



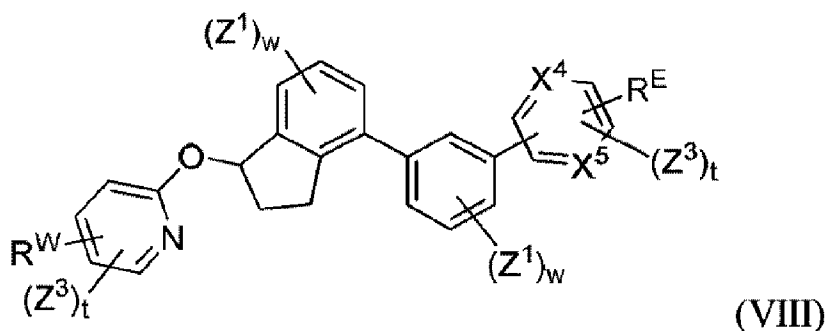
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(72) Inventeurs/Inventors:
AKTOUDIANAKIS, EVANGELOS, US;
APPLEBY, TODD, US;
CHO, AESOP, US;
DU, ZHIMIN, US;
GRAUPE, MICHAEL, US;
...

(73) Propriétaire/Owner:

(54) Titre : INHIBITEURS PD-1/PD-L1
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(57) Abrégé/Abstract:

The present invention pertains to compounds according to formula (VIII) or a pharmaceutically acceptable salt thereof.

(see formula VIII).

The invention also pertains to the use of said compounds singly or in combination with additional agents for inhibiting PD-1, PD-L1 and/or the PD-1/PD-L1 interaction or in the treatment of cancer and compositions of said compounds.



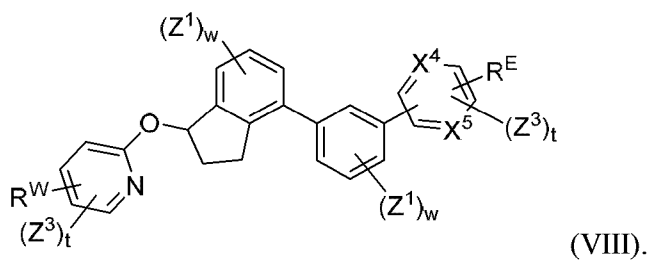
(72) **Inventeurs(suite)/Inventors(continued)**: GUERRERO, JUAN A., US; JABRI, SALMAN Y., US; LAD, LATESHKUMAR THAKORLAL, US; MACHICAO TELLO, PAULO A., US; MEDLEY, JONATHAN WILLIAM, US; METOBO, SAMUEL E., US; MUKHERJEE, PRASENJIT KUMAR, US; NADUTHAMBI, DEVAN, US; NOTTE, GREGORY, US; PARKHILL, ERIC Q., US; PHILLIPS, BARTON W., US; SIMONOVICH, SCOTT PRESTON, US; SQUIRES, NEIL H., US; VENKATARAMANI, CHANDRASEKAR, US; WANG, PEIYUAN, US; WATKINS, WILLIAM J., US; XU, JIE, US; YANG, KIN SHING, US; ZIEBENHAUS, CHRISTOPHER ALLEN, US

(73) **Propriétaires(suite)/Owners(continued)**: GILEAD SCIENCES, INC., US

(74) **Agent**: ROBIC AGENCE PI S.E.C./ROBIC IP AGENCY LP

ABSTRACT

The present invention pertains to compounds according to formula (VIII) or a pharmaceutically acceptable salt thereof:



The invention also pertains to the use of said compounds singly or in combination with additional agents for inhibiting PD-1, PD-L1 and/or the PD-1/PD-L1 interaction or in the treatment of cancer and compositions of said compounds.

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 4
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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

PD-1/PD-L1 INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATION

FIELD

The present disclosure generally relates to compounds useful as inhibitors of PD-1, PD-L1 or the PD-1/PD-L1 interaction. Provided herein are compounds, compositions comprising such compounds, and methods for their use.

BACKGROUND

Programmed death-1 (CD279) is a receptor on T cells that has been shown to suppress activating signals from the T cell receptor when bound by either of its ligands, Programmed death-ligand 1 (PD-L1, CD274, B7-H1) or PD-L2 (CD273, B7-DC). When PD-1 expressing T cells contact cells expressing its ligands, functional activities in response to antigenic stimuli, including proliferation, cytokine secretion, and cytotoxicity are reduced. PD-1/PD-Ligand interactions down regulate immune responses during resolution of an infection or tumor, or during the development of self-tolerance. Chronic antigen stimulation, such as that which occurs during tumor disease or chronic infections, results in T cells that express elevated levels of PD-1 and are dysfunctional with respect to activity towards the chronic antigen. This is termed "T cell exhaustion." B cells also display PD-1/PD-ligand suppression and "exhaustion."

Blockade of the PD-1/PD-L1 ligation using antibodies to PD-L1 has been shown to restore and augment T cell activation in many systems. Patients with advanced cancer benefit from therapy with a monoclonal antibody to PD-L1. Preclinical animal models of tumors and chronic infections have shown that blockade of the PD-1/PD-L1 pathway by monoclonal antibodies can enhance the immune response and result in tumor rejection or control of infection. Antitumor immunotherapy via PD-1/PD-L1 blockade may augment therapeutic immune response to a number of histologically distinct tumors.

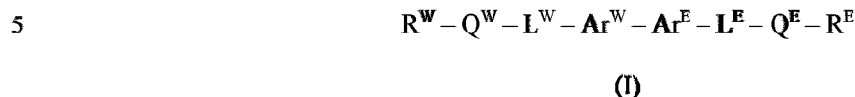
Interference with the PD-1/PD-L1 interaction has also shown enhanced T cell activity in chronic infection systems. Chronic lymphocytic chorio meningitis virus infection of mice also exhibits improved virus clearance and restored immunity with blockade of PD-L1. Humanized mice infected with HIV-1 show enhanced protection against viremia and viral depletion of CD4+ T cells. Blockade of PD-1/PD-L1 through monoclonal antibodies to PD-L1 can restore in vitro antigen-specific functionality to T cells from HIV patients, HCV patients or HBV.

Accordingly, agents that block PD-1, PD-L1 and/or the PD-1/PD-L1 interaction are desired. Small molecule agents that block or inhibit PD-1, PD-L1 and/or the PD-1/PD-L1 interaction are particularly desired. Applicants have discovered small molecule compounds that have activity as

inhibitors of PD-1, PD-L1 or inhibitors of the interaction of PD-1 with PD-L1, and thus may be useful for treating patients having cancer.

SUMMARY

The present disclosure provides a compound of formula (I):



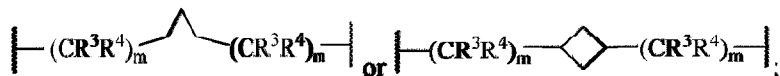
wherein:

Ar^E and Ar^W are each independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, $-OR^a$, $-NO_2$, $-CN$, $-NR^aR^b$, $-N_3$, $-SO_2R^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-OC_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-6}$ alkyl C_{3-8} cycloalkyl;

wherein each alkyl, alkenyl, alkynyl, and cycloalkyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

L^E and L^W are each independently a bond, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-(CR^3R^4)_m-$, $-(CR^3R^4)_mO(CR^3R^4)_m-$, $-(CR^3R^4)_mS(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3(CR^3R^4)_m-$, $-C(O)-$, $-(CR^3R^4)_mC(O)(CR^3R^4)_m-$, $-(CR^3R^4)_mC(O)NR^3(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3C(O)(CR^3R^4)_m-$, C_{2-6} alkenylene, C_{2-6} alkynylene,



wherein

each m is independently 0, 1, 2, 3 or 4;

Q^E and Q^W are each independently aryl, heteroaryl, or heterocyclyl,

wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, oxo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

wherein each alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic

group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

wherein

R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)OR^1$, $-SC_{1-6}$

alkyl NR^1R^2 , $-C_{1-6}$ alkyl OR^a , or $L^1-V-L^2-\textcircled{A}$;

wherein

L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, C_{3-8} cycloalkyl, and C_{1-6} alkyl C_{3-8} cycloalkyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $IN^+R^1R^2R^3$, $-SC_{1-6}$ alkyl NR^1R^2 , $-C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_uSO_2NR^1R^2$, $-(CH_2)_uNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}$ alkyl NR^1R^2 , $-NR^aSO_2C_{1-6}$ alkyl NR^1R^2 , $-(CH_2)_uC(O)NR^aSO_2NR^aR^b$, $-(CH_2)_uN^+R^1R^2O^-$, $-(CH_2)_uP^+R^bR^cR^d$, $-(CH_2)_uP^+R^cR^dO^-$, $-(CH_2)_uP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_uNR^cP(O)(OR^c)_2$, $-(CH_2)_uNR^c(CH_2)_uP(O)(OR^c)_2$, $-(CH_2)_uCH_2OP(O)(OR^c)(OR^d)$, $-(CH_2)_uOP(O)(OR^c)(OR^d)$, $-(CH_2)_uOP(O)NR^aR^b(OR^a)$, or $-V^2-(CR^cR^d)_p-L^3-\textcircled{B}-(T)_z$;

wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

ring **B** is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently H, OR^a , $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^e$, $(CH_2)_qOR^a$, or $(CH_2)_qC(O)R^e$;

p is independently 0, 1, 2, 3, 4, or 5;

5 **q** is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4; and

z is 0, 1, 2, or 3;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from NR^aR^b , halo, cyano, oxo, OR^a , $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl NR^aR^b , $-C_{1-6}$ alkylOH, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;

provided that at least one of V^2 , L^3 , ring **B** and **T** contains a nitrogen atom;

R^1 is independently selected from H, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl $C(O)OR^a$, $-C_{2-6}$ alkenyl $C(O)OR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-C(O)NR^aSO_2R^a$, and $-C_{1-6}$ alkyl C_{3-8} cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from OR^a , $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $NR^aC(O)OR^b$, $-C_{1-6}$ alkyl INR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, $-C_{1-6}$ alkyl $C(O)NR^aSO_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}$ alkyl $INR^aC(O)R^b$;

R^2 is independently selected from H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl OR^a , $-C_{1-6}$ alkyl $C(O)OR^a$, and $-C_{2-6}$ alkenyl $C(O)OR^a$;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkyl INR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$ and $-NR^aC(O)R^b$;

or R^1 and R^2 combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1

to 3 groups independently selected from oxo, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, and -C₁₋₆ alkylSO₂NR^aR^b;

- 5 R³ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or -C₂₋₆ alkenylC(O)OR^a;

R⁴ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or

- 10 -C₂₋₆ alkenylC(O)OR^a;

R^a is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

R^b is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

- 15 or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, -C₁₋₆ alkylOR^f, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^f, -C₁₋₆ alkylC(O)R^f, -C(O)OR^f, -C₁₋₆ alkylC(O)OR^f, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆ alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆ alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆ alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and
- 20 -NR^fC(O)R^g;

R^c is independently selected from H, OH, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

R^d is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

- 25 R^e is independently selected from H, -C₁₋₆ alkyl, -OC₁₋₆alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -OC₃₋₈ cycloalkyl, -Oaryl, -Oheteroaryl, -Oheterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆ alkylC(O)NR^fR^g, -NHSO₂R^f, -C₁₋₆ alkylSO₂R^f, and -C₁₋₆ alkylSO₂NR^fR^g;

R^f is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,

- 30 -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl; and

R^g is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

The present disclosure further provides a compound of formula (I):



(I)

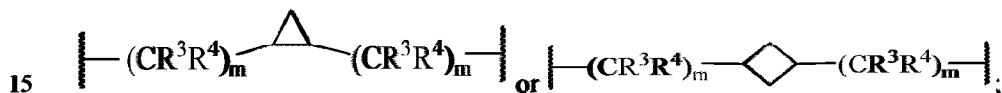
wherein:

5 Ar^E and Ar^W are each independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, $-OR^a$, $-NO_2$, $-CN$, $-NR^aR^b$, $-N_3$, $-SO_2R^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-OC_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-6}$ alkyl C_{3-8} cycloalkyl;

10 wherein each alkyl, alkenyl, alkynyl, and cycloalkyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

L^E and L^W are each independently a bond, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-(CR^3R^4)_m-$, $-(CR^3R^4)_mO(CR^3R^4)_m-$, $-(CR^3R^4)_mS(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3(CR^3R^4)_m-$, $-C(O)-$, $-(CR^3R^4)_mC(O)(CR^3R^4)_m-$, $-(CR^3R^4)_mC(O)NR^3(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3C(O)(CR^3R^4)_m-$, C_{2-6} alkenylene, C_{2-6} alkynylene,



wherein

each m is independently 1, 2, 3 or 4;

provided that when one of Ar^E and Ar^W is optionally substituted phenyl and the other is optionally substituted phenyl or optionally substituted 2,3-dihydrobenzo[b][1,4]dioxine, and one of L^E and L^W is $-CH_2O-$, $-CH_2CH_2-$, $-CHCH-$, and $-C(O)N-$; then the other of L^E and L^W is a bond, $-O-$ or $-CH_2O-$ of the formula $Ar-CH_2O-Q$;

20

Q^E and Q^W are each independently aryl, heteroaryl, or heterocyclyl,

wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, oxo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, and R^N ;

25

wherein each alkyl, alkenyl, alkynyl, is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkyl CN , $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

30

wherein

R^N is independently $-C_{1-6}alkylINR^1R^2$, $-OC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylINR^1R^2$,
 $-NR^aC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)OR^1$,
 $-SC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOR^a$, or

$$L^1-V-L^2-\textcircled{A};$$

wherein

5 L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, and $C_{2-6}alkynyl$;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted
 with OR^a , halo, cyano, $-NR^aR^b$ or $-C_{3-8}cycloalkyl$;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

10 provided at least one of L^1 , V and L^2 is other than a bond;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally
 substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$,
 halo, cyano, $-C_{1-6}alkyl$, $-C_{1-6}haloalkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-OC_{1-6}$
 15 haloalkyl, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}alkylCN$, $-C(O)NR^aR^b$,
 $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$,
 $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $C_{3-8}cycloalkyl$,
 and $C_{1-6}alkylC_{3-8}cycloalkyl$;

wherein each alkyl, alkenyl, or alkynyl is optionally independently
 20 substituted with OR^a , halo, cyano, $-NR^aR^b$ and $-C_{3-8}cycloalkyl$;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}alkylINR^1R^2$, $-OC_{1-6}alkylINR^1R^2$,
 $-C_{1-6}alkylOC_{1-6}alkylINR^1R^2$, $-NR^aC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylIN^+R^1R^2R^3$, $-SC_{1-6}alkylINR^1R^2$,
 $-C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_uSO_2NR^1R^2$, $-(CH_2)_uNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}alkylINR^1R^2$,
 $-NR^aSO_2C_{1-6}alkylINR^1R^2$, $-(CH_2)_uC(O)NR^aSO_2NR^aR^b$, $-(CH_2)_uN^+R^1R^2O^-$, $-(CH_2)_uP^+R^bR^cR^d$,
 25 $-(CH_2)_uP^+R^cR^dO^-$, $-(CH_2)_uP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_uNR^cP(O)(OR^c)_2$, $-(CH_2)_uNR^c(CH_2)_uP(O)(OR^c)_2$,
 $-(CH_2)_uCH_2OP(O)(OR^c)(OR^d)$, $-(CH_2)_uOP(O)(OR^c)(OR^d)$, $-(CH_2)_uOP(O)NR^aR^b(OR^a)$, or
 $-V^2-(CR^cR^d)_p-L^3-\textcircled{B}-(T)_z$;

wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

30 L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

ring B is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently H, OR^a, (CH₂)_qNR^aR², (CH₂)_qNR^aC(O)R^e, (CH₂)_qOR^a, or (CH₂)_qC(O)R^e;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4; and

5 z is 0, 1, 2, or 3;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 3 substituents independently selected from NR^aR^b, halo, cyano, oxo, OR^a, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylNR^aR^b, -C₁₋₆ alkylOH, -C₃₋₈ cycloalkyl, and -C₁₋₃ alkylC₃₋₈cycloalkyl;

10 provided that at least one of V², L³, ring B and T contains a nitrogen atom, and when each of V² and L³ is a bond and p is 0, then either (i) neither of L^E or L^W is a bond or (ii) ring B is not a 5,6-membered fused heteroaryl where the 5-membered ring of the fused heteroaryl is bound to the corresponding Q^E or Q^W;

R¹ is independently selected from H, -C₁₋₈ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl, 15 heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₁₋₆ alkylC(O)OR^a, -C₂₋₆ alkenylC(O)OR^a, -SO₂R^a, -SO₂NR^aR^b, -C(O)NR^aSO₂R^a, and C₁₋₆ alkylC₃₋₈cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆ alkyl, -C₁₋₆ alkylOR^a, 20 -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkyl C(O)R^a, -C(O)OR^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, NR^aC(O)OR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆ alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆ alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and -C₁₋₆ alkylNR^aC(O)R^b;

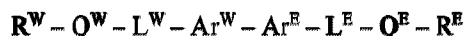
25 R² is independently selected from H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, and -C₂₋₆ alkenylC(O)OR^a;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆ alkyl, 30 -C₁₋₆ alkylOR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C(O)OR^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆ alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b and -NR^aC(O)R^b;

- or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a,
 5 C₁₋₆ alkylC(O)R^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆ alkylSO₂NR^aR^b;
- R³ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or -C₂₋₆ alkenylC(O)OR^a;
- R⁴ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl,
 10 -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or -C₂₋₆ alkenylC(O)OR^a;
- R^a is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;
- R^b is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;
- 15 or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, -C₁₋₆ alkylOR^f, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^f, -C₁₋₆ alkylC(O)R^f, -C(O)OR^f, -C₁₋₆ alkylC(O)OR^f, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆ alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆ alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆ alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and
 20 -NR^fC(O)R^g;
- R^c is independently selected from H, OH, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;
- R^d is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;
- 25 R^e is independently selected from H, -C₁₋₆ alkyl, -OC₁₋₆alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -OC₃₋₈ cycloalkyl, -Oaryl, -Oheteroaryl, -Oheterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆ alkylC(O)NR^fR^g, -NHSO₂R^f, -C₁₋₆ alkylSO₂R^f, and -C₁₋₆ alkylSO₂NR^fR^g;
- R^f is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
 30 -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl; and
- R^g is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

The present disclosure further provides a compound of formula (I):



(I)

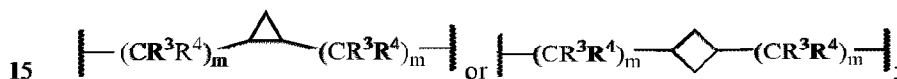
wherein:

5 Ar^E and Ar^W are each independently a cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, $-OR^a$, $-NO_2$, $-CN$, $-NR^aR^b$, $-N_3$, $-SO_2R^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-OC_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-6}$ alkyl C_{3-8} cycloalkyl; and

10 wherein each alkyl, alkenyl, alkynyl, and cycloalkyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

L^E and L^W are each independently a bond, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-(CR^3R^4)_m-$, $-(CR^3R^4)_mO(CR^3R^4)_m-$, $-(CR^3R^4)_mS(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3(CR^3R^4)_m-$, $-C(O)-$, $-(CR^3R^4)_mC(O)(CR^3R^4)_m-$, $-(CR^3R^4)_mC(O)NR^3(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3C(O)(CR^3R^4)_m-$, C_{2-6} alkenylene, C_{2-6} alkynylene,



wherein each m is independently 0, 1, 2, 3 or 4;

Q^E and Q^W are each independently aryl, heteroaryl, or heterocyclyl;

wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, oxo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ; and

25 wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ cyanoalkyl, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and further wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

30

R^N is independently $-C_{1-6}alkyl|NR^1R^2$, $-OC_{1-6}alkyl|NR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkyl|NR^1R^2$,
 $-NR^aC_{1-6}alkyl|NR^1R^2$, $-C_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)OR^1$,
 $-SC_{1-6}alkyl|NR^1R^2$, $-C_{1-6}alkyl|OR^a$, or

$$L^1-V-L^2-\textcircled{A};$$

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

5 V is independently selected from a bond, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, and $C_{2-6}alkynyl$;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted
 with OR^a , halo, cyano, $-NR^aR^b$ or $-C_{3-8}cycloalkyl$;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

10 wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally
 substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$,
 halo, cyano, $-C_{1-6}alkyl$, $-C_{1-6}haloalkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-OC_{1-6}$
 $haloalkyl$, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}alkylCN$, $-C(O)NR^aR^b$,
 $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$,
 15 $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $C_{3-8}cycloalkyl$,
 and $C_{1-6}alkylC_{3-8}cycloalkyl$; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently
 substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}cycloalkyl$;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}alkyl|NR^1R^2$, $-OC_{1-6}alkyl|NR^1R^2$,
 20 $-C_{1-6}alkylOC_{1-6}alkyl|NR^1R^2$, $-NR^aC_{1-6}alkyl|NR^1R^2$, $-C_{1-6}alkyl|NR^1R^2R^3$, $-SC_{1-6}alkyl|NR^1R^2$,
 $-C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_nSO_2NR^1R^2$, $-(CH_2)_nNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}alkyl|NR^1R^2$, $-NR^aSO_2C_{1-6}$
 $alkyl|NR^1R^2$, $-(CH_2)_nC(O)NR^aSO_2NR^aR^b$, $-(CH_2)_nN^+R^1R^2O^-$, $-(CH_2)_nP^+R^bR^cR^d$, $-(CH_2)_nP^+R^cR^dO^-$,
 $-(CH_2)_nP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_nNR^aP(O)(OR^c)_2$, $-(CH_2)_nCH_2OP(O)(OR^c)(OR^d)$,
 $-(CH_2)_nOP(O)(OR^c)(OR^d)$, $-(CH_2)_nOP(O)NR^aR^b(OR^a)$, or

25 $-V^2-(CR^cR^d)_p-L^3-\textcircled{B}-(T)_z$;

wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

ring B is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

30 T is independently H, OR^a , $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^c$, or $(CH_2)_qC(O)R^c$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted

5 with 1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a , $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl NR^aR^b , $-C_{1-6}$ alkylOH, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

10 R^1 is independently selected from H, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkylC(O) OR^a , $-C_{2-6}$ alkenylC(O) OR^a , $-SO_2R^a$, $-SO_2NR^aR^b$, $-C(O)NR^aSO_2R^a$, and $-C_{1-6}$ alkyl C_{3-8} cycloalkyl;

15 wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkylC(O) R^a , $-C(O)OR^a$, $-C_{1-6}$ alkylC(O) OR^a , $-NR^aR^b$, $-OC(O)NR^aR^b$, $NR^aC(O)OR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkylC(O) NR^aR^b , $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, $-C_{1-6}$ alkylC(O) $NR^aSO_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}$ alkyl $NR^aC(O)R^b$;

R^2 is independently selected from H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl OR^a , $-C_{1-6}$ alkylC(O) OR^a , and $-C_{2-6}$ alkenylC(O) OR^a ;

25 wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkylC(O) R^a , $-C(O)OR^a$, $-C_{1-6}$ alkylC(O) OR^a , $-NR^aR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, C_{1-6} alkylC(O) NR^aR^b , $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$ and $-NR^aC(O)R^b$;

30 or R^1 and R^2 combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OR^a$, $-C(O)OR^a$, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ haloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, C_{1-6} alkylC(O) R^a , $-C_{1-6}$ alkylC(O) OR^a , $-NR^aR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkylC(O) NR^aR^b , $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, and C_{1-6} alkyl $SO_2NR^aR^b$;

R^3 is independently H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, or $-C_{2-6}$ alkenylC(O)OR^a;

R^4 is independently H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl,
5 $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, or $-C_{2-6}$ alkenylC(O)OR^a;

R^a is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^b is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl,
10 $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, $-C_{1-6}$ alkylOR^f, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^f$, $-C_{1-6}$ alkylC(O)R^f, $-C(O)OR^f$, $-C_{1-6}$ alkylC(O)OR^f, $-NR^fR^g$, $-C_{1-6}$ alkylINR^fR^g, $-C(O)NR^fR^g$,
15 $-C_{1-6}$ alkylC(O)NR^fR^g, $-SO_2R^f$, $-C_{1-6}$ alkylSO₂R^f, $-SO_2NR^fR^g$, $-C_{1-6}$ alkylSO₂NR^fR^g, $-C(O)NR^fSO_2R^g$ and $-NR^fC(O)R^g$;

R^c is independently selected from H, OH, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^d is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl,
20 $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^e is independently selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkylINR^fR^g, $-C(O)NR^fR^g$, $-C_{1-6}$ alkylC(O)NR^fR^g, $-NH$ SO₂R^f, $-C_{1-6}$ alkylSO₂R^f, and $-C_{1-6}$ alkylSO₂NR^fR^g;

R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl,
25 $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and

R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer
30 thereof.

In one embodiment of formula (I), both Ar^E and Ar^W are optionally substituted bicyclic rings, wherein neither is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring. In one embodiment of formula (I), both L^E and L^W are -O-. In one embodiment of formula (I), both L^E and L^W are -Q-O-CH₂-Ar-. In one embodiment of formula (I), each of Ar^E, Ar^W, Q^E, and Q^W are monocyclic,

provided at least two are heteroaryl, and neither of R^E , and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring. In one embodiment of formula (I), at least one L is a bond, and none of Ar^E , Ar^W , Q^E , Q^W , R^E , and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring. In one embodiment of formula (I), at least one of the following occurs: a) both Ar^E and Ar^W are optionally substituted bicyclic rings, wherein neither is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring; or both L^E and L^W are -O-; b) both L^E and L^W are -Q-O-CH₂-Ar-; c) each of Ar^E , Ar^W , Q^E , and Q^W are monocyclic, provided at least two are heteroaryl, and neither of R^E , and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring; or d) at least one L is a bond, and none of Ar^E , Ar^W , Q^E , Q^W , R^E , and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

10 The present disclosure provides a method of inhibiting PD-1, PD-L1 and/or the PD-1/PD-L1 interaction comprising administering a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, to a patient in need thereof.

The present disclosure provides a method of treating cancer comprising administering a therapeutically effective amount of a compound formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof, to a patient in need thereof.

15 One embodiment provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, for the treatment of cancer or a condition in a patient that is amenable to treatment by inhibiting PD-1, PD-L1 or the PD-1/PD-L1 interaction comprising administering said compound of formula (I) to said patient in need thereof.

20 In one embodiment, provided is a method for treating a cancer wherein the cancer is pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft tissue sarcoma, non-small cell lung cancer, small-cell lung cancer or colon cancer, comprising administering a therapeutically effective amount of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof to a patient in need thereof.

25 In one embodiment, provided is a method for treating a cancer or a condition in a patient that is amenable to treatment by inhibiting PD-1, PD-L1 or the PD-1/PD-L1 interaction selected from pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft tissue sarcoma, non-small cell lung cancer, small-cell lung cancer and colon cancer comprising administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof to a patient in need thereof, further comprising at least one additional anticancer agent or therapy selected from nivolumab, pembrolizumab,

atezolizumab, ipilimumab, chemotherapy, radiation therapy, and resection therapy, to a patient in need thereof.

In one embodiment, provided is a method for treating HBV, comprising administering a therapeutically effective amount of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof to a patient in need thereof.

In one embodiment, provided is a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, for the treatment of cancer or a condition in a patient selected from lymphoma, multiple myeloma, and leukemia. Additional diseases or conditions that may be treated include, but are not limited to acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myeloid leukemia (CML), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma, Waldstrom's macroglobulinemia (WM), T-cell lymphoma, B-cell lymphoma and diffuse large B-cell lymphoma (DLBCL).

In one embodiment, the present disclosure provides a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, in combination with at least one additional anti-cancer agent selected from rituxan, doxorubicin, gemcitabine, nivolumab, pembrolizumab, and ipilimumab.

In one embodiment, the present disclosure provides a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, in combination with at least one additional check-point inhibitor selected from nivolumab, pembrolizumab, atezolizumab, and ipilimumab.

In one embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, and a pharmaceutically acceptable carrier or excipient.

In one embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, and at least one additional anticancer agent and at least one pharmaceutically acceptable carrier or excipient.

In one embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, at least one additional therapeutic agent suitable for treating an HBV infection, and at least one pharmaceutically acceptable carrier or excipient.

In one embodiment, the present disclosure provides a kit that includes a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, a label

and/or instructions for use of the compound in the treatment of cancer or a disease or condition mediated by PD-1, PD-L1 activity or the PD-1/PD-L1 interaction.

In one embodiment, the present disclosure provides a kit that includes a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, at least one additional anticancer agent, a label(s) and/or instructions for use of the compound(s) in the treatment of a disease or condition mediated by PD-1, PD-L1 activity or PD-1/PD-L1 interaction.

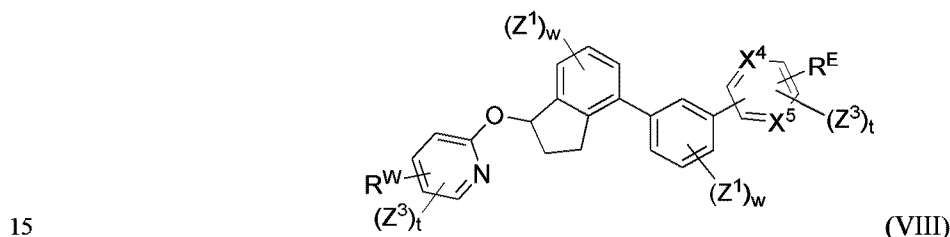
In one embodiment, the present disclosure provides articles of manufacture that include a compound of formula (I) or a pharmaceutically acceptable salt, or solvate thereof; and a container. In one embodiment, the container may be a vial, jar, ampoule, preloaded syringe, or an intravenous bag.

In one embodiment, the present disclosure provides a compound of formula (I) for use in therapy.

In another embodiment, the present disclosure provides a compound of formula (I) for use in the manufacture of a medicament for treating cancer.

The following embodiments are provided:

Embodiment 1. A compound of formula (VIII):



wherein:

each of X^4 and X^5 are independently N, CH or CZ^3 ;

each Z^1 is independently halo, $-OR^a$, or $-C_{1-6}$ alkyl;

wherein each alkyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

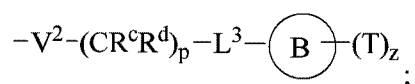
each w is independently 0, 1 or 2;

each Z^3 is independently halo, $-OR^a$ or $-C_{1-6}$ alkyl; and

wherein the alkyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-O-C_{1-6}$ cyanoalkyl, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

each t is independently 0, 1 or 2;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}$ alkyl NR^1R^2 , $-O-C_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^a-C_{1-6}$ alkyl NR^1R^2 , or



wherein:

V^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

L^3 is independently a bond, O, NR^a , S, SO, or SO_2 ;

5 ring B is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently H, OR^a , $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^e$, or $(CH_2)_qC(O)R^e$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

z is 0, 1, or 2; and

10 wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a , $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl NR^aR^b , $-C_{1-6}$ alkylOH, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;

provided that at least one of V^2 , L^3 , ring B, and T contains a nitrogen atom;

15 each R^1 is independently selected from H, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl $C(O)OR^a$, $-C_{2-6}$ alkenyl $C(O)OR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-C(O)NR^aSO_2R^a$, and $-C_{1-6}$ alkyl C_{3-8} cycloalkyl;

20 wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $NR^aC(O)OR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, $-C_{1-6}$ alkyl $C(O)NR^aSO_2R^b$, $-NR^aC(O)R^b$, and

25 $-C_{1-6}$ alkyl $NR^aC(O)R^b$;

each R^2 is independently selected from H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl $-OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, and $-C_{2-6}$ alkenyl $C(O)OR^a$;

30 wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkyl NR^aR^b ,

-C(O)NR^aR^b, C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆ alkylSO₂NR^aR^b,
-C(O)NR^aSO₂R^b and -NR^aC(O)R^b;

or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional
heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1
5 to 3 groups independently selected from oxo, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl,
-OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a,
C₁₋₆ alkylC(O)R^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b,
-SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆ alkylSO₂NR^aR^b;

each R^a is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
10 -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

each R^b is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S;
wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo,
15 -C₁₋₆ alkylOR^f, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^f,
-C₁₋₆ alkylC(O)R^f, -C(O)OR^f, -C₁₋₆ alkylC(O)OR^f, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g,
-C₁₋₆ alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆ alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆ alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and
-NR^fC(O)R^g;

each R^c is independently selected from H, OH, -C₁₋₆ alkyl, and -C₃₋₈ cycloalkyl;

20 R^d is independently selected from H, -C₁₋₆ alkyl, and -C₃₋₈ cycloalkyl;

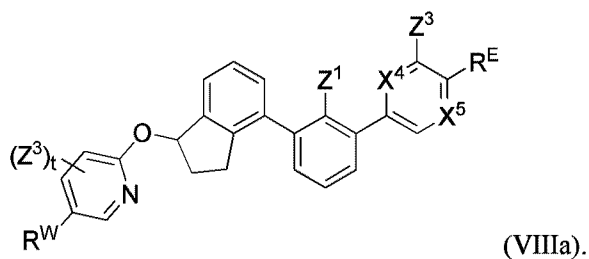
each R^e is independently selected from H, -C₁₋₆ alkyl, -O-C₁₋₆alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl,
heterocyclyl, -O-C₃₋₈ cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl,
-C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆ alkylC(O)NR^fR^g,
-NH₂SO₂R^f, -C₁₋₆ alkylSO₂R^f, and -C₁₋₆ alkylSO₂NR^fR^g;

25 each R^f is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈ cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl; and

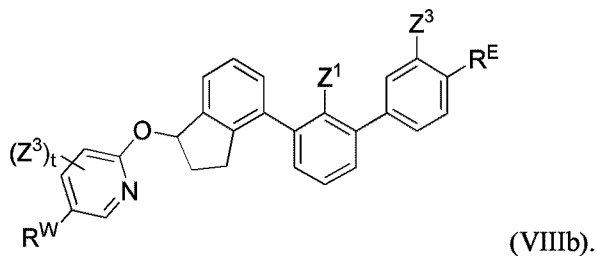
each R^g is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈ cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

or a pharmaceutically acceptable salt thereof.

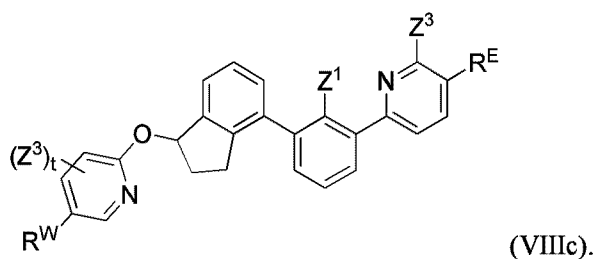
30 Embodiment 2. The compound of embodiment 1, wherein the compound is represented by a compound
of formula (VIIIa):



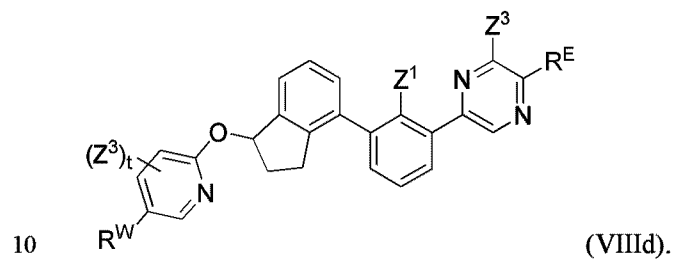
Embodiment 3. The compound of embodiment 1, wherein the compound is represented by a compound of formula (VIIIb):



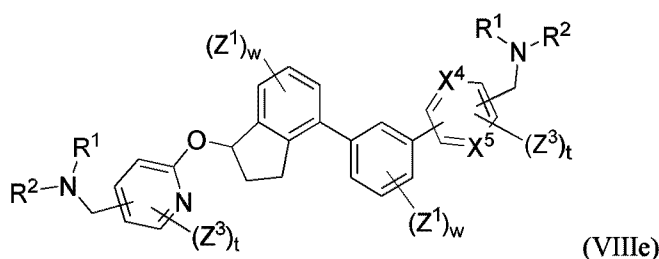
- 5 Embodiment 4. The compound of embodiment 1, wherein the compound is represented by a compound of formula (VIIIc):



Embodiment 5. The compound of embodiment 1, wherein the compound is represented by a compound of formula (VIId):



Embodiment 6. The compound of embodiment 1, wherein the compound is represented by a compound of formula (VIIE):



wherein:

each of X^4 and X^5 are independently N, CH or CZ^3 ;

each Z^1 is independently halo, $-OR^a$, or $-C_{1-6}$ alkyl;

5 each w is independently 0, 1 or 2;

each Z^3 is independently halo, $-OR^a$ or $-C_{1-6}$ alkyl, ; and

wherein the alkyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-O-C_{1-6}$ cyanoalkyl, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, -
 10 $C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

each t is independently 0, 1 or 2;

each R^1 is independently selected from H, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkylC(O) OR^a , $-C_{2-6}$ alkenylC(O) OR^a , $-SO_2R^a$, $-SO_2NR^aR^b$, $-C(O)NR^aSO_2R^a$, and C_{1-6} alkylC<sub>3-
 15 8cycloalkyl;</sub>

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkylC(O) R^a , $-C(O)OR^a$, $-C_{1-6}$ alkylC(O) OR^a , $-NR^aR^b$, $-OC(O)NR^aR^b$, $-NR^aC(O)OR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkylC(O)NR^aR^b, $-SO_2R^a$, $-C_{1-6}$ alkylSO₂R^a, $-SO_2NR^aR^b$, $-C_{1-6}$ alkylSO₂NR^aR^b, $-C(O)NR^aSO_2R^b$, $-C_{1-6}$ alkylC(O)NR^aSO₂R^b, $-NR^aC(O)R^b$, and $-C_{1-6}$ alkylNR^aC(O)R^b;

each R^2 is independently selected from H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a,
 25 $-C_{1-6}$ alkylC(O) OR^a , and $-C_{2-6}$ alkenylC(O) OR^a ;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkylC(O) R^a , $-C(O)OR^a$, $-C_{1-6}$ alkylC(O) OR^a , $-NR^aR^b$, $-C_{1-6}$ alkylNR^aR^b,

-C(O)NR^aR^b, C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆ alkylSO₂NR^aR^b,
-C(O)NR^aSO₂R^b and -NR^aC(O)R^b;

or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional
heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1
5 to 3 groups independently selected from oxo, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl,
-OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a,
C₁₋₆ alkylC(O)R^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b,
-SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆ alkylSO₂NR^aR^b;

each R^a is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
10 -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

each R^b is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

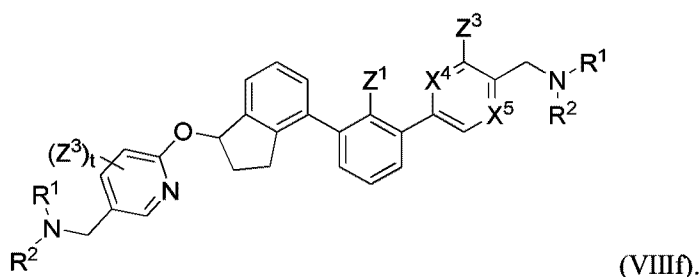
or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S;
wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo,
15 -C₁₋₆ alkylOR^f, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^f,
-C₁₋₆ alkylC(O)R^f, -C(O)OR^f, -C₁₋₆ alkylC(O)OR^f, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g,
-C₁₋₆ alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆ alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆ alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and
-NR^fC(O)R^g;

each R^f is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
20 -C₁₋₃ alkylC₃₋₈ cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl; and

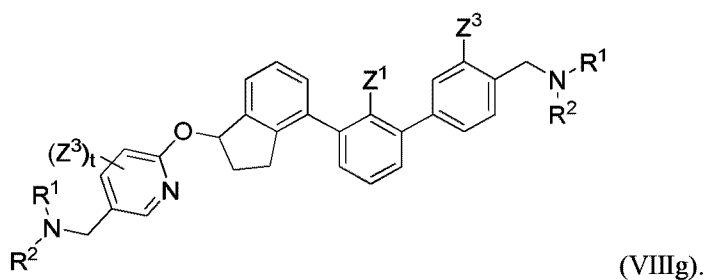
each R^g is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈ cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

or a pharmaceutically acceptable salt thereof.

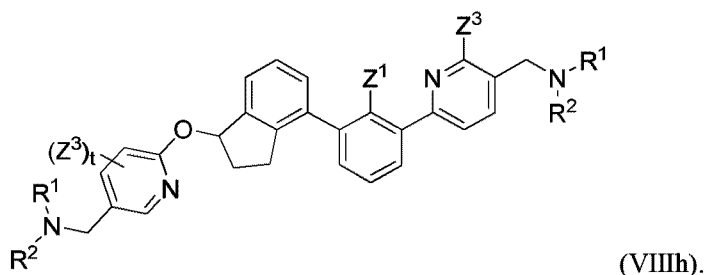
Embodiment 7. The compound of embodiment 6, wherein the compound is represented by a compound
25 of formula (VIIIf):



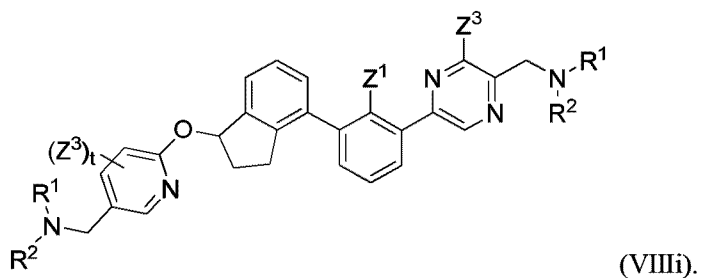
Embodiment 8. The compound of embodiment 1, wherein the compound is represented by a compound
of formula (VIIIg):



Embodiment 9. The compound of embodiment 1, wherein the compound is represented by a compound of formula (VIIIh):



- 5 Embodiment 10. The compound of embodiment 1, wherein the compound is represented by a compound of formula (VIIIi):



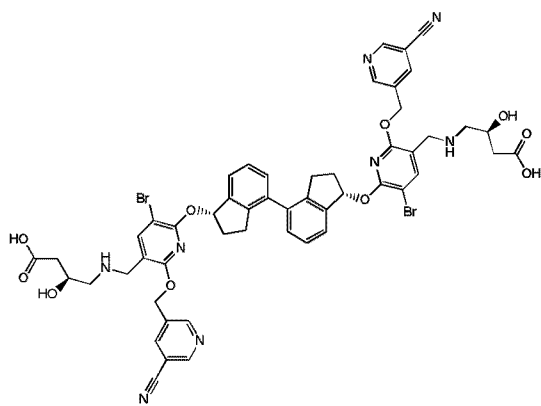
Embodiment 11. The compound of any one of embodiments 1 to 10, wherein each Z^1 is independently halo.

- 10 Embodiment 12. The compound of any one of embodiments 1 to 11, wherein each Z^3 is independently halo or C_{1-6} alkoxy.

Embodiment 13. The compound of any one of embodiments 1 to 12, wherein each Z^1 is independently chloro.

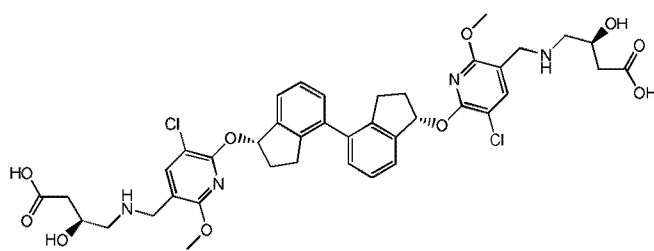
- Embodiment 14. The compound of any one of embodiments 1 to 13, wherein each Z^3 is independently chloro or methoxy.
- 15

Embodiment 15. The compound



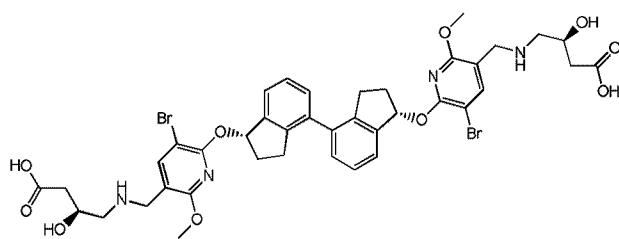
or a pharmaceutically acceptable salt thereof.

Embodiment 16. The compound



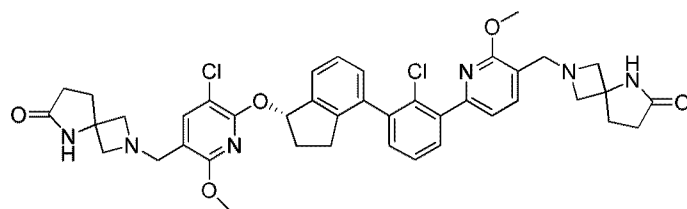
5 or a pharmaceutically acceptable salt thereof.

Embodiment 17. The compound



or a pharmaceutically acceptable salt thereof.

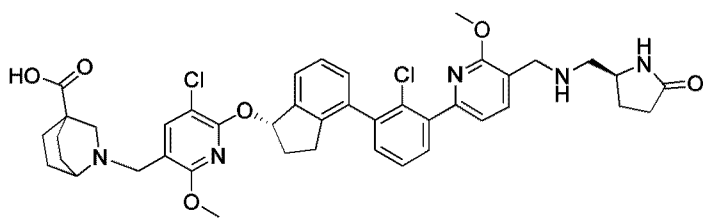
Embodiment 18. The compound of embodiment 1, having the structure:



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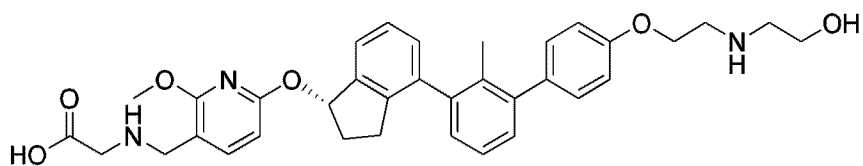
or a pharmaceutically acceptable salt thereof.

Embodiment 19. The compound of embodiment 1 having the structure:

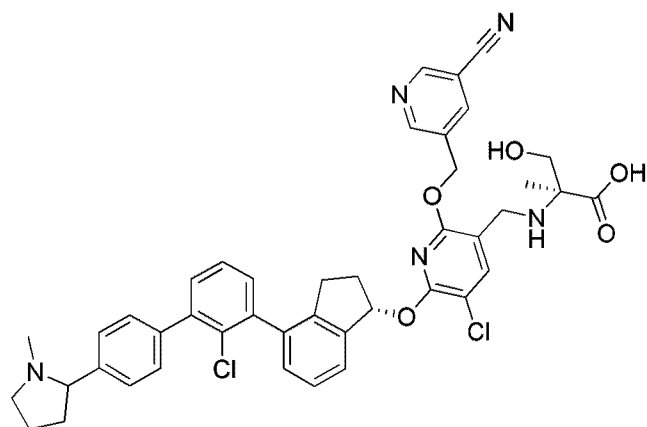
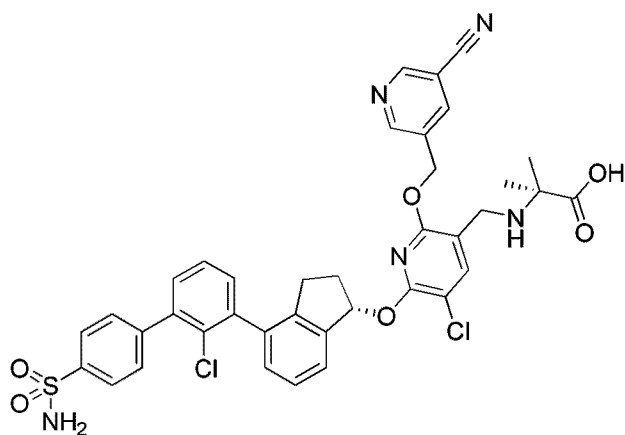
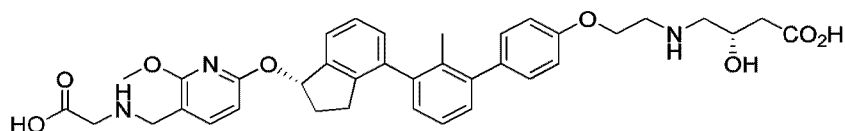


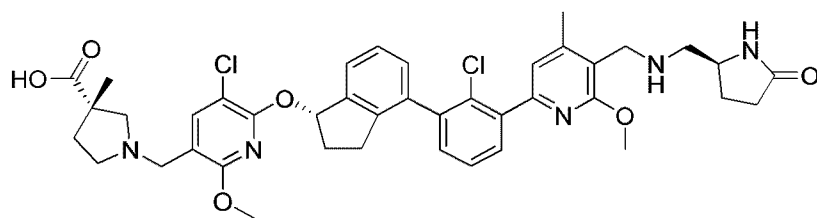
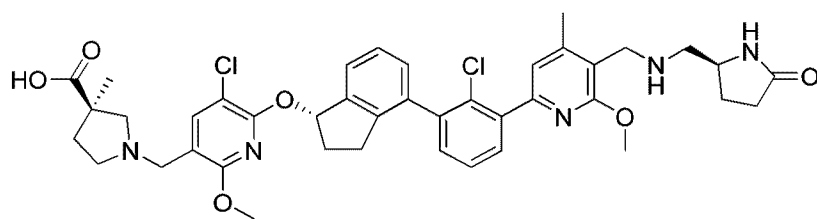
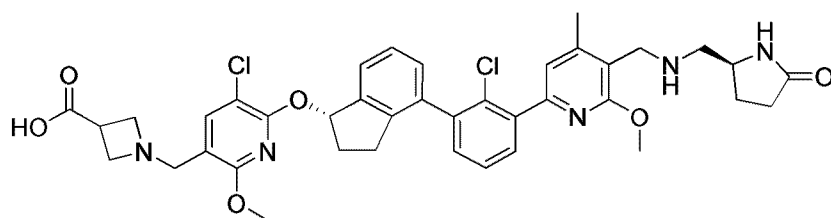
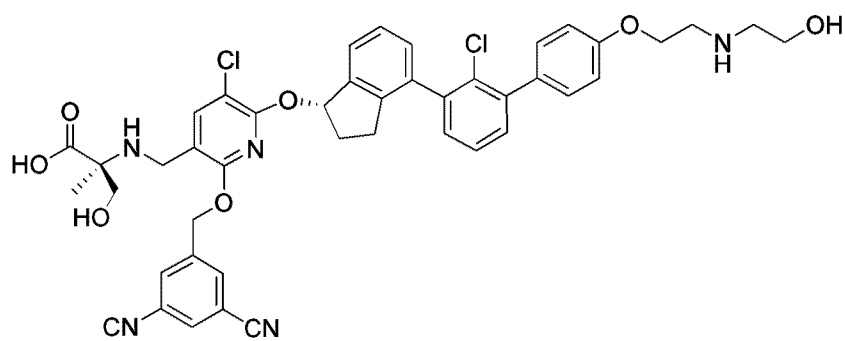
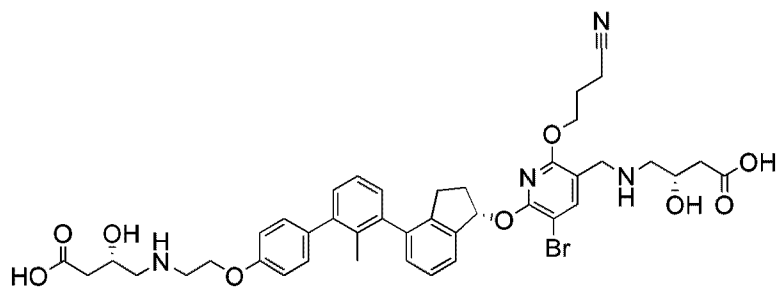
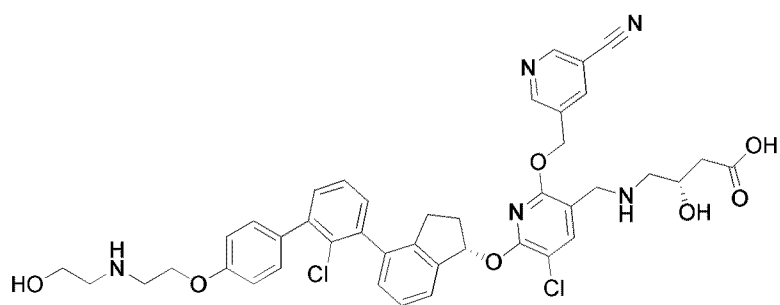
or a pharmaceutically acceptable salt thereof.

Embodiment 20. A compound of formula:

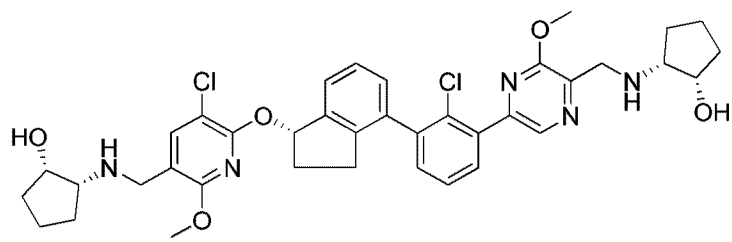
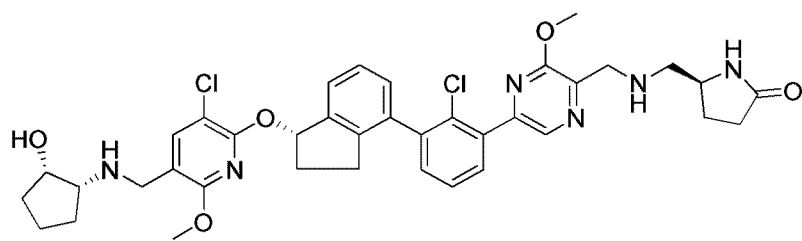
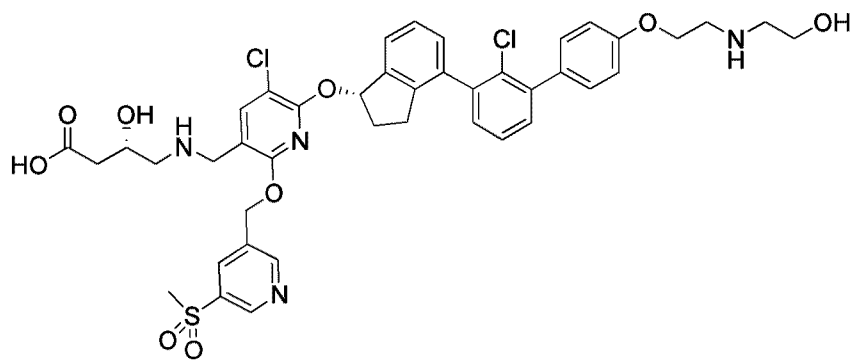
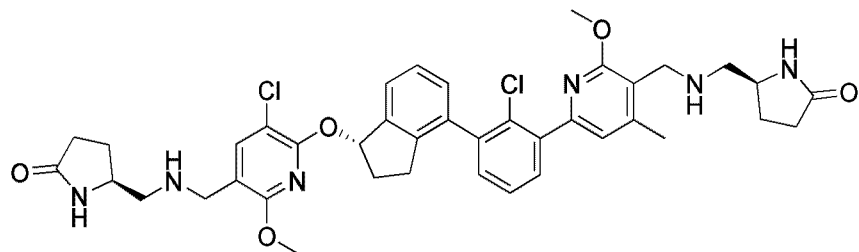
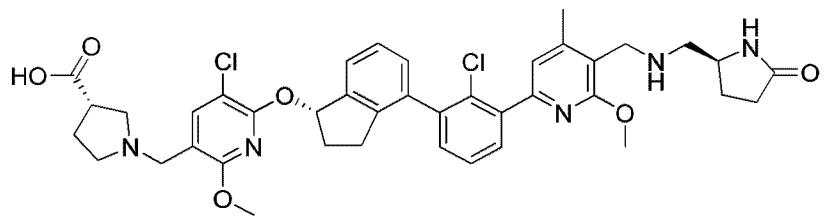
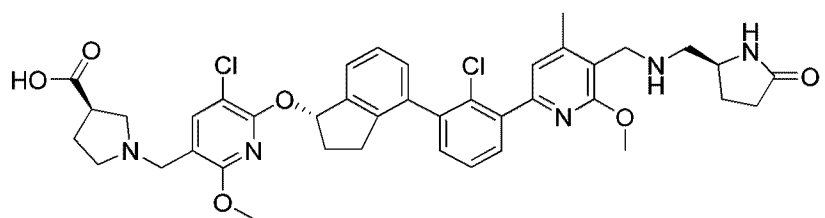


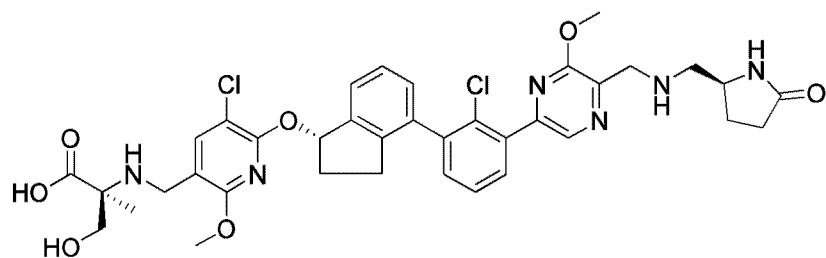
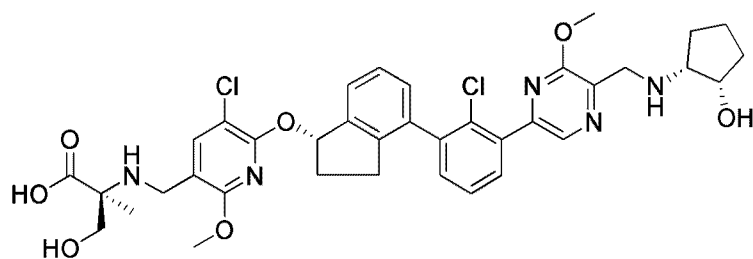
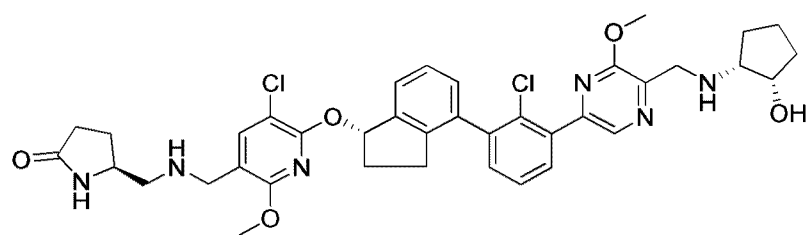
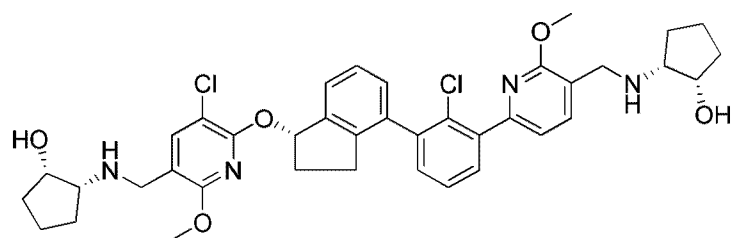
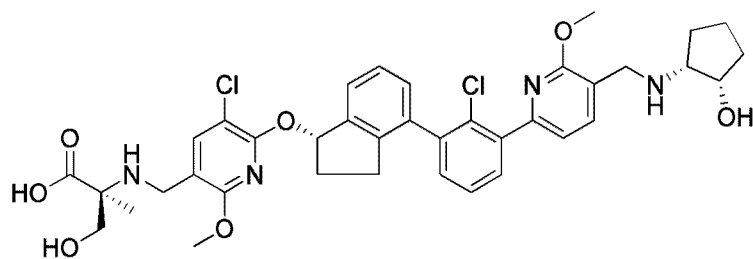
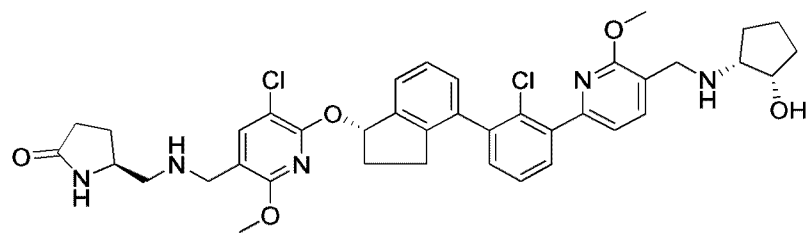
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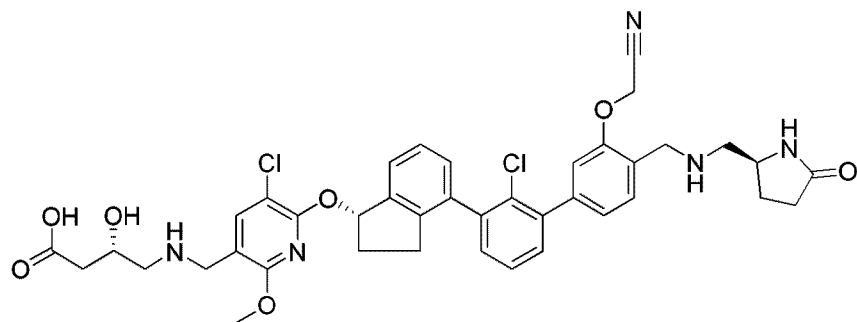
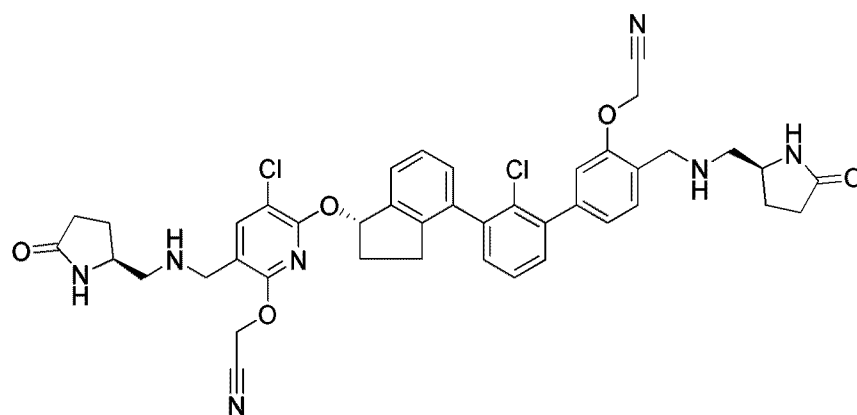
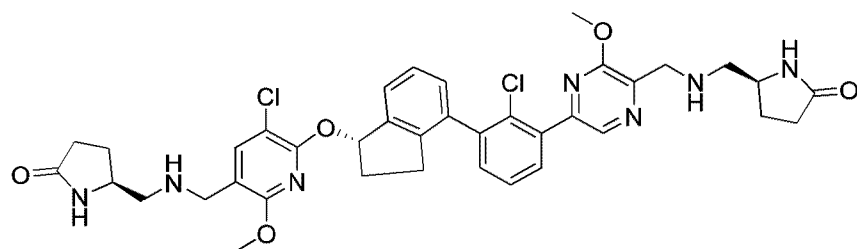
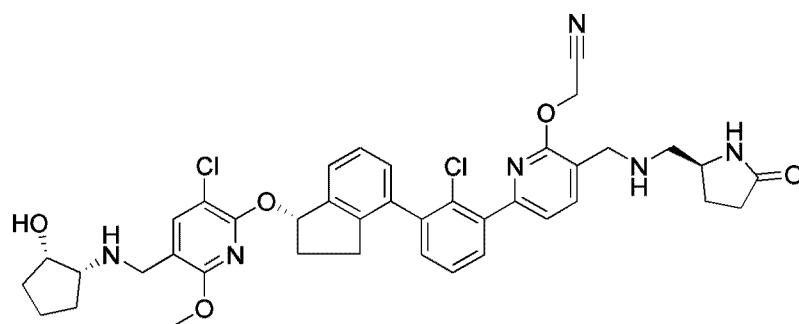
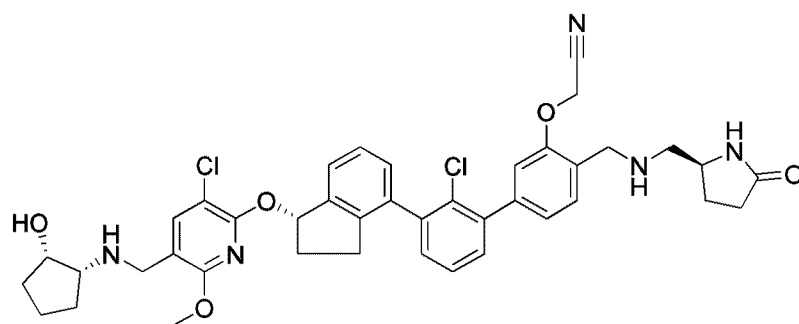


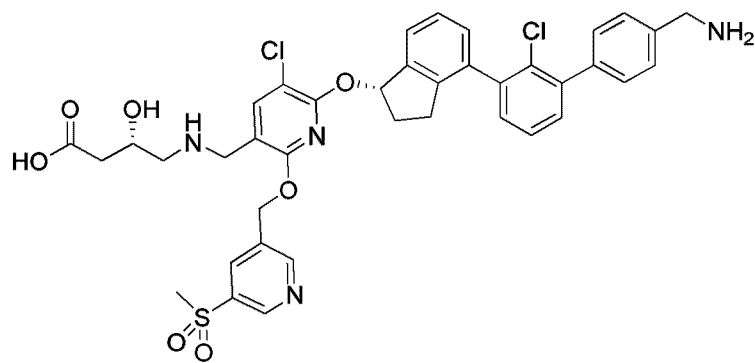
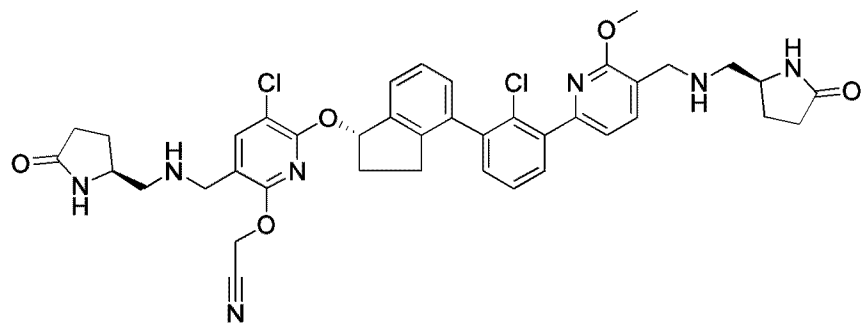
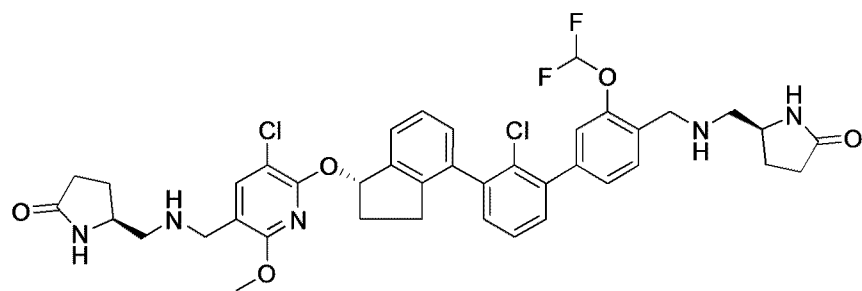
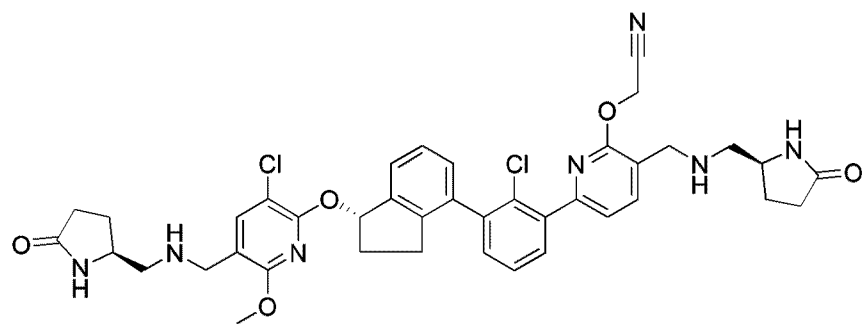
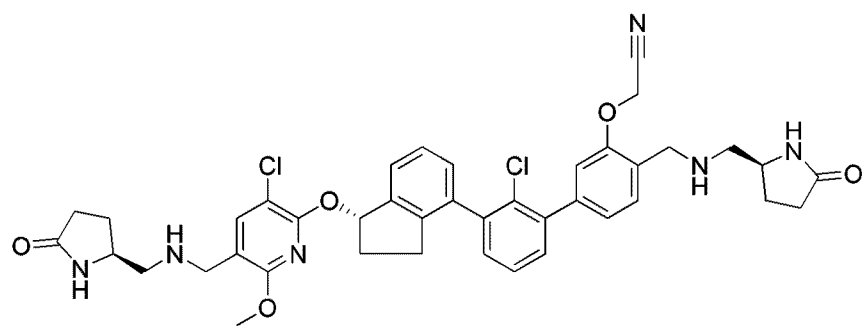


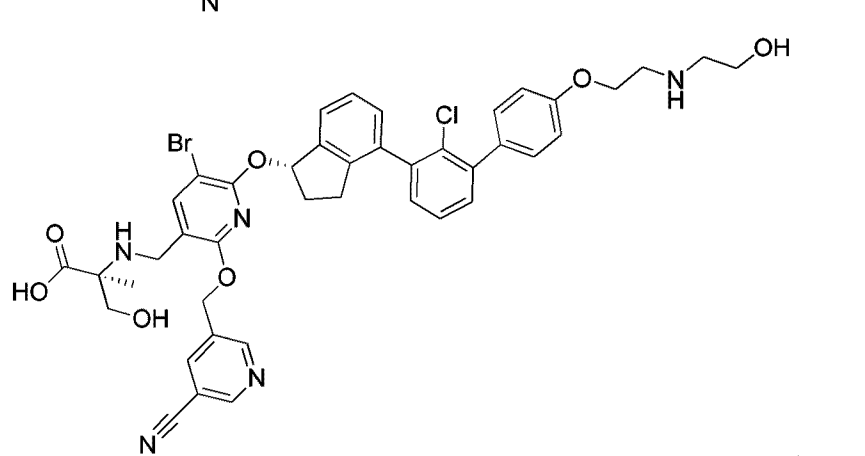
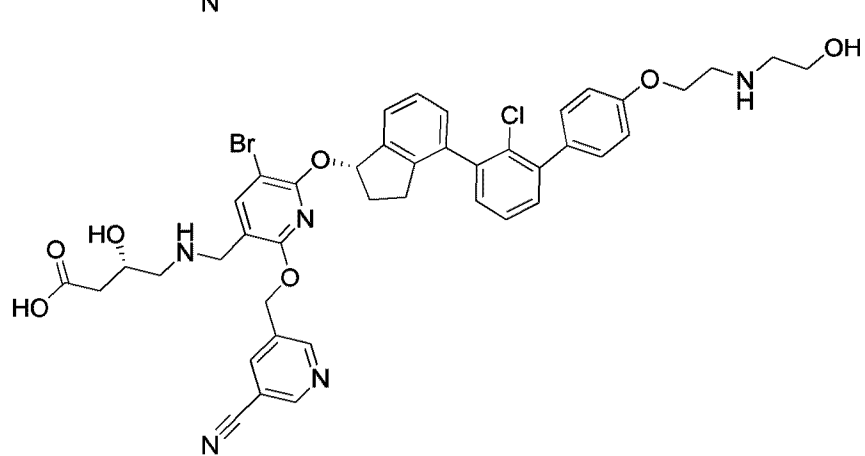
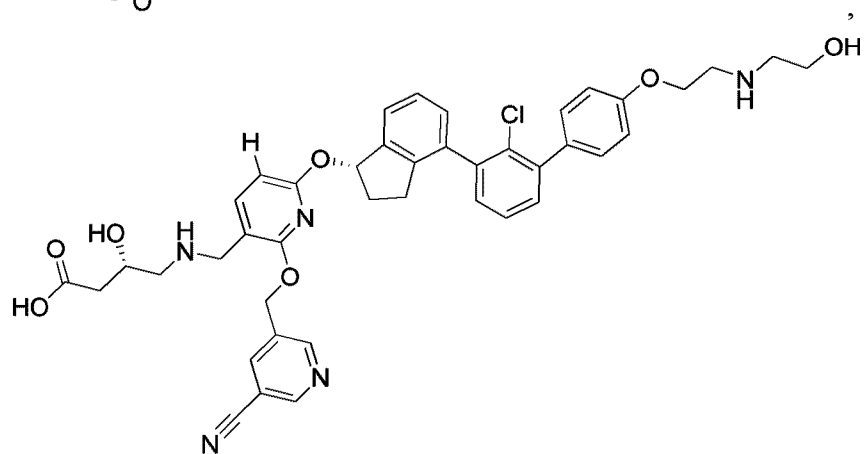
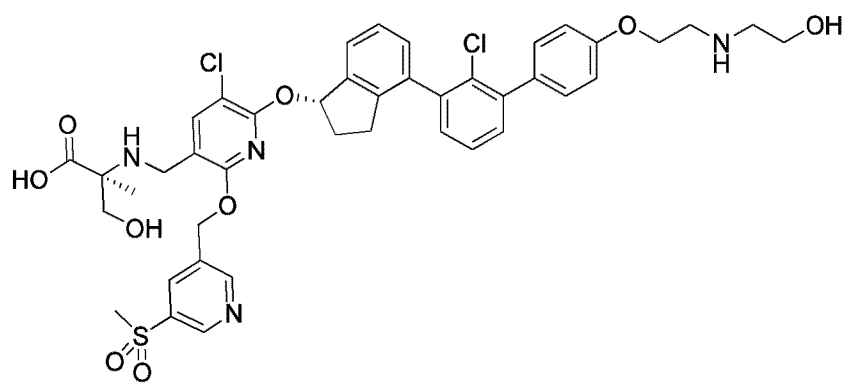
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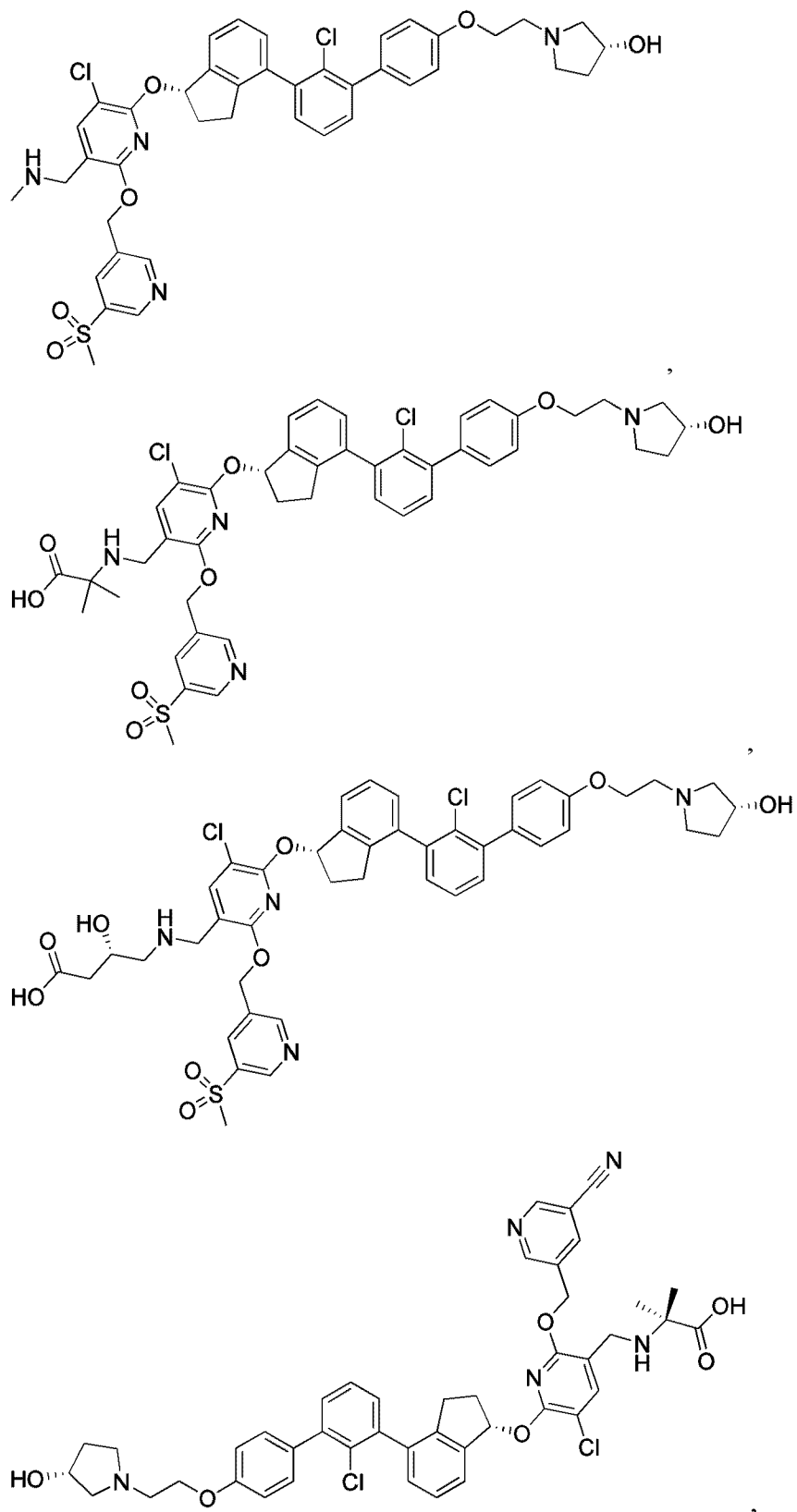


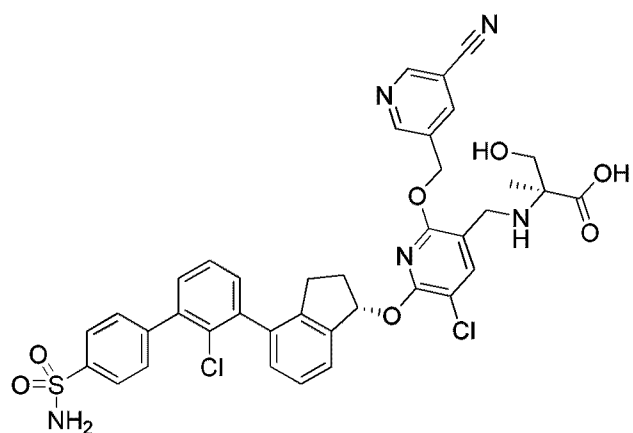
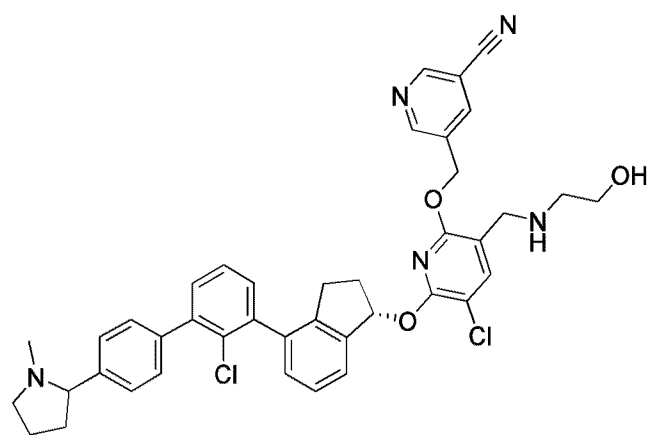
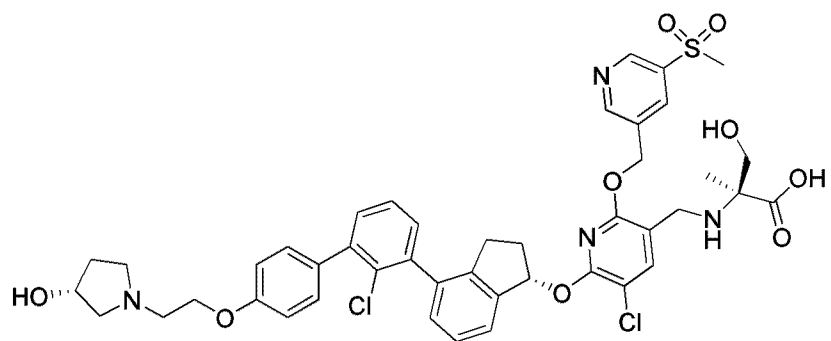
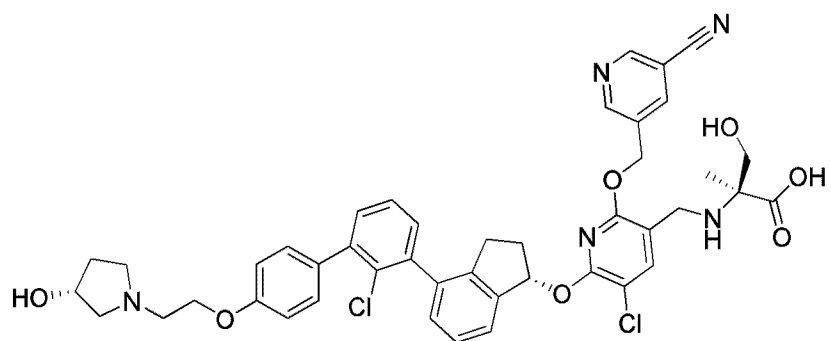


