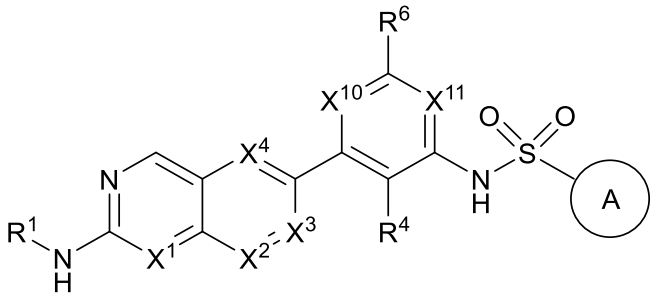
demonstrated to prevent amino acid deprivation (AAD)-induced expression of Vascular Endothelial Growth Factor (VEGF) which tumors use to enhance nutrient supply via increased vascularization. Thus, activation of the GCN2/ATF4 pathway promotes tumor growth and angiogenesis through AAD-mediated VEGF expression. Abrogation of ATF4 or GCN2 expression significantly inhibited tumor growth in vivo.

[0013] Therefore, selective inhibition of GCN2 can both increase the activity of the immune system and decrease vascularization in the tumor microenvironment. The GCN2-eIF2□-ATF4 pathway is critical for maintaining metabolic homeostasis in tumor cells under conditions of stress, and for maintaining an immunosuppressed immune cell microenvironment. The PERK-ATF4 pathway is also critical for maintaining homeostasis in tumors cells under conditions of stress. It has been reported that there is cross talk regulation of both the GCN2 and PERK signaling pathways, such that inhibition of GCN2 can activate PERK as a compensatory mechanism, and vice versa, that inhibition of PERK an activate GCN2 as a compensatory mechanism.

[0014] There is a need for inhibitors of GCN2 and/or PERK that block the pro-tumoral aspects of GCN2 and/or PERK, both in the tumor cell (tumor cell autonomous) and in the tumor immune cell microenvironment.

SUMMARY

[0014a] In an aspect of the present disclosure, there is provided a compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring;

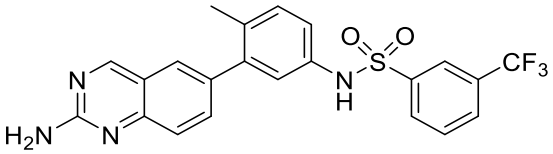
L^2 is selected from the group consisting of a direct bond and alkyl, wherein alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

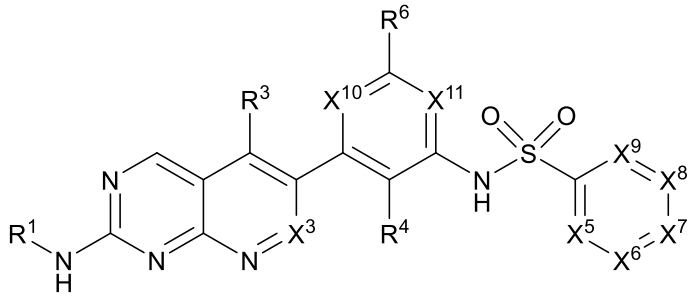
E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2; provided that the compound is not:



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[0014b] In another aspect of the present disclosure, there is provided a compound represented by Formula I-A:



Formula I-A

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^5 is selected from the group consisting of CR^8 and N;

X^6 is selected from the group consisting of CR^9 and N;

X^7 is selected from the group consisting of CR^{10} and N;

X^8 is selected from the group consisting of CR^{11} and N;

X^9 is selected from the group consisting of CR^8 and N,

provided that not more than three of X^5, X^6, X^7, X^8, and X^9 is N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

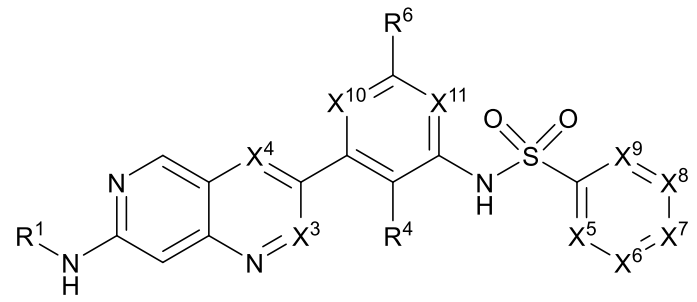
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014c] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-B:



Formula I-B

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^4 is selected from the group consisting of CR^3 and N;

X^5 is selected from the group consisting of CR^8 and N;

X^6 is selected from the group consisting of CR^9 and N;

X^7 is selected from the group consisting of CR^{10} and N;

X^8 is selected from the group consisting of CR^{11} and N;

X^9 is selected from the group consisting of CR^8 and N,

provided that not more than three of X^5, X^6, X^7, X^8, and X^9 is N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,

alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

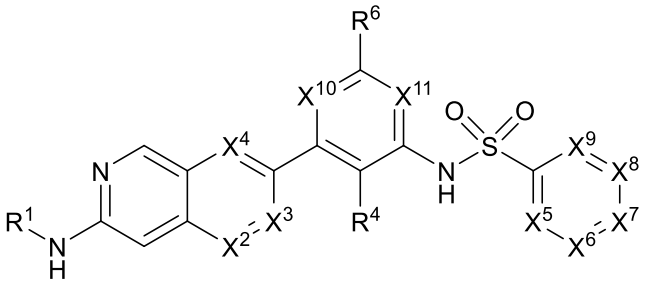
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014d] In another aspect of the present disclosure, there is provided a compound represented by Formula I-C:



Formula I-C

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^5 is selected from the group consisting of CR^8 and N;

X^6 is selected from the group consisting of CR^9 and N;

X^7 is selected from the group consisting of CR^{10} and N;

X^8 is selected from the group consisting of CR^{11} and N;

X^9 is selected from the group consisting of CR^8 and N,

provided that not more than three of X^5, X^6, X^7, X^8, and X^9 is N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

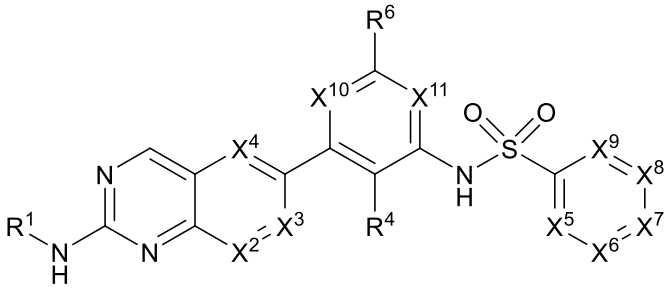
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014e] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-D:



Formula I-D

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^5 is selected from the group consisting of CR^8 and N;

X^6 is selected from the group consisting of CR^9 and N;

X^7 is selected from the group consisting of CR^{10} and N;

