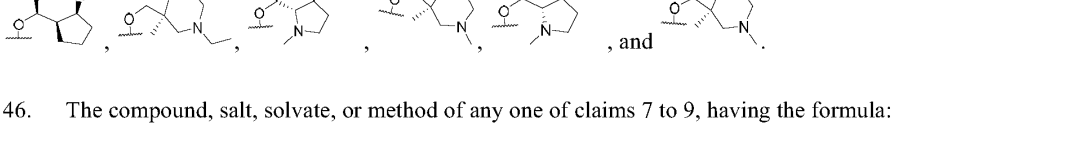
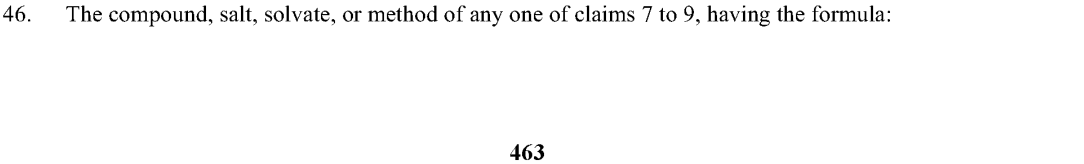
R^{B8} is halogen.

45. The compound, salt, solvate, or method of any one of claims 1, 2 and 7, having the formula:

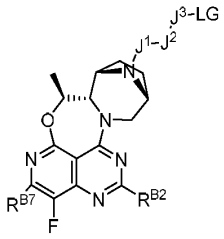


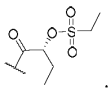
(A-7), wherein:-J^1-J^2-J^3-DG is  ;

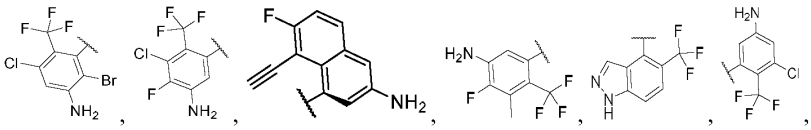
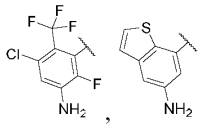
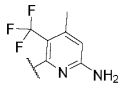
R^{B7} is selected from  ,  ,  ,  ,  ,  ,  ,  , and  ; and

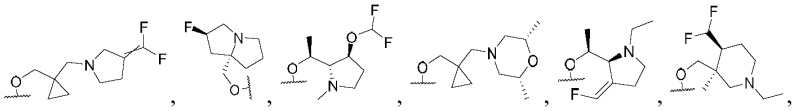
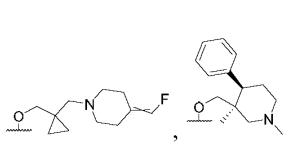
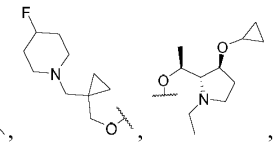
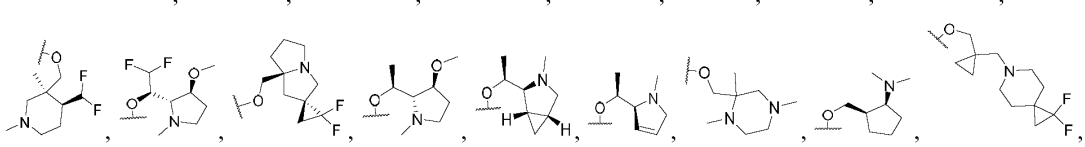
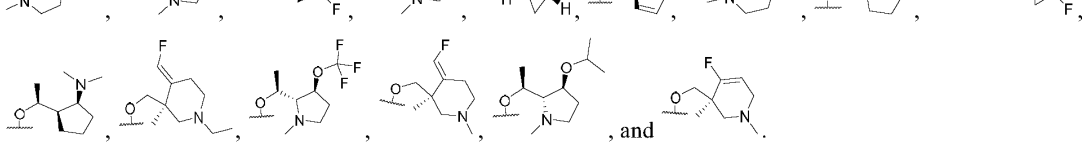
R^{B2} is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , and .

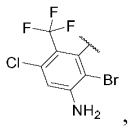
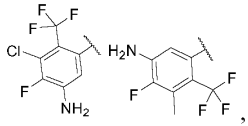
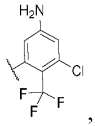
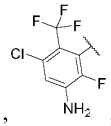
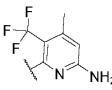
46. The compound, salt, solvate, or method of any one of claims 7 to 9, having the formula:

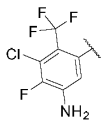
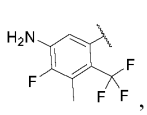
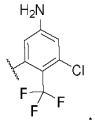


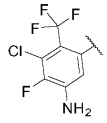
(a-7), wherein -J^1-J^2-J^3-LG is  .