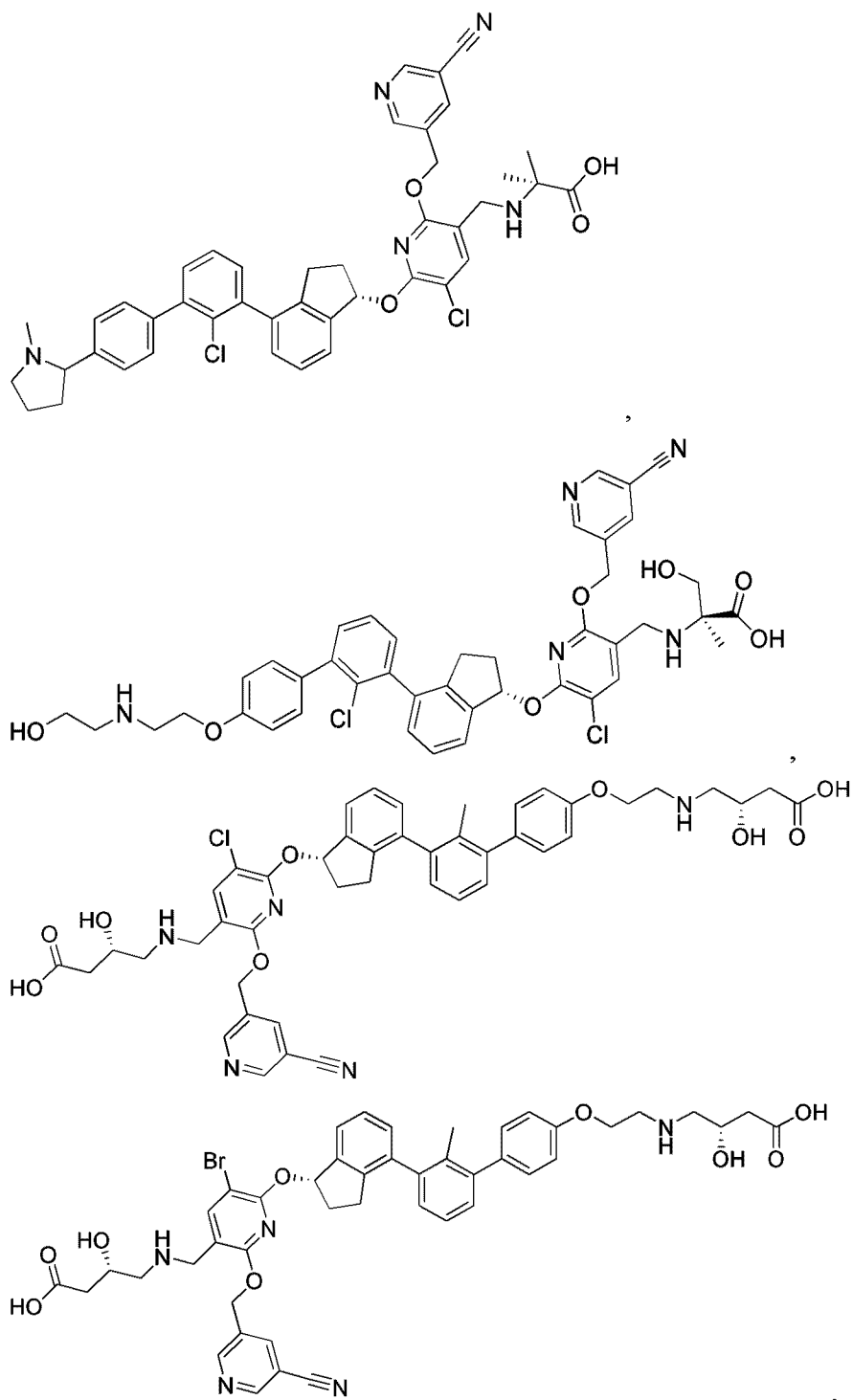


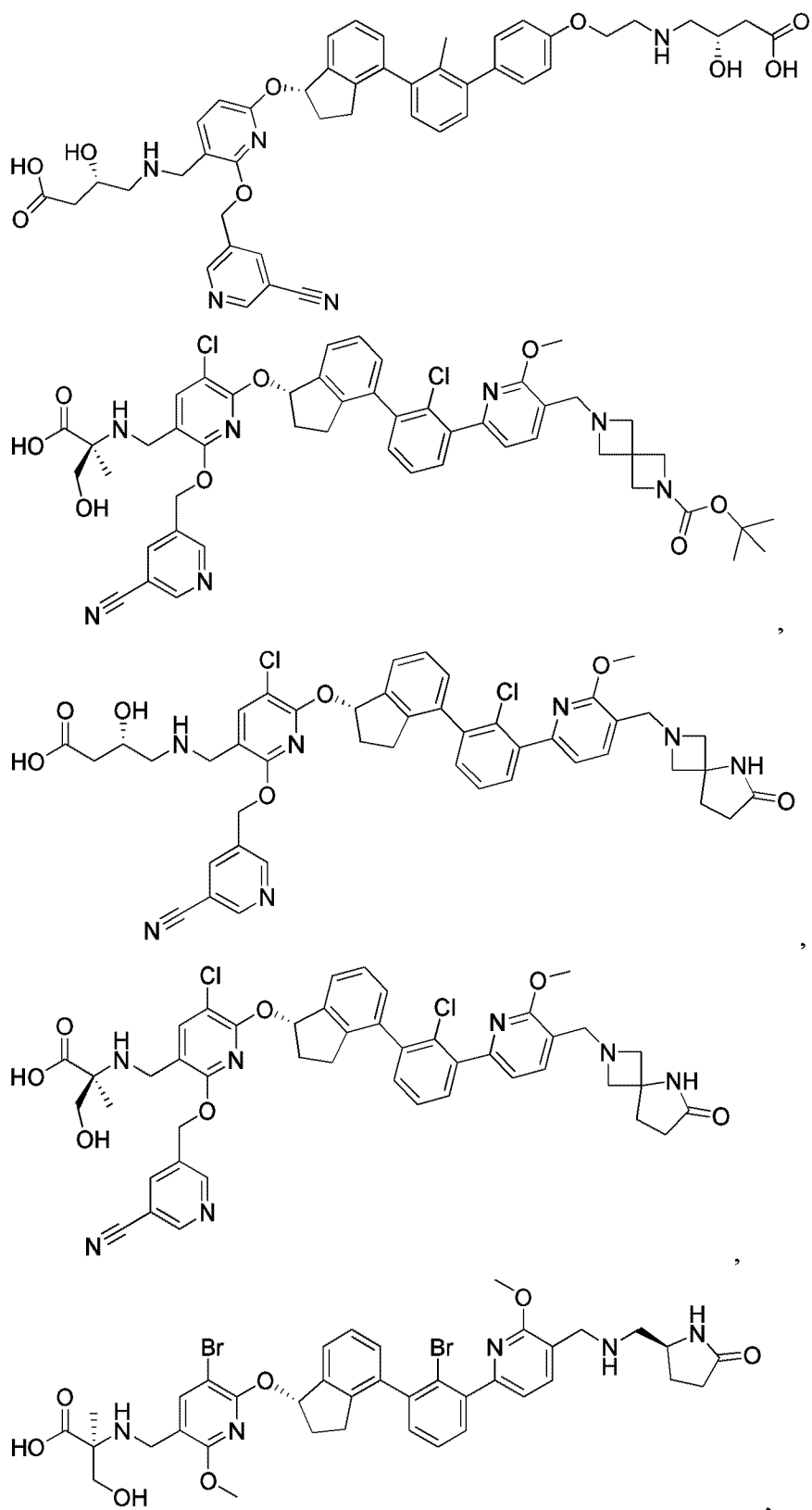


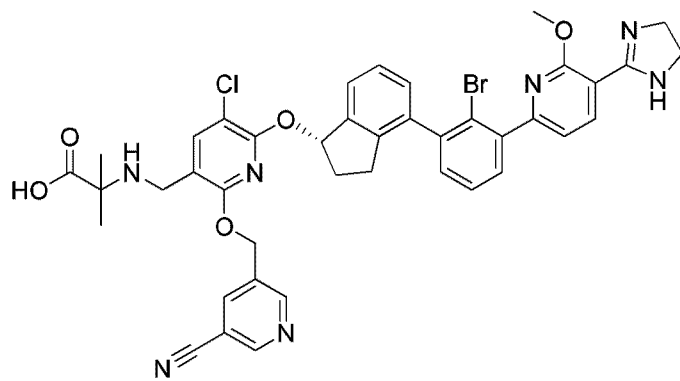
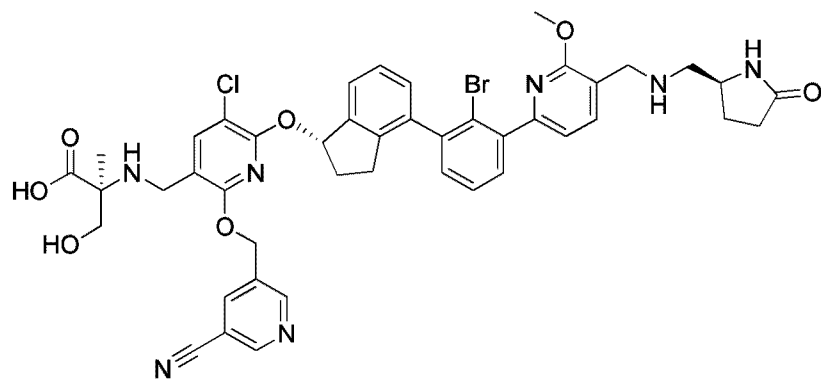
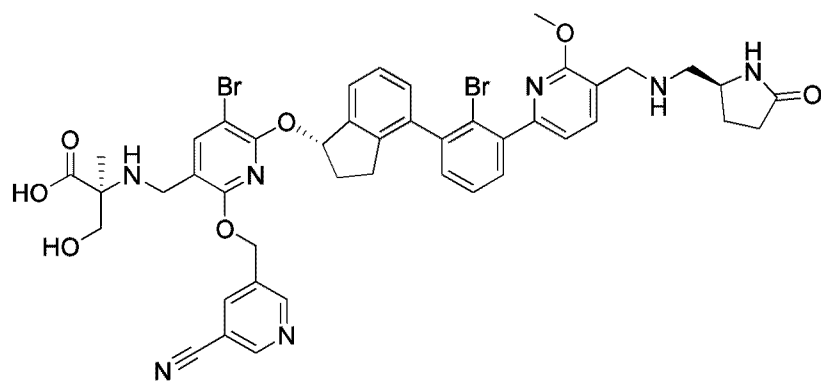
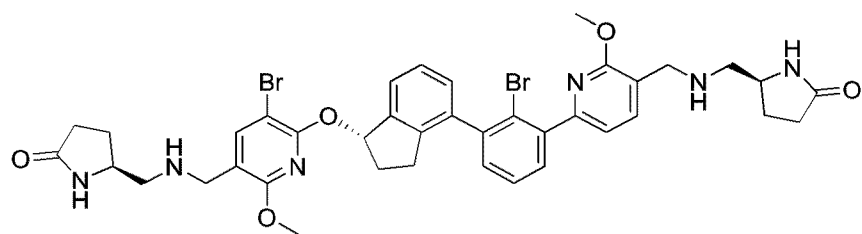


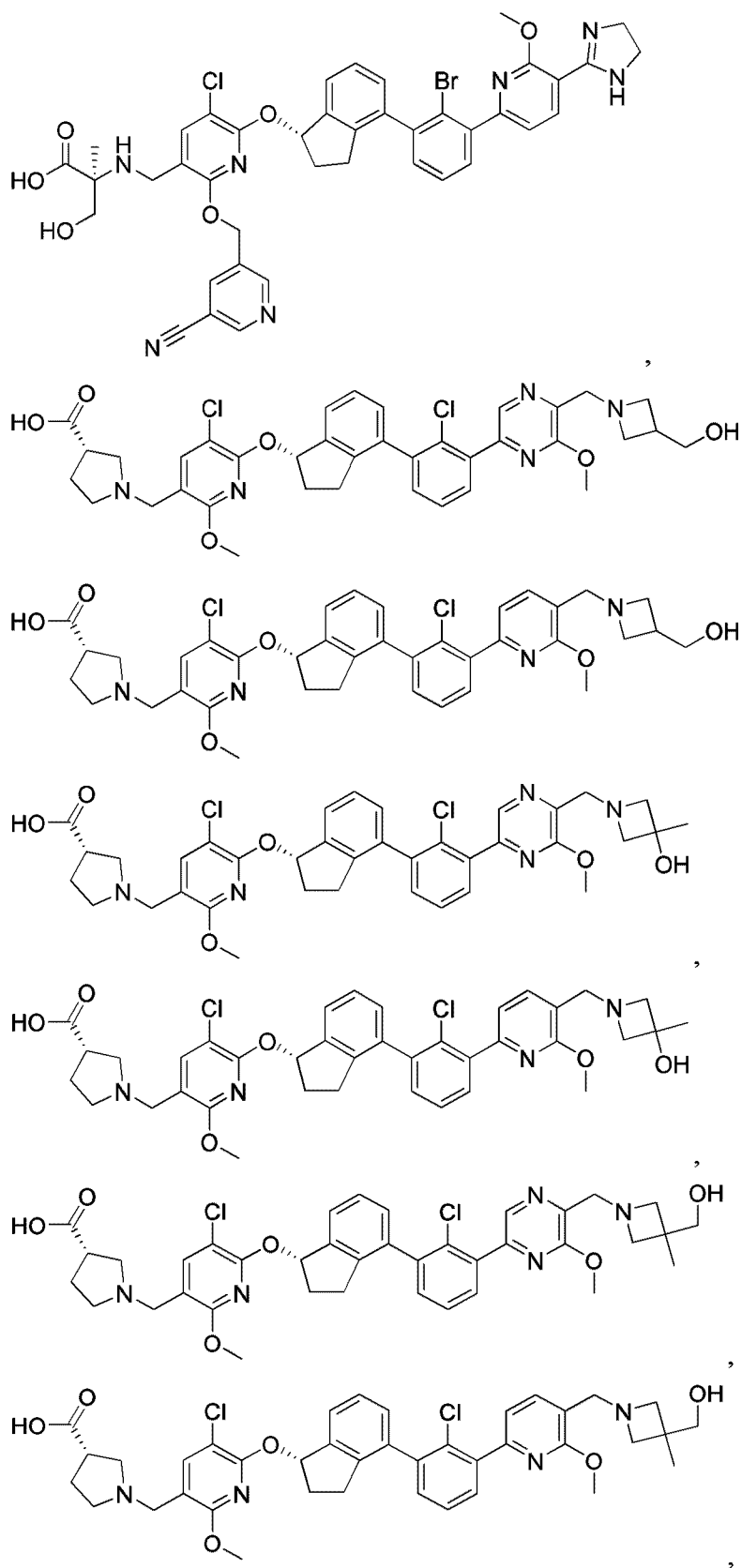


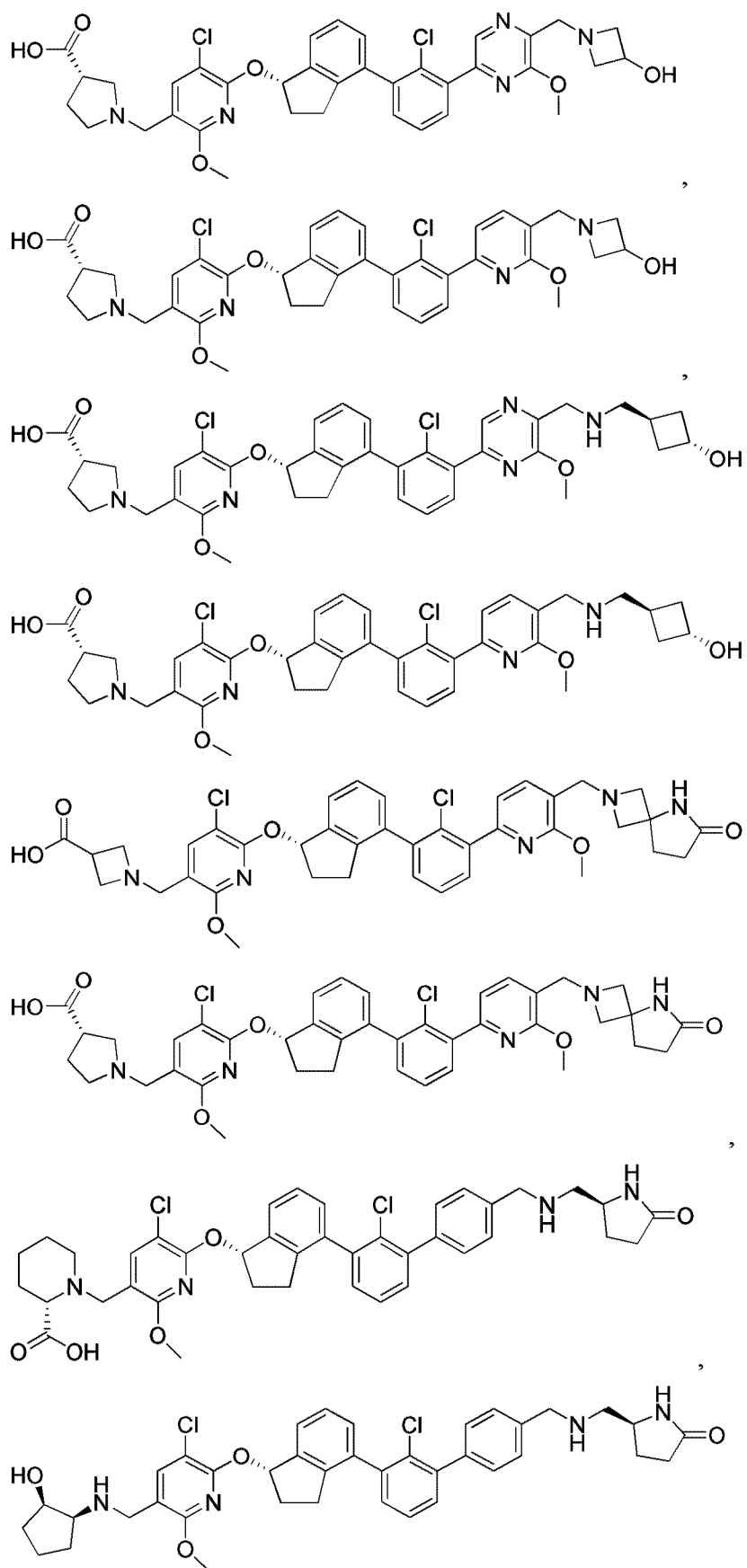


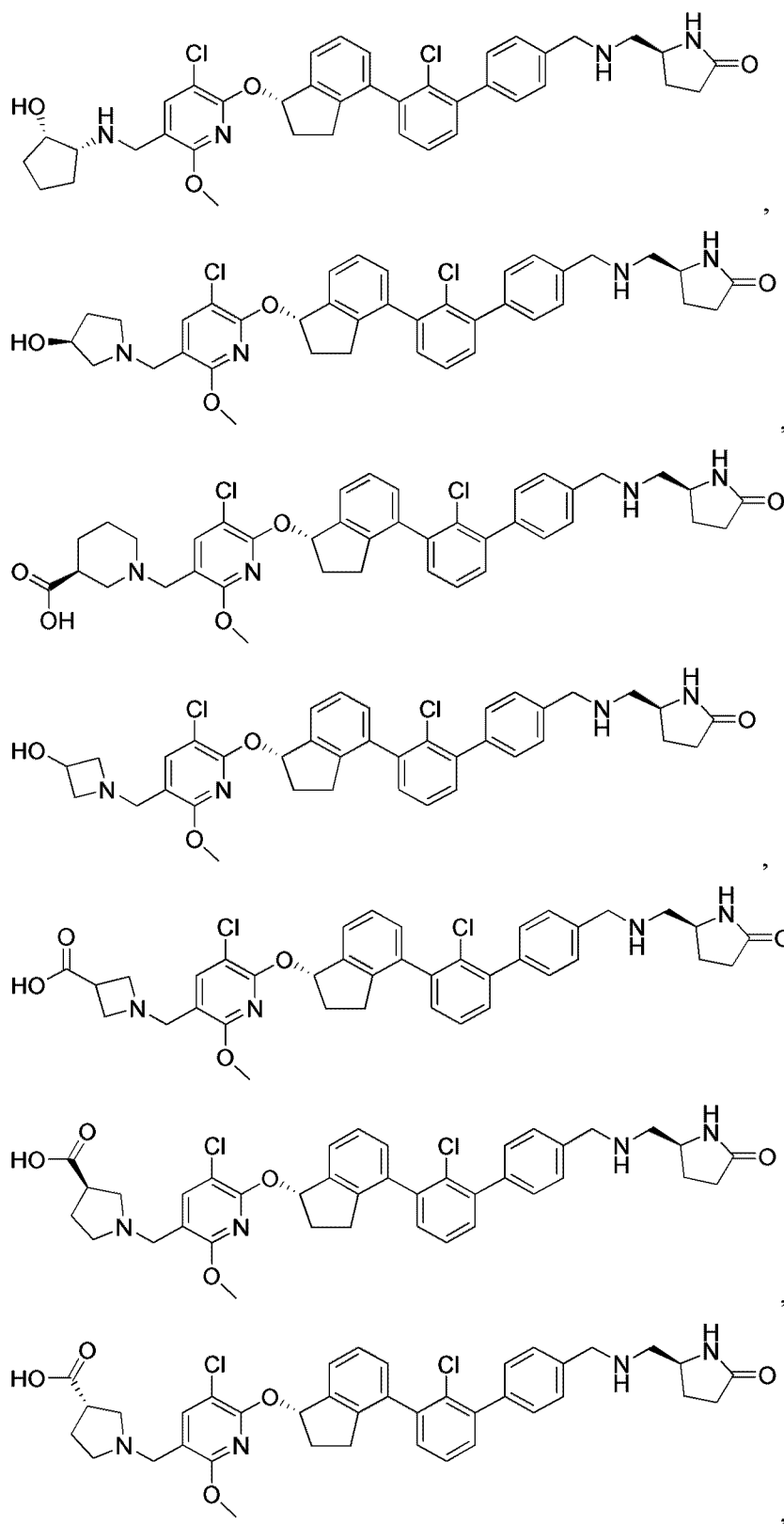


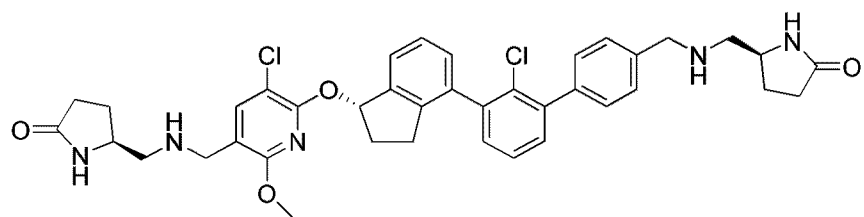
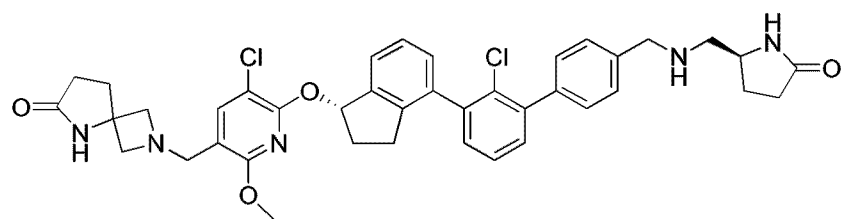
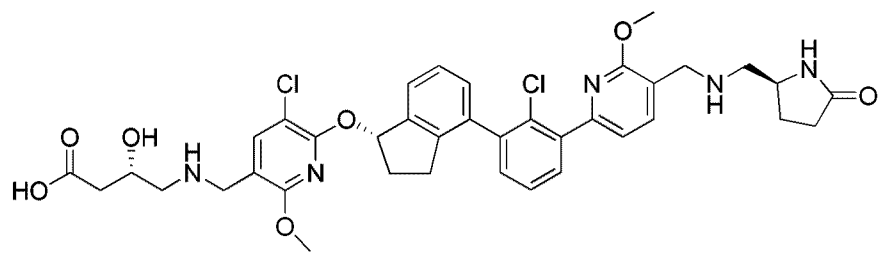
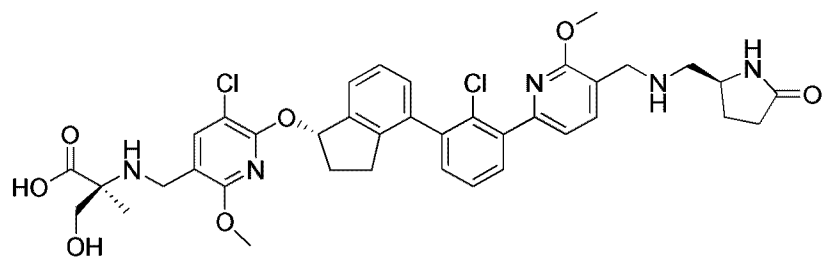
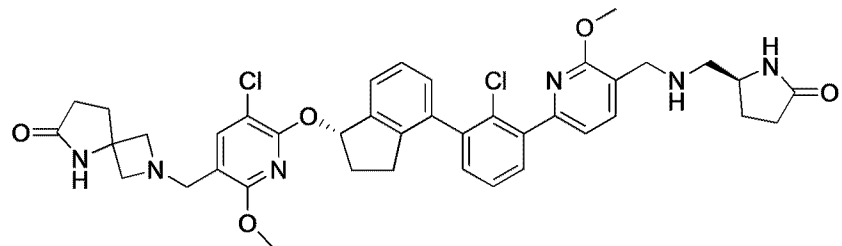
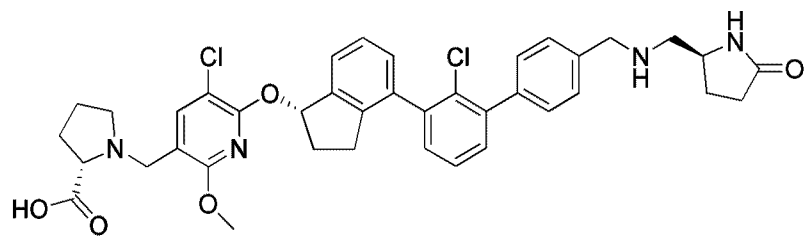
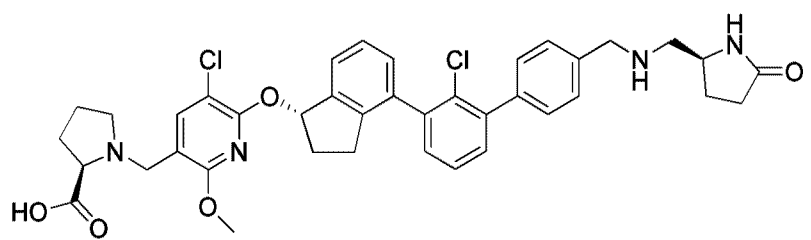


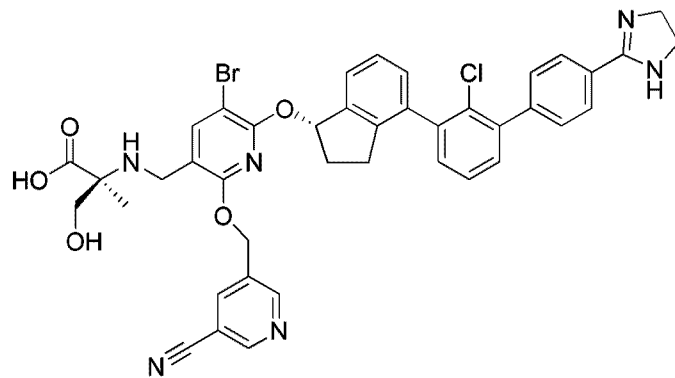
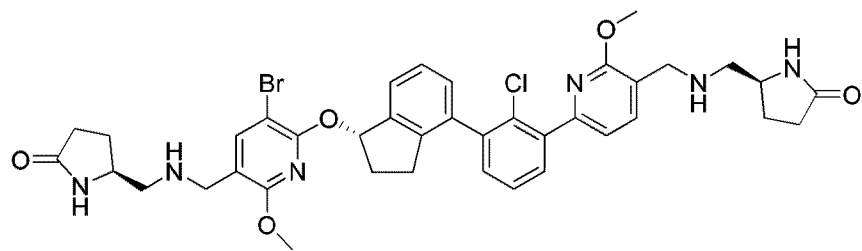
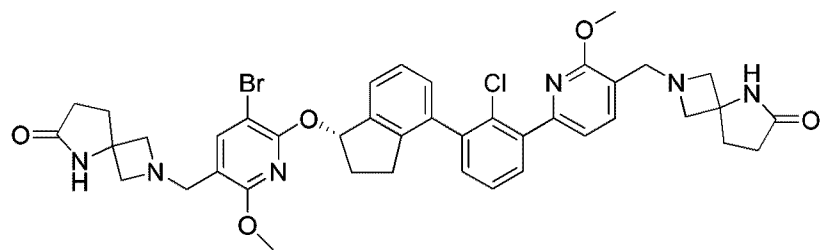
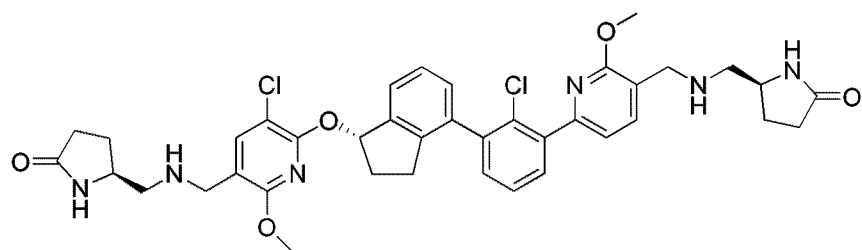
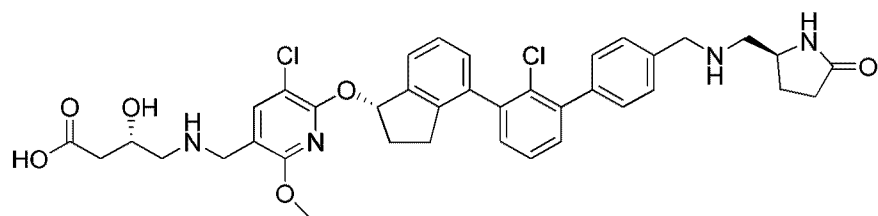
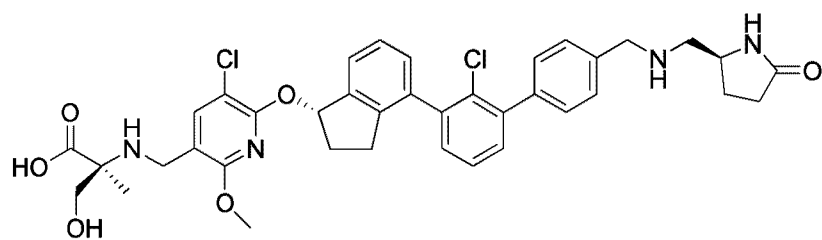


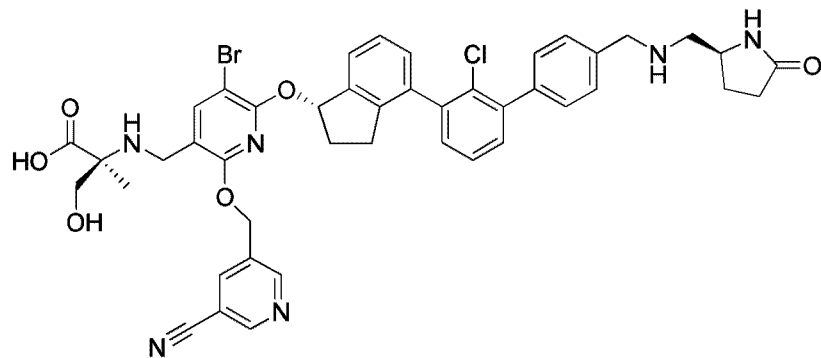
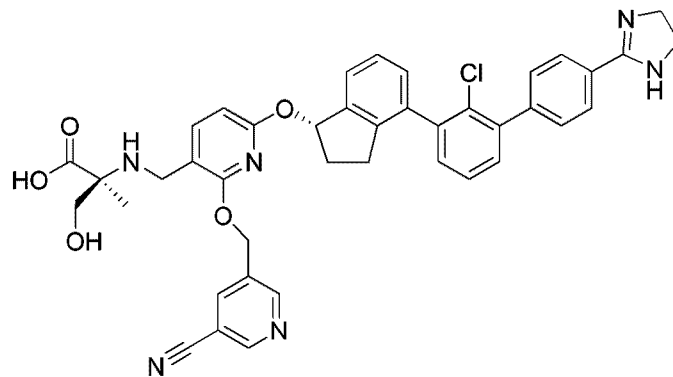
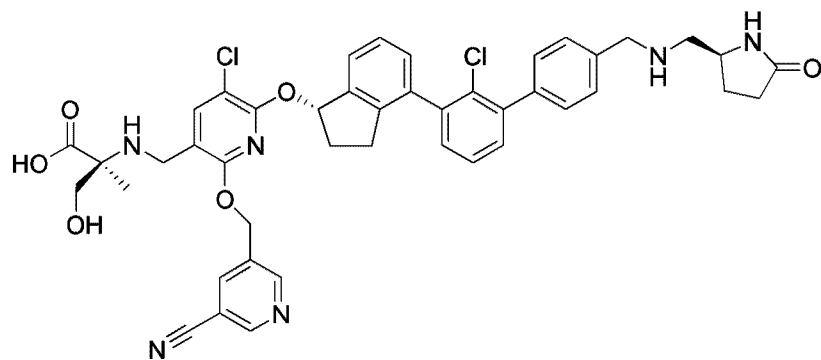
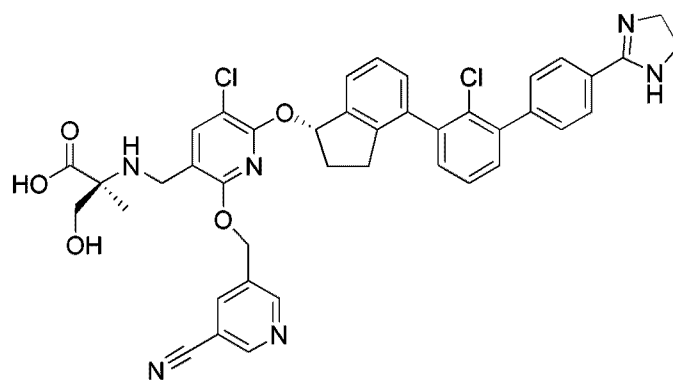


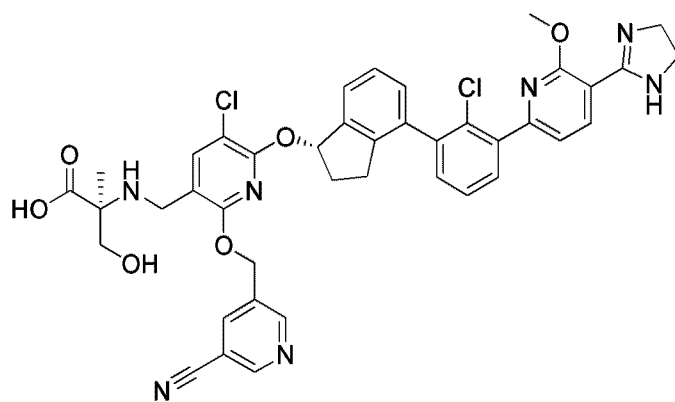
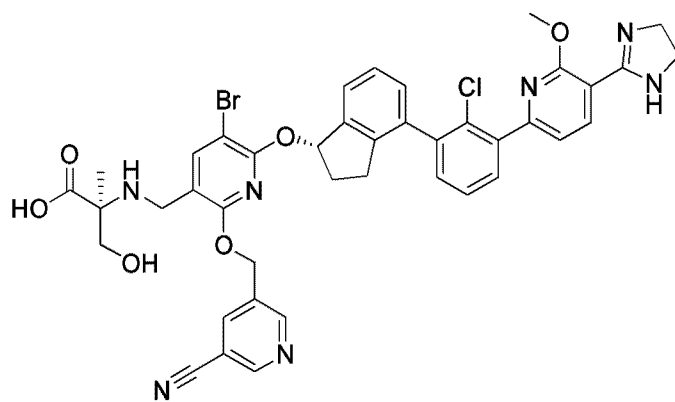
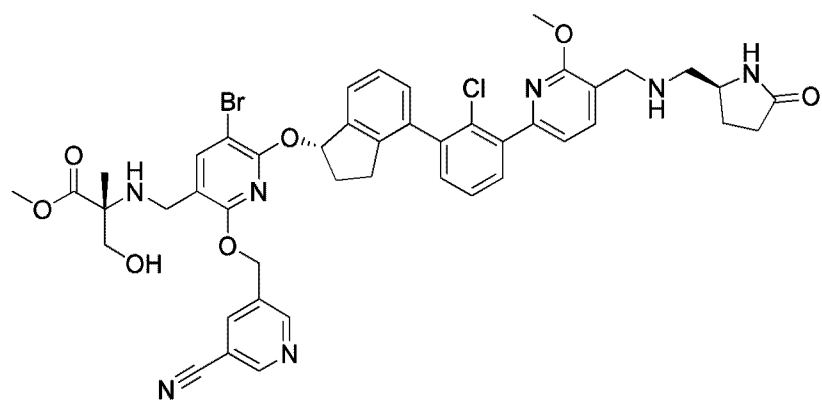
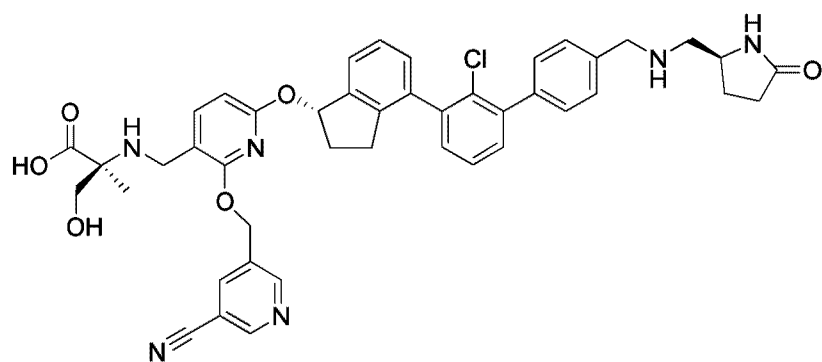


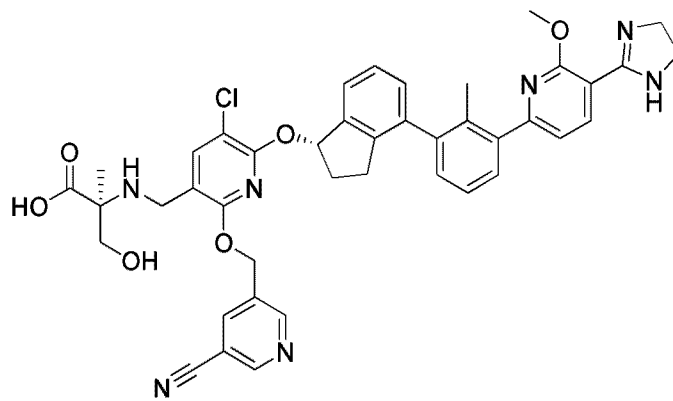
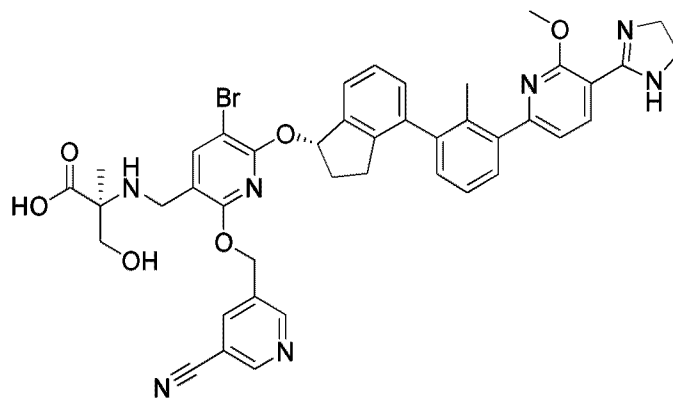
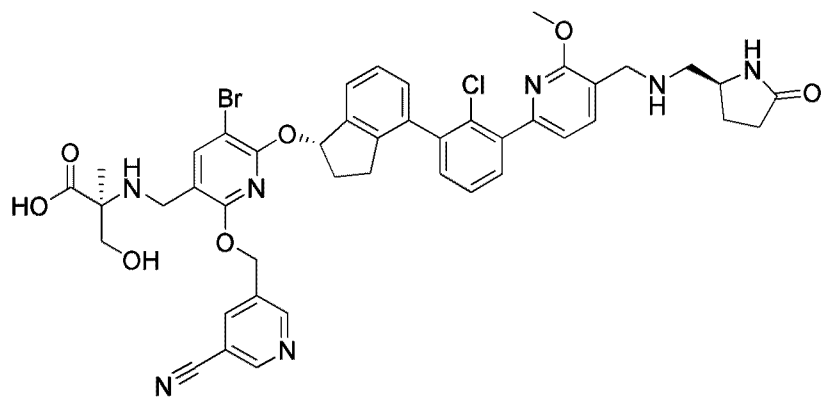
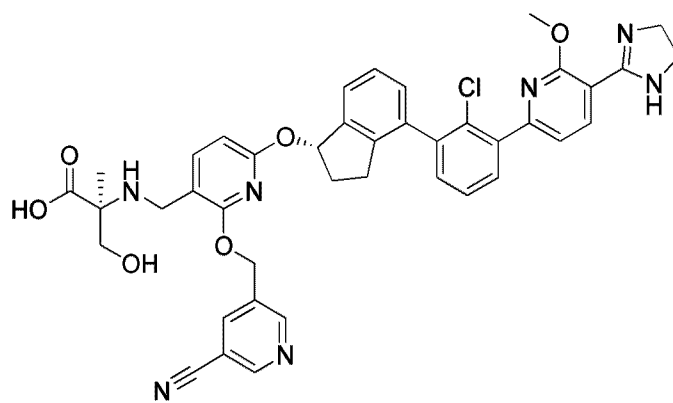


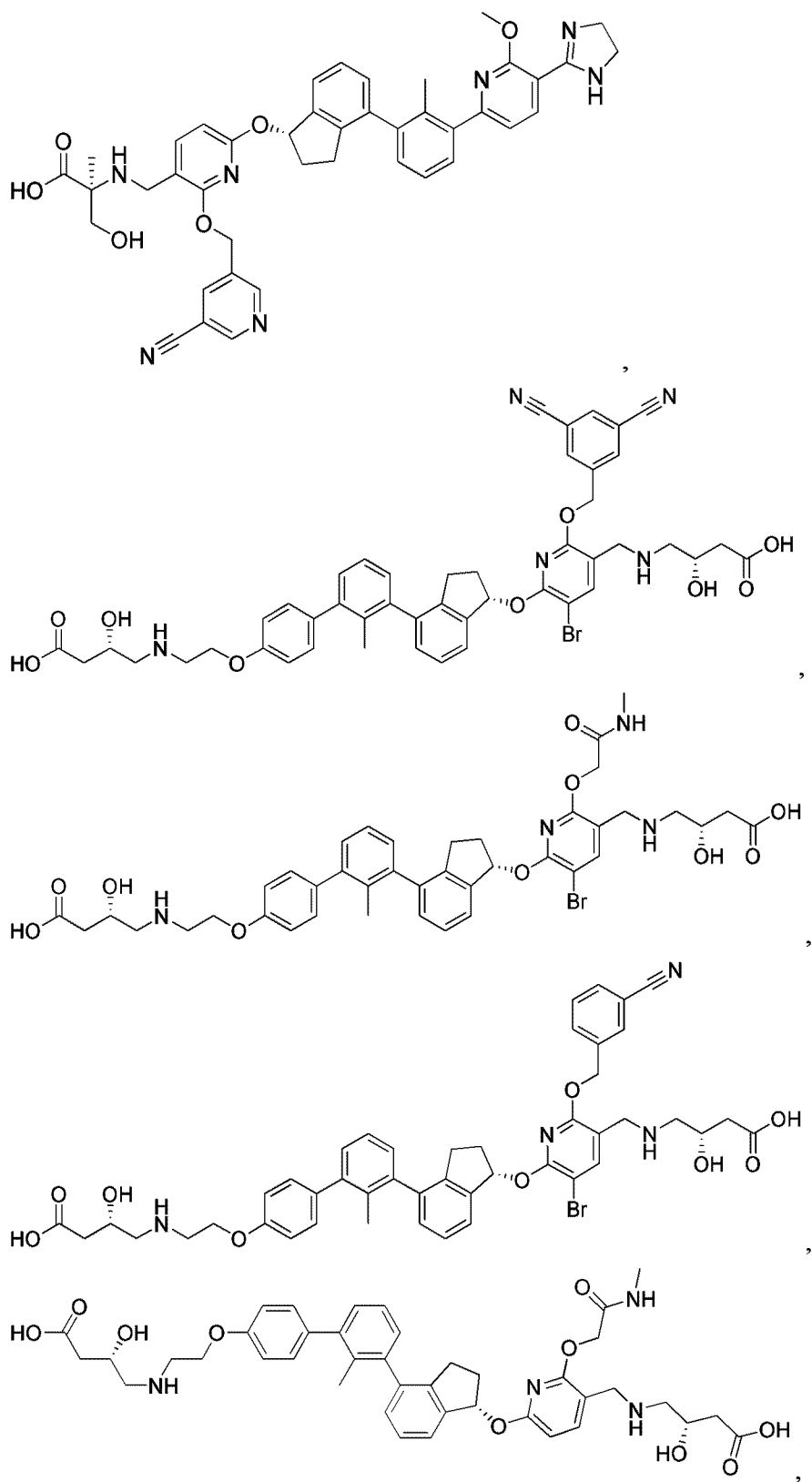


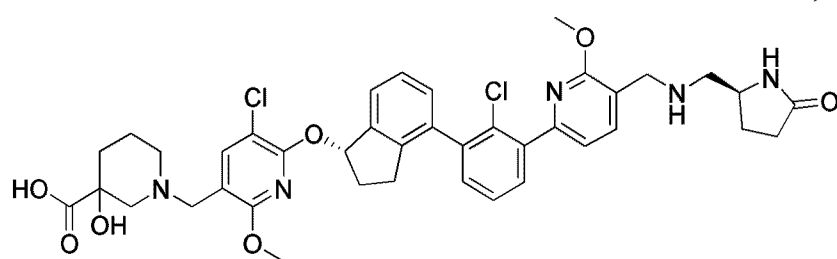
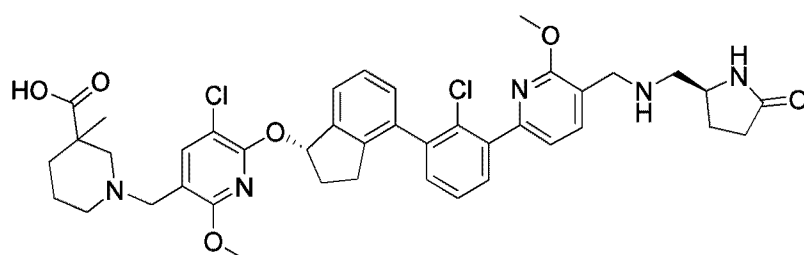
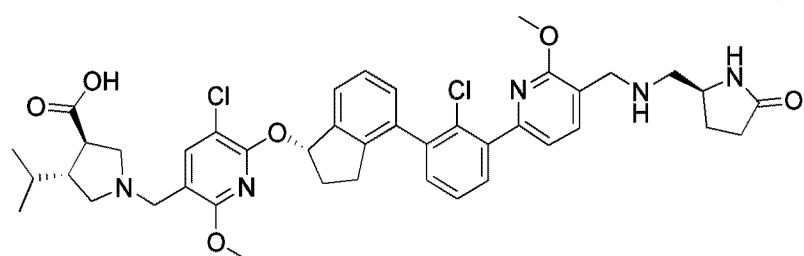
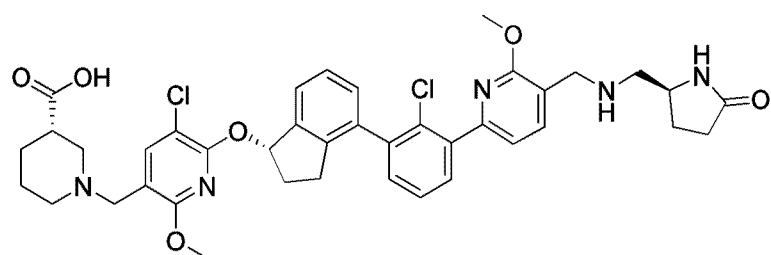
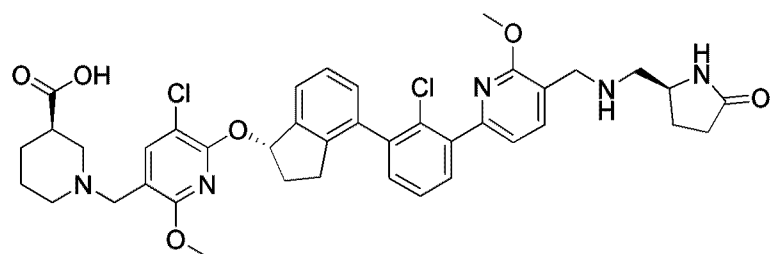
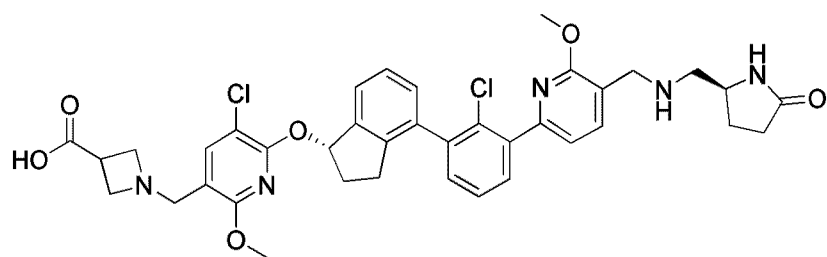


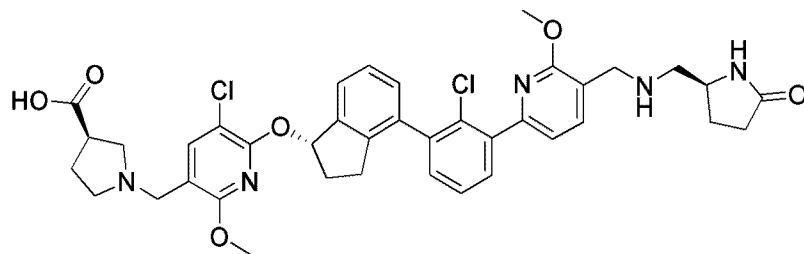
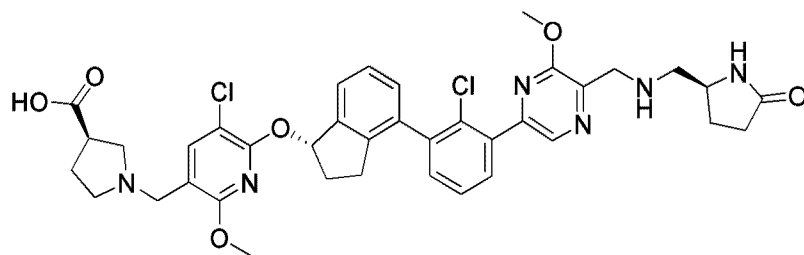
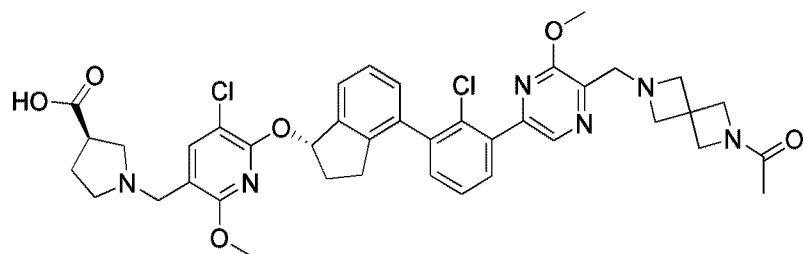
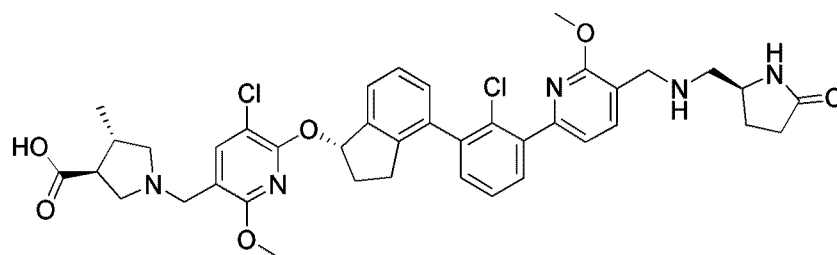
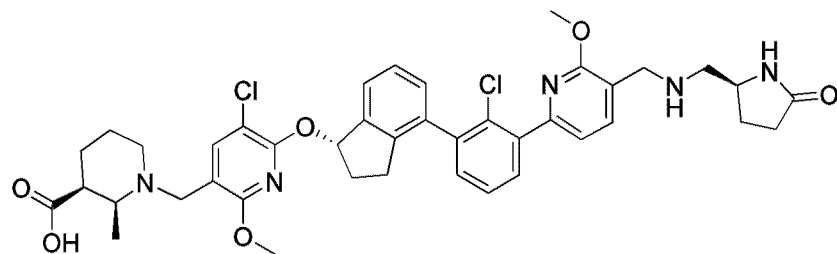
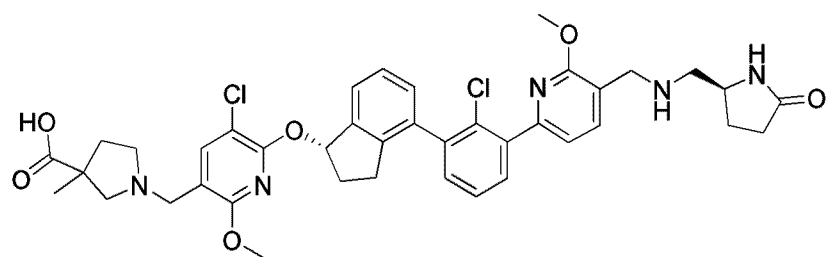


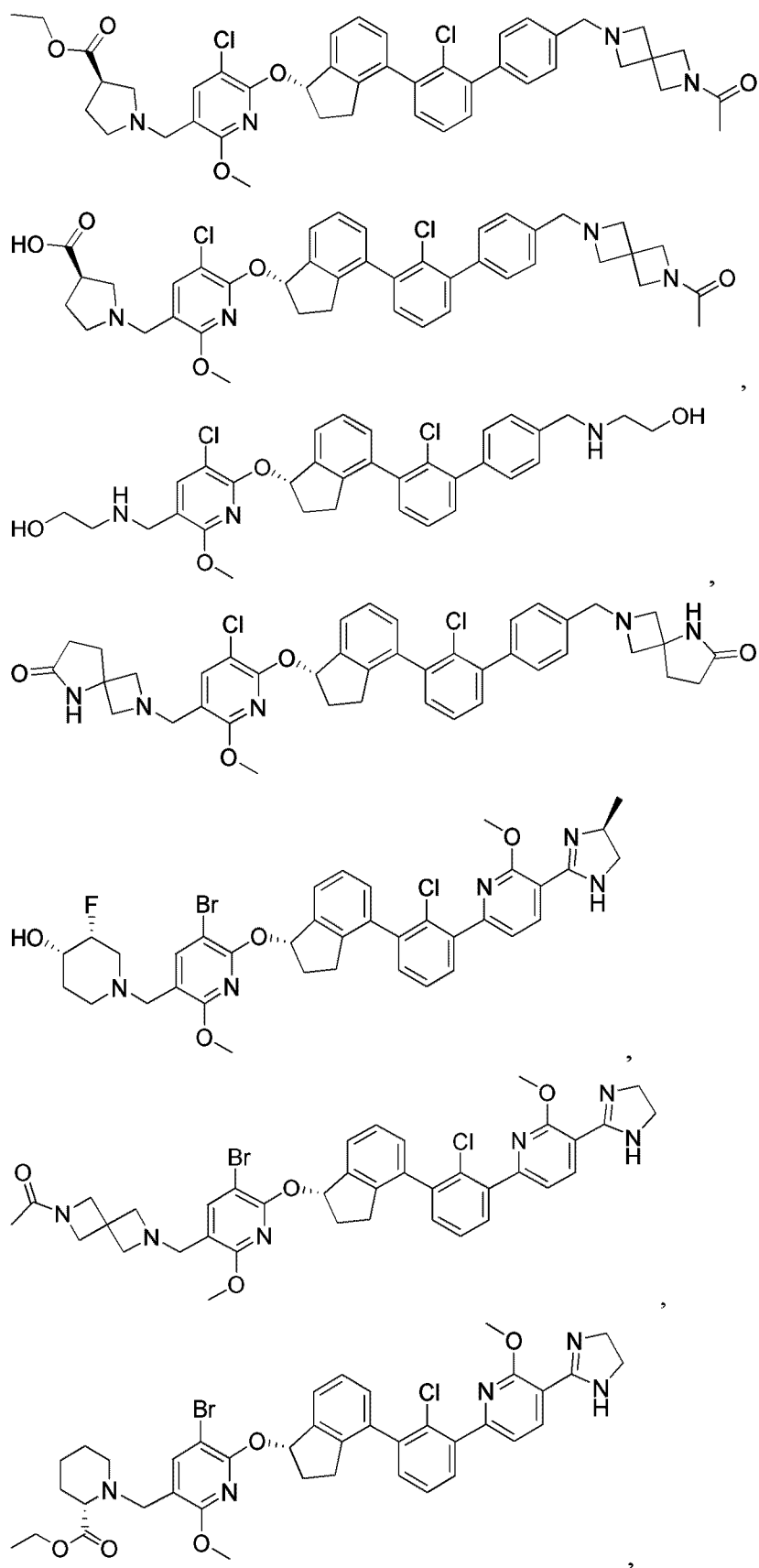


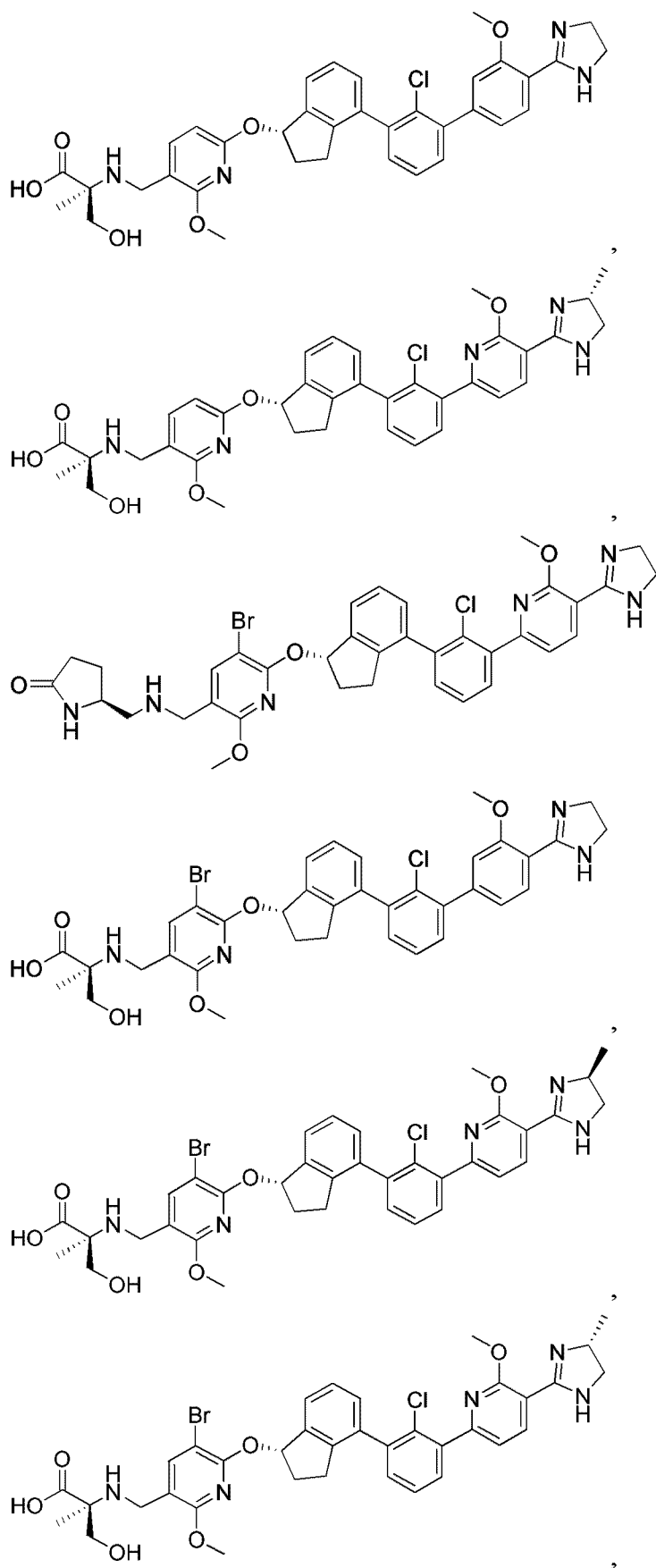


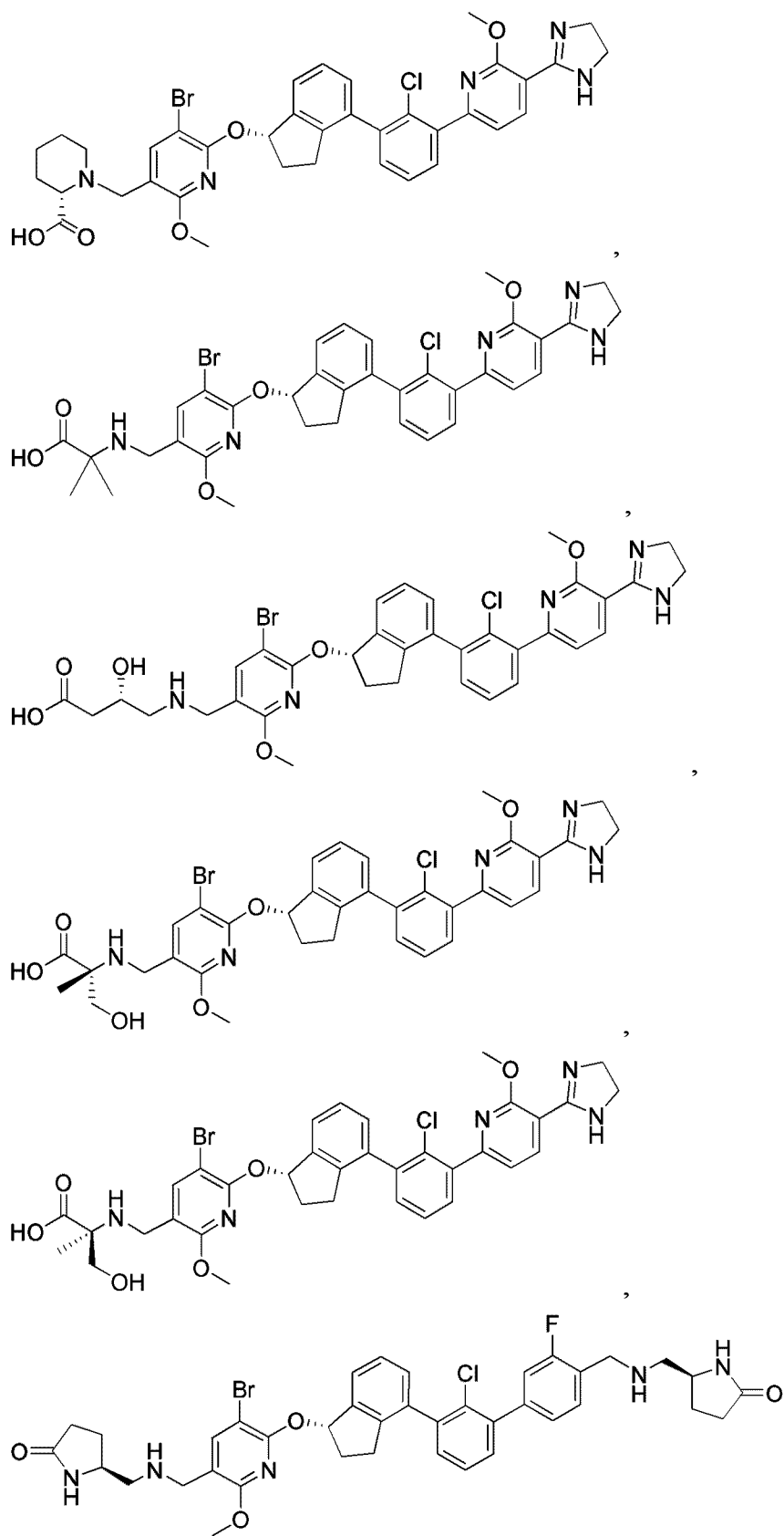


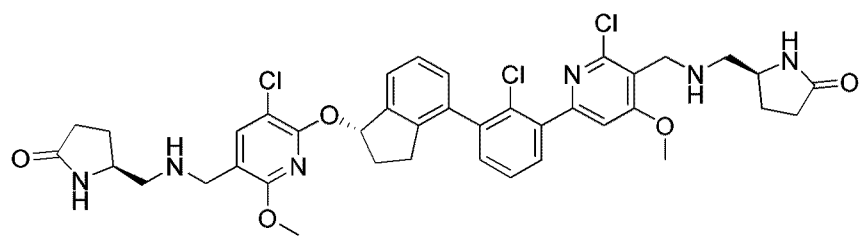
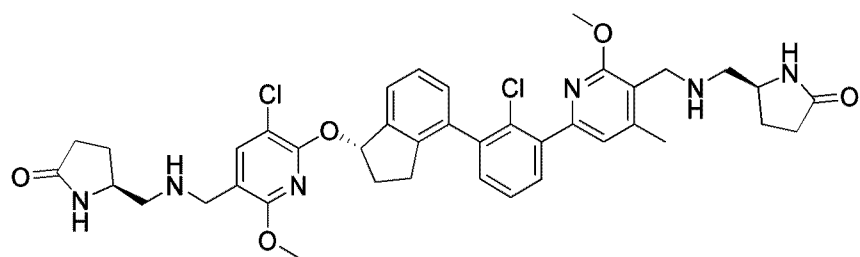
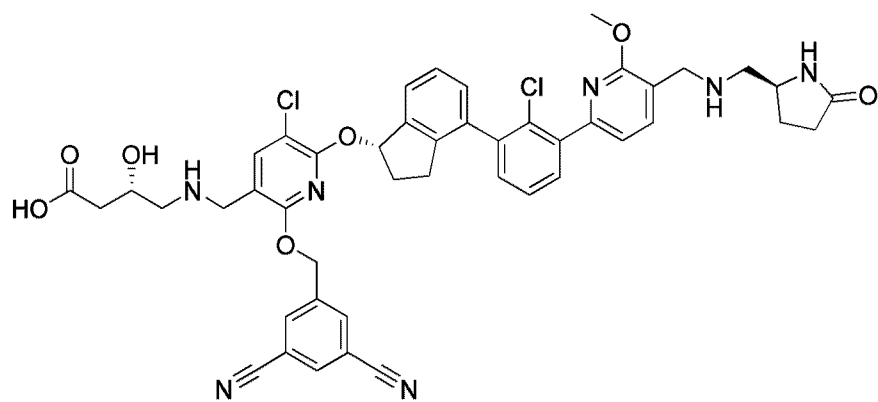
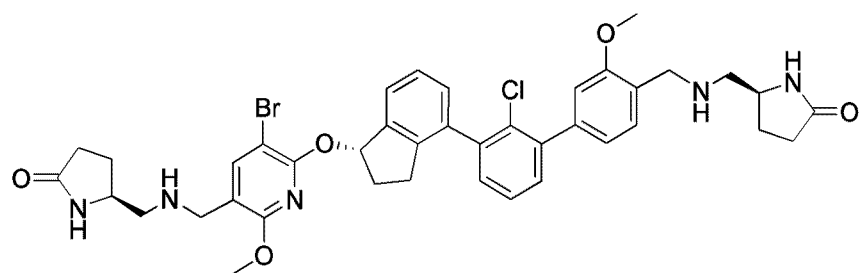
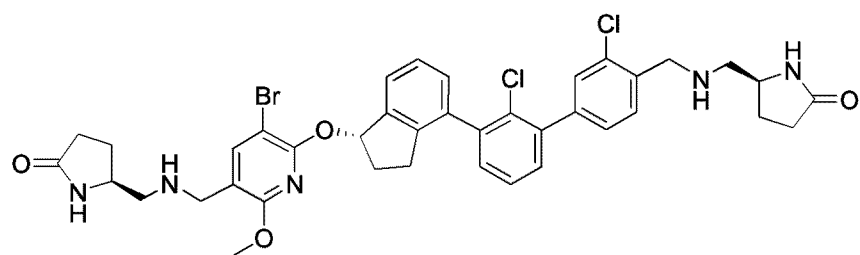












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- Embodiment 29. A pharmaceutical composition comprising a compound according to any one of embodiments 1 to 20 or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.
- Embodiment 30. The pharmaceutical composition according to embodiment 29, further
5 comprising at least one additional agent which is an anticancer agent selected from rituxan, doxorubicin, gemcitabine, nivolumab, pembrolizumab, and ipilimumab.
- Embodiment 31. The pharmaceutical composition according to embodiment 29, further comprising an additional agent which is an anticancer agent, wherein the additional anticancer agent is nivolumab, pembrolizumab, atezolizumab, or ipilimumab.
- 10 Embodiment 32. A compound according to any one of embodiments 1 to 20 or a pharmaceutically acceptable salt thereof for use in therapy.
- Embodiment 33. A compound according to any one of embodiments 1 to 20 or a pharmaceutically acceptable salt thereof for use in inhibiting PD-1, PD-L1 and/or the PD-1/PD-L1 interaction.
- Embodiment 34. A compound according to any one of embodiments 1 to 20 or a pharmaceutically
15 acceptable salt thereof, for use in treating cancer.
- Embodiment 35. The compound for use according to embodiment 34, wherein the cancer is pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft
20 tissue sarcoma, non-small cell lung cancer, small-cell lung cancer, or colon cancer.
- Embodiment 36. The compound for use according to embodiment 34, wherein the cancer is acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myeloid leukemia (CML), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL),
25 mantle cell lymphoma (MCL), follicular lymphoma, Waldestrom's macroglobulinemia (WM), T-cell lymphoma, B-cell lymphoma, or diffuse large B-cell lymphoma (DLBCL).
- Embodiment 37. The compound for use according to any one of embodiments 32 to 36, for use in combination with at least one additional anticancer agent or therapy selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, ipilimumab, chemotherapy, radiation therapy, and resection
30 therapy.
- Embodiment 38. The compound for use according to embodiment 37, wherein the additional anticancer agent or therapy is nivolumab, pembrolizumab, atezolizumab, or ipilimumab.
- Embodiment 39. A compound according to any one of embodiments 1 to 20 or a pharmaceutically acceptable salt thereof, and at least one additional agent which is an anticancer agent selected from
35 rituxan, doxorubicin, gemcitabine, nivolumab, pembrolizumab, and ipilimumab for use in treating cancer.

Embodiment 40. The compound for use according to embodiment 39, wherein the cancer is pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft
5 tissue sarcoma, non-small cell lung cancer, small-cell lung cancer, or colon cancer.

Embodiment 41. The compound for use according to embodiment 39, wherein the cancer is acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myeloid leukemia (CML), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL),
10 mantle cell lymphoma (MCL), follicular lymphoma, Waldstrom's macroglobulinemia (WM), T-cell lymphoma, B-cell lymphoma, or diffuse large B-cell lymphoma (DLBCL).

DETAILED DESCRIPTION

Definitions

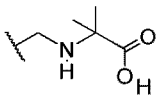
15 As used in the present disclosure, the following words and phrases are generally intended to have the meanings as set forth below unless expressly indicated otherwise or the context in which they are used indicates otherwise.

The following description sets forth exemplary methods, parameters and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present
20 disclosure but is instead provided as a description of exemplary embodiments.

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

A dash ("—") that is not between two letters or symbols is used to indicate a point of attachment
25 for a substituent. For example, -C(O)NH_2 is attached through the carbon atom. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. Unless chemically or structurally required, no directionality is indicated or implied by the order in which a chemical group is written or named.

A squiggly line on a chemical group as shown below, for example,

30  indicates a point of attachment, i.e., it shows the broken bond by which the group is connected to another described group.

The prefix “C_{u-v}” indicates that the following group has from u to v carbon atoms. For example, “C₁₋₆ alkyl” indicates that the alkyl group has from 1 to 6 carbon atoms.

Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter *per se*. In certain embodiments, the term “about” includes the indicated amount $\pm 10\%$. In other embodiments, the term “about” includes the indicated amount $\pm 5\%$. In certain other embodiments, the term “about” includes the indicated amount $\pm 1\%$. Also, to the term “about X” includes description of “X”. Also, the singular forms “a” and “the” include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to “the compound” includes a plurality of such compounds and reference to “the assay” includes reference to one or more assays and equivalents thereof known to those skilled in the art.

The term “substituted” means that any one or more hydrogen atoms on the designated atom or group is replaced with one or more substituents other than hydrogen, provided that the designated atom’s normal valence is not exceeded. The one or more substituents include, but are not limited to, alkyl, alkenyl, alkynyl, alkoxy, acyl, amino, amido, amidino, aryl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, haloalkyl, heteroalkyl, heteroaryl, heterocycloalkyl, hydroxy, hydrazino, imino, oxo, nitro, alkylsulfinyl, sulfonic acid, alkylsulfonyl, thiocyanate, thiol, thione, or combinations thereof. Polymers or similar indefinite structures arrived at by defining substituents with further substituents appended ad infinitum (e.g., a substituted aryl having a substituted alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Unless otherwise noted, the maximum number of serial substitutions in compounds described herein is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to ((substituted aryl)substituted aryl) substituted aryl. Similarly, the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluorines or heteroaryl groups having two adjacent oxygen ring atoms). Such impermissible substitution patterns are well known to the skilled artisan. When used to modify a chemical group, the term “substituted” may describe other chemical groups defined herein. For example, the term “substituted aryl” includes, but is not limited to, “alkylaryl.” Unless specified otherwise, where a group is described as optionally substituted, any substituents of the group are themselves unsubstituted.

A “substituted” group also includes embodiments in which a monoradical substituent is bound to a single atom of the substituted group (e.g., forming a branch), and also includes embodiments in which the substituent may be a diradical bridging group bound to two adjacent atoms of the substituted group, thereby forming a fused ring on the substituted group.

“Alkyl” refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (i.e., C₁₋₂₀ alkyl), 1 to 8 carbon atoms (i.e., C₁₋₈ alkyl), 1 to 6 carbon atoms (i.e., C₁₋₆ alkyl), or 1 to 4 carbon atoms (i.e., C₁₋₄ alkyl). Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl,

2-hexyl, 3-hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example, "butyl" includes n-butyl (i.e., $-(CH_2)_3CH_3$), sec-butyl (i.e., $-CH(CH_3)CH_2CH_3$), isobutyl (i.e., $-CH_2CH(CH_3)_2$) and tert-butyl (i.e., $-C(CH_3)_3$); and "propyl" includes n-propyl (i.e., $-(CH_2)_2CH_3$) and isopropyl (i.e., $-CH(CH_3)_2$).

"Alkenyl" refers to an aliphatic group containing at least one carbon-carbon double bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkenyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkenyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkenyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkenyl). Examples of alkenyl groups include ethenyl, propenyl, butadienyl (including 1,2-butadienyl, and 1,3-butadienyl).

"Alkynyl" refers to an aliphatic group containing at least one carbon-carbon triple bond and having from 2 to 20 carbon atoms (i.e., C_{2-20} alkynyl), 2 to 8 carbon atoms (i.e., C_{2-8} alkynyl), 2 to 6 carbon atoms (i.e., C_{2-6} alkynyl), or 2 to 4 carbon atoms (i.e., C_{2-4} alkynyl). The term "alkynyl" also includes those groups having one triple bond and one double bond.

"Alkoxy" refers to the group "alkyl-O-" or "-O-alkyl". Examples of alkoxy groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy.

"Haloalkoxy" refers to an alkoxy group as defined above, wherein one or more hydrogen atoms are replaced by a halogen.

"Amino" refers to the group $-NR^yR^z$ wherein R^y and R^z are independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl; each of which may be optionally substituted.

"Aryl" refers to a monoradical or diradical aromatic carbocyclic group having a single ring (e.g., monocyclic) or multiple rings (e.g., bicyclic or tricyclic) including fused ring systems wherein one or more fused rings is/are fully or partially unsaturated. As used herein, aryl has 6 to 20 ring carbon atoms (i.e., C_{6-20} aryl), 6 to 12 carbon ring atoms (i.e., C_{6-12} aryl), or 6 to 10 carbon ring atoms (i.e., C_{6-10} aryl). Non-limiting examples of aryl groups as used herein include phenyl, naphthyl, fluorenyl, indanyl, tetrahydroindanyl, and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl ring, the resulting ring system is heteroaryl. The classification of mono or diradical indicates whether the aryl group terminates the chain (monoradical) or is within a chain (diradical). The above definition does not preclude additional substituents on the aryl group. For example, as used herein, the aryl group in "A-aryl-B" is a diradical whereas the aryl group in "A-B-aryl" is monoradical, though additional substituents may be present on each aryl group.

The term "alkylsulfinyl" refers to the group $-SO$ -alkyl, where alkyl is as defined above, and includes optionally substituted alkyl groups as also defined above.

The term “alkylsulfonyl” refers to the group -SO₂-alkyl, where alkyl is as defined above, and includes optionally substituted alkyl groups as also defined above.

“Cycloalkyl” refers to a saturated or partially saturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C₃₋₂₀ cycloalkyl), 3 to 12 ring carbon atoms (i.e., C₃₋₁₂ cycloalkyl), 3 to 10 ring carbon atoms (i.e., C₃₋₁₀ cycloalkyl), 3 to 8 ring carbon atoms (i.e., C₃₋₈ cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C₃₋₆ cycloalkyl). Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

As used herein the term “cycloalkenyl” groups means the non-aromatic carbocyclic group having at least one double bond.

“Cyanoalkyl” refers to an alkyl group substituted with cyano (CN).

“Halogen” or “halo” includes fluoro, chloro, bromo, and iodo.

The term “haloalkyl” refers to a monoradical or diradical having the indicated carbon atoms of the alkyl group wherein one or more hydrogen atoms have been substituted by a halogen. Examples of haloalkyl groups include -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, -CHFCH₂F, -CF₂-, -CHF-, and the like. Similarly, the term “haloalkoxy”, e.g., -O-C₁₋₃haloalkyl, refers to an alkoxy group wherein one or more hydrogen atoms of the alkyl group have been substituted by a halogen. Examples of haloalkoxy groups include -OCH₂F, -OCHF₂, -OCF₃, -OCH₂CF₃, -OCHFCH₂F, and the like. One of skill in the art is aware that similar definitions apply for the alkenyl and alkynyl analogs (e.g., C₂₋₄haloalkenyl, -O-C₂₋₄haloalkynyl) of the above.

“Heteroalkyl” refers to an alkyl group in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic group. The term “heteroalkyl” includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, -NR-, -O-, -S-, -SO-, -SO₂-, and the like, where R is H, alkyl, aryl, cycloalkyl, heteroalkyl, heteroaryl, or heterocycloalkyl, each of which may be optionally substituted. Examples of heteroalkyl groups include -OCH₃, -CH₂OCH₃, -SCH₃, -CH₂SCH₃, -NRCH₃, and -CH₂NRCH₃, where R is hydrogen, alkyl, aryl, arylalkyl, heteroalkyl, or heteroaryl, each of which may be optionally substituted. As used herein, heteroalkyl includes 1 to 10 carbon atoms, 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom.

“Heteroaryl” refers to a monoradical or diradical aromatic group having a single ring, multiple rings, or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. The term includes fused ring systems wherein one or more fused rings is/are fully or partially unsaturated. As used herein, heteroaryl include 1 to 20 ring carbon atoms (i.e., C₁₋₂₀ heteroaryl), 3 to 12 ring carbon atoms (i.e., C₃₋₁₂ heteroaryl), or 3 to 8 carbon ring atoms (i.e., C₃₋₈ heteroaryl); and 1

to 5 heteroatoms, 1 to 4 heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. Non-limiting examples of heteroaryl groups include pyrimidinyl, purinyl, pyridyl, pyridazinyl, benzothiazolyl, benzodioxanyl, indolinyl, and pyrazolyl. The classification of mono or diradical indicates whether the heteroaryl group terminates the chain (monoradical) or is within a chain (diradical). The above definition does not preclude additional substituents on the heteroaryl group. For example, the heteroaryl group in “A-heteroaryl-B” is a diradical whereas the heteroaryl group in “A-B-heteroaryl” is monoradical, though additional substituents may be present on each heteroaryl group. Heteroaryl does not encompass or overlap with aryl as defined above.

“Heterocycloalkyl” refers to a saturated or unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. A heterocycloalkyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro. As used herein, heterocycloalkyl has 2 to 20 ring carbon atoms (i.e., C₂₋₂₀ heterocycloalkyl), 2 to 12 ring carbon atoms (i.e., C₂₋₁₂ heterocycloalkyl), 2 to 10 ring carbon atoms (i.e., C₂₋₁₀ heterocycloalkyl), 2 to 8 ring carbon atoms (i.e., C₂₋₈ heterocycloalkyl), 3 to 12 ring carbon atoms (i.e., C₃₋₁₂ heterocycloalkyl), 3 to 8 ring carbon atoms (i.e., C₃₋₈ heterocycloalkyl), or 3 to 6 ring carbon atoms (i.e., C₃₋₆ heterocycloalkyl); having 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur or oxygen. Examples of heterocycloalkyl groups include pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, dioxolanyl, azetidiny, and morpholinyl. As used herein, the term “bridged-heterocycloalkyl” refers to a four- to ten-membered cyclic moiety connected at two non-adjacent atoms of the heterocycloalkyl with one or more (e.g., 1 or 2) four- to ten-membered cyclic moiety having at least one heteroatom where each heteroatom is independently selected from nitrogen, oxygen, and sulfur. As used herein, bridged-heterocycloalkyl includes bicyclic and tricyclic ring systems. Also used herein, the term “spiro-heterocycloalkyl” refers to a ring system in which a three- to ten-membered heterocycloalkyl has one or more additional ring, wherein the one or more additional ring is three- to ten-membered cycloalkyl or three- to ten-membered heterocycloalkyl, where a single atom of the one or more additional ring is also an atom of the three- to ten-membered heterocycloalkyl. Examples of spiro-heterocycloalkyl include bicyclic and tricyclic ring systems, such as 2-oxa-7-azaspiro[3.5]nonanyl, 2-oxa-6-azaspiro[3.4]octanyl, and 6-oxa-1-azaspiro[3.3]heptanyl.