X^8 is selected from the group consisting of CR^{11} and N;

X^9 is selected from the group consisting of CR^8 and N,

provided that not more than three of X^5, X^6, X^7, X^8, and X^9 is N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

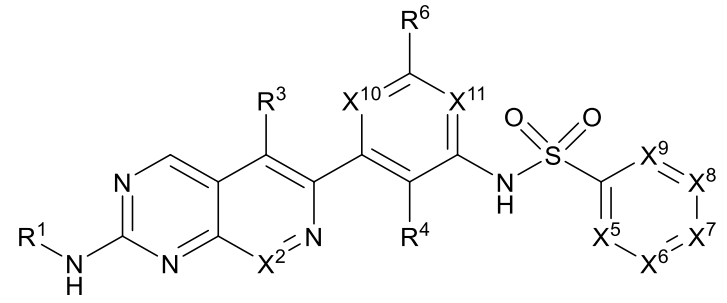
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014f] In another aspect of the present disclosure, there is provided a compound represented by Formula I-E:



Formula I-E

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^5 is selected from the group consisting of CR^8 and N;

X^6 is selected from the group consisting of CR^9 and N;

X^7 is selected from the group consisting of CR^{10} and N;

X^8 is selected from the group consisting of CR^{11} and N;

X^9 is selected from the group consisting of CR^8 and N,

provided that not more than three of X^5, X^6, X^7, X^8, and X^9 is N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

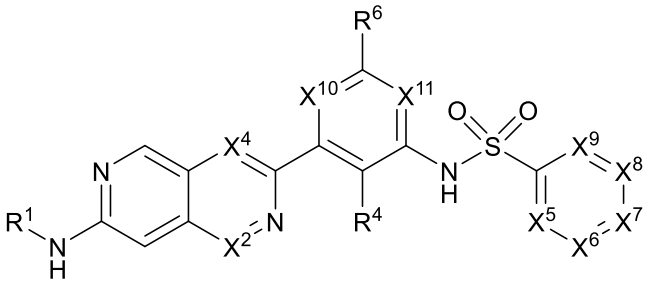
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014g] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-F:



Formula I-F

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^4 is selected from the group consisting of CR^3 and N;

X^5 is selected from the group consisting of CR^8 and N;

X^6 is selected from the group consisting of CR^9 and N;

X^7 is selected from the group consisting of CR^{10} and N;

X^8 is selected from the group consisting of CR^{11} and N;

X^9 is selected from the group consisting of CR^8 and N,

provided that not more than three of X^5, X^6, X^7, X^8, and X^9 is N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

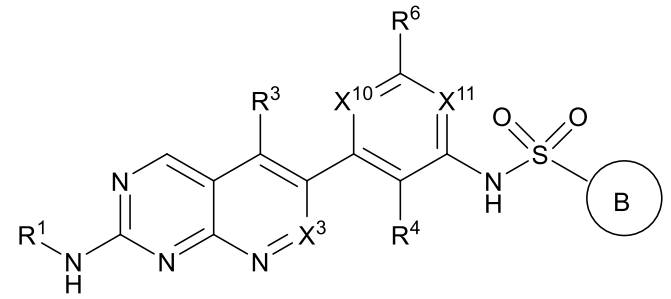
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014h] In another aspect of the present disclosure, there is provided a compound represented by Formula I-G:



Formula I-G

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

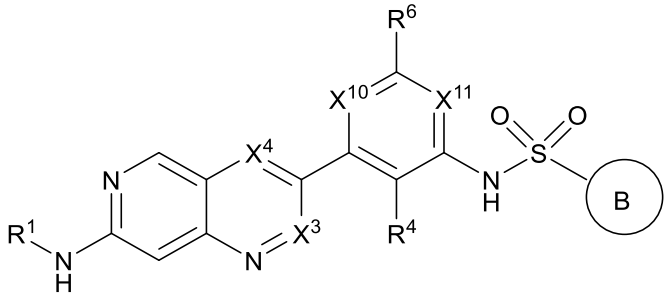
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

and each p is independently 0, 1 or 2.

[0014i] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-H:



Formula I-H

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

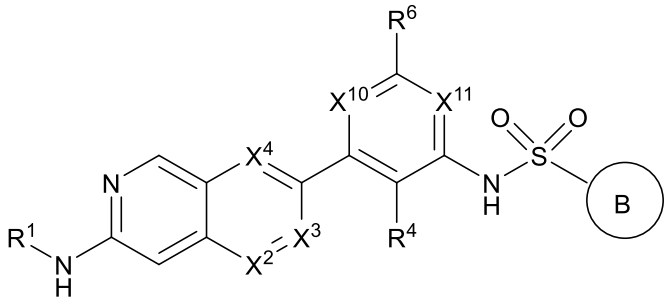
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014j] In another aspect of the present disclosure, there is provided a compound represented by Formula I-J:



Formula I-J

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

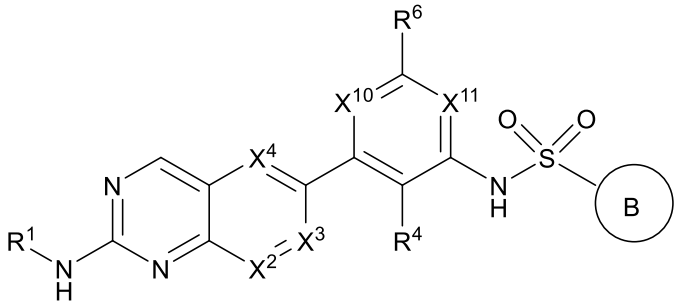
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014k] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-K:



Formula I-K

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

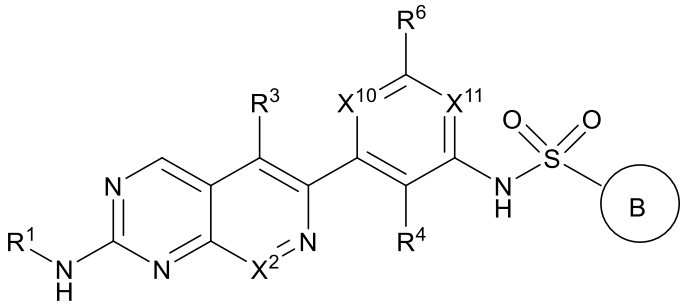
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014l] In another aspect of the present disclosure, there is provided a compound represented by Formula I-L:



Formula I-L

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

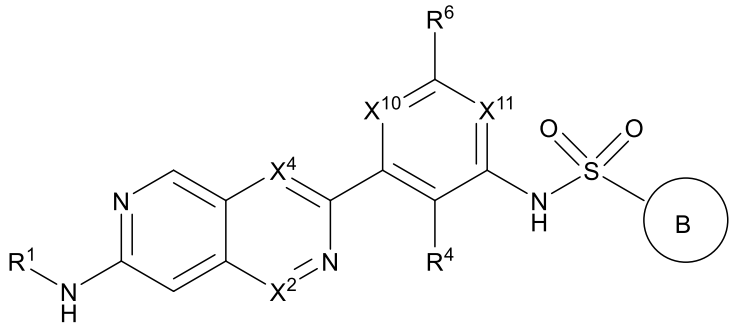
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014m] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-M:



Formula I-M

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

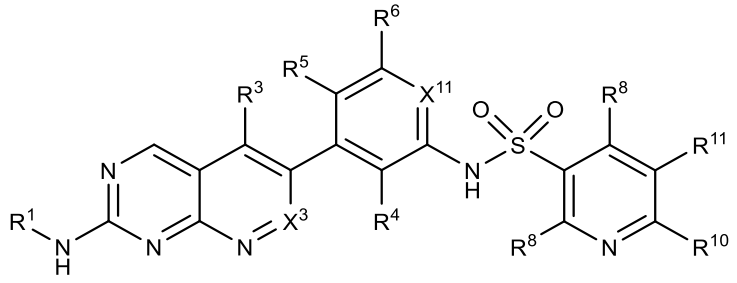
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014n] In another aspect of the present disclosure, there is provided a compound represented by Formula I-N:



Formula I-N

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F; R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl; R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

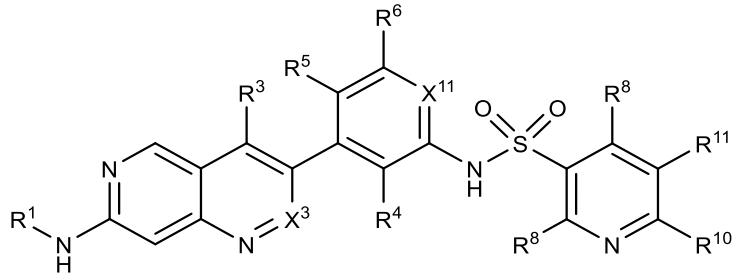
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014o] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-O:



Formula I-O

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl; R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl; R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

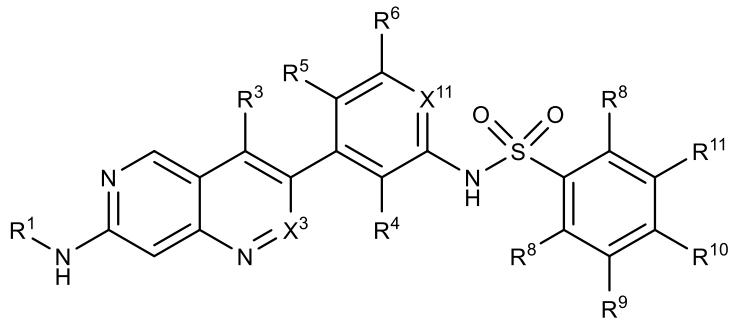
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014p] In another aspect of the present disclosure, there is provided a compound represented by Formula I-P:



Formula I-P

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^9, R^{10}, and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

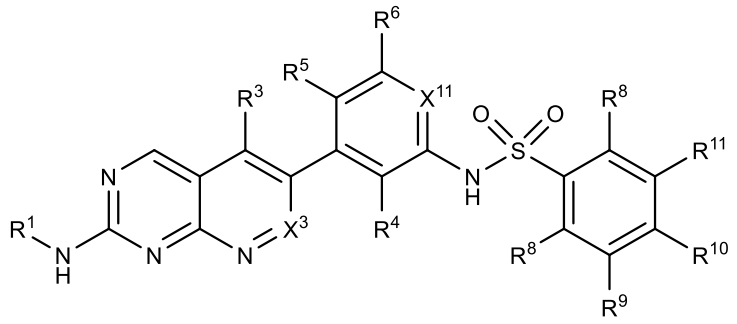
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014q] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-Q:



Formula I-Q

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^9, R^{10}, and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

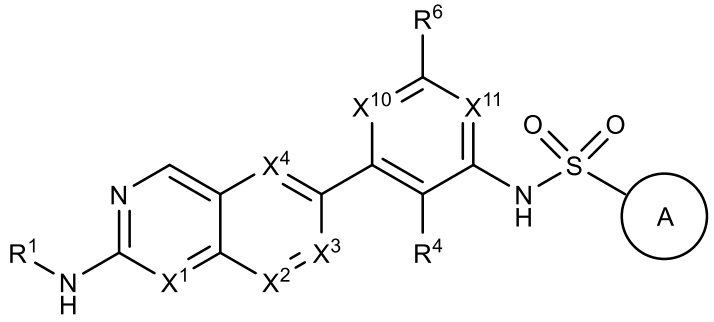
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014r] In another aspect of the present disclosure, there is provided a compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring;

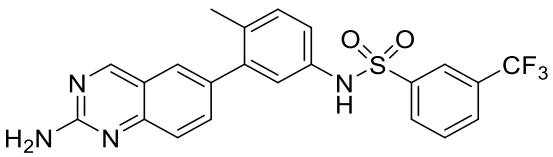
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

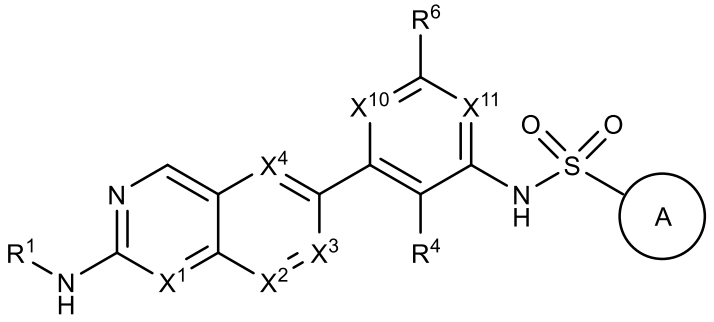
E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2; provided that the compound is not:



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[0014s] In a further aspect of the present disclosure, there is provided a compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^2 is selected from the group consisting of N, CH, C-O-L^2-E^2, and C-L^2-E^2;

X^3 is C-N(R^2)-L^2-E^2;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,

alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

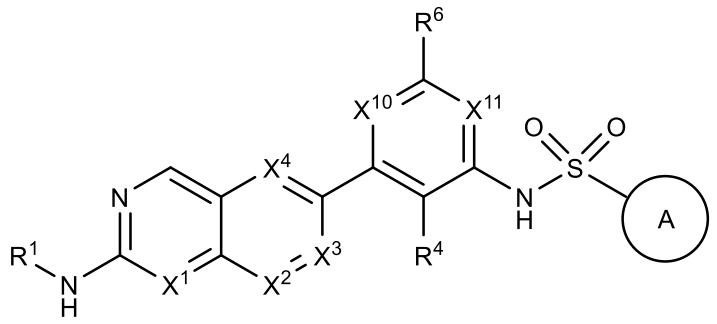
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014t] In another aspect of the present disclosure, there is provided a compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is CH;