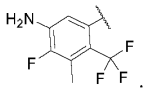
R^{B7} is selected from  ,  , and  ; and

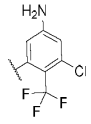
R^{B2} is selected from  ,  ,  ,  ,  , and .

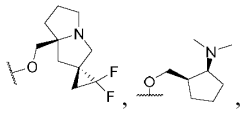
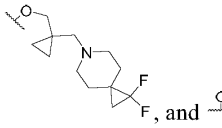
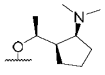
47. The compound, salt, solvate, or method of claim 45 or 46, wherein R^{B7} is selected from  ,  ,  ,  , and  .

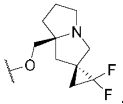
48. The compound, salt, solvate, or method of claim 45 or 46, wherein R^{B7} is selected from  ,  , and  .

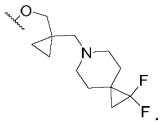
49. The compound, salt, solvate, or method of claim 45 or 46, wherein R^{B7} is  .

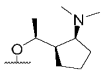
50. The compound, salt, solvate, or method of claim 45 or 46, wherein R^{B7} is  .

51. The compound, salt, solvate, or method of claim 45 or 46, wherein R^{B7} is  .

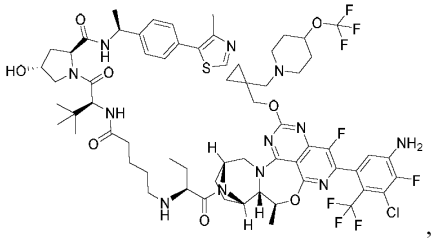
52. The compound, salt, solvate, or method of any one of claims 45 to 51, wherein R^{B2} is selected from  , ,  , and  .

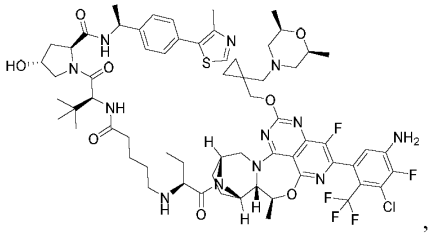
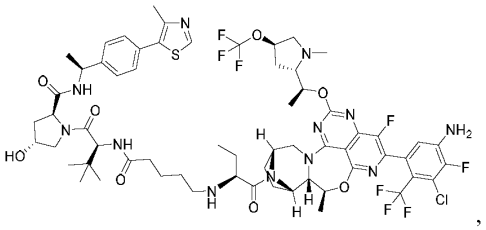
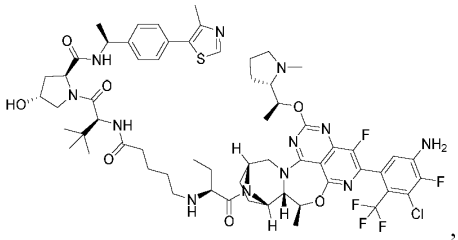
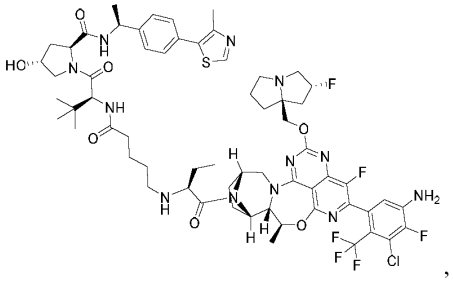
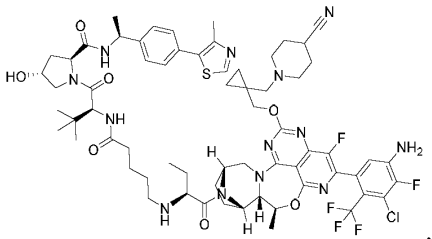
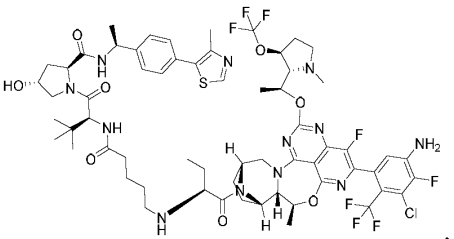
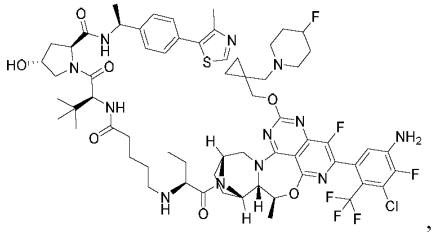
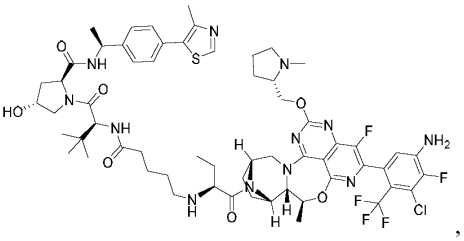
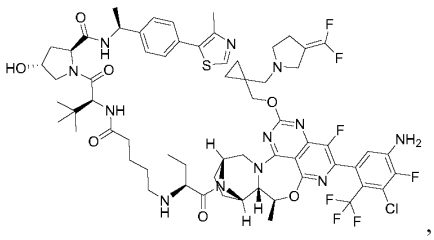
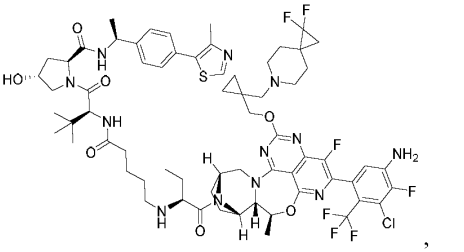
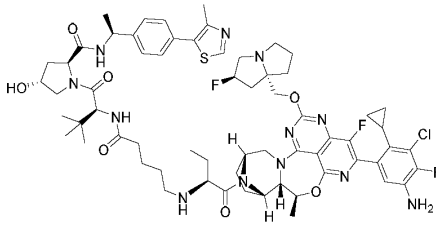
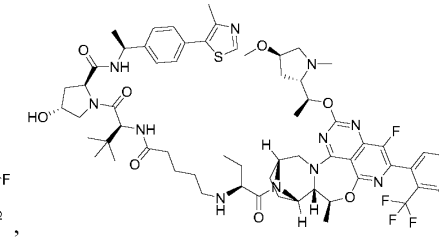
53. The compound, salt, solvate, or method of any one of claims 45 to 51, wherein R^{B2} is  .