The term “heterocyclyl,” “heterocycle,” or “heterocyclic” refers to a monoradical or diradical saturated or unsaturated group having a single ring or multiple condensed rings, having from 3 to 12 carbon atoms, from 1 to 6 hetero atoms, or from 1 to 4 heteroatoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring. Where the group does not terminate the molecule, it is a diradical and is construed as such i.e., also referred to as heterocyclylene or heterocyclene.

Exemplary “heterocyclyl” groups include, but are not limited to, pyrrolidin-2-one, azetidine, piperidine, pynrolidine, 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine, morpholine, piperazin-2-one, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octan-7-one, 2,5-diazaspiro[3.4]octan-6-one, 2,7-

diazaspiro[4.4]nonan-3-one, 2,9-diazaspiro[5.5]undecan-1-one, 1,7-diazaspiro[3.5]nonan-2-one, 2,8-diazaspiro[4.5]decan-3-one, piperazine, 2-azaspiro[3.3]heptane, and 2-azabicyclo[2.2.2]octane.

The term “heterocyclyl” includes heterocycloalkenyl groups (i.e., the heterocyclyl group having at least one double bond), bridged-heterocyclyl groups, fused-heterocyclyl groups, and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro. Any non-aromatic ring containing at least one heteroatom is considered a heterocyclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to an aryl or heteroaryl ring, regardless of the attachment to the remainder of the molecule. A heterocyclyl may contain one or more oxo and/or thioxo groups.

“Acyl” refers to a group $-C(=O)R$, wherein R is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of acyl include formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethyl-carbonyl, and benzoyl.

The term “N-alkylated” means an alkyl group is substituted for one of the hydrogen atoms of a mono substituted amine, or a di-substituted amine group or a tri substituted amine group. When the alkylation is on a tri-substituted amine group an alkonium salt is generated i.e., a positive charge is generated on the nitrogen atom. N-alkylation is commonly associated with alkyl substitution on a ring nitrogen atom.

The term “oxo” refers to a group $=O$.

The term “carboxy” refers to a group $-C(O)-OH$.

The term “ester” or “carboxyl ester” refers to the group $-C(O)OR$, where R is alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl, which may be optionally further substituted, for example, by alkyl, alkoxy, halogen, CF_3 , amino, substituted amino, cyano or $-SO_nR^f$, in which R^f is alkyl, aryl, or heteroaryl, and n is 0, 1 or 2.

The term “substituted amino” refers to the group $-NRR$, where each R is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which may be optionally substituted, or a group as described or exemplified herein, or where both R groups are joined to form a heterocyclic group (e.g., morpholino) as described or exemplified herein, which also may be optionally substituted.

The term “amido” refers to the group $-C(O)NRR$ where each R is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which may be optionally substituted, or a group as described or exemplified herein, or where both R groups are joined to form a heterocyclic group (e.g., morpholino) as described or exemplified herein, which also may be optionally substituted.

The term “sulfoxide” refers to a group $-SOR$, in which R is alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which may be optionally substituted.

The term “sulfone” refers to a group $\text{-SO}_2\text{R}$, in which R is alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which may be optionally substituted.

As used herein, the terms “alkylcycloalkyl,” “alkylaryl,” “alkylheteroaryl” and “alkylheterocyclyl” are intended to refer to a cycloalkyl, aryl, heteroaryl or heterocyclyl group which is bound to the remainder of the molecule via an alkyl moiety, where the terms “alkyl,” “cycloalkyl,” “aryl,” “heteroaryl” and “heterocyclyl” are as defined herein. Exemplary alkylaryl groups include benzyl, phenethyl, and the like.

“Optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not.

Certain commonly used alternative chemical names may be used. For example, a divalent group such as a divalent “alkyl” group, a divalent “aryl” group, etc., may also be referred to as an “alkylene” group or an “alkylenyl” group, an “arylene” group or an “arylenyl” group, respectively. Also, unless indicated explicitly otherwise, where combinations of groups are referred to herein as one moiety, e.g., arylalkyl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule.

Where a group is represented by a bond, multiple adjacent groups whether the same or different, when represented by bonds, constitute a single bond. For example the group “ $\text{-L}^1\text{-V}^1\text{-L}^2\text{-}$ ” constitutes a single bond if each of L^1 , V^1 and L^2 is a bond.

Where a given group (moiety) is described herein as being attached to a second group and the site of attachment is not explicit, the given group may be attached at any available site of the given group or to any available site of the second group. For example, an “alkyl-substituted phenyl”, where the attachment sites are not explicit, may have any available site of the alkyl group attached to any available site of the phenyl group. In this regard, an “available site” is a site of the group at which hydrogen of the group may be replaced with a substituent.

It is understood that in all substituted groups defined above, polymers arrived at by defining substituents with further substituents to themselves (e.g., substituted aryl having a substituted aryl group as a substituent which is itself substituted with a substituted aryl group, etc.) are not intended for inclusion herein. Also not included are infinite numbers of substituents, whether the substituents are the same or different. In such cases, the maximum number of such substituents is three. Each of the above definitions is thus constrained by a limitation that, for example, substituted aryl groups are limited to -substituted aryl-(substituted aryl)-substituted aryl.

“Isomers” are different compounds that have the same molecular formula. Isomers include stereoisomers, enantiomers and diastereomers.

“Stereoisomers” are isomers that differ only in the way the atoms are arranged in space.

“Enantiomers” are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a “racemic” mixture. The term “(±)” is used to designate a racemic mixture where appropriate.

5 **“Diastereoisomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.**

The compounds of the disclosure may possess one or more asymmetric centers and may be produced as a racemic mixture or as individual enantiomers or diastereoisomers. The number of stereoisomers present in any given compound of a given formula depends upon the number of asymmetric centers present (there are 2^n stereoisomers possible where n is the number of asymmetric centers). The individual stereoisomers may be obtained by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis or by resolution of the compound by conventional means. The individual stereoisomers (including individual enantiomers and diastereoisomers) as well as racemic and non-racemic mixture of stereoisomers are encompassed within the scope of the present disclosure, all of which are intended to be depicted by the structures of this specification unless otherwise specifically indicated.

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The absolute stereochemistry is specified according to the Cahn Ingold Prelog R S system. When the compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either R or S. A resolved compound whose absolute configuration is unknown may be designated (+) or (-) depending on the direction (dextro- or laevorotary) that it rotates the plane of polarized light at the wavelength of the sodium D line.

20

Some of the compounds exist as tautomeric isomers. Tautomeric isomers are in equilibrium with one another. For example, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown, and regardless of the nature of the equilibrium among tautomers, the compounds are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, the amide containing compounds are understood to include their imidic acid tautomers. Likewise, the imidic acid containing compounds are understood to include their amide tautomers.

25

The term “polymorph” refers to different crystal structures of a crystalline compound. The different polymorphs may result from differences in crystal packing (packing polymorphism) or differences in packing between different conformers of the same molecule (conformational polymorphism).

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The term “solvate” refers to a complex formed by combining a compound of formula (I), or any other formula as disclosed herein and a solvent.

The term “hydrate” refers to the complex formed by the combining of a compound of formula (I), or any formula disclosed herein, and water.

35

The term “prodrug” refers to compounds of formula (I), or derivatives of formula (I) disclosed herein, that include chemical groups which, *in vivo*, can be converted and/or can be split off from the remainder of the molecule to provide for the active drug. Pharmaceutically acceptable salts or biologically active metabolites thereof of the prodrug of a compound of formula (I) are also within the
 5 ambit of the present disclosure.

Any formula or structure given herein, including formula (I), or any formula disclosed herein, is intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an isotope having a selected atomic mass or mass
 10 number. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as, but not limited to ^2H (deuterium, D), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl , and ^{125}I . Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as
 15 ^3H , ^{13}C and ^{14}C are incorporated, are within the ambit of the present disclosure. Such isotopically labeled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in treatment of patients. Such isotopically labeled analogs of compounds of the present disclosure may also be useful for treatment of diseases disclosed
 20 herein because they may provide improved pharmacokinetic and/or pharmacodynamic properties over the unlabeled forms of the same compounds. Such isotopically leveled forms of or analogs of compounds herein are within the ambit of the present disclosure. One of skill in the art is able to prepare and use such isotopically labeled forms following procedures for isotopically labeling compounds or aspects of compounds to arrive at isotopic or radiolabeled analogs of compounds disclosed herein.

The term “pharmaceutically acceptable salt” of a given compound refers to salts that retain the biological effectiveness and properties of the given compound, and which are not biologically or otherwise undesirable. Pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include,
 30 but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines, di-substituted cycloalkyl amine, tri-substituted cycloalkyl amines,
 35 cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, di-substituted cycloalkenyl amine, tri-substituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic

amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group. Amines are of general structure $N(R^{30})(R^{31})(R^{32})$, wherein mono-substituted amines have two of the three substituents on nitrogen (R^{30} , R^{31} , and R^{32}) as hydrogen, di-substituted amines have one of the three substituents on nitrogen (R^{30} , R^{31} , and R^{32}) as hydrogen, whereas tri-substituted amines have none of the three substituents on nitrogen (R^{30} , R^{31} , and R^{32}) as hydrogen. R^{30} , R^{31} , and R^{32} are selected from a variety of substituents such as hydrogen, optionally substituted alkyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl, and the like.

Specific examples of suitable amines include, by way of example only, isopropyl amine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, diethanolamine, 2-dimethylamino ethanol, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like.

As used herein, "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial, and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, or unless otherwise indicated herein, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The term "anticancer agent" is any drug that is effective in the treatment of a malignant, or cancerous disease. Effectiveness may mean inhibition, partial, or full remission, prolongation of life, improvement in quality of life, or cure. There are several major classes of anticancer drugs including chemical compositions as disclosed herein or known to one of skill in the art e.g., PD-1, PD-L1, PD-1/PD-L1 interaction inhibitors, alkylating agents, antimetabolites, natural products, and hormones.

The term "additional anticancer agent" as used herein means the use or combination of a second, third, fourth, fifth, etc., anticancer agent(s) in addition to a compound according to formula (I) disclosed herein.

The term “anticancer therapy” means any currently known therapeutic methods for the treatment of cancer.

The term “blockade agent” or “check point inhibitors” are classes of immune oncology agents that inhibit PD-1, PD-L1, or the PD-1/PD-L1 interaction.

5 The term “treatment” or “treating” means any administration of a compound or compounds according to the present disclosure to a subject (e.g., a human) having or susceptible to a condition or disease disclosed herein for the purpose of: 1) preventing or protecting against the disease or condition, that is, causing the clinical symptoms not to develop; 2) inhibiting the disease or condition, that is, arresting or suppressing the development of clinical symptoms; or 3) relieving the disease or condition
10 that is causing the regression of clinical symptoms. In some embodiments, the term “treatment” or “treating” refers to relieving the disease or condition or causing the regression of clinical symptoms.

As used herein, the term “preventing” refers to the prophylactic treatment of a patient in need thereof. The prophylactic treatment can be accomplished by providing an appropriate dose of a therapeutic agent to a subject at risk of suffering from an ailment, thereby substantially averting onset of
15 the ailment. The presence of a genetic mutation or the predisposition to having a mutation may not be alterable. However, prophylactic treatment (prevention) as used herein has the potential to avoid/ameliorate the symptoms or clinical consequences of having the disease engendered by such genetic mutation or predisposition.

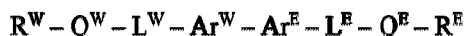
It will be understood by those of ordinary skill in the art that in human medicine, it is not always
20 possible to distinguish between “preventing” and “suppressing” since the ultimate inductive event or events may be unknown, latent, or the patient is not ascertained until well after the occurrence of the event or events. Therefore, as used herein, the term “prophylaxis” is intended as an element of “treatment” to encompass both “preventing” and “suppressing” as defined herein. The term “protection,” as used herein, is meant to include “prophylaxis.”

25 The term “patient” typically refers to a “mammal” which includes, without limitation, human, monkeys, rabbits, mice, domestic animals, such as dogs and cats, farm animals, such as cows, horses, or pigs, and laboratory animals. In some embodiments, the term patient refers to a human in need of treatment as defined herein.

Compounds

30 Provided herein are compounds that function as PD-1 inhibitors, PD-L1 inhibitors, and/or PD-1/PD-L1 interaction inhibitors, methods of using such compounds and compositions comprising such compounds optionally in combination with one or more additional anticancer agents or therapies. In all embodiments discussed herein where there is more than one occurrence of a group or variable, it is intended that the group or variable is independently selected the list that follows. It is further
35 contemplated that all embodiments directed to compounds include any pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, prodrug or tautomer thereof.

The present disclosure provides a compound of formula (I):



(I)

wherein:

5 Ar^E and Ar^W are each independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, $-OR^a$, $-NO_2$, $-CN$, $-NR^aR^b$, $-N_3$, $-SO_2R^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-OC_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-6}$ alkyl C_{3-8} cycloalkyl;

10 wherein each alkyl, alkenyl, alkynyl, and cycloalkyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

L^E and L^W are each independently a bond, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-(CR^3R^4)_m-$, $-(CR^3R^4)_mO(CR^3R^4)_m-$, $-(CR^3R^4)_mS(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3(CR^3R^4)_m-$, $-C(O)-$, $-(CR^3R^4)_mC(O)(CR^3R^4)_m-$, $-(CR^3R^4)_mC(O)NR^3(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3C(O)(CR^3R^4)_m-$, C_{2-6} alkenylene, C_{2-6} alkynylene,



wherein

each m is independently 0, 1, 2, 3 or 4;

Q^E and Q^W are each independently aryl, heteroaryl, or heterocyclyl,

20 wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, oxo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

25 wherein each alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

30

wherein

R^N is independently $-C_{1-6}alkylINR^1R^2$, $-OC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylINR^1R^2$, $-NR^aC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)OR^1$, $-SC_{1-6}$

$alkylINR^1R^2$, $-C_{1-6}alkylOR^a$, or $L^1-V-L^2-\textcircled{A}$;

wherein

5 L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, and $C_{2-6}alkynyl$;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ or $-C_{3-8}cycloalkyl$;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

10 ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}alkyl$, $-C_{1-6}haloalkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-OC_{1-6}haloalkyl$, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}alkylCN$, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $C_{3-8}cycloalkyl$, and $C_{1-6}alkylC_{3-8}cycloalkyl$;

15

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ and $-C_{3-8}cycloalkyl$;

20 R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}alkylINR^1R^2$, $-OC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylINR^1R^2$, $-NR^aC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylIN^+R^1R^2R^3$, $-SC_{1-6}alkylINR^1R^2$, $-C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_nSO_2NR^1R^2$, $-(CH_2)_nNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}alkylINR^1R^2$, $-NR^aSO_2C_{1-6}alkylINR^1R^2$, $-(CH_2)_nC(O)NR^aSO_2NR^aR^b$, $-(CH_2)_nN^+R^1R^2O^-$, $-(CH_2)_nP^+R^bR^cR^d$, $-(CH_2)_nP^+R^cR^dO^-$, $-(CH_2)_nP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_nNR^cP(O)(OR^c)_2$, $-(CH_2)_nNR^c(CH_2)_nP(O)(OR^c)_2$, $-(CH_2)_nCH_2OP(O)(OR^c)(OR^d)$, $-(CH_2)_nOP(O)(OR^c)(OR^d)$, $-(CH_2)_nOP(O)NR^aR^b(OR^a)$, or $-V^2-(CR^cR^d)_p-L^3-\textcircled{B}-(T)_z$;

25

wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

30

ring B is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently H, OR^a , $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^e$, $(CH_2)_qOR^a$, or $(CH_2)_qC(O)R^e$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4; and

z is 0, 1, 2, or 3;

5 wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from NR^aR^b , halo, cyano, oxo, OR^a , $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl NR^aR^b , $-C_{1-6}$ alkylOH, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

10 R^1 is independently selected from H, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl $C(O)OR^a$, $-C_{2-6}$ alkenyl $C(O)OR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-C(O)NR^aSO_2R^a$, and C_{1-6} alkyl C_{3-8} cycloalkyl;

15 wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $NR^aC(O)OR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, $-C_{1-6}$ alkyl $C(O)NR^aSO_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}$ alkyl $NR^aC(O)R^b$;

20 R^2 is independently selected from H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl OR^a , $-C_{1-6}$ alkyl $C(O)OR^a$, and $-C_{2-6}$ alkenyl $C(O)OR^a$;

25 wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$ and $-NR^aC(O)R^b$;

30 or R^1 and R^2 combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OR^a$, $-C(O)OR^a$, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ haloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, C_{1-6} alkyl $C(O)R^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, and C_{1-6} alkyl $SO_2NR^aR^b$;

R^3 is independently H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, or $-C_{2-6}$ alkenylC(O)OR^a;

R^4 is independently H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl,
5 $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, or $-C_{2-6}$ alkenylC(O)OR^a;

R^a is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^b is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl,
10 $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from $-OR^f$, $-CN$, halo, $-C_{1-6}$ alkylOR^f, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^f$, $-C_{1-6}$ alkylC(O)R^f, $-C(O)OR^f$, $-C_{1-6}$ alkylC(O)OR^f, $-NR^fR^g$, $-C_{1-6}$ alkylNR^fR^g, $-C(O)NR^fR^g$,
15 $-C_{1-6}$ alkylC(O)NR^fR^g, $-SO_2R^f$, $-C_{1-6}$ alkylSO₂R^f, $-SO_2NR^fR^g$, $-C_{1-6}$ alkylSO₂NR^fR^g, $-C(O)NR^fSO_2R^g$ and $-NR^fC(O)R^g$;

R^c is independently selected from H, OH, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^d is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl,
20 $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

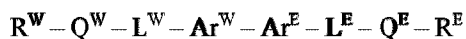
R^e is independently selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkylNR^fR^g, $-C(O)NR^fR^g$, $-C_{1-6}$ alkylC(O)NR^fR^g, $-NHSO_2R^f$, $-C_{1-6}$ alkylSO₂R^f, and $-C_{1-6}$ alkylSO₂NR^fR^g;

R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl,
25 $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and

R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer
30 thereof.

The present disclosure further provides a compound of formula (I):



(I)

wherein:

Ar^E and Ar^W are each independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, $-\text{OR}^a$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^a\text{R}^b$, $-\text{N}_3$, $-\text{SO}_2\text{R}^a$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ haloalkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-\text{OC}_{1-6}$ haloalkyl, $-\text{C}_{3-8}$ cycloalkyl, and $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl;

wherein each alkyl, alkenyl, alkynyl, and cycloalkyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, and cyano;

L^E and L^W are each independently a bond, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{O}(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{S}(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{NR}^3(\text{CR}^3\text{R}^4)_m-$, $-\text{C}(\text{O})-$, $-(\text{CR}^3\text{R}^4)_m\text{C}(\text{O})(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{C}(\text{O})\text{NR}^3(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{NR}^3\text{C}(\text{O})(\text{CR}^3\text{R}^4)_m-$, C_{2-6} alkenylene, C_{2-6} alkynylene,



wherein

each m is independently 1, 2, 3 or 4;

provided that when one of Ar^E and Ar^W is optionally substituted phenyl and the other is optionally substituted phenyl or optionally substituted 2,3-dihydrobenzo[b][1,4]dioxine, and one of L^E and L^W is $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CHCH}-$, and $-\text{C}(\text{O})\text{N}-$; then the other of L^E and L^W is a bond, $-\text{O}-$ or $-\text{CH}_2\text{O}-$ of the formula $\text{Ar}-\text{CH}_2\text{O}-\text{Q}$;

Q^E and Q^W are each independently aryl, heteroaryl, or heterocyclyl,

wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, oxo, $-\text{OR}^a$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl, and R^N ;

wherein each alkyl, alkenyl, alkynyl, is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}$ alkyl CN , $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$ and $-\text{C}_{3-8}$ cycloalkyl;

wherein

R^N is independently $-\text{C}_{1-6}$ alkyl NR^1R^2 , $-\text{OC}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-\text{NR}^a\text{C}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^1$,



wherein

L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

5 wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

provided at least one of L^1 , V or L^2 is other than a bond;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

10 wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, C_{3-8} cycloalkyl, and C_{1-6} alkyl C_{3-8} cycloalkyl;

15

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $IN^+R^1R^2R^3$, $-SC_{1-6}$ alkyl NR^1R^2 , $-C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_nSO_2NR^1R^2$, $-(CH_2)_nNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}$ alkyl NR^1R^2 , $-NR^aSO_2C_{1-6}$ alkyl NR^1R^2 , $-(CH_2)_nC(O)NR^aSO_2NR^aR^b$, $-(CH_2)_nN^+R^1R^2O^-$, $-(CH_2)_nP^+R^bR^cR^d$, $-(CH_2)_nP^+R^cR^dO^-$, $-(CH_2)_nP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_nNR^aP(O)(OR^c)_2$, $-(CH_2)_nNR^c(CH_2)_nP(O)(OR^c)_2$, $-(CH_2)_nCH_2OP(O)(OR^c)(OR^d)$, $-(CH_2)_nOP(O)(OR^c)(OR^d)$, $-(CH_2)_nOP(O)NR^aR^b(OR^a)$, or $-V^2-(CR^cR^d)_p-L^3-\textcircled{B}-(T)_z$;

20

25 wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

ring B is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently H, OR^a , $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^e$, $(CH_2)_qOR^a$, or $(CH_2)_qC(O)R^e$;

30 p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4; and

z is 0, 1, 2, or 3;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 3 substituents independently selected from NR^aR^b , halo, cyano, oxo, OR^a , $-\text{C}_{1-6}$ alkyl,

5 $-\text{C}_{1-6}$ haloalkyl, $-\text{C}_{1-6}$ cyanoalkyl, $-\text{C}_{1-6}$ alkyl NR^aR^b , $-\text{C}_{1-6}$ alkylOH, $-\text{C}_{3-8}$ cycloalkyl, and $-\text{C}_{1-3}$ alkyl C_{3-8} cycloalkyl;

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom, and when each of V^2 and L^3 is a bond and p is 0, then either (i) neither of L^E or L^W is a bond or (ii) ring B is not a 5,6-membered fused heteroaryl where the 5-membered ring of the fused heteroaryl is bound to the

10 corresponding Q^E or Q^W ;

R^1 is independently selected from H, $-\text{C}_{1-8}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{C}_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-6}$ alkylaryl, $-\text{C}_{1-6}$ alkylheteroaryl, $-\text{C}_{1-6}$ alkylheterocyclyl, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^a$, $-\text{C}_{2-6}$ alkenyl $\text{C}(\text{O})\text{OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{R}^a$, and C_{1-6} alkyl C_{3-8} cycloalkyl;

15 wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-\text{OR}^a$, $-\text{CN}$, halo, C_{1-6} alkyl, $-\text{C}_{1-6}$ alkyl OR^a , $-\text{C}_{1-6}$ cyanoalkyl, $-\text{C}_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-\text{C}_{1-3}$ alkyl C_{3-8} cycloalkyl, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{R}^b$, $-\text{OC}(\text{O})\text{NR}^a\text{R}^b$, $\text{NR}^a\text{C}(\text{O})\text{OR}^b$, $-\text{C}_{1-6}$ alkyl NR^aR^b , $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{SO}_2\text{R}^a$, $-\text{C}_{1-6}$ alkyl SO_2R^a , $-\text{SO}_2\text{NR}^a\text{R}^b$,
20 $-\text{C}_{1-6}$ alkyl $\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{R}^b$, and $-\text{C}_{1-6}$ alkyl $\text{NR}^a\text{C}(\text{O})\text{R}^b$;

R^2 is independently selected from H, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{C}_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-6}$ alkylaryl, $-\text{C}_{1-6}$ alkylheteroaryl, $-\text{C}_{1-6}$ alkylheterocyclyl, $-\text{C}_{2-6}$ alkyl $-\text{OR}^a$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^a$, and $-\text{C}_{2-6}$ alkenyl $\text{C}(\text{O})\text{OR}^a$;

25 wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-\text{OR}^a$, $-\text{CN}$, halo, C_{1-6} alkyl, $-\text{C}_{1-6}$ alkyl OR^a , $-\text{C}_{1-6}$ cyanoalkyl, $-\text{C}_{1-6}$ haloalkyl, $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-3}$ alkyl C_{3-8} cycloalkyl, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}$ alkyl NR^aR^b , $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{SO}_2\text{R}^a$, $-\text{C}_{1-6}$ alkyl SO_2R^a , $-\text{SO}_2\text{NR}^a\text{R}^b$,
30 $-\text{C}_{1-6}$ alkyl $\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{R}^b$ and $-\text{NR}^a\text{C}(\text{O})\text{R}^b$;

or R^1 and R^2 combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OR}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}_{1-6}$ cyanoalkyl, $-\text{C}_{1-6}$ alkyl OR^a , $-\text{C}_{1-6}$ haloalkyl, $-\text{C}_{1-3}$ alkyl C_{3-8} cycloalkyl, $-\text{C}(\text{O})\text{R}^a$,

C_{1-6} alkylC(O)R^a, $-C_{1-6}$ alkylC(O)OR^a, $-NR^aR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkylC(O)NR^aR^b, $-SO_2R^a$, $-C_{1-6}$ alkylSO₂R^a, $-SO_2NR^aR^b$, and C_{1-6} alkylSO₂NR^aR^b;

R³ is independently H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, or $-C_{2-6}$ alkenylC(O)OR^a;

- 5 R⁴ is independently H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, or $-C_{2-6}$ alkenylC(O)OR^a;

R^a is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

- 10 R^b is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from $-OR^f$, $-CN$, halo, $-C_{1-6}$ alkylOR^f, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^f$, $-C_{1-6}$ alkylC(O)R^f, $-C(O)OR^f$, $-C_{1-6}$ alkylC(O)OR^f, $-NR^fR^g$, $-C_{1-6}$ alkylNR^fR^g, $-C(O)NR^fR^g$, $-C_{1-6}$ alkylC(O)NR^fR^g, $-SO_2R^f$, $-C_{1-6}$ alkylSO₂R^f, $-SO_2NR^fR^g$, $-C_{1-6}$ alkylSO₂NR^fR^g, $-C(O)NR^fSO_2R^g$ and $-NR^fC(O)R^g$;

- 15 R^c is independently selected from H, OH, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

- 20 R^d is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

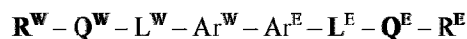
R^e is independently selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkylNR^fR^g, $-C(O)NR^fR^g$, $-C_{1-6}$ alkylC(O)NR^fR^g, $-NHSO_2R^f$, $-C_{1-6}$ alkylSO₂R^f, and $-C_{1-6}$ alkylSO₂NR^fR^g;

- 25 R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and

R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

- 30 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

The present disclosure further provides a compound of formula (I):



(I)

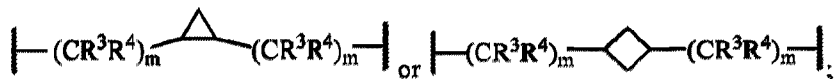
wherein:

Ar^E and Ar^W are each independently a cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, $-\text{OR}^a$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^a\text{R}^b$, $-\text{N}_3$, $-\text{SO}_2\text{R}^a$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ haloalkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-\text{OC}_{1-6}$ haloalkyl, $-\text{C}_{3-8}$ cycloalkyl, and $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl; and

wherein each alkyl, alkenyl, alkynyl, and cycloalkyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, and cyano;

L^E and L^W are each independently a bond, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{O}(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{S}(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{NR}^3(\text{CR}^3\text{R}^4)_m-$, $-\text{C}(\text{O})-$, $-(\text{CR}^3\text{R}^4)_m\text{C}(\text{O})(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{C}(\text{O})\text{NR}^3(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{NR}^3\text{C}(\text{O})(\text{CR}^3\text{R}^4)_m-$, C_{2-6} alkenylene, C_{2-6} alkynylene,



wherein each m is independently 0, 1, 2, 3 or 4;

Q^E and Q^W are each independently aryl, heteroaryl, or heterocyclyl;

wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, oxo, $-\text{OR}^a$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ; and

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}$ cyanoalkyl, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$ and $-\text{C}_{3-8}$ cycloalkyl; and further wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-\text{C}_{1-6}$ alkyl NR^1R^2 , $-\text{OC}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-\text{NR}^a\text{C}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^1$,

$-\text{SC}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl OR^a , or $\text{L}^1-\text{V}-\text{L}^2-\text{A}$;

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a, halo, cyano, -NR^aR^b or -C₃₋₈ cycloalkyl;

L² is independently a bond, O, NR^a, S, SO, or SO₂;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

5 wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo, cyano, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OC₁₋₆ haloalkyl, NR^aR^b, -C(O)R^a, -C(O)OR^a, -OC₁₋₆ alkylCN, -C(O)NR^aR^b, -NR^aC(O)R^a, -NR^aC(O)OR^a, -NR^aC(O)OR^a, -C(O)N(R^a)OR^b, -SO₂R^a,
10 -SO₂NR^aR^b, -NR^aSO₂R^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b, C₃₋₈cycloalkyl, and C₁₋₆alkylC₃₋₈cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with -OR^a, halo, cyano, -NR^aR^b or -C₃₋₈ cycloalkyl;

R^E and R^W are each independently -NR¹R², -C₁₋₆alkylNR¹R², -OC₁₋₆alkylNR¹R²,
15 -C₁₋₆alkylOC₁₋₆alkylNR¹R², -NR^aC₁₋₆alkylNR¹R², -C₁₋₆alkylIN⁺R¹R²R³, -SC₁₋₆alkylNR¹R², -C(O)NR¹R², -SO₂R^a, -(CH₂)_uSO₂NR¹R², -(CH₂)_uNR^aSO₂NR^aR^b, -SO₂NR^aC₁₋₆alkylNR¹R², -NR^aSO₂C₁₋₆alkylNR¹R², -(CH₂)_uC(O)NR^aSO₂NR^aR^b, -(CH₂)_uN⁺R¹R²O⁻, -(CH₂)_uP⁺R^bR^cR^d, -(CH₂)_uP⁺R^cR^dO⁻, -(CH₂)_uP⁺O[NR^aR^b][NR^cR^d], -(CH₂)_uNR^cP(O)(OR^e)₂, -(CH₂)_uCH₂OP(O)(OR^e)(OR^d), -(CH₂)_uOP(O)(OR^e)(OR^d), -(CH₂)_uOP(O)NR^aR^b(OR^a), or

20
$$-V^2-(CR^cR^d)_p-L^3-\textcircled{B}-(T)_z;$$

wherein:

V² is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹R², or NR^aSO₂;

L³ is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹R², or NR^aSO₂;

ring B is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

25 T is independently H, OR^a, (CH₂)_qNR¹R², (CH₂)_qNR^aC(O)R^e, or (CH₂)_qC(O)R^e;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

30 wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b, halo,

cyano, oxo, OR^a, -C₁₋₆alkyl, -C₁₋₆haloalkyl, -C₁₋₆cyanoalkyl, -C₁₋₆alkylNR^aR^b,
-C₁₋₆alkylOH, -C₃₋₈cycloalkyl, and -C₁₋₃alkylC₃₋₈cycloalkyl;

provided that at least one of V², L³, ring B and T contains a nitrogen atom;

- R¹** is independently selected from H, -C₁₋₈alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₆cycloalkyl, aryl,
5 heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl,
-C₁₋₆alkylC(O)OR^a, -C₂₋₆alkenylC(O)OR^a, -SO₂R^a, -SO₂NR^aR^b, -C(O)NR^aSO₂R^a, and
C₁₋₆alkylC₃₋₈cycloalkyl;

- wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted
with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a,
10 -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a,
-C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, NR^aC(O)OR^b,
-C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b,
-C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and
-C₁₋₆alkylNR^aC(O)R^b;

- R²** is independently selected from H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₆cycloalkyl, aryl,
15 heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a,
-C₁₋₆alkylC(O)OR^a, and -C₂₋₆alkenylC(O)OR^a;

- wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally
substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl,
20 -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl,
-C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b,
-C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b,
-C(O)NR^aSO₂R^b and -NR^aC(O)R^b;

- or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional
25 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1
to 3 groups independently selected from oxo, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl,
-OR^a, -C(O)OR^a, -C₁₋₆cyanoalkyl, -C₁₋₆alkylOR^a, -C₁₋₆haloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a,
C₁₋₆alkylC(O)R^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b,
-SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆alkylSO₂NR^aR^b;

- R³** is independently H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl,
30 -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, or
-C₂₋₆alkenylC(O)OR^a;

- R⁴** is independently H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, or
35 -C₂₋₆alkenylC(O)OR^a;

R^a is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

R^b is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

- 5 or **R^a** and **R^b** may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, -C₁₋₆alkylOR^f, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^f, -C₁₋₆alkylC(O)R^f, -C(O)OR^f, -C₁₋₆alkylC(O)OR^f, -NR^fR^g, -C₁₋₆alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and
10 -NR^fC(O)R^g;

R^c is independently selected from H, OH, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

R^d is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

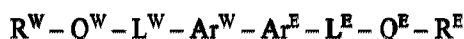
- 15 **R^e** is independently selected from H, -C₁₋₆alkyl, -OC₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -OC₃₋₈cycloalkyl, -Oaryl, -Oheteroaryl, -Oheterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -NR^fR^g, -C₁₋₆alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆alkylC(O)NR^fR^g, -NHSO₂R^f, -C₁₋₆alkylSO₂R^f, and -C₁₋₆alkylSO₂NR^fR^g;

- R^f** is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl; and
20

R^g is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof.

- 25 In one embodiment, provided is a compound of formula (I):



(I)

wherein:

Ar^E and **Ar^W** are each independently a cycloalkyl, aryl, heteroaryl, or heterocyclyl;

- 30 wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from halo, -OR^a, -NO₂, -CN, -NR^aR^b, -N₃, -SO₂R^a, -C₁₋₆alkyl, -C₁₋₆haloalkyl, OC₁₋₆alkyl, -OC₁₋₆haloalkyl, and -C₃₋₈cycloalkyl;

wherein each alkyl, and cycloalkyl group is optionally substituted with 1 to 4 groups independently selected from NO₂, -N₃, -OR^a, halo, and cyano.

In one embodiment, Ar^E and Ar^W are each independently an aryl, heteroaryl, or heterocyclyl; wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from halo, -OR^a, CN, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, and -OC₁₋₆ alkyl; and

wherein each alkyl group is optionally substituted with 1 to 4 groups independently selected from OR^a, halo, or cyano.

In one embodiment, Ar^W and Ar^E are each independently selected from phenyl, pyridinyl, indanyl, and indolinyl;

wherein each phenyl, pyridinyl, indanyl, and indolinyl is optionally substituted with 1 to 2 groups independently selected from halo, cyano, -OR^a, -C₁₋₆alkyl, -C₁₋₆alkyl-OR^a, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, and -C₁₋₆cyanoalkyl.

In one embodiment, Ar^W is the same as Ar^E and is selected from phenyl, pyridinyl, indanyl, and indolinyl;

wherein each phenyl, pyridinyl, indanyl, and indolinyl is optionally substituted with 1 to 3 groups independently selected from halo, cyano, -OR^a, -C₁₋₆ alkyl, -C₁₋₆alkyl-OR^a, -C₁₋₆haloalkyl, and -C₁₋₆cyanoalkyl.

In one embodiment, the group Ar^W is selected from phenyl, pyridinyl, indanyl, naphthyl, indazolyl, indolinyl, quinolinyl, quinazolinyl, benzimidazolyl, benzthiazolyl, thiazolyl, and thienyl. In another embodiment, the group Ar^W is selected from phenyl, pyridinyl, indanyl, indolinyl, quinolinyl, and benzimidazolyl.

In one embodiment, the group Ar^E is selected from phenyl, pyridinyl, indanyl, naphthyl, indazolyl, indolinyl, quinolinyl, quinazolinyl, benzimidazolyl, benzthiazolyl, thiazolyl, and thienyl. In another embodiment, the group Ar^E is selected from phenyl, pyridinyl, indanyl, indolinyl, quinolinyl, and benzimidazolyl.

In one embodiment, the groups Ar^W and Ar^E are the same. In one embodiment, the groups Ar^W and Ar^E are the same and have the same substituents. In one embodiment, the groups Ar^W and Ar^E are both phenyl each optionally substituted with methyl. In one embodiment, the groups Ar^W and Ar^E are both phenyl each optionally substituted with chloro. In one embodiment, the groups Ar^W and Ar^E are both indanyl each optionally substituted with methyl. In one embodiment, the groups Ar^W and Ar^E are both indolinyl each optionally substituted with methyl. In one embodiment, the groups Ar^W and Ar^E are both benzimidazole each optionally substituted with methyl. In one embodiment, the groups Ar^W and Ar^E are both indolyl. In one embodiment, the groups Ar^W and Ar^E are both indolyl each optionally

substituted with methyl. In another embodiment of the disclosure, the groups Ar^W and Ar^E are different and are independently selected from phenyl, indanyl, thienyl, benzimidazolyl, indolyl, and indolinyl.

In one embodiment, the optional substituents on Ar^W and Ar^E are independently selected from halo, cyano, C_1 -alkyl, C_1 -haloalkyl, C_2 -alkynyl, and $-O-C_1$ -alkyl.

- 5 In one embodiment, Ar^E is the same as Ar^W and each is optionally substituted with 1 to 2 groups independently selected from methyl, chloro, bromo, CN, $-OCF_3$, CF_3 , CH_2CF_3 , and ethyl.

In one embodiment, Ar^E is different from Ar^W and each is optionally substituted with 1 to 2 groups independently selected from methyl, chloro, bromo, CN, $-OCF_3$, CF_3 , CH_2CF_3 , and ethyl.

- 10 In one embodiment, Ar^W is indolinyl and Ar^E is indolinyl each optionally substituted with 1 to 2 groups independently selected from methyl, ethyl, methoxy, chloro, and CF_3 .

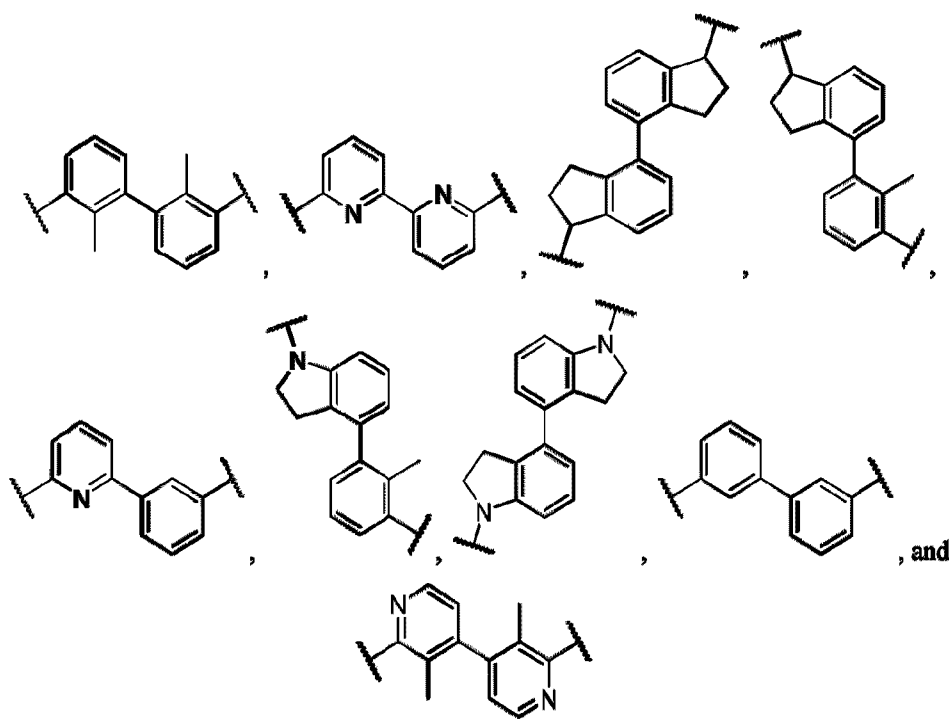
In one embodiment, Ar^W is phenyl and Ar^E is phenyl each optionally substituted with 1 to 2 groups independently selected from methyl, ethyl, methoxy, chloro, and CF_3 .

In another embodiment of the disclosure, the optional substituents on Ar^W and Ar^E are independently selected from CN, Cl, F, $-OCF_3$, $-O-CH_3$, CH_3 , and C_2H_5 .

- 15 In another embodiment of the disclosure, the optional substituents on Ar^W and Ar^E are independently selected from CN, Cl, F, $-OCF_3$, $-OCH_3$, $-CH_3$, and $-C_2H_5$.

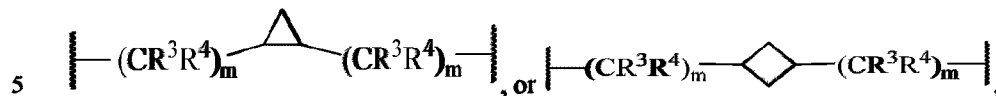
In another embodiment of the disclosure, the optional substituents on Ar^W and Ar^E is CH_3 .

In one embodiment, the present disclosure provides a compound of formula (I) wherein the group $-Ar^W-Ar^E-$ is selected from:



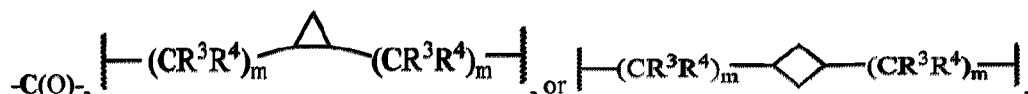
wherein each ring is optionally substituted with 1 or 2 groups independently selected from halo, cyano, C₁₋₆alkyl, C₁₋₃haloalkyl, -OC₁₋₆alkyl, and -OC₁₋₃haloalkyl.

In one embodiment, L^E and L^W are each independently a bond, -O-, -(CR³R⁴)_m-, -(CR³R⁴)_mO(CR³R⁴)_m-, -(CR³R⁴)_mNR³(CR³R⁴)_m-, -C(O)-, C₂₋₆alkenylene, C₂₋₆alkynylene,



wherein each m is independently 0, 1, 2, 3 or 4.

In one embodiment, L^E and L^W are each independently a bond, -(CR³R⁴)_m-, -(CR³R⁴)_mO(CR³R⁴)_m-,



wherein

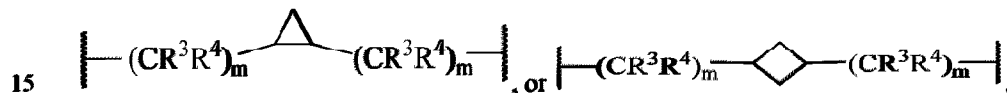
10 each m is independently 0, 1, 2 or 3;

R³ is independently H, -C₁₋₆alkyl, -OH, -OCH₃, or -OCH₂CH₃; and

R⁴ is independently H, halo, -C₁₋₆alkyl, -OH, -OCH₃, or -OCH₂CH₃.

In one embodiment,

L^E and L^W are each independently a bond, -(CR³R⁴)_m-, -(CR³R⁴)_mO(CR³R⁴)_m-, -C(O)-,



wherein

each m is independently 0, 1 or 2;

R³ is independently H, -C₁₋₆alkyl, -OH, -OCH₃, or -OCH₂CH₃; and

R⁴ is independently H, halo, -C₁₋₆alkyl, -OH, -OCH₃, or -OCH₂CH₃.

20 In one embodiment, L^E and L^W are each independently O-, -S-, -SO-, -SO₂-,

-(CR³R⁴)_mNR³(CR³R⁴)_m-, -C(O)-, -(CR³R⁴)_mC(O)NR³(CR³R⁴)_m-, or -(CR³R⁴)_mNR³C(O)(CR³R⁴)_m-,

wherein

each m is independently 0, 1, or 2; and

R³ and R⁴ are each independently H, or -C₁₋₆alkyl.

25 In one embodiment, L^E and L^W are each independently a bond, -(CR³R⁴)_m-, -O(CR³R⁴)_m-,

-(CR³R⁴)_mO, or -C(O)-,

wherein

m is independently 0, 1, 2, or 3; and

R³ and R⁴ are each independently H, -C₁₋₆alkyl, -OH, -OCH₃, or -OCH₂CH₃.

In one embodiment, L^E and L^W are each independently a bond, -(CR³R⁴)_m-, -O(CR³R⁴)_m-, (CR³R⁴)_mO, or -C(O)-:

5 wherein

m is independently 0, 1 or 2; and

R³ and R⁴ are each independently H, or -C₁₋₆alkyl.

In one embodiment, L^E and L^W are each independently a bond, -CH₂-, -OCH₂-, -CH₂O- or -C(O)-.

In one embodiment, L^W is -O(CR³R⁴)_m- or -(CR³R⁴)_mO-.

10 In another embodiment, L^W is -(CR³R⁴)_m-. In another embodiment, L^W is -NR³(CHR⁴)_n or -(CHR⁴)_nNR³-. In another embodiment, L^W is -NR³(CHR⁴)_m-. In another embodiment, the group L^W is -C(O)-. In yet another embodiment, L^W is a bond.

In one embodiment, L^E is -(CR³R⁴)_mO- or -(CR³R⁴)_mO-.

15 In another embodiment, L^E is -(CR³R⁴)_m-. In another embodiment, L^E is -NR³(CHR⁴)_n or -(CHR⁴)_nNR³-. In another embodiment, L^E is -NR³(CHR⁴)_m-. In another embodiment, the group L^E is -C(O)-. In yet another embodiment, L^E is a bond.

In one embodiment, one of L^W and L^E is a bond and the other is -OCH₂- or -CH₂O-.

In one embodiment, Q^E and Q^W are each independently an aryl, heteroaryl, or heterocyclyl;

20 wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from halo, oxo, -OR^a, -N₃, -NO₂, -CN, -NR¹R², -SO₂R^a, -SO₂NR^aR^b, -NR^aSO₂R^a, -NR^aC(O)R^a, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OC₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₁₋₆ alkylC₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N;

25 wherein the alkyl, alkenyl, alkynyl, C₃₋₈ cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo, cyano, -NR^aR^b, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, NR^aC(O)R^a, -NR^aC(O)OR^a, -SO₂R^a, -NR^aSO₂R^b, -SO₂NR^aR^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b and -C₃₋₈ cycloalkyl;

30 wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide, or may be C₁₋₆ alkylated to form a N-C₁₋₆ alkylated ion, or oxidized on a sulfur atom to form a sulfoxide or sulfone;

wherein

R^N is independently $-C_{1-6}alkylINR^1R^2$, $-OC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylINR^1R^2$,
 $-NR^aC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)OR^1$,
 $-SC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOR^a$, or

$$L^1-V-L^2-\textcircled{A};$$

wherein L^1 is independently a bond, O, NR^a or S;

5 wherein L^2 is independently a bond, O, NR^a or S;

V is independently selected from a bond, $C_{1-6}alkyl$, and $C_{2-6}alkenyl$; and

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

10 wherein the cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally independently substituted with 1 to 3 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}alkylCN$, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $C_{3-8}cycloalkyl$.

In one embodiment, Q^E and Q^W are each independently an aryl, heteroaryl, or heterocyclyl optionally substituted with R^N ;

15 wherein R^N is independently $-C_{1-6}alkylINR^1R^2$, $-OC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylINR^1R^2$,
 $-NR^aC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOR^a$, or

$$L^1-V-L^2-\textcircled{A};$$

wherein

L^1 is independently a bond, O, NR^a or S;

L^2 is independently a bond, O, NR^a or S;

20 V is independently selected from a bond, $C_{1-6}alkyl$, and $C_{2-6}alkenyl$;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

25 wherein the cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally independently substituted with 1 to 3 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}alkylCN$, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $C_{3-8}cycloalkyl$.

In one embodiment, Q^E and Q^W are each independently an aryl, or heteroaryl group optionally substituted with R^N ; wherein

R^N is independently $-C_{1-6}alkylNR^1R^2$, $-OC_{1-6}alkylNR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylNR^1R^2$,

$-NR^aC_{1-6}alkylNR^1R^2$, $-C_{1-6}alkylOR^a$, or $L^1-V-L^2-\textcircled{A}$;

wherein

L^1 is independently a bond, O, NR^a or S;

5 L^2 is independently a bond, O, NR^a or S;

V is independently selected from a bond, $C_{1-6}alkyl$, and $C_{2-6}alkenyl$; and

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein the cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally independently substituted with 1 to 3 groups independently selected from oxo,
10 $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}alkylCN$,
 $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$,
 $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and
 $C_{3-8}cycloalkyl$.

15 In one embodiment, Q^E and Q^W are each independently phenyl, pyridine, indanyl, naphthyl, indolyl, indolinyl, benzthiazolyl, indazolyl, benzimidazolyl, imidazolyl, thiazolyl, or thienyl;

wherein each phenyl, pyridine, indanyl, naphthyl, indolyl, indolinyl, benzthiazolyl, indazolyl, benzimidazolyl, imidazolyl, thiazolyl, or thienyl is optionally substituted with 1 to 3 groups independently selected from halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^aR^b$, $-C_{1-6}alkyl$, $C_{3-8}cycloalkyl$, and $-C_{1-6}alkylC_{3-8}cycloalkyl$.

20 In one embodiment, Q^E and Q^W are each independently phenyl, pyridine, indanyl, naphthyl, indolyl, indolinyl, benzthiazolyl, indazolyl, benzimidazolyl, imidazolyl, thiazolyl, or thienyl;

wherein each phenyl, pyridine, indanyl, naphthyl, indolyl, indolinyl, benzthiazolyl, indazolyl, benzimidazolyl, imidazolyl, thiazolyl, or thienyl is optionally substituted with 1 to 3 groups independently selected from halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^aR^b$, $-C_{1-6}alkyl$, $C_{3-8}cycloalkyl$,
25 $-C_{1-6}alkylC_{3-8}cycloalkyl$, and R^N ;

wherein

R^N is independently $-C_{1-6}alkylNR^1R^2$, $-OC_{1-6}alkylNR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylNR^1R^2$,
 $-NR^aC_{1-6}alkylNR^1R^2$, $-C_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)NR^1R^2$,

$-OC_{1-6}alkylC(O)OR^1$, $-SC_{1-6}alkylNR^1R^2$, $-C_{1-6}alkylOR^a$, or $L^1-V-L^2-\textcircled{A}$;

30 L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a, halo, cyano, -NR^aR^b or -C₃₋₈cycloalkyl; and

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

5 wherein the cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo, -CN, NR^aR^b, -C(O)R^a, -C(O)OR^a, -OC₁₋₆alkylCN, -C(O)NR^aR^b, -NR^aC(O)R^a, -NR^aC(O)OR^a, -NR^aC(O)OR^a, -C(O)N(R^a)OR^b, -SO₂R^a, -SO₂NR^aR^b, -NR^aSO₂R^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b and C₃₋₈cycloalkyl.

10 In one embodiment, Q^E and Q^W are each independently phenyl, pyridine, indanyl, naphthyl, indolyl, indolinyl, benzthiazolyl, indazolyl, benzimidazolyl, or benzthiazolyl;

wherein each group is optionally substituted with 1 to 3 groups independently selected from halo, -OR^a, -N₃, -NO₂, -CN, -NR^aR^b, -C₁₋₆alkyl, C₃₋₈cycloalkyl, -C₁₋₆alkylC₃₋₈cycloalkyl, and R^N;

wherein

15 R^N is independently -C₁₋₆alkylNR¹R², -OC₁₋₆alkylNR¹R², -C₁₋₆alkylOC₁₋₆alkylNR¹R², -NR^aC₁₋₆alkylNR¹R², -C₁₋₆alkylC(O)NR¹R², -OC₁₋₆alkylC(O)NR¹R²,

-OC₁₋₆alkylC(O)OR¹, -SC₁₋₆alkylNR¹R², -C₁₋₆alkylOR^a, or $L^1-V-L^2-\textcircled{A}$;

wherein

L¹ is independently a bond, O, NR^a, S, SO, or SO₂;

20 L² is independently a bond, O, NR^a, S, SO, or SO₂;

V is independently selected from a bond, C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl;

wherein the alkyl, alkenyl, or alkynyl is optionally independently substituted with -OR^a, halo, cyano, -NR^aR^b or -C₃₋₈cycloalkyl;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

25 wherein the cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo, CN, -NR^aR^b, -C(O)R^a, -C(O)OR^a, -OC₁₋₆alkylCN, -C(O)NR^aR^b, -NR^aC(O)R^a, -NR^aC(O)OR^a, -NR^aC(O)OR^a, -C(O)N(R^a)OR^b, -SO₂R^a, -SO₂NR^aR^b, -NR^aSO₂R^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b and C₃₋₈cycloalkyl.

30 In one embodiment, Q^E and Q^W are each independently phenyl, indanyl, naphthyl, indolyl, indolinyl, benzthiazolyl, indazolyl, benzimidazolyl, or benzthiazolyl;

wherein each phenyl, indanyl, naphthyl, indolyl, indolinyl, benzthiazolyl, indazolyl, benzimidazolyl, or benzthiazolyl is optionally substituted with 1 to 3 groups independently selected from halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^aR^b$, $-C_{1-6}$ alkyl, C_{3-8} cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, and R^N ;

5 wherein

R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$

alkyl $C(O)OR^1$, $-SC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OR^a , or $L^1-V-L^2-\textcircled{A}$;

wherein

10 L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$, or $-C_{3-8}$ cycloalkyl; and

15 ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein the cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, $-CN$, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, and C_{3-8} cycloalkyl.

20

In one embodiment, Q^E and Q^W are each independently phenyl, pyridine, indazolyl, thiazolyl, or indolinyl;

25 wherein each phenyl, pyridine, indazolyl, thiazolyl, or indolinyl is optionally substituted with 1 to 3 groups independently selected from halo, $-OR^a$, $-CN$, $-NR^aR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-8}$ cycloalkyl, and R^N ;

wherein

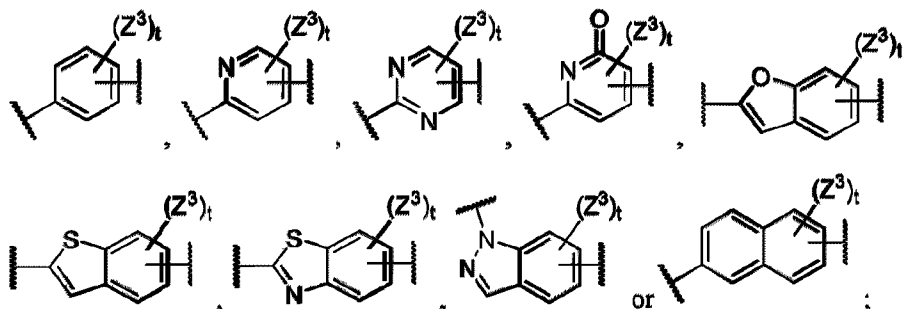
R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 ,

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$-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OR^a , or $L^1-V-L^2-\textcircled{A}$;

wherein

30 In one embodiment, Q^W and Q^E are each independently



wherein each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkylC $_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N , and

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and further wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)OR^1$,

$-SC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OR^a , or $L^1-V-L^2-\textcircled{A}$;

wherein

L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$, or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

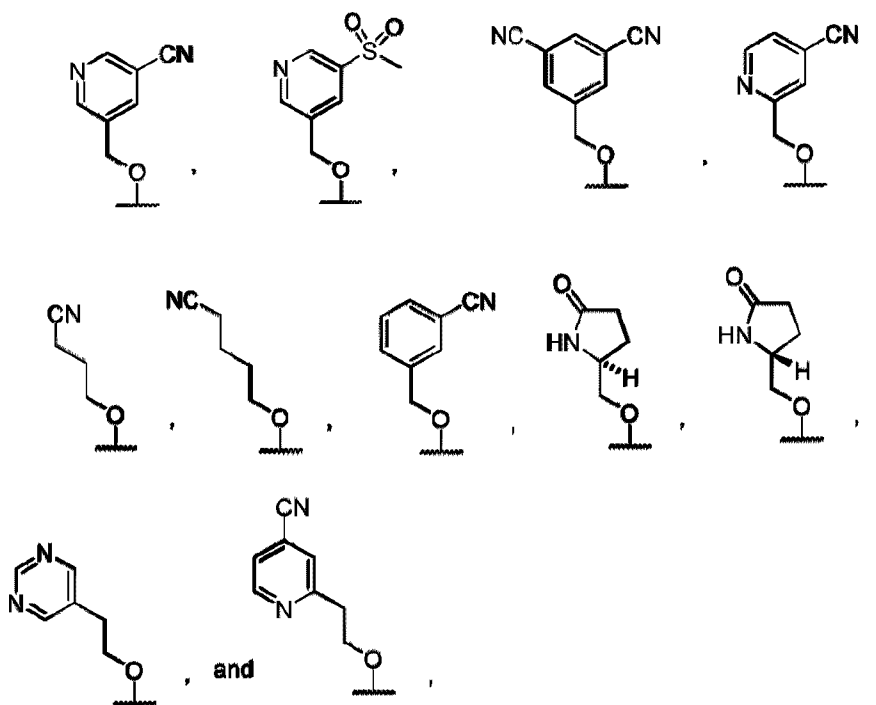
wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$,

-NR^aC(O)OR^a, -NR^aC(O)OR^a, -C(O)N(R^a)OR^b, -SO₂R^a, -SO₂NR^aR^b, -NR^aSO₂R^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b, C₃₋₈cycloalkyl, and C₁₋₆alkylC₃₋₈cycloalkyl; and

5 wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with -OR^a, halo, cyano, -NR^aR^b, or -C₃₋₈cycloalkyl.

In one embodiment, t is 0, 1, 2 or 3. In one embodiment, t is 1, 2 or 3. In one embodiment, t is 0, 1 or 2. In one embodiment, t is 0. In one embodiment, t is 1. In one embodiment, t is 2. In one embodiment, t is 3.

In one embodiment, substituents on Q^W or Q^E are independently selected from



10

or a pharmaceutically acceptable salt thereof.

In one embodiment, Q^E and Q^W are each optionally substituted with halo. In one embodiment, Q^E and Q^W are each optionally substituted with -C₁₋₆alkyl. In one embodiment, Q^E and Q^W are each optionally substituted with -OC₁₋₆alkyl. In one embodiment, Q^E and Q^W are each optionally substituted with methoxy.

15

In one embodiment, Q^E and Q^W are different and each is optionally substituted with 1 to 3 groups independently selected from OH, halo, CN, -SO₂R^a, -C₁₋₆alkyl, and -OC₁₋₆alkyl.

In one embodiment, Q^E and Q^W are the same and each is optionally substituted with 1 to 3 groups independently selected from OH, halo, CN, -SO₂R^a, -C₁₋₆alkyl, and -OC₁₋₆alkyl.

In one embodiment, R^E and R^W are independently selected from $-NR^1R^2$, $-C_{1-6}alkylINR^1R^2$, $-OC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylINR^1R^2$, $-NR^aC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylIN^+R^1R^2R^3$, $-SC_{1-6}alkylINR^1R^2$, $-C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_uSO_2NR^1R^2$, $-(CH_2)_uNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}alkylINR^1R^2$, $-NR^aSO_2C_{1-6}alkylINR^1R^2$, $-(CH_2)_uC(O)NR^aSO_2NR^aR^b$, $-(CH_2)_uN^+R^1R^2O^-$,
 5 $-(CH_2)_uP^+R^bR^cR^d$, $-(CH_2)_uP^+R^cR^dO^-$, $-(CH_2)_uP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_uNR^cP(O)(OR^c)_2$, $-(CH_2)_uCH_2OP(O)(OR^c)(OR^d)$, $-(CH_2)_uOP(O)(OR^c)(OR^d)$, and $-(CH_2)_uOP(O)NR^aR^b(OR^a)$; wherein

R^1 is selected from H, $-C_{1-6}alkyl$, $-C_{3-6}cycloalkyl$, heterocyclyl, $-C_{2-6}alkyl-OR^a$, or $-C_{1-6}alkylC(O)OR^a$;

wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2
 10 groups independently selected from $-OR^a$, $-CN$, halo, $-C_{1-6}alkylOR^a$, $-C_{1-6}cyanoalkyl$, $-C_{1-3}haloalkyl$, $-C(O)R^a$, $-C_{1-6}alkylC(O)R^a$, $-C(O)OR^a$, $-C_{1-6}alkylC(O)OR^a$, $-C(O)NR^aR^b$, and $-C_{1-6}alkylC(O)NR^aR^b$;

R^2 is selected from $-C_{1-6}alkyl$, $-C_{3-6}cycloalkyl$, heterocyclyl, $-C_{2-6}alkyl-OR^a$, and $-C_{1-6}alkylC(O)OR^a$;

wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2
 15 groups independently selected from $-OR^a$, $-CN$, $-C_{1-6}alkylOR^a$, $-C_{1-6}cyanoalkyl$, $-C_{1-3}haloalkyl$, $-C_{3-8}cycloalkyl$, $-C_{1-3}alkylC_{3-8}cycloalkyl$, $-C(O)R^a$, $-C_{1-6}alkylC(O)R^a$, $-C(O)OR^a$, $-C_{1-6}alkylC(O)OR^a$, $-C(O)NR^aR^b$, and $-C_{1-6}alkylC(O)NR^aR^b$;

or R^1 and R^2 combine to form a heterocyclyl group optionally containing an additional
 20 heteroatom selected from oxygen, sulfur or nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}alkyl$, $-OR^a$, $-C(O)OR^a$, $-C(O)R^a$, $-C_{1-6}alkylC(O)R^a$, $-C_{1-6}alkylC(O)OR^a$, $-NR^aR^b$, $-C_{1-6}alkylINR^aR^b$, and $-C(O)NR^aR^b$;

R^3 is independently H, $-C_{1-6}alkyl$, $-C_{2-6}alkenyl$, $-C_{3-6}cycloalkyl$, aryl, heteroaryl, heterocyclyl, $-C_{1-6}alkylaryl$;

25 R^a is independently H or $-C_{1-6}alkyl$;

R^b is independently H or $-C_{1-6}alkyl$;

R^c is independently selected from H, $-C_{1-6}alkyl$, $-C_{3-8}cycloalkyl$, and $-C_{1-3}alkylC_{3-8}cycloalkyl$;

R^d is independently selected from H, $-C_{1-6}alkyl$, $-C_{3-8}cycloalkyl$, and $-C_{1-3}alkylC_{3-8}cycloalkyl$;
 and

30 u is 0, 1, 2, or 3.

In one embodiment, R^E and R^W are independently selected from $-C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_uSO_2NR^1R^2$, $-(CH_2)_uNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}alkylINR^1R^2$, $-NR^aSO_2C_{1-6}alkylINR^1R^2$, and $-(CH_2)_uC(O)NR^aSO_2NR^aR^b$; wherein

R^1 is selected from H, -C₁₋₆alkyl, -C₃₋₆cycloalkyl, heterocyclyl, -C₂₋₆alkyl-OR^a, or -C₁₋₆alkylC(O)OR^a;

wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from -OR^a, -CN, halo, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₃haloalkyl, -C(O)R^a, -C₁₋₆alkyl C(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -C(O)NR^aR^b, and -C₁₋₆alkylC(O)NR^aR^b;

R^2 is selected from -C₁₋₆alkyl, -C₃₋₆cycloalkyl, heterocyclyl, -C₂₋₆alkyl-OR^a, and -C₁₋₆alkylC(O)OR^a;

wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from -OR^a, -CN, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₃haloalkyl, -C₃₋₆cycloalkyl, -C₁₋₃alkylC₃₋₆cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -C(O)NR^aR^b, and -C₁₋₆alkylC(O)NR^aR^b;

or R^1 and R^2 combine to form a heterocyclyl optionally containing an additional heteroatom selected from oxygen, sulfur or nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆alkyl, -OR^a, -C(O)OR^a, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, and -C(O)NR^aR^b;

R^a is independently H or -C₁₋₆alkyl;

R^b is independently H or -C₁₋₆alkyl; and

u is 0, 1, 2, or 3.

In one embodiment, R^E and R^W are independently selected from -(CH₂)_uN⁺R¹R²O⁻, -(CH₂)_uP⁺R^bR^cR^d, -(CH₂)_uP⁺R^cR^dO⁻, -(CH₂)_uP⁺O[NR^aR^b][NR^cR^d], -(CH₂)_uNR^cP(O)(OR^c)₂, -(CH₂)_uCH₂OP(O)(OR^c)(OR^d), -(CH₂)_uOP(O)(OR^c)(OR^d), and -(CH₂)_uOP(O)NR^aR^b(OR^a); wherein

R^1 is selected from H, -C₁₋₆alkyl, -C₃₋₆cycloalkyl, heterocyclyl, -C₂₋₆alkyl-OR^a, and -C₁₋₆alkylC(O)OR^a;

wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from -OR^a, -CN, halo, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₃haloalkyl, -C(O)R^a, -C₁₋₆alkyl C(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -C(O)NR^aR^b, and -C₁₋₆alkylC(O)NR^aR^b;

R^2 is selected from -C₁₋₆alkyl, -C₃₋₆cycloalkyl, heterocyclyl, -C₂₋₆alkyl-OR^a, and -C₁₋₆alkylC(O)OR^a;

wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from -OR^a, -CN, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₃haloalkyl, -C₃₋₆cycloalkyl, -C₁₋₃alkylC₃₋₆cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -C(O)NR^aR^b, and -C₁₋₆alkylC(O)NR^aR^b;

or R^1 and R^2 combine to form a heterocyclyl optionally containing an additional heteroatom selected from oxygen, sulfur or nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-OR^a$, $-C(O)OR^a$, $-C(O)R^a$, C_{1-6} alkylC(O) R^a , $-C_{1-6}$ alkylC(O) OR^a , $-NR^aR^b$, $-C_{1-6}$ alkylNR $^aR^b$, and $-C(O)NR^aR^b$;

5 R^a is independently H or $-C_{1-6}$ alkyl;

R^b is independently H or $-C_{1-6}$ alkyl;

R^c is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkylC $_{3-8}$ cycloalkyl;

R^d is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkylC $_{3-8}$ cycloalkyl; and

10 u is 0, 1, 2 or 3.

In one embodiment, R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}$ alkylNR $^1R^2$, $-OC_{1-6}$ alkylNR $^1R^2$,

$-C_{1-6}$ alkylOC $_{1-6}$ alkylNR $^1R^2$, $-NR^aC_{1-6}$ alkylNR $^1R^2$, or $-V^2-(CR^cR^d)_p-L^3-\textcircled{B}-(T)_z$;

wherein

15 V^2 is independently a bond, O, NR^a , S, SO or SO_2 ;

R^c is independently selected from H, OH, $-C_{1-6}$ alkyl, and $-C_{3-8}$ cycloalkyl;

R^d is independently selected from H, $-C_{1-6}$ alkyl, and $-C_{3-8}$ cycloalkyl;

L^3 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring B is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

20 T is independently H, OR^a , $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^e$ or $(CH_2)_qC(O)R^e$;

R^e is independently selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkylC $_{3-8}$ cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkylNR $^fR^g$, $-C(O)NR^fR^g$, $-C_{1-6}$ alkylC(O)NR $^fR^g$, $-NHSO_2R^f$, $-C_{1-6}$ alkylSO $_2R^f$, and $-C_{1-6}$ alkylSO $_2$ NR $^fR^g$;

25 p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5; and

z is 0, 1, or 2;

and wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally

30 substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, OR^a , $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkylNR $^aR^b$, $-C_{1-6}$ alkylOH, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkylC $_{3-8}$ cycloalkyl;

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

R^1 is selected from H, $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, heterocyclyl, $-C_{2-6}$ alkyl-OR^a, or $-C_{1-6}$ alkylC(O)OR^a;

wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from -OR^a, -CN, halo, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-3}$ haloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl C(O)R^a, $-C(O)OR^a$, $-C_{1-6}$ alkylC(O)OR^a, $-C(O)NR^aR^b$, and $-C_{1-6}$ alkylC(O)NR^aR^b;

R^2 is selected from $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, heterocyclyl, $-C_{2-6}$ alkyl-OR^a, and $-C_{1-6}$ alkylC(O)OR^a;

wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from -OR^a, -CN, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-3}$ haloalkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-3}$ alkylC₃₋₆cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkylC(O)R^a, $-C(O)OR^a$, $-C_{1-6}$ alkylC(O)OR^a, $-C(O)NR^aR^b$, and $-C_{1-6}$ alkylC(O)NR^aR^b;

or R^1 and R^2 combine to form a heterocyclyl group optionally containing an additional heteroatom selected from oxygen, sulfur or nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, -OR^a, $-C(O)OR^a$, $-C(O)R^a$, $-C_{1-6}$ alkylC(O)R^a, $-C_{1-6}$ alkylC(O)OR^a, $-NR^aR^b$, $-C_{1-6}$ alkylNR^aR^b, and $-C(O)NR^aR^b$;

R^a is independently H or $-C_{1-6}$ alkyl; and

R^b is independently H or $-C_{1-6}$ alkyl.

In one embodiment,

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}$ alkylNR¹R², $-OC_{1-6}$ alkylNR¹R²,

$-C_{1-6}$ alkylOC₁₋₆alkylNR¹R², $-NR^aC_{1-6}$ alkylNR¹R², or $-V^2-(CR^cR^d)_p-L^3-\textcircled{B}-(T)_z$;

wherein

V^2 is independently a bond, O, NR^a, S, SO or SO₂;

L^3 is independently a bond, O, NR^a, S, SO, or SO₂;

ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently H, OR^a, $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^c$ or $(CH_2)_qC(O)R^c$;

p is independently 0, 1, 2, or 3;

q is independently 0, 1, 2, or 3;

z is 0, 1, 2, or 3;

and wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b,

halo, cyano, OR^a , $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ haloalkyl, $-\text{C}_{1-6}$ cyanoalkyl, $-\text{C}_{1-6}$ alkyl NR^aR^b , $-\text{C}_{1-6}$ alkylOH, $-\text{C}_{3-8}$ cycloalkyl, and $-\text{C}_{1-3}$ alkyl C_{3-8} cycloalkyl;

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

R^1 is selected from H, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{3-6}$ cycloalkyl, heterocyclyl, $-\text{C}_{2-6}$ alkyl- OR^a , or $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^a$;

5 wherein each alkyl, cycloalkyl, or heterocyclyl group is optionally substituted with 1 to 2 groups independently selected from $-\text{OR}^a$, $-\text{CN}$, halo, $-\text{C}_{1-6}$ alkyl OR^a , $-\text{C}_{1-6}$ cyanoalkyl, $-\text{C}_{1-3}$ haloalkyl, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, and $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^a\text{R}^b$;

R^2 is selected from $-\text{C}_{1-6}$ alkyl, $-\text{C}_{3-6}$ cycloalkyl, heterocyclyl, $-\text{C}_{2-6}$ alkyl- OR^a , and $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^a$;

10 wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from $-\text{OR}^a$, $-\text{CN}$, $-\text{C}_{1-6}$ alkyl OR^a , $-\text{C}_{1-6}$ cyanoalkyl, $-\text{C}_{1-3}$ haloalkyl, $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-3}$ alkyl C_{3-8} cycloalkyl, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, and $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^a\text{R}^b$;

or R^1 and R^2 combine to form a heterocyclyl optionally containing an additional heteroatom selected
15 from oxygen, sulfur or nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-\text{C}_{1-6}$ alkyl, $-\text{OR}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{R}^a$, C_{1-6} alkyl $\text{C}(\text{O})\text{R}^a$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}$ alkyl NR^aR^b , and $-\text{C}(\text{O})\text{NR}^a\text{R}^b$;

R^a is independently H or $-\text{C}_{1-6}$ alkyl;

R^b is independently H or $-\text{C}_{1-6}$ alkyl;

20 R^c is independently selected from H, OH, $-\text{C}_{1-6}$ alkyl, and $-\text{C}_{3-8}$ cycloalkyl;

R^d is independently selected from H, $-\text{C}_{1-6}$ alkyl, and $-\text{C}_{3-8}$ cycloalkyl;

R^e is selected from H, $-\text{C}_{1-6}$ alkyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-\text{OC}_{3-8}$ cycloalkyl, $-\text{Oaryl}$, $-\text{Oheteroaryl}$, $-\text{Oheterocyclyl}$, $-\text{C}_{1-3}$ alkyl C_{3-8} cycloalkyl, $-\text{C}_{1-6}$ alkylaryl, $-\text{C}_{1-6}$ alkylheteroaryl, $-\text{NR}^f\text{R}^g$, $-\text{C}_{1-6}$ alkyl NR^fR^g , $-\text{C}(\text{O})\text{NR}^f\text{R}^g$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^f\text{R}^g$, $-\text{NHSO}_2\text{R}^f$,
25 $-\text{C}_{1-6}$ alkyl SO_2R^f , and $-\text{C}_{1-6}$ alkyl $\text{SO}_2\text{NR}^f\text{R}^g$;

R^f is independently selected from H, $-\text{C}_{1-6}$ alkyl, and $-\text{C}_{3-8}$ cycloalkyl;

R^g is independently selected from H, $-\text{C}_{1-6}$ alkyl, and $-\text{C}_{3-8}$ cycloalkyl.

In one embodiment, R^E and R^W are each $-\text{V}^2-(\text{CR}^c\text{R}^d)_p-\text{L}^3-\text{B}-(\text{T})_z$;

wherein

30 V^2 is independently a bond, O, NR^a , S, SO or SO_2 ;

R^c is independently selected from H, OH, $-\text{C}_{1-6}$ alkyl, and $-\text{C}_{3-8}$ cycloalkyl;

R^d is independently selected from H, $-C_{1-6}$ alkyl, and $-C_{3-6}$ cycloalkyl;

L^3 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently H, OR^a , $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^e$ or $(CH_2)_qC(O)R^e$;

- 5 R^e is selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkyl NR^fR^g , $-C(O)NR^fR^g$, $-C_{1-6}$ alkyl $C(O)NR^fR^g$, $-NHSO_2R^f$, $-C_{1-6}$ alkyl SO_2R^f , and $-C_{1-6}$ alkyl $SO_2NR^fR^g$;

R^f is independently selected from H, $-C_{1-6}$ alkyl, and $-C_{3-8}$ cycloalkyl;

- 10 R^g is independently selected from H, $-C_{1-6}$ alkyl, and $-C_{3-8}$ cycloalkyl;

p is independently 0, 1, 2, or 3;

q is independently 0, 1, 2, or 3;

z is 0, 1, 2, or 3;

- 15 and wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with

1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, OR^a , $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl NR^aR^b , $-C_{1-6}$ alkylOH, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom.

- 20 In one embodiment, R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}$ alkyl NR^1R^2 , or $-OC_{1-6}$ alkyl NR^1R^2 ;

R^1 is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, heterocyclyl, $-C_{2-6}$ alkyl- OR^a , or $-C_{1-6}$ alkyl $C(O)OR^a$;

- 25 wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from $-OR^a$, $-CN$, halo, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-3}$ haloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-C(O)NR^aR^b$, and $-C_{1-6}$ alkyl $C(O)NR^aR^b$;

R^2 is independently selected from $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, heterocyclyl, $-C_{2-6}$ alkyl- OR^a , and $-C_{1-6}$ alkyl $C(O)OR^a$;

- 30 wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from $-OR^a$, $-CN$, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-3}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-C(O)NR^aR^b$, and $-C_{1-6}$ alkyl $C(O)NR^aR^b$;

or R^1 and R^2 combine to form a heterocyclyl optionally containing 1 or 2 additional heteroatoms independently selected from oxygen, sulfur or nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-OR^a$, $-C(O)OR^a$, $-C(O)R^a$, C_{1-6} alkylC(O) R^a , $-C_{1-6}$ alkylC(O) OR^a , $-NR^aR^b$, $-C_{1-6}$ alkylNR $^aR^b$, and $-C(O)NR^aR^b$;

5 R^a is independently H or $-C_{1-6}$ alkyl;

R^b is independently H or $-C_{1-6}$ alkyl.

In one embodiment, R^E and R^W are each $-C_{1-6}$ alkylOC $_{1-6}$ alkylNR $^1R^2$;

R^1 is selected from H, $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, heterocyclyl, $-C_{2-6}$ alkyl- OR^a , and $-C_{1-6}$ alkylC(O) OR^a ;

10 wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from $-OR^a$, $-CN$, halo, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-3}$ haloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl C(O) R^a , $-C(O)OR^a$, $-C_{1-6}$ alkylC(O) OR^a , $-C(O)NR^aR^b$, and $-C_{1-6}$ alkylC(O)NR $^aR^b$;

R^2 is selected from $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, heterocyclyl, $-C_{2-6}$ alkyl- OR^a , and $-C_{1-6}$ alkylC(O) OR^a ;

15 wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from $-OR^a$, $-CN$, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-3}$ haloalkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-3}$ alkylC $_{3-8}$ cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkylC(O) R^a , $-C(O)OR^a$, $-C_{1-6}$ alkylC(O) OR^a , $-C(O)NR^aR^b$, and C_{1-6} alkylC(O)NR $^aR^b$; or

20 R^1 and R^2 combine to form a heterocyclyl optionally containing 1 or 2 additional heteroatoms independently selected from oxygen, sulfur or nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-OR^a$, $-C(O)OR^a$, $-C(O)R^a$, C_{1-6} alkylC(O) R^a , $-C_{1-6}$ alkylC(O) OR^a , $-NR^aR^b$, $-C_{1-6}$ alkylNR $^aR^b$, and $-C(O)NR^aR^b$;

R^a is independently H or $-C_{1-6}$ alkyl; and

R^b is independently H or $-C_{1-6}$ alkyl.

In one embodiment, provided is a compound of formula (I), wherein

25 R^E and R^W are each $-OC_{1-6}$ alkylNR $^1R^2$;

R^1 is selected from H, $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, heterocyclyl, $-C_{2-6}$ alkyl- OR^a , and $-C_{1-6}$ alkylC(O) OR^a ;

30 wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from $-OR^a$, $-CN$, halo, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-3}$ haloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl C(O) R^a , $-C(O)OR^a$, $-C_{1-6}$ alkylC(O) OR^a , $-C(O)NR^aR^b$, and $-C_{1-6}$ alkylC(O)NR $^aR^b$;

R^2 is selected from $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, heterocyclyl, $-C_{2-6}$ alkyl- OR^a , and $-C_{1-6}$ alkylC(O) OR^a ;

wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from $-OR^a$, $-CN$, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-3}$ haloalkyl,

$-C_{3-8}\text{cycloalkyl}$, $-C_{1-3}\text{alkyl}C_{3-8}\text{cycloalkyl}$, $-C(O)R^a$, $-C_{1-6}\text{alkyl}C(O)R^a$, $-C(O)OR^a$,
 $-C_{1-6}\text{alkyl}C(O)OR^a$, $-C(O)NR^aR^b$, and $C_{1-6}\text{alkyl}C(O)NR^aR^b$; or

R^1 and R^2 combine to form a heterocyclyl group optionally containing 1 or 2 additional heteroatoms
independently selected from oxygen, sulfur or nitrogen, and optionally substituted with 1 to 3 groups
5 independently selected from oxo, $-C_{1-6}\text{alkyl}$, $-OR^a$, $-C(O)OR^a$, $-C(O)R^a$, $C_{1-6}\text{alkyl}C(O)R^a$,
 $-C_{1-6}\text{alkyl}C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}\text{alkyl}NR^aR^b$, and $-C(O)NR^aR^b$;

R^a is independently H or $-C_{1-6}\text{alkyl}$; and

R^b is independently H or $-C_{1-6}\text{alkyl}$.

In one embodiment,

10 R^E and R^W are each $-NR^1R^2$;

R^1 is selected from H, $-C_{1-6}\text{alkyl}$, $-C_{3-6}\text{cycloalkyl}$, heterocyclyl, $-C_{2-6}\text{alkyl}-OR^a$, and $-C_{1-6}\text{alkyl}C(O)OR^a$;

wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with 1 to 2 groups
independently selected from $-OR^a$, $-CN$, halo, $-C_{1-6}\text{alkyl}OR^a$, $-C_{1-6}\text{cyanoalkyl}$, $-C_{1-3}\text{haloalkyl}$,
 $-C(O)R^a$, $-C_{1-6}\text{alkyl}C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}\text{alkyl}C(O)OR^a$, $-C(O)NR^aR^b$, and $-C_{1-}$
15 $6\text{alkyl}C(O)NR^aR^b$;

R^2 is selected from $-C_{1-6}\text{alkyl}$, $-C_{3-6}\text{cycloalkyl}$, heterocyclyl, $-C_{2-6}\text{alkyl}-OR^a$, and $-C_{1-6}\text{alkyl}C(O)OR^a$;

wherein each alkyl, cycloalkyl, or heterocyclyl group is optionally substituted with 1 to 2 groups
independently selected from $-OR^a$, $-CN$, $-C_{1-6}\text{alkyl}OR^a$, $-C_{1-6}\text{cyanoalkyl}$, $-C_{1-3}\text{haloalkyl}$,
 $-C_{3-8}\text{cycloalkyl}$, $-C_{1-3}\text{alkyl}C_{3-8}\text{cycloalkyl}$, $-C(O)R^a$, $-C_{1-6}\text{alkyl}C(O)R^a$, $-C(O)OR^a$,
20 $-C_{1-6}\text{alkyl}C(O)OR^a$, $-C(O)NR^aR^b$, and $C_{1-6}\text{alkyl}C(O)NR^aR^b$;

or R^1 and R^2 combine to form a heterocyclyl group optionally containing an additional heteroatom
selected from oxygen, sulfur or nitrogen, and optionally substituted with 1 to 3 groups independently
selected from oxo, $-C_{1-6}\text{alkyl}$, $-OR^a$, $-C(O)OR^a$, $-C(O)R^a$, $C_{1-6}\text{alkyl}C(O)R^a$, $-C_{1-6}\text{alkyl}C(O)OR^a$, $-NR^aR^b$,
 $-C_{1-6}\text{alkyl}NR^aR^b$, and $-C(O)NR^aR^b$;

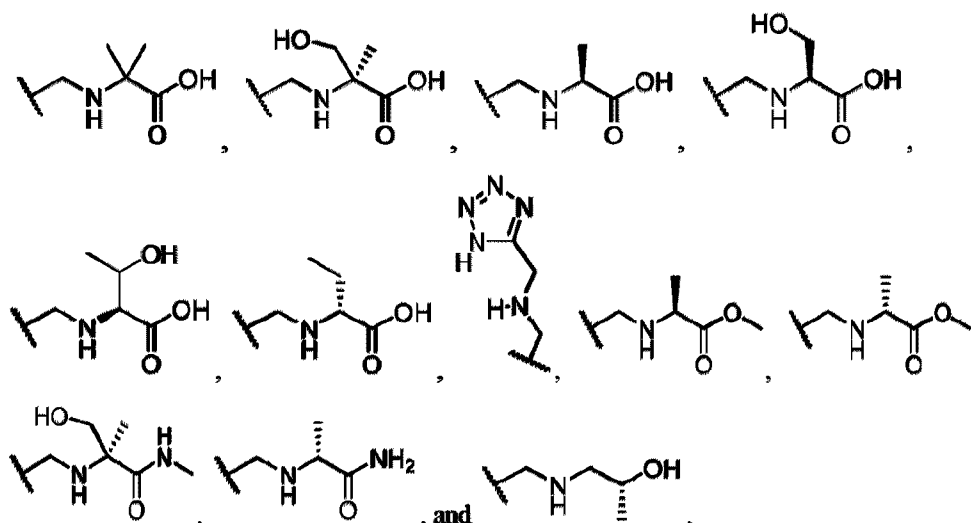
25 R^a is independently H or $-C_{1-6}\text{alkyl}$; and

R^b is independently H or $-C_{1-6}\text{alkyl}$.