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

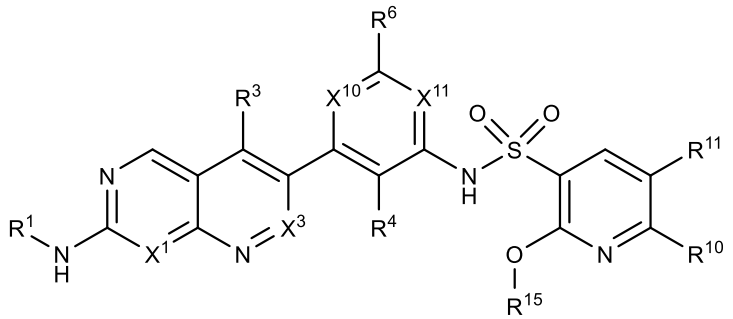
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

[0014u] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-R, Formula I-S, Formula I-T, Formula I-U, Formula I-V, Formula I-W, Formula I-X, or Formula I-Y:



Formula I-R

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,

alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

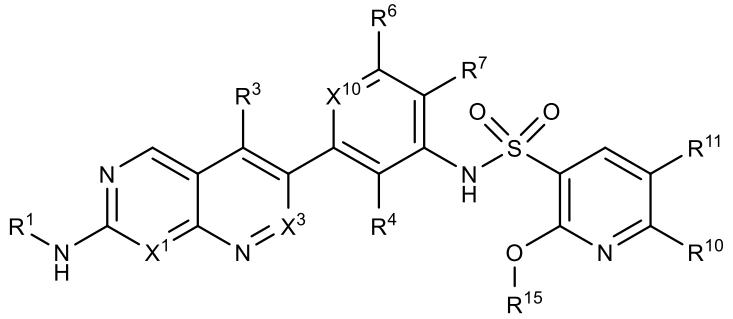
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;



Formula I-S

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

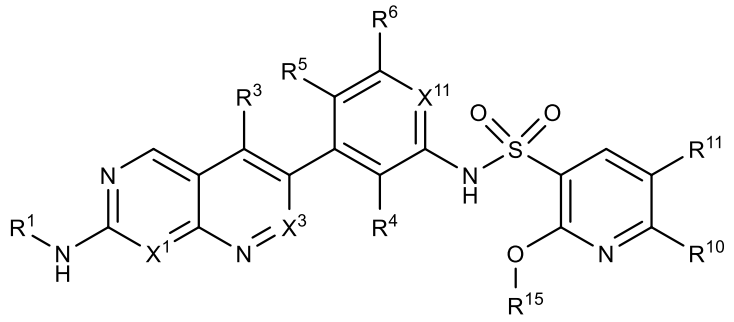
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;



Formula I-T

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

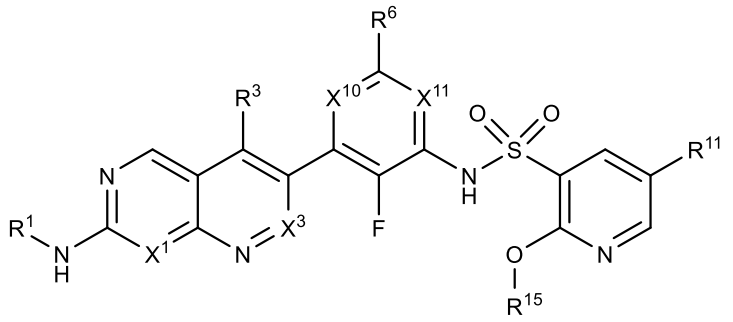
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;



Formula I-U

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

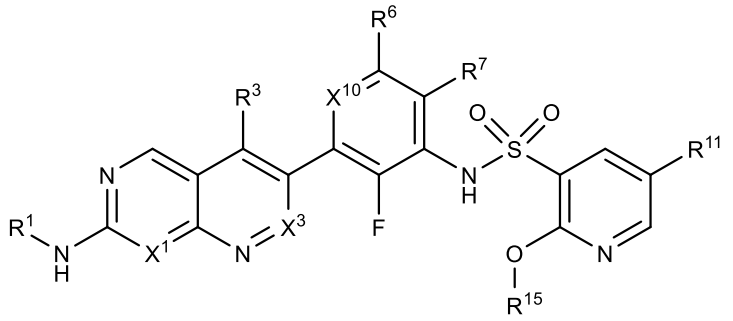
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;



Formula I-V

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

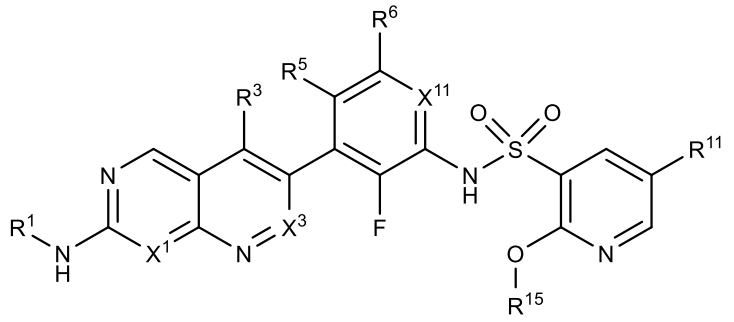
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;



Formula I-W

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

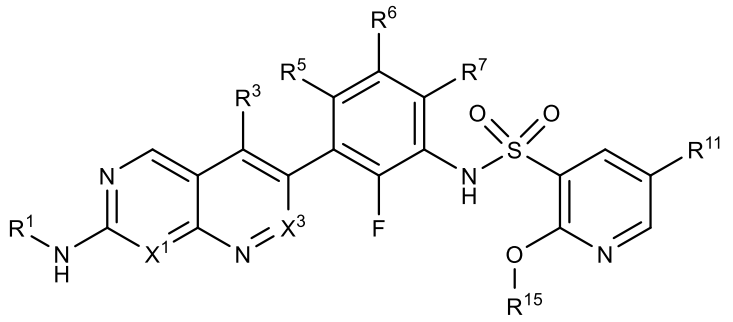
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;



Formula I-X

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

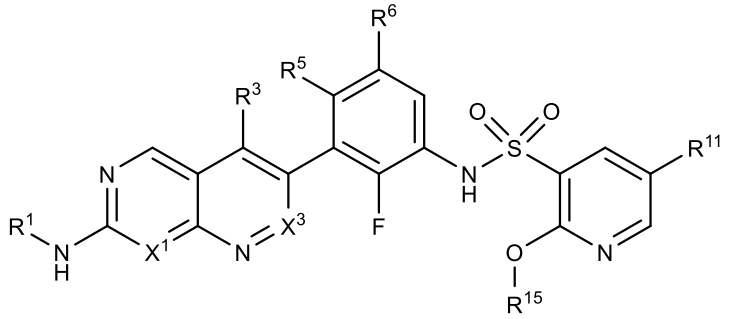
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2; or