54. The compound, salt, solvate, or method of any one of claims 45 to 51, wherein R^{B2} is  .

55. The compound, salt, solvate, or method of any one of claims 45 to 51, wherein R^{B2} is  .

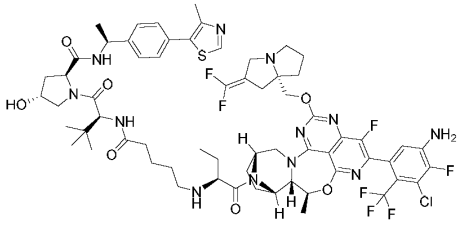
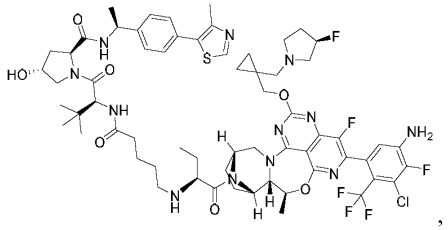
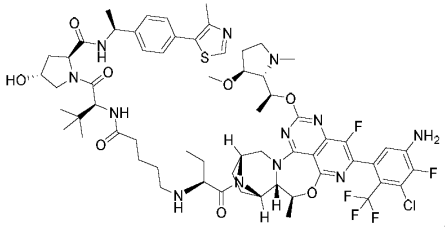
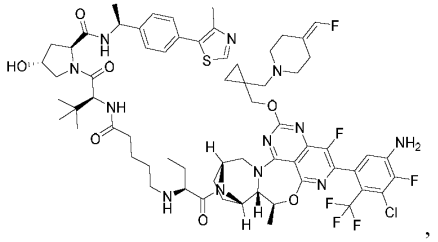
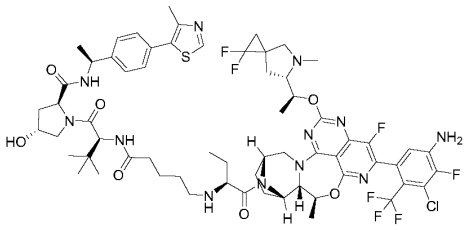
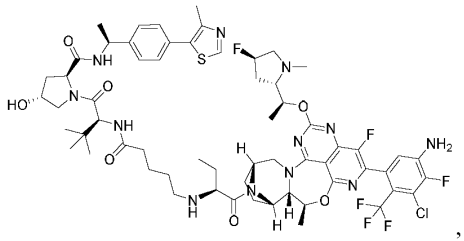
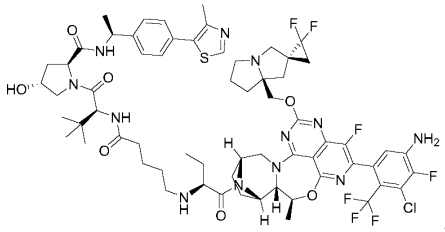
56. The compound, salt, solvate, or method of any one of claims 1, 7, and 8, wherein the compound is selected from a compound of Table 1.