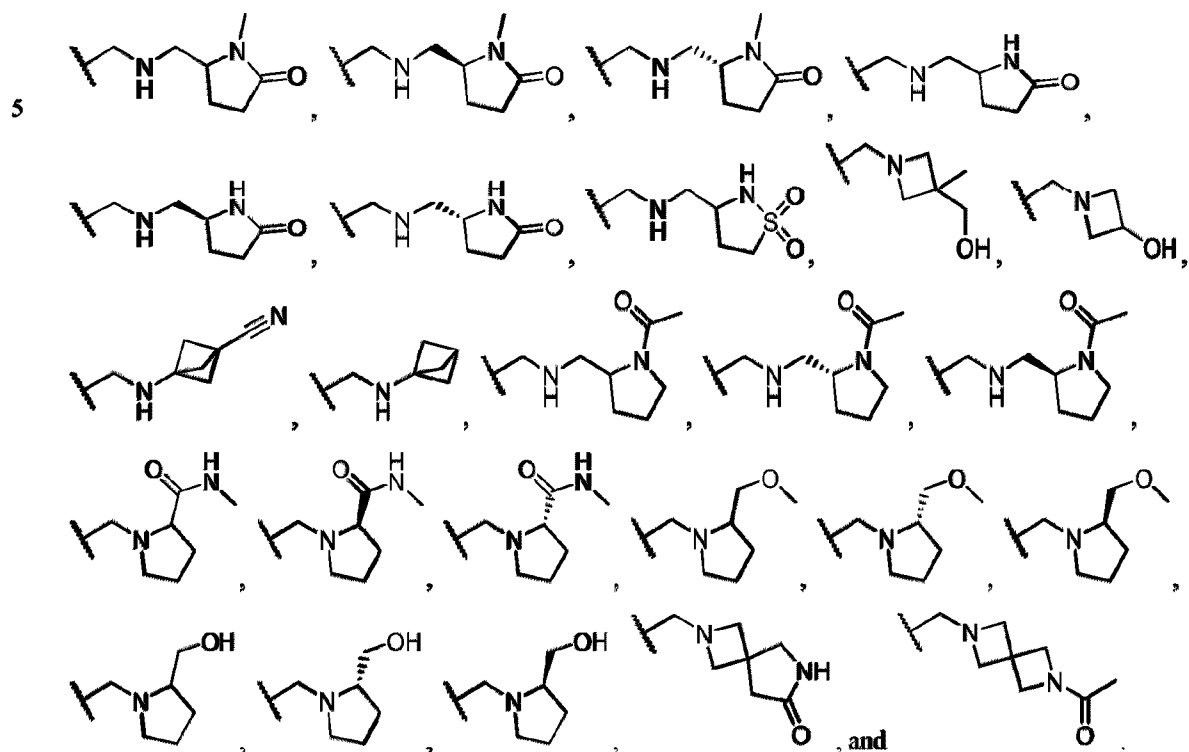
In one embodiment, R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}\text{alkyl}NR^1R^2$, or
 $-OC_{1-6}\text{alkyl}NR^1R^2$; wherein

R^b is independently H or -C₁₋₆ alkyl.

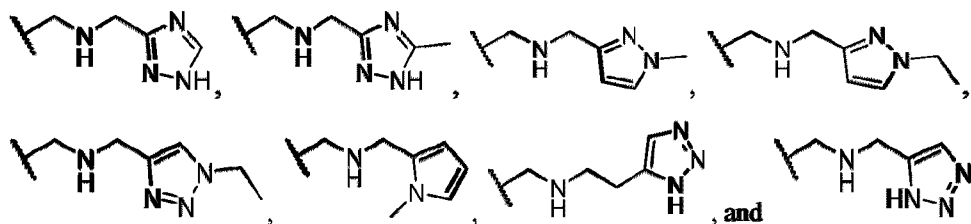
15 In one embodiment, each R^W and R^E is independently selected from:



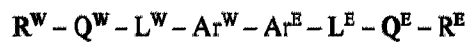
In one embodiment, each R^W and R^E is independently selected from:



10 In one embodiment, each R^W and R^E is independently selected from:



In another embodiment of the disclosure, provided is a compound of formula (I):



(I)

wherein:

Ar^E and Ar^W are each independently aryl, heteroaryl, or heterocyclyl,

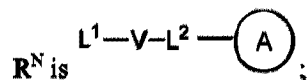
- 5 wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from halo, $-OR^a$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, and $-C_{3-8}$ cycloalkyl;

L^E and L^W are each independently a bond, $-O-$, $-(CR^3R^4)_m-$, $-O(CR^3R^4)_m$, $-(CR^3R^4)_mO$, $-(CR^3R^4)_mNR^3-$, $-NR^3(CR^3R^4)_m-$, or $-C(O)-$,

- 10 m is independently 0, 1, 2, 3 or 4;

Q^E and Q^W are each independently aryl, heteroaryl, or heterocyclyl, wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^aR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, and R^N ;

- 15 wherein



wherein

L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

- 20 wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

- 25 wherein the cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally independently substituted with 1 to 2 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, C_{3-8} cycloalkyl, and C_{1-6} alkyl C_{3-8} cycloalkyl;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}alkylINR^1R^2$, $-OC_{1-6}alkylINR^1R^2$,
 $-C_{1-6}alkylOC_{1-6}alkylINR^1R^2$, $-NR^aC_{1-6}alkylINR^1R^2$, $-C(O)NR^1R^2$, $-(CH_2)_uSO_2NR^1R^2$,
 $-SO_2NR^aC_{1-6}alkylINR^1R^2$, $-NR^aSO_2C_{1-6}alkylINR^1R^2$ or

$$-V^2-(CR^cR^d)_p-L^3-\textcircled{B}-(T)_z;$$

wherein

5 V^2 is independently a bond, O, NR^a , S, SO or SO_2

L^3 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is $(CH_2)_qNR^1R^2$ or $(CH_2)_qC(O)R^a$;

p is 0, 1, 2, or 3;

10 q is 0, 1, 2, or 3;

u is 0, 1, 2, or 3;

and wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with
 1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a ,
 $-C_{1-6}alkyl$, $-C_{1-6}haloalkyl$, $-C_{1-6}cyanoalkyl$, $-C_{1-6}alkylINR^aR^b$, $-C_{1-6}alkylOH$, $-C_{3-8}cycloalkyl$, and
 15 $-C_{1-3}alkylC_{3-8}cycloalkyl$;

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

R^1 is independently selected from H, $-C_{1-6}alkylaryl$, heterocyclyl, $-C_{1-6}alkylheteroaryl$,
 $-C_{1-6}alkylheterocyclyl$, $-C_{1-6}alkylC(O)OR^a$, $-C_{2-6}alkenylC(O)OR^a$, and $-C_{1-6}alkylC_{3-8}cycloalkyl$;

wherein each alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to
 20 2 groups independently selected from $-OR^a$, oxo, $-CN$, halo, $C_{1-6}alkyl$, $-C_{1-6}alkylOR^a$,
 $-C_{1-6}cyanoalkyl$, $-C_{1-6}haloalkyl$, $C_{3-8}cycloalkyl$, $-C_{1-3}alkylC_{3-8}cycloalkyl$, $-C(O)R^a$,
 $-C_{1-6}alkylC(O)R^a$, $-C(O)OR^a$, $-C_{1-6}alkylC(O)OR^a$, $-NR^aR^b$, $-C_{1-6}alkylINR^aR^b$, $-C(O)NR^aR^b$,
 $-C_{1-6}alkylC(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}alkylSO_2R^a$, $-SO_2NR^aR^b$, $-C_{1-6}alkylSO_2NR^aR^b$,
 $-C(O)NR^aSO_2R^b$, $-C_{1-6}alkylC(O)NR^aSO_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}alkylINR^aC(O)R^b$;

25 R^2 is selected from $-C_{1-6}alkyl$, $-C_{2-6}alkenyl$, $-C_{3-6}cycloalkyl$, aryl, heteroaryl, heterocyclyl,
 $-C_{1-6}alkylaryl$, $-C_{1-6}alkylheteroaryl$, $-C_{1-6}alkylheterocyclyl$, $-C_{2-6}alkyl-OR^a$, $-C_{1-6}alkylC(O)OR^a$, and
 $-C_{2-6}alkenylC(O)OR^a$;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycle is optionally substituted
 with 1 to 3 groups independently selected from $-OR^a$, $-CN$, halo, $-C_{1-6}alkylOR^a$, $-C_{1-6}$
 30 $cyanoalkyl$, $-C_{1-6}haloalkyl$, $-C_{3-8}cycloalkyl$, $-C_{1-3}alkylC_{3-8}cycloalkyl$, $-C(O)R^a$, $-C_{1-6}$
 $alkylC(O)R^a$,

$-\text{C}(\text{O})\text{OR}^a$, $-\text{C}_{1-6}\text{alkylC}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}\text{alkylNR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}\text{alkylC}(\text{O})\text{NR}^a\text{R}^b$,
 $-\text{SO}_2\text{R}^a$, $-\text{C}_{1-6}\text{alkylSO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}\text{alkylSO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{R}^b$ and $-\text{NR}^a\text{C}(\text{O})\text{R}^b$;

or R^1 and R^2 combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur or nitrogen, and optionally substituted with 1 to
 5 3 groups independently selected from oxo, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{OR}^a$,
 $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}_{1-6}\text{cyanoalkyl}$, $-\text{C}_{1-6}\text{alkylOR}^a$, $-\text{C}_{1-6}\text{haloalkyl}$, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}(\text{O})\text{R}^a$,
 $\text{C}_{1-6}\text{alkylC}(\text{O})\text{R}^a$, $-\text{C}_{1-6}\text{alkylC}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}\text{alkylNR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}\text{alkylC}(\text{O})\text{NR}^a\text{R}^b$,
 $-\text{SO}_2\text{R}^a$, $-\text{C}_{1-6}\text{alkylSO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, and $\text{C}_{1-6}\text{alkylSO}_2\text{NR}^a\text{R}^b$;

R^3 is independently H, halo, $-\text{C}_{1-6}\text{alkyl}$, $-\text{OH}$, $-\text{OCH}_3$, or $-\text{OCH}_2\text{CH}_3$;

10 R^4 is independently H, halo, $-\text{C}_{1-6}\text{alkyl}$, $-\text{OH}$, $-\text{OCH}_3$, or $-\text{OCH}_2\text{CH}_3$;

R^a is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, and $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$;

R^b is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, and $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$;

R^c is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, and $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$;

R^d is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, and $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$;

15 or wherein any two R^e , any two R^d or any R^e and R^d optionally combine to form a 3-6 membered cycloalkyl ring;

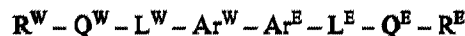
R^e is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{OC}_{3-8}\text{cycloalkyl}$, $-\text{Oaryl}$, $-\text{Oheteroaryl}$, $-\text{Oheterocyclyl}$, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$,
 $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, $-\text{NR}^f\text{R}^g$, $-\text{C}_{1-6}\text{alkylNR}^f\text{R}^g$, $\text{C}_{1-6}\text{alkylC}(\text{O})\text{NR}^f\text{R}^g$, $-\text{NHSO}_2\text{R}^f$,
 20 $-\text{C}_{1-6}\text{alkylSO}_2\text{R}^f$, and $-\text{C}_{1-6}\text{alkylSO}_2\text{NR}^f\text{R}^g$;

R^f is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, and $-\text{C}_{1-6}\text{alkylheterocyclyl}$;

R^g is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, and $-\text{C}_{1-6}\text{alkylheterocyclyl}$;

25 or a pharmaceutically acceptable salt thereof.

In another embodiment of the disclosure, provided is a compound of formula (I)



(I)

wherein:

30 Ar^E and Ar^W are each independently aryl, heteroaryl, or heterocyclyl;

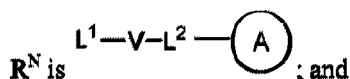
wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from halo, $-OR^a$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, and $-C_{3-8}$ cycloalkyl;

L^E and L^W are each independently a bond, $-O-$, $-(CR^3R^4)_m-$, $-O(CR^3R^4)_m$, $-(CR^3R^4)_mO$, $-(CR^3R^4)_mNR^3-$,
 5 $-NR^3(CR^3R^4)_m-$, or $-C(O)-$;

m is independently 0, 1, 2, 3, or 4;

Q^E and Q^W are each independently an aryl or heteroaryl, wherein each aryl or heteroaryl is optionally substituted with 1 to 4 groups independently selected from halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^aR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, and R^N ;

10 wherein



L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

15 wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

wherein ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

20 wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally independently substituted with 1 to 2 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, C_{3-8} cycloalkyl, and C_{1-6} alkyl C_{3-8} cycloalkyl;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}$ alkyl INR^1R^2 , $-OC_{1-6}$ alkyl INR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl INR^1R^2 , $-NR^aC_{1-6}$ alkyl INR^1R^2 , $-C(O)NR^1R^2$, $-(CH_2)_uSO_2NR^1R^2$,

25 $-SO_2NR^aC_{1-6}$ alkyl INR^1R^2 , $-NR^aSO_2C_{1-6}$ alkyl INR^1R^2 , or $-V^2-(CR^cR^d)_p-L^3-\textcircled{B}-\textcircled{T}_z$;

wherein

V^2 is independently a bond, O, NR^a , S, SO, or SO_2

L^3 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl;

30 T is $(CH_2)_qNR^1R^2$, or $(CH_2)_qC(O)R^a$;

p is 0, 1, 2, or 3;

q is 0, 1, 2, or 3;

u is 0, 1, 2, or 3;

and wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 3 substituents independently selected from the group consisting of $-NR^aR^b$, halo, cyano, oxo, OR^a , $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl NR^aR^b , $-C_{1-6}$ alkylOH, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

R^1 is selected from H, $-C_{1-6}$ alkylaryl, heterocyclyl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl $C(O)OR^a$, $-C_{2-6}$ alkenyl $C(O)OR^a$, and $-C_{1-6}$ alkyl C_{3-8} cycloalkyl;

wherein each alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from $-OR^a$, oxo, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, $-C_{1-6}$ alkyl $C(O)NR^aSO_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}$ alkyl $NR^aC(O)R^b$;

R^2 is selected from $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl- OR^a , $-C_{1-6}$ alkyl $C(O)OR^a$, and $-C_{2-6}$ alkenyl $C(O)OR^a$;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycle is optionally substituted with 1 to 3 groups independently selected from $-OR^a$, $-CN$, halo, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, and $-NR^aC(O)R^b$;

or R^1 and R^2 combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur or nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OR^a$, $-C(O)OR^a$, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ haloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, and $-C_{1-6}$ alkyl $SO_2NR^aR^b$;

R^3 is independently H, halo, $-C_{1-6}$ alkyl, $-OH$, $-OCH_3$, or $-OCH_2CH_3$;

R^4 is independently H, halo, $-C_{1-6}$ alkyl, $-OH$, $-OCH_3$, or $-OCH_2CH_3$;

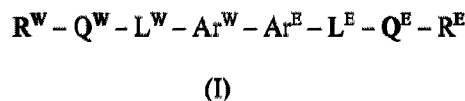
R^a is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;

R^b is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;
 R^c is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;
 R^d is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;
 and wherein any two R^c , any two R^d or any R^c and R^d optionally combine to form a 3-6 membered
 5 cycloalkyl ring;

R^e is independently selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkyl NR^fR^g , C_{1-6} alkyl $C(O)NR^fR^g$, $-NHSO_2R^f$, $-C_{1-6}$ alkyl SO_2R^f , and $-C_{1-6}$ alkyl $SO_2NR^fR^g$;

10 R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;
 R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl,
 or a pharmaceutically acceptable salt thereof.

15 In another embodiment of the disclosure is provided a compound of formula (I)



wherein:

Ar^E and Ar^W are each independently aryl, heteroaryl, or heterocyclyl;

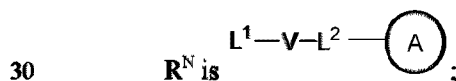
20 wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from halo, $-OR^a$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, and $-C_{3-8}$ cycloalkyl;

L^E and L^W are each independently a bond, $-O-$, $-(CR^3R^4)_m-$, $-O(CR^3R^4)_m$, $-(CR^3R^4)_mO$, $-(CR^3R^4)_mNR^3-$, $-NR^3(CR^3R^4)_m-$, or $-C(O)-$

25 m is independently 0, 1, 2, 3 or 4; and

Q^E and Q^W are each an aryl group optionally substituted with 1 to 4 groups independently selected from halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^aR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, and R^N ;

wherein



wherein

L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

5 L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally independently substituted with 1 to 2 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, C_{3-8} cycloalkyl, and C_{1-6} alkyl C_{3-8} cycloalkyl;

10

R^B and R^W are each independently $-NR^1R^2$, $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C(O)NR^1R^2$, $-(CH_2)_uSO_2NR^1R^2$,

$-SO_2NR^aC_{1-6}$ alkyl NR^1R^2 , $-NR^aSO_2C_{1-6}$ alkyl NR^1R^2 or $-V^2-(CR^cR^d)_p-L^3-\textcircled{B}-(T)_z$;

15

wherein

V^2 is independently a bond, O, NR^a , S, SO, or SO_2

L^3 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is $(CH_2)_qNR^1R^2$ or $(CH_2)_qC(O)R^e$;

20

p is 0, 1, 2, or 3;

q is 0, 1, 2, or 3;

u is 0, 1, 2, or 3;

and wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a , $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl NR^aR^b , $-C_{1-6}$ alkylOH, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;

25

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

R^1 is selected from H, $-C_{1-6}$ alkylaryl, heterocyclyl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl $C(O)OR^a$, $-C_{2-6}$ alkenyl $C(O)OR^a$, and C_{1-6} alkyl C_{3-8} cycloalkyl;

30

wherein each alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 groups independently selected from $-OR^a$, oxo, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkylOR^a,

-C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a,
 -C₁₋₆ alkylC(O)R^a, -C(O)OR^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b,
 -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆ alkylSO₂NR^aR^b,
 -C(O)NR^aSO₂R^b, -C₁₋₆ alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and -C₁₋₆ alkylNR^aC(O)R^b;

- 5 **R² is selected from -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, and -C₂₋₆ alkenylC(O)OR^a;**

- 10 **wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 3 groups independently selected from -OR^a, -CN, halo, -C₁₋₆ alkylOR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C(O)OR^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆ alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, and -NR^aC(O)R^b;**

- 15 **or R¹ and R² combine to form a heterocyclyl optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur or nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, and -C₁₋₆ alkylSO₂NR^aR^b;**

- 20 **R³ is independently H, halo, -C₁₋₆ alkyl, -OH, -OCH₃, or -OCH₂CH₃;**

R⁴ is independently H, halo, -C₁₋₆ alkyl, -OH, -OCH₃, or -OCH₂CH₃;

R^a is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, and -C₁₋₃ alkylC₃₋₈cycloalkyl;

R^b is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, and -C₁₋₃ alkylC₃₋₈cycloalkyl;

R^c is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, and -C₁₋₃ alkylC₃₋₈cycloalkyl;

- 25 **R^d is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, and -C₁₋₃ alkylC₃₋₈cycloalkyl;**
and wherein any two R^c, any two R^d or any R^c and R^d optionally combine to form a 3-6 membered cycloalkyl ring;

- R^e is independently selected from H, -C₁₋₆ alkyl, -OC₁₋₆alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -OC₃₋₈ cycloalkyl, -Oaryl, -Oheteroaryl, -Oheterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C₁₋₆ alkylC(O)NR^fR^g, -NHSO₂R^f, -C₁₋₆ alkylSO₂R^f, and -C₁₋₆ alkylSO₂NR^fR^g;**

- 30 **R^f is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;**

R^E is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl, or a pharmaceutically acceptable salt thereof.

In one embodiment, at least one of Ar^E and Ar^W is other than optionally substituted aryl. In one embodiment, at least one of Ar^E and Ar^W is other than optionally substituted phenyl.

In one embodiment, when both of Ar^E and Ar^W are optionally substituted aryl, then the moiety $-L^E-Ar^E-Ar^W-L^W-$ is $-O-(CR^3R^4)_m-Ar^E-Ar^W-L^W-(CR^3R^4)_m-O-$. In one embodiment, the moiety $-L^E-Ar^E-Ar^W-L^W-$ is $-O-(CR^3R^4)_m-Ar^E-Ar^W-L^W-(CR^3R^4)_m-O-$.

In one embodiment, both of Q^E and Q^W are independently optionally substituted aryl. In one embodiment, both of Q^E and Q^W are independently optionally substituted phenyl. In one embodiment, both of Q^E and Q^W are independently optionally substituted pyridyl.

In one embodiment of any compound described herein, both Ar^E and Ar^W are optionally substituted bicyclic rings, wherein neither is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring. In one embodiment of any compound described herein, both L^E and L^W are $-O-$. In one embodiment of any compound described herein, both L^E and L^W are $-Q-O-CH_2-Ar-$. In one embodiment of any compound described herein, each of Ar^E , Ar^W , Q^E , and Q^W are monocyclic, provided at least two are heteroaryl, and neither of R^E , and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring. In one embodiment of any compound described herein, at least one L is a bond, and none of Ar^E , Ar^W , Q^E , Q^W , R^E , and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring. In one embodiment of any compound described herein, at least one of the following occurs: a) both Ar^E and Ar^W are optionally substituted bicyclic rings, wherein neither is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring; b) both L^E and L^W are $-O-$; c) both L^E and L^W are $-Q-O-CH_2-Ar-$; d) each of Ar^E , Ar^W , Q^E , and Q^W are monocyclic, provided at least two are heteroaryl, and neither of R^E , and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring; or e) at least one L is a bond, and none of Ar^E , Ar^W , Q^E , Q^W , R^E , and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment provided is a compound selected from Example 92, 209, 124, 121, 402, 123, 43, 122, 16, 240, 167, 90, 210, 178, 42, 148, 93, 32, 111, 74, 172, 166, 160, 183, 225, 125, 162, 214, 40, 220, 213, 114, 41, 127, 113, 185, 34, 144, 94, 143, 286, 128, 142, 140, 279, 29, 49, 221, 241, 112, 133, 242, 35, 253, 168, 66, 161, 126, 153, 232, 252, 163, 57, 165, 110, 145, 79, 75, 244, 132, 138, 243, 78, 48, 215, 258, 182, 234, 282, 260, 157, 281, 164, 47, 259, 216, 91, 136, 159, 248, 68, 219, 217, 280, 152, 227, 95, 12, 179, 257, 134, 109, 28, 149, 218, 31, 254, 203, 116, 53, 256, 226, 247, 117, 175, 135, 230, 58, 118, 404, 222, 200, 37, 70, 96, 204, 231, 131, 268, 54, 71, 76, 36, 201, 246, 147, 405, 59, 264, 120, 67, 21, 266, 184, 137, 284, 55, 207, 17, 83, 82, 69, 202, 276, 22, 199, 146, 73, 38, 261, 245, 88, 236, 19, 15, 155, 61, 265, 85, 64, 84, 233, 14, 62, 1394, 158, 272, 30, 77, 150, 80, 151, 81, 154, 255, 235, 56, 141, 23, 86, 104, 39, 60, 269, 87, 115, 173, 174, 270, 271, 223, 273, 406, 237, 277, 249, 170, 18, 63, 105, ((5-

bromo-6-((3'-(((3-bromo-5-(((carboxymethyl)amino)methyl)-6-(((R)-5-oxopyrrolidin-2-yl)methoxy)pyridin-2-yl)oxy)methyl)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2-(((S)-5-oxopyrrolidin-2-yl)methoxy)pyridin-3-yl)methyl)glycine, (S)-4-(((5-(3'-(((4-(((S)-3-carboxy-2-hydroxypropyl)amino)methyl)-2-chloro-5-((5-cyanopyridin-3-yl)methoxy)phenoxy)methyl)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)benzo[b]thiophen-2-yl)methyl)amino)-3-hydroxybutanoic acid, and (S)-4-(((5-bromo-4-((3'-((2-bromo-4-(((S)-3-carboxy-2-hydroxypropyl)amino)methyl)-5-((5-cyanopyridin-3-yl)methoxy)phenoxy)methyl)-2,2'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2-((5-isocyanopyridin-3-yl)methoxy)benzyl)amino)-3-hydroxybutanoic acid, or a pharmaceutically acceptable salt thereof.

In one embodiment provided is a compound selected from Example 191, 198, 197, 193, 189, 196, 192, 195, 190, 20, 194, 186, 188, 72, 187, 25, and 285, or a pharmaceutically acceptable salt thereof.

In one embodiment provided is a compound selected from Example 4, 5, 3, 7, 6, 8, 9, 2, 10, 1, 407, and 13, or a pharmaceutically acceptable salt thereof.

In one embodiment provided is a compound selected from Example 267, 180, 181, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, and 420, or a pharmaceutically acceptable salt thereof.

In one embodiment provided is a compound selected from Example 191, 198, 197, 193, 189, 196, 192, 195, 190, 20, 194, 186, 188, 72, 187, 25, and 285, or a pharmaceutically acceptable salt thereof.

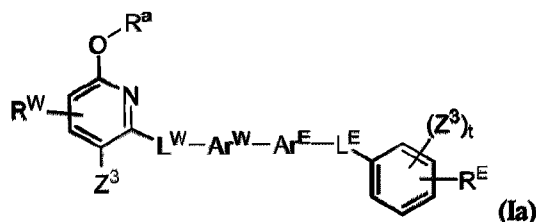
In one embodiment provided is a compound selected from Example 287, 102, 103, 27, 251, and 107, or a pharmaceutically acceptable salt thereof.

In one embodiment provided is a compound selected from Example 239 and 238, or a pharmaceutically acceptable salt thereof.

In one embodiment provided is a compound selected from Example 97, 44, 98, 50, 51, 45, 99, 169, 100, 89, 274, 422, 24, 176, 65, 171, 26, 52, 156, and 263, or a pharmaceutically acceptable salt thereof.

In one embodiment provided is a compound selected from Example 423, 29, 113, 34, 240, 6, 7, 66, 16, and 19, or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound is represented by formula (Ia):



where,

each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$,

$-\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^{N} ;

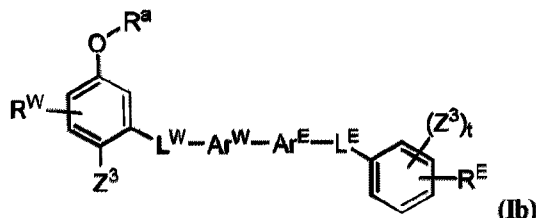
wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^{\text{a}}$, halo, cyano, $-\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{C}(\text{O})\text{OR}^{\text{a}}$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $\text{NR}^{\text{a}}\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(\text{O})\text{OR}^{\text{a}}$, $-\text{SO}_2\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{SO}_2\text{R}^{\text{b}}$, $-\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$ and $-\text{C}_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone; and

t is 0, 1 or 2; and

each of Ar^{E} , Ar^{W} , R^{E} , R^{W} , L^{E} , L^{W} , R^{N} , R^{a} , and R^{b} are as defined herein.

In one embodiment of formula (Ia), L^{E} is other than $-\text{CH}_2\text{O}-$, $-(\text{CH}_2)_2-$, $-\text{CH}=\text{CH}-$, and $-\text{C}(\text{O})\text{NH}-$. In one embodiment of formula (Ia), none of Ar^{E} , Ar^{W} , Q^{E} , Q^{W} , R^{E} , and R^{W} is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by any one of formula (Ib):



where

each Z^3 is independently halo, $-\text{OR}^{\text{a}}$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{SO}_2\text{R}^{\text{a}}$, $-\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{NR}^{\text{a}}\text{SO}_2\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{C}(\text{O})\text{OR}^{\text{a}}$, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{NR}^{\text{a}}\text{C}(\text{O})\text{OR}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(\text{O})\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{OC}(\text{O})\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^{N} ;

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^{\text{a}}$, halo, cyano, $-\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{C}(\text{O})\text{OR}^{\text{a}}$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $\text{NR}^{\text{a}}\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(\text{O})\text{OR}^{\text{a}}$, $-\text{SO}_2\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{SO}_2\text{R}^{\text{b}}$, $-\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$ and $-\text{C}_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone; and

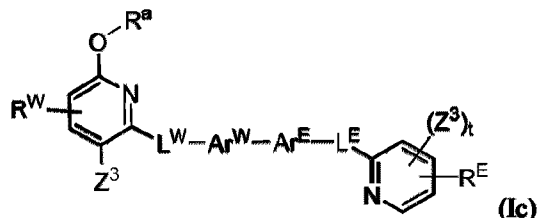
t is 0, 1 or 2; and

each of Ar^{E} , Ar^{W} , R^{E} , R^{W} , L^{E} , L^{W} , R^{N} , R^{a} , and R^{b} are as defined herein.

In one embodiment of formula (Ib), L^{W} and L^{E} are other than $-\text{CH}_2\text{O}-$, $-(\text{CH}_2)_2-$, $-\text{CH}=\text{CH}-$, and $-\text{C}(\text{O})\text{NH}-$. In one embodiment of formula (Ib), L^{E} is other than $-\text{CH}_2\text{O}-$, $-(\text{CH}_2)_2-$, $-\text{CH}=\text{CH}-$, and

-C(O)NH-. In one embodiment of formula (Ib), L^W is other than $-\text{CH}_2\text{O}-$, $-(\text{CH}_2)_2-$, $-\text{CH}=\text{CH}-$, and $-\text{C(O)NH}-$. In one embodiment of formula (Ib), none of Ar^E , Ar^W , Q^E , Q^W , R^E , and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromeric ring.

In one embodiment, the compound is represented by formula (Ic):



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where

each Z^3 is independently halo, $-\text{OR}^a$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{C(O)R}^a$, $-\text{C(O)R}^a$, $-\text{C(O)OR}^a$, $-\text{C(O)NR}^a\text{R}^b$, $-\text{NR}^a\text{C(O)OR}^a$, $-\text{NR}^a\text{C(O)NR}^1\text{R}^2$, $-\text{OC(O)NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C(O)NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl,

10 $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, $-\text{C(O)R}^a$, $-\text{C(O)OR}^a$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C(O)NR}^a\text{R}^b$, $\text{NR}^a\text{C(O)R}^a$, $-\text{NR}^a\text{C(O)OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C(O)NR}^a\text{SO}_2\text{NR}^a\text{R}^b$ and $-\text{C}_{3-8}$ cycloalkyl; and

15 wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone; and

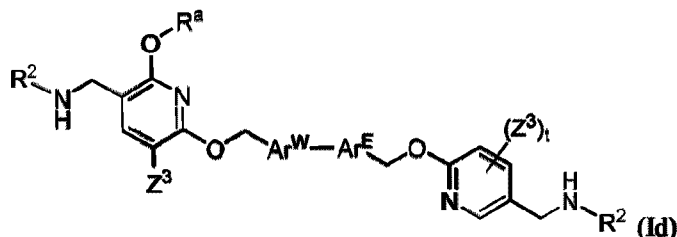
t is 0, 1 or 2; and

each of Ar^E , Ar^W , R^E , R^W , L^E , L^W , R^N , R^a , and R^b are as defined herein.

In one embodiment of formula (Ic), none of Ar^E , Ar^W , Q^E , Q^W , R^E , and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromeric ring.

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In one embodiment, the compound is represented by formula (Id):



where

each Z^3 is independently halo, $-\text{OR}^a$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{C(O)R}^a$, $-\text{C(O)R}^a$, $-\text{C(O)OR}^a$, $-\text{C(O)NR}^a\text{R}^b$, $-\text{NR}^a\text{C(O)OR}^a$, $-\text{NR}^a\text{C(O)NR}^1\text{R}^2$, $-\text{OC(O)NR}^a\text{R}^b$,

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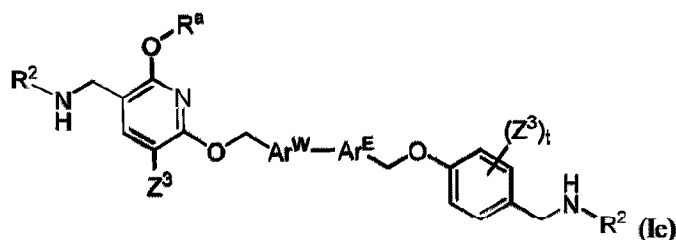
$-\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^{N} ;

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^{\text{a}}$, halo, cyano, $-\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{C}(\text{O})\text{OR}^{\text{a}}$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $\text{NR}^{\text{a}}\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(\text{O})\text{OR}^{\text{a}}$, $-\text{SO}_2\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{SO}_2\text{R}^{\text{b}}$, $-\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$ and $-\text{C}_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

t is 0, 1 or 2; and

each Ar^{E} , Ar^{W} , R^2 , R^{N} , R^{a} , and R^{b} are as defined herein.

In one embodiment, the compound is represented by formulas (Ic):



where

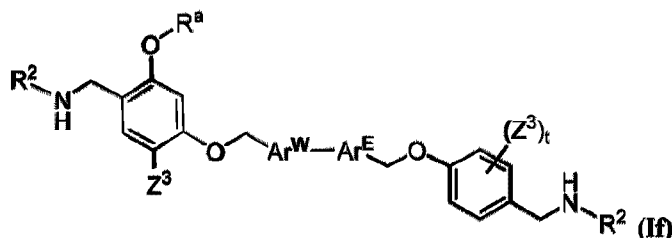
each Z^3 is independently halo, $-\text{OR}^{\text{a}}$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^{\text{a}}\text{R}^2$, $-\text{SO}_2\text{R}^{\text{a}}$, $-\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{NR}^{\text{a}}\text{SO}_2\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{C}(\text{O})\text{OR}^{\text{a}}$, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{NR}^{\text{a}}\text{C}(\text{O})\text{OR}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(\text{O})\text{NR}^{\text{a}}\text{R}^2$, $-\text{OC}(\text{O})\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^{N} ;

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^{\text{a}}$, halo, cyano, $-\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{C}(\text{O})\text{OR}^{\text{a}}$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $\text{NR}^{\text{a}}\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(\text{O})\text{OR}^{\text{a}}$, $-\text{SO}_2\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{SO}_2\text{R}^{\text{b}}$, $-\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{C}(\text{O})\text{NR}^{\text{a}}\text{SO}_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$ and $-\text{C}_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

t is 0, 1 or 2; and

each Ar^{E} , Ar^{W} , R^2 , R^{N} , R^{a} , and R^{b} are as defined herein.

In one embodiment, the compound is represented by formula (If):



where

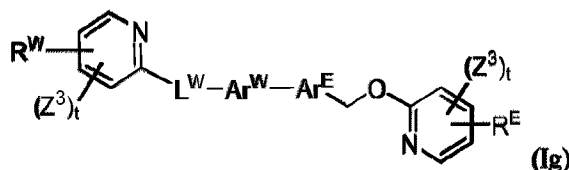
- each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$,
 5 $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

- wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$,
 10 $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

t is 0, 1 or 2; and

each Ar^E , Ar^W , R^2 , R^N , R^a , and R^b are as defined herein.

- 15 In one embodiment, the compound is represented by formula (Ig):



where

- each Z^3 is independently halo, OR^a , $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$,
 20 $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

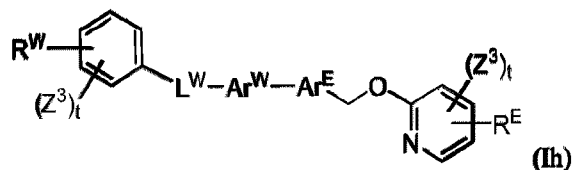
- wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$,
 25 $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

each t is independently 0, 1 or 2; and

each L^W , Ar^E , Ar^W , R^E , R^W , R^N , R^a , and R^b are as defined herein.

In one embodiment of formula (Ig), none of Ar^E , Ar^W , R^E , and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

5 In one embodiment, the compound is represented by formula (Ih):



where

each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$,
 10 $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl,
 $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

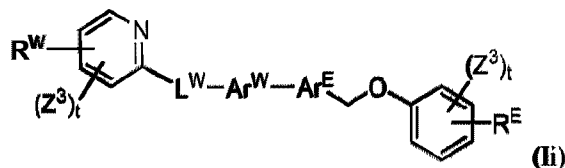
wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$,
 15 $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and
 wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

each t is independently 0, 1 or 2; and

each L^W , Ar^E , Ar^W , R^E , R^W , R^N , R^a , and R^b are as defined herein.

20 In one embodiment of formula (Ig), none of Ar^E , Ar^W , R^E , and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formula (Ii):



where

25 each Z^3 is independently halo, OR^a , $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$,

$-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

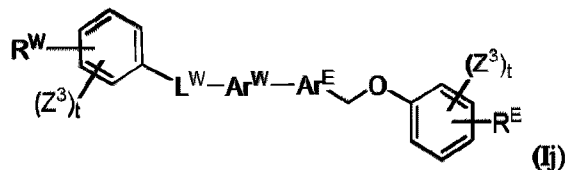
wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$ and $-\text{C}_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

each t is independently 0, 1 or 2; and

each L^W , Ar^E , Ar^W , R^E , R^W , R^N , R^a , and R^b are as defined herein.

In one embodiment of formula (Ii), L^W is a bond, $-\text{O}-$, or $-\text{CH}_2\text{O}-$, where the O is bonded to the pyridine ring and the $-\text{CH}_2-$ is bonded to Ar^W . In one embodiment of formula (Ii), none of Ar^E , Ar^W , R^E and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formula (Ij):



where

each Z^3 is independently halo, OR^a , $-\text{N}_3$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

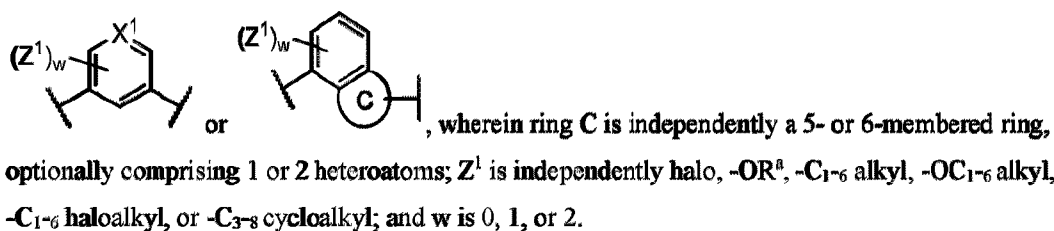
wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$ and $-\text{C}_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

each t is independently 0, 1 or 2; and

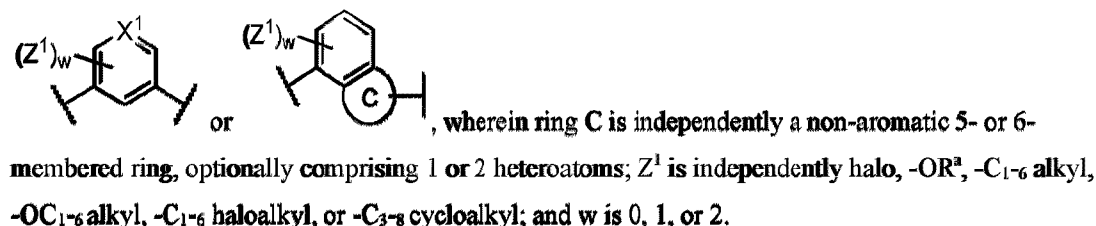
each L^W , Ar^E , Ar^W , R^E , R^W , R^N , R^a , and R^b are as defined herein.

In one embodiment of formula (Ij), L^W is a bond, $-\text{O}-$, or $-\text{CH}_2\text{O}-$, where the O is bonded to the pyridine ring and the $-\text{CH}_2-$ is bonded to Ar^W . In one embodiment of formula (Ij), none of Ar^E , Ar^W , R^E and R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

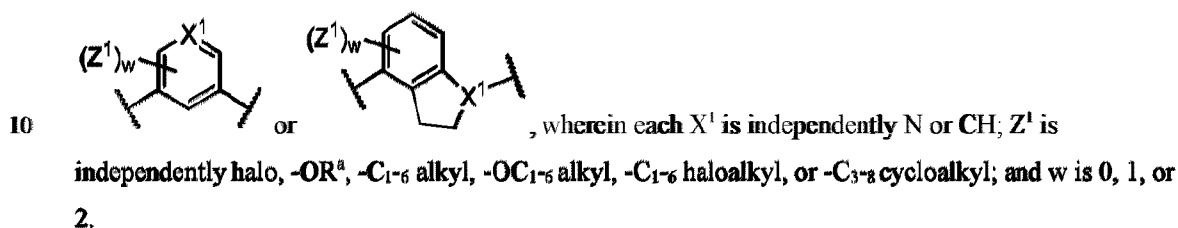
In one embodiment, Ar^W and Ar^E are each independently



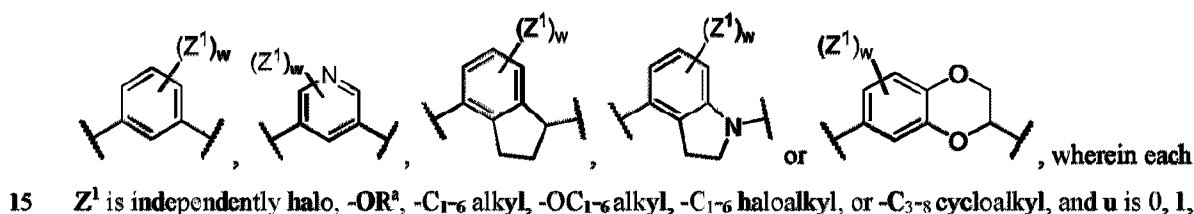
5 In one embodiment, Ar^W and Ar^E are each independently



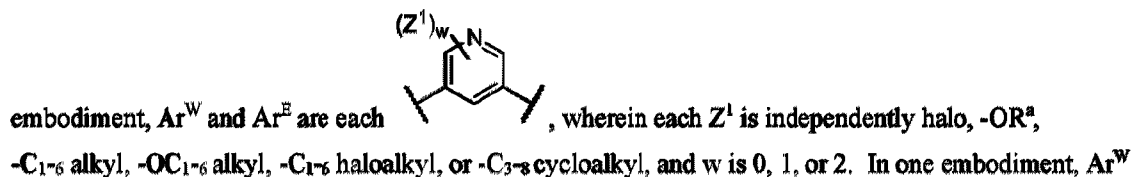
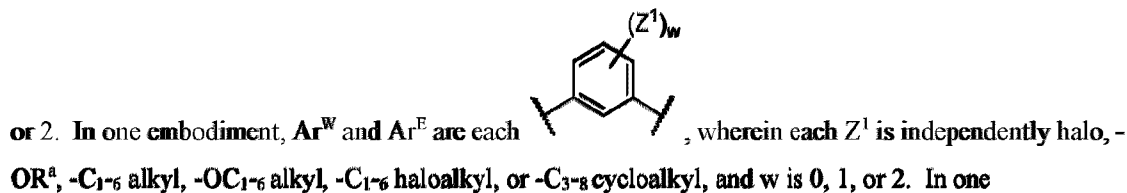
In one embodiment, Ar^W and Ar^E are each independently

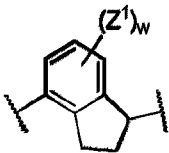


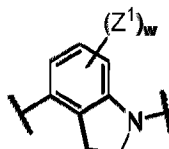
In one embodiment, Ar^W and Ar^E are each independently

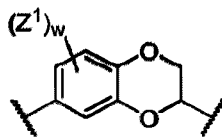


15 Z^1 is independently halo, $-OR^a$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, or $-C_{3-8}$ cycloalkyl, and u is 0, 1,

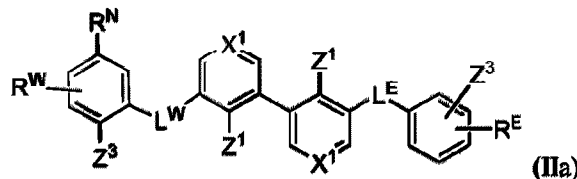


and Ar^E are each , wherein each Z^1 is independently halo, $-\text{OR}^a$, $-\text{C}_{1-6}$ alkyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{1-6}$ haloalkyl, or $-\text{C}_{3-8}$ cycloalkyl, and w is 0, 1, or 2. In one embodiment, Ar^W and Ar^E are each

, wherein each Z^1 is independently halo, $-\text{OR}^a$, $-\text{C}_{1-6}$ alkyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{1-6}$ haloalkyl,

or $-\text{C}_{3-8}$ cycloalkyl, and w is 0, 1, or 2. In one embodiment, Ar^W and Ar^E are each , wherein each Z^1 is independently halo, $-\text{OR}^a$, $-\text{C}_{1-6}$ alkyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{1-6}$ haloalkyl, or $-\text{C}_{3-8}$ cycloalkyl, and w is 0, 1, or 2.

In one embodiment, the compound is represented by formula (IIa):



wherein

each X^1 is independently N or CH;

each Z^1 is independently halo, $-\text{OR}^a$, $-\text{C}_{1-6}$ alkyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{1-6}$ haloalkyl, or $-\text{C}_{3-8}$ cycloalkyl;

each Z^3 is independently halo, $-\text{OR}^a$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl,

$-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-6}$ alkyl $-\text{C}_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ,

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$ and $-\text{C}_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-C_{1-6}alkylNR^1R^2$, $-OC_{1-6}alkylNR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylNR^1R^2$,
 $-NR^aC_{1-6}alkylNR^1R^2$, $-C_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)OR^1$,
 $-SC_{1-6}alkylNR^1R^2$, $-C_{1-6}alkylOR^a$, or

$$L^1-V-L^2-\textcircled{A};$$

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

5 V is independently selected from a bond, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, and $C_{2-6}alkynyl$;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted
 with OR^a , halo, cyano, $-NR^aR^b$ and $-C_{3-8}cycloalkyl$;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

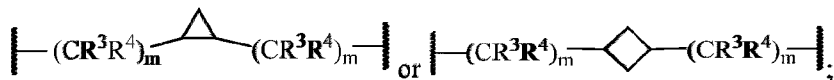
ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

10 wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally
 substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$,
 halo, cyano, $-C_{1-6}alkyl$, $-C_{1-6}haloalkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-OC_{1-6}$
 $haloalkyl$, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}alkylCN$, $-C(O)NR^aR^b$, -
 $NR^aC(O)R^a$,

15 $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, -
 $NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $C_{3-8}cycloalkyl$, and C_{1-6}
 $alkylC_{3-8}cycloalkyl$; and

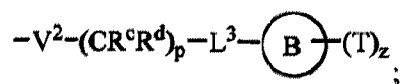
wherein the alkyl, alkenyl, or alkynyl group is optionally independently
 substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}cycloalkyl$

20 L^E and L^W are each independently a bond, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-(CR^3R^4)_m-$, $-(CR^3R^4)_mO(CR^3R^4)_m-$,
 $-(CR^3R^4)_mS(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3(CR^3R^4)_m-$, $-C(O)-$, $-(CR^3R^4)_mC(O)(CR^3R^4)_m-$,
 $-(CR^3R^4)_mC(O)NR^3(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3C(O)(CR^3R^4)_m-$, $C_{2-6}alkenylene$, $C_{2-6}alkynylene$,



each m is independently 0, 1, 2, 3 or 4;

25 R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}alkylNR^1R^2$, $-OC_{1-6}alkylNR^1R^2$,
 $-C_{1-6}alkylOC_{1-6}alkylNR^1R^2$, $-NR^aC_{1-6}alkylNR^1R^2$, $-C_{1-6}alkylIN^+R^1R^2R^3$, $-SC_{1-6}alkylNR^1R^2$, -
 $C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_nSO_2NR^1R^2$, $-(CH_2)_nNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}alkylNR^1R^2$, $-NR^aSO_2C_{1-6}$
 $alkylNR^1R^2$,
 $-(CH_2)_nC(O)NR^aSO_2NR^aR^b$, $-(CH_2)_nP^+R^1R^2O^-$, $-(CH_2)_nP^+R^bR^cR^d$, $-(CH_2)_nP^+R^cR^dO^-$,
 30 $-(CH_2)_nP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_nNR^aP(O)(OR^e)_2$, $-(CH_2)_nCH_2OP(O)(OR^e)(OR^d)$,
 $-(CH_2)_nOP(O)(OR^e)(OR^d)$, $-(CH_2)_nOP(O)NR^aR^b(OR^e)$, or



wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

5 ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a , $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^e$ or $(CH_2)_qC(O)R^e$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

10 z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a , $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl NR^aR^b , $-C_{1-6}$ alkylOH, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;

15 provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

R^1 is independently selected from H, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl $C(O)OR^a$, $-C_{2-6}$ alkenyl $C(O)OR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-C(O)NR^aSO_2R^a$, and C_{1-6} alkyl C_{3-8} cycloalkyl;

20 wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $NR^aC(O)OR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, $-C_{1-6}$ alkyl $C(O)NR^aSO_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}$ alkyl $NR^aC(O)R^b$;

25

R^2 is independently selected from H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl $-OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, and $-C_{2-6}$ alkenyl $C(O)OR^a$;

30 wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl,

-C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C(O)OR^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b,
 -C(O)NR^aR^b, C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆ alkylSO₂NR^aR^b,
 -C(O)NR^aSO₂R^b, and -NR^aC(O)R^b;

or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional

5 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆ alkylSO₂NR^aR^b;

10 R³ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or -C₂₋₆ alkenylC(O)OR^a;

R⁴ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or
 15 -C₂₋₆ alkenylC(O)OR^a;

R^a is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

R^b is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

20 or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, -C₁₋₆ alkylOR^f, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^f, -C₁₋₆ alkylC(O)R^f, -C(O)OR^f, -C₁₋₆ alkylC(O)OR^f, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆ alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆ alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆ alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and
 25 -NR^fC(O)R^g;

R^c is independently selected from H, OH, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

R^d is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

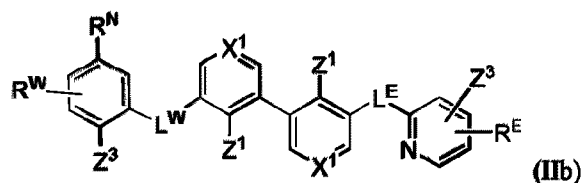
30 R^e is independently selected from H, -C₁₋₆ alkyl, -OC₁₋₆alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -OC₃₋₈ cycloalkyl, -Oaryl, -Oheteroaryl, -Oheterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆ alkylC(O)NR^fR^g, -NH₂SO₂R^f, -C₁₋₆ alkylSO₂R^f, and -C₁₋₆ alkylSO₂NR^fR^g;

R^f is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
 35 -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl; and

R^E is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

In one embodiment of formula (IIa), when one of L^E or L^W is $-\text{CH}_2\text{O}-$, $-(\text{CH}_2)_2-$, $-\text{CH}=\text{CH}-$, or $-\text{C}(\text{O})\text{NH}-$; then the other of L^E and L^W is a bond, $-\text{O}-$, or $-\text{O}-\text{CH}_2-$, where the oxygen is bonded to the Q ring and the $-\text{CH}_2-$ is bonded to the Ar ring. In one embodiment of formula (IIa), both L^E and L^W are $-\text{O}-\text{CH}_2-$, where the oxygen is bonded to the Q ring and the CH_2 is bonded to the Ar ring. In one embodiment of formula (IIa), one or both of L^E or L^W is a bond or $-\text{O}-$. In one embodiment of formula (IIa), one or both of X^1 is N. In one embodiment of formula (IIa), neither of R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formula (IIb):



wherein

each X^1 is independently N or CH;

each Z^1 is independently halo, $-\text{OR}^a$, $-C_{1-6}$ alkyl, $-\text{OC}_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, or $-C_{3-8}$ cycloalkyl;

each Z^3 is independently halo, $-\text{OR}^a$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$ and $-C_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-\text{OC}_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-\text{NR}^a\text{C}_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^1$,

$-\text{SC}_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OR^a , or $\text{L}^1-\text{V}-\text{L}^2-\text{A}$;

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a, halo, cyano, -NR^aR^b and -C₃₋₈ cycloalkyl;

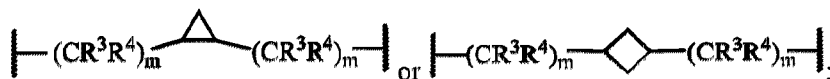
L² is independently a bond, O, NR^a, S, SO, or SO₂;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

- 5 wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo, cyano, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OC₁₋₆ haloalkyl, NR^aR^b, -C(O)R^a, -C(O)OR^a, -OC₁₋₆ alkylCN, -C(O)NR^aR^b, -NR^aC(O)R^a,
 10 -NR^aC(O)OR^a, -NR^aC(O)OR^a, -C(O)N(R^a)OR^b, -SO₂R^a, -SO₂NR^aR^b, -NR^aSO₂R^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b, C₃₋₈cycloalkyl, and C₁₋₆alkylC₃₋₈ cycloalkyl; and

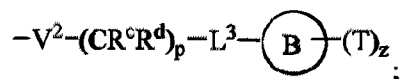
wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with -OR^a, halo, cyano, -NR^aR^b or -C₃₋₈ cycloalkyl

- 15 L^E and L^W are each independently a bond, -O-, -S-, -SO-, -SO₂-, -(CR³R⁴)_m-, -(CR³R⁴)_mO(CR³R⁴)_m-, -(CR³R⁴)_mS(CR³R⁴)_m-, -(CR³R⁴)_mNR³(CR³R⁴)_m-, -C(O)-, -(CR³R⁴)_mC(O)(CR³R⁴)_m-, -(CR³R⁴)_mC(O)NR³(CR³R⁴)_m-, -(CR³R⁴)_mNR³C(O)(CR³R⁴)_m-, C₂₋₆ alkenylene, C₂₋₆ alkynylene,



each m is independently 0, 1, 2, 3 or 4;

- 20 R^E and R^W are each independently -NR¹R², -C₁₋₆alkylNR¹R², -OC₁₋₆alkylNR¹R², -C₁₋₆alkylOC₁₋₆alkylNR¹R², -NR^aC₁₋₆alkylNR¹R², -C₁₋₆alkylIN⁺R¹R²R³, -SC₁₋₆alkylNR¹R², -C(O)NR¹R², -SO₂R^a, -(CH₂)_nSO₂NR¹R², -(CH₂)_nNR^aSO₂NR^aR^b, -SO₂NR^aC₁₋₆alkylNR¹R², -NR^aSO₂C₁₋₆alkylNR¹R²,
 25 -(CH₂)_nC(O)NR^aSO₂NR^aR^b, -(CH₂)_nN⁺R¹R²O⁻, -(CH₂)_nP⁺R^bR^cR^d, -(CH₂)_nP⁺R^cR^dO⁻,
 -(CH₂)_nP⁺O[NR^aR^b][NR^cR^d], -(CH₂)_nNR^aP(O)(OR^e)₂, -(CH₂)_nCH₂OP(O)(OR^e)(OR^d),
 -(CH₂)_nOP(O)(OR^e)(OR^d), -(CH₂)_nOP(O)NR^aR^b(OR^a), or



wherein:

V² is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹R², or NR^aSO₂;

- 30 L³ is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹R², or NR^aSO₂;

ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently H, OR^a, (CH₂)_nNR¹R², (CH₂)_nNR^aC(O)R^e or (CH₂)_nC(O)R^e;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

- 5 wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a , $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl NR^aR^b , $-C_{1-6}$ alkylOH, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

- 10 R^1 is independently selected from H, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl $C(O)OR^a$, $-C_{2-6}$ alkenyl $C(O)OR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-C(O)NR^aSO_2R^a$, and C_{1-6} alkyl C_{3-8} cycloalkyl;

- 15 wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $NR^aC(O)OR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, $-C_{1-6}$ alkyl $C(O)NR^aSO_2R^b$, $-NR^aC(O)R^b$, and
- 20 $-C_{1-6}$ alkyl $NR^aC(O)R^b$;

R^2 is independently selected from H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl OR^a , $-C_{1-6}$ alkyl $C(O)OR^a$, and $-C_{2-6}$ alkenyl $C(O)OR^a$;

- 25 wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, C_{1-6} alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, and $-NR^aC(O)R^b$;

- 30 or R^1 and R^2 combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OR^a$, $-C(O)OR^a$, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ haloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, and C_{1-6} alkyl $SO_2NR^aR^b$;
- 35

R³ is independently **H**, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, or -C₂₋₆alkenylC(O)OR^a;

R⁴ is independently **H**, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, or -C₂₋₆alkenylC(O)OR^a;

R^a is independently selected from **H**, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

R^b is independently selected from **H**, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

or **R^a** and **R^b** may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, -C₁₋₆alkylOR^f, -C₁₋₆cianoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^f, -C₁₋₆alkylC(O)R^f, -C(O)OR^f, -C₁₋₆alkylC(O)OR^f, -NR^fR^g, -C₁₋₆alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and -NR^fC(O)R^g;

R^c is independently selected from **H**, OH, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

R^d is independently selected from **H**, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

R^e is independently selected from **H**, -C₁₋₆alkyl, -OC₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -OC₃₋₈cycloalkyl, -Oaryl, -Oheteroaryl, -Oheterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -NR^fR^g, -C₁₋₆alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆alkylC(O)NR^fR^g, -NH₂SO₂R^f, -C₁₋₆alkylSO₂R^f, and -C₁₋₆alkylSO₂NR^fR^g;

R^f is independently selected from **H**, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl; and

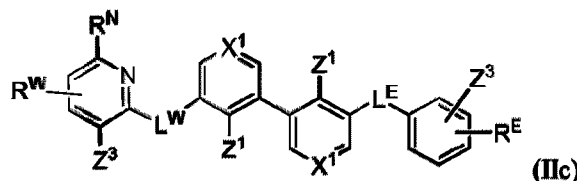
R^g is independently selected from **H**, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

In one embodiment of formula (IIb), **L^w** is other than -CH₂O-, -(CH₂)₂-, -CH=CH-, and -C(O)NH-. In one embodiment of formula (IIb), **L^E** is -O-CH₂-, where the oxygen is bonded to the Q group and the CH₂ is bonded to the Ar group. In one embodiment of formula (IIb), **L^E** is a bond. In one embodiment of formula (IIb), one or both of **L^E** or **L^w** is a bond or -O-. In one embodiment of formula

(IIb), one or both of X^1 is N. In one embodiment of formula (IIb), neither of R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formula (IIc):



5 wherein

each X^1 is independently N or CH;

each Z^1 is independently halo, $-OR^a$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, or $-C_{3-8}$ cycloalkyl;

each Z^2 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$,

10 $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

15 R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)OR^1$,

20 $-SC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OR^a , or $L^1-V-L^2-\text{A}$;

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

25 L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

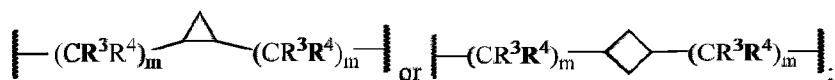
ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$

haloalkyl, NR^aR^b , $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}\text{alkylCN}$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{N}(\text{R}^a)\text{OR}^b$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, C_3 - s -cycloalkyl, and $\text{C}_{1-6}\text{alkylC}_3$ - s -cycloalkyl; and

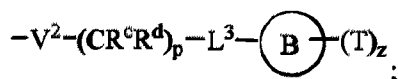
wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$ or $-\text{C}_3$ - s -cycloalkyl

L^E and L^W are each independently a bond, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{O}(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{S}(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{NR}^3(\text{CR}^3\text{R}^4)_m-$, $-\text{C}(\text{O})-$, $-(\text{CR}^3\text{R}^4)_m\text{C}(\text{O})(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{C}(\text{O})\text{NR}^3(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{NR}^3\text{C}(\text{O})(\text{CR}^3\text{R}^4)_m-$, C_{2-6} alkenylene, C_{2-6} alkynylene,



each m is independently 0, 1, 2, 3 or 4;

R^E and R^W are each independently $-\text{NR}^1\text{R}^2$, $-\text{C}_{1-6}\text{alkylINR}^1\text{R}^2$, $-\text{OC}_{1-6}\text{alkylINR}^1\text{R}^2$, $-\text{C}_{1-6}\text{alkylOC}_{1-6}\text{alkylINR}^1\text{R}^2$, $-\text{NR}^a\text{C}_{1-6}\text{alkylINR}^1\text{R}^2$, $-\text{C}_{1-6}\text{alkylIN}^+\text{R}^1\text{R}^2\text{R}^3$, $-\text{SC}_{1-6}\text{alkylINR}^1\text{R}^2$, $-\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-(\text{CH}_2)_u\text{SO}_2\text{NR}^1\text{R}^2$, $-(\text{CH}_2)_u\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{C}_{1-6}\text{alkylINR}^1\text{R}^2$, $-\text{NR}^a\text{SO}_2\text{C}_{1-6}\text{alkylINR}^1\text{R}^2$, $-(\text{CH}_2)_u\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-(\text{CH}_2)_u\text{N}^+\text{R}^1\text{R}^2\text{O}^-$, $-(\text{CH}_2)_u\text{P}^+\text{R}^b\text{R}^c\text{R}^d$, $-(\text{CH}_2)_u\text{P}^+\text{R}^c\text{R}^d\text{O}^-$, $-(\text{CH}_2)_u\text{P}^+\text{O}[\text{NR}^a\text{R}^b][\text{NR}^c\text{R}^d]$, $-(\text{CH}_2)_u\text{NR}^c\text{P}(\text{O})(\text{OR}^e)_2$, $-(\text{CH}_2)_u\text{CH}_2\text{OP}(\text{O})(\text{OR}^e)(\text{OR}^d)$, $-(\text{CH}_2)_u\text{OP}(\text{O})(\text{OR}^e)(\text{OR}^d)$, $-(\text{CH}_2)_u\text{OP}(\text{O})\text{NR}^a\text{R}^b(\text{OR}^a)$, or



wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $\text{C}(\text{O})\text{NR}^a$, $\text{NR}^a\text{C}(\text{O})$, $\text{SO}_2\text{NR}^1\text{R}^2$, or NR^aSO_2 ;

L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $\text{C}(\text{O})\text{NR}^a$, $\text{NR}^a\text{C}(\text{O})$, $\text{SO}_2\text{NR}^1\text{R}^2$, or NR^aSO_2 ;

ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a , $(\text{CH}_2)_q\text{NR}^1\text{R}^2$, $(\text{CH}_2)_q\text{NR}^a\text{C}(\text{O})\text{R}^e$ or $(\text{CH}_2)_q\text{C}(\text{O})\text{R}^e$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with

1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano,

oxo, OR^a, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylNR^aR^b, -C₁₋₆ alkylOH, -C₃₋₈ cycloalkyl, and -C₁₋₃ alkylC₃₋₈cycloalkyl;

provided that at least one of V², L³, ring B and T contains a nitrogen atom;

- R¹** is independently selected from H, -C₁₋₈ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₁₋₆ alkylC(O)OR^a, -C₂₋₆ alkenylC(O)OR^a, -SO₂R^a, -SO₂NR^aR^b, -C(O)NR^aSO₂R^a, and C₁₋₆ alkylC₃₋₈cycloalkyl;

- wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, NR^aC(O)OR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and -C₁₋₆alkylNR^aC(O)R^b;

- R²** is independently selected from H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, and -C₂₋₆ alkenylC(O)OR^a;

- wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, and -NR^aC(O)R^b;

- or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C(O)OR^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆ alkylSO₂NR^aR^b;

- R³** is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or -C₂₋₆ alkenylC(O)OR^a;

- R⁴** is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or -C₂₋₆ alkenylC(O)OR^a;

R^a is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^b is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

- 5 or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from $-OR^f$, $-CN$, halo, $-C_{1-6}$ alkyl OR^f , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^f$, $-C_{1-6}$ alkyl $C(O)R^f$, $-C(O)OR^f$, $-C_{1-6}$ alkyl $C(O)OR^f$, $-NR^fR^g$, $-C_{1-6}$ alkyl NR^fR^g , $-C(O)NR^fR^g$, $-C_{1-6}$ alkyl $C(O)NR^fR^g$, $-SO_2R^f$, $-C_{1-6}$ alkyl SO_2R^f , $-SO_2NR^fR^g$, $-C_{1-6}$ alkyl $SO_2NR^fR^g$, $-C(O)NR^fSO_2R^g$ and
- 10 $-NR^fC(O)R^g$;

R^c is independently selected from H, OH, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^d is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

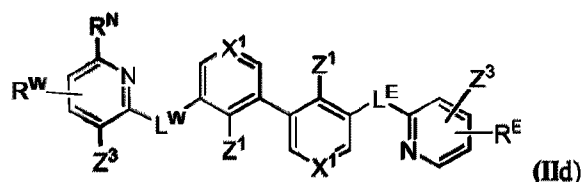
- 15 R^e is independently selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkyl NR^fR^g , $-C(O)NR^fR^g$, $-C_{1-6}$ alkyl $C(O)NR^fR^g$, $-NHSO_2R^f$, $-C_{1-6}$ alkyl SO_2R^f , and $-C_{1-6}$ alkyl $SO_2NR^fR^g$;

- R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and
- 20 R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

- In one embodiment of formula (IIc), L^E is other than $-CH_2O-$, $-(CH_2)_2-$, $-CH=CH-$, and -
- 25 $C(O)NH-$. In one embodiment of formula (IIc), L^W is $-O-CH_2-$, where the oxygen is bonded to the Q ring and the CH_2 is bonded to the Ar ring. In certain embodiments of formula (IIc), one or both of L^E or L^W is a bond or $-O-$. In certain embodiments of formula (IIc), one or both of X^1 is N. In certain embodiments of formula (IIc), neither of R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

- 30 In one embodiment, the compound is represented by formula (IIId):



wherein

each X^1 is independently N or CH;

each Z^1 is independently halo, $-OR^a$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, or $-C_{3-8}$ cycloalkyl;

each Z^2 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$,
 5 $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$,
 $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl,
 $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is
 optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo,
 10 cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$,
 $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and
 wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an
 N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 ,
 15 $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)OR^1$,
 $-SC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OR^a , or



wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted
 20 with OR^a , halo, cyano, $-NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

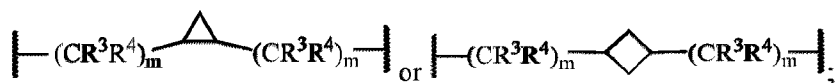
ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally
 substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$,
 25 halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$
 haloalkyl, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$,
 $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$,
 $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, C_{3-8} cycloalkyl,
 and C_{1-6} alkyl C_{3-8} cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently
 30 substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl

L^E and L^W are each independently a bond, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-(CR^3R^4)_m-$, $-(CR^3R^4)_mO(CR^3R^4)_m-$,
 $-(CR^3R^4)_mS(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3(CR^3R^4)_m-$, $-C(O)-$, $-(CR^3R^4)_mC(O)(CR^3R^4)_m-$,

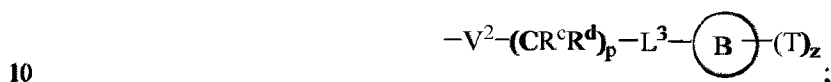
$-(\text{CR}^3\text{R}^4)_m\text{C}(\text{O})\text{NR}^3(\text{CR}^3\text{R}^4)_m$, $-(\text{CR}^3\text{R}^4)_m\text{NR}^3\text{C}(\text{O})(\text{CR}^3\text{R}^4)_m$, C_{2-6} alkenylene, C_{2-6} alkynylene,



each m is independently 0, 1, 2, 3 or 4;

R^E and R^W are each independently $-\text{NR}^1\text{R}^2$, $-\text{C}_{1-6}$ alkyl NR^1R^2 , $-\text{OC}_{1-6}$ alkyl NR^1R^2 ,

- 5 $-\text{C}_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-\text{NR}^a\text{C}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl $\text{IN}^+\text{R}^1\text{R}^2\text{R}^3$, $-\text{SC}_{1-6}$ alkyl NR^1R^2 , $-\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-(\text{CH}_2)_u\text{SO}_2\text{NR}^1\text{R}^2$, $-(\text{CH}_2)_u\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{C}_{1-6}$ alkyl NR^1R^2 , $-\text{NR}^a\text{SO}_2\text{C}_{1-6}$ alkyl NR^1R^2 , $-(\text{CH}_2)_u\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-(\text{CH}_2)_u\text{N}^+\text{R}^1\text{R}^2\text{O}^-$, $-(\text{CH}_2)_u\text{P}^+\text{R}^b\text{R}^c\text{R}^d$, $-(\text{CH}_2)_u\text{P}^+\text{R}^c\text{R}^d\text{O}^-$, $-(\text{CH}_2)_u\text{P}^+\text{O}[\text{NR}^a\text{R}^b][\text{NR}^c\text{R}^d]$, $-(\text{CH}_2)_u\text{NR}^c\text{P}(\text{O})(\text{OR}^e)_2$, $-(\text{CH}_2)_u\text{CH}_2\text{OP}(\text{O})(\text{OR}^e)(\text{OR}^d)$, $-(\text{CH}_2)_u\text{OP}(\text{O})(\text{OR}^e)(\text{OR}^d)$, $-(\text{CH}_2)_u\text{OP}(\text{O})\text{NR}^a\text{R}^b(\text{OR}^e)$, or



wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $\text{C}(\text{O})\text{NR}^a$, $\text{NR}^a\text{C}(\text{O})$, $\text{SO}_2\text{NR}^1\text{R}^2$, or NR^aSO_2 ;

L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $\text{C}(\text{O})\text{NR}^a$, $\text{NR}^a\text{C}(\text{O})$, $\text{SO}_2\text{NR}^1\text{R}^2$, or NR^aSO_2 ;

- 15 ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a , $(\text{CH}_2)_q\text{NR}^1\text{R}^2$, $(\text{CH}_2)_q\text{NR}^a\text{C}(\text{O})\text{R}^e$ or $(\text{CH}_2)_q\text{C}(\text{O})\text{R}^e$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

- 20 wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1

to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a , $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ haloalkyl, $-\text{C}_{1-6}$ cyanoalkyl, $-\text{C}_{1-6}$ alkyl NR^aR^b , $-\text{C}_{1-6}$ alkylOH, $-\text{C}_{3-8}$ cycloalkyl, and $-\text{C}_{1-3}$ alkyl C_{3-8} cycloalkyl;

- 25 provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

R^1 is independently selected from H, $-\text{C}_{1-8}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{C}_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-6}$ alkylaryl, $-\text{C}_{1-6}$ alkylheteroaryl, $-\text{C}_{1-6}$ alkylheterocyclyl, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^a$, $-\text{C}_{2-6}$ alkenyl $\text{C}(\text{O})\text{OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{R}^a$, and C_{1-6} alkyl C_{3-8} cycloalkyl;

- 30 wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-\text{OR}^a$, $-\text{CN}$, halo, C_{1-6} alkyl, $-\text{C}_{1-6}$ alkyl OR^a ,

-C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a,
 -C₁₋₆ alkylC(O)R^a, -C(O)OR^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, NR^aC(O)OR^b,
 -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b,
 -C₁₋₆ alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆ alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and
 5 -C₁₋₆ alkylNR^aC(O)R^b;

R² is independently selected from H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl,
 heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a,
 -C₁₋₆ alkylC(O)OR^a, and -C₂₋₆ alkenylC(O)OR^a;

10 wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally
 substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl,
 -C₁₋₆ alkylOR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl,
 -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C(O)OR^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b,
 -C(O)NR^aR^b, C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆ alkylSO₂NR^aR^b,
 -C(O)NR^aSO₂R^b, and -NR^aC(O)R^b;

15 or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional
 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1
 to 3 groups independently selected from oxo, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl,
 -OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a,
 -C₁₋₆ alkylC(O)R^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b,
 20 -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆ alkylSO₂NR^aR^b;

R³ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl,
 -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or
 -C₂₋₆ alkenylC(O)OR^a;

25 R⁴ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆
 alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or -C₂₋₆
 alkenylC(O)OR^a;

R^a is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
 -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

30 R^b is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
 -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S;
 wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN,
 halo, -C₁₋₆ alkylOR^f, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl,
 -C(O)R^f, -C₁₋₆ alkylC(O)R^f, -C(O)OR^f, -C₁₋₆ alkylC(O)OR^f, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g,

$-\text{C}_{1-6}\text{alkylC}(\text{O})\text{NR}^f\text{R}^g$, $-\text{SO}_2\text{R}^f$, $-\text{C}_{1-6}\text{alkylSO}_2\text{R}^f$, $-\text{SO}_2\text{NR}^f\text{R}^g$, $-\text{C}_{1-6}\text{alkylSO}_2\text{NR}^f\text{R}^g$, $-\text{C}(\text{O})\text{NR}^f\text{SO}_2\text{R}^g$ and $-\text{NR}^f\text{C}(\text{O})\text{R}^g$;

R^c is independently selected from H, OH, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, and $-\text{C}_{1-6}\text{alkylheterocyclyl}$;

- 5 R^d is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, and $-\text{C}_{1-6}\text{alkylheterocyclyl}$;

R^e is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{OC}_{3-8}\text{cycloalkyl}$, $-\text{Oaryl}$, $-\text{Oheteroaryl}$, $-\text{Oheterocyclyl}$, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, $-\text{NR}^f\text{R}^g$, $-\text{C}_{1-6}\text{alkylNR}^f\text{R}^g$, $-\text{C}(\text{O})\text{NR}^f\text{R}^g$, $-\text{C}_{1-6}\text{alkylC}(\text{O})\text{NR}^f\text{R}^g$,
10 $-\text{NHSO}_2\text{R}^f$, $-\text{C}_{1-6}\text{alkylSO}_2\text{R}^f$, and $-\text{C}_{1-6}\text{alkylSO}_2\text{NR}^f\text{R}^g$;

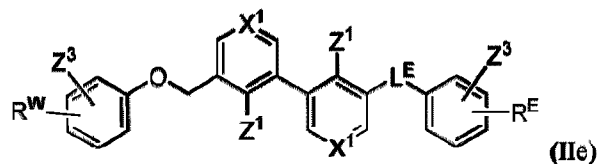
R^f is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, and $-\text{C}_{1-6}\text{alkylheterocyclyl}$; and

R^g is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, and $-\text{C}_{1-6}\text{alkylheterocyclyl}$;

- 15 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

In one embodiment of formula (IId), neither of R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by any one of formula (IIe):



- 20 wherein

each X^1 is independently N or CH;

each Z^1 is independently halo, $-\text{OR}^a$, $-\text{C}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{alkyl}$, $-\text{C}_{1-6}\text{haloalkyl}$, or $-\text{C}_{3-8}\text{cycloalkyl}$;

each Z^3 is independently halo, $-\text{OR}^a$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}(\text{O})\text{NR}^a\text{R}^b$,

- 25 $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{OC}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylC}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, and R^N ;

wherein the alkyl, alkenyl, alkynyl, $\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}\text{alkylCN}$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$,
30 $-\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$ and $-\text{C}_{3-8}\text{cycloalkyl}$; and

wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-C_{1-6}alkylINR^1R^2$, $-OC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylINR^1R^2$, $-NR^aC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)OR^1$,

5 $-SC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOR^a$, or $L^1-V-L^2-\textcircled{A}$;

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, and $C_{2-6}alkynyl$;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ and $-C_{3-8}cycloalkyl$;

10 L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}alkyl$, $-C_{1-6}haloalkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-OC_{1-6}haloalkyl$, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}alkylCN$, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $C_{3-8}cycloalkyl$, and $C_{1-6}alkylC_{3-8}cycloalkyl$; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}cycloalkyl$

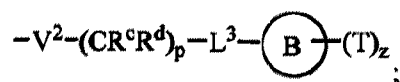
L^E is a bond, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-(CR^3R^4)_m-$, $-(CR^3R^4)_mO(CR^3R^4)_m-$, $-(CR^3R^4)_mS(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3(CR^3R^4)_m-$, $-C(O)-$, $-(CR^3R^4)_mC(O)(CR^3R^4)_m-$, $-(CR^3R^4)_mC(O)NR^3(CR^3R^4)_m-$,

$-(CR^3R^4)_mNR^3C(O)(CR^3R^4)_m-$, $C_{2-6}alkenylene$, $C_{2-6}alkynylene$, $\left|-(CR^3R^4)_m-\triangle-(CR^3R^4)_m\right|$ or $\left|-(CR^3R^4)_m-\diamond-(CR^3R^4)_m\right|$,

25 each m is independently 0, 1, 2, 3 or 4;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}alkylINR^1R^2$, $-OC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylINR^1R^2$, $-NR^aC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylIN^+R^1R^2R^3$, $-SC_{1-6}alkylINR^1R^2$, $-C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_uSO_2NR^1R^2$, $-(CH_2)_uNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}alkylINR^1R^2$, $-NR^aSO_2C_{1-6}alkylINR^1R^2$, $-(CH_2)_uC(O)NR^aSO_2NR^aR^b$, $-(CH_2)_uN^+R^1R^2O^-$, $-(CH_2)_uP^+R^bR^cR^d$, $-(CH_2)_uP^+R^bR^dO^-$, $-(CH_2)_uP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_uNR^cP(O)(OR^c)_2$, $-(CH_2)_uCH_2OP(O)(OR^c)(OR^d)$, $-(CH_2)_uOP(O)(OR^c)(OR^d)$, $-(CH_2)_uOP(O)NR^aR^b(OR^a)$, or

30



wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

5 ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a , $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^e$ or $(CH_2)_qC(O)R^e$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

10 z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with

1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a , $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl NR^aR^b , $-C_{1-6}$ alkylOH, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

R^1 is independently selected from H, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl $C(O)OR^a$, $-C_{2-6}$ alkenyl $C(O)OR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-C(O)NR^aSO_2R^a$, and C_{1-6} alkyl C_{3-8} cycloalkyl;

20 wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $NR^aC(O)OR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, $-C_{1-6}$ alkyl $C(O)NR^aSO_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}$ alkyl $NR^aC(O)R^b$;

R^2 is independently selected from H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl OR^a , $-C_{1-6}$ alkyl $C(O)OR^a$, and $-C_{2-6}$ alkenyl $C(O)OR^a$;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl,

-C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, and -NR^aC(O)R^b;

- 5 or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -OR^a, -C(O)OR^a, -C₁₋₆cyanoalkyl, -C₁₋₆alkylOR^a, -C₁₋₆haloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b,
10 -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, and -C₁₋₆alkylSO₂NR^aR^b;

R³ is independently H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, or -C₂₋₆alkenylC(O)OR^a;

- R⁴ is independently H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl,
15 -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, or -C₂₋₆alkenylC(O)OR^a;

R^a is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

- R^b is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl,
20 -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

- or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, -C₁₋₆alkylOR^f, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^f, -C₁₋₆alkylC(O)R^f, -C(O)OR^f, -C₁₋₆alkylC(O)OR^f, -NR^fR^g, -C₁₋₆alkylNR^fR^g, -C(O)NR^fR^g,
25 -C₁₋₆alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and -NR^fC(O)R^g;

R^c is independently selected from H, OH, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

- R^d is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl,
30 -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

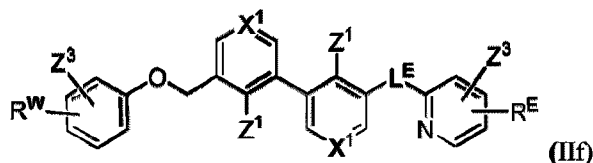
R^e is independently selected from H, -C₁₋₆alkyl, -OC₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -OC₃₋₈cycloalkyl, -Oaryl, -Oheteroaryl, -Oheterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -NR^fR^g, -C₁₋₆alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆alkylC(O)NR^fR^g, -NHSO₂R^f, -C₁₋₆alkylSO₂R^f, and -C₁₋₆alkylSO₂NR^fR^g;

R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

5 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

In one embodiment of formula (Ile), L^E is a bond, $-O-$, or $-O-CH_2-$, where the oxygen is bonded to the Q ring and the CH_2 is bonded to the Ar ring. In one embodiment of formula (Ile), one or both X^1 is N. In one embodiment of formula (Ile), neither of R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

10 In one embodiment, the compound is represented by formula (IIf):



wherein

each X^1 is independently N or CH ;

each Z^1 is independently halo, $-OR^a$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, or $-C_{3-8}$ cycloalkyl;