Formula I-Y

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

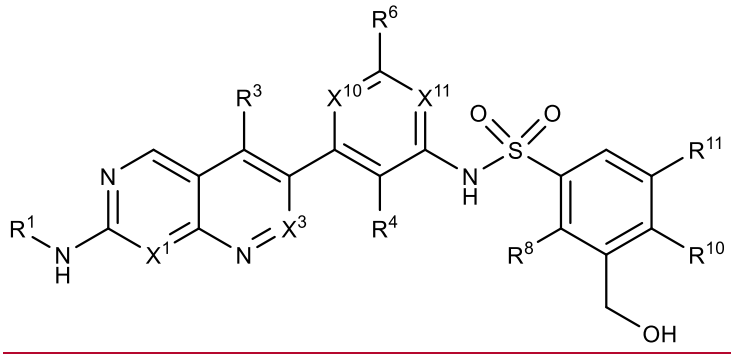
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2.

[0014v] In another aspect of the present disclosure, there is provided a compound represented by Formula I-Z, Formula I-AA, Formula I-AB, Formula I-AC, Formula I-AD, Formula I-AE, Formula I-AF, or Formula I-AG:



Formula I-Z

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

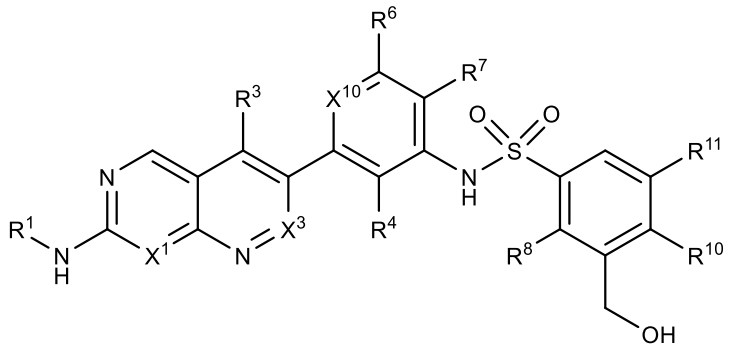
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;



Formula I-AA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

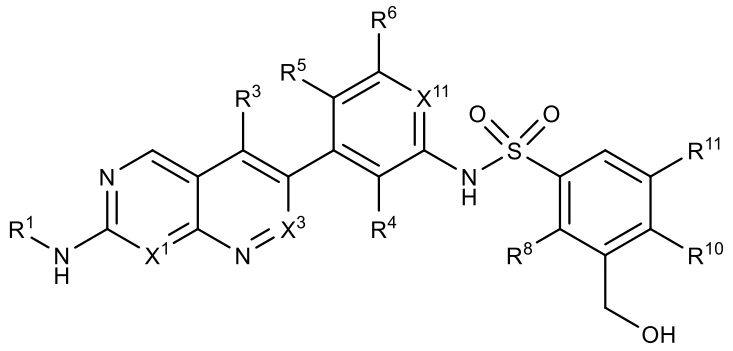
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;



Formula I-AB

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

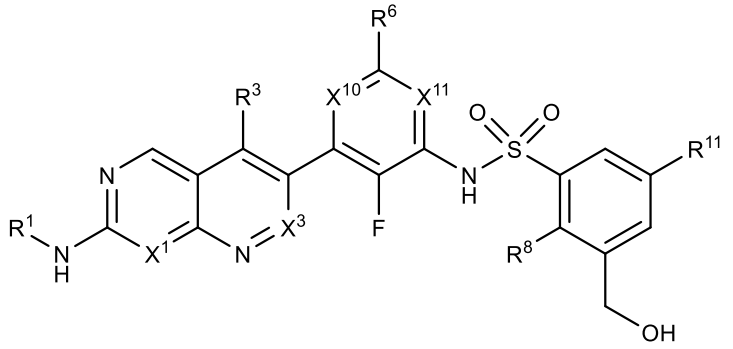
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;



Formula I-AC

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

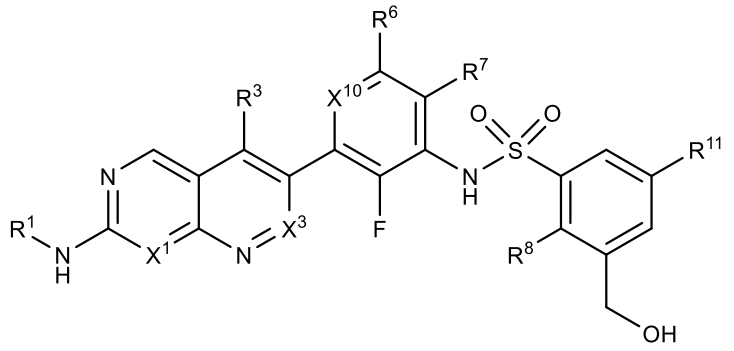
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;



Formula I-AD

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano,

alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

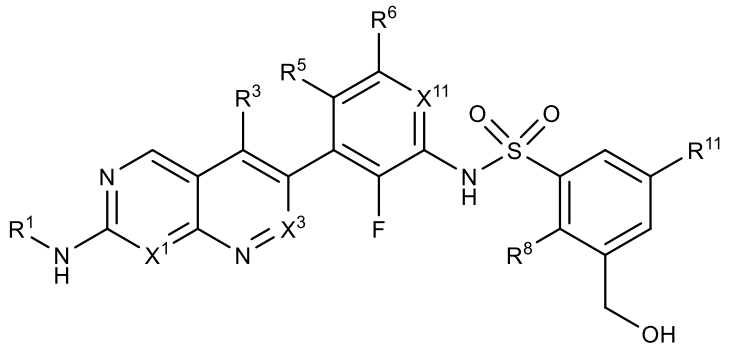
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;



Formula I-AE

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

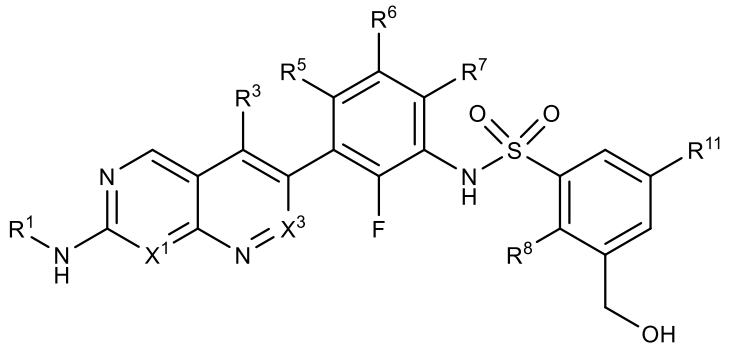
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;