57. A compound selected from  ,

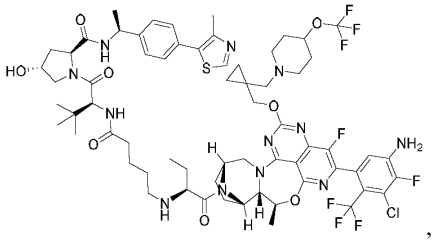
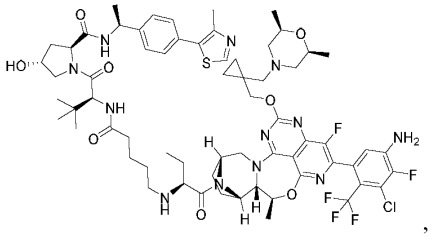
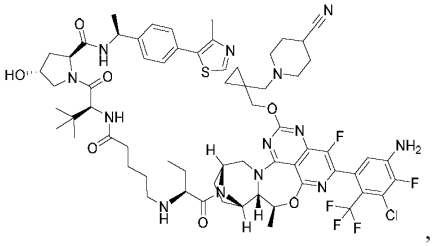

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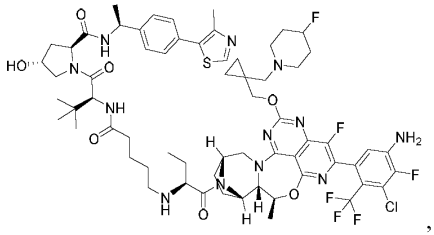
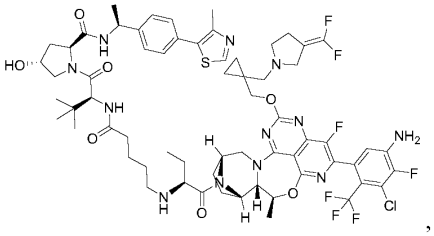
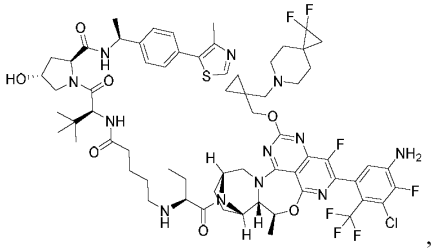
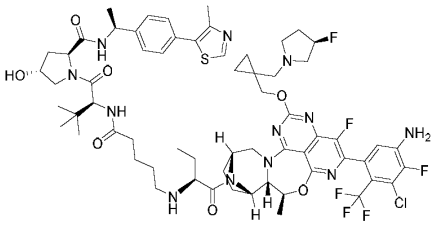
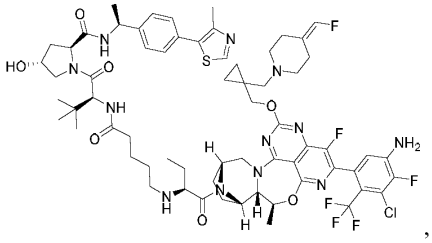
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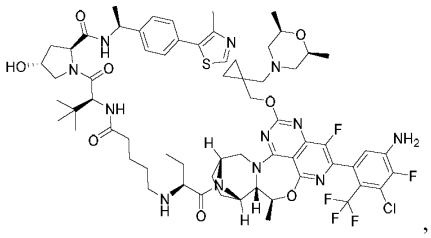
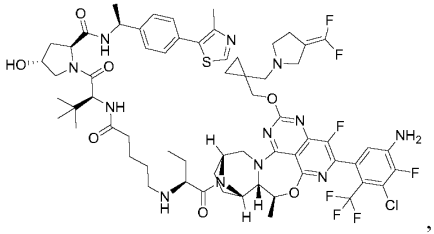
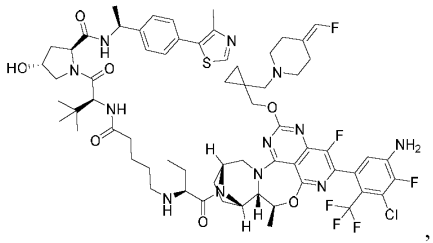
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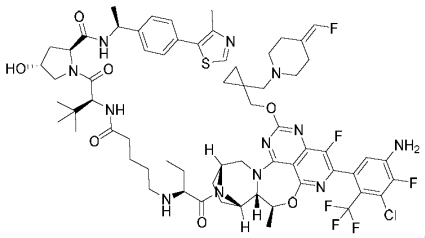