15 each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

20 wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

25 R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)OR^1$,



wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

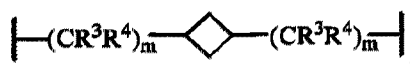
wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a, halo, cyano, -NR^aR^b and -C₃₋₈ cycloalkyl;

L² is independently a bond, O, NR^a, S, SO, or SO₂;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

5 wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo, cyano, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OC₁₋₆ haloalkyl, NR^aR^b, -C(O)R^a, -C(O)OR^a, -OC₁₋₆ alkylCN, -C(O)NR^aR^b, -NR^aC(O)R^a, -NR^aC(O)OR^a, -NR^aC(O)OR^a, -C(O)N(R^a)OR^b, -SO₂R^a,
10 -SO₂NR^aR^b, -NR^aSO₂R^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b, C₃₋₈cycloalkyl, and C₁₋₆alkylC₃₋₈cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with -OR^a, halo, cyano, -NR^aR^b or -C₃₋₈ cycloalkyl;

L^E is a bond, -O-, -S-, -SO-, -SO₂-, -(CR³R⁴)_m-, -(CR³R⁴)_mO(CR³R⁴)_m-, -(CR³R⁴)_mS(CR³R⁴)_m-,
15 -(CR³R⁴)_mNR³(CR³R⁴)_m-, -C(O)-, -(CR³R⁴)_mC(O)(CR³R⁴)_m-, -(CR³R⁴)_mC(O)NR³(CR³R⁴)_m-,
-(CR³R⁴)_mNR³C(O)(CR³R⁴)_m-, C₂₋₆ alkenylene, C₂₋₆ alkynylene,  or
;

each m is independently 0, 1, 2, 3 or 4;

R^E and R^W are each independently -NR¹R², -C₁₋₆ alkylNR¹R², -OC₁₋₆ alkylNR¹R²,
20 -C₁₋₆ alkylOC₁₋₆ alkylNR¹R², -NR^aC₁₋₆ alkylNR¹R², -C₁₋₆ alkylIN⁺R¹R²R³, -SC₁₋₆ alkylNR¹R², -C(O)NR¹R², -SO₂R^a, -(CH₂)_nSO₂NR¹R², -(CH₂)_nNR^aSO₂NR^aR^b, -SO₂NR^aC₁₋₆ alkylNR¹R², -NR^aSO₂C₁₋₆ alkylNR¹R², -(CH₂)_nC(O)NR^aSO₂NR^aR^b, -(CH₂)_nN⁺R¹R²O⁻, -(CH₂)_nP⁺R^bR^cR^d, -(CH₂)_nP⁺R^cR^dO⁻,
-(CH₂)_nP⁺O[NR^aR^b][NR^cR^d], -(CH₂)_nNR^cP(O)(OR^e)₂, -(CH₂)_nCH₂OP(O)(OR^e)(OR^d),
-(CH₂)_nOP(O)(OR^e)(OR^d), -(CH₂)_nOP(O)NR^aR^b(OR^a), or

25
$$-V^2-(CR^cR^d)_p-L^3-\textcircled{B}-\textcircled{T}_z$$
;

wherein:

V² is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹R², or NR^aSO₂;

L³ is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹R², or NR^aSO₂;

30 ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a, (CH₂)_qNR¹R², (CH₂)_qNR^aC(O)R^c or (CH₂)_qC(O)R^c;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a , $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl NR^aR^b , $-C_{1-6}$ alkylOH, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

R^1 is independently selected from H, $-C_{1-8}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{1-6}$ alkyl $C(O)OR^a$, $-C_{2-6}$ alkenyl $C(O)OR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-C(O)NR^aSO_2R^a$, and C_{1-6} alkyl C_{3-8} cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, C_{3-8} cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $NR^aC(O)OR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, $-C_{1-6}$ alkyl $C(O)NR^aSO_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}$ alkyl $NR^aC(O)R^b$;

R^2 is independently selected from H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl OR^a , $-C_{1-6}$ alkyl $C(O)OR^a$, and $-C_{2-6}$ alkenyl $C(O)OR^a$;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, C_{1-6} alkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkyl $C(O)R^a$, $-C(O)OR^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, C_{1-6} alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, $-C_{1-6}$ alkyl $SO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, and $-NR^aC(O)R^b$;

or R^1 and R^2 combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OR^a$, $-C(O)OR^a$, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl OR^a , $-C_{1-6}$ haloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^a$, C_{1-6} alkyl $C(O)R^a$, $-C_{1-6}$ alkyl $C(O)OR^a$, $-NR^aR^b$, $-C_{1-6}$ alkyl NR^aR^b , $-C(O)NR^aR^b$, $-C_{1-6}$ alkyl $C(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}$ alkyl SO_2R^a , $-SO_2NR^aR^b$, and C_{1-6} alkyl $SO_2NR^aR^b$;

R^3 is independently H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, or $-C_{2-6}$ alkenylC(O)OR^a;

R^4 is independently H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl,
5 $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, or $-C_{2-6}$ alkenylC(O)OR^a;

R^a is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^b is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl,
10 $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from $-OR^f$, $-CN$, halo, $-C_{1-6}$ alkylOR^f, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^f$, $-C_{1-6}$ alkylC(O)R^f, $-C(O)OR^f$, $-C_{1-6}$ alkylC(O)OR^f, $-NR^fR^g$, $-C_{1-6}$ alkylNR^fR^g, $-C(O)NR^fR^g$,
15 $-C_{1-6}$ alkylC(O)NR^fR^g, $-SO_2R^f$, $-C_{1-6}$ alkylSO₂R^f, $-SO_2NR^fR^g$, $-C_{1-6}$ alkylSO₂NR^fR^g, $-C(O)NR^fSO_2R^g$ and $-NR^fC(O)R^g$;

R^c is independently selected from H, OH, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^d is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl,
20 $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^e is independently selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkylNR^fR^g, $-C(O)NR^fR^g$, $-C_{1-6}$ alkylC(O)NR^fR^g, $-NH$ SO₂R^f, $-C_{1-6}$ alkylSO₂R^f, and $-C_{1-6}$ alkylSO₂NR^fR^g;

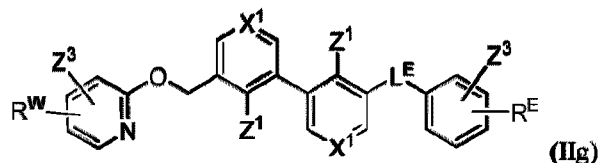
R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl,
25 $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and

R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

30 In one embodiment of formula (II^f), L^E is a bond, $-O-$, or $-O-CH_2-$, where the oxygen is bonded to the Q ring and the CH_2 is bonded to the Ar ring. In one embodiment of formula (II^f), one or both of X^1 is N. In one embodiment of formula (II^f), neither of R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formula (II^g):



wherein

each X^1 is independently N or CH;

each Z^1 is independently halo, $-OR^a$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, or $-C_{3-8}$ cycloalkyl;

- 5 each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

- 10 wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

- 15 R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)OR^1$,



wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

- 20 wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

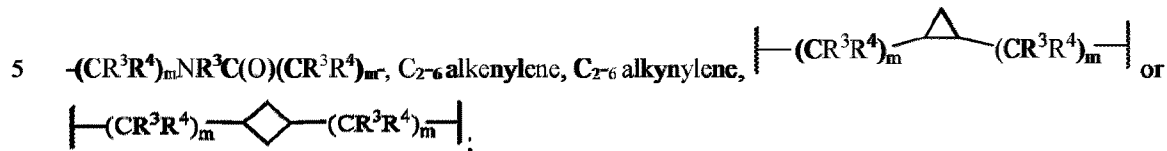
L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

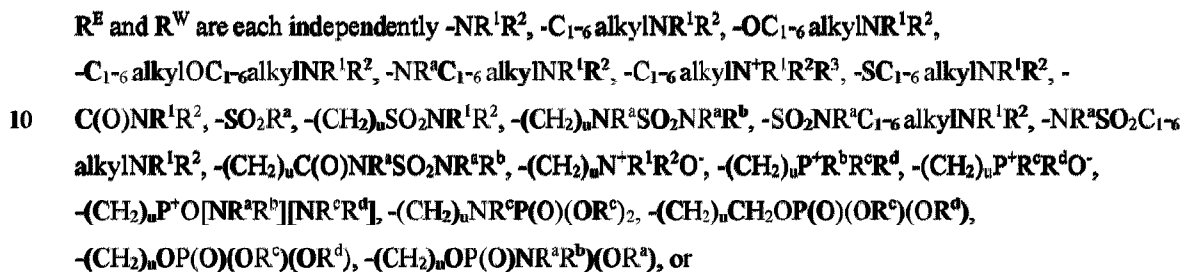
- 25 wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, C_{3-8} cycloalkyl, and C_{1-6} alkyl C_{3-8} cycloalkyl; and
- 30

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with -OR^a, halo, cyano, -NR^aR^b or -C₃₋₈ cycloalkyl

L^E is a bond, -O-, -S-, -SO-, -SO₂-, -(CR³R⁴)_m-, -(CR³R⁴)_mO(CR³R⁴)_m-, -(CR³R⁴)_mS(CR³R⁴)_m-, -(CR³R⁴)_mNR³(CR³R⁴)_m-, -C(O)-, -(CR³R⁴)_mC(O)(CR³R⁴)_m-, -(CR³R⁴)_mC(O)NR³(CR³R⁴)_m-,



each m is independently 0, 1, 2, 3 or 4;



15 wherein:

V² is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹R², or NR^aSO₂;

L³ is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹R², or NR^aSO₂;

ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a, (CH₂)_qNR¹R², (CH₂)_qNR^aC(O)R^b or (CH₂)_qC(O)R^c;

20 p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

25 wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b, halo, cyano, oxo, OR^a, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylNR^aR^b, -C₁₋₆ alkylOH, -C₃₋₈ cycloalkyl, and -C₁₋₃ alkylC₃₋₈ cycloalkyl;

provided that at least one of V², L³, ring B and T contains a nitrogen atom;

30 R¹ is independently selected from H, -C₁₋₈ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl,

$-C_{1-6}$ alkylC(O)OR^a, $-C_{2-6}$ alkenylC(O)OR^a, $-SO_2R^a$, $-SO_2NR^aR^b$, $-C(O)NR^aSO_2R^a$, and $-C_{1-6}$ alkylC₃₋₈cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkylC(O)R^a, $-C(O)OR^a$, $-C_{1-6}$ alkylC(O)OR^a, $-NR^aR^b$, $-OC(O)NR^aR^b$, $NR^aC(O)OR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkylC(O)NR^aR^b, $-SO_2R^a$, $-C_{1-6}$ alkylSO₂R^a, $-SO_2NR^aR^b$, $-C_{1-6}$ alkylSO₂NR^aR^b, $-C(O)NR^aSO_2R^b$, $-C_{1-6}$ alkylC(O)NR^aSO₂R^b, $-NR^aC(O)R^b$, and $-C_{1-6}$ alkylNR^aC(O)R^b;

10 R² is independently selected from H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, and $-C_{2-6}$ alkenylC(O)OR^a;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkylC(O)R^a, $-C(O)OR^a$, $-C_{1-6}$ alkylC(O)OR^a, $-NR^aR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkylC(O)NR^aR^b, $-SO_2R^a$, $-C_{1-6}$ alkylSO₂R^a, $-SO_2NR^aR^b$, $-C_{1-6}$ alkylSO₂NR^aR^b, $-C(O)NR^aSO_2R^b$, and $-NR^aC(O)R^b$;

or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OR^a$, $-C(O)OR^a$, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ haloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkylC(O)R^a, $-C_{1-6}$ alkylC(O)OR^a, $-NR^aR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkylC(O)NR^aR^b, $-SO_2R^a$, $-C_{1-6}$ alkylSO₂R^a, $-SO_2NR^aR^b$, and $-C_{1-6}$ alkylSO₂NR^aR^b;

25 R³ is independently H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, or $-C_{2-6}$ alkenylC(O)OR^a;

R⁴ is independently H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, or $-C_{2-6}$ alkenylC(O)OR^a;

R^a is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^b is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from $-OR^f$, $-CN$, halo, $-C_{1-6}$ alkylOR^f, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^f$, $-C_{1-6}$ alkylC(O)R^f, $-C(O)OR^f$, $-C_{1-6}$ alkylC(O)OR^f, $-NR^fR^g$, $-C_{1-6}$ alkylNR^fR^g, $-C(O)NR^fR^g$, $-C_{1-6}$ alkylC(O)NR^fR^g, $-SO_2R^f$, $-C_{1-6}$ alkylSO₂R^f, $-SO_2NR^fR^g$, $-C_{1-6}$ alkylSO₂NR^fR^g, $-C(O)NR^fSO_2R^g$ and $-NR^fC(O)R^g$;

R^c is independently selected from H, OH, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^d is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^e is independently selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkylNR^fR^g, $-C(O)NR^fR^g$, $-C_{1-6}$ alkylC(O)NR^fR^g, $-NHSO_2R^f$, $-C_{1-6}$ alkylSO₂R^f, and $-C_{1-6}$ alkylSO₂NR^fR^g;

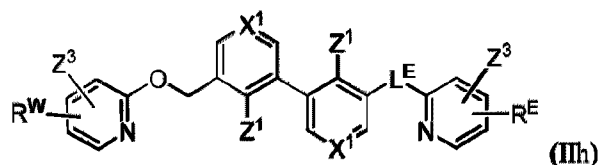
R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and

R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

In one embodiment of formula (IIg), neither of R^B or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formula (IIIh):



wherein

each X^1 is independently N or CH;

each Z^1 is independently halo, $-OR^a$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, or $-C_{3-8}$ cycloalkyl;

each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl,

$-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkylC₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

wherein the alkyl, alkenyl, alkynyl, C₃₋₈ cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo, cyano, -NR^aR^b, -C(O)R^a, -C(O)OR^a, -OC₁₋₆ alkylCN, -C(O)NR^aR^b, NR^aC(O)R^a, -NR^aC(O)OR^a, -SO₂R^a, -NR^aSO₂R^b, -SO₂NR^aR^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b and -C₃₋₈ cycloalkyl; and

5 wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently -C₁₋₆ alkylNR¹R², -OC₁₋₆ alkylNR¹R², -C₁₋₆ alkylOC₁₋₆ alkylNR¹R², -NR^aC₁₋₆ alkylNR¹R², -C₁₋₆ alkylC(O)NR¹R², -OC₁₋₆ alkylC(O)NR¹R², -OC₁₋₆ alkylC(O)OR¹,

-SC₁₋₆ alkylNR¹R², -C₁₋₆ alkylOR^a, or $L^1 - V - L^2 - \textcircled{A}$;

10 wherein: L¹ is independently a bond, O, NR^a, S, SO, or SO₂;

V is independently selected from a bond, C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a, halo, cyano, -NR^aR^b and -C₃₋₈ cycloalkyl;

L² is independently a bond, O, NR^a, S, SO, or SO₂;

15 ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo, cyano, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OC₁₋₆ haloalkyl, NR^aR^b, -C(O)R^a, -C(O)OR^a, -OC₁₋₆ alkylCN, -C(O)NR^aR^b, -NR^aC(O)R^a, -NR^aC(O)OR^a, -NR^aC(O)OR^a, -C(O)N(R^a)OR^b, -SO₂R^a, -SO₂NR^aR^b, -NR^aSO₂R^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b, C₃₋₈ cycloalkyl, and C₁₋₆ alkylC₃₋₈ cycloalkyl; and

20

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with -OR^a, halo, cyano, -NR^aR^b or -C₃₋₈ cycloalkyl

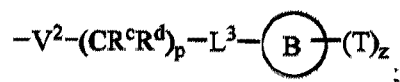
25 L^B is a bond, -O-, -S-, -SO-, -SO₂-, -(CR³R⁴)_m-, -(CR³R⁴)_mO(CR³R⁴)_m-, -(CR³R⁴)_mS(CR³R⁴)_m-, -(CR³R⁴)_mNR³(CR³R⁴)_m-, -C(O)-, -(CR³R⁴)_mC(O)(CR³R⁴)_m-, -(CR³R⁴)_mC(O)NR³(CR³R⁴)_m-,

-(CR³R⁴)_mNR³C(O)(CR³R⁴)_m-, C₂₋₆ alkenylene, C₂₋₆ alkynylene, $\left[\text{---}(\text{CR}^3\text{R}^4)_m \text{---} \triangle \text{---} (\text{CR}^3\text{R}^4)_m \text{---} \right]$ or $\left[\text{---}(\text{CR}^3\text{R}^4)_m \text{---} \diamond \text{---} (\text{CR}^3\text{R}^4)_m \text{---} \right]$;

each m is independently 0, 1, 2, 3 or 4;

30 R^E and R^W are each independently -NR¹R², -C₁₋₆ alkylNR¹R², -OC₁₋₆ alkylNR¹R², -C₁₋₆ alkylOC₁₋₆ alkylNR¹R², -NR^aC₁₋₆ alkylNR¹R², -C₁₋₆ alkylNR¹R²R³, -SC₁₋₆ alkylNR¹R², -C(O)NR¹R², -SO₂R^a, -(CH₂)_nSO₂NR¹R², -(CH₂)_nNR^aSO₂NR^aR^b, -SO₂NR^aC₁₋₆ alkylNR¹R², -NR^aSO₂C₁₋₆

alkylNR¹R², -(CH₂)_uC(O)NR^aSO₂NR^aR^b, -(CH₂)_uN⁺R¹R²O⁻, -(CH₂)_uP⁺R^bR^cR^d, -(CH₂)_uP⁺R^cR^dO⁻,
 -(CH₂)_uP⁺O[NR^aR^b][NR^cR^d], -(CH₂)_uNR^cP(O)(OR^e)₂, -(CH₂)_uCH₂OP(O)(OR^e)(OR^d),
 -(CH₂)_uOP(O)(OR^e)(OR^d), -(CH₂)_uOP(O)NR^aR^b(OR^a), or



5 wherein:

V² is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹R², or NR^aSO₂;

L³ is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹R², or NR^aSO₂;

ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently H, OR^a, (CH₂)_qNR¹R², (CH₂)_qNR^aC(O)R^c or (CH₂)_qC(O)R^c;

10 p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

15 wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b, halo, cyano, oxo, OR^a, -C₁₋₆alkyl, -C₁₋₆haloalkyl, -C₁₋₆cyanoalkyl, -C₁₋₆alkylNR^aR^b, -C₁₋₆alkylOH, -C₃₋₈cycloalkyl, and -C₁₋₃alkylC₃₋₈cycloalkyl;

provided that at least one of V², L³, ring B and T contains a nitrogen atom;

20 R¹ is independently selected from H, -C₁₋₈alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₁₋₆alkylC(O)OR^a, -C₂₋₆alkenylC(O)OR^a, -SO₂R^a, -SO₂NR^aR^b, -C(O)NR^aSO₂R^a, and C₁₋₆alkylC₃₋₈cycloalkyl;

25 wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkyl C(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, NR^aC(O)OR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and -C₁₋₆alkylNR^aC(O)R^b;

30 R² is independently selected from H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, and -C₂₋₆alkenylC(O)OR^a;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b,
 5 -C(O)NR^aR^b, C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, and -NR^aC(O)R^b;

or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl,
 10 -OR^a, -C(O)OR^a, -C₁₋₆cyanoalkyl, -C₁₋₆alkylOR^a, -C₁₋₆haloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆alkylSO₂NR^aR^b;

R³ is independently H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, or
 15 -C₂₋₆alkenylC(O)OR^a;

R⁴ is independently H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, or -C₂₋₆alkenylC(O)OR^a;

R^a is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;
 20

R^b is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, -C₁₋₆alkylOR^f, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl,
 25 -C(O)R^f, -C₁₋₆alkylC(O)R^f, -C(O)OR^f, -C₁₋₆alkylC(O)OR^f, -NR^fR^g, -C₁₋₆alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and -NR^fC(O)R^g;

R^c is independently selected from H, OH, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;
 30

R^d is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

R^e is independently selected from H, -C₁₋₆alkyl, -OC₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -OC₃₋₈cycloalkyl, -Oaryl, -Oheteroaryl, -Oheterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl,

$-\text{C}_{1-6}$ alkylaryl, $-\text{C}_{1-6}$ alkylheteroaryl, $-\text{NR}^f\text{R}^g$, $-\text{C}_{1-6}$ alkyl NR^fR^g , $-\text{C}(\text{O})\text{NR}^f\text{R}^g$, $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^f\text{R}^g$, $-\text{NH}\text{SO}_2\text{R}^f$, $-\text{C}_{1-6}$ alkyl SO_2R^f , and $-\text{C}_{1-6}$ alkyl $\text{SO}_2\text{NR}^f\text{R}^g$;

R^f is independently selected from H, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-3}$ alkyl C_{3-8} cycloalkyl, $-\text{C}_{1-6}$ alkylaryl, $-\text{C}_{1-6}$ alkylheteroaryl, and $-\text{C}_{1-6}$ alkylheterocyclyl; and

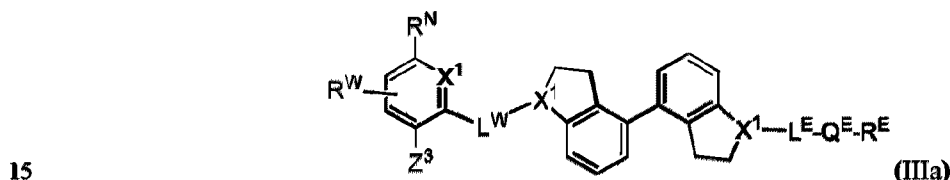
5 R^g is independently selected from H, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-3}$ alkyl C_{3-8} cycloalkyl, $-\text{C}_{1-6}$ alkylaryl, $-\text{C}_{1-6}$ alkylheteroaryl, and $-\text{C}_{1-6}$ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

In one embodiment of formula (IIg), neither of R^B or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

10 In one embodiment of formulas (IIe), (IIf), (IIg), or (IIh), L^B is $-\text{O}-\text{CH}_2-$, where the oxygen is bonded to the Q ring and the $-\text{CH}_2-$ is bonded to the Ar ring. In one embodiment of formulas (IIe), (IIf), (IIg), or (IIh), L^B is a bond. In one embodiment of formulas (IIe), (IIf), (IIg), or (IIh), L^B is $-\text{O}-\text{CH}_2-$, neither of R^B or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formula (IIIa):



wherein

each X^1 is independently N or CH;

Z^3 is halo, $-\text{OR}^a$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

20

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$ and $-\text{C}_{3-8}$ cycloalkyl; and

25

wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-\text{C}_{1-6}$ alkyl NR^1R^2 , $-\text{OC}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-\text{NR}^a\text{C}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^1$,

30 $-\text{SC}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl OR^a , or $\text{L}^1-\text{V}-\text{L}^2-\text{A}$;

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

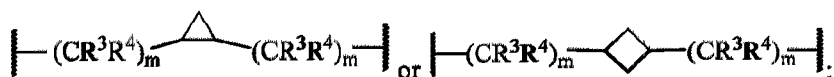
5 L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, C_{3-8} cycloalkyl, and C_{1-6} alkyl C_{3-8} cycloalkyl; and

15 wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

L^E and L^W are each independently a bond, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-(CR^3R^4)_m-$, $-(CR^3R^4)_mO(CR^3R^4)_m-$, $-(CR^3R^4)_mS(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3(CR^3R^4)_m-$, $-C(O)-$, $-(CR^3R^4)_mC(O)(CR^3R^4)_m-$, $-(CR^3R^4)_mC(O)NR^3(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3C(O)(CR^3R^4)_m-$, C_{2-6} alkenylene, C_{2-6} alkynylene,



20 wherein each m is independently 0, 1, 2, 3 or 4;

Q^E is aryl, heteroaryl, or heterocyclyl;

wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, oxo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ; and

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and further wherein the heteroaryl or

30

heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-C_{1-6}alkylINR^1R^2$, $-OC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylINR^1R^2$, $-NR^aC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)NR^1R^2$, $-OC_{1-6}alkylC(O)OR^1$,

5 $-SC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOR^a$, or $L^1-V-L^2-\textcircled{A}$;

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, and $C_{2-6}alkynyl$;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ or $-C_{3-8}cycloalkyl$;

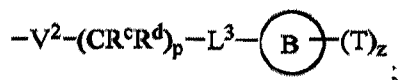
10 L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}alkyl$, $-C_{1-6}haloalkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-OC_{1-6}haloalkyl$, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}alkylCN$, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $C_{3-8}cycloalkyl$, and $C_{1-6}alkylC_{3-8}cycloalkyl$; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}cycloalkyl$;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}alkylINR^1R^2$, $-OC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylINR^1R^2$, $-NR^aC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylIN^+R^1R^2R^3$, $-SC_{1-6}alkylINR^1R^2$, $-C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_nSO_2NR^1R^2$, $-(CH_2)_nNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}alkylINR^1R^2$, $-NR^aSO_2C_{1-6}alkylINR^1R^2$, $-(CH_2)_nC(O)NR^aSO_2NR^aR^b$, $-(CH_2)_nN^+R^1R^2O^-$, $-(CH_2)_nP^+R^bR^cR^d$, $-(CH_2)_nP^+R^cR^dO^-$, $-(CH_2)_nP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_nNR^aP(O)(OR^c)_2$, $-(CH_2)_nCH_2OP(O)(OR^c)(OR^d)$, $-(CH_2)_nOP(O)(OR^c)(OR^d)$, $-(CH_2)_nOP(O)NR^aR^b(OR^a)$, or



wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

30 L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a, (CH₂)_qNR¹R², (CH₂)_qNR^aC(O)R^e or (CH₂)_qC(O)R^e;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

5 u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b, halo, cyano, oxo, OR^a, -C₁₋₆alkyl, -C₁₋₆haloalkyl, -C₁₋₆cyanoalkyl, -C₁₋₆alkylNR^aR^b, -C₁₋₆alkylOH, -C₃₋₈cycloalkyl, and -C₁₋₃alkylC₃₋₈cycloalkyl;

provided that at least one of V², L³, ring B and T contains a nitrogen atom;

R¹ is independently selected from H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₁₋₆alkylC(O)OR^a, -C₂₋₆alkenylC(O)OR^a, -SO₂R^a, -SO₂NR^aR^b, -C(O)NR^aSO₂R^a, and C₁₋₆alkylC₃₋

15 cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, NR^aC(O)OR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and -C₁₋₆alkylNR^aC(O)R^b;

20

R² is independently selected from H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, and -C₂₋₆alkenylC(O)OR^a;

25

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, and -NR^aC(O)R^b;

30

or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl,

-OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆ alkylSO₂NR^aR^b;

R³ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl,
 5 **-C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or -C₂₋₆ alkenylC(O)OR^a;**

R⁴ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or -C₂₋₆ alkenylC(O)OR^a;

10 **R^a is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;**

R^b is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S;
 15 **wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, -C₁₋₆ alkylOR^f, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^f, -C₁₋₆ alkylC(O)R^f, -C(O)OR^f, -C₁₋₆ alkylC(O)OR^f, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆ alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆ alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆ alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and -NR^fC(O)R^g;**

20 **R^c is independently selected from H, OH, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;**

R^d is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

R^e is independently selected from H, -C₁₋₆ alkyl, -OC₁₋₆alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl,
 25 **heterocyclyl, -OC₃₋₈ cycloalkyl, -Oaryl, -Oheteroaryl, -Oheterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆ alkylC(O)NR^fR^g, -NH₂SO₂R^f, -C₁₋₆ alkylSO₂R^f, and -C₁₋₆ alkylSO₂NR^fR^g;**

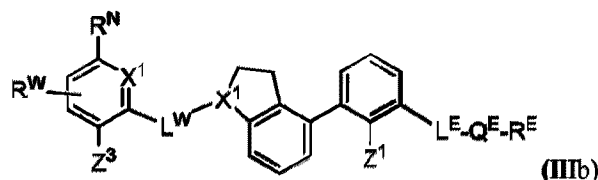
R^f is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl; and

30 **R^g is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;**

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

In one embodiment of formula (IIIa), neither of R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formula (IIIb):



wherein

each X^1 is independently N or CH;

- 5 Z^1 is halo, $-OR^a$, $-NO_2$, $-CN$, $-NR^aR^b$, $-N_3$, $-SO_2R^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-OC_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-6}$ alkyl C_{3-8} cycloalkyl;

wherein each alkyl, alkenyl, alkynyl, and cycloalkyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

- 10 Z^3 is halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

- 15 wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

- 20 R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)OR^1$, $-SC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OR^a , or



wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

- 25 wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$,

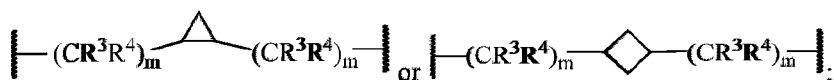
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halo, cyano, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OC₁₋₆ haloalkyl, -NR^aR^b, -C(O)R^a, -C(O)OR^a, -OC₁₋₆ alkylCN, -C(O)NR^aR^b, -NR^aC(O)R^a, -NR^aC(O)OR^a, -NR^aC(O)OR^a, -C(O)N(R^a)OR^b, -SO₂R^a, -SO₂NR^aR^b, -NR^aSO₂R^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b, C₃₋₈ cycloalkyl, and C₁₋₆alkylC₃₋₈ cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with -OR^a, halo, cyano, -NR^aR^b or -C₃₋₈ cycloalkyl;

L^E and L^W are each independently a bond, -O-, -S-, -SO-, -SO₂-, -(CR³R⁴)_m-, -(CR³R⁴)_mO(CR³R⁴)_m-, -(CR³R⁴)_mS(CR³R⁴)_m-, -(CR³R⁴)_mNR³(CR³R⁴)_m-, -C(O)-, -(CR³R⁴)_mC(O)(CR³R⁴)_m-,

10 -(CR³R⁴)_mC(O)NR³(CR³R⁴)_m-, -(CR³R⁴)_mNR³C(O)(CR³R⁴)_m-, C₂₋₆ alkenylene, C₂₋₆ alkynylene,



wherein each m is independently 0, 1, 2, 3 or 4;

Q^E is aryl, heteroaryl, or heterocyclyl;

wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups

15 independently selected from halo, oxo, -OR^a, -N₃, -NO₂, -CN, -NR¹R², -SO₂R^a, -SO₂NR^aR^b, -NR^aSO₂R^a, -NR^aC(O)R^a, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -NR^aC(O)OR^a, -NR^aC(O)NR¹R², -OC(O)NR^aR^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OC₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₁₋₆ alkylC₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N, and

20 wherein the alkyl, alkenyl, alkynyl, C₃₋₈ cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo, cyano, -NR^aR^b, -C(O)R^a, -C(O)OR^a, -OC₁₋₆ alkylCN, -C(O)NR^aR^b, -NR^aC(O)R^a, -NR^aC(O)OR^a, -SO₂R^a, -NR^aSO₂R^b, -SO₂NR^aR^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b and -C₃₋₈ cycloalkyl; and further wherein the

25 heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently -C₁₋₆ alkylNR¹R², -OC₁₋₆ alkylNR¹R², -C₁₋₆ alkylOC₁₋₆ alkylNR¹R², -NR^aC₁₋₆ alkylNR¹R², -C₁₋₆ alkylC(O)NR¹R², -OC₁₋₆ alkylC(O)NR¹R², -OC₁₋₆ alkylC(O)OR¹,



30

wherein: L¹ is independently a bond, O, NR^a, S, SO, or SO₂;

V is independently selected from a bond, C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a, halo, cyano, -NR^aR^b or -C₃₋₈ cycloalkyl;

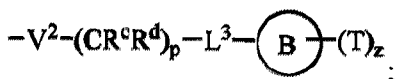
L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, C_{3-8} cycloalkyl, and C_{1-6} alkyl C_{3-8} cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $IN^+R^1R^2R^3$, $-SC_{1-6}$ alkyl NR^1R^2 , $-C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_uSO_2NR^1R^2$, $-(CH_2)_uNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}$ alkyl NR^1R^2 , $-NR^aSO_2C_{1-6}$ alkyl NR^1R^2 , $-(CH_2)_uC(O)NR^aSO_2NR^aR^b$, $-(CH_2)_uN^+R^1R^2O^-$, $-(CH_2)_uP^+R^bR^cR^d$, $-(CH_2)_uP^+R^cR^dO^-$, $-(CH_2)_uP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_uNR^cP(O)(OR^e)_2$, $-(CH_2)_uCH_2OP(O)(OR^e)(OR^d)$, $-(CH_2)_uOP(O)(OR^e)(OR^d)$, $-(CH_2)_uOP(O)NR^aR^b(OR^e)$, or



wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a , $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^e$ or $(CH_2)_qC(O)R^e$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a , $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkyl NR^aR^b , $-C_{1-6}$ alkylOH, $-C_{3-8}$ cycloalkyl, and $-C_{1-3}$ alkyl C_{3-8} cycloalkyl;

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

R¹ is independently selected from H, -C₁₋₈ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₁₋₆ alkylC(O)OR^a, -C₂₋₆ alkenylC(O)OR^a, -SO₂R^a, -SO₂NR^aR^b, -C(O)NR^aSO₂R^a, and C₁₋₆ alkylC₃₋₈cycloalkyl;

- 5 wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆ alkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C(O)OR^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, NR^aC(O)OR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆ alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆ alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and -C₁₋₆ alkylNR^aC(O)R^b;
- 10

R² is independently selected from H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, and -C₂₋₆ alkenylC(O)OR^a;

- 15 wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆ alkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C(O)OR^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆ alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, and -NR^aC(O)R^b;
- 20

or **R¹** and **R²** combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆ alkylSO₂NR^aR^b;

25

R³ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or -C₂₋₆ alkenylC(O)OR^a;

- 30 **R⁴** is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or -C₂₋₆ alkenylC(O)OR^a;

R^a is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

R^b is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from $-OR^f$, $-CN$,

5 halo, $-C_{1-6}$ alkyl OR^f , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^f$, $-C_{1-6}$ alkyl $C(O)R^f$, $-C(O)OR^f$, $-C_{1-6}$ alkyl $C(O)OR^f$, $-NR^fR^g$, $-C_{1-6}$ alkyl NR^fR^g , $-C(O)NR^fR^g$, $-C_{1-6}$ alkyl $C(O)NR^fR^g$, $-SO_2R^f$, $-C_{1-6}$ alkyl SO_2R^f , $-SO_2NR^fR^g$, $-C_{1-6}$ alkyl $SO_2NR^fR^g$, $-C(O)NR^fSO_2R^g$ and $-NR^fC(O)R^g$;

10 R^c is independently selected from H, OH, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^d is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

15 R^e is independently selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkyl NR^fR^g , $-C(O)NR^fR^g$, $-C_{1-6}$ alkyl $C(O)NR^fR^g$, $-NH$ SO_2R^f , $-C_{1-6}$ alkyl SO_2R^f , and $-C_{1-6}$ alkyl $SO_2NR^fR^g$;

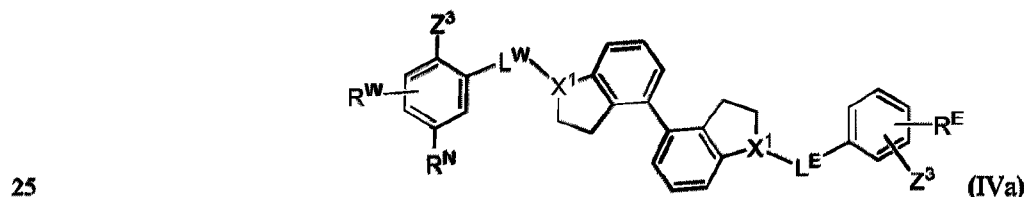
R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and

20 R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

In one embodiment of formula (IIIb), none of Q^E , R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formula (IVa):



wherein

each X^1 is independently N or CH;

each Z^1 is independently halo, $-OR^a$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, or $-C_{3-8}$ cycloalkyl;

30 each Z^2 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$,

$-\text{NR}^a\text{SO}_2\text{NR}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^b$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^b$ and $-\text{C}_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-\text{C}_{1-6}$ alkyl NR^1R^2 , $-\text{OC}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-\text{NR}^a\text{C}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^1$,

$-\text{SC}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl OR^a , or $\text{L}^1-\text{V}-\text{L}^2-\text{A}$;

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-\text{NR}^a\text{R}^b$, or $-\text{C}_{3-8}$ cycloalkyl;

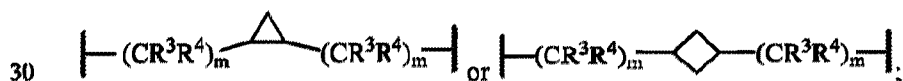
L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ haloalkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ haloalkyl, NR^aR^b , $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{N}(\text{R}^a)\text{OR}^b$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^b$, C_{3-8} cycloalkyl, and C_{1-6} alkyl C_{3-8} cycloalkyl; and

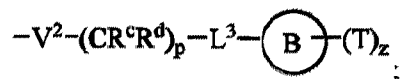
wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, or $-\text{C}_{3-8}$ cycloalkyl;

L^E and L^W are each independently a bond, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{O}(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{S}(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{NR}^3(\text{CR}^3\text{R}^4)_m-$, $-\text{C}(\text{O})-$, $-(\text{CR}^3\text{R}^4)_m\text{C}(\text{O})(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{C}(\text{O})\text{NR}^3(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{NR}^3\text{C}(\text{O})(\text{CR}^3\text{R}^4)_m-$, C_{2-6} alkenylene, C_{2-6} alkynylene,



each m is independently 0, 1, 2, 3 or 4;

- R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}alkylINR^1R^2$, $-OC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylINR^1R^2$, $-NR^aC_{1-6}alkylINR^1R^2$, $-C_{1-6}alkylIN^+R^1R^2R^3$, $-SC_{1-6}alkylINR^1R^2$, $-C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_uSO_2NR^1R^2$, $-(CH_2)_uNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}alkylINR^1R^2$, $-NR^aSO_2C_{1-6}alkylINR^1R^2$, $-(CH_2)_uC(O)NR^aSO_2NR^aR^b$, $-(CH_2)_uN^+R^1R^2O^-$, $-(CH_2)_uP^+R^bR^cR^d$, $-(CH_2)_uP^+R^cR^dO^-$,
 5 $-(CH_2)_uP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_uNR^cP(O)(OR^e)_2$, $-(CH_2)_uCH_2OP(O)(OR^e)(OR^d)$, $-(CH_2)_uOP(O)(OR^e)(OR^d)$, $-(CH_2)_uOP(O)NR^aR^b(OR^a)$, or



wherein:

- V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;
 10 L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;
 ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a , $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^e$, or $(CH_2)_qC(O)R^e$;
 p is independently 0, 1, 2, 3, 4, or 5;
 q is independently 0, 1, 2, 3, 4, or 5;
 15 u is 0, 1, 2, 3, or 4;
 z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with

- 1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a , $-C_{1-6}alkyl$, $-C_{1-6}haloalkyl$, $-C_{1-6}cyanoalkyl$, $-C_{1-6}alkylINR^aR^b$, $-C_{1-6}alkylOH$, $-C_{3-8}cycloalkyl$, and $-C_{1-3}alkylC_{3-8}cycloalkyl$;
 20

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

- R^1 is independently selected from H, $-C_{1-8}alkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-C_{3-6}cycloalkyl$, aryl, heteroaryl, heterocyclyl, $-C_{1-6}alkylaryl$, $-C_{1-6}alkylheteroaryl$, $-C_{1-6}alkylheterocyclyl$, $-C_{1-6}alkylC(O)OR^a$, $-C_{2-6}alkenylC(O)OR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-C(O)NR^aSO_2R^a$, and $C_{1-6}alkylC_{3-8}cycloalkyl$;
 25

- wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, $C_{1-6}alkyl$, $-C_{1-6}alkylOR^a$, $-C_{1-6}cyanoalkyl$, $-C_{1-6}haloalkyl$, $C_{3-8}cycloalkyl$, $-C_{1-3}alkylC_{3-8}cycloalkyl$, $-C(O)R^a$, $-C_{1-6}alkylC(O)R^a$, $-C(O)OR^a$, $-C_{1-6}alkylC(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $NR^aC(O)OR^b$, $-C_{1-6}alkylINR^aR^b$, $-C(O)NR^aR^b$, $-C_{1-6}alkylC(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}alkylSO_2R^a$, $-SO_2NR^aR^b$, $-C_{1-6}alkylSO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, $-C_{1-6}alkylC(O)NR^aSO_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}alkylINR^aC(O)R^b$;
 30

R² is independently selected from H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, and -C₂₋₆alkenylC(O)OR^a;

5 wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b and -NR^aC(O)R^b;

10 or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -OR^a, -C(O)OR^a, -C₁₋₆cyanoalkyl, -C₁₋₆alkylOR^a, -C₁₋₆haloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b,
15 -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆alkylSO₂NR^aR^b;

R³ is independently H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, or -C₂₋₆alkenylC(O)OR^a;

R⁴ is independently H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, or -C₂₋₆alkenylC(O)OR^a;

R^a is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

R^b is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

25 or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, -C₁₋₆alkylOR^f, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^f, -C₁₋₆alkylC(O)R^f, -C(O)OR^f, -C₁₋₆alkylC(O)OR^f, -NR^fR^g, -C₁₋₆alkylNR^fR^g, -C(O)NR^fR^g,
30 -C₁₋₆alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and -NR^fC(O)R^g;

R^c is independently selected from H, OH, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

R^d is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

R^e is independently selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkyl NR^fR^g , $-C(O)NR^fR^g$, $-C_{1-6}$ alkyl $C(O)NR^fR^g$, $-NHSO_2R^f$, $-C_{1-6}$ alkyl SO_2R^f , and $-C_{1-6}$ alkyl $SO_2NR^fR^g$;

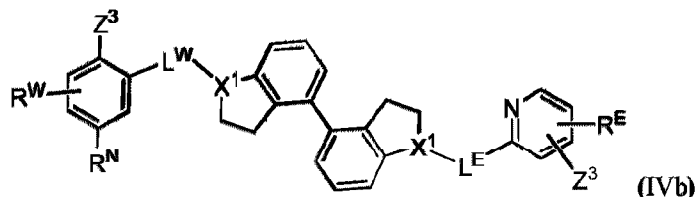
- 5 R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and

R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

- 10 In one embodiment of formula (IVa), neither of R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formulas (IVb):



wherein

- 15 each X^1 is independently N or CH_2 ;
- each Z^1 is independently halo, $-OR^a$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, or $-C_{3-8}$ cycloalkyl;
- each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl,
- 20 $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and

25 wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)OR^1$,

$-SC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OR^a , or

$L^1-V-L^2-\text{A}$;

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$, or $-C_{3-8}$ cycloalkyl;

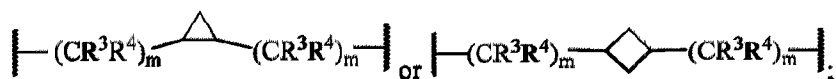
5 L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, C_{3-8} cycloalkyl, and C_{1-6} alkyl C_{3-8} cycloalkyl; and

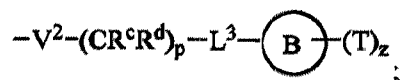
15 wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$, or $-C_{3-8}$ cycloalkyl

L^E and L^W are each independently a bond, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-(CR^3R^4)_m-$, $-(CR^3R^4)_mO(CR^3R^4)_m-$, $-(CR^3R^4)_mS(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3(CR^3R^4)_m-$, $-C(O)-$, $-(CR^3R^4)_mC(O)(CR^3R^4)_m-$, $-(CR^3R^4)_mC(O)NR^3(CR^3R^4)_m-$, $-(CR^3R^4)_mNR^3C(O)(CR^3R^4)_m-$, C_{2-6} alkenylene, C_{2-6} alkynylene,



20 each m is independently 0, 1, 2, 3 or 4;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $IN^+R^1R^2R^3$, $-SC_{1-6}$ alkyl NR^1R^2 , $-C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_nSO_2NR^1R^2$, $-(CH_2)_nNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}$ alkyl NR^1R^2 , $-NR^aSO_2C_{1-6}$ alkyl NR^1R^2 , $-(CH_2)_nC(O)NR^aSO_2NR^aR^b$, $-(CH_2)_nN^+R^1R^2O^-$, $-(CH_2)_nP^+R^bR^cR^d$, $-(CH_2)_nP^+R^cR^dO^-$, $-(CH_2)_nP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_nNR^cP(O)(OR^e)_2$, $-(CH_2)_nCH_2OP(O)(OR^e)(OR^d)$, $-(CH_2)_nOP(O)(OR^e)(OR^d)$, $-(CH_2)_nOP(O)NR^aR^b(OR^a)$, or



wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

30 L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;

ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a, (CH₂)_qNR¹R², (CH₂)_qNR^aC(O)R^e, or (CH₂)_qC(O)R^e;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

5 u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b, halo, cyano, oxo, OR^a, -C₁₋₆alkyl, -C₁₋₆haloalkyl, -C₁₋₆cyanoalkyl, -C₁₋₆alkylNR^aR^b, -C₁₋₆alkylOH, -C₃₋₈cycloalkyl, and -C₁₋₃alkylC₃₋₈cycloalkyl;

provided that at least one of V², L³, ring B and T contains a nitrogen atom;

R¹ is independently selected from H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₁₋₆alkylC(O)OR^a, -C₂₋₆alkenylC(O)OR^a, -SO₂R^a, -SO₂NR^aR^b, -C(O)NR^aSO₂R^a, and

15 -C₁₋₆alkylC₃₋₈cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, NR^aC(O)OR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and -C₁₋₆alkylNR^aC(O)R^b;

R² is independently selected from H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, and -C₂₋₆alkenylC(O)OR^a;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b and -NR^aC(O)R^b;

or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl,

-OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆ alkylSO₂NR^aR^b;

R³ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl,
5 -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or
-C₂₋₆ alkenylC(O)OR^a;

R⁴ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or
-C₂₋₆ alkenylC(O)OR^a;

10 R^a is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

R^b is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S;
15 wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN,
halo, -C₁₋₆ alkylOR^f, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl,
-C(O)R^f, -C₁₋₆ alkylC(O)R^f, -C(O)OR^f, -C₁₋₆ alkylC(O)OR^f, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g,
-C₁₋₆ alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆ alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆ alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and
-NR^fC(O)R^g;

20 R^c is independently selected from H, OH, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

R^d is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

R^e is independently selected from H, -C₁₋₆ alkyl, -OC₁₋₆alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl,
25 heterocyclyl, -OC₃₋₈ cycloalkyl, -Oaryl, -Oheteroaryl, -Oheterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl,
-C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆ alkylC(O)NR^fR^g,
-NH₂SO₂R^f, -C₁₋₆ alkylSO₂R^f, and -C₁₋₆ alkylSO₂NR^fR^g;

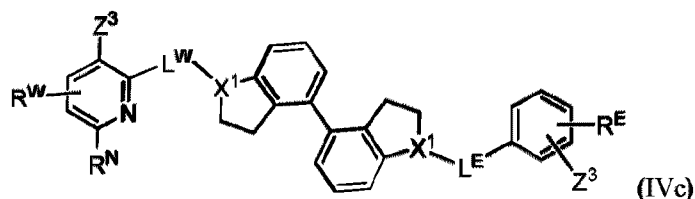
R^f is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl; and

30 R^g is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
-C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

In one embodiment of formula (IVb), neither of R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formula (IVc):



wherein

each X^1 is independently N or CH;

5 each Z^1 is independently halo, $-OR^a$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, or $-C_{3-8}$ cycloalkyl;

each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

10 wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

15 R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)OR^1$,

$-SC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OR^a , or $L^1-V-L^2-\textcircled{A}$;

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

20 V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$, or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

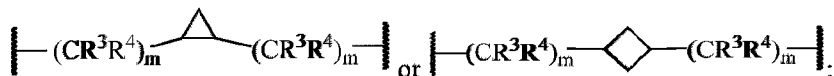
ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

25 wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$,

$-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $\text{C}_3\text{-8 cycloalkyl}$,
and $\text{C}_{1-6}\text{alkylC}_{3-8}\text{cycloalkyl}$; and

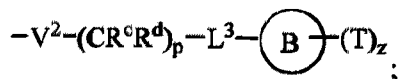
wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, or $-\text{C}_{3-8}\text{cycloalkyl}$;

- 5 L^E and L^W are each independently a bond, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{O}(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{S}(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{NR}^3(\text{CR}^3\text{R}^4)_m-$, $-\text{C}(\text{O})-$, $-(\text{CR}^3\text{R}^4)_m\text{C}(\text{O})(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{C}(\text{O})\text{NR}^3(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{NR}^3\text{C}(\text{O})(\text{CR}^3\text{R}^4)_m-$, $\text{C}_{2-6}\text{ alkenylene}$, $\text{C}_{2-6}\text{ alkynylene}$,



each m is independently 0, 1, 2, 3 or 4;

- 10 R^E and R^W are each independently $-\text{NR}^1\text{R}^2$, $-\text{C}_{1-6}\text{alkylNR}^1\text{R}^2$, $-\text{OC}_{1-6}\text{alkylNR}^1\text{R}^2$, $-\text{C}_{1-6}\text{alkylOC}_{1-6}\text{alkylNR}^1\text{R}^2$, $-\text{NR}^a\text{C}_{1-6}\text{alkylNR}^1\text{R}^2$, $-\text{C}_{1-6}\text{alkylNR}^1\text{R}^2\text{R}^3$, $-\text{SC}_{1-6}\text{alkylNR}^1\text{R}^2$, $-\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-(\text{CH}_2)_u\text{SO}_2\text{NR}^1\text{R}^2$, $-(\text{CH}_2)_u\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{C}_{1-6}\text{alkylNR}^1\text{R}^2$, $-\text{NR}^a\text{SO}_2\text{C}_{1-6}\text{alkylNR}^1\text{R}^2$, $-(\text{CH}_2)_u\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-(\text{CH}_2)_u\text{N}^+\text{R}^1\text{R}^2\text{O}^-$, $-(\text{CH}_2)_u\text{P}^+\text{R}^b\text{R}^c\text{R}^d$, $-(\text{CH}_2)_u\text{P}^+\text{R}^c\text{R}^d\text{O}^-$, $-(\text{CH}_2)_u\text{P}^+\text{O}[\text{NR}^a\text{R}^b][\text{NR}^c\text{R}^d]$, $-(\text{CH}_2)_u\text{NR}^c\text{P}(\text{O})(\text{OR}^e)_2$, $-(\text{CH}_2)_u\text{CH}_2\text{OP}(\text{O})(\text{OR}^e)(\text{OR}^d)$,
15 $-(\text{CH}_2)_u\text{OP}(\text{O})(\text{OR}^e)(\text{OR}^d)$, $-(\text{CH}_2)_u\text{OP}(\text{O})\text{NR}^a\text{R}^b(\text{OR}^a)$, or



wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $\text{C}(\text{O})\text{NR}^a$, $\text{NR}^a\text{C}(\text{O})$, $\text{SO}_2\text{NR}^1\text{R}^2$, or NR^aSO_2 ;

L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $\text{C}(\text{O})\text{NR}^a$, $\text{NR}^a\text{C}(\text{O})$, $\text{SO}_2\text{NR}^1\text{R}^2$, or NR^aSO_2 ;

- 20 ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a , $(\text{CH}_2)_q\text{NR}^1\text{R}^2$, $(\text{CH}_2)_q\text{NR}^a\text{C}(\text{O})\text{R}^e$, or $(\text{CH}_2)_q\text{C}(\text{O})\text{R}^e$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

- 25 z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a , $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{1-6}\text{haloalkyl}$, $-\text{C}_{1-6}\text{cyanoalkyl}$, $-\text{C}_{1-6}\text{alkylNR}^a\text{R}^b$, $-\text{C}_{1-6}\text{alkylOH}$, $-\text{C}_{3-8}\text{cycloalkyl}$, and $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$;

- 30 provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

R¹ is independently selected from H, -C₁₋₈ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₁₋₆ alkylC(O)OR^a, -C₂₋₆ alkenylC(O)OR^a, -SO₂R^a, -SO₂NR^aR^b, -C(O)NR^aSO₂R^a, and -C₁₋₆ alkylC₃₋₈cycloalkyl;

- 5 wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, NR^aC(O)OR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and -C₁₋₆alkylNR^aC(O)R^b;
- 10

R² is independently selected from H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, and -C₂₋₆ alkenylC(O)OR^a;

- 15 wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b and -NR^aC(O)R^b;
- 20

- or **R¹** and **R²** combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆alkylSO₂NR^aR^b;
- 25

R³ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or -C₂₋₆ alkenylC(O)OR^a;

- 30 **R⁴** is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or -C₂₋₆ alkenylC(O)OR^a;

R^a is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

R^b is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from $-OR^f$, $-CN$,

5 halo, $-C_{1-6}$ alkyl OR^f , $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C(O)R^f$, $-C_{1-6}$ alkyl $C(O)R^f$, $-C(O)OR^f$, $-C_{1-6}$ alkyl $C(O)OR^f$, $-NR^fR^g$, $-C_{1-6}$ alkyl NR^fR^g , $-C(O)NR^fR^g$, $-C_{1-6}$ alkyl $C(O)NR^fR^g$, $-SO_2R^f$, $-C_{1-6}$ alkyl SO_2R^f , $-SO_2NR^fR^g$, $-C_{1-6}$ alkyl $SO_2NR^fR^g$, $-C(O)NR^fSO_2R^g$ and $-NR^fC(O)R^g$;

R^c is independently selected from H, OH, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^d is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^e is independently selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkyl NR^fR^g , $-C(O)NR^fR^g$, $-C_{1-6}$ alkyl $C(O)NR^fR^g$, $-NH$ SO_2R^f , $-C_{1-6}$ alkyl SO_2R^f , and $-C_{1-6}$ alkyl $SO_2NR^fR^g$;

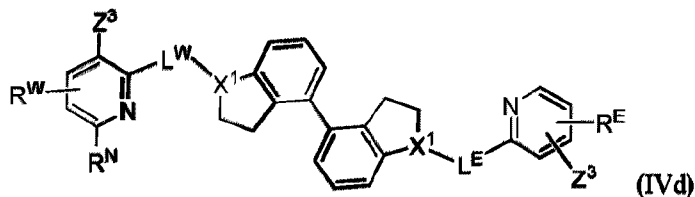
R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and

R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

In one embodiment of formula (IVc), neither of R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formula or (IVd):



25

wherein

each X^1 is independently N or CH;

each Z^1 is independently halo, $-OR^a$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, or $-C_{3-8}$ cycloalkyl;

each Z^2 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$,

30

$-\text{NR}^a\text{SO}_2\text{NR}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^b$, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ alkyl, $-\text{C}_{3-8}$ cycloalkyl, $-\text{C}_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^b$ and $-\text{C}_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-\text{C}_{1-6}$ alkyl NR^1R^2 , $-\text{OC}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-\text{NR}^a\text{C}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}$ alkyl $\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}$ alkyl $\text{C}(\text{O})\text{OR}^1$,

$-\text{SC}_{1-6}$ alkyl NR^1R^2 , $-\text{C}_{1-6}$ alkyl OR^a , or $\text{L}^1-\text{V}-\text{L}^2-\text{A}$;

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-\text{NR}^a\text{R}^b$, or $-\text{C}_{3-8}$ cycloalkyl;

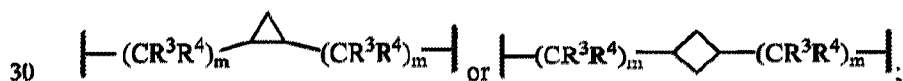
L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{C}_{1-6}$ alkyl, $-\text{C}_{1-6}$ haloalkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, $-\text{OC}_{1-6}$ haloalkyl, NR^aR^b , $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}$ alkylCN, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{N}(\text{R}^a)\text{OR}^b$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^b$, C_{3-8} cycloalkyl, and C_{1-6} alkyl C_{3-8} cycloalkyl; and

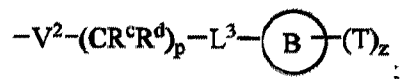
wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, or $-\text{C}_{3-8}$ cycloalkyl

L^E and L^W are each independently a bond, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{O}(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{S}(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{NR}^3(\text{CR}^3\text{R}^4)_m-$, $-\text{C}(\text{O})-$, $-(\text{CR}^3\text{R}^4)_m\text{C}(\text{O})(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{C}(\text{O})\text{NR}^3(\text{CR}^3\text{R}^4)_m-$, $-(\text{CR}^3\text{R}^4)_m\text{NR}^3\text{C}(\text{O})(\text{CR}^3\text{R}^4)_m-$, C_{2-6} alkenylene, C_{2-6} alkynylene,



each m is independently 0, 1, 2, 3 or 4;

- R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}alkylNR^1R^2$, $-OC_{1-6}alkylNR^1R^2$, $-C_{1-6}alkylOC_{1-6}alkylNR^1R^2$, $-NR^aC_{1-6}alkylNR^1R^2$, $-C_{1-6}alkylIN^+R^1R^2R^3$, $-SC_{1-6}alkylNR^1R^2$, $-C(O)NR^1R^2$, $-SO_2R^a$, $-(CH_2)_uSO_2NR^1R^2$, $-(CH_2)_uNR^aSO_2NR^aR^b$, $-SO_2NR^aC_{1-6}alkylNR^1R^2$, $-NR^aSO_2C_{1-6}alkylNR^1R^2$, $-(CH_2)_uC(O)NR^aSO_2NR^aR^b$, $-(CH_2)_uN^+R^1R^2O^-$, $-(CH_2)_uP^+R^bR^cR^d$, $-(CH_2)_uP^+R^cR^dO^-$, $-(CH_2)_uP^+O[NR^aR^b][NR^cR^d]$, $-(CH_2)_uNR^cP(O)(OR^e)_2$, $-(CH_2)_uCH_2OP(O)(OR^e)(OR^d)$, $-(CH_2)_uOP(O)(OR^e)(OR^d)$, $-(CH_2)_uOP(O)NR^aR^b(OR^a)$, or



wherein:

- V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;
 L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $C(O)NR^a$, $NR^aC(O)$, $SO_2NR^1R^2$, or NR^aSO_2 ;
 ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a , $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^e$, or $(CH_2)_qC(O)R^e$;
 p is independently 0, 1, 2, 3, 4, or 5;
 q is independently 0, 1, 2, 3, 4, or 5;
 u is 0, 1, 2, 3, or 4;
 z is 0, 1, 2, or 3; and

- wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a , $-C_{1-6}alkyl$, $-C_{1-6}haloalkyl$, $-C_{1-6}cyanoalkyl$, $-C_{1-6}alkylNR^aR^b$, $-C_{1-6}alkylOH$, $-C_{3-8}cycloalkyl$, and $-C_{1-3}alkylC_{3-8}cycloalkyl$;

provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

- R^1 is independently selected from H, $-C_{1-8}alkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-C_{3-6}cycloalkyl$, aryl, heteroaryl, heterocyclyl, $-C_{1-6}alkylaryl$, $-C_{1-6}alkylheteroaryl$, $-C_{1-6}alkylheterocyclyl$, $-C_{1-6}alkylC(O)OR^a$, $-C_{2-6}alkenylC(O)OR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-C(O)NR^aSO_2R^a$, and $-C_{1-6}alkylC_{3-8}cycloalkyl$;

- wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-OR^a$, $-CN$, halo, $C_{1-6}alkyl$, $-C_{1-6}alkylOR^a$, $-C_{1-6}cyanoalkyl$, $-C_{1-6}haloalkyl$, $C_{3-8}cycloalkyl$, $-C_{1-3}alkylC_{3-8}cycloalkyl$, $-C(O)R^a$, $-C_{1-6}alkylC(O)R^a$, $-C(O)OR^a$, $-C_{1-6}alkylC(O)OR^a$, $-NR^aR^b$, $-OC(O)NR^aR^b$, $NR^aC(O)OR^b$, $-C_{1-6}alkylNR^aR^b$, $-C(O)NR^aR^b$, $-C_{1-6}alkylC(O)NR^aR^b$, $-SO_2R^a$, $-C_{1-6}alkylSO_2R^a$, $-SO_2NR^aR^b$, $-C_{1-6}alkylSO_2NR^aR^b$, $-C(O)NR^aSO_2R^b$, $-C_{1-6}alkylC(O)NR^aSO_2R^b$, $-NR^aC(O)R^b$, and $-C_{1-6}alkylNR^aC(O)R^b$;

R^2 is independently selected from H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, and $-C_{2-6}$ alkenylC(O)OR^a;

5 wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C_{1-6} alkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkylC(O)R^a, $-C(O)OR^a$, $-C_{1-6}$ alkylC(O)OR^a, $-NR^aR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, C_{1-6} alkylC(O)NR^aR^b, $-SO_2R^a$, $-C_{1-6}$ alkylSO₂R^a, $-SO_2NR^aR^b$, $-C_{1-6}$ alkylSO₂NR^aR^b, $-C(O)NR^aSO_2R^b$ and $-NR^aC(O)R^b$;

10 or R^1 and R^2 combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, -OR^a, $-C(O)OR^a$, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ alkylOR^a, $-C_{1-6}$ haloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^a$, $-C_{1-6}$ alkylC(O)R^a, $-C_{1-6}$ alkylC(O)OR^a, $-NR^aR^b$, $-C_{1-6}$ alkylNR^aR^b, $-C(O)NR^aR^b$, $-C_{1-6}$ alkylC(O)NR^aR^b, $-SO_2R^a$, $-C_{1-6}$ alkylSO₂R^a, $-SO_2NR^aR^b$, and C_{1-6} alkylSO₂NR^aR^b;

R^3 is independently H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, or $-C_{2-6}$ alkenylC(O)OR^a;

20 R^4 is independently H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, or $-C_{2-6}$ alkenylC(O)OR^a;

R^a is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

25 R^b is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, $-C_{1-6}$ alkylOR^f, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^f$, $-C_{1-6}$ alkylC(O)R^f, $-C(O)OR^f$, $-C_{1-6}$ alkylC(O)OR^f, $-NR^fR^g$, $-C_{1-6}$ alkylNR^fR^g, $-C(O)NR^fR^g$, $-C_{1-6}$ alkylC(O)NR^fR^g, $-SO_2R^f$, $-C_{1-6}$ alkylSO₂R^f, $-SO_2NR^fR^g$, $-C_{1-6}$ alkylSO₂NR^fR^g, $-C(O)NR^fSO_2R^g$ and $-NR^fC(O)R^g$;

R^c is independently selected from H, OH, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

35 R^d is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^e is independently selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkyl NR^fR^g , $-C(O)NR^fR^g$, $-C_{1-6}$ alkyl $C(O)NR^fR^g$, $-NHSO_2R^f$, $-C_{1-6}$ alkyl SO_2R^f , and $-C_{1-6}$ alkyl $SO_2NR^fR^g$;

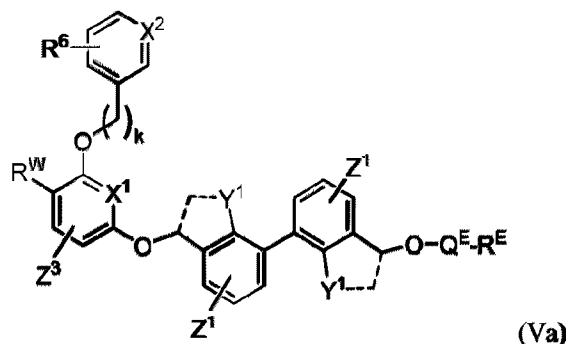
- 5 R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and

R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

- 10 In one embodiment of formula (IVd), neither of R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formula or (Va):



wherein

- 15 the dotted lines are optionally a single bond or absent, such that when the dotted lines are absent, each Y^1 is independently halo, $-OR^a$, $-NO_2$, $-CN$, $-NR^aR^b$, $-N_3$, $-SO_2R^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-OC_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-6}$ alkyl C_{3-8} cycloalkyl;

wherein each alkyl, alkenyl, alkynyl, and cycloalkyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

- 20 or the dotted lines are single bonds and Y^1 is CH_2 , such that they form a fused 5-membered ring;

k is 0, 1, 2, 3, 4, 5, or 6;

each X^1 is independently N or CH;

X^2 is N or CH;

each Z^1 is independently halo, $-OR^a$, $-NO_2$, $-CN$, $-NR^aR^b$, $-N_3$, $-SO_2R^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl,

- 25 $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-OC_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-6}$ alkyl C_{3-8} cycloalkyl;

wherein each alkyl, alkenyl, alkynyl, and cycloalkyl is optionally substituted with 1 to 4 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo, and cyano;

each Z³ is independently halo, -OR^a, -N₃, -NO₂, -CN, -NR¹R², -SO₂R^a, -SO₂NR^aR^b, -NR^aSO₂R^a, -NR^aC(O)R^a, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -NR^aC(O)OR^a, -NR^aC(O)NR¹R², -OC(O)NR^aR^b,
 5 -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OC₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₁₋₆ alkylC₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N;

wherein the alkyl, alkenyl, alkynyl, C₃₋₈ cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo, cyano, -NR^aR^b, -C(O)R^a, -C(O)OR^a, -OC₁₋₆ alkylCN, -C(O)NR^aR^b, NR^aC(O)R^a, -NR^aC(O)OR^a,
 10 -SO₂R^a, -NR^aSO₂R^b, -SO₂NR^aR^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b and -C₃₋₈ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently -C₁₋₆ alkylNR¹R², -OC₁₋₆ alkylNR¹R², -C₁₋₆ alkylOC₁₋₆ alkylNR¹R², -NR^aC₁₋₆ alkylNR¹R², -C₁₋₆ alkylC(O)NR¹R², -OC₁₋₆ alkylC(O)NR¹R², -OC₁₋₆ alkylC(O)OR¹,

15 -SC₁₋₆ alkylNR¹R², -C₁₋₆ alkylOR^a, or $L^1-V-L^2-\textcircled{A}$;

wherein: L¹ is independently a bond, O, NR^a, S, SO, or SO₂;

V is independently selected from a bond, C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a, halo, cyano, -NR^aR^b, or -C₃₋₈ cycloalkyl;

20 L² is independently a bond, O, NR^a, S, SO, or SO₂;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo, cyano, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OC₁₋₆ haloalkyl, NR^aR^b, -C(O)R^a, -C(O)OR^a, -OC₁₋₆ alkylCN, -C(O)NR^aR^b,
 25 -NR^aC(O)R^a, -NR^aC(O)OR^a, -NR^aC(O)OR^a, -C(O)N(R^a)OR^b, -SO₂R^a, -SO₂NR^aR^b, -NR^aSO₂R^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b, C₃₋₈ cycloalkyl, and C₁₋₆ alkylC₃₋₈ cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with -OR^a, halo, cyano, -NR^aR^b, or -C₃₋₈ cycloalkyl
 30

R⁶ is -NO₂, -N₃, -OR^a, halo, cyano, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OC₁₋₆ haloalkyl, NR^aR^b, -C(O)R^a, -C(O)OR^a, -OC₁₋₆ alkylCN, -C(O)NR^aR^b, -NR^aC(O)R^a, -

$\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{N}(\text{R}^a)\text{OR}^b$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $\text{C}_{3-8}\text{cycloalkyl}$, and $\text{C}_{1-6}\text{alkylC}_{3-8}\text{cycloalkyl}$;

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$ or $-\text{C}_{3-8}\text{cycloalkyl}$;

5 Q^E is aryl, heteroaryl, or heterocyclyl;

wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, oxo, $-\text{OR}^a$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{CN}$, $-\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{OC}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylC}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, and R^N ; and

wherein the alkyl, alkenyl, alkynyl, $\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}\text{alkylCN}$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$ and $-\text{C}_{3-8}\text{cycloalkyl}$; and further wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-\text{C}_{1-6}\text{alkylNR}^1\text{R}^2$, $-\text{OC}_{1-6}\text{alkylNR}^1\text{R}^2$, $-\text{C}_{1-6}\text{alkylOC}_{1-6}\text{alkylNR}^1\text{R}^2$, $-\text{NR}^a\text{C}_{1-6}\text{alkylNR}^1\text{R}^2$, $-\text{C}_{1-6}\text{alkylC}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}\text{alkylC}(\text{O})\text{NR}^1\text{R}^2$, $-\text{OC}_{1-6}\text{alkylC}(\text{O})\text{OR}^1$,

$-\text{SC}_{1-6}\text{alkylNR}^1\text{R}^2$, $-\text{C}_{1-6}\text{alkylOR}^a$, or $\text{L}^1-\text{V}-\text{L}^2-\text{A}$;

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, and $\text{C}_{2-6}\text{alkynyl}$;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-\text{NR}^a\text{R}^b$ or $-\text{C}_{3-8}\text{cycloalkyl}$;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

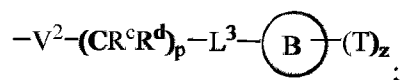
ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-\text{NO}_2$, $-\text{N}_3$, $-\text{OR}^a$, halo, cyano, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{1-6}\text{haloalkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{OC}_{1-6}\text{haloalkyl}$, NR^aR^b , $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{OC}_{1-6}\text{alkylCN}$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{N}(\text{R}^a)\text{OR}^b$, $-\text{SO}_2\text{R}^a$,

$-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{R}^b$, $-\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $\text{C}_{3-8}\text{cycloalkyl}$,
and $\text{C}_{1-6}\text{alkylC}_{3-8}\text{cycloalkyl}$; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-\text{OR}^a$, halo, cyano, $-\text{NR}^a\text{R}^b$ or $-\text{C}_{3-8}\text{cycloalkyl}$;

- 5 R^E and R^W are each independently $-\text{NR}^1\text{R}^2$, $-\text{C}_{1-6}\text{alkylINR}^1\text{R}^2$, $-\text{OC}_{1-6}\text{alkylINR}^1\text{R}^2$,
 $-\text{C}_{1-6}\text{alkylOC}_{1-6}\text{alkylINR}^1\text{R}^2$, $-\text{NR}^a\text{C}_{1-6}\text{alkylINR}^1\text{R}^2$, $-\text{C}_{1-6}\text{alkylIN}^+\text{R}^1\text{R}^2\text{R}^3$, $-\text{SC}_{1-6}\text{alkylINR}^1\text{R}^2$,
 $-\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{SO}_2\text{R}^a$, $-(\text{CH}_2)_u\text{SO}_2\text{NR}^1\text{R}^2$, $-(\text{CH}_2)_u\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{SO}_2\text{NR}^a\text{C}_{1-6}\text{alkylINR}^1\text{R}^2$, $-\text{NR}^a\text{SO}_2\text{C}_{1-6}$
 $\text{alkylINR}^1\text{R}^2$, $-(\text{CH}_2)_u\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{NR}^a\text{R}^b$, $-(\text{CH}_2)_u\text{N}^+\text{R}^1\text{R}^2\text{O}^-$, $-(\text{CH}_2)_u\text{P}^+\text{R}^b\text{R}^c\text{R}^d$, $-(\text{CH}_2)_u\text{P}^+\text{R}^c\text{R}^d\text{O}^-$,
 $-(\text{CH}_2)_u\text{P}^+\text{O}[\text{NR}^a\text{R}^b][\text{NR}^c\text{R}^d]$, $-(\text{CH}_2)_u\text{NR}^c\text{P}(\text{O})(\text{OR}^c)_2$, $-(\text{CH}_2)_u\text{CH}_2\text{OP}(\text{O})(\text{OR}^c)(\text{OR}^d)$,
10 $-(\text{CH}_2)_u\text{OP}(\text{O})(\text{OR}^c)(\text{OR}^d)$, $-(\text{CH}_2)_u\text{OP}(\text{O})\text{NR}^a\text{R}^b(\text{OR}^a)$, or



wherein:

V^2 is independently a bond, O, NR^a , S, SO, SO_2 , $\text{C}(\text{O})\text{NR}^a$, $\text{NR}^a\text{C}(\text{O})$, $\text{SO}_2\text{NR}^1\text{R}^2$, or NR^aSO_2 ;

L^3 is independently a bond, O, NR^a , S, SO, SO_2 , $\text{C}(\text{O})\text{NR}^a$, $\text{NR}^a\text{C}(\text{O})$, $\text{SO}_2\text{NR}^1\text{R}^2$, or NR^aSO_2 ;

- 15 ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a , $(\text{CH}_2)_q\text{NR}^1\text{R}^2$,
 $(\text{CH}_2)_q\text{NR}^a\text{C}(\text{O})\text{R}^e$, or $(\text{CH}_2)_q\text{C}(\text{O})\text{R}^e$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

- 20 z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b , halo, cyano, oxo, OR^a , $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{1-6}\text{haloalkyl}$, $-\text{C}_{1-6}\text{cyanoalkyl}$, $-\text{C}_{1-6}\text{alkylINR}^a\text{R}^b$, $-\text{C}_{1-6}\text{alkylOH}$, $-\text{C}_{3-8}\text{cycloalkyl}$, and $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$;

- 25 provided that at least one of V^2 , L^3 , ring B and T contains a nitrogen atom;

R^1 is independently selected from H, $-\text{C}_{1-3}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{C}_{3-6}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, $-\text{C}_{1-6}\text{alkylheterocyclyl}$, $-\text{C}_{1-6}\text{alkylC}(\text{O})\text{OR}^a$, $-\text{C}_{2-6}\text{alkenylC}(\text{O})\text{OR}^a$, $-\text{SO}_2\text{R}^a$, $-\text{SO}_2\text{NR}^a\text{R}^b$, $-\text{C}(\text{O})\text{NR}^a\text{SO}_2\text{R}^a$, and $\text{C}_{1-6}\text{alkylC}_{3-8}\text{cycloalkyl}$;

- 30 wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from $-\text{OR}^a$, $-\text{CN}$, halo, $\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{1-6}\text{alkylOR}^a$, $-\text{C}_{1-6}\text{cyanoalkyl}$, $-\text{C}_{1-6}\text{haloalkyl}$, $\text{C}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}(\text{O})\text{R}^a$,

-C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, NR^aC(O)OR^b,
 -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b,
 -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and
 -C₁₋₆alkylNR^aC(O)R^b;

- 5 **R² is independently selected from H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, and -C₂₋₆alkenylC(O)OR^a;**

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl,

- 10 -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b and -NR^aC(O)R^b;

or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional

- 15 **heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -OR^a, -C(O)OR^a, -C₁₋₆cyanoalkyl, -C₁₋₆alkylOR^a, -C₁₋₆haloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, and -C₁₋₆alkylSO₂NR^aR^b;**

- 20 **R³ is independently H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, or -C₂₋₆alkenylC(O)OR^a;**

R⁴ is independently H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, or

- 25 **-C₂₋₆alkenylC(O)OR^a;**

R^a is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

R^b is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

- 30 **or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, -C₁₋₆alkylOR^f, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^f, -C₁₋₆alkylC(O)R^f, -C(O)OR^f, -C₁₋₆alkylC(O)OR^f, -NR^fR^g, -C₁₋₆alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and**
 35 **-NR^fC(O)R^g;**

R^c is independently selected from H, OH, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

R^d is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

- 5 R^e is independently selected from H, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-OC_{3-8}$ cycloalkyl, $-O$ aryl, $-O$ heteroaryl, $-O$ heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-NR^fR^g$, $-C_{1-6}$ alkyl NR^fR^g , $-C(O)NR^fR^g$, $-C_{1-6}$ alkyl $C(O)NR^fR^g$, $-NHSO_2R^f$, $-C_{1-6}$ alkyl SO_2R^f , and $-C_{1-6}$ alkyl $SO_2NR^fR^g$;

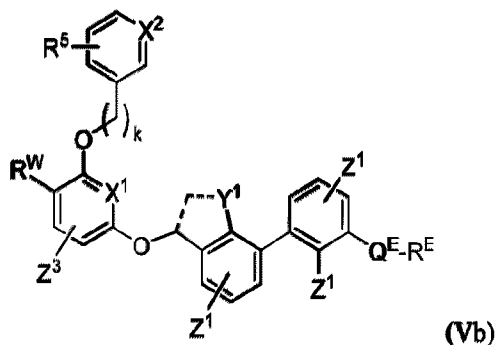
- R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl,
10 $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and

R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

- In one embodiment of formula (Va), neither of R^E or R^W is an optionally substituted fused
15 5,6-aromatic or 5,6-heteromatic ring.

In one embodiment, the compound is represented by formula or (Vb):



wherein

- the dotted lines are optionally a single bond or absent, such that when the dotted lines are absent, Y^1 is
20 halo, $-OR^a$, $-NO_2$, $-CN$, $-NR^aR^b$, $-N_3$, $-SO_2R^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-OC_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-6}$ alkyl C_{3-8} cycloalkyl;

wherein each alkyl, alkenyl, alkynyl, and cycloalkyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

or the dotted lines are single bonds and Y^1 is CH_2 , such that they form a fused 5-membered ring;

- 25 k is 0, 1, 2, 3, 4, 5, or 6;

each X^1 is independently N or CH ;

X^2 is N or CH;

each Z^1 is independently halo, $-OR^a$, $-NO_2$, $-CN$, $-NR^aR^b$, $-N_3$, $-SO_2R^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-OC_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, and $-C_{1-6}$ alkyl C_{3-8} cycloalkyl;

5 wherein each alkyl, alkenyl, alkynyl, and cycloalkyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

each Z^2 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ;

10 wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

15 R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)OR^1$, $-SC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OR^a , or

$$L^1-V-L^2-\textcircled{A};$$

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

20 V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$, or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

25 wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, C_{3-8} cycloalkyl, and C_{1-6} alkyl C_{3-8} cycloalkyl; and

30 wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$, or $-C_{3-8}$ cycloalkyl

R^6 is $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $-NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)OR^a$, $-C(O)N(R^a)OR^b$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, C_{3-8} cycloalkyl, and C_{1-6} alkyl C_{3-8} cycloalkyl;

- 5 wherein the alkyl, alkenyl, or alkynyl group is optionally independently substituted with $-OR^a$, halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

Q^v is aryl, heteroaryl, or heterocyclyl;

- wherein each aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from halo, oxo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ; and

- 15 wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and further wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^aC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)NR^1R^2$, $-OC_{1-6}$ alkyl $C(O)OR^1$,

$-SC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OR^a , or $L^1-V-L^2-\textcircled{A}$;

wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

- 25 V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

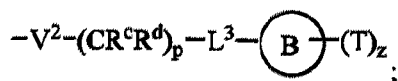
ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

- 30 wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-OC_{1-6}$ haloalkyl, NR^aR^b , $-C(O)R^a$, $-C(O)OR^a$, $-OC_{1-6}$ alkylCN, $-C(O)NR^aR^b$,

-NR^aC(O)R^a, -NR^aC(O)OR^a, -NR^aC(O)OR^a, -C(O)N(R^a)OR^b, -SO₂R^a,
 -SO₂NR^aR^b, -NR^aSO₂R^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b, C₃₋₈cycloalkyl,
 and C₁₋₆alkylC₃₋₈cycloalkyl; and

5 wherein the alkyl, alkenyl, or alkynyl group is optionally independently
 substituted with -OR^a, halo, cyano, -NR^aR^b or -C₃₋₈cycloalkyl;

R^E and R^W are each independently -NR¹R², -C₁₋₆alkylNR¹R², -OC₁₋₆alkylNR¹R²,
 -C₁₋₆alkylOC₁₋₆alkylNR¹R², -NR^aC₁₋₆alkylNR¹R², -C₁₋₆alkylIN⁺R¹R²R³, -SC₁₋₆alkylNR¹R², -
 C(O)NR¹R², -SO₂R^a, -(CH₂)_uSO₂NR¹R², -(CH₂)_uNR^aSO₂NR^aR^b, -SO₂NR^aC₁₋₆alkylNR¹R², -NR^aSO₂C₁₋₆
 alkylNR¹R², -(CH₂)_uC(O)NR^aSO₂NR^aR^b, -(CH₂)_uN⁺R¹R²O⁻, -(CH₂)_uP⁺R^bR^cR^d, -(CH₂)_uP⁺R^cR^dO⁻,
 10 -(CH₂)_uP⁺O[NR^aR^b][NR^cR^d], -(CH₂)_uNR^cP(O)(OR^e)₂, -(CH₂)_uCH₂OP(O)(OR^e)(OR^d),
 -(CH₂)_uOP(O)(OR^e)(OR^d), -(CH₂)_uOP(O)NR^aR^b(OR^a), or



wherein:

V² is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹R², or NR^aSO₂;
 15 L³ is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹R², or NR^aSO₂;
 ring B is cycloalkyl, aryl, heteroaryl, or heterocyclyl; T is independently H, OR^a, (CH₂)_qNR¹R²,
 (CH₂)_qNR^aC(O)R^e, or (CH₂)_qC(O)R^e;
 p is independently 0, 1, 2, 3, 4, or 5;
 q is independently 0, 1, 2, 3, 4, or 5;
 20 u is 0, 1, 2, 3, or 4;
 z is 0, 1, 2, or 3; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted
 with 1 to 3 substituents independently selected from the group consisting of NR^aR^b, halo,
 cyano, oxo, OR^a, -C₁₋₆alkyl, -C₁₋₆haloalkyl, -C₁₋₆cyanoalkyl, -C₁₋₆alkylNR^aR^b, -C₁₋₆
 25 alkylOH, -C₃₋₈cycloalkyl, and -C₁₋₃alkylC₃₋₈cycloalkyl;

provided that at least one of V², L³, ring B and T contains a nitrogen atom;

R¹ is independently selected from H, -C₁₋₈alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₆cycloalkyl, aryl,
 heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₁₋₆
 alkylC(O)OR^a, -C₂₋₆alkenylC(O)OR^a, -SO₂R^a, -SO₂NR^aR^b, -C(O)NR^aSO₂R^a, and
 30 C₁₋₆alkylC₃₋₈cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted
 with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a,

-C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a,
 -C₁₋₆ alkylC(O)R^a, -C(O)OR^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, NR^aC(O)OR^b,
 -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b,
 -C₁₋₆ alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆ alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and
 5 -C₁₋₆ alkylNR^aC(O)R^b;

R² is independently selected from H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl,
 heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a,
 -C₁₋₆ alkylC(O)OR^a, and -C₂₋₆ alkenylC(O)OR^a;

10 wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally
 substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl,
 -C₁₋₆ alkylOR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl,
 -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C(O)OR^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b,
 -C(O)NR^aR^b, C₁₋₆ alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆ alkylSO₂NR^aR^b,
 -C(O)NR^aSO₂R^b and -NR^aC(O)R^b;

15 or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional
 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1
 to 3 groups independently selected from oxo, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl,
 -OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a,
 -C₁₋₆ alkylC(O)R^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆ alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆ alkylC(O)NR^aR^b,
 20 -SO₂R^a, -C₁₋₆ alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆ alkylSO₂NR^aR^b;

R³ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl,
 -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or
 -C₂₋₆ alkenylC(O)OR^a;

25 R⁴ is independently H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl,
 -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, or
 -C₂₋₆ alkenylC(O)OR^a;

R^a is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
 -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

30 R^b is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl,
 -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S;
 wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN,
 halo, -C₁₋₆ alkylOR^f, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl,
 -C(O)R^f, -C₁₋₆ alkylC(O)R^f, -C(O)OR^f, -C₁₋₆ alkylC(O)OR^f, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g,

$-\text{C}_{1-6}\text{alkylC(O)NR}^f\text{R}^g$, $-\text{SO}_2\text{R}^f$, $-\text{C}_{1-6}\text{alkylSO}_2\text{R}^f$, $-\text{SO}_2\text{NR}^f\text{R}^g$, $-\text{C}_{1-6}\text{alkylSO}_2\text{NR}^f\text{R}^g$, $-\text{C(O)NR}^f\text{SO}_2\text{R}^g$ and $-\text{NR}^f\text{C(O)R}^g$;

R^c is independently selected from H, OH, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, and $-\text{C}_{1-6}\text{alkylheterocyclyl}$;

- 5 R^d is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, and $-\text{C}_{1-6}\text{alkylheterocyclyl}$;

R^e is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{OC}_{3-8}\text{cycloalkyl}$, $-\text{Oaryl}$, $-\text{Oheteroaryl}$, $-\text{Oheterocyclyl}$, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, $-\text{NR}^f\text{R}^g$, $-\text{C}_{1-6}\text{alkylNR}^f\text{R}^g$, $-\text{C(O)NR}^f\text{R}^g$, $-\text{C}_{1-6}\text{alkylC(O)NR}^f\text{R}^g$, $-\text{NH}\text{SO}_2\text{R}^f$, $-\text{C}_{1-6}\text{alkylSO}_2\text{R}^f$, and $-\text{C}_{1-6}\text{alkylSO}_2\text{NR}^f\text{R}^g$;

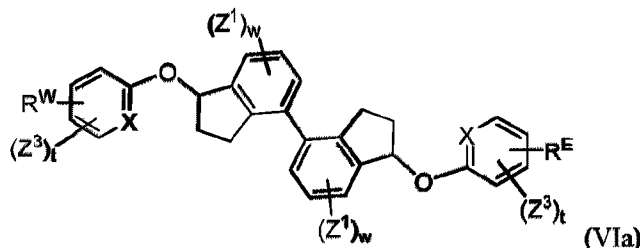
R^f is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, and $-\text{C}_{1-6}\text{alkylheterocyclyl}$; and

R^g is independently selected from H, $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{3-8}\text{cycloalkyl}$, aryl, heteroaryl, heterocyclyl, $-\text{C}_{1-3}\text{alkylC}_{3-8}\text{cycloalkyl}$, $-\text{C}_{1-6}\text{alkylaryl}$, $-\text{C}_{1-6}\text{alkylheteroaryl}$, and $-\text{C}_{1-6}\text{alkylheterocyclyl}$;

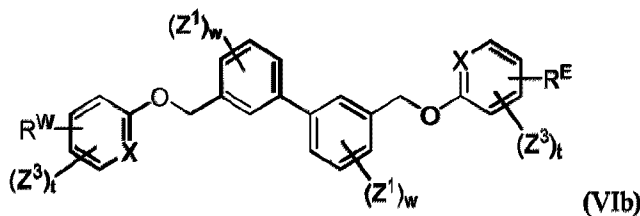
- 15 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or tautomer thereof.