Formula I-AF

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

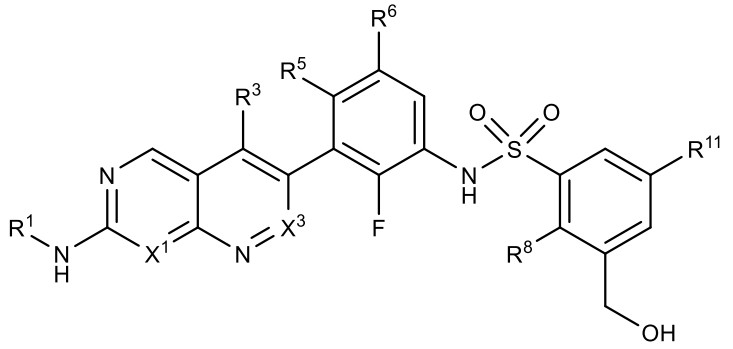
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2; or



Formula I-AG

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

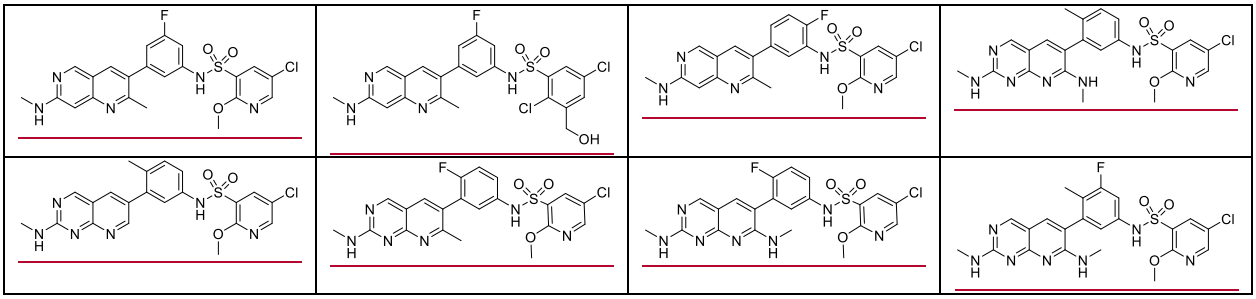
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

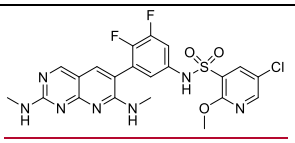
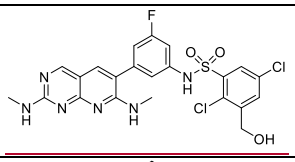
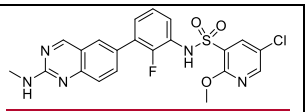
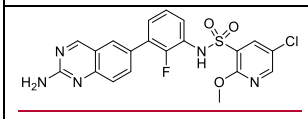
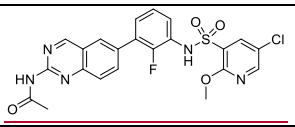
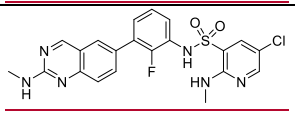
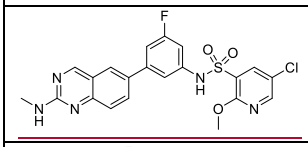
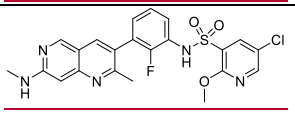
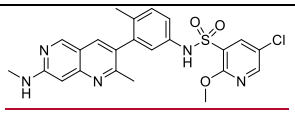
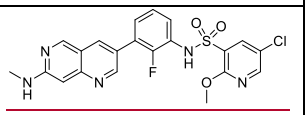
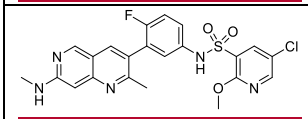
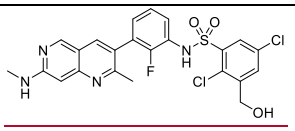
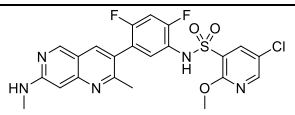
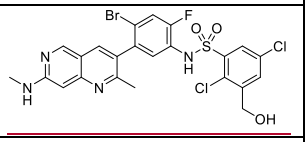
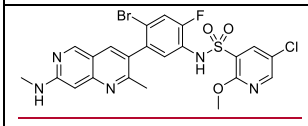
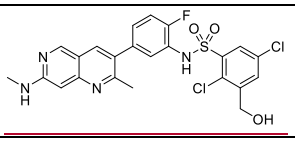
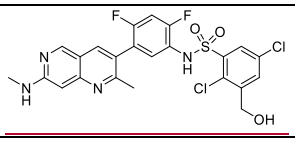
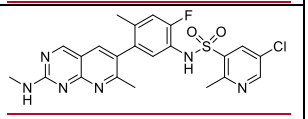
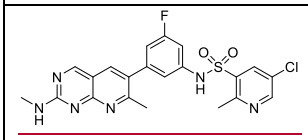
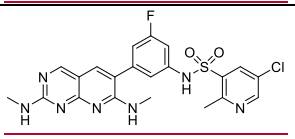
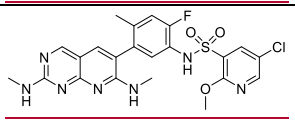
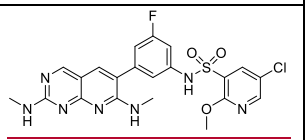
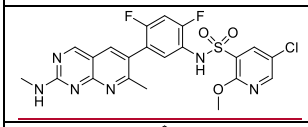
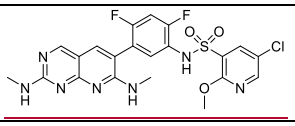
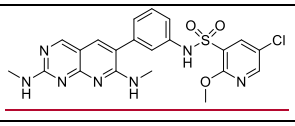
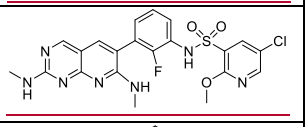
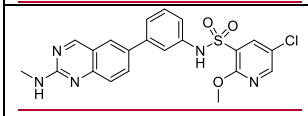
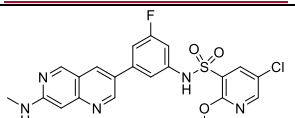
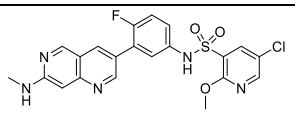
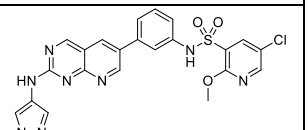
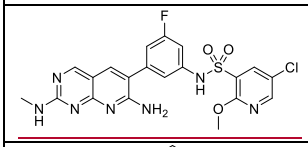
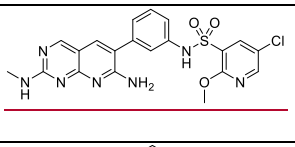
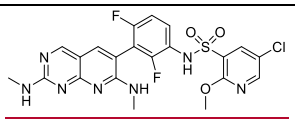
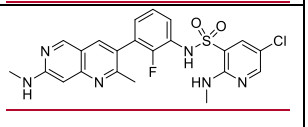
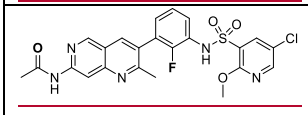
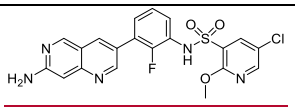
wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