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, or a pharmaceutically acceptable salt or solvate thereof.

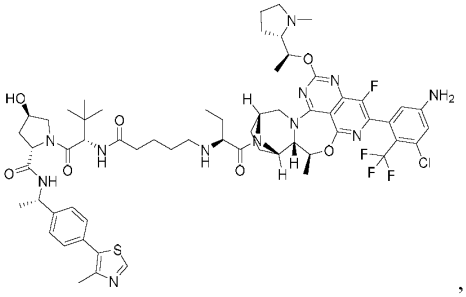
58. A compound selected from

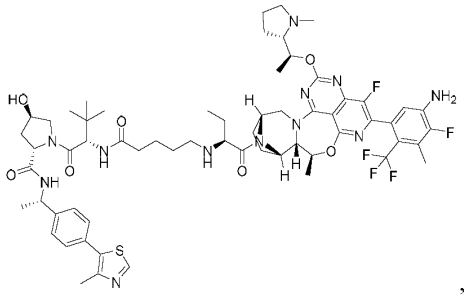
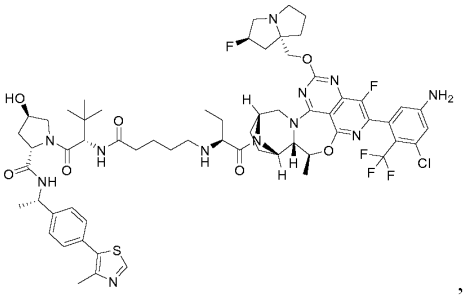
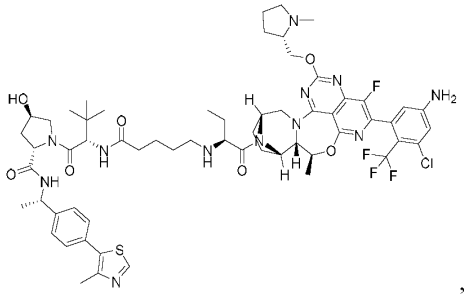

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, and

, or a pharmaceutically acceptable salt or solvate thereof.

59. A compound selected from

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, and

, or a pharmaceutically acceptable salt or solvate thereof.

60. A compound having the formula

, or a pharmaceutically acceptable salt or solvate thereof.

61. A compound selected from  ,

 ,  , and  , or a pharmaceutically acceptable salt or solvate thereof.

62. A pharmaceutical composition comprising a compound of any one of claims 1 to 6 or 8 to 61, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

63. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 6 or 8 to 61, or a pharmaceutically acceptable salt or solvate thereof.

64. A method of treating cancer in a subject comprising a Ras mutant protein, the method comprising: inhibiting the Ras mutant protein of said subject by administering to said subject a compound of any one of claims 1 to 6 or 8 to 61, wherein the compound is characterized in that upon contacting the Ras mutant protein, said Ras mutant protein exhibits reduced Ras signaling output.

65. The method of claim 63 or 64, wherein the cancer is a solid tumor or a hematological cancer.

66. A method of reducing signaling output of a Ras protein, comprising contacting a Ras protein with an effective amount of a compound of any one of claims 1 to 6 or 8 to 61, or a pharmaceutically acceptable salt or solvate thereof, thereby reducing the signaling output of the Ras protein.

67. The method of claim 66, wherein the compound binds covalently or non-covalently to the Ras protein,

thereby reducing the signaling output of the Ras protein.

68. A method of inhibiting cell growth, comprising administering an effective amount of a compound of any one of claims 1 to 6 or 8 to 61, or a pharmaceutically acceptable salt or solvate thereof, to a cell expressing a Ras protein, thereby inhibiting growth of said cells.

69. The method of any one of claims 63 to 68, comprising administering an additional agent.