In one embodiment of formula (Vb), neither of R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring.

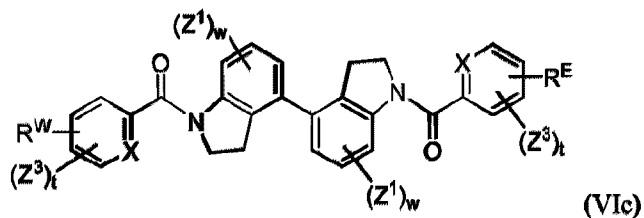
In one embodiment, provided is a compound of formula (VIa):



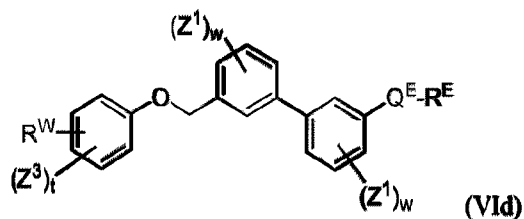
- 20 wherein R^E , R^W , Z^1 and Z^3 are as defined herein, each w is independently 0, 1 or 2, each t is independently 0, 1 or 2, and each X is independently CZ^3 , CH or N. In one embodiment, provided is a compound of formula (VIb):



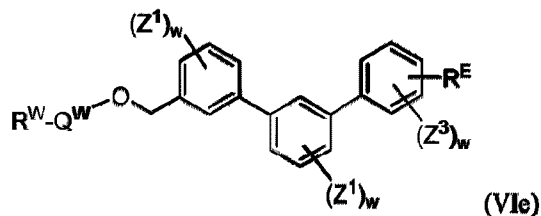
wherein R^E , R^W , Z^1 and Z^3 are as defined herein, each w is independently 0, 1 or 2, each t is independently 0, 1 or 2, and each X is independently CZ^3 , CH or N. In one embodiment, provided is a compound of formula (VIc):



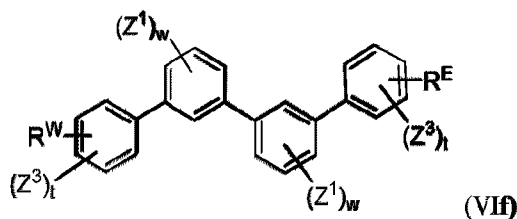
- 5 wherein R^E , R^W , Z^1 and Z^3 are as defined herein, each w is independently 0, 1 or 2, each t is independently 0, 1 or 2, and each X is independently CZ^3 , CH or N. In one embodiment, provided is a compound of formula (VIId):



- wherein R^E , R^W , Z^1 and Z^3 are as defined herein, each w is independently 0, 1 or 2, each t is independently 0, 1 or 2, and Q^E is heteroaryl. In one embodiment, provided is a compound of formula (VId):

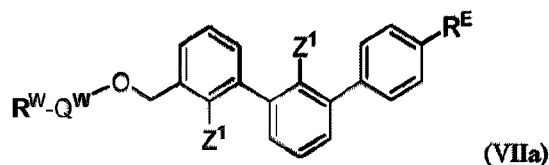


wherein R^E , R^W , Z^1 , Z^3 and Q^W are as defined herein, each w is independently 0, 1 or 2, each t is independently 0, 1 or 2. In one embodiment, provided is a compound of formula (VIf):

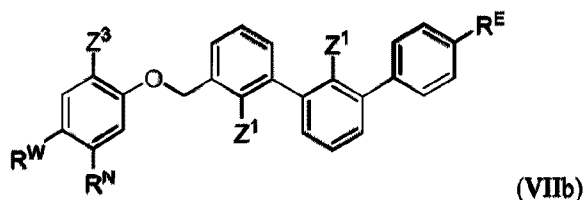


15

wherein R^E , R^W , Z^1 and Z^3 are as defined herein, each w is independently 0, 1 or 2, each t is independently 0, 1 or 2. In one embodiment, provided is a compound of formula (VIIa):



wherein R^W , Q^W , Z^1 and R^E are as defined herein. In one embodiment, provided is a compound of formula (VIIb):



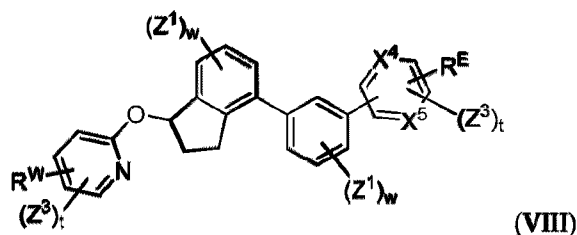
5 wherein R^W , R^N , Z^3 , Z^1 and R^E are as defined herein.

In certain embodiments of any one of formulas (VIa)-(VI f) or formulas (VIIa)-(VIIb), each Z^1 is independently halo. In certain embodiments of any one of formulas (VIa)-(VI f) or formulas (VIIa)-(VIIb), each Z^3 is independently C_{1-6} alkoxy.

10 In certain embodiments of any one of formulas (VIa)-(VI f) or formulas (VIIa)-(VIIb), each Z^1 is chloro. In certain embodiments of any one of formulas (VIa)-(VI f) or formulas (VIIa)-(VIIb), each Z^3 is methoxy.

In certain embodiments of formula (VIa)-(VI f) or formulas (VIIa)-(VIIb), neither of R^E or R^W is an optionally substituted fused 5,6-aromatic or 5,6-heteromatic ring directly bound to the Q ring via a covalent bond.

15 In one embodiment, provided is a compound of formula (VIII):



wherein:

each of X^4 and X^5 are independently N, CH or CZ^3 ;

20 each Z^1 is independently is halo, $-OR^a$, $-NO_2$, $-CN$, $-NR^aR^b$, $-N_3$, $-SO_2R^a$, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$ alkyl, $-O-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, or $-C_{1-6}$ alkyl C_{3-8} cycloalkyl; and

wherein each alkyl, alkenyl, alkynyl, and cycloalkyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

each w is independently 0, 1 or 2;

each Z³ is independently halo, -OR^a, -N₃, -NO₂, -CN, -NR¹R², -SO₂R^a, -SO₂NR^aR^b,
-NR^aSO₂R^a, -NR^aC(O)R^a, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -NR^aC(O)OR^a, -NR^aC(O)NR¹R²,
-OC(O)NR^aR^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl,
5 -O-C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₁₋₆ alkylC₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N; and

wherein the alkyl, alkenyl, alkynyl, C₃₋₈ cycloalkyl, aryl, heteroaryl, or heterocyclyl group is
optionally substituted with 1 to 4 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo,
cyano, -NR^aR^b, -C(O)R^a, -C(O)OR^a, -O-C₁₋₆cyanoalkyl, -C(O)NR^aR^b, NR^aC(O)R^a,
-NR^aC(O)OR^a, -SO₂R^a, -NR^aSO₂R^b, -SO₂NR^aR^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b and -C₃₋₈
10 cycloalkyl; and further wherein the heteroaryl or heterocyclic group may be oxidized on a
nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently -C₁₋₆ alkylNR¹R², -OC₁₋₆ alkylNR¹R², -C₁₋₆ alkylOC₁₋₆ alkylNR¹R²,
-NR^aC₁₋₆ alkylNR¹R², -C₁₋₆ alkylC(O)NR¹R², -OC₁₋₆ alkylC(O)NR¹R², -OC₁₋₆ alkylC(O)OR¹,
-SC₁₋₆ alkylNR¹R², -C₁₋₆ alkylOR^a, or



15 wherein: L¹ is independently a bond, O, NR^a, S, SO, or SO₂;

V is independently selected from a bond, C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted
with OR^a, halo, cyano, -NR^aR^b or -C₃₋₈ cycloalkyl;

L² is independently a bond, O, NR^a, S, SO, or SO₂;

20 ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

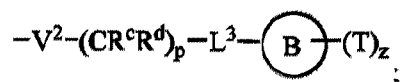
wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally
substituted with 1 to 4 groups independently selected from oxo, -NO₂, -N₃, -OR^a,
halo, cyano, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -O-C₁₋₆
haloalkyl, NR^aR^b, -C(O)R^a, -C(O)OR^a, -OC₁₋₆ alkylCN, -C(O)NR^aR^b,
25 -NR^aC(O)R^a, -NR^aC(O)OR^a, -NR^aC(O)OR^a, -C(O)N(R^a)OR^b, -SO₂R^a,
-SO₂NR^aR^b, -NR^aSO₂R^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b, C₃₋₈cycloalkyl,
and C₁₋₆alkylC₃₋₈ cycloalkyl; and

wherein the alkyl, alkenyl, or alkynyl group is optionally independently
substituted with -OR^a, halo, cyano, -NR^aR^b or -C₃₋₈ cycloalkyl;

30 each t is independently 0, 1 or 2;

R^E and R^W are each independently -NR¹R², -C₁₋₆ alkylNR¹R², -O-C₁₋₆ alkylNR¹R²,
-C₁₋₆ alkylOC₁₋₆ alkylNR¹R², -NR^a-C₁₋₆ alkylNR¹R², -C₁₋₆ alkylIN⁺R¹R²R³, -S-C₁₋₆ alkylNR¹R², -
C(O)NR¹R², -SO₂R^a, -(CH₂)_nSO₂NR¹R², -(CH₂)_nNR^aSO₂NR^aR^b, -SO₂NR^aC₁₋₆ alkylNR¹R², -NR^aSO₂C₁₋₆

alkylNR¹R², -(CH₂)_uC(O)NR^aSO₂NR^aR^b, -(CH₂)_uN⁺R¹R²O⁻, -(CH₂)_uP⁺R^bR^cR^d, -(CH₂)_uP⁺R^cR^dO⁻,
 -(CH₂)_uP⁺O[NR^aR^b][NR^cR^d], -(CH₂)_uNR^aP(O)(OR^e)₂, -(CH₂)_uCH₂OP(O)(OR^e)(OR^d),
 -(CH₂)_uOP(O)(OR^e)(OR^d), -(CH₂)_uOP(O)NR^aR^b(OR^a), or



5 wherein:

V² is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹, or NR^aSO₂;

L³ is independently a bond, O, NR^a, S, SO, SO₂, C(O)NR^a, NR^aC(O), SO₂NR¹, or NR^aSO₂;

ring B is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently H, OR^a, (CH₂)_qNR¹R², (CH₂)_qNR^aC(O)R^c, or (CH₂)_qC(O)R^c;

10 p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

u is 0, 1, 2, 3, or 4;

z is 0, 1, 2, or 3; and

15 wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b, halo, cyano, oxo, OR^a, -C₁₋₆alkyl, -C₁₋₆haloalkyl, -C₁₋₆cyanoalkyl, -C₁₋₆alkylNR^aR^b, -C₁₋₆alkylOH, -C₃₋₈cycloalkyl, and -C₁₋₃alkylC₃₋₈cycloalkyl;

provided that at least one of V², L³, ring B and T contains a nitrogen atom;

20 each R¹ is independently selected from H, -C₁₋₈alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₁₋₆alkylC(O)OR^a, -C₂₋₆alkenylC(O)OR^a, -SO₂R^a, -SO₂NR^aR^b, -C(O)NR^aSO₂R^a, and -C₁₋₆alkylC₃₋₈cycloalkyl;

25 wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, NR^aC(O)OR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and -C₁₋₆alkylNR^aC(O)R^b;

30 each R² is independently selected from H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, and -C₂₋₆alkenylC(O)OR^a;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b,
 5 -C(O)NR^aR^b, C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b and -NR^aC(O)R^b;

or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl,
 10 -OR^a, -C(O)OR^a, -C₁₋₆cyanoalkyl, -C₁₋₆alkylOR^a, -C₁₋₆haloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, C₁₋₆alkylC(O)R^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, and C₁₋₆alkylSO₂NR^aR^b;

each R³ is independently H, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₃₋₆cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -C₁₋₆alkylheterocyclyl, -C₂₋₆alkyl-OR^a, -C₁₋₆alkylC(O)OR^a, or
 15 -C₂₋₆alkenylC(O)OR^a;

each R^a is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

R^b is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, -C₁₋₆alkylOR^f, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^f, -C₁₋₆alkylC(O)R^f, -C(O)OR^f, -C₁₋₆alkylC(O)OR^f, -NR^fR^g, -C₁₋₆alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and
 25 -NR^fC(O)R^g;

each R^c is independently selected from H, OH, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

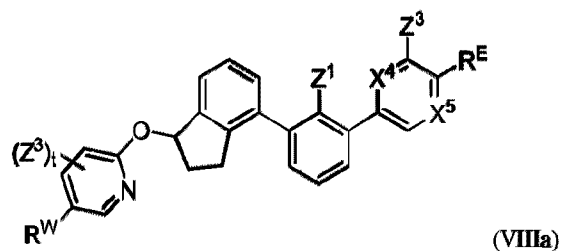
each R^d is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

each R^e is independently selected from H, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -O-C₃₋₈cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, -NR^fR^g, -C₁₋₆alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆alkylC(O)NR^fR^g, -NH₂SO₂R^f, -C₁₋₆alkylSO₂R^f, and -C₁₋₆alkylSO₂NR^fR^g;

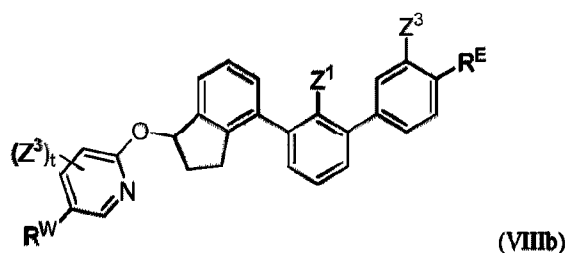
each R^f is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl; and
 35

each R^E is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkyl C_{3-8} cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof.

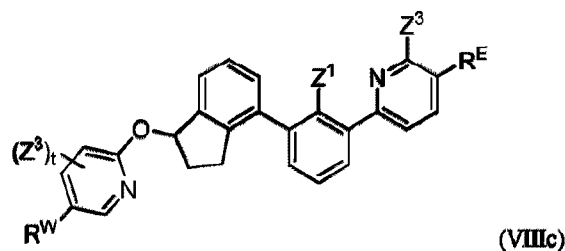
5 In one embodiment, provided is a compound of formula (VIIIa):



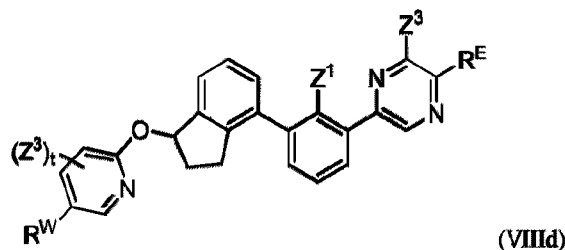
wherein X^4 , X^5 , Z^1 , Z^3 , t , R^W and R^E are as defined herein. In one embodiment, provided is a compound of formula (VIIIb):



10 wherein Z^1 , Z^3 , t , R^W and R^E are as defined herein. In one embodiment, provided is a compound of formula (VIIIc):



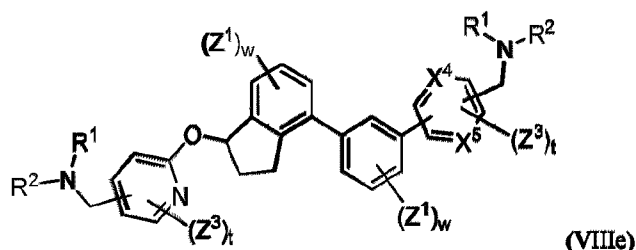
wherein Z^1 , Z^3 , t , R^W and R^E are as defined herein. In one embodiment, provided is a compound of formula (VIId):



15

wherein Z^1 , Z^3 , t , R^W and R^E are as defined herein.

In one embodiment, provided is a compound of formula (VIIIe):



wherein:

each of X^4 and X^5 are independently N, CH or CZ^3 ;

5 each Z^1 is independently halo, $-OR^a$, $-CN$, or $-C_{1-6}$ alkyl;

each w is independently 0, 1 or 2;

each Z^3 is independently halo, $-OR^a$, $-N_3$, $-NO_2$, $-CN$, $-NR^1R^2$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aSO_2R^a$, $-NR^aC(O)R^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^1R^2$, $-OC(O)NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl,

10 $-O-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, and R^N ; and

wherein the alkyl, alkenyl, alkynyl, C_{3-8} cycloalkyl, aryl, heteroaryl, or heterocyclyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-O-C_{1-6}$ cyanoalkyl, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl; and further wherein the heteroaryl or heterocyclic group may be oxidized on a nitrogen atom to form an N-oxide or oxidized on a sulfur atom to form a sulfoxide or sulfone;

R^N is independently $-C_{1-6}$ alkyl NR^1R^2 , $-OC_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^a-C_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-O-C_{1-6}$ alkyl $C(O)NR^1R^2$, $-O-C_{1-6}$ alkyl $C(O)OR^1$,

$-S-C_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OR^a , or $L^1-V-L^2-\text{A}$;

20 wherein: L^1 is independently a bond, O, NR^a , S, SO, or SO_2 ;

V is independently selected from a bond, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl;

wherein each alkyl, alkenyl, or alkynyl is optionally independently substituted with OR^a , halo, cyano, $-NR^aR^b$ or $-C_{3-8}$ cycloalkyl;

L^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

25 ring A is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

wherein each cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $-O-C_{1-6}$

each R^3 is independently H, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{3-6}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, $-C_{1-6}$ alkylheterocyclyl, $-C_{2-6}$ alkyl-OR^a, $-C_{1-6}$ alkylC(O)OR^a, or $-C_{2-6}$ alkenylC(O)OR^a;

each R^a is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

each R^b is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, $-C_{1-6}$ alkylOR^f, $-C_{1-6}$ cyanoalkyl, $-C_{1-6}$ haloalkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C(O)R^f$, $-C_{1-6}$ alkylC(O)R^f, $-C(O)OR^f$, $-C_{1-6}$ alkylC(O)OR^f, $-NR^fR^g$, $-C_{1-6}$ alkylINR^fR^g, $-C(O)NR^fR^g$, $-C_{1-6}$ alkylC(O)NR^fR^g, $-SO_2R^f$, $-C_{1-6}$ alkylSO₂R^f, $-SO_2NR^fR^g$, $-C_{1-6}$ alkylSO₂NR^fR^g, $-C(O)NR^fSO_2R^g$ and $-NR^fC(O)R^g$;

each R^f is independently selected from H, OH, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

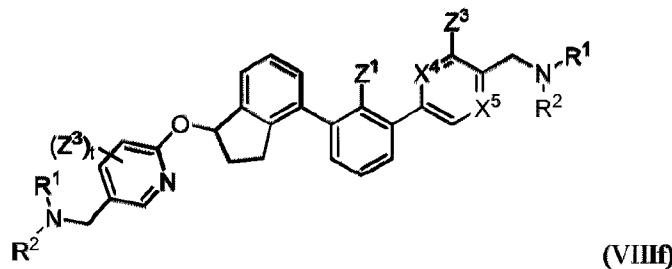
R^d is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

each R^f is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl; and

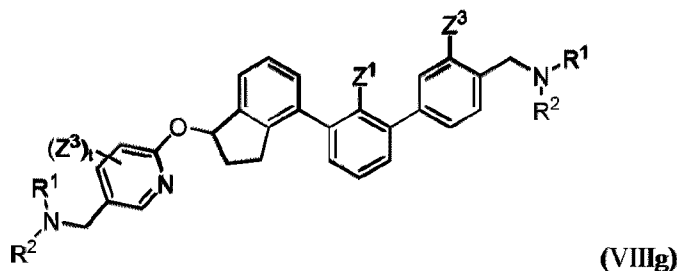
each R^g is independently selected from H, $-C_{1-6}$ alkyl, $-C_{3-8}$ cycloalkyl, aryl, heteroaryl, heterocyclyl, $-C_{1-3}$ alkylC₃₋₈cycloalkyl, $-C_{1-6}$ alkylaryl, $-C_{1-6}$ alkylheteroaryl, and $-C_{1-6}$ alkylheterocyclyl;

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, solvate, or tautomer thereof.

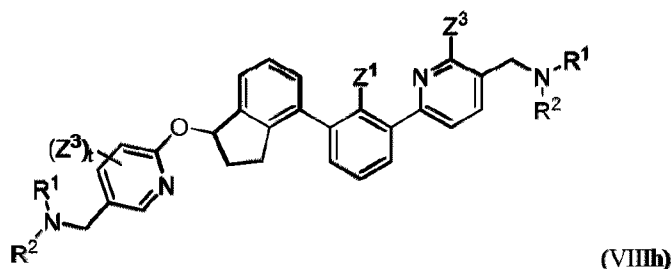
In one embodiment, provided is a compound of formula (VIIIf):



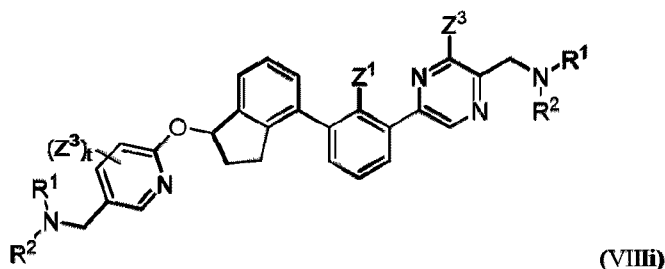
wherein X^4 , X^5 , Z^1 , Z^2 , Z^3 , t , R^1 and R^2 are as defined herein. In one embodiment, provided is a compound of formula (VIIIg):



wherein Z^1 , Z^3 , t , R^1 and R^2 are as defined herein. In one embodiment, provided is a compound of formula (VIIIh):



5 wherein Z^1 , Z^3 , t , R^1 and R^2 are as defined herein. In one embodiment, provided is a compound of formula (VIIIi):



wherein Z^1 , Z^3 , t , R^1 and R^2 are as defined herein.

In certain embodiments of any one of formulas (VIII)-(VIIIi), each Z^1 is independently halo. In
10 certain embodiments of any one of formulas (VIII)-(VIIIi), each Z^3 is independently halo or C_{1-6} alkoxy.

In certain embodiments of any one of formulas (VIII)-(VIIIi), each Z^1 is independently chloro.
In certain embodiments of any one of formulas (VIII)-(VIIIi), each Z^3 is independently chloro or methoxy.

In one embodiment provided is a compound selected from Examples 637-803.

15 In certain embodiments, the compound as provided herein has a molecular weight of less than about 1200 g/mol, or less than about 1100 g/mol, or less than about 1000 g/mol, or less than about 900 g/mol, or less than about 800 g/mol, or between about 1200 to about 600 g/mol, or between about 1000 to about 700 g/mol, or between about 1000 to about 800 g/mol.

One of skill in the art is aware that each and every embodiment of a group (e.g., Ar^E) disclosed herein may be combined with any other embodiment of each of the remaining groups (e.g., Q^E, Ar^W, Q^W, etc.) to generate a complete compound of formula (I) as disclosed herein; each of which is deemed within the ambit of the present disclosure.

5 ***Formulations and Methods***

Methods

In one embodiment, the present disclosure provides a compound of formula (I) useful as an inhibitor of PD-1, PD-L1 and/or the PD-1/PD-L1 interaction. In some embodiments, compounds disclosed herein inhibit the PD-1/PD-L1 interaction by dimerizing PD-L1, or by inducing or stabilizing PD-L1 dimer formation.

In one embodiment, the present disclosure provides a method of treating cancer comprising administering a compound of formula (I) in combination with one or more check-point inhibitors selected from nivolumab, pembrolizumab, and atezolizumab.

15 In one embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

In one embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, and at least one additional anticancer agent and at least one pharmaceutically acceptable excipient.

20 The present disclosure provides a compound of formula (I) for use in therapy.

In another embodiment, the present disclosure provides a compound of formula (I) for use in the manufacture of a medicament for treating cancer.

In one embodiment, provided is a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, useful for the treatment of cancer or a condition in a patient that is amenable to treatment by inhibiting PD-1, PD-L1 or the PD-1/PD-L1 interaction. Cancers that may be treated with the compounds of formula (I) disclosed herein include pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft tissue sarcoma, non-small cell lung cancer, small-cell lung cancer and colon cancer.

30 In one embodiment, provided is a compound of formula (I) or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof, useful for the treatment of cancer or a condition in a patient that is amenable to treatment by inhibiting PD-1, PD-L1 or the PD-1/PD-L1 interaction including, but not limited to, lymphoma, multiple myeloma, and leukemia. Additional diseases or conditions that may be treated include, but are not limited to acute lymphocytic leukemia

(ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myeloid leukemia (CML), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma, Waldstrom's macroglobulinemia (WM), T-cell lymphoma, B-cell lymphoma and diffuse large B-cell lymphoma (DLBCL).

In one embodiment, provided is a method of treating HBV, comprising administering to a patient in need thereof a compound of formula (I), or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers or tautomer thereof.

"Administering" or "administration" refers to the delivery of one or more therapeutic agents to a patient. In one embodiment, the administration is a monotherapy wherein a compound of formula (I) is the only active ingredient administered to the patient in need of therapy. In another embodiment, the administration is co-administration such that two or more therapeutic agents are delivered together during the course of the treatment. In one embodiment, two or more therapeutic agents may be co-formulated into a single dosage form or "combined dosage unit", or formulated separately and subsequently combined into a combined dosage unit, as is typically for intravenous administration or oral administration as a mono or bilayer tablet or capsule.

In one embodiment, the compound of formula (I) or a pharmaceutically acceptable salt thereof is administered to a human patient in need thereof in an effective amount, such as, from about 0.1 mg to about 1000 mg per day of said compound. In one embodiment, the effective amount is from about 0.1 mg to about 200 mg per day. In one embodiment, the effective amount is from about 1 mg to about 100 mg per day. In other embodiments, the effective amount is about 1 mg, about 3 mg, about 5 mg, about 10 mg, about 15 mg, about 18 mg, about 20 mg, about 30 mg, about 40 mg, about 60 mg, about 80 mg, or about 100 mg per day.

In one embodiment, the compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one additional anticancer agent is administered to a human patient in need thereof in an effective amount of each agent, independently from about 0.1 mg to about 1000 mg per compound or formulation per day per compounds. In one embodiment, the effective amount of the combination treatment of a compound of formula (I) and an additional compound is independently from about 0.1 mg to about 200 mg per compound per day. In one embodiment, the effective amount of the combination treatment of a compound of formula (I) and an additional compound is independently from about 1 mg to about 100 mg per compound per day. In other embodiments, the effective amount of the combination treatment of a compound of formula (I) and an additional compound is for each component, about 1 mg, about 3 mg, about 5 mg, about 10 mg, about 15 mg, about 18 mg, about 20 mg, about 30 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 200 mg, or about 500 mg each per day.

In one embodiment, the compound of formula (I) and/or a combination of the compound of formula (I) and an additional anticancer agent or a pharmaceutically acceptable salt thereof is

administered once a day. In yet another embodiment, the compound of formula (I) and/or an additional anticancer agent or a pharmaceutically acceptable salt thereof is administered as a loading dose of from about 10 mg to about 500 mg per compound on the first day and each day or on alternate days or weekly for up to a month followed by a regular regimen of a compound of formula (I) and/or one or more additional anticancer agents or therapies. The maintenance dose may be 1-500 mg daily or weekly for each component of a multi component drug regimen. A qualified care giver or treating physician is aware of what dose regimen is best for a particular patient or particular presenting conditions and will make appropriate treating regimen decisions for that patient. Thus, in another embodiment, the qualified caregiver is able to tailor a dose regimen of the compound of formula (I) and/or an additional agent(s) as disclosed herein to fit with the particular needs of the patient. Thus, it will be understood that the amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof and the amount of an additional agent actually administered will usually be determined by a physician, in light of the relevant circumstances, including the condition(s) to be treated, the chosen route of administration, the actual compound (e.g., salt or free base) administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

Co-administration may also include administering component drugs e.g., one on more compounds of formula (I) and one or more additional (e.g., a second, third, fourth or fifth) anticancer or other therapeutic agent(s). Such combination of one on more compounds of formula (I) and one or more additional anticancer or other therapeutic agent(s) may be administered simultaneously or in sequence (one after the other) within a reasonable period of time of each administration (e.g., about 1 minute to 24 hours) depending on the pharmacokinetic and/or pharmacodynamics properties of each agent or the combination. Co-administration may also involve treatment with a fixed combination wherein agents of the treatment regimen are combinable in a fixed dosage or combined dosage medium e.g., solid, liquid or aerosol. In one embodiment, a kit may be used to administer the drug or drug components.

Thus, one embodiment of the present disclosure is a method of treating a disease amenable to treatment with a PD-1, PD-L1 inhibitor or a PD-1/PD-L1 interaction inhibitor e.g., cancer comprising administering therapeutically effective amounts of formulations of one on more compounds of formula (I) and one or more additional anticancer agents, including for example, via a kit to a patient in need thereof. It will be understood that a qualified care giver will administer or direct the administration of a therapeutically effective amount of any of the compound(s) or combinations of compounds of the present disclosure.

"Intravenous administration" is the administration of substances directly into a vein, or "intravenously." Compared with other routes of administration, the intravenous (IV) route is a faster way to deliver fluids and medications throughout the body. An infusion pump can allow precise control over the flow rate and total amount of medication delivered. However, in cases where a change in the flow rate would not have serious consequences, or if pumps are not available, the drip is often left to flow simply by placing the bag above the level of the patient and using the clamp to regulate the rate.

Alternatively, a rapid infuser can be used if the patient requires a high flow rate and the IV access device is of a large enough diameter to accommodate it. This is either an inflatable cuff placed around the fluid bag to force the fluid into the patient or a similar electrical device that may also heat the fluid being infused. When a patient requires medications only at certain times, intermittent infusion is used which
 5 does not require additional fluid. It can use the same techniques as an intravenous drip (pump or gravity drip), but after the complete dose of medication has been given, the tubing is disconnected from the IV access device. Some medications are also given by IV push or bolus, meaning that a syringe is connected to the IV access device and the medication is injected directly (slowly, if it might irritate the vein or cause a too-rapid effect). Once a medicine has been injected into the fluid stream of the IV tubing there
 10 must be some means of ensuring that it gets from the tubing to the patient. Usually this is accomplished by allowing the fluid stream to flow normally and thereby carry the medicine into the bloodstream; however, a second fluid injection is sometimes used, as a "flush", following the injection to push the medicine into the bloodstream more quickly. Thus in one embodiment, compound(s) or combination of compounds described herein may be administered by IV administration alone or in combination with
 15 administration of certain components of the treatment regimen by oral or parenteral routes.

"Oral administration" is a route of administration where a substance is taken through the mouth, and includes buccal, sub labial, and sublingual administration, as well as enteral administration and that through the respiratory tract, unless made through e.g., tubing so the medication is not in direct contact with any of the oral mucosa. Typical form for the oral administration of therapeutic agents includes the
 20 use of tablets or capsules. Thus in one embodiment, compound(s) or combination of compounds described herein may be administered by oral route alone or in combination with administration of certain components of the treatment regimen by IV or parenteral routes.

Pharmaceutical Formulations

The compound(s) of formula (I) or a pharmaceutically acceptable salt thereof may be
 25 administered in a pharmaceutical formulation. Pharmaceutical formulations/compositions contemplated by the present disclosure comprise, in addition to a carrier, the compound of formula (I), or a pharmaceutically acceptable salt thereof, or a combination of compound of formula (I), or a pharmaceutically acceptable salt thereof, optionally in combination with an additional agent such as for example, ipilimumab, or a pharmaceutically acceptable salt thereof.

30 Pharmaceutical formulations/compositions contemplated by the present disclosure may also be intended for administration by injection and include aqueous solutions, oil suspensions, emulsions (with sesame oil, corn oil, cottonseed oil, or peanut oil) as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles. Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and
 35 the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin,

by the maintenance of the required particle size in the case of dispersion and/or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

5 Sterile injectable solutions are prepared by incorporating the component compound(s) in the required amount in the appropriate solvent with various other ingredients as enumerated above or as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and
10 freeze-drying techniques which yield a powder of the active ingredient(s) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

In making pharmaceutical compositions that comprise compound of formula (I), or a pharmaceutically acceptable salt thereof, optionally in combination with an additional agent/therapy useful for the purpose or pharmaceutically acceptable salt thereof, the active ingredient is usually diluted
15 by an excipient or carrier and/or enclosed or mixed with such a carrier that may be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material (as above), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments
20 containing, for example, up to 20% by weight of the active compounds, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations
25 can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents.

The compositions of the disclosure may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures
30 known in the art. In one embodiment, sustained release formulations are used. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations.

Certain compositions are preferably formulated in a unit dosage form. The term "unit dosage forms" or "combined dosage unit" refers to physically discrete units suitable as unitary dosages for
35 human subjects and other mammals, each unit containing a predetermined quantity of one or more of the active materials (e.g., compound (I), optionally in combination with an additional agent calculated to

produce the desired effect, in association with a suitable pharmaceutical excipient in for example, a tablet, capsule, ampoule or vial for injection. It will be understood, however, that the amount of each active agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual
5 compounds administered and their relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient(s) is /are mixed with a pharmaceutical excipient to form a solid pre-formulation composition containing a homogeneous mixture of a compound of the present disclosure. When referring to these pre-formulation compositions
10 as homogeneous, it is meant that the active ingredient(s) are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

The tablets or pills comprising compound of formula (I) or a pharmaceutically acceptable salt thereof of the present disclosure optionally in combination with the second agent may be coated or
15 otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acidic conditions of the stomach. For example, the tablet or pill can comprise an inner dosage and an outer dosage element, the latter being in the form of an envelope over the former. In one embodiment, the inner dosage element may comprise the compound (I) and the outer dosage element may comprise the second or additional agent or *vice versa*. Alternatively, the combined dosage unit may
20 be side by side configuration as in a capsule or tablet where one portion or half of the tablet or capsule is filled with a formulation of the compound of formula (I) while the other portion or half of the table or capsule comprises the additional agent

A variety of materials may be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol,
25 and cellulose acetate. One of ordinary skill in the art is aware of techniques and materials used in the manufacture of dosages of formulations disclosed herein.

A "sustained release formulation" or "extended release formulation" is a formulation which is designed to slowly release a therapeutic agent into the body over an extended period of time, whereas an "immediate release formulation" is a formulation which is designed to quickly release a therapeutic agent
30 into the body over a shortened period of time. In some cases the immediate release formulation may be coated such that the therapeutic agent is only released once it reaches the desired target in the body (e.g., the stomach). One of ordinary skill in the art is able to develop sustained release formulations of the presently disclosed compounds without undue experimentation. Thus in one embodiment, compound(s) or combination of compounds described herein may be delivered via sustained released formulations
35 alone or in combination with administration of certain components of the treatment regimen by oral, IV or parenteral routes.

A lyophilized formulation may also be used to administer a compound of formula (I) singly or in combination with an additional anticancer agent. One of skill in the art is aware of how to make and use lyophilized formulations of drug substances amenable to lyophilization.

5 Spray-dried formulation may also be used to administer a compound of formula (I) singly or in combination with an additional anti-cancer agent. One of skill in the art is aware of how to make and use spray-dried formulations of drug substances amenable to spray-drying. Other known formulation techniques may also be employed to formulate a compound or combination of compounds disclosed herein.

Combination Therapy

10 Also provided are methods of treatment in which a compound of formula (I) or a pharmaceutically acceptable salt thereof, is given to a patient in combination with one or more additional active agents or therapy.

Thus in one embodiment, a method of treating cancer and/or diseases or symptoms that co-present or are exacerbated or triggered by the cancer e.g., an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction, comprises administering to a patient
15 in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, optionally in combination with an additional agent (e.g., a second, third, fourth or fifth active agent) which can be useful for treating a cancer, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction incident to or co-presenting with a cancer.
20 Treatment with the second, third, fourth or fifth active agent may be prior to, concomitant with, or following treatment with a compound of formula (I) or a pharmaceutically acceptable salt thereof. In one embodiment, a compound of formula (I) or a pharmaceutically acceptable salt thereof is combined with another active agent in a single dosage form. Suitable antitumor or anticancer therapeutics that may be used in combination with a compound of formula (I) or a pharmaceutically acceptable salt thereof
25 include, but are not limited to, chemotherapeutic agents, for example mitomycin C, carboplatin, taxol, cisplatin, paclitaxel, etoposide, doxorubicin, or a combination comprising at least one of the foregoing chemotherapeutic agents. Radiotherapeutic antitumor agents may also be used, alone or in combination with chemotherapeutic agents.

A compound of formula (I) or a pharmaceutically acceptable salt thereof can be useful as chemo-
30 sensitizing agents, and thus, can be useful in combination with other chemotherapeutic drugs, in particular, drugs that induce apoptosis. Thus, in one embodiment, the present disclosure provides a method for increasing sensitivity of cancer cells to chemotherapy, comprising administering to a patient in need of or undergoing chemotherapy, a chemotherapeutic agent together with a compound of formula (I), or a pharmaceutically acceptable salt thereof in an amount sufficient to increase the sensitivity of
35 cancer cells to the chemotherapeutic agent.

Examples of other chemotherapeutic drugs that can be used in combination with compounds of formula (I), or a pharmaceutically acceptable salt thereof include topoisomerase I inhibitors (camptothecin or topotecan), topoisomerase II inhibitors (e.g., daunomycin and etoposide), alkylating agents (e.g., cyclophosphamide, melphalan and BCNU), tubulin directed agents (e.g., taxol and vinblastine), and biological agents (e.g., antibodies such as anti CD20 antibody, IDEC 8, immunotoxins, and cytokines).

In some embodiments, the compound(s) of formula (I), or a pharmaceutically acceptable salt thereof is used in combination with Rituxan® (Rituximab) and/or other agents that work by selectively depleting CD20+ B-cells.

Included herein are methods of treatment in which a compound of formula (I), or a pharmaceutically acceptable salt thereof is administered in combination with an anti-inflammatory agent. Anti-inflammatory agents include but are not limited to NSAIDs, non-specific and COX-2 specific cyclooxygenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor receptor (TNF) receptors antagonists, immunosuppressants and methotrexate.

Examples of NSAIDs include, but are not limited to ibuprofen, flurbiprofen, naproxen and naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, and hydroxychloroquine. Examples of NSAIDs also include COX-2 specific inhibitors (i.e., a compound that inhibits COX-2 with an IC_{50} that is at least 50-fold lower than the IC_{50} for COX-1) such as celecoxib, valdecoxib, lumiracoxib, etoricoxib and/or rofecoxib.

In a further embodiment, the anti-inflammatory agent is a salicylate. Salicylates include but are not limited to acetylsalicylic acid or aspirin, sodium salicylate, and choline and magnesium salicylates.

The anti-inflammatory agent may also be a corticosteroid. For example, the corticosteroid may be chosen from cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, and prednisone.

In some embodiments, the anti-inflammatory therapeutic agent is a gold compound such as gold sodium thiomalate or auranofin.

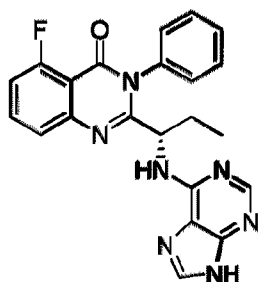
In some embodiments, the anti-inflammatory agent is a metabolic inhibitor such as a dihydrofolate reductase inhibitor, such as methotrexate or a dihydroorotate dehydrogenase inhibitor, such as leflunomide.

In one embodiment, the compound(s) of formula (I), or a pharmaceutically acceptable salt thereof is used in combination with at least one anti-inflammatory compound that is an anti-C5 monoclonal antibody (such as eculizumab or pexelizumab), a TNF antagonist, such as etanercept, or infliximab, which is an anti-TNF alpha monoclonal antibody.

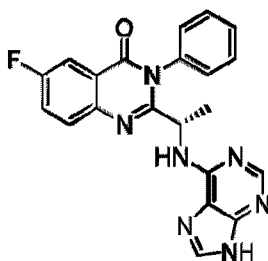
In one embodiment, the compound(s) of formula (I), or a pharmaceutically acceptable salt thereof is used in combination with at least one active agent that is an immunosuppressant compound such as methotrexate, leflunomide, cyclosporine, tacrolimus, azathioprine, or mycophenolate mofetil.

In other embodiments, the compound(s) of formula (I), or a pharmaceutically acceptable salt thereof is used in combination with one or more phosphatidylinositol 3-kinase (PI3K) inhibitors, including for example, Compounds A, B and C (whose structures are provided below), or a pharmaceutically acceptable salt thereof.

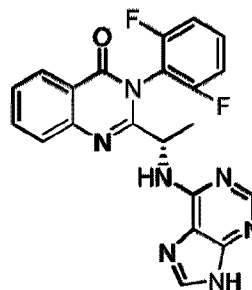
Compound A



Compound B



Compound C



Compounds A, B and C are disclosed in WO2015/017460 and WO2015/100217. Additional examples of PI3K inhibitors include, but are not limited to, ACP-319, AEZA-129, AMG-319, AS252424, AZD8186, BAY 10824391, BEZ235, buparlisib (BKM120), BYL719 (alpelisib), CH5132799, copanlisib (BAY 80-6946), duvelisib, GDC-0941, GDC-0980, GSK2636771, GSK2269557, idelalisib (Zydelig®), IPI-145, IPI-443, IPI-549, KAR4141, LY294002, LY3023414, MLN1117, OXY111A, PA799, PX-866, RG7604, rigosertib, RP5090, taselisib, TG100115, TGR-1202, TGX221, WX-037, X-339, X-414, XL147 (SAR245408), XL499, XL756, wortmannin, ZSTK474, and the compounds described in WO 2005/113556 (ICOS), WO 2013/052699 (Gilead Calistoga), WO 2013/116562 (Gilead Calistoga), WO 2014/100765 (Gilead Calistoga), WO 2014/100767 (Gilead Calistoga), and WO 2014/201409 (Gilead Sciences).

In yet another embodiment, the compound(s) of formula (I) may be used in combination with Spleen Tyrosine Kinase (SYK) Inhibitors. Examples of SYK inhibitors include, but are not limited to, 6-(1H-indazol-6-yl)-N-(4-morpholinophenyl)imidazo[1,2-a]pyrazin-8-amine, BAY-61-3606, cerdulatinib (PRT-062607), entospletinib, fostamatinib (R788), HMPL-523, NVP-QAB 205 AA, R112, R343, taminib (R406), and those described in U.S. 8450321 (Gilead Connecticut) and those described in U.S. 2015/0175616.

In yet another embodiment, the compounds of formula (I) may be used in combination with Tyrosine-kinase Inhibitors (TKIs). TKIs may target epidermal growth factor receptors (EGFRs) and receptors for fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF). Examples of TKIs include, but are not limited to, afatinib, ARQ-087, asp5878, AZD3759, AZD4547, bosutinib, brigatinib, cabozantinib, cediranib, crenolanib, dacomitinib,

dasatinib, dovitinib, E-6201, erdafitinib, erlotinib, gefitinib, gilteritinib (ASP-2215), FP-1039, HM61713, icotinib, imatinib, KX2-391 (Src), lapatinib, lestaurtinib, midostaurin, nintedanib, ODM-203, osimertinib (AZD-9291), ponatinib, poziotinib, quizartinib, radotinib, rociletinib, sulfatinib (HMPL-012), sunitinib, and TH-4000.

In yet other embodiments, the compound(s) of formula (I), or a pharmaceutically acceptable salt thereof is used in combination with one or more inhibitors of lysyl oxidase-like 2 (LOXL) or a substance that binds to LOXL, including for example, a humanized monoclonal antibody (mAb) with an immunoglobulin IgG4 isotype directed against human LOXL2. Examples of LOXL inhibitors include, but are not limited to, the antibodies described in WO 2009/017833 (Arresto Biosciences). Examples of LOXL2 inhibitors include, but are not limited to, the antibodies described in WO 2009/017833 (Arresto Biosciences), WO 2009/035791 (Arresto Biosciences), and WO 2011/097513 (Gilead Biologics).

In yet another embodiment, the compounds of formula (I) may be used in combination with Toll-like receptor 8 (TLR8) inhibitors. Examples of TLR8 inhibitors include, but are not limited to, E-6887, IMO-4200, IMO-8400, IMO-9200, MCT-465, MEDI-9197, motolimod, resiquimod, VTX-1463, and VTX-763.

In yet another embodiment, the compounds of formula (I) may be used in combination with Toll-like receptor (TLR9) inhibitors. Examples of TLR9 inhibitors include, but are not limited to, IMO-2055, IMO-2125, lefitolimod, litemimod, MGN-1601, and PUL-042.

In one embodiment, the compound of formula (I) is useful for the treatment of cancer in combination with a BTK (Bruting's Tyrosine kinase) inhibitor. An example of such BTK inhibitor is a compound disclosed in U.S. patent 7,405,295. Additional examples of BTK inhibitors include, but are not limited to, (S)-6-amino-9-(1-(but-2-ynoyl)pyrrolidin-3-yl)-7-(4-phenoxyphenyl)-7H-purin-8(9H)-one, acalabrutinib (ACP-196), BGB-3111, HM71224, ibrutinib, M-2951, tirabrutinib (ONO-4059), PRN-1008, spebrutinib (CC-292), and TAK-020.

In one embodiment, the compound of formula (I) is useful for the treatment of cancer in combination with a BET inhibitor. An example of such BET inhibitor is a compound disclosed in WO2014/182929.

In one embodiment, the compound of formula (I) is useful for the treatment of cancer in combination with a TBK (Tank Binding kinase) inhibitor. An example of such TBK inhibitor is a compound disclosed in WO2016/049211.

In one embodiment, the compound of formula (I) is useful for the treatment of cancer in combination with a OX40 inhibitor. An example of such OX40 inhibitor is a compound disclosed in U.S. 8,450,460.

In one embodiment, the compound of formula (I) is useful for the treatment of cancer in combination with a JAK-1 inhibitor. An example of such JAK-1 inhibitor is a compound disclosed in

WO2008/109943. Examples of other JAK inhibitors include, but are not limited to, AT9283, AZD1480, baricitinib, BMS-911543, fedratinib, filgotinib (GLPG0634), gandotinib (LY2784544), INCB039110, lestaurtinib, momelotinib (CYT0387), NS-018, pacritinib (SB1518), peficitinib (ASP015K), ruxolitinib, tofacitinib (formerly tasocitinib), and XL019.

5 In one embodiment, the compound of formula (I) is useful for the treatment of cancer in combination with an Indoleamine-pyrrole-2,3-dioxygenase (IDO) inhibitors. An example of such IDO inhibitor is a compound disclosed in WO2016/186967. In one embodiment, the compounds of formula (I) are useful for the treatment of cancer in combination with IDO1 inhibitors including but not limited to BLV-0801, epacadostat, F-001287, GBV-1012, GBV-1028, GDC-0919, indoximod, NKTR-218, NLG-
10 919-based vaccine, PF-06840003, pyranonaphthoquinone derivatives (SN-35837), resminostat, SBLK-200802, and shIDO-ST.

In one embodiment, the compound of formula (I) is useful for the treatment of cancer in combination with a Mitogen-activated Protein Kinase (MEK) Inhibitors. MEK inhibitors useful for combination treatment with a compound(s) of formula (I) includes antroquinonol, binimetinib,
15 cobimetinib (GDC-0973, XL-518), MT-144, selumetinib (AZD6244), sorafenib, trametinib (GSK1120212), uprosertib and trametinib.

In one embodiment, the compound of formula (I) is useful for the treatment of cancer in combination with an Apoptosis Signal-Regulating Kinase (ASK) Inhibitors: ASK inhibitors include but are not limited to those described in WO 2011/008709 (Gilead Sciences) and WO 2013/112741 (Gilead
20 Sciences) including for example selonsertib.

In one embodiment, the compounds of formula (I) may be combined with Cluster of Differentiation 47 (CD47) inhibitors. Examples of CD47 inhibitors include, but are not limited to anti-CD47 mAbs (Vx-1004), anti-human CD47 mAbs (CNTO-7108), CC-90002, CC-90002-ST-001, humanized anti-CD47 antibody (Hu5F9-G4), NI-1701, NI-1801, RCT-1938, and TTI-621.

25 In one embodiment, the compounds of formula (I) may be combined with Cyclin-dependent Kinase (CDK) Inhibitors. CDK inhibitors include inhibitors of CDK 1, 2, 3, 4, 6 and 9, such as abemaciclib, alvociclib (HMR-1275, flavopiridol), AT-7519, FLX-925, LEE001, palbociclib, ribociclib, rigosertib, selinexor, UCN-01, and TG-02.

In one embodiment, the compounds of formula (I) may be combined with Discoidin Domain
30 Receptor (DDR) Inhibitors for the treatment of cancer. DDR inhibitors include inhibitors of DDR1 and/or DDR2. Examples of DDR inhibitors include, but are not limited to, those disclosed in WO 2014/047624 (Gilead Sciences), US 2009-0142345 (Takeda Pharmaceutical), US 2011-0287011 (Oncomed Pharmaceuticals), WO 2013/027802 (Chugai Pharmaceutical), and WO 2013/034933 (Imperial Innovations).

35 In one embodiment, the compounds of formula (I) may be combined with Histone Deacetylase (HDAC) Inhibitors such as those disclosed in U.S. patent 8,575,353 and equivalents thereof. Additional

examples of HDAC inhibitors include, but are not limited to, abexinostat, ACY-241, AR-42, BEBT-908, belinostat, CKD-581, CS-055 (HBI-8000), CUDC-907, entinostat, givinostat, mocetinostat, panobinostat, pracinostat, quisinostat (JNJ-26481585), resminostat, ricolinostat, SHP-141, valproic acid (VAL-001), vorinostat.

5 In one embodiment, the compound of formula (I) is useful for the treatment of cancer in combination with a standard of care in the treatment of the respective cancer. One of skill in the art is aware of the standard of care as of a given date in the particular field of cancer therapy or with respect to a given cancer.

10 Certain embodiments of the present application include or use one or more additional therapeutic agent. The one or more additional therapeutic agent may be an agent useful for the treatment of cancer, inflammation, autoimmune disease and/or related conditions. The one or more additional therapeutic agent may be a chemotherapeutic agent, an anti-angiogenic agent, an antifibrotic agent, an anti-inflammatory agent, an immune modulating agent, an immunotherapeutic agent, a therapeutic antibody, a radiotherapeutic agent, an anti-neoplastic agent, an anti-cancer agent, an anti-proliferation agent, or any
15 combination thereof. In some embodiments, the compound(s) described herein may be used or combined with a chemotherapeutic agent, an anti-angiogenic agent, an anti-fibrotic agent, an anti-inflammatory agent, an immune modulating agent, an immunotherapeutic agent, a therapeutic antibody, a radiotherapeutic agent, an antineoplastic agent or an anti-cancer agent, an anti-proliferation agent, or any combination thereof.

20 In one embodiment, a compound(s) of formula (I) optionally in combination with an additional anticancer agent described herein, may be used or combined with an anti-neoplastic agent or an anti-cancer agent, anti-fibrotic agent, an anti-anti-inflammatory agent, or an immune modulating agent.

 In one embodiment, provided are kits comprising a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, or a compound of formula (I) and at least
25 one additional anticancer agent, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier. In one embodiment, the kit comprises instructions for use in the treatment of cancer or inflammatory conditions. In one embodiment, the instructions in the kit are directed to use of the pharmaceutical composition for the treatment of cancer selected from pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular
30 cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft tissue sarcoma, non-small cell lung cancer, small-cell lung cancer and colon cancer.

 The application also provides method for treating a subject who is undergoing one or more standard therapies, such as chemotherapy, radiotherapy, immunotherapy, surgery, or combination thereof
35 comprising administering or co-administering a compound of formula (I) to said subject. Accordingly, one or more compound(S) of formula (I), or pharmaceutically acceptable salt thereof, may be

administered before, during, or after administration of a chemotherapy, radiotherapy, immunotherapy, surgery or combination thereof.

In one embodiment, the subject may be a human who is (i) substantially refractory to at least one chemotherapy treatment, or (ii) in relapse after treatment with chemotherapy, or both (i) and (ii). In some
5 of embodiments, the subject is refractory to at least two, at least three, or at least four chemotherapy treatments (including standard or experimental chemotherapies).

In one embodiment, the subject is refractory to at least one, at least two, at least three, or at least four chemotherapy treatment (including standard or experimental chemotherapy) selected from fludarabine, rituximab, obinutuzumab, alkylating agents, alemtuzumab and other chemotherapy
10 treatments such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); R-CHOP (rituximab-CHOP); hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine); R-hyperCVAD (rituximab-hyperCVAD); FCM (fludarabine, cyclophosphamide, mitoxantrone); R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantrone); bortezomib and rituximab; temsirolimus and rituximab; temsirolimus and Velcade®; Iodine-131
15 tositumomab (Bexxar®) and CHOP; CVP (cyclophosphamide, vincristine, prednisone); R-CVP (rituximab-CVP); ICE (ifosfamide, carboplatin, etoposide); R-ICE (rituximab-ICE); FCR (fludarabine, cyclophosphamide, rituximab); FR (fludarabine, rituximab); and D.T. PACE (dexamethasone, thalidomide, cisplatin, Adriamycin®, cyclophosphamide, etoposide).

Other examples of chemotherapy treatments (including standard or experimental
20 chemotherapies) are described below. In addition, treatment of certain lymphomas is reviewed in Cheson, B.D., Leonard, J.P., "Monoclonal Antibody Therapy for B-Cell Non-Hodgkin's Lymphoma" *The New England Journal of Medicine* 2008, 359(6), p. 613-626; and Wierda, W.G., "Current and Investigational Therapies for Patients with CLL" *Hematology* 2006, p. 285-294. Lymphoma incidence patterns in the United States is profiled in Morton, L.M., *et al.* "Lymphoma Incidence Patterns by WHO
25 Subtype in the United States, 1992-2001" *Blood* 2006, 107(1), p. 265-276.

Examples of immunotherapeutic agents treating lymphoma or leukemia include, but are not limited to, rituximab (such as Rituxan), alemtuzumab (such as Campath, MabCampath), anti-CD19 antibodies, anti-CD20 antibodies, anti-MN-14 antibodies, anti-TRAIL, Anti-TRAIL DR4 and DR5 antibodies, anti-CD74 antibodies, apolizumab, bevacizumab, CHIR-12.12, epratuzumab (hLL2- anti-
30 CD22 humanized antibody), galiximab, ha20, ibritumomab tiuxetan, lumiliximab, milatuzumab, ofatumumab, PRO131921, SGN-40, WT-1 analog peptide vaccine, WT1 126-134 peptide vaccine, tositumomab, autologous human tumor-derived HSPPC-96, and velutuzumab. Additional immunotherapy agents includes using cancer vaccines based upon the genetic makeup of an individual patient's tumor, such as lymphoma vaccine example is GTOP-99 (MyVax®).

35 Examples of chemotherapy agents for treating lymphoma or leukemia include aldesleukin, alvociclib, antineoplaston AS2-1, antineoplaston A10, anti-thymocyte globulin, amifostine trihydrate,

aminocamptothecin, arsenic trioxide, beta alethine, Bcl-2 family protein inhibitor ABT-263, BMS-345541, bortezomib (Velcade®), bryostatins, busulfan, carboplatin, campath-1H, CC-5103, carmustine, caspofungin acetate, clofarabine, cisplatin, Cladribine (Leustarin), Chlorambucil (Leukeran), Curcumin, cyclosporine, Cyclophosphamide (Cytoxan, Endoxan, Endoxana, Cyclostin), cytarabine, denileukin

5 diftitox, dexamethasone, DT PACE, docetaxel, dolastatin 10, Doxorubicin (Adriamycin®, Adriblastine), doxorubicin hydrochloride, enzastaurin, epoetin alfa, etoposide, Everolimus (RAD001), fenretinide, filgrastim, melphalan, mesna, Flavopiridol, Fludarabine (Fludara), Geldanamycin (17-AAG), ifosfamide, irinotecan hydrochloride, ixabepilone, Lenalidomide (Revlimid®, CC-5013), lymphokine-activated killer cells, melphalan, methotrexate, mitoxantrone hydrochloride, motexafin gadolinium, mycophenolate

10 mofetil, nelarabine, oblimersen (Genasense) Obatoclax (GX15-070), oblimersen, octreotide acetate, omega-3 fatty acids, oxaliplatin, paclitaxel, PD0332991, PEGylated liposomal doxorubicin hydrochloride, pegfilgrastim, Pentastatin (Nipent), perfosine, Prednisolone, Prednisone, R-roscovitine (Seliciclib, CYC202), recombinant interferon alfa, recombinant interleukin-12, recombinant interleukin-11, recombinant flt3 ligand, recombinant human thrombopoietin, rituximab, sargramostim, sildenafil

15 citrate, simvastatin, sirolimus, Styryl sulphones, tacrolimus, tanespimycin, Temsirolimus (CCI-779), Thalidomide, therapeutic allogeneic lymphocytes, thiotepa, tipifarnib, Velcade® (bortezomib or PS-341), Vincristine (Oncovin), vincristine sulfate, vinorelbine ditartrate, Vorinostat (SAHA), vorinostat, and FR (fludarabine, rituximab), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CVP (cyclophosphamide, vincristine and prednisone), FCM (fludarabine, cyclophosphamide, mitoxantrone),

20 FCR (fludarabine, cyclophosphamide, rituximab), hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine), ICE (cyclophosphamide, carboplatin and etoposide), MCP (mitoxantrone, chlorambucil, and prednisolone), R-CHOP (rituximab plus CHOP), R-CVP (rituximab plus CVP), R-FCM (rituximab plus FCM), R-ICE (rituximab-ICE), and R-MCP (Rituximab-MCP).

25 In some embodiments, the cancer is melanoma. Suitable agents for use in combination with the compounds described herein include, without limitation, dacarbazine (DTIC), optionally, along with other chemotherapy drugs such as carmustine (BCNU) and cisplatin; the "Dartmouth regimen," which consists of DTIC, BCNU, cisplatin and tamoxifen; a combination of cisplatin, vinblastine, and DTIC, temozolomide or YERVOY™. Compounds disclosed herein may also be combined with immunotherapy

30 drugs, including cytokines such as interferon alpha, interleukin 2, and tumor necrosis factor (TNF) in the treatment of melanoma.

Compounds described here may also be used in combination with vaccine therapy in the treatment of melanoma. Anti-melanoma vaccines are, in some ways, similar to the anti-virus vaccines which are used to prevent diseases caused by viruses such as polio, measles, and mumps. Weakened

35 melanoma cells or parts of melanoma cells called antigens may be injected into a patient to stimulate the body's immune system to destroy melanoma cells.

Melanomas that are confined to the arms or legs may also be treated with a combination of agents including one or more compounds described herein, using for example, a hyperthermic isolated limb perfusion technique. This treatment protocol temporarily separates the circulation of the involved limb from the rest of the body and injects high doses of chemotherapy into the artery feeding the limb, thus providing high doses to the area of the tumor without exposing internal organs to these doses that might otherwise cause severe side effects. Usually the fluid is warmed to 102° to 104° F. Melphalan is the drug most often used in this chemotherapy procedure. This can be given with another agent called tumor necrosis factor (TNF) and optionally in combination with a compound of formula (I).

The therapeutic treatments can be supplemented or combined with any of the aforementioned therapies with stem cell transplantation or treatment. One example of modified approach is radioimmunotherapy, wherein a monoclonal antibody is combined with a radioisotope particle, such as indium In 111, yttrium Y 90, iodine I-131. Examples of combination therapies include, but are not limited to, Iodine-131 tositumomab (Bexxar®), Yttrium-90 ibritumomab tiuxetan (Zevalin®), Bexxar® with CHOP.

Other therapeutic procedures useful in combination with treatment with a compound of formula (I) include peripheral blood stem cell transplantation, autologous hematopoietic stem cell transplantation, autologous bone marrow transplantation, antibody therapy, biological therapy, enzyme inhibitor therapy, total body irradiation, infusion of stem cells, bone marrow ablation with stem cell support, *in vitro*-treated peripheral blood stem cell transplantation, umbilical cord blood transplantation, immunoenzyme technique, pharmacological study, low-LET cobalt-60 gamma ray therapy, bleomycin, conventional surgery, radiation therapy, and nonmyeloablative allogeneic hematopoietic stem cell transplantation.

In some embodiments, the application provides pharmaceutical compositions comprising a compound of formula (I) in combination with an MMP9 binding protein and/or one or more additional therapeutic agent, and a pharmaceutically acceptable diluent, carrier or excipient. In one embodiment, the pharmaceutical compositions comprise an MMP9 binding protein, one or more additional therapeutic agent, and a pharmaceutically acceptable excipient, carrier or diluent. In some embodiments, the pharmaceutical compositions comprise the compound of formula (I) and anti-MMP9 antibody AB0045.

In one embodiment, the pharmaceutical compositions comprise the compound of formula (I), anti-MMP9 antibody AB0045, at least one additional therapeutic agent that is an immunomodulating agent, and a pharmaceutically acceptable diluent, carrier or excipient. In certain other embodiments, the pharmaceutical compositions comprise the anti-MMP9 antibody AB0045, at least one additional therapeutic agent that is an anti-inflammatory agent, and a pharmaceutically acceptable diluent, carrier or excipient. In certain other embodiments, the pharmaceutical compositions comprise compound of formula (I), the anti-MMP9 antibody AB0045, at least one additional therapeutic agent that is an antineoplastic agent or anti-cancer agent, and a pharmaceutically acceptable diluent, carrier or excipient. In one embodiment, MMP9 compounds useful for combination treatment with a compound of formula (I)

include but are not limited to marimastat (BB-2516), cipemastat (Ro 32-3555) and those described in WO 2012/027721 (Gilead Biologics).

In one embodiment, the one or more additional therapeutic agent is an immune modulating agent, e.g., an immunostimulant or an immunosuppressant. In certain other embodiments, an immune
 5 modulating agent is an agent capable of altering the function of immune checkpoints, including the CTLA-4, LAG-3, B7-H3, B7-H4, Tim3, BTLA, KIR, A2aR, CD200 and/or PD-1 pathways. In other embodiments, the immune modulating agent is immune checkpoint modulating agents. Exemplary immune checkpoint modulating agents include anti-CTLA-4 antibody (e.g., ipilimumab), anti-LAG-3
 10 antibody, anti-B7-H3 antibody, anti-B7-H4 antibody, anti-Tim3 antibody, anti-BTLA antibody, anti-KIR antibody, anti-A2aR antibody, anti CD200 antibody, anti-PD-1 antibody, anti-PD-L1 antibody, anti-CD28 antibody, anti-CD80 or -CD86 antibody, anti-B7RP1 antibody, anti-B7-H3 antibody, anti-HVEM antibody, anti-CD137 or -CD137L antibody, anti-OX40 or -OX40L antibody, anti-CD40 or -CD40L antibody, anti-GAL9 antibody, anti-IL-10 antibody and A2aR drug. For certain such immune pathway
 15 gene products, the use of either antagonists or agonists of such gene products is contemplated, as are small molecule modulators of such gene products. In one embodiment, the immune modulatory agent is an anti-PD-1 or anti-PD-L1 antibody. In some embodiments, immune modulating agents include those agents capable of altering the function of mediators in cytokine mediated signaling pathways.

In some embodiments, the one or more additional therapy or anti-cancer agent is cancer gene therapy or cell therapy. Cancer gene therapy and cell therapy include the insertion of a normal gene into
 20 cancer cells to replace a mutated or altered gene; genetic modification to silence a mutated gene; genetic approaches to directly kill the cancer cells; including the infusion of immune cells designed to replace most of the patient's own immune system to enhance the immune response to cancer cells, or activate the patient's own immune system (T cells or Natural Killer cells) to kill cancer cells, or find and kill the cancer cells; genetic approaches to modify cellular activity to further alter endogenous immune
 25 responsiveness against cancer. Non limiting examples are Algenpantucel-L (2 pancreatic cell lines), Sipuleucel-T, SGT-53 liposomal nanodelivery (scL) of gene p53; T-cell therapy, such as CD19 CAR-T tisagenlecleucel-T (CTL019) WO2012079000, WO2017049166, axicabtagene ciloleucel (KTE-C19) US7741465, US6319494, JCAR-015 US7446190, JCAR-014, JCAR-020, JCAR-024, JCAR-023, JTCR-016, JCAR-018 WO2016090190, JCAR-017, (WO2016196388, WO2016033570, WO2015157386),
 30 BPX-501 US9089520, WO2016100236, AU-105, UCART-22, ACTR-087, P-BCMA-101; activated allogeneic natural killer cells CNDO-109-AANK, FATE-NK100, LFU-835 hematopoietic stem cells.

In one embodiment, the one or more additional therapeutic agent is an immune checkpoint inhibitor. Tumors subvert the immune system by taking advantage of a mechanism known as T-cell exhaustion, which results from chronic exposure to antigens and is characterized by the up-regulation of
 35 inhibitory receptors. These inhibitory receptors serve as immune checkpoints in order to prevent uncontrolled immune reactions.

PD-1 and co-inhibitory receptors such as cytotoxic T-lymphocyte antigen 4 (CTLA-4, B and T Lymphocyte Attenuator (BTLA; CD272), T cell Immunoglobulin and Mucin domain-3 (Tim-3), Lymphocyte Activation Gene-3 (Lag-3; CD223), and others are often referred to as a checkpoint regulators. They act as molecular determinants to influence whether cell cycle progression and other intracellular signaling processes should proceed based upon extracellular information.

In addition to specific antigen recognition through the T-cell receptor (TCR), T-cell activation is regulated through a balance of positive and negative signals provided by costimulatory receptors. These surface proteins are typically members of either the TNF receptor or B7 superfamilies. Agonistic antibodies directed against activating co-stimulatory molecules and blocking antibodies against negative co-stimulatory molecules may enhance T-cell stimulation to promote tumor destruction.

Programmed Cell Death Protein 1, (PD-1 or CD279), a 55-kD type 1 transmembrane protein, is a member of the CD28 family of T cell co-stimulatory receptors that include immunoglobulin superfamily member CD28, CTLA-4, inducible co-stimulator (ICOS), and BTLA. PD-1 is highly expressed on activated T cells and B cells. PD-1 expression can also be detected on memory T-cell subsets with variable levels of expression. Two ligands specific for PD-1 have been identified: programmed death- ligand 1 (PD-L1, also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or CD273). PD-L1 and PD-L2 have been shown to down-regulate T cell activation upon binding to PD-1 in both mouse and human systems (Okazaki et al., *Int. Immunol.*, 2007; 19: 813-824). The interaction of PD-1 with its ligands, PD-L1 and PD-L2, which are expressed on antigen-presenting, cells (APCs) and dendritic cells (DCs), transmits negative regulatory stimuli to down-modulate the activated T cell immune response. Blockade of PD-1 suppresses this negative signal and amplifies T cell responses. Numerous studies indicate that the cancer microenvironment manipulates the PD-L1/PD-1 signaling pathway and that induction of PD-L1 expression is associated with inhibition of immune responses against cancer, thus permitting cancer progression and metastasis. The PD-L1/ PD-1 signaling pathway is a primary mechanism of cancer immune evasion for several reasons. This pathway is involved in negative regulation of immune responses of activated T effector cells found in the periphery. PD-L1 is up-regulated in cancer microenvironments, while PD-1 is also up-regulated on activated tumor infiltrating T cells, thus possibly potentiating a vicious cycle of inhibition. This pathway is also intricately involved in both innate and adaptive immune regulation through bi-directional signaling. These factors make the PD-1/PD-L1 complex a central point through which cancer can manipulate immune responses and promote its own progression.

The first immune-checkpoint inhibitor to be tested in a clinical trial was ipilimumab (Yervoy, Bristol-Myers Squibb), a CTLA-4 mAb. CTLA-4 belongs to the immunoglobulin superfamily of receptors, which also includes PD-1, BTLA, TIM-3, and V-domain immunoglobulin suppressor of T cell activation (VISTA). Anti-CTLA-4 mAb is a powerful checkpoint inhibitor which removes "the break" from both naive and antigen-experienced cells.

Therapy enhances the antitumor function of CD8+ T cells, increases the ratio of CD8+ T cells to Foxp3+ T regulatory cells, and inhibits the suppressive function of T regulatory cells. TIM-3 has been identified as another important inhibitory receptor expressed by exhausted CD8+ T cells. In mouse models of cancer, it has been shown that the most dysfunctional tumor-infiltrating CD8+ T cells actually co-express PD-1 and LAG-3. LAG-3 is another recently identified inhibitory receptor that acts to limit effector T-cell function and augment the suppressive activity of T regulatory cells. It has recently been revealed that PD-1 and LAG-3 are extensively co-expressed by tumor-infiltrating T cells in mice, and that combined blockade of PD-1 and LAG-3 provokes potent synergistic antitumor immune responses in mouse models of cancer.

Thus in one embodiment, the present disclosure provides the use of immune checkpoint inhibitors of formula (I) disclosed herein in combination with one or more additional immune checkpoint inhibitors. In one embodiment, the present disclosure provides the use of immune checkpoint inhibitors of formula (I) disclosed herein in combination with one or more additional immune checkpoint inhibitors and an anti-MMP9 antibody or antigen binding fragment thereof to treat or prevent cancer. In some embodiments, the immune checkpoint inhibitors may be an anti-PD-1 and/or an anti-PD-L1 antibody or an anti PD-1/PD-L1 interaction inhibitor. In some embodiments, the anti-PD-L1 antibody may be B7-H1 antibody, BMS 936559 antibody, MPDL3280A (atezolizumab) antibody, MEDI-4736 antibody, MSB0010718C antibody or combinations thereof. According to another embodiment, the anti-PD-1 antibody may be nivolumab antibody, pembrolizumab antibody, pidilizumab antibody or combinations thereof.

In addition, PD-1 may also be targeted with AMP-224, which is a PD-L2-IgG recombinant fusion protein. Additional antagonists of inhibitory pathways in the immune response include IMP321, a soluble LAG-3 Ig fusion protein and MHC class II agonist, which is used to increase an immune response to tumors. Lirilumab is an antagonist to the KIR receptor and BMS 986016 is an antagonist of LAG3. The TIM-3-Galectin-9 pathway is another inhibitory checkpoint pathway that is also a promising target for checkpoint inhibition. RX518 targets and activates the glucocorticoid-induced tumor necrosis factor receptor (GITR), a member of the TNF receptor superfamily that is expressed on the surface of multiple types of immune cells, including regulatory T cells, effector T cells, B cells, natural killer (NK) cells, and activated dendritic cells. Thus, in one embodiment, the compound(s) of formula (I) may be used in combination with IMP321, Lirilumab and/or BMS 986016.

Anti-PD-1 antibodies that may be used in the compositions and methods described herein include but are not limited to: Nivolumab /MDX-1106/BMS-936558/ONO1152, a fully human IgG4 anti-PD-1 monoclonal antibody; pidilizumab (MDV9300/CT-011), a humanized IgG1 monoclonal antibody; pembrolizumab (MK-3475/ pembrolizumab /lambrolizumab), a humanized monoclonal IgG4 antibody; durvalumab (MEDI-4736) and atezolizumab. Anti-PD-L1 antibodies that may be used in compositions and methods described herein include but are not limited to: avelumab; BMS-936559, a

fully human IgG4 antibody; atezolizumab (MPDL3280A/RG-7446), a human monoclonal antibody; MEDI4736; MSB0010718C, and MDX1105-01.

In one embodiment, the compound of formula (I) is administered in combination with the anti-PD-1 antibody nivolumab, pembrolizumab, and/or pidilizumab to a patient in need thereof. In one embodiment, the anti-PD-L1 antibody useful for combination treatment with a compound of formula (I) is BMS-936559, atezolizumab, or avelumab. In one embodiment, the immune modulating agent inhibits an immune checkpoint pathway. In another embodiment, the immune checkpoint pathway is selected from CTLA-4, LAG-3, B7-H3, B7-H4, Tim3, BTLA, KIR, A2aR, CD200 and PD-1. Additional antibodies that may be used in combination with a compound of formula (I) in compositions and methods described herein include the anti-PD-1 and anti-PD-L1 antibodies disclosed in U.S. Patent Nos. 8,008,449 and 7,943,743, respectively.

In one embodiment, the one or more additional therapeutic agent is an anti-inflammatory agent. In certain other embodiments, the anti-inflammatory agent is a tumor necrosis factor alpha (TNF- α) inhibitor. As used herein, the terms "TNF alpha," "TNF- α ," and "TNF α ," are interchangeable. TNF- α is a pro-inflammatory cytokine secreted primarily by macrophages but also by a variety of other cell types including lymphoid cells, mast cells, endothelial cells, cardiac myocytes, adipose tissue, fibroblasts, and neuronal tissue. TNF- α is also known as endotoxin-induced factor in serum, cachectin, and differentiation inducing factor. The tumor necrosis factor (TNF) family includes TNF alpha, TNF beta, CD40 ligand (CD40L), Fas ligand (FasL), TNF-related apoptosis inducing ligand (TRAIL), and LIGHT (homologous to lymphotoxins, exhibits inducible expression, and competes with HSV glycoprotein D for HVEM, a receptor expressed by T lymphocytes), some of the most important cytokines involved in, among other physiological processes, systematic inflammation, tumor lysis, apoptosis and initiation of the acute phase reaction.

The above therapeutic agents when employed in combination with a compound(s) disclosed herein, may be used, for example, in those amounts indicated in the referenced manuals e.g., Physicians Desk Reference or in amounts generally known to a qualified care giver, i.e., one of ordinary skill in the art. In the methods of the present disclosure, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the compound(s) of formula (I). Certain other therapeutic agents may be combined into a single formulation or kit when amenable to such. For example, tablet, capsule or liquid formulations may be combined with other tablet, capsule or liquid formulations into one fixed or combined dose formulation or regimen. Other combinations may be given separately, contemporaneously or otherwise.

In one embodiment, the instructions are directed to use of the pharmaceutical composition for the treatment of cancer, including for example, leukemia or lymphoma. In specific embodiments, the cancer is acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), myelodysplastic syndrome (MDS), myeloproliferative

disease (MPD), chronic myeloid leukemia (CML), multiple myeloma (MM), indolent non-Hodgkin's lymphoma (iNHL), refractory iNHL, non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma, Waldstrom's macroglobulinemia (WM), T-cell lymphoma, B-cell lymphoma, and diffuse large B-cell lymphoma (DLBCL). In one embodiment, the cancer is T-cell acute lymphoblastic leukemia (T-ALL), or B-cell acute lymphoblastic leukemia (B-ALL). The non-Hodgkin lymphoma encompasses the indolent B-cell diseases that include, for example, follicular lymphoma, lymphoplasmacytic lymphoma, Waldenstrom macroglobulinemia, and marginal zone lymphoma, as well as the aggressive lymphomas that include, for example, Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL). In one embodiment, the cancer is indolent non-Hodgkin's lymphoma (iNHL)

In a particular variation, the instructions are directed to use of the pharmaceutical composition for the treatment of an autoimmune disease. Specific embodiments of an autoimmune disease include asthma, rheumatoid arthritis, multiple sclerosis, and lupus.

Combination Therapy for HBV

In certain embodiments, a method for treating or preventing an HBV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents. In one embodiment, a method for treating an HBV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents.

In certain embodiments, the present disclosure provides a method for treating an HBV infection, comprising administering to a patient in need thereof a therapeutically effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more (e.g., one, two, three, four, one or two, one to three, or one to four) additional therapeutic agents which are suitable for treating an HBV infection.

In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four, or more additional therapeutic agents. In certain embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with four additional therapeutic agents. The one, two, three, four, or more additional therapeutic agents

can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents.

Administration of HBV Combination Therapy

In certain embodiments, when a compound disclosed herein is combined with one or more additional therapeutic agents as described above, the components of the composition are administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

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

Co-administration includes administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more additional therapeutic agents. The compound disclosed herein may be administered within seconds, minutes, or hours of the administration of one or more additional therapeutic agents. For example, in some embodiments, a unit dose of a compound disclosed herein is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein within seconds or minutes. In some embodiments, a unit dose of a compound disclosed herein is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound disclosed herein.

In certain embodiments, a compound disclosed herein is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a patient, for example as a solid dosage form for oral administration.

In certain embodiments a compound of Formula (I) is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HBV. In certain embodiments, the tablet can contain another active ingredient for treating HBV.

In certain embodiments, such tablets are suitable for once daily dosing.

The compounds described herein may be used or combined with one or more of a chemotherapeutic agent, an immunomodulator, an immunotherapeutic agent, a therapeutic antibody, a therapeutic vaccine, a bispecific antibody and "antibody-like" therapeutic protein (such as DARTs®, Duobodies®, Bites®, XmAbs®, TandAbs®, Fab derivatives), an antibody-drug conjugate (ADC), gene modifiers or gene editors (such as CRISPR Cas9, zinc finger nucleases, homing endonucleases, synthetic

nucleases, TALENs), cell therapies such as CAR-T (chimeric antigen receptor T-cell), and TCR-T (an engineered T cell receptor) agent or any combination thereof.

In the above embodiments, the additional therapeutic agent may be an anti-HBV agent. For example, the additional therapeutic agent may be selected from the group consisting of HBV combination
 5 drugs, other drugs for treating HBV, 3-dioxygenase (IDO) inhibitors, antisense oligonucleotide targeting viral mRNA, Apolipoprotein A1 modulator, arginase inhibitors, B- and T-lymphocyte attenuator inhibitors, Bruton's tyrosine kinase (BTK) inhibitors, CCR2 chemokine antagonist, CD137 inhibitors, CD160 inhibitors, CD305 inhibitors, CD4 agonist and modulator, compounds targeting HBcAg, compounds targeting hepatitis B core antigen (HBcAg), covalently closed circular DNA (cccDNA)
 10 inhibitors, cyclophilin inhibitors, cytokines, cytotoxic T-lymphocyte-associated protein 4 (ip4) inhibitors, DNA polymerase inhibitor, Endonuclease modulator, epigenetic modifiers, Farnesoid X receptor agonist, gene modifiers or editors, HBsAg inhibitors, HBsAg secretion or assembly inhibitors, HBV antibodies, HBV DNA polymerase inhibitors, HBV replication inhibitors, HBV RNase inhibitors, HBV vaccines, HBV viral entry inhibitors, HBx inhibitors, Hepatitis B large envelope protein modulator,
 15 Hepatitis B large envelope protein stimulator, Hepatitis B structural protein modulator, hepatitis B surface antigen (HBsAg) inhibitors, hepatitis B surface antigen (HBsAg) secretion or assembly inhibitors, hepatitis B virus E antigen inhibitors, hepatitis B virus replication inhibitors, Hepatitis virus structural protein inhibitor, HIV-1 reverse transcriptase inhibitor, Hyaluronidase inhibitor, IAPs inhibitors, IL-2 agonist, IL-7 agonist, Immunoglobulin agonist, Immunoglobulin G modulator,
 20 immunomodulators, indoleamine-2, inhibitors of ribonucleotide reductase, Interferon agonist, Interferon alpha 1 ligand, Interferon alpha 2 ligand, Interferon alpha 5 ligand modulator, Interferon alpha ligand, Interferon alpha ligand modulator, interferon alpha receptor ligands, Interferon beta ligand, Interferon ligand, Interferon receptor modulator, Interleukin-2 ligand, ipi4 inhibitors, lysine demethylase inhibitors, histone demethylase inhibitors, KDM5 inhibitors, KDM1 inhibitors, killer cell lectin-like receptor
 25 subfamily G member 1 inhibitors, lymphocyte-activation gene 3 inhibitors, lymphotoxin beta receptor activators, microRNA (miRNA) gene therapy agents, modulators of Axl, modulators of B7-H3, modulators of B7-H4, modulators of CD160, modulators of CD161, modulators of CD27, modulators of CD47, modulators of CD70, modulators of GITR, modulators of HEVEM, modulators of ICOS, modulators of Mer, modulators of NKG2A, modulators of NKG2D, modulators of OX40, modulators of
 30 SIRPalpha, modulators of TIGIT, modulators of Tim-4, modulators of Tyro, Na⁺-taurocholate cotransporting polypeptide (NTCP) inhibitors, natural killer cell receptor 2B4 inhibitors, NOD2 gene stimulator, Nucleoprotein inhibitor, nucleoprotein modulators, PD-1 inhibitors, PD-L1 inhibitors, PEG-Interferon Lambda, Peptidylprolyl isomerase inhibitor, phosphatidylinositol-3 kinase (PI3K) inhibitors, recombinant scavenger receptor A (SRA) proteins, recombinant thymosin alpha-1, Retinoic acid-inducible gene 1 stimulator, Reverse transcriptase inhibitor, Ribonuclease inhibitor, RNA DNA
 35 polymerase inhibitor, short interfering RNAs (siRNA), short synthetic hairpin RNAs (sshRNAs), SLC10A1 gene inhibitor, SMAC mimetics, Src tyrosine kinase inhibitor, stimulator of interferon gene

(STING) agonists, stimulators of NOD1, T cell surface glycoprotein CD28 inhibitor, T-cell surface glycoprotein CD8 modulator, Thymosin agonist, Thymosin alpha 1 ligand, Tim-3 inhibitors, TLR-3 agonist, TLR-7 agonist, TLR-9 agonist, TLR9 gene stimulator, toll-like receptor (TLR) modulators, Viral ribonucleotide reductase inhibitor, zinc finger nucleases or synthetic nucleases (TALENs), and combinations thereof.

In certain embodiments, a compound of Formula (I) is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HBV. In certain embodiments, the tablet can contain another active ingredient for treating HBV, such as 3-dioxygenase (IDO) inhibitors, Apolipoprotein A1 modulator, arginase inhibitors, B- and T-lymphocyte attenuator inhibitors, Bruton's tyrosine kinase (BTK) inhibitors, CCR2 chemokine antagonist, CD137 inhibitors, CD160 inhibitors, CD305 inhibitors, CD4 agonist and modulator, compounds targeting HBcAg, compounds targeting hepatitis B core antigen (HBcAg), core protein allosteric modulators, covalently closed circular DNA (cccDNA) inhibitors, cyclophilin inhibitors, cytotoxic T-lymphocyte-associated protein 4 (ip4) inhibitors, DNA polymerase inhibitor, Endonuclease modulator, epigenetic modifiers, Farnesoid X receptor agonist, HBsAg inhibitors, HBsAg secretion or assembly inhibitors, HBV DNA polymerase inhibitors, HBV replication inhibitors, HBV RNase inhibitors, HBV viral entry inhibitors, HBx inhibitors, Hepatitis B large envelope protein modulator, Hepatitis B large envelope protein stimulator, Hepatitis B structural protein modulator, hepatitis B surface antigen (HBsAg) inhibitors, hepatitis B surface antigen (HBsAg) secretion or assembly inhibitors, hepatitis B virus E antigen inhibitors, hepatitis B virus replication inhibitors, Hepatitis virus structural protein inhibitor, HIV-1 reverse transcriptase inhibitor, Hyaluronidase inhibitor, IAPs inhibitors, IL-2 agonist, IL-7 agonist, immunomodulators, indoleamine-2 inhibitors, inhibitors of ribonucleotide reductase, Interleukin-2 ligand, ipi4 inhibitors, lysine demethylase inhibitors, histone demethylase inhibitors, KDM1 inhibitors, KDM5 inhibitors, killer cell lectin-like receptor subfamily G member 1 inhibitors, lymphocyte-activation gene 3 inhibitors, lymphotoxin beta receptor activators, modulators of Axl, modulators of B7-H3, modulators of B7-H4, modulators of CD160, modulators of CD161, modulators of CD27, modulators of CD47, modulators of CD70, modulators of GITR, modulators of HEVEM, modulators of ICOS, modulators of Mer, modulators of NKG2A, modulators of NKG2D, modulators of OX40, modulators of SIRPalpha, modulators of TIGIT, modulators of Tim-4, modulators of Tyro, Na⁺-taurocholate cotransporting polypeptide (NTCP) inhibitors, natural killer cell receptor 2B4 inhibitors, NOD2 gene stimulator, Nucleoprotein inhibitor, nucleoprotein modulators, PD-1 inhibitors, PD-L1 inhibitors, Peptidylprolyl isomerase inhibitor, phosphatidylinositol-3 kinase (PI3K) inhibitors, Retinoic acid-inducible gene 1 stimulator, Reverse transcriptase inhibitor, Ribonuclease inhibitor, RNA DNA polymerase inhibitor, SLC10A1 gene inhibitor, SMAC mimetics, Src tyrosine kinase inhibitor, stimulator of interferon gene (STING) agonists, stimulators of NOD1, T cell surface glycoprotein CD28 inhibitor, T-cell surface glycoprotein CD8 modulator, Thymosin agonist, Thymosin alpha 1 ligand, Tim-3 inhibitors, TLR-3

agonist, TLR-7 agonist, TLR-9 agonist, TLR9 gene stimulator, toll-like receptor (TLR) modulators, Viral ribonucleotide reductase inhibitor, and combinations thereof.

In certain embodiments, a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, is combined with one, two, three, four or more additional therapeutic agents selected from
 5 HBV combination drugs, HBV vaccines, HBV DNA polymerase inhibitors, immunomodulators toll-like receptor (TLR) modulators, interferon alpha receptor ligands, hyaluronidase inhibitors, hepatitis b surface antigen (HBsAg) inhibitors, cytotoxic T-lymphocyte-associated protein 4 (ipi4) inhibitors, cyclophilin inhibitors, HBV viral entry inhibitors, antisense oligonucleotide targeting viral mRNA, short interfering RNAs (siRNA) and ddRNAi endonuclease modulators, ribonucleotide reductase inhibitors, HBV E
 10 antigen inhibitors, covalently closed circular DNA (cccDNA) inhibitors, farnesoid X receptor agonists, HBV antibodies, CCR2 chemokine antagonists, thymosin agonists, cytokines, nucleoprotein modulators, retinoic acid-inducible gene 1 stimulators, NOD2 stimulators, phosphatidylinositol 3-kinase (PI3K) inhibitors, indoleamine-2, 3-dioxygenase (IDO) pathway inhibitors, PD-1 inhibitors, PD-L1 inhibitors, recombinant thymosin alpha-1, bruton's tyrosine kinase (BTK) inhibitors, KDM inhibitors, HBV
 15 replication inhibitors, arginase inhibitors, and other HBV drugs.

HBV Combination Drugs

Examples of combination drugs for the treatment of HBV include TRUVADA® (tenofovir disoproxil fumarate and emtricitabine); ABX-203, lamivudine, and PEG-IFN-alpha; ABX-203 adefovir, and PEG-IFNalpha; and INO-1800 (INO-9112 and RG7944).

Other HBV Drugs

Examples of other drugs for the treatment of HBV include alpha-hydroxytropolones, amdoxovir, beta-hydroxycytosine nucleosides, AL-034, CCC-0975, elvucitabine, ezetimibe, cyclosporin A, gentiopiricin (gentiopicroside), JNJ-56136379, nitazoxanide, birinapant, NJK14047, NOV-205 (molixan, BAM-205), oligotide, mivofilate, feron, GST-HG-131, levamisole, Ka Shu Ning, alloferon, WS-007, Y-
 25 101 (Ti Fen Tai), rSIFN-co, PEG-IFN α m, KW-3, BP-Inter-014, oleanolic acid, HepB-nRNA, cTP-5 (rTP-5), HSK-II-2, HEISCO-106-1, HEISCO-106, Hepbarna, IBPB-006IA, Hepuyinfein, DasKloster 0014-01, ISA-204, Jiangantai (Ganxikang), MIV-210, OB-AI-004, PF-06, picroside, DasKloster-0039, hepulantai, IMB-2613, TCM-800B, reduced glutathione, RO-6864018, RG-7834, UB-551, and ZH-2N, and the compounds disclosed in US20150210682, (Roche), US 2016/0122344 (Roche), WO2015173164,
 30 WO2016023877, US2015252057A (Roche), WO16128335A1 (Roche), WO16120186A1 (Roche), US2016237090A (Roche), WO16107833A1 (Roche), WO16107832A1 (Roche), US2016176899A (Roche), WO16102438A1 (Roche), WO2016012470A1 (Roche), US2016220586A (Roche), and US2015031687A (Roche).

HBV Vaccines

35 HBV vaccines include both prophylactic and therapeutic vaccines. Examples of HBV prophylactic vaccines include Vaxelis, Hexaxim, Heplisav, Mosquirix, DTwP-HBV vaccine, Bio-Hep-B,

D/T/P/HBV/M (LBVP-0101; LBVW-0101), DTwP-Hepb-Hib-IPV vaccine, Heberpenta L, DTwP-HepB-Hib, V-419, CVI-HBV-001, Tetrabhay, hepatitis B prophylactic vaccine (Advax Super D), Hepatrol-07, GSK-223192A, ENGERIX B®, recombinant hepatitis B vaccine (intramuscular, Kangtai Biological Products), recombinant hepatitis B vaccine (Hansenula polymorpha yeast, intramuscular, Hualan Biological Engineering), recombinant hepatitis B surface antigen vaccine, Bimmugen, Euforavac, Eutravac, anrix-DTaP-IPV-Hep B, HBAI-20, Infanrix-DTaP-IPV-Hep B-Hib, Pentabio Vaksin DTP-HB-Hib, Comvac 4, Twinrix, Euvax-B, Tritanrix HB, Infanrix Hep B, Comvac, DTP-Hib-HBV vaccine, DTP-HBV vaccine, Yi Tai, Heberbiovac HB, Trivac HB, GerVax, DTwP-Hep B-Hib vaccine, Bilive, Hepavax-Genex, SUPERVAX, Comvac5, Shanvac-B, Hebsulin, Recombivax HB, Revac B mcf, Revac B+, Fendrix, DTwP-HepB-Hib, DNA-001, Shan5, Shan6, rhHBsAG vaccine, HBI pentavalent vaccine, LBVD, Infanrix HeXa, and DTaP-rHB-Hib vaccine.

Examples of HBV therapeutic vaccines include HBsAG-HBIG complex, ARB-1598, Bio-Hep-B, NASVAC, abi-HB (intravenous), ABX-203, Tetrabhay, GX-110E, GS-4774, peptide vaccine (epsilonPA-44), Hepatrol-07, NASVAC (NASTERAP), IMP-321, BEVAC, Revac B mcf, Revac B+, MGN-1333, KW-2, CVI-HBV-002, AltraHepB, VGX-6200, FP-02, FP-02.2, TG-1050, NU-500, HBVax, im/TriGrid/antigen vaccine, Mega-CD40L-adjuvanted vaccine, HepB-v, RG7944 (INO-1800), recombinant VLP-based therapeutic vaccine (HBV infection, VLP Biotech), AdTG-17909, AdTG-17910 AdTG-18202, ChronVac-B, TG-1050, and Lm HBV.

HBV DNA Polymerase Inhibitors

Examples of HBV DNA polymerase inhibitors include adefovir (HEPSERA®), emtricitabine (EMTRIVA®), tenofovir disoproxil fumarate (VIREAD®), tenofovir alafenamide, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, tenofovir dipivoxil, tenofovir dipivoxil fumarate, tenofovir octadecyloxyethyl ester, CMX-157, besifovir, entecavir (BARACLUDE®), entecavir maleate, telbivudine (TYZEKA®), pradevovir, clevudine, ribavirin, lamivudine (EPIVIR-HBV®), phosphazide, famciclovir, fusolin, metacavir, SNC-019754, FMCA, AGX-1009, AR-II-04-26, HIP-1302, tenofovir disoproxil aspartate, tenofovir disoproxil orotate, and HS-10234.

Immunomodulators

Examples of immunomodulators include rintatolimod, imidol hydrochloride, ingaron, dermaVir, plaquenil (hydroxychloroquine), proleukin, hydroxyurea, mycophenolate mofetil (MPA) and its ester derivative mycophenolate mofetil (MMF), WF-10, ribavirin, IL-12, INO-9112, polymer polyethyleneimine (PEI), Gepon, VGV-1, MOR-22, BMS-936559, RO-7011785, RO-6871765, AIC-649, and IR-103.

Toll-like Receptor (TLR) Modulators

TLR modulators include modulators of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, TLR11, TLR12, and TLR13. Examples of TLR3 modulators include rintatolimod, poly-ICLC, RIBOXXON®, Apoxsim, RIBOXXIM®, IPH-33, MCT-465, MCT-475, GS-9688 and ND-1.1.

Examples of TLR7 modulators include GS-9620, GSK-2245035, imiquimod, resiquimod, DSR-6434, DSP-3025, IMO-4200, MCT-465, MEDI-9197, 3M-051, SB-9922, 3M-052, Limtop, TMX-30X, TMX-202, RG-7863, RG-7795, RG-7854, and the compounds disclosed in US20100143301 (Gilead Sciences), US20110098248 (Gilead Sciences), and US20090047249 (Gilead Sciences).

5 Examples of TLR8 modulators include motolimod, resiquimod, 3M-051, 3M-052, MCT-465, IMO-4200, VTX-763, VTX-1463, and the compounds disclosed in US20140045849 (Janssen), US20140073642 (Janssen), WO2014/056953 (Janssen), WO2014/076221 (Janssen), WO2014/128189 (Janssen), US20140350031 (Janssen), WO2014/023813 (Janssen), US20080234251 (Array Biopharma), US20080306050 (Array Biopharma), US20100029585 (Ventirx Pharma), US20110092485 (Ventirx
10 Pharma), US20110118235 (Ventirx Pharma), US20120082658 (Ventirx Pharma), US20120219615 (Ventirx Pharma), US20140066432 (Ventirx Pharma), US20140088085 (Ventirx Pharma), US20140275167 (Novira Therapeutics), and US20130251673 (Novira Therapeutics).

 Examples of TLR9 modulators include BB-001, BB-006, CYT-003, IMO-2055, IMO-2125, IMO-3100, IMO-8400, IR-103, IMO-9200, agatolimod, DIMS-9054, DV-1079, DV-1179, AZD-1419,
15 leftolimod (MGN-1703), litemimod, and CYT-003-QbG10.

Interferon Alpha Receptor Ligands

 Examples of interferon alpha receptor ligands include interferon alpha-2b (INTRON A®), pegylated interferon alpha-2a (PEGASYS®), PEGylated interferon alpha-1b, interferon alpha 1b (HAPGEN®), Veldona, Infradure, Roferon-A, YPEG-interferon alfa-2a (YPEG-rhIFNalpha-2a), P-1101,
20 Algeon, Alfaona, Ingaron (interferon gamma), rSIFN-co (recombinant super compound interferon), Ypeginterferon alfa-2b (YPEG-rhIFNalpha-2b), MOR-22, peginterferon alfa-2b (PEG-INTRON®), Bioferon, Novaferon, Inmutag (Inferon), MULTIFERON®, interferon alfa-n1 (HUMOFERON®), interferon beta-1a (AVONEX®), Shaferon, interferon alfa-2b (Axxo), Alfaferone, interferon alfa-2b (BioGeneric Pharma), interferon-alpha 2 (CJ), Laferonum, VIPEG, BLAUFERON-A, BLAUFERON-B,
25 Intermix Alpha, Realdiron, Lanstion, Pegaferon, PDferon-B PDferon-B, interferon alfa-2b (IFN, Laboratorios Bioprofarma), alfainterferona 2b, Kalferon, Pagnano, Feronsure, PegiHep, interferon alfa 2b (Zydus-Cadila), interferon alfa 2a, Optipeg A, Realfa 2B, Reliferon, interferon alfa-2b (Amega), interferon alfa-2b (Virchow), ropeginterferon alfa-2b, rHSA-IFN alpha-2a (recombinant human serum albumin interferon alpha 2a fusion protein), rHSA-IFN alpha 2b, recombinant human interferon alpha-
30 (1b, 2a, 2b), peginterferon alfa-2b (Amega), peginterferon alfa-2a, Reaferon-EC, Proquiferon, Uniferon, Unifron, interferon alfa-2b (Changchun Institute of Biological Products), Anterferon, Shanferon, Layfferon, Shang Sheng Lei Tai, INTEFEN, SINOGEN, Fukangtai, Pegstat, rHSA-IFN alpha-2b, SFR-9216, and Interapo (Interapa).

Hyaluronidase Inhibitors

35 Examples of hyaluronidase inhibitors include astodimer.

Hepatitis B Surface Antigen (HBsAg) Inhibitors

Examples of HBsAg inhibitors include HBF-0259, PBHBV-001, PBHBV-2-15, PBHBV-2-1, REP-9AC, REP-9C, REP-9, REP-2139, REP-2139-Ca, REP-2165, REP-2055, REP-2163, REP-2165, REP-2053, REP-2031 and REP-006, and REP-9AC'.

5 Examples of HBsAg secretion inhibitors include BM601.

Cytotoxic T-lymphocyte-associated protein 4 (ipi4) inhibitors

Examples of Cytotoxic T-lymphocyte-associated protein 4 (ipi4) inhibitors include AGEN-2041, AGEN-1884, ipilimumab, belatacept, PSI-001, PRS-010, Probody mAbs, tremelimumab, and JHL-1155.

Cyclophilin Inhibitors

10 Examples of cyclophilin inhibitors include CPI-431-32, EDP-494, OCB-030, SCY-635, NVP-015, NVP-018, NVP-019, STG-175, and the compounds disclosed in US8513184 (Gilead Sciences), US20140030221 (Gilead Sciences), US20130344030 (Gilead Sciences), and US20130344029 (Gilead Sciences).

HBV Viral Entry Inhibitors

15 Examples of HBV viral entry inhibitors include Myrcludex B.

Antisense Oligonucleotide Targeting Viral mRNA

Examples of antisense oligonucleotide targeting viral mRNA include ISIS-HBVRx, IONIS-HBVRx, IONIS-GSK6-LRx, GSK-3389404, RG-6004.

Short Interfering RNAs (siRNA) and ddRNAi.

20 Examples of siRNA include TKM-HBV (TKM-HepB), ALN-HBV, SR-008, HepB-nRNA., and ARC-520, ARC-521, ARB-1740, ARB-1467.

Examples of DNA-directed RNA interference (ddRNAi) include BB-HB-331.

Endonuclease Modulators

Examples of endonuclease modulators include PGN-514.

25 *Ribonucleotide Reductase Inhibitors*

Examples of inhibitors of ribonucleotide reductase include Trimidox.

HBV E Antigen Inhibitors

Examples of HBV E antigen inhibitors include wogonin.

Covalently Closed Circular DNA (cccDNA) Inhibitors

30 Examples of cccDNA inhibitors include BSBI-25, and CHR-101.

Farnesoid X receptor agonist

Example of farnesoid x receptor agonist such as EYP-001.

HBV Antibodies

Examples of HBV antibodies targeting the surface antigens of the hepatitis B virus include GC-1102, XTL-17, XTL-19, KN-003, IV Hepabulin SN, and fully human monoclonal antibody therapy (hepatitis B virus infection, Humabs BioMed). Examples of HBV antibodies, including monoclonal antibodies and polyclonal antibodies, include Zutectra, Shang Sheng Gan Di, Uman Big (Hepatitis B Hyperimmune), Omri-Hep-B, Nabi-HB, Hepatect CP, HepaGam B, igantibc, Niuliva, CT-P24, hepatitis B immunoglobulin (intravenous, pH4, HBV infection, Shanghai RAAS Blood Products), and Fovepta (BT-088). Fully human monoclonal antibodies such as HBC-34.

CCR2 Chemokine Antagonists

Examples of CCR2 chemokine antagonists include propagermanium.

Thymosin Agonists

Examples of thymosin agonists include Thymalfasin, recombinant thymosin alpha 1 (GeneScience).

Cytokines

Examples of cytokines include recombinant IL-7, CYT-107, interleukin-2 (IL-2, Immunex), recombinant human interleukin-2 (Shenzhen Neptunus), IL-15, IL-21, IL-24, and cclmoleukin.

Nucleoprotein modulators

Nucleoprotein modulators may be either HBV core or capsid protein inhibitors. Examples of nucleoprotein modulators include AB-423, AT-130, GLS4, NVR-1221, NVR-3778, BAY 41-4109, morphothiadine mesilate, JNJ-379, RG-7907, ABI-H0731, ABI-H2158 and DVR-23.

Examples of capsid inhibitors include the compounds disclosed in US20140275167 (Novira Therapeutics), US20130251673 (Novira Therapeutics), US20140343032 (Roche), WO2014037480 (Roche), US20130267517 (Roche), WO2014131847 (Janssen), WO2014033176 (Janssen), WO2014033170 (Janssen), WO2014033167 (Janssen), WO2015/059212 (Janssen), WO2015118057 (Janssen), WO2015011281 (Janssen), WO2014184365 (Janssen), WO2014184350 (Janssen), WO2014161888 (Janssen), WO2013096744 (Novira), US20150225355 (Novira), US20140178337 (Novira), US20150315159 (Novira), US20150197533 (Novira), US20150274652 (Novira), US20150259324, (Novira), US20150132258 (Novira), US9181288 (Novira), WO2014184350 (Janssen), WO2013144129 (Roche).

Retinoic Acid-inducible Gene 1 Stimulators

Examples of stimulators of retinoic acid-inducible gene 1 include SB-9200, SB-40, SB-44, ORI-7246, ORI-9350, ORI-7537, ORI-9020, ORI-9198, and ORI-7170, RGT-100.

NOD2 Stimulators

5 Examples of stimulators of NOD2 include SB-9200.

Phosphatidylinositol 3-kinase (PI3K) Inhibitors

Examples of PI3K inhibitors include idelalisib, ACP-319, AZD-8186, AZD-8835, buparlisib, CDZ-173, CLR-457, pictilisib, neratinib, rigosertib, rigosertib sodium, EN-3342, TGR-1202, alpelisib, duvelisib, IPI-549, UCB-5857, taselisib, XL-765, gedatolisib, ME-401, VS-5584, copanlisib, CAI
10 orotate, perifosine, RG-7666, GSK-2636771, DS-7423, panulisib, GSK-2269557, GSK-2126458, CUDC-907, PQR-309, INCB-40093, pilaralisib, BAY-1082439, puquitinib mesylate, SAR-245409, AMG-319, RP-6530, ZSTK-474, MLN-1117, SF-1126, RV-1729, sonolisib, LY-3023414, SAR-260301, TAK-117, HMPL-689, tenalisib, voxalisib, and CLR-1401.

Indoleamine-2, 3-dioxygenase (IDO) Pathway Inhibitors

15 Examples of IDO inhibitors include epacadostat (INCB24360), resminostat (4SC-201), indoximod, F-001287, SN-35837, NLG-919, GDC-0919, GBV-1028, GBV-1012, NKTR-218, and the compounds disclosed in US20100015178 (Incyte), US2016137652 (Flexus Biosciences, Inc.), WO2014073738 (Flexus Biosciences, Inc.), and WO2015188085 (Flexus Biosciences, Inc.).

PD-1 Inhibitors

20 Examples of PD-1 inhibitors include nivolumab, pembrolizumab, pidilizumab, BGB-108, SHR-1210, PDR-001, PF-06801591, IBI-308, GB-226, STI-1110, and mDX-400.

PD-L1 Inhibitors

Examples of PD-L1 inhibitors include atezolizumab, avelumab, AMP-224, MEDI-0680, RG-7446, GX-P2, durvalumab, KY-1003, KD-033, MSB-0010718C, TSR-042, ALN-PDL, STI-A1014, CX-
25 072, and BMS-936559.

In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with compounds such as those disclosed in WO2018026971, US20180044329, US20180044305, US20180044304, US20180044303, US20180044350, US20180057455, US20180057486, US20180045142, WO20180044963, WO2018044783, WO2018009505,
30 WO20180044329, WO2017066227, WO2017087777, US20170145025, WO2017079669, WO2017070089, US2017107216, WO2017222976, US20170262253, WO2017205464, US20170320875, WO2017192961, WO2017112730, US20170174679, WO2017106634, WO2017202744, WO2017202275, WO2017202273, WO2017202274, WO2017202276,

WO2017180769, WO2017118762, WO2016041511, WO2016039749, WO2016142835, WO2016142852, WO2016142886, WO2016142894, and WO2016142833.

Recombinant Thymosin Alpha-1

Examples of recombinant thymosin alpha-1 include NL-004 and PEGylated thymosin alpha-1.

5 *Bruton's Tyrosine Kinase (BTK) Inhibitors*

Examples of BTK inhibitors include ABBV-105, acalabrutinib (ACP-196), ARQ-531, BMS-986142, dasatinib, ibrutinib, GDC-0853, PRN-1008, SNS-062, ONO-4059, BGB-3111, ML-319, MSC-2364447, RDX-022, X-022, AC-058, RG-7845, spebrutinib, TAS-5315, TP-0158, TP-4207, HM-71224, KBP-7536, M-2951, TAK-020, AC-0025, and the compounds disclosed in US20140330015 (Ono
10 Pharmaceutical), US20130079327 (Ono Pharmaceutical), and US20130217880 (Ono Pharmaceutical).

KDM Inhibitors

Examples of KDM5 inhibitors include the compounds disclosed in WO2016057924 (Genentech/Constellation Pharmaceuticals), US20140275092 (Genentech/Constellation Pharmaceuticals), US20140371195 (Epitherapeutics) and US20140371214 (Epitherapeutics),
15 US20160102096 (Epitherapeutics), US20140194469 (Quantice), US20140171432, US20140213591 (Quantice), US20160039808 (Quantice), US20140275084 (Quantice), WO2014164708 (Quantice).

Examples of KDM1 inhibitors include the compounds disclosed in US9186337B2 (Oryzon Genomics), and GSK-2879552, RG-6016, ORY-2001.

HBV Replication Inhibitors

20 Examples of hepatitis B virus replication inhibitors include isothiafludine, IQP-HBV, RM-5038, and Xingantic.

Arginase inhibitors

Examples of Arginase inhibitors include CB-1158, C-201, and resminostat.

Gene Therapy and Cell Therapy

25 Gene Therapy and Cell Therapy including the genetic modification to silence a gene; genetic approaches to directly kill the infected cells; the infusion of immune cells designed to replace most of the patient's own immune system to enhance the immune response to infected cells, or activate the patient's own immune system to kill infected cells, or find and kill the infected cells; genetic approaches to modify cellular activity to further alter endogenous immune responsiveness against the infection.

30 *Gene Editors*

The genome editing system is selected from the group consisting of: a CRISPR/Cas9 system, a zinc finger nuclease system, a TALEN system, a homing endonucleases system, and a meganuclease system; e.g., cccDNA elimination via targeted cleavage, and altering one or more of the hepatitis B virus

(HBV) viral genes. Altering (e.g., knocking out and/or knocking down) the *PreC*, *C*, *X*, *PreS1*, *PreS2*, *S*, *P* or *SP* gene refers to (1) reducing or eliminating *PreC*, *C*, *X*, *PreS1*, *PreS2*, *S*, *P* or *SP* gene expression, (2) interfering with Precore, Core, X protein, Long surface protein, middle surface protein, S protein (also known as HBs antigen and HBsAg), polymerase protein, and/or Hepatitis B spliced protein function (HBe, HBc, HBx, PreS1, PreS2, S, Pol, and/or HBSP or (3) reducing or eliminating the intracellular, serum and/or intraparenchymal levels of HBe, HBc, HBx, LHBs, MHBs, SHBs, Pol, and/or HBSP proteins. Knockdown of one or more of the *PreC*, *C*, *X*, *PreS1*, *PreS2*, *S*, *P* and/or *SP* gene(s) is performed by targeting the gene(s) within HBV cccDNA and/or integrated HBV DNA.

CAR-T cell therapy

10 A population of immune effector cells engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an HBV antigen-binding domain. The immune effector cell is a T cell or an NK cell. In some embodiments, the T cell is a CD4+ T cell, a CD8+ T cell, or a combination thereof. Cells can be autologous or allogeneic.

TCR-T cell therapy

15 T cells expressing HBV-specific T cell receptors. TCR-T cells are engineered to target HBV derived peptides presented on the surface of virus-infected cells.

T-Cells expressing HBV surface antigen (HBsAg)-specific TCR.

TCR-T therapy directed to treatment of HBV, such as LTCR-H2-1

HBV Combination Therapy

20 In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with one, two, three, or four additional therapeutic agent selected from the group consisting of adefovir (HEPSERA®), tenofovir disoproxil fumarate (VIREAD®), tenofovir alafenamide, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, entecavir (BARACLUDE®), telbivudine (TYZEKA®), or lamivudine (EPIVIR-HBV®). In a particular

25 embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of adefovir (HEPSERA®), tenofovir disoproxil fumarate (VIREAD®), tenofovir alafenamide, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, entecavir (BARACLUDE®), telbivudine (TYZEKA®), or lamivudine (EPIVIR-HBV®). In one embodiment, pharmaceutical

30 compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, four, one or two, or one to three, or one to four) additional therapeutic agents and a pharmaceutically acceptable carrier, diluent, or excipient are provided.

HBV DNA Polymerase Inhibitor Combination Therapy

In a specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HBV DNA polymerase inhibitor. In another specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HBV DNA polymerase inhibitor and at least one additional therapeutic agent selected from the group consisting of: immunomodulators, TLR modulators, interferon alpha receptor ligands, hyaluronidase inhibitors, recombinant IL-7, HBsAg inhibitors, HBsAg secretion or assembly inhibitors, compounds targeting HBcAg, cyclophilin inhibitors, HBV vaccines, HBV viral entry inhibitors, NTCP inhibitors, antisense oligonucleotide targeting viral mRNA, siRNA, miRNA gene therapy agents, endonuclease modulators, inhibitors of ribonucleotide reductase, hepatitis B virus E antigen inhibitors, recombinant SRA proteins, src kinase inhibitors, HBx inhibitors, cccDNA inhibitors, sshRNAs, HBV antibodies including HBV antibodies targeting the surface antigens of the hepatitis B virus and bispecific antibodies and "antibody-like" therapeutic proteins (such as DARTs[®], DUOBODIES[®], BITES[®], XmAbs[®], TandAbs[®], Fab derivatives, or TCR-like antibodies), CCR2 chemokine antagonists, thymosin agonists, cytokines, nucleoprotein modulators (HBV core or capsid protein modulators), stimulators of retinoic acid-inducible gene 1, stimulators of RIG-I like receptors, stimulators of NOD2, stimulators of NOD1, Arginase inhibitors, STING agonists, PI3K inhibitors, lymphotoxin beta receptor activators, natural killer cell receptor 2B4 inhibitors, Lymphocyte-activation gene 3 inhibitors, CD160 inhibitors, cytotoxic T-lymphocyte-associated protein 4 (ip4) inhibitors, CD137 inhibitors, Killer cell lectin-like receptor subfamily G member 1 inhibitors, TIM-3 inhibitors, B- and T-lymphocyte attenuator inhibitors, CD305 inhibitors, PD-1 inhibitors, PD-L1 inhibitors, PEG-Interferon Lambda, recombinant thymosin alpha-1, BTK inhibitors, modulators of TIGIT, modulators of CD47, modulators of SIRPalpha, modulators of ICOS, modulators of CD27, modulators of CD70, modulators of OX40, epigenetic modifiers, modulators of NKG2D, modulators of Tim-4, modulators of B7-H4, modulators of B7-H3, modulators of NKG2A, modulators of GITR, modulators of CD160, modulators of HEVEM, modulators of CD161, modulators of Axl, modulators of Mer, modulators of Tyro, gene modifiers or editors such as CRISPR (including CRISPR Cas9), zinc finger nucleases or synthetic nucleases (TALENs), IAPs inhibitors, SMAC mimetics, KDM5 inhibitors, IDO inhibitors, and hepatitis B virus replication inhibitors.

In another specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HBV DNA polymerase inhibitor, one or two additional therapeutic agents selected from the group consisting of immunomodulators, TLR modulators, HBsAg inhibitors, HBsAg secretion or assembly inhibitors, HBV therapeutic vaccines, HBV antibodies including HBV antibodies targeting the surface antigens of the hepatitis B virus and bispecific antibodies and "antibody-like" therapeutic proteins (such as DARTs[®], DUOBODIES[®], BITES[®], XmAbs[®], TandAbs[®], Fab derivatives, or TCR-like antibodies), cyclophilin inhibitors, stimulators of retinoic acid-inducible gene 1, stimulators of RIG-I like receptors, PD-1 inhibitors, PD-L1 inhibitors, Arginase inhibitors, PI3K inhibitors, IDO inhibitors, and stimulators of NOD2, and one or two additional therapeutic agents

selected from the group consisting of HBV viral entry inhibitors, NTCP inhibitors, HBx inhibitors, cccDNA inhibitors, HBV antibodies targeting the surface antigens of the hepatitis B virus, siRNA, miRNA gene therapy agents, sshRNAs, KDM5 inhibitors, and nucleoprotein modulators (HBV core or capsid protein modulators).

5 In another specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with an HBV DNA polymerase inhibitor and at least a second additional therapeutic agent selected from the group consisting of: immunomodulators, TLR modulators, HBsAg inhibitors, HBV therapeutic vaccines, HBV antibodies including HBV antibodies targeting the surface antigens of the hepatitis B virus and bispecific antibodies and “antibody-like” therapeutic proteins (such
10 as DARTs®, DUOBODIES®, BITES®, XmAbs®, TandAbs®, Fab derivatives, or TCR-like antibodies), cyclophilin inhibitors, stimulators of retinoic acid-inducible gene 1, stimulators of RIG-I like receptors, PD-1 inhibitors, PD-L1 inhibitors, Arginase inhibitors, PI3K inhibitors, IDO inhibitors, and stimulators of NOD2.

In another specific embodiment, a compound disclosed herein, or a pharmaceutically acceptable
15 salt thereof, is combined with an HBV DNA polymerase inhibitor and at least a second additional therapeutic agent selected from the group consisting of: HBV viral entry inhibitors, NTCP inhibitors, HBx inhibitors, cccDNA inhibitors, HBV antibodies targeting the surface antigens of the hepatitis B virus, siRNA, miRNA gene therapy agents, sshRNAs, KDM5 inhibitors, and nucleoprotein modulators (HBV core or capsid protein inhibitors).

20 *HBV Drug Combination Therapy*

In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of adefovir (HEPSERA®), tenofovir disoproxil fumarate (VIREAD®), tenofovir alafenamide, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, entecavir
25 (BARACLUDE®), telbivudine (TYZEKA®), or lamivudine (EPIVIR-HBV®), and at least a second additional therapeutic agent selected from the group consisting of immunomodulators, TLR modulators, interferon alpha receptor ligands, hyaluronidase inhibitors, recombinant IL-7, HBsAg inhibitors, HBsAg secretion or assembly inhibitors, compounds targeting HBcAg, cyclophilin inhibitors, HBV vaccines, HBV viral entry inhibitors, NTCP inhibitors, antisense oligonucleotide targeting viral mRNA, siRNA,
30 miRNA gene therapy agents, endonuclease modulators, inhibitors of ribonucleotide reductase, hepatitis B virus E antigen inhibitors, recombinant SRA proteins, src kinase inhibitors, HBx inhibitors, cccDNA inhibitors, sshRNAs, HBV antibodies including HBV antibodies targeting the surface antigens of the hepatitis B virus and bispecific antibodies and “antibody-like” therapeutic proteins (such as DARTs®, DUOBODIES®, BITES®, XmAbs®, TandAbs®, Fab derivatives, and TCR-like antibodies), CCR2
35 chemokine antagonists, thymosin agonists, cytokines, nucleoprotein modulators (HBV core or capsid protein modulators), stimulators of retinoic acid-inducible gene 1, stimulators of RIG-I like receptors,

stimulators of NOD2, stimulators of NOD1, IDO inhibitors, recombinant thymosin alpha-1, Arginase inhibitors, STING agonists, PI3K inhibitors, lymphotoxin beta receptor activators, natural killer cell receptor 2B4 inhibitors, Lymphocyte-activation gene 3 inhibitors, CD160 inhibitors, ipi4 inhibitors, CD137 inhibitors, killer cell lectin-like receptor subfamily G member 1 inhibitors, TIM-3 inhibitors, B- and T-lymphocyte attenuator inhibitors, epigenetic modifiers, CD305 inhibitors, PD-1 inhibitors, PD-L1 inhibitors, PEG-Interferon Lambda, BTK inhibitors, modulators of TIGIT, modulators of CD47, modulators of SIRPalpha, modulators of ICOS, modulators of CD27, modulators of CD70, modulators of OX40, modulators of NKG2D, modulators of Tim-4, modulators of B7-H4, modulators of B7-H3, modulators of NKG2A, modulators of GITR, modulators of CD160, modulators of HEVEM, modulators of CD161, modulators of Axl, modulators of Mer, modulators of Tyro, gene modifiers or editors such as CRISPR (including CRISPR Cas9), zinc finger nucleases or synthetic nucleases (TALENs), IAPs inhibitors, SMAC mimetics, KDM5 inhibitors, and hepatitis B virus replication inhibitors.

In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of adefovir (HEPSERA®), tenofovir disoproxil fumarate (VIREAD®), tenofovir alafenamide, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, entecavir (BARACLUDE®), telbivudine (TYZEKA®) or lamivudine (EPIVIR-HBV®) and at least a second additional therapeutic agent selected from the group consisting of peginterferon alfa-2b (PEG-INTRON®), MULTIFERON®, interferon alpha 1b (HAPGEN®), interferon alpha-2b (INTRON A®), pegylated interferon alpha-2a (PEGASYS®), interferon alfa-n1 (HUMOFERON®), ribavirin, interferon beta-1a (AVONEX®), Bioferon, Ingaron, Inmutag (Inferon), Algeron, Roferon-A, Oligotide, Zutectra, Shaferon, interferon alfa-2b (AXXO), Alfaferone, interferon alfa-2b (BioGeneric Pharma), Feron, interferon-alpha 2 (CJ), BEVAC, Laferonum, VIPEG, BLAUFERON-B, BLAUFERON-A, Intermix Alpha, Realdiron, Lanstion, Pegaferon, PDferon-B, interferon alfa-2b (IFN, Laboratorios Bioprofarma), alfainterferona 2b, Kalferon, Pegnano, Feronsure, PegiHep, interferon alfa 2b (Zydus-Cadila), Optipeg A, Realfa 2B, Reliferon, interferon alfa-2b (Amega), interferon alfa-2b (Virchow), peginterferon alfa-2b (Amega), Reaferon-EC, Proquiferon, Uniferon, Urifron, interferon alfa-2b (Changchun Institute of Biological Products), Anterferon, Shanferon, MOR-22, interleukin-2 (IL-2, Immunex), recombinant human interleukin-2 (Shenzhen Neptunus), Layfferon, Ka Shu Ning, Shang Sheng Lei Tai, INTEFEN, SINOGEN, Fukangtai, Alloferon, and celmoleukin.

In a particular embodiment, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, is combined with a first additional therapeutic agent selected from the group consisting of adefovir (HEPSERA®), tenofovir disoproxil fumarate (VIREAD®), tenofovir alafenamide, tenofovir, tenofovir disoproxil, tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, entecavir (BARACLUDE®), telbivudine (TYZEKA®), or lamivudine (EPIVIR-HBV®), and at least a second additional therapeutic agent selected from the group consisting of immunomodulators, TLR modulators, HBsAg inhibitors, HBsAg secretion or assembly inhibitors, HBV therapeutic vaccines, HBV antibodies

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 4
CONTAINING PAGES 1 TO 222

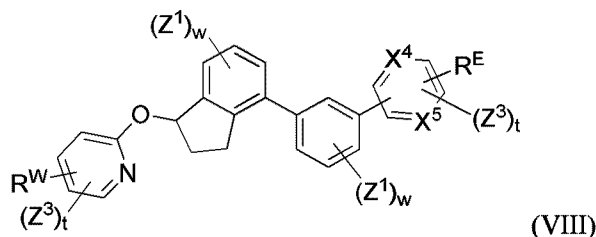
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Claims

1. A compound of formula (VIII):



wherein:

each of X^4 and X^5 are independently N, CH or CZ^3 ;

each Z^1 is independently halo, $-OR^a$, or $-C_{1-6}$ alkyl;

wherein each alkyl is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, and cyano;

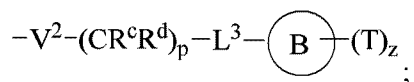
each w is independently 0, 1 or 2;

each Z^3 is independently halo, $-OR^a$ or $-C_{1-6}$ alkyl; and

wherein the alkyl group is optionally substituted with 1 to 4 groups independently selected from oxo, $-NO_2$, $-N_3$, $-OR^a$, halo, cyano, $-NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-O-C_{1-6}$ cyanoalkyl, $-C(O)NR^aR^b$, $NR^aC(O)R^a$, $-NR^aC(O)OR^a$, $-SO_2R^a$, $-NR^aSO_2R^b$, $-SO_2NR^aR^b$, $-NR^aSO_2NR^aR^b$, $-C(O)NR^aSO_2NR^aR^b$ and $-C_{3-8}$ cycloalkyl;

each t is independently 0, 1 or 2;

R^E and R^W are each independently $-NR^1R^2$, $-C_{1-6}$ alkyl NR^1R^2 , $-O-C_{1-6}$ alkyl NR^1R^2 , $-C_{1-6}$ alkyl OC_{1-6} alkyl NR^1R^2 , $-NR^a-C_{1-6}$ alkyl NR^1R^2 , or



wherein:

V^2 is independently a bond, O, NR^a , S, SO, or SO_2 ;

L^3 is independently a bond, O, NR^a , S, SO, or SO_2 ;

ring B is independently cycloalkyl, aryl, heteroaryl, or heterocyclyl;

T is independently H, OR^a , $(CH_2)_qNR^1R^2$, $(CH_2)_qNR^aC(O)R^e$, or $(CH_2)_qC(O)R^e$;

p is independently 0, 1, 2, 3, 4, or 5;

q is independently 0, 1, 2, 3, 4, or 5;

z is 0, 1, or 2; and

wherein the alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl of R^E or R^W is optionally substituted with 1 to 3 substituents independently selected from the group consisting of NR^aR^b, halo, cyano, oxo, OR^a, -C₁₋₆ alkyl, -C₁₋₆ haloalkyl, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylNR^aR^b, -C₁₋₆ alkylOH, -C₃₋₈ cycloalkyl, and -C₁₋₃ alkylC₃₋₈cycloalkyl;

provided that at least one of V², L³, ring B, and T contains a nitrogen atom;

each R¹ is independently selected from H, -C₁₋₈ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₁₋₆ alkylC(O)OR^a, -C₂₋₆ alkenylC(O)OR^a, -SO₂R^a, -SO₂NR^aR^b, -C(O)NR^aSO₂R^a, and -C₁₋₆ alkylC₃₋₈cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, NR^aC(O)OR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and -C₁₋₆alkylNR^aC(O)R^b;

each R² is independently selected from H, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, and -C₂₋₆ alkenylC(O)OR^a;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b and -NR^aC(O)R^b;

or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OR^a, -C(O)OR^a, -C₁₋₆ cyanoalkyl, -C₁₋₆ alkylOR^a, -C₁₋₆ haloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆ alkylC(O)R^a, -C₁₋₆ alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, and -C₁₋₆alkylSO₂NR^aR^b;

each R^a is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

each R^b is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, -C₁₋₆ alkylOR^f, -C₁₋₆ cyanoalkyl, -C₁₋₆ haloalkyl, -C₃₋₈ cycloalkyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C(O)R^f, -C₁₋₆ alkylC(O)R^f, -C(O)OR^f, -C₁₋₆ alkylC(O)OR^f, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆ alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆ alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆ alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and -NR^fC(O)R^g;

each R^c is independently selected from H, OH, -C₁₋₆ alkyl, and -C₃₋₈ cycloalkyl;

R^d is independently selected from H, -C₁₋₆ alkyl, and -C₃₋₈cycloalkyl;

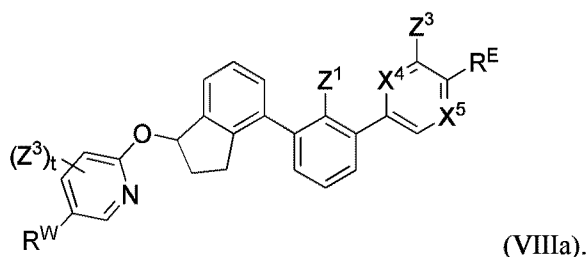
each R^e is independently selected from H, -C₁₋₆ alkyl, -O-C₁₋₆alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -O-C₃₋₈ cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocyclyl, -C₁₋₃ alkylC₃₋₈cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆alkylheteroaryl, -NR^fR^g, -C₁₋₆ alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆ alkylC(O)NR^fR^g, -NHSO₂R^f, -C₁₋₆ alkylSO₂R^f, and -C₁₋₆ alkylSO₂NR^fR^g;

each R^f is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈ cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl; and

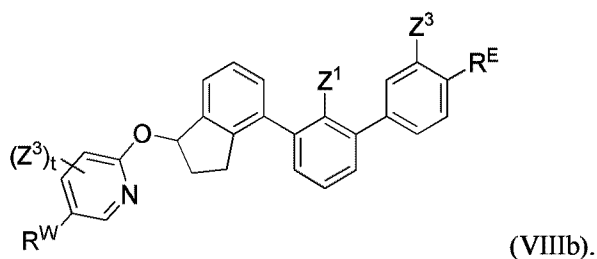
each R^g is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈ cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl;

or a pharmaceutically acceptable salt thereof.

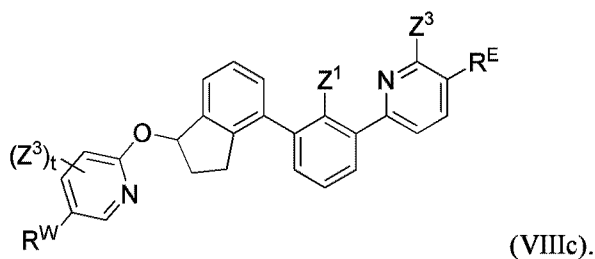
2. The compound of claim 1, wherein the compound is represented by a compound of formula (VIIIa):



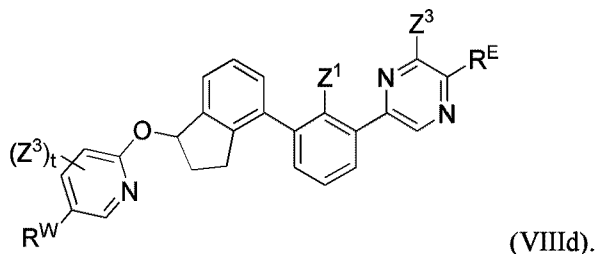
3. The compound of claim 1, wherein the compound is represented by a compound of formula (VIIIb):



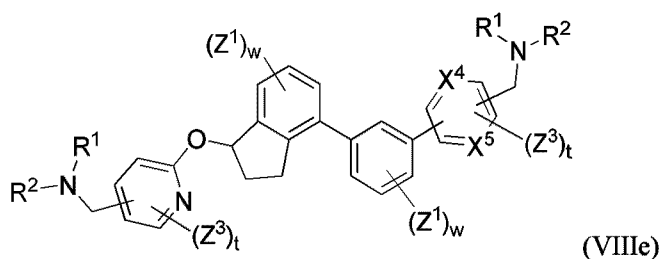
4. The compound of claim 1, wherein the compound is represented by a compound of formula (VIIIc):



5. The compound of claim 1, wherein the compound is represented by a compound of formula (VIIId):



6. The compound of claim 1, wherein the compound is represented by a compound of formula (VIIIe):



wherein:

each of X⁴ and X⁵ are independently N, CH or CZ³;

each Z¹ is independently halo, -OR^a, or -C₁₋₆ alkyl;

each w is independently 0, 1 or 2;

each Z³ is independently halo, -OR^a or -C₁₋₆ alkyl, ; and

wherein the alkyl group is optionally substituted with 1 to 4 groups independently selected from oxo, -NO₂, -N₃, -OR^a, halo, cyano, -NR^aR^b, -C(O)R^a, -C(O)OR^a, -O-C₁₋₆cyanoalkyl, -C(O)NR^aR^b, NR^aC(O)R^a, -NR^aC(O)OR^a, -SO₂R^a, -NR^aSO₂R^b, -SO₂NR^aR^b, -NR^aSO₂NR^aR^b, -C(O)NR^aSO₂NR^aR^b and -C₃₋₈ cycloalkyl;

each t is independently 0, 1 or 2;

each R¹ is independently selected from H, -C₁₋₈ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₁₋₆

alkylC(O)OR^a, -C₂₋₆ alkenylC(O)OR^a, -SO₂R^a, -SO₂NR^aR^b, -C(O)NR^aSO₂R^a, and C₁₋₆ alkylC₃₋₈cycloalkyl;

wherein each alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -OC(O)NR^aR^b, -NR^aC(O)OR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b, -C₁₋₆alkylC(O)NR^aSO₂R^b, -NR^aC(O)R^b, and -C₁₋₆alkylNR^aC(O)R^b;

each R² is independently selected from H, -C₁₋₆alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -C₃₋₆ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, -C₁₋₆ alkylheterocyclyl, -C₂₋₆ alkyl-OR^a, -C₁₋₆ alkylC(O)OR^a, and -C₂₋₆ alkenylC(O)OR^a;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 4 groups independently selected from -OR^a, -CN, halo, C₁₋₆alkyl, -C₁₋₆alkylOR^a, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C(O)OR^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, -C₁₋₆alkylSO₂NR^aR^b, -C(O)NR^aSO₂R^b and -NR^aC(O)R^b;

or R¹ and R² combine to form a heterocyclyl group optionally containing 1, 2, or 3 additional heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 3 groups independently selected from oxo, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, -OR^a, -C(O)OR^a, -C₁₋₆cyanoalkyl, -C₁₋₆alkylOR^a, -C₁₋₆haloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^a, -C₁₋₆alkylC(O)R^a, -C₁₋₆alkylC(O)OR^a, -NR^aR^b, -C₁₋₆alkylNR^aR^b, -C(O)NR^aR^b, -C₁₋₆alkylC(O)NR^aR^b, -SO₂R^a, -C₁₋₆alkylSO₂R^a, -SO₂NR^aR^b, and -C₁₋₆alkylSO₂NR^aR^b;

each R^a is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

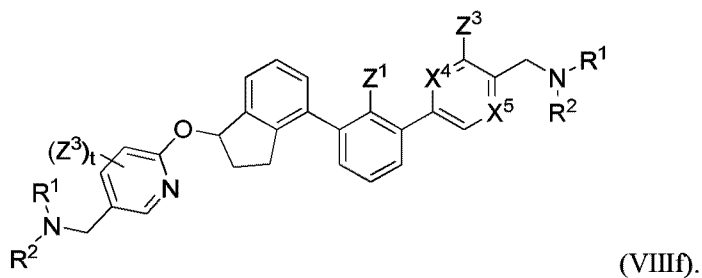
each R^b is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl;

or R^a and R^b may combine together to form a ring consisting of 3-8 ring atoms that are C, N, O, or S; wherein the ring is optionally substituted with 1 to 4 groups independently selected from -OR^f, -CN, halo, -C₁₋₆alkylOR^f, -C₁₋₆cyanoalkyl, -C₁₋₆haloalkyl, -C₃₋₈cycloalkyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C(O)R^f, -C₁₋₆alkylC(O)R^f, -C(O)OR^f, -C₁₋₆alkylC(O)OR^f, -NR^fR^g, -C₁₋₆alkylNR^fR^g, -C(O)NR^fR^g, -C₁₋₆alkylC(O)NR^fR^g, -SO₂R^f, -C₁₋₆alkylSO₂R^f, -SO₂NR^fR^g, -C₁₋₆alkylSO₂NR^fR^g, -C(O)NR^fSO₂R^g and -NR^fC(O)R^g;

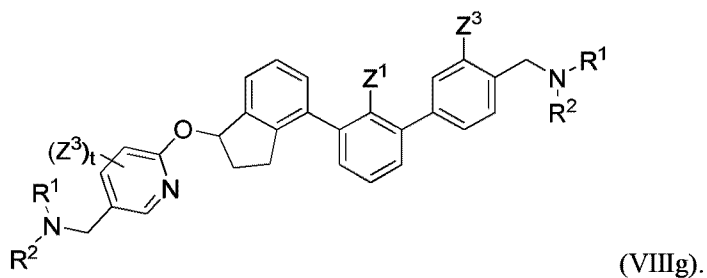
each R^f is independently selected from H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃alkylC₃₋₈cycloalkyl, -C₁₋₆alkylaryl, -C₁₋₆alkylheteroaryl, and -C₁₋₆alkylheterocyclyl; and

each R⁸ is independently selected from H, -C₁₋₆ alkyl, -C₃₋₈ cycloalkyl, aryl, heteroaryl, heterocyclyl, -C₁₋₃ alkylC₃₋₈ cycloalkyl, -C₁₋₆ alkylaryl, -C₁₋₆ alkylheteroaryl, and -C₁₋₆ alkylheterocyclyl; or a pharmaceutically acceptable salt thereof.

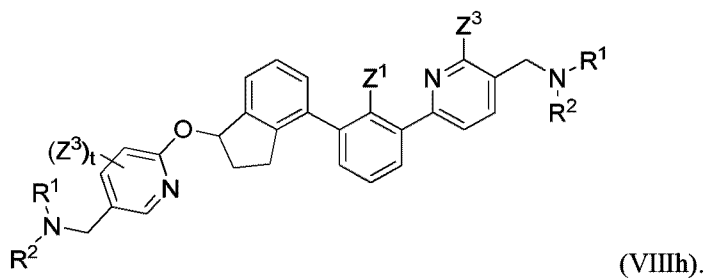
7. The compound of claim 6, wherein the compound is represented by a compound of formula (VIIIf):



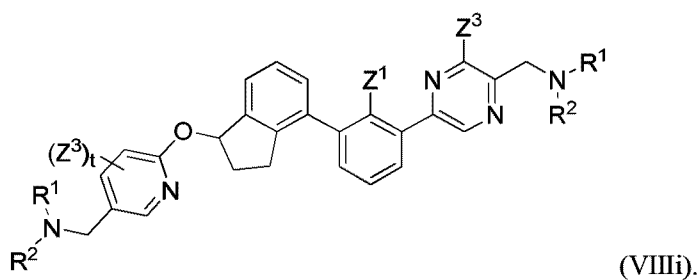
8. The compound of claim 1, wherein the compound is represented by a compound of formula (VIIIg):



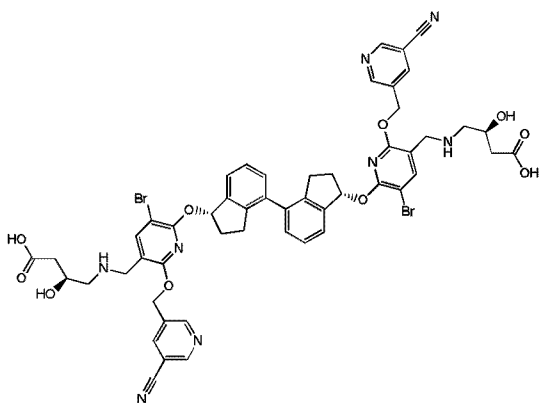
9. The compound of claim 1, wherein the compound is represented by a compound of formula (VIIIh):



10. The compound of claim 1, wherein the compound is represented by a compound of formula (VIIIi):

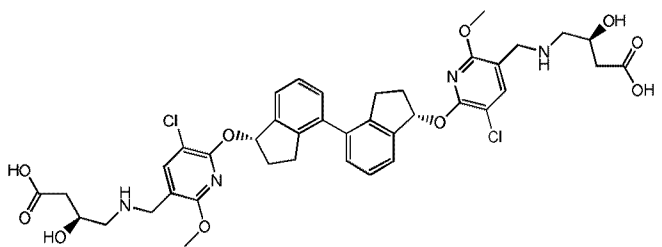


11. The compound of any one of claims 1 to 10, wherein each Z^1 is independently halo.
12. The compound of any one of claims 1 to 11, wherein each Z^3 is independently halo or C_{1-6} alkoxy.
13. The compound of any one of claims 1 to 12, wherein each Z^1 is independently chloro.
14. The compound of any one of claims 1 to 13, wherein each Z^3 is independently chloro or methoxy.
15. The compound



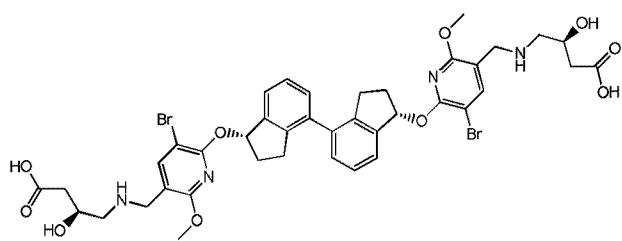
or a pharmaceutically acceptable salt thereof.

16. The compound



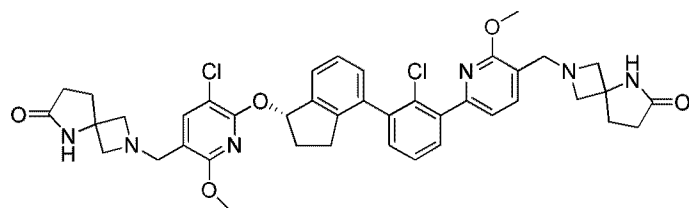
or a pharmaceutically acceptable salt thereof.

17. The compound



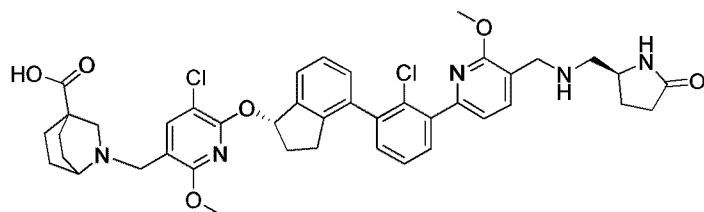
or a pharmaceutically acceptable salt thereof.

18. The compound of claim 1, having the structure:



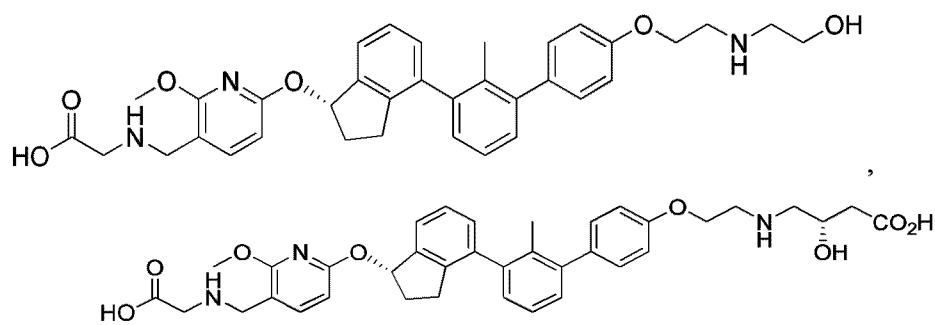
or a pharmaceutically acceptable salt thereof.

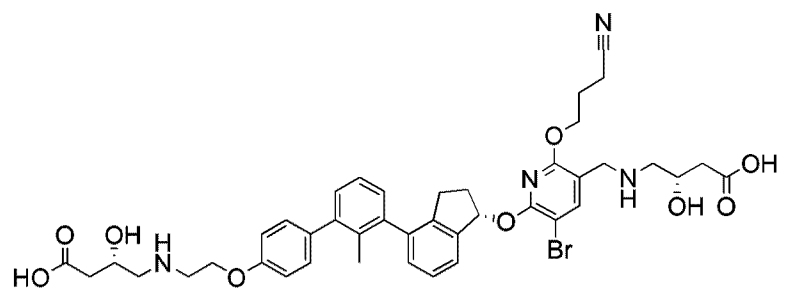
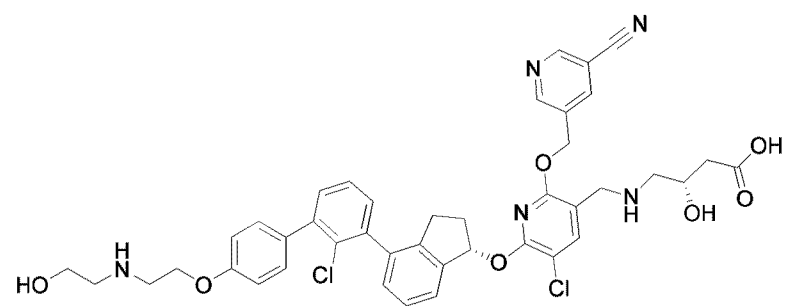
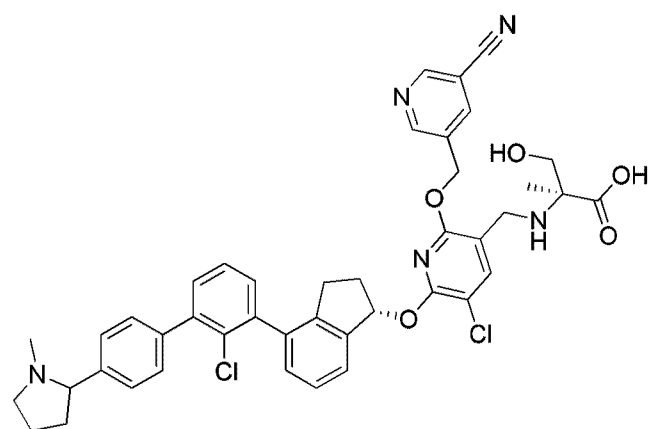
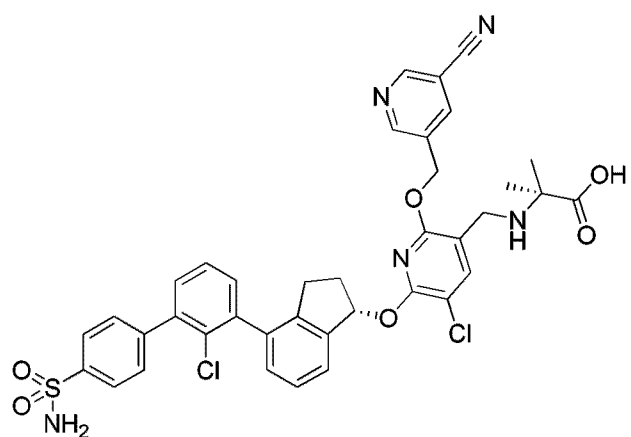
19. The compound of claim 1 having the structure:

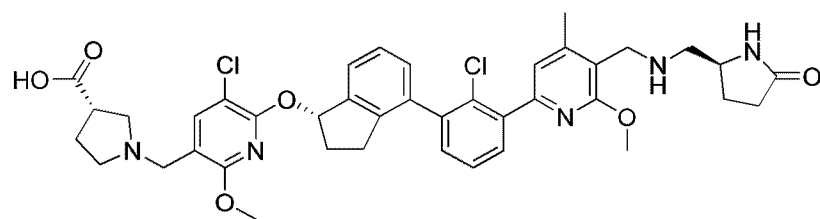
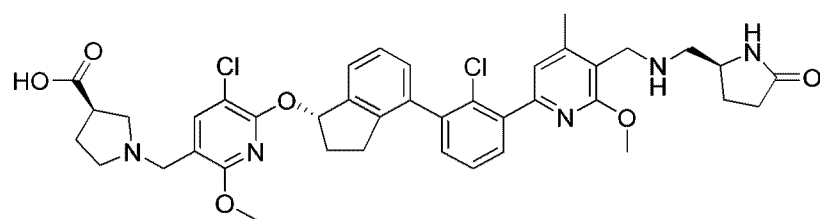
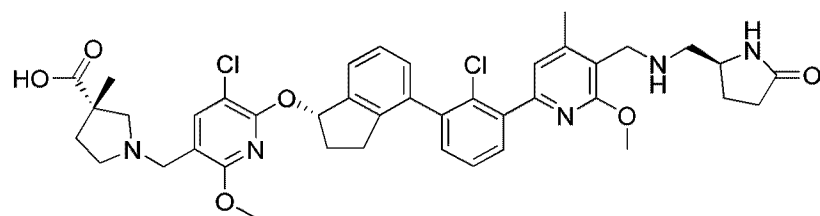
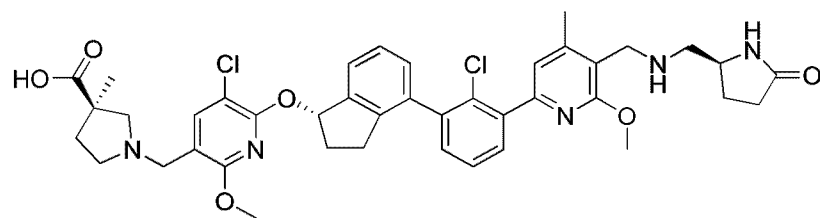
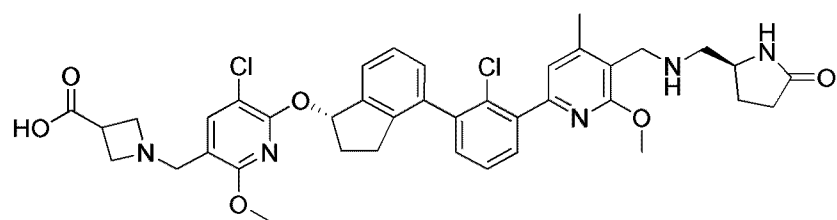
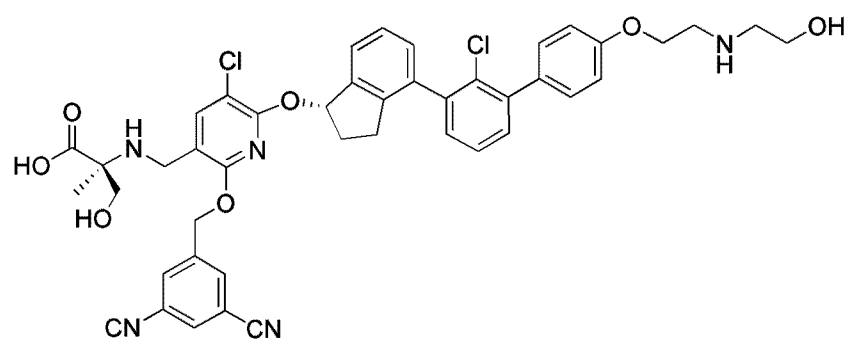


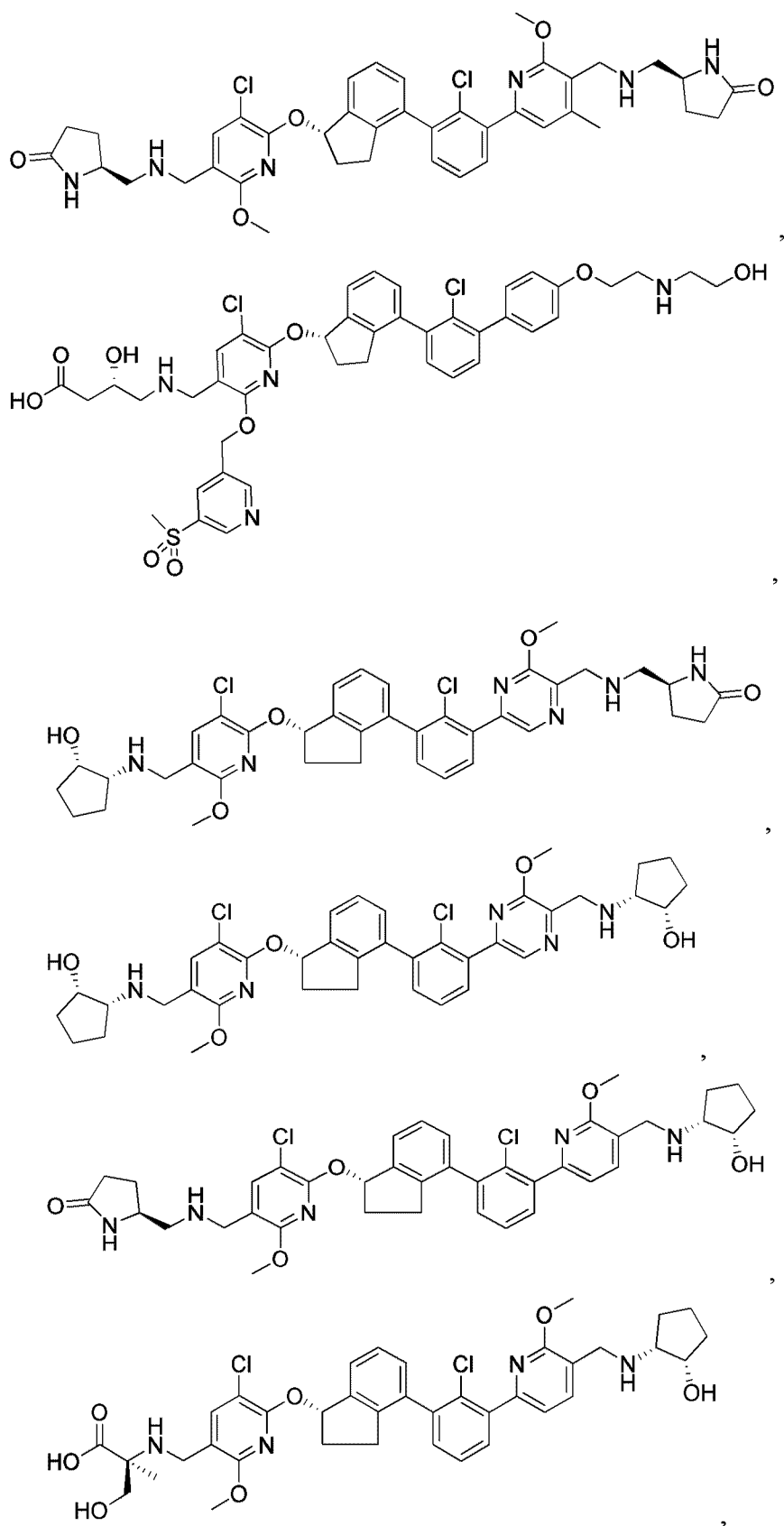
or a pharmaceutically acceptable salt thereof.

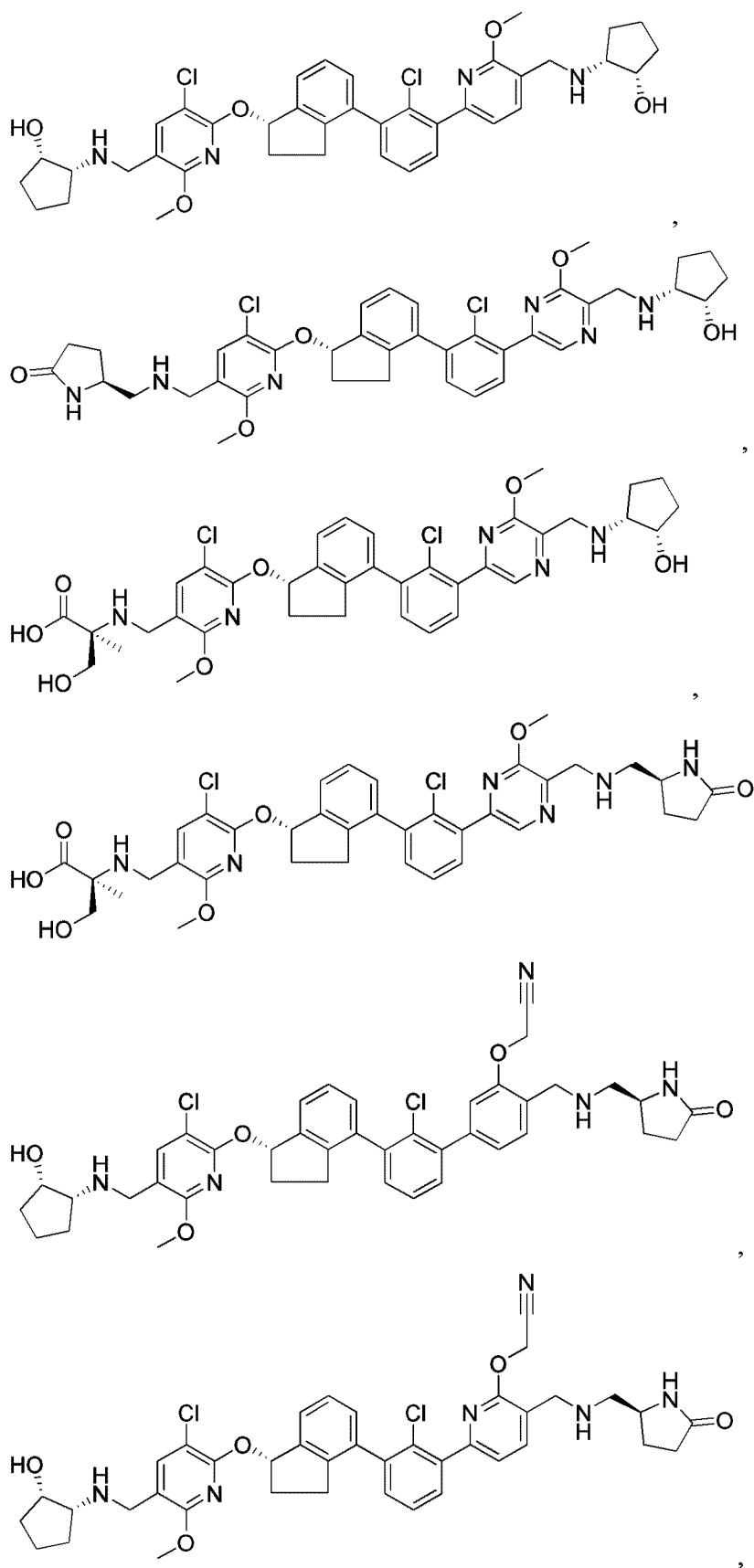
20. A compound of formula:

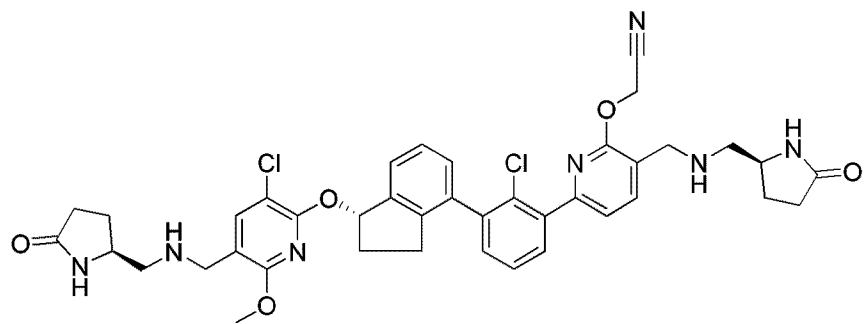
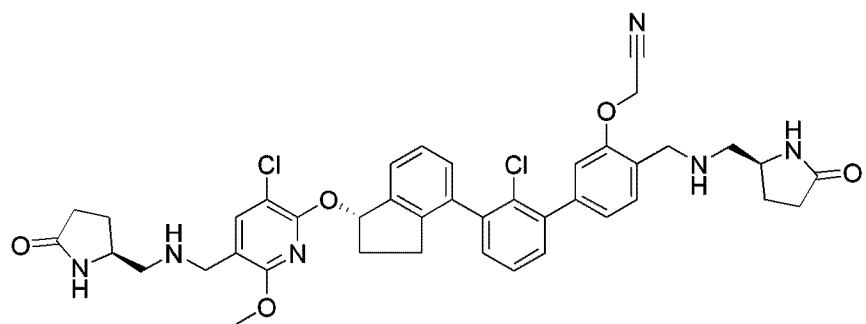
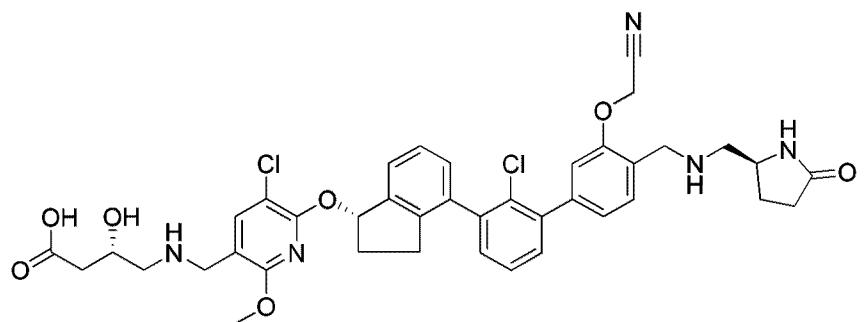
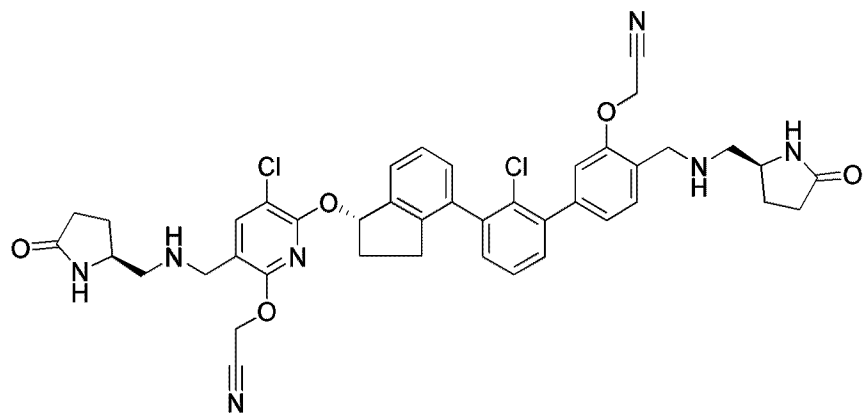
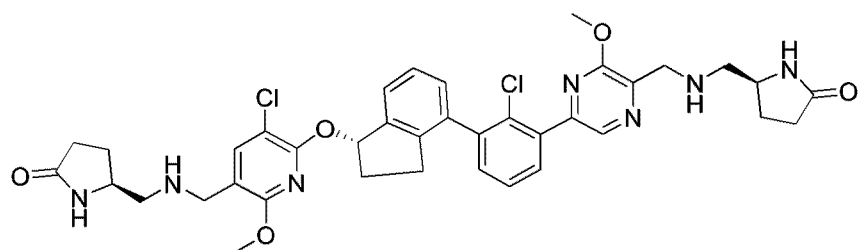


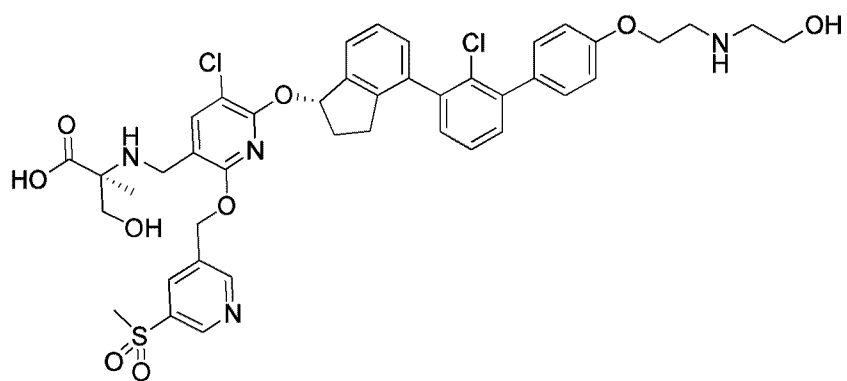
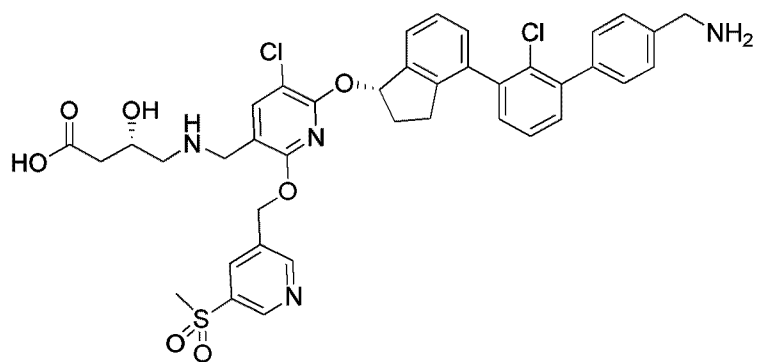
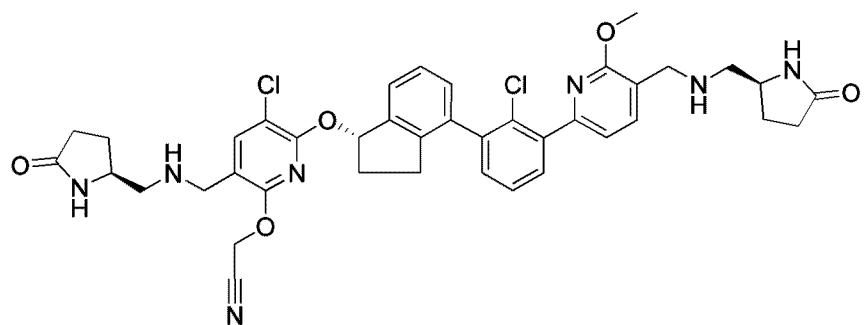
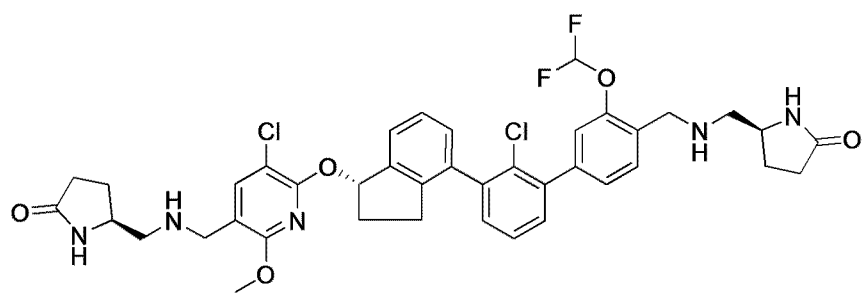


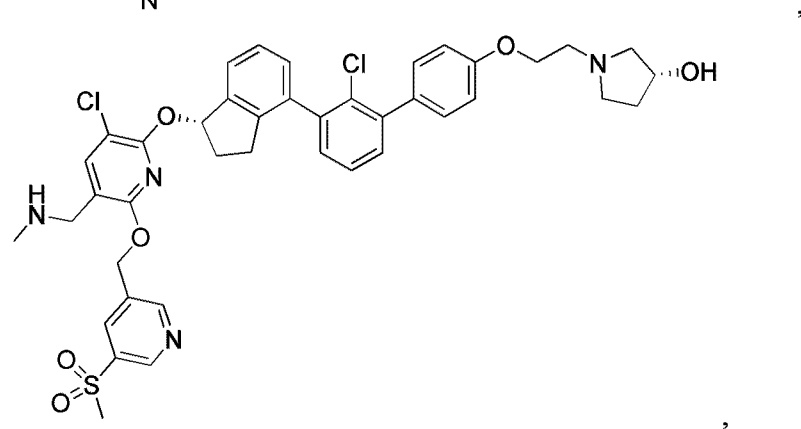
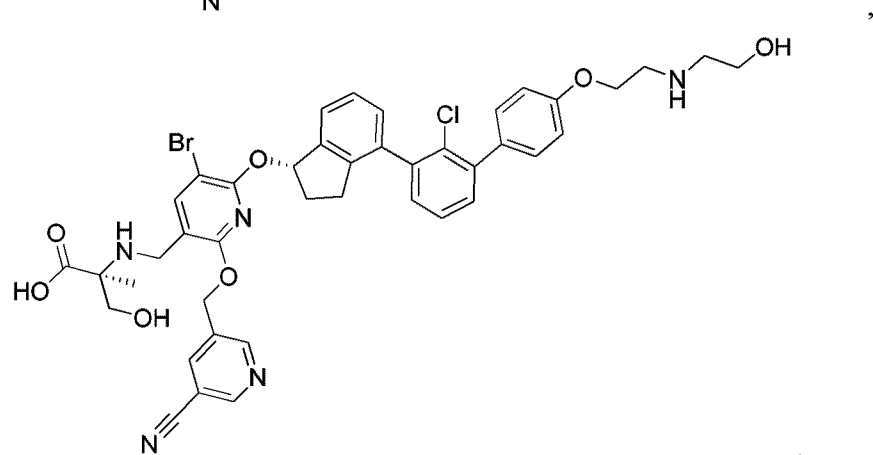
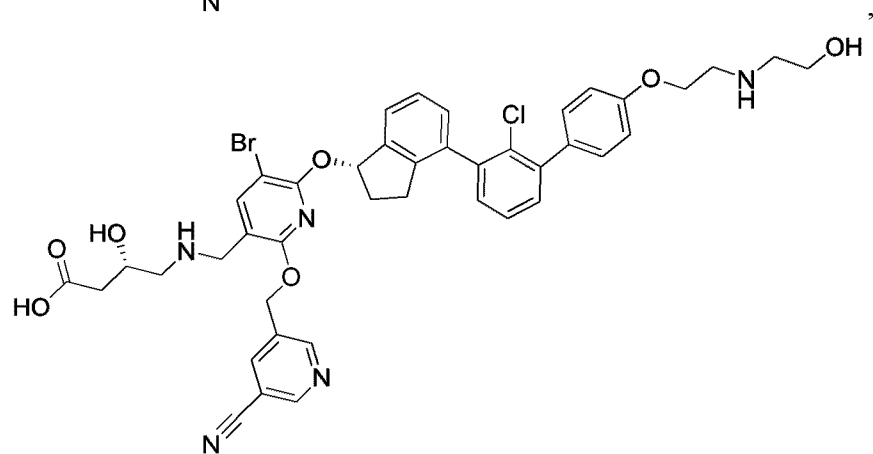
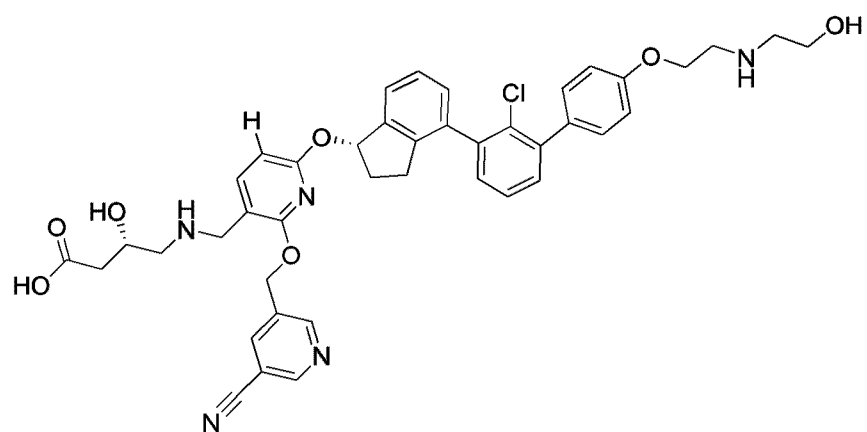


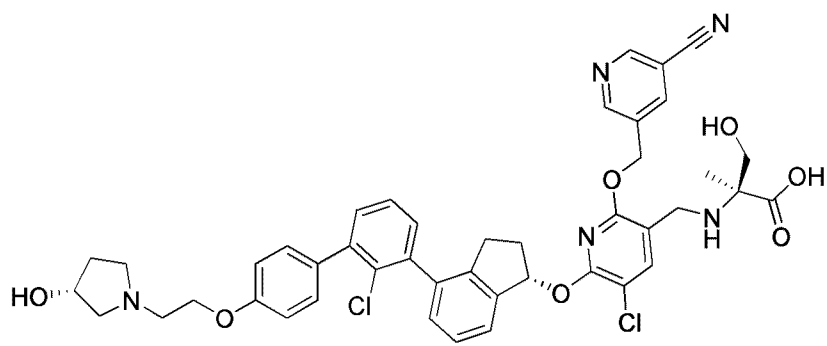
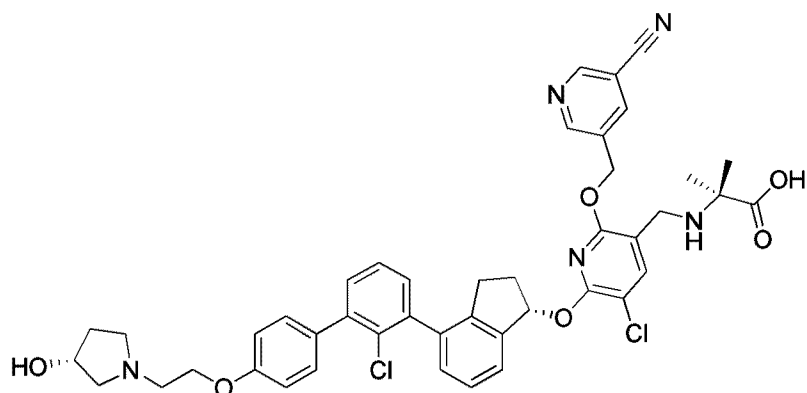
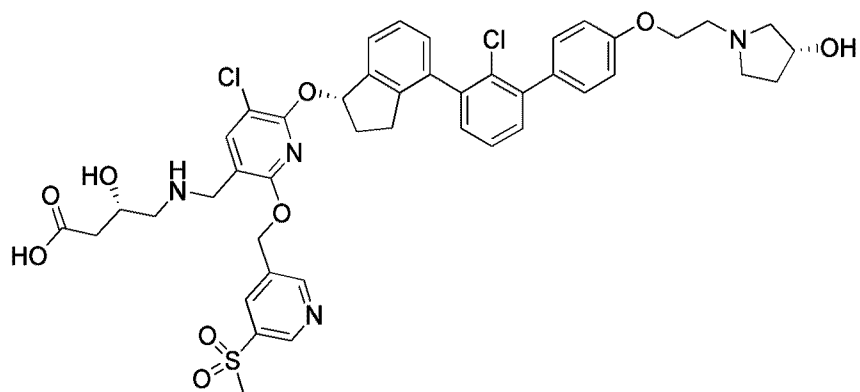
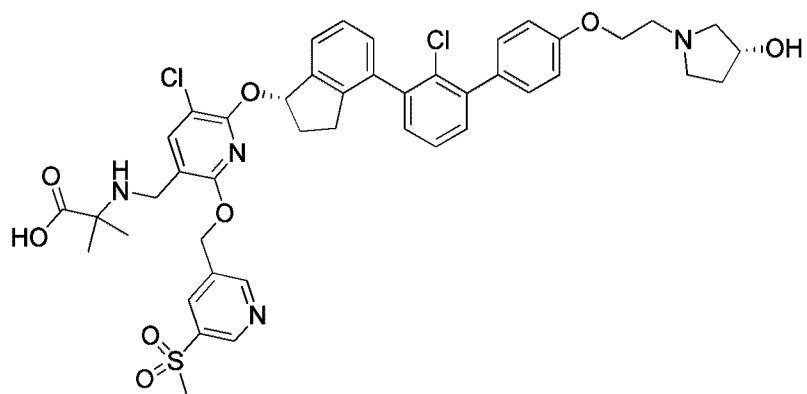


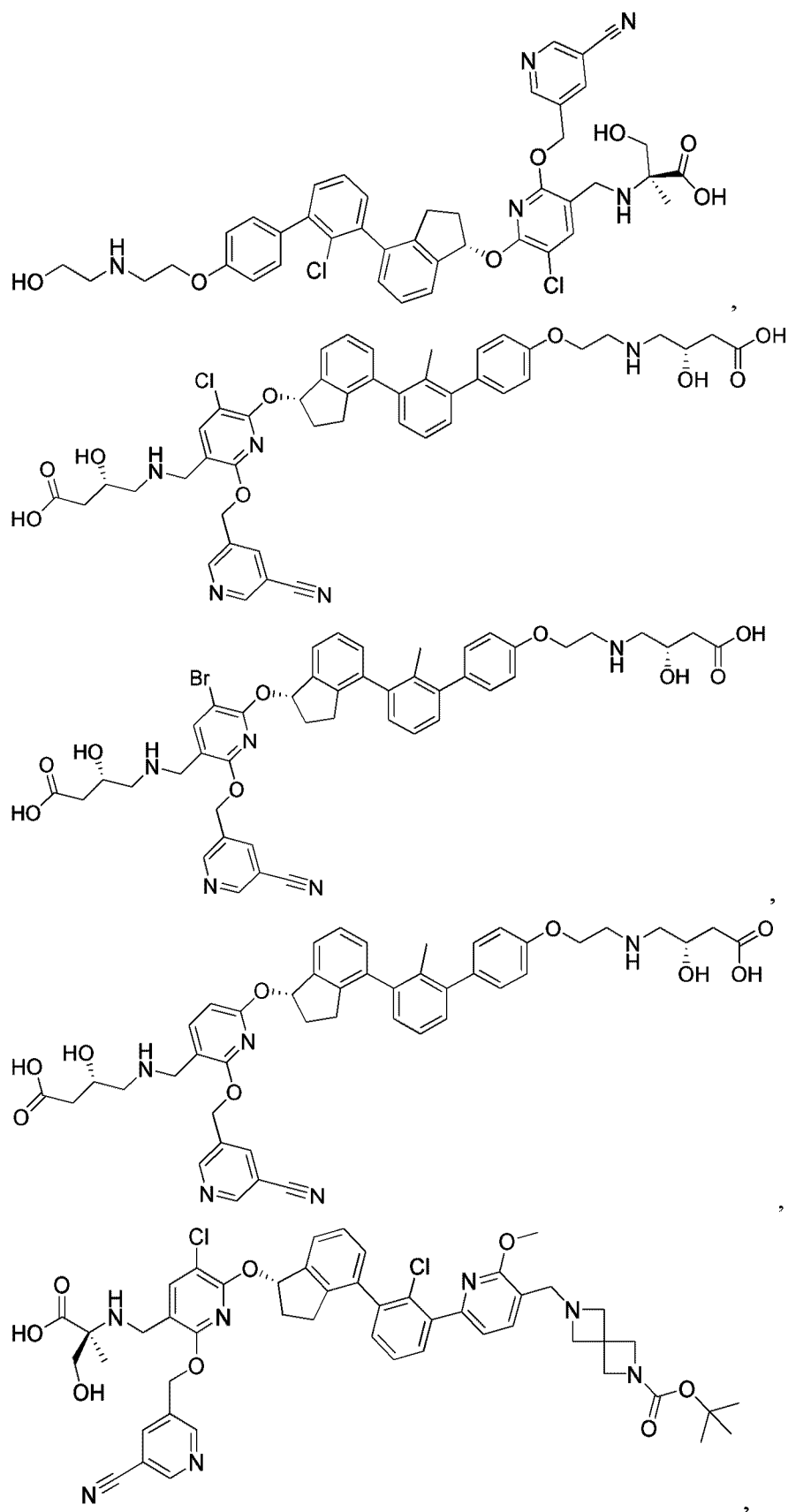


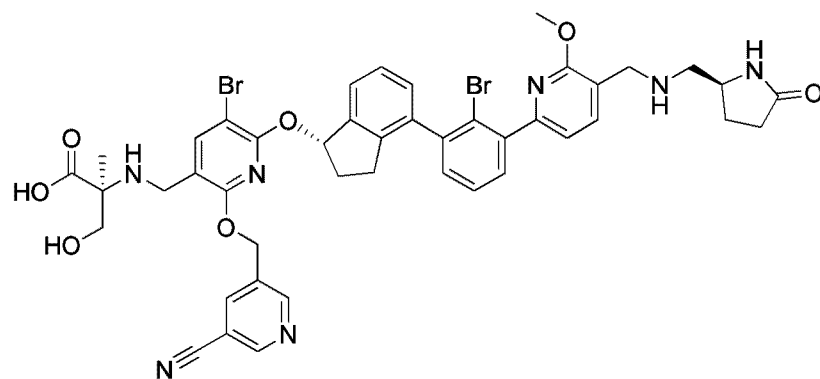
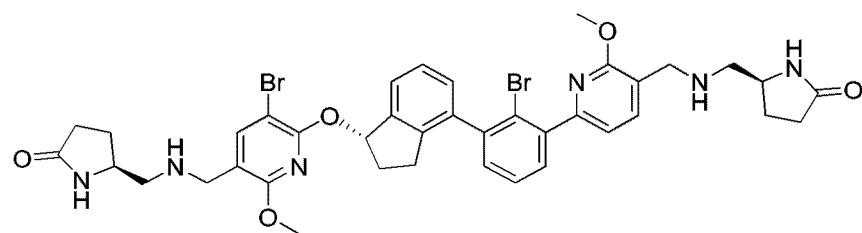
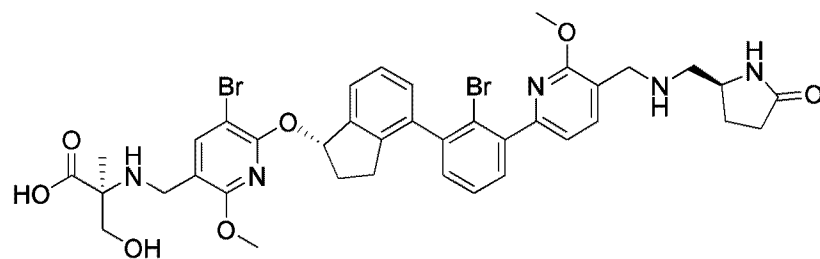
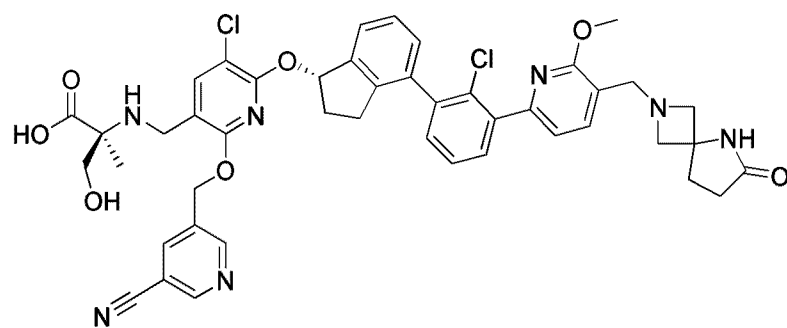
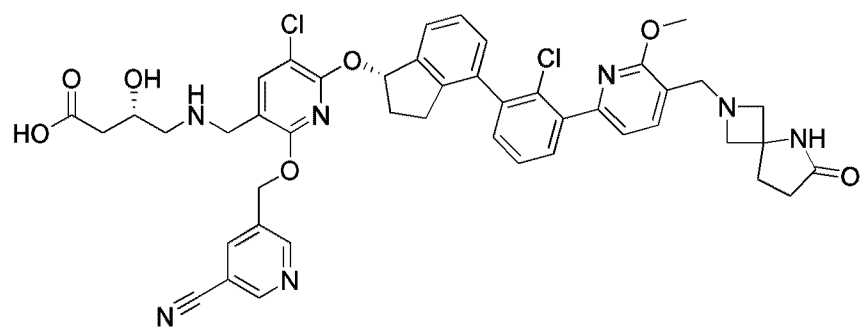


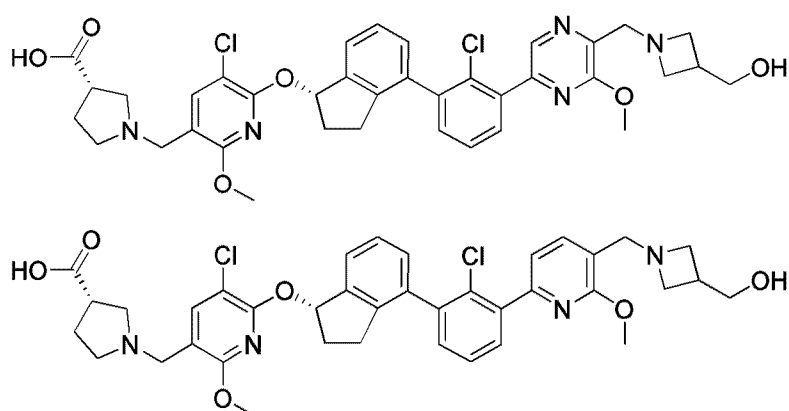
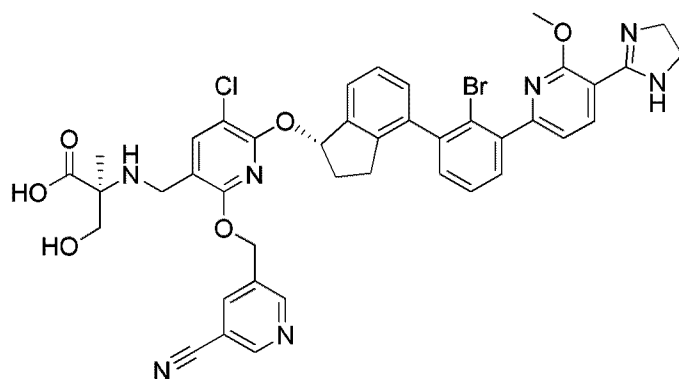
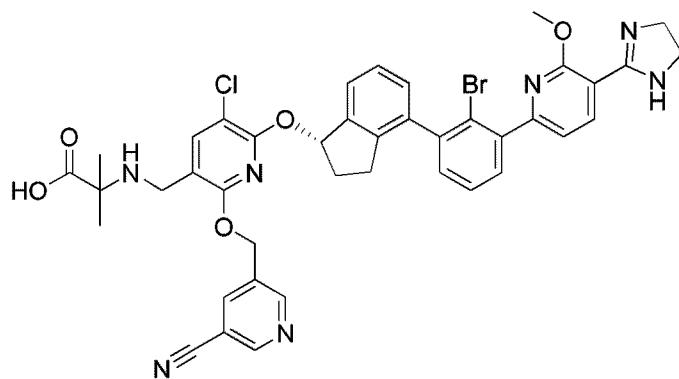
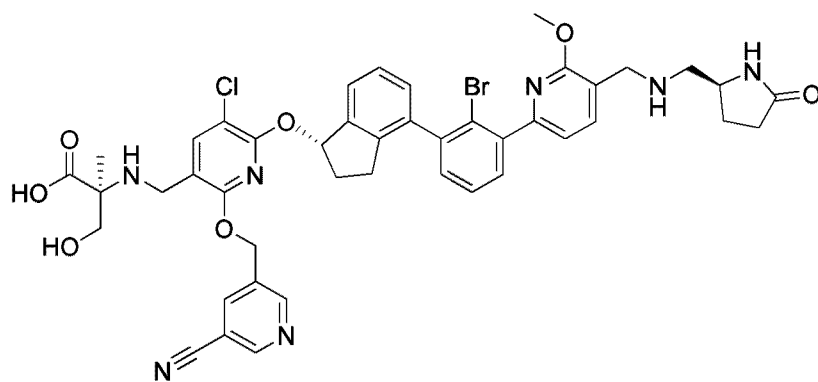


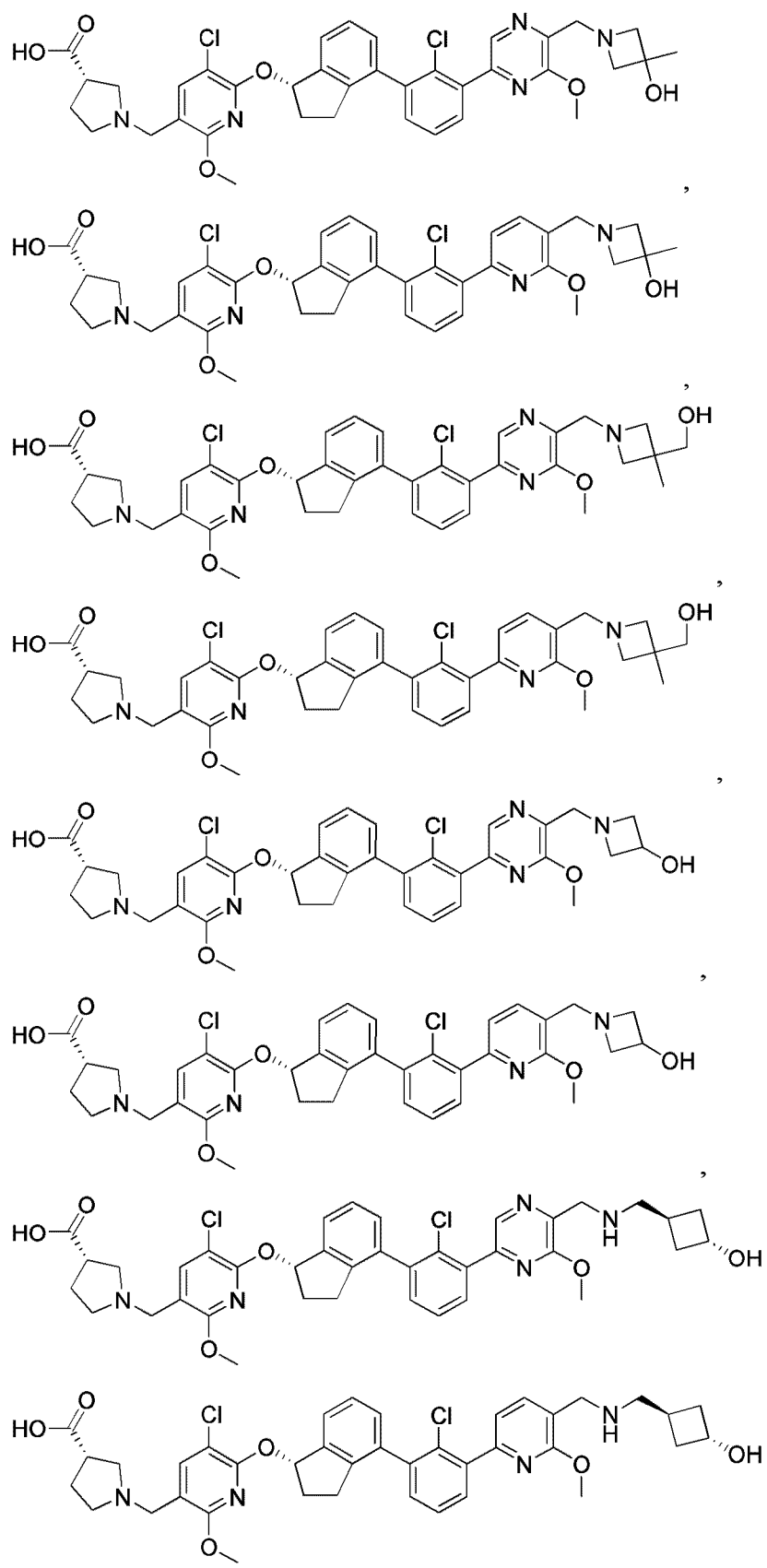


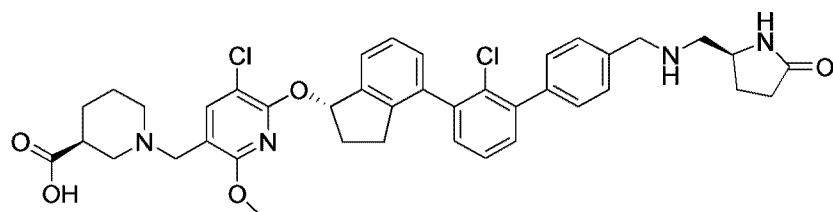
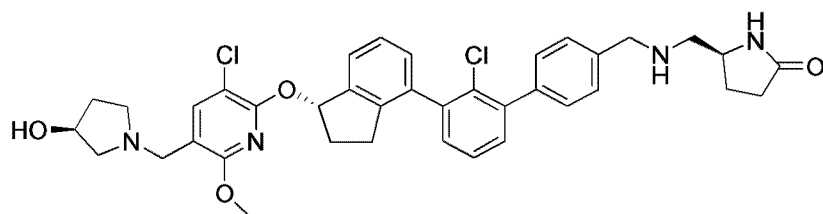
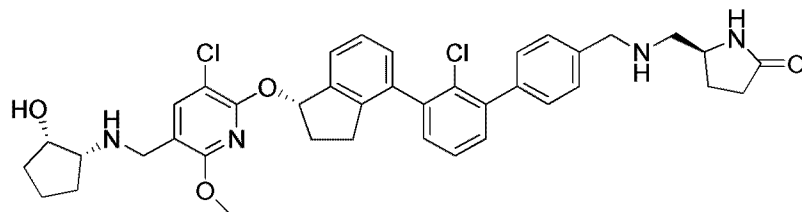
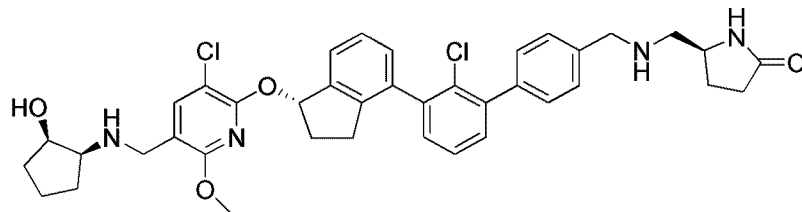
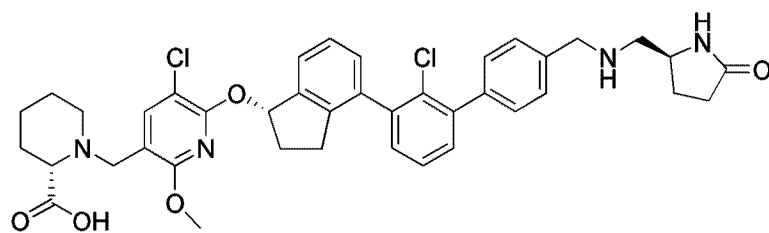
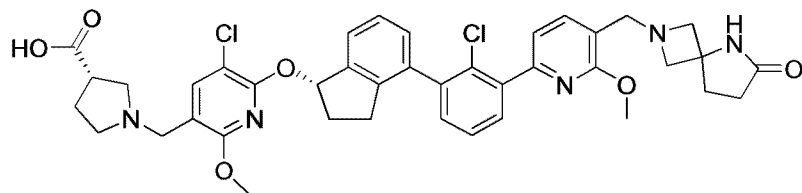
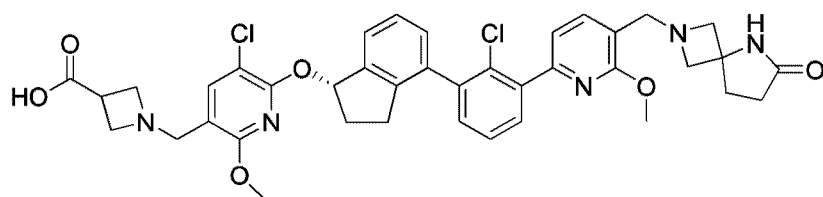


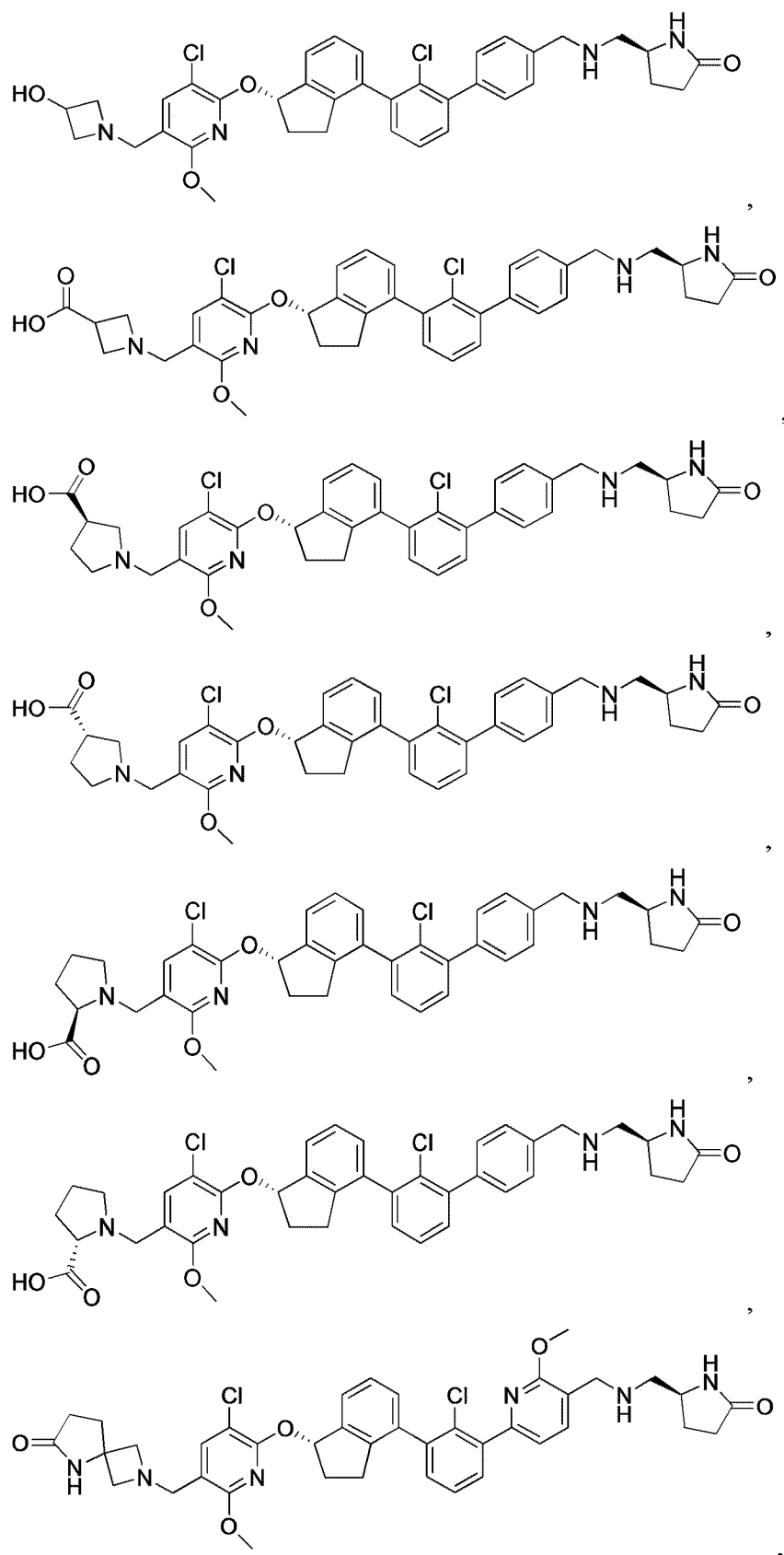


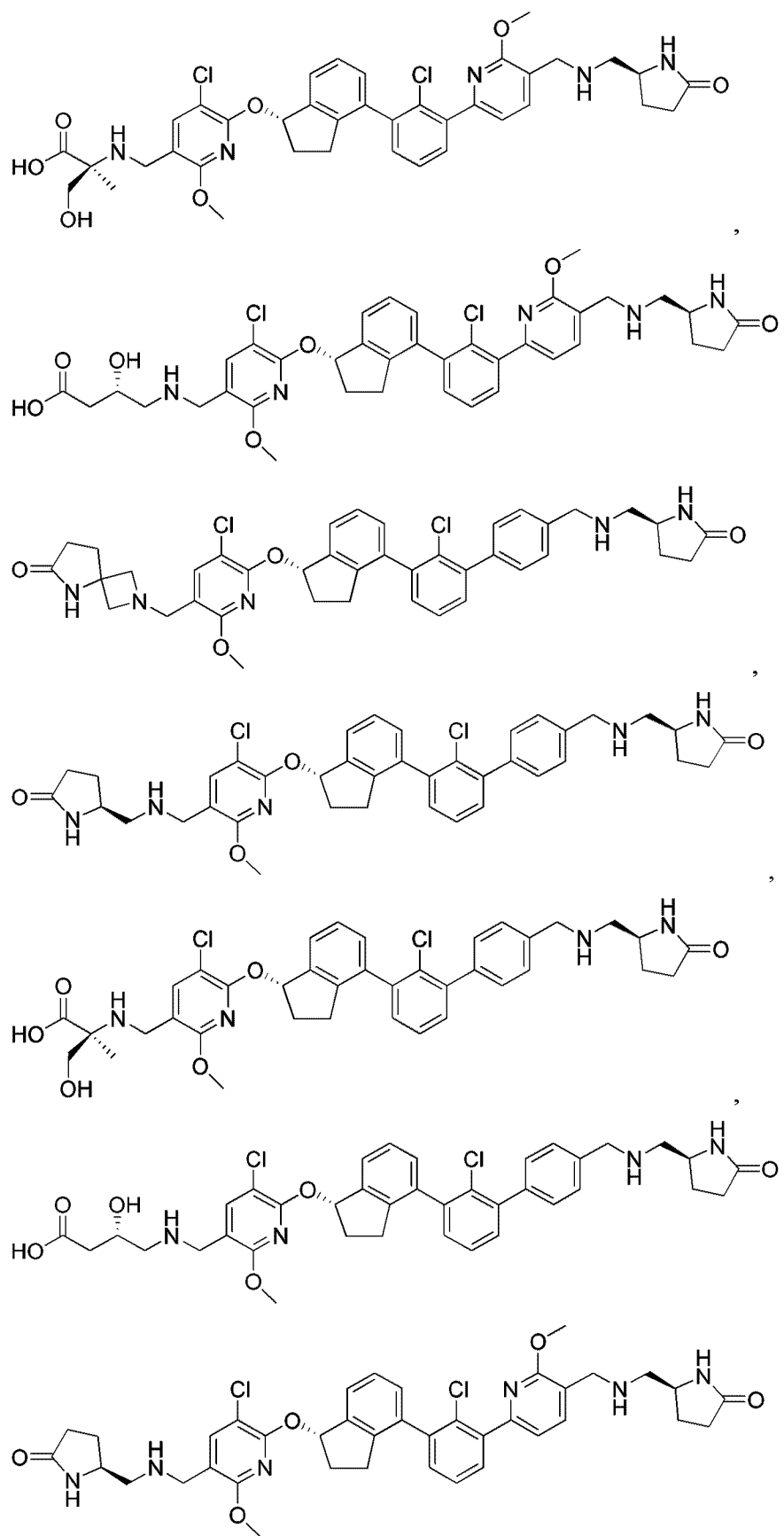


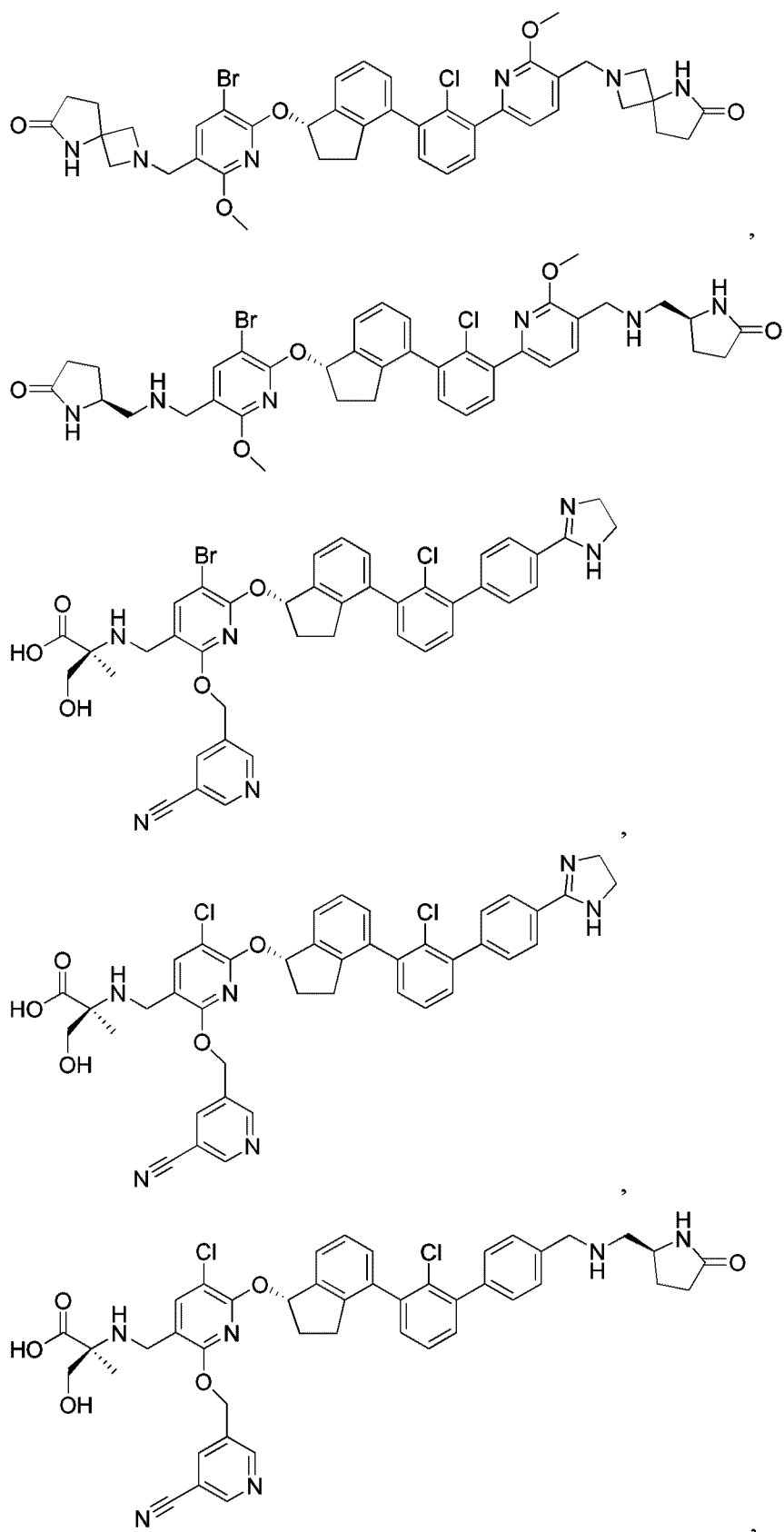


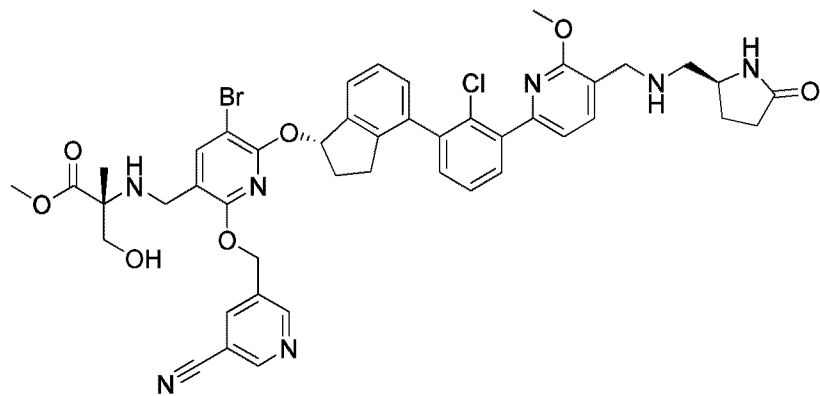
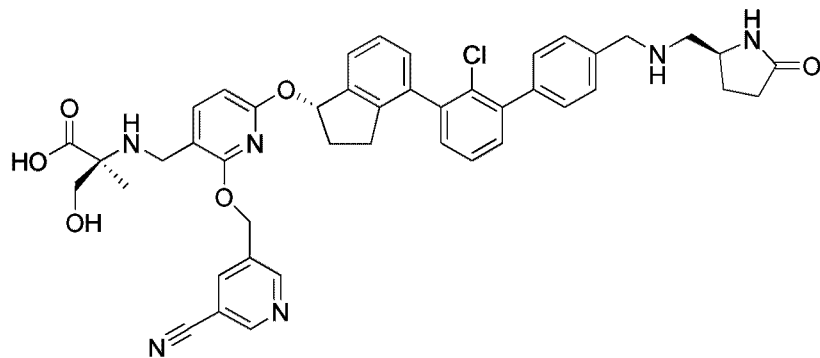
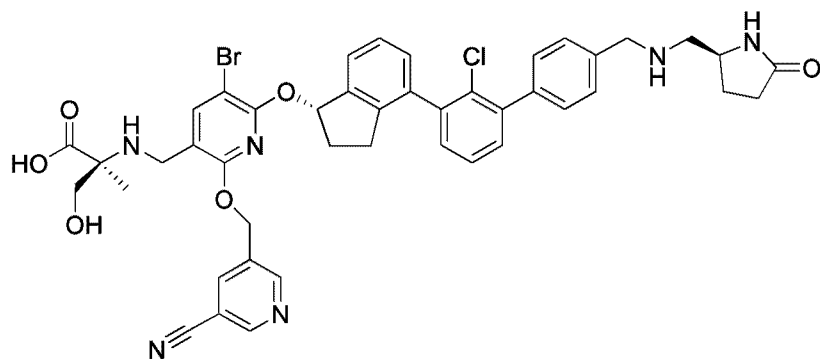
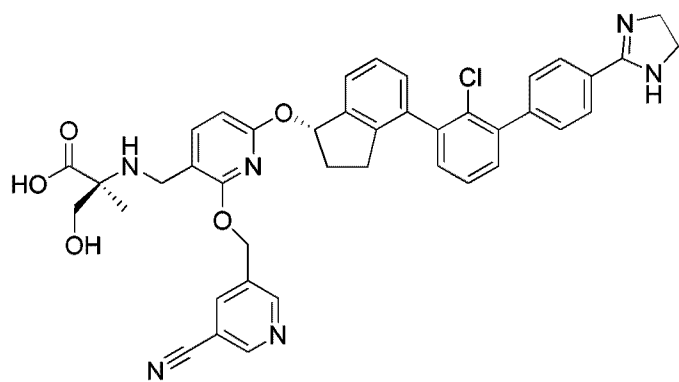


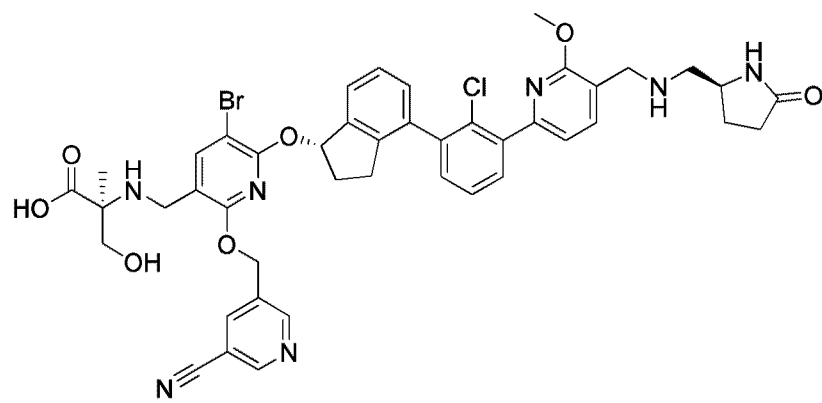
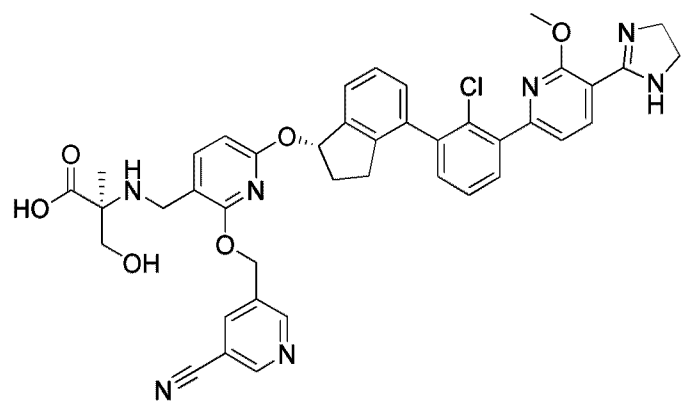
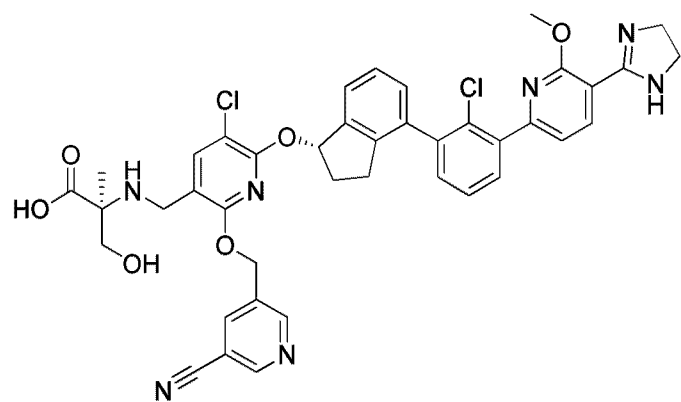
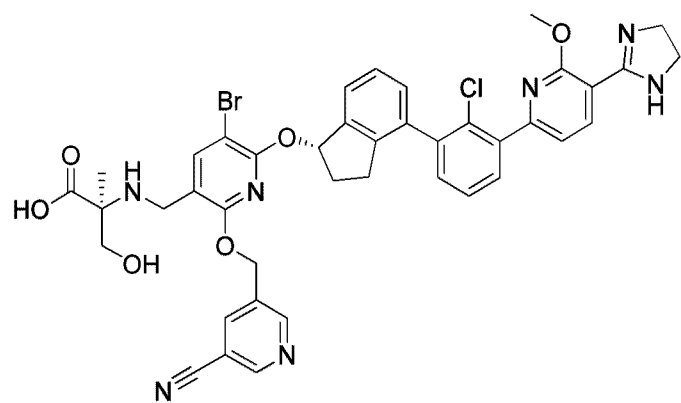


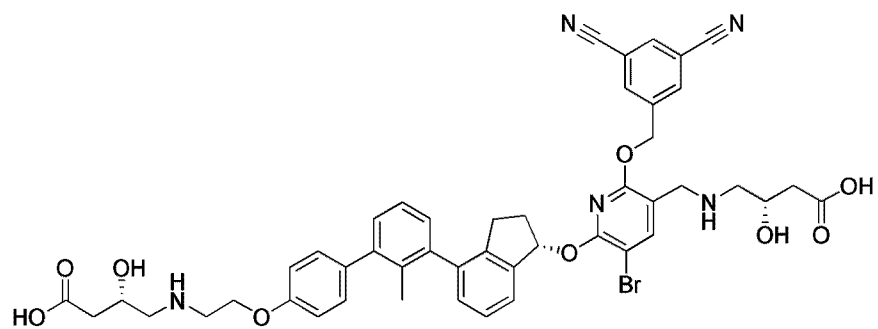
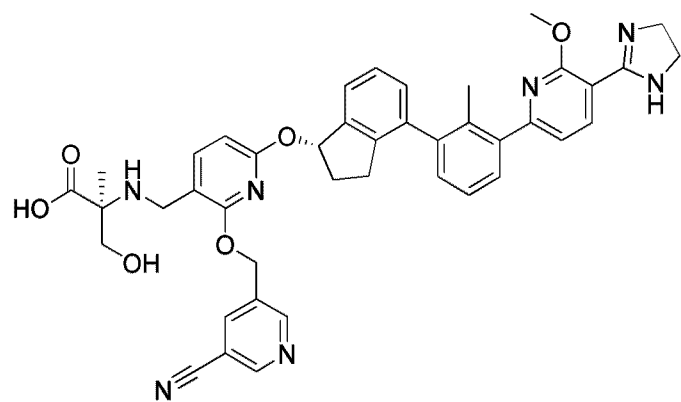
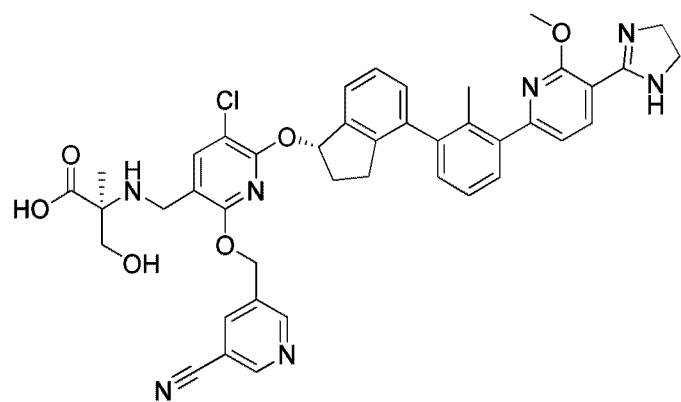
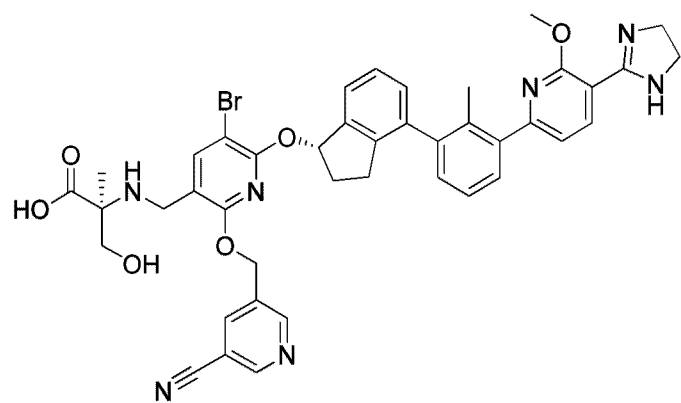


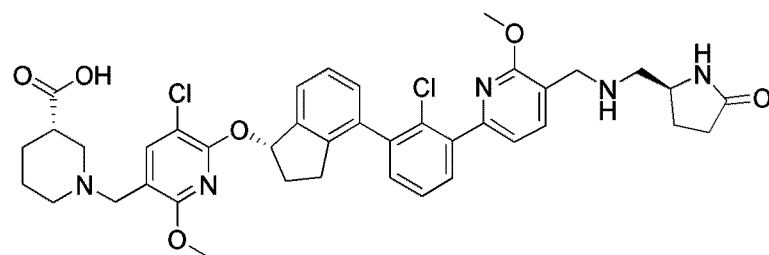
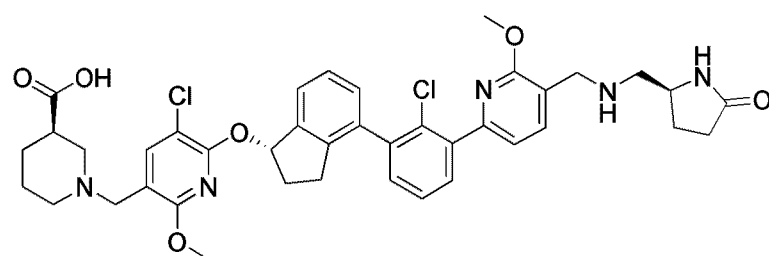
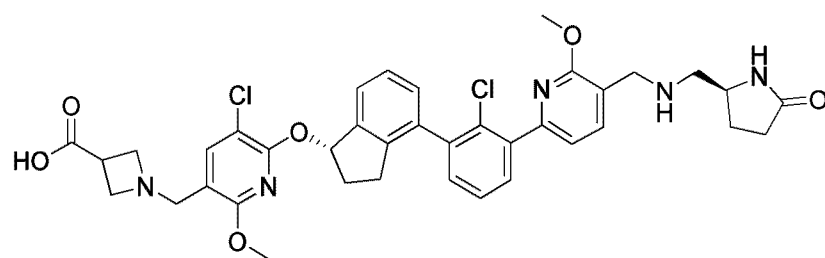
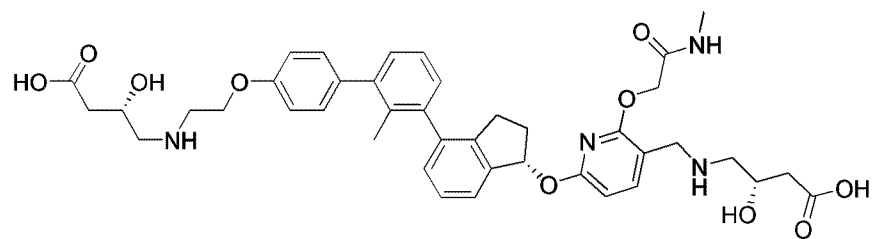
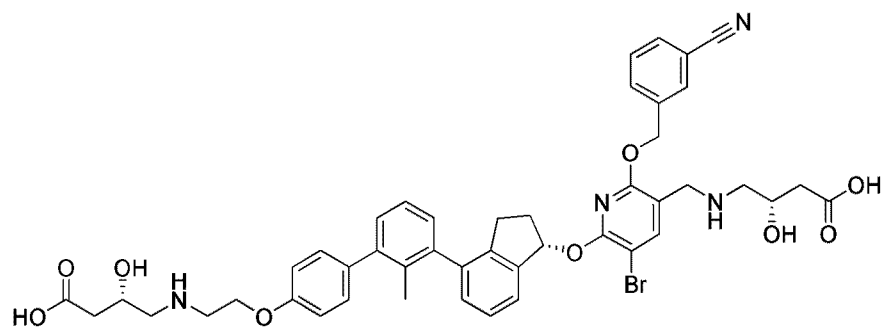
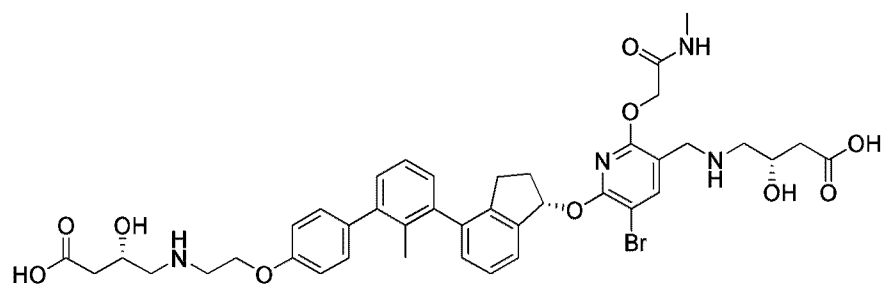


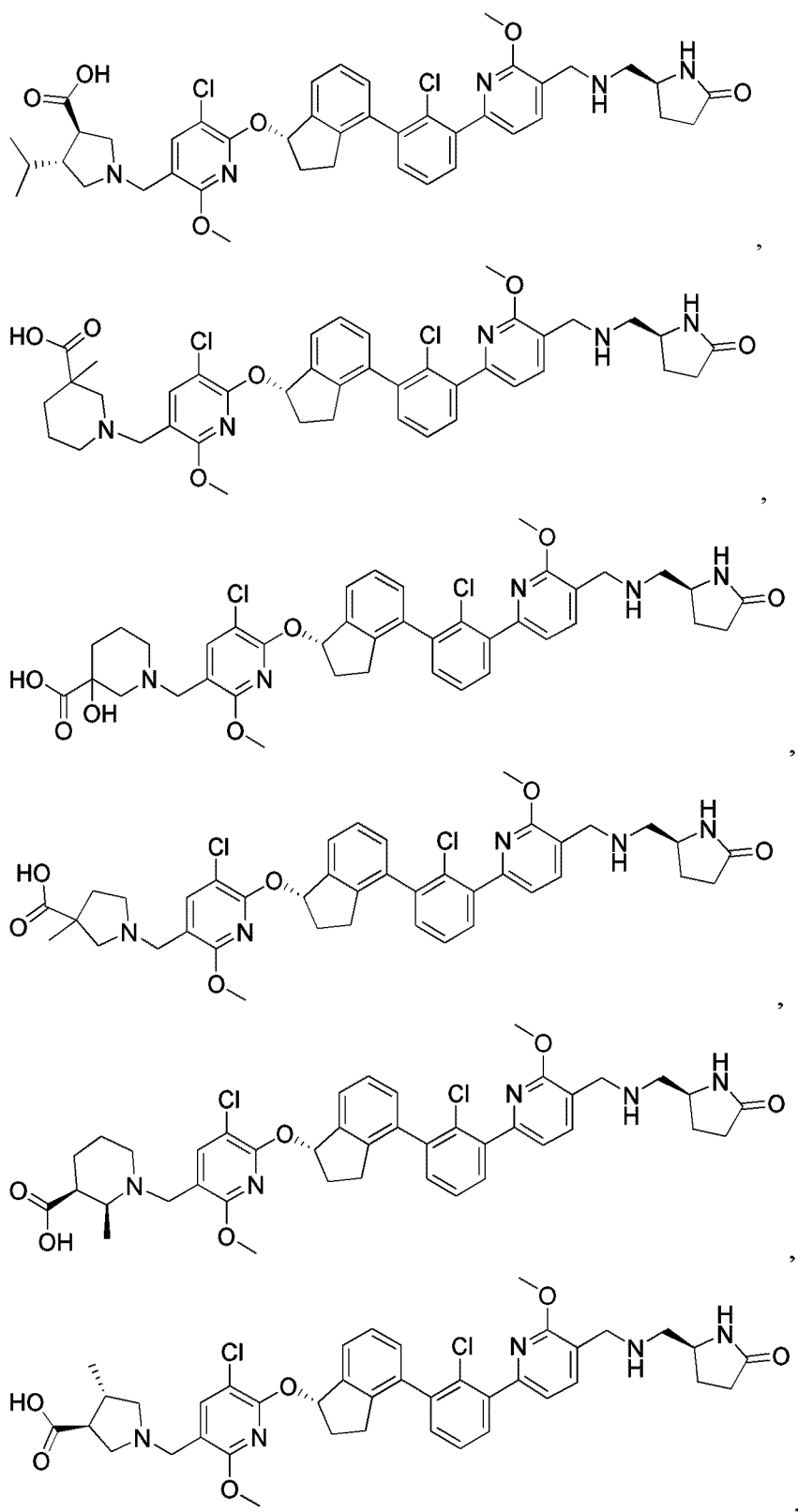


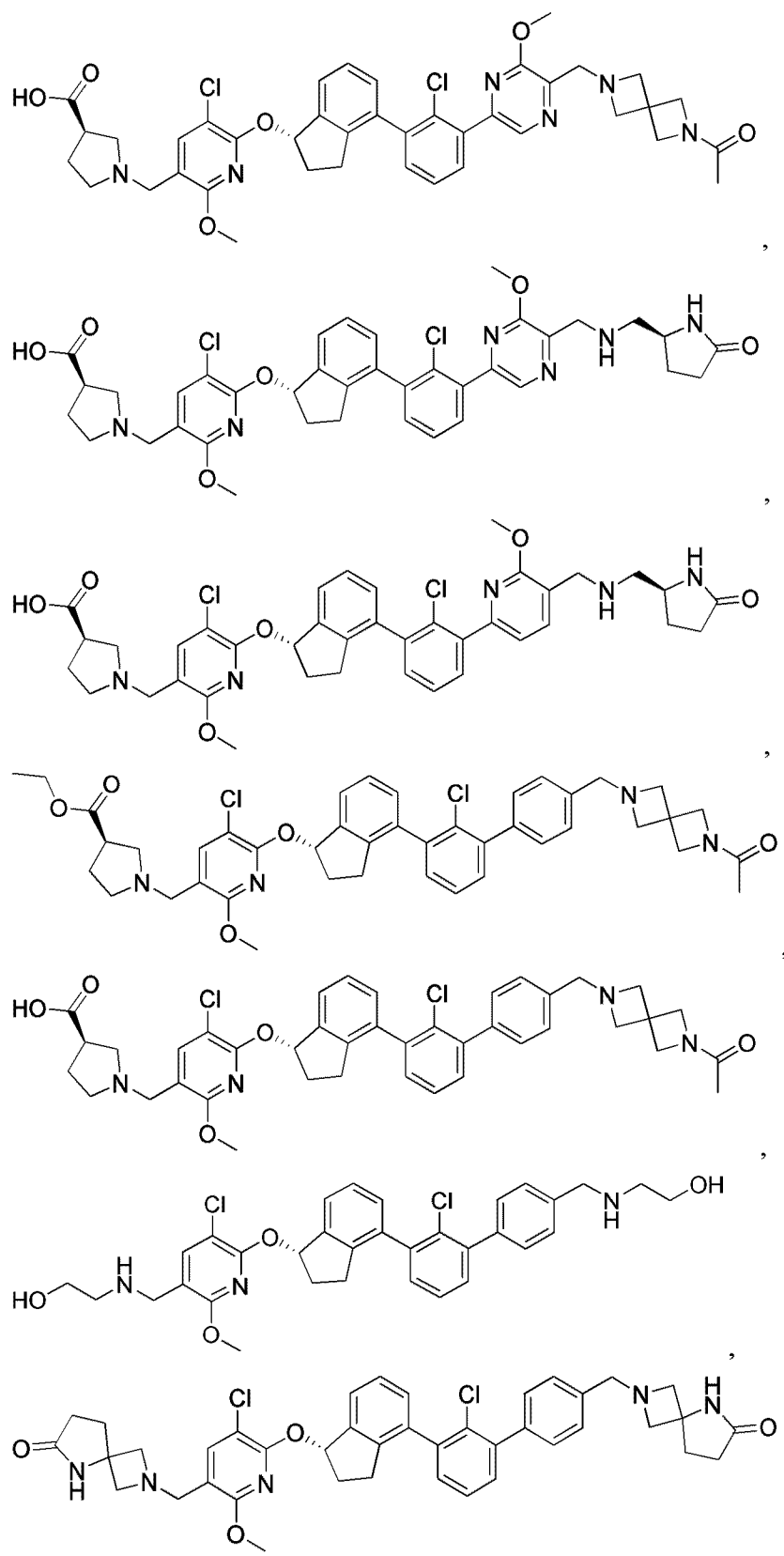


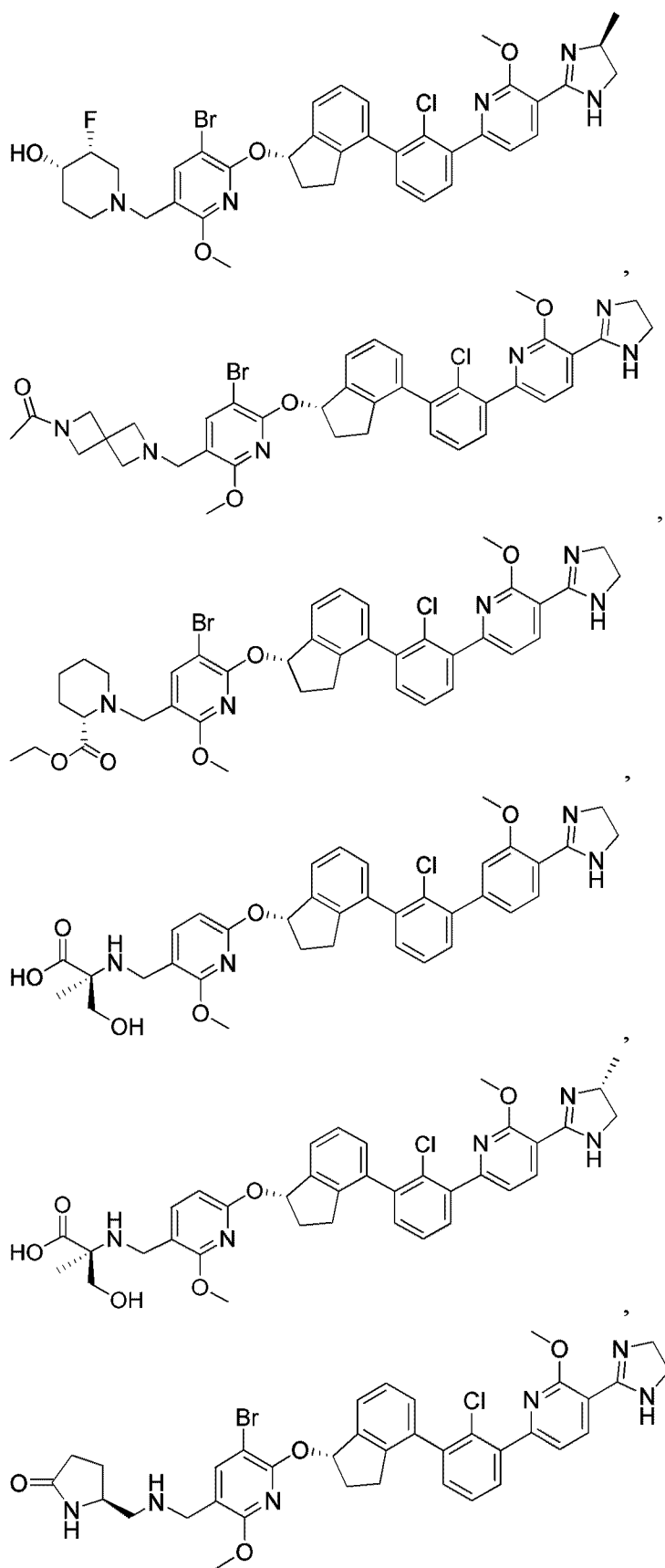


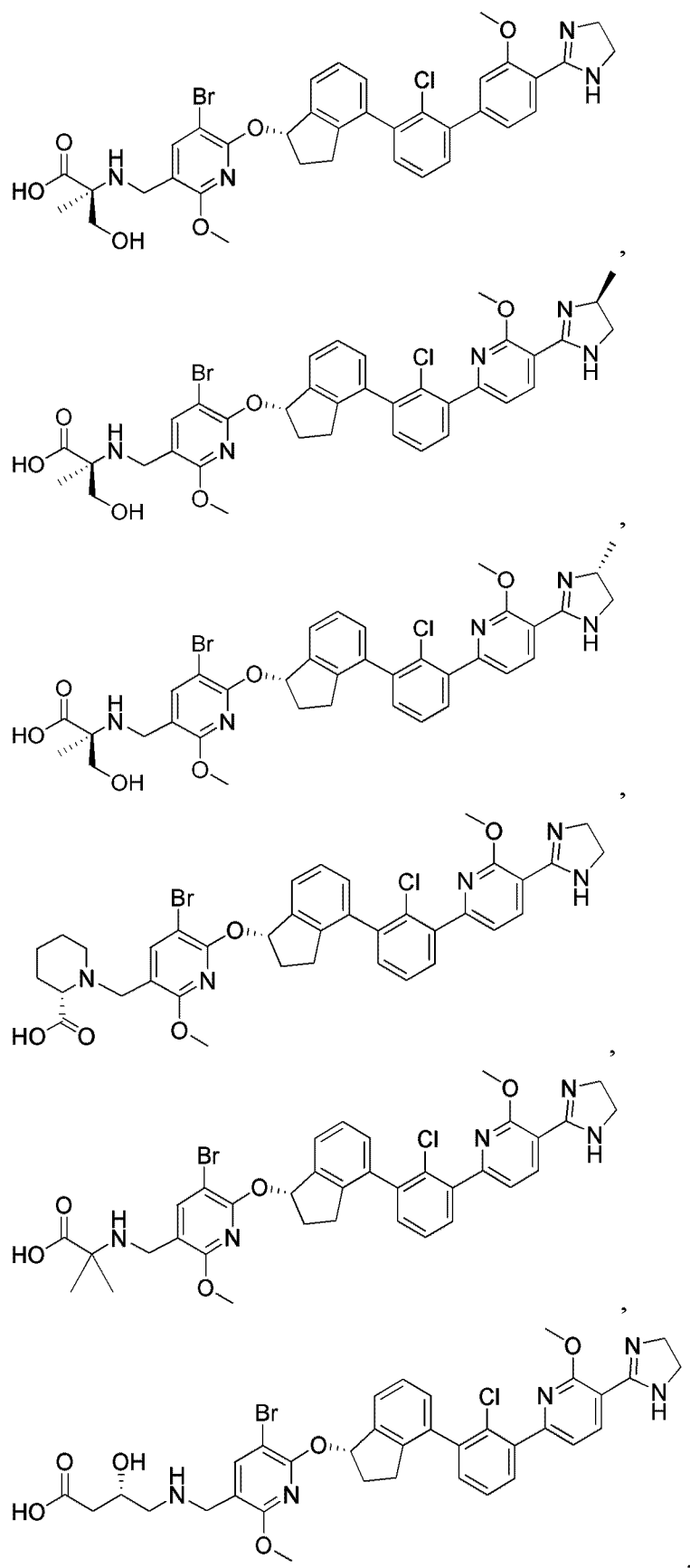


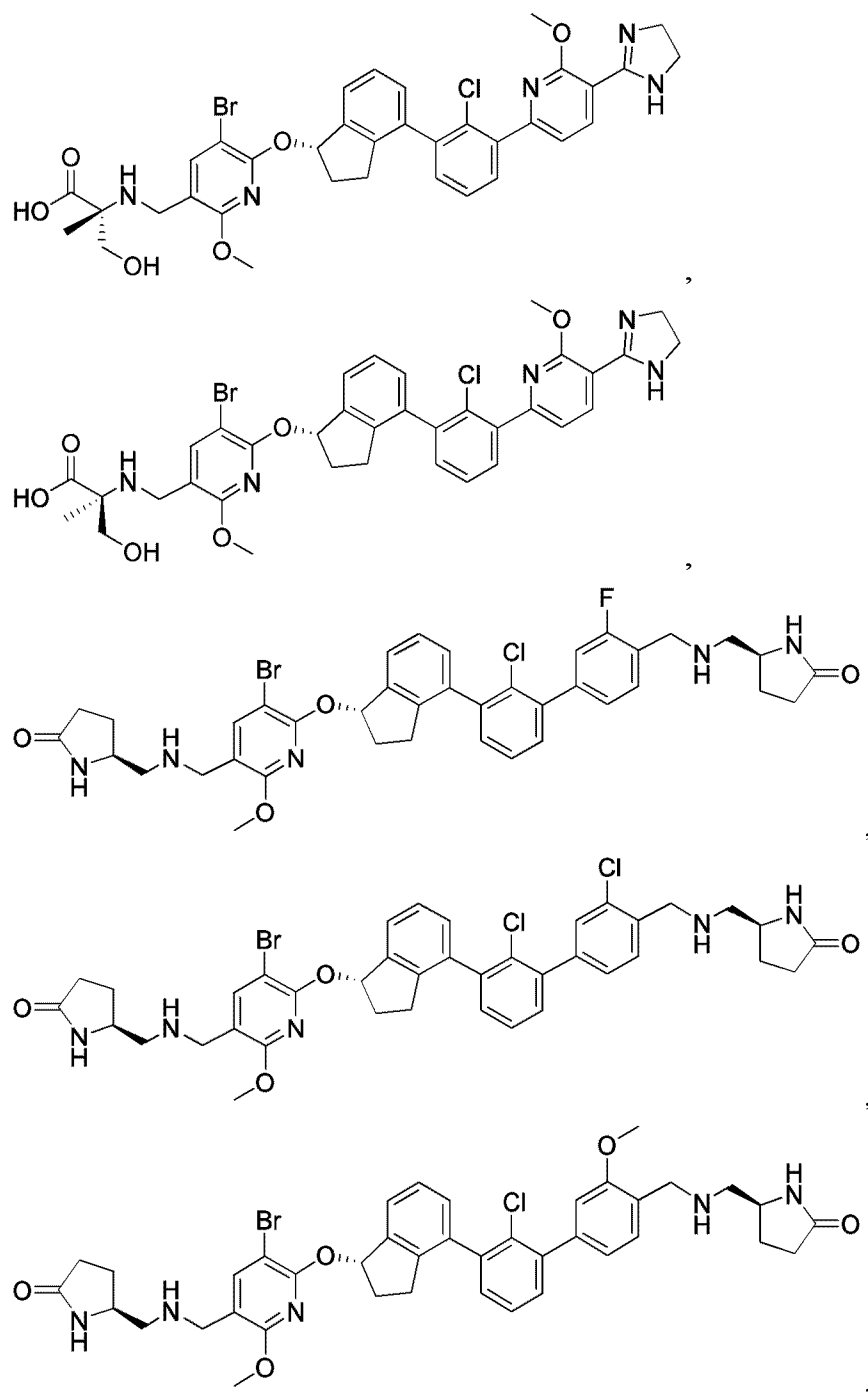


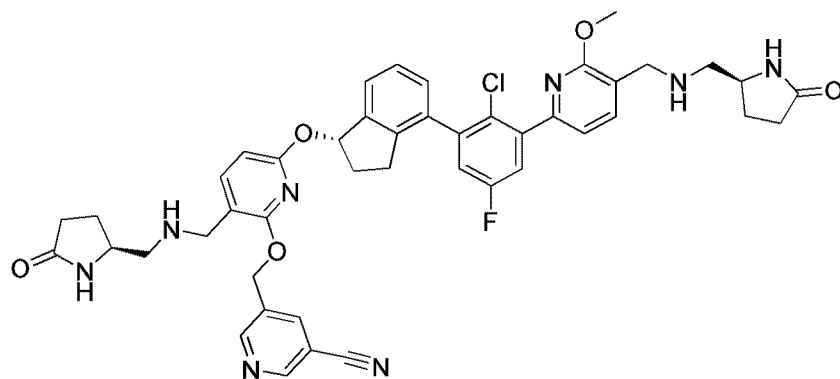
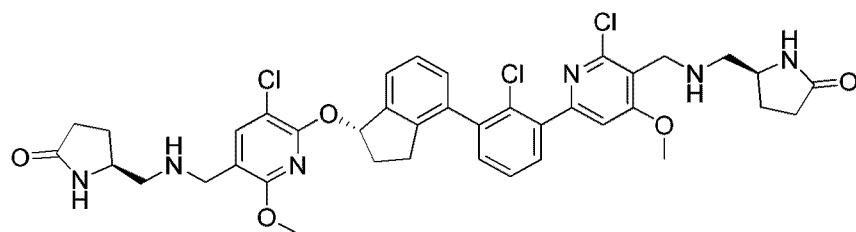
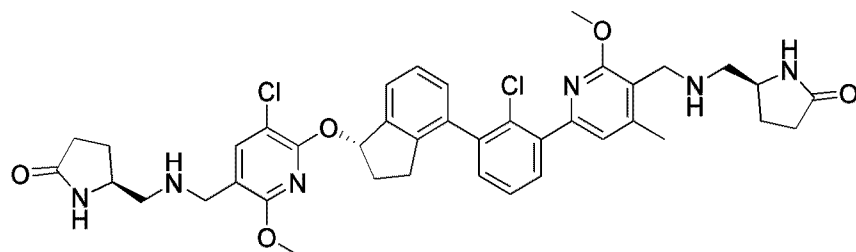
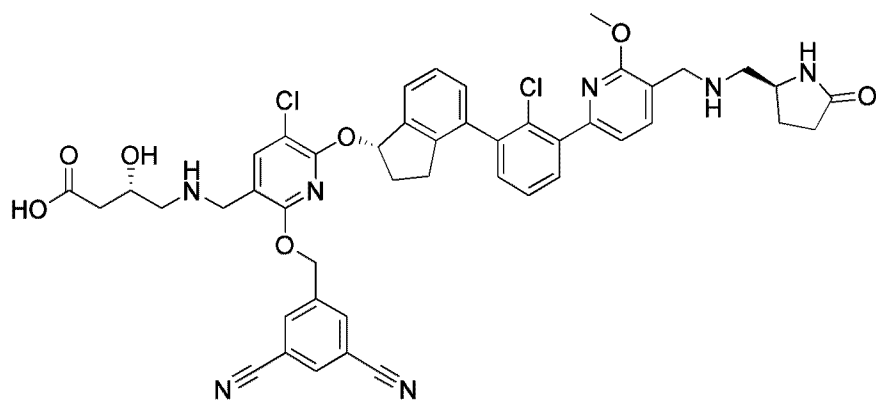












or a pharmaceutically acceptable salt thereof.

21. Use of a compound according to any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof for inhibiting PD-1, PD-L1 and/or the PD-1/PD-L1 interaction.

22. Use of a compound according to any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting PD-1, PD-L1 and/or the PD-1/PD-L1 interaction.

23. Use of a compound according to any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof for treating cancer.

24. Use of a compound according to any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating cancer.
25. The use according to claim 23 or 24, wherein the cancer is pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft tissue sarcoma, non-small cell lung cancer, small-cell lung cancer, or colon cancer.
26. The use according to claim 23 or 24, wherein the cancer is acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myeloid leukemia (CML), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma, Waldstrom's macroglobulinemia (WM), T-cell lymphoma, B-cell lymphoma, or diffuse large B-cell lymphoma (DLBCL).
27. The use according to any one of claims 21 to 26, wherein the compound is for use in combination with at least one additional anticancer agent or therapy selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, ipilimumab, chemotherapy, radiation therapy, and resection therapy.
28. The use according to claim 27, wherein the additional anticancer agent or therapy is nivolumab, pembrolizumab, atezolizumab, or ipilimumab.
29. A pharmaceutical composition comprising a compound according to any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.
30. The pharmaceutical composition according to claim 29, further comprising at least one additional agent which is an anticancer agent selected from rituxan, doxorubicin, gemcitabine, nivolumab, pembrolizumab, and ipilimumab.
31. The pharmaceutical composition according to claim 29, further comprising an additional agent which is an anticancer agent, wherein the additional anticancer agent is nivolumab, pembrolizumab, atezolizumab, or ipilimumab.
32. A compound according to any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof for use in therapy.
33. A compound according to any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof for use in inhibiting PD-1, PD-L1 and/or the PD-1/PD-L1 interaction.
34. A compound according to any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof, for use in treating cancer.
35. The compound for use according to claim 34, wherein the cancer is pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma,

neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft tissue sarcoma, non-small cell lung cancer, small-cell lung cancer, or colon cancer.

36. The compound for use according to claim 34, wherein the cancer is acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myeloid leukemia (CML), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma, Waldstrom's macroglobulinemia (WM), T-cell lymphoma, B-cell lymphoma, or diffuse large B-cell lymphoma (DLBCL).

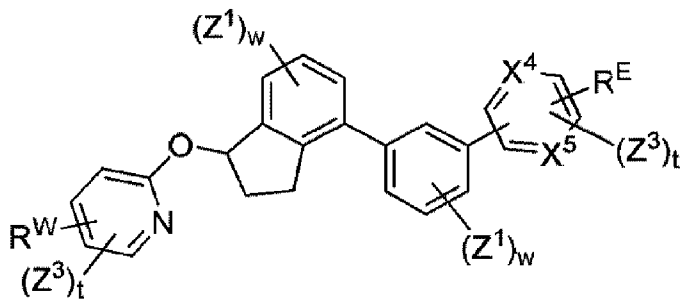
37. The compound for use according to any one of claims 32 to 36, for use in combination with at least one additional anticancer agent or therapy selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, ipilimumab, chemotherapy, radiation therapy, and resection therapy.

38. The compound for use according to claim 37, wherein the additional anticancer agent or therapy is nivolumab, pembrolizumab, atezolizumab, or ipilimumab.

39. A compound according to any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof, and at least one additional agent which is an anticancer agent selected from rituxan, doxorubicin, gemcitabine, nivolumab, pembrolizumab, and ipilimumab for use in treating cancer.

40. The compound for use according to claim 39, wherein the cancer is pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft tissue sarcoma, non-small cell lung cancer, small-cell lung cancer, or colon cancer.

41. The compound for use according to claim 39, wherein the cancer is acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myeloid leukemia (CML), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma, Waldstrom's macroglobulinemia (WM), T-cell lymphoma, B-cell lymphoma, or diffuse large B-cell lymphoma (DLBCL).



(VIII)