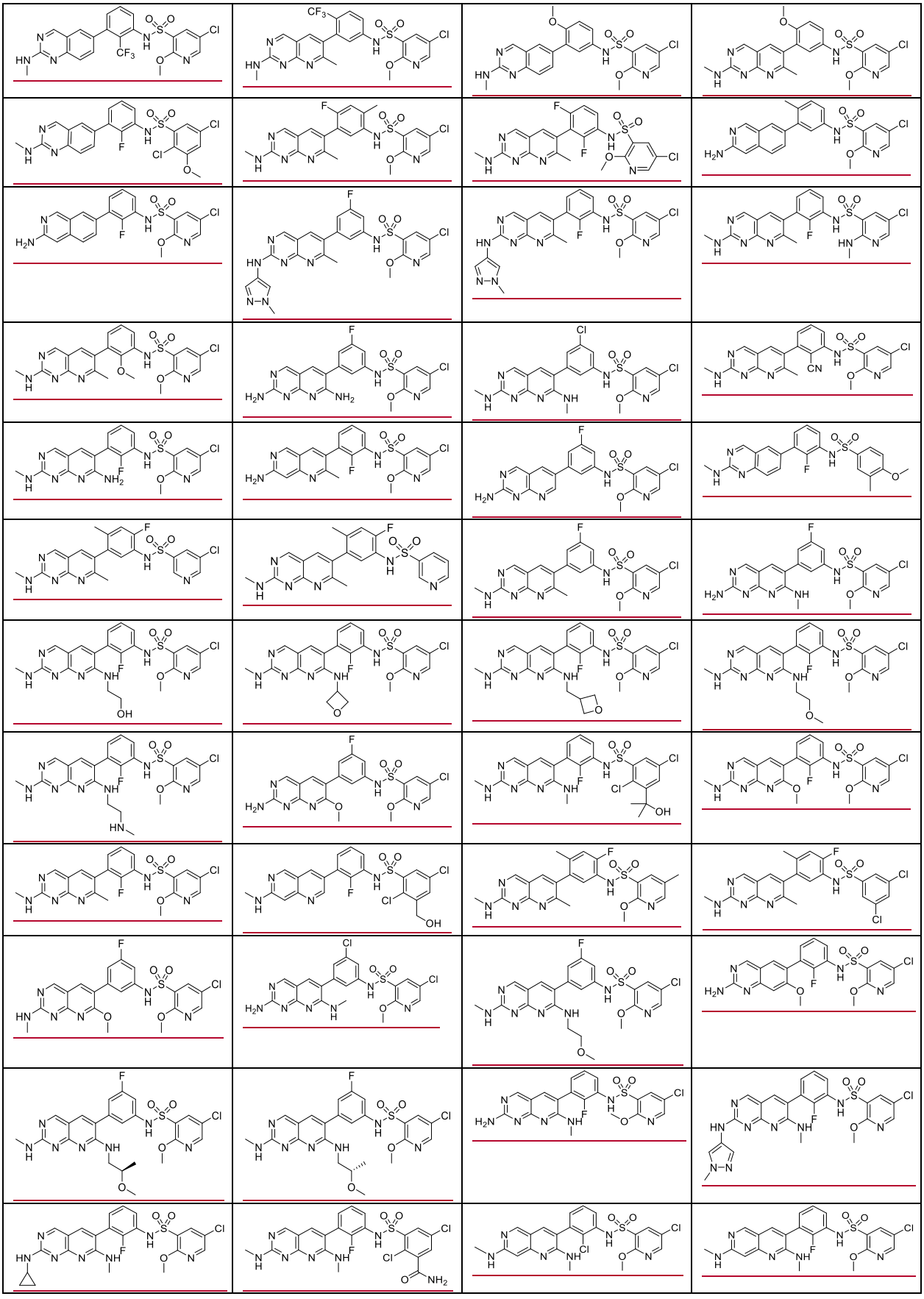
each p is independently 0, 1 or 2.

[0014w] In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of:

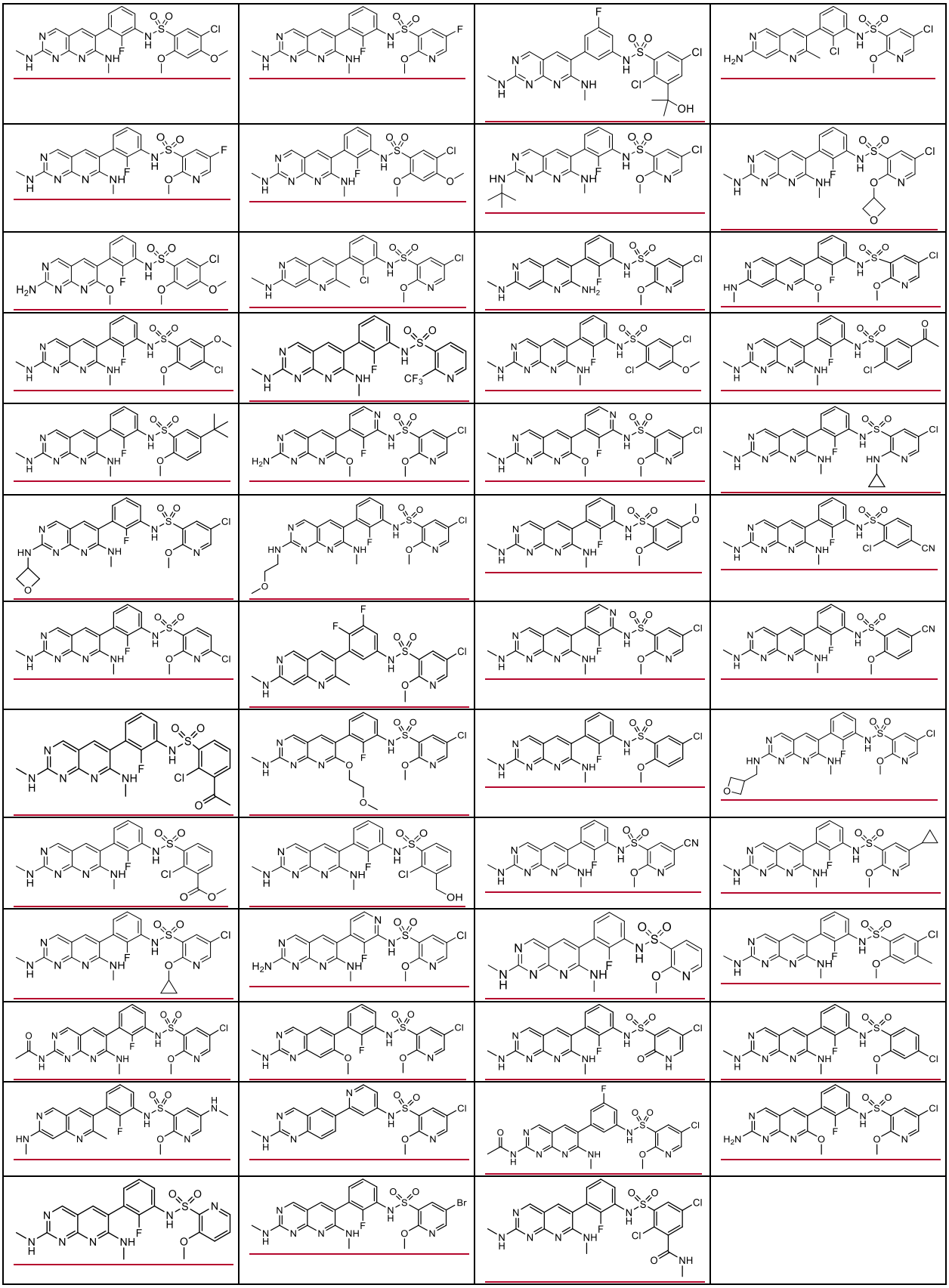


4bm



4bn



and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

4bo

[0014x] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0014y] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a disease caused by a dysregulation of an integrated stress response and/or an unfolded protein response in a patient in need thereof.

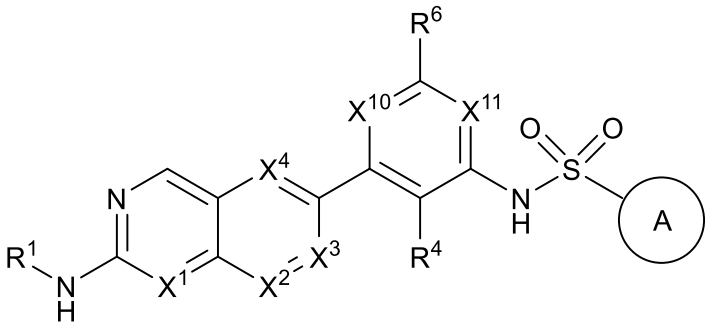
[0014z] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a cancer in a patient in need thereof, optionally wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocyctic lymphoma, waldenstrom macroglobulinemia, light chain amyloidosis, and malignant lymphoma.

[0014aa] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating amyloidosis in a patient in need thereof.

[0014ab] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, for use in therapy.

[0015] Described herein are compounds which display inhibitory activity of the GCN2 (general control nonderepressible 2) kinase and/or PERK (PKR-like ER kinase) kinase and methods of use thereof for the treatment of disorders, including GCN2 or PERK associated diseases.

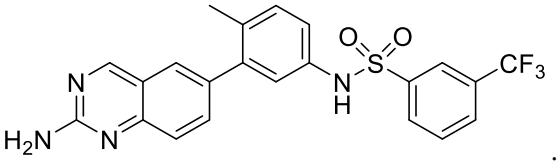
[0016] In one ~~embodiment~~example, described herein is a compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N; X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2, provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2,and C-N(R^2)-L^2-E^2; provided that X^2 is selected from the group consisting of



[0017] In another ~~embodiment~~example, described herein is a pharmaceutical composition comprising a compound described herein (e.g., a compound of Formula I described herein) and a pharmaceutically acceptable carrier or excipient.

[0018] In another example~~embodiment~~, described herein is a method of treating a disease caused by a dysregulation of an integrated stress response in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0019] In another example~~embodiment~~, described herein is a method of treating a disease caused by a dysregulation of an integrated stress response and/or an unfolded protein response in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0020] In another example~~embodiment~~, described herein is a method of modulating the activity of GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0021] In another example~~embodiment~~, described herein is a method of activating GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0022] In another example~~embodiment~~, described herein is a method of modulating the activity of PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0023] In another example~~embodiment~~, described herein is a method of activating PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0024] In another example~~embodiment~~, described herein is a method of inhibiting GCN2 kinase and inhibiting PERK kinase in a patient in need thereof, comprising administering to the patient a

therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0025] In another example~~embodiment~~, described herein is a method of modulating the activity of GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0026] In another example~~embodiment~~, described herein is a method of inhibiting the activity of PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0027] In another example~~embodiment~~, described herein is a method of treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or of a pharmaceutical composition described herein.

[0028] In another example~~embodiment~~, described herein is a method of treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of one or more therapeutic agents.

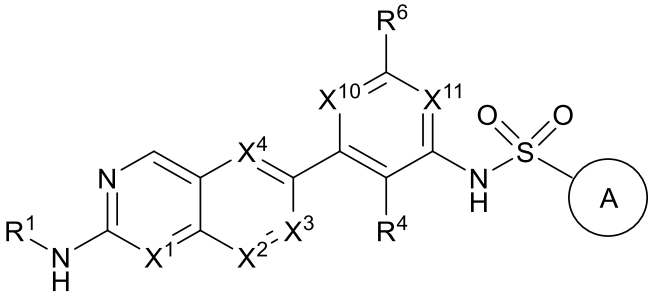
[0029] In another example~~embodiment~~, described herein is a method of treating a cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein (e.g., a compound of Formula I described herein) or a pharmaceutically acceptable salt thereof, or pharmaceutical composition described herein.

[0030] In another example~~embodiment~~, described herein is a method of treating a disorder selected from the group consisting of melanoma, fibrosarcoma, thyroid cancer, ovarian cancer, colon cancer, pancreatic cancer, lung cancer, bladder cancer, gastrointestinal stromal tumors, solid tumors, blood-borne cancers, acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL) and other cancers caused by activation of the GCN2 signaling pathway in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound described herein (e.g., a compound of Formula I described herein) or a pharmaceutically acceptable salt thereof.

CLAIMS

What is claimed is:

1. A compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring;

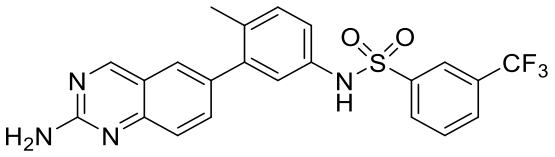
L^2 is selected from the group consisting of a direct bond and alkyl, wherein alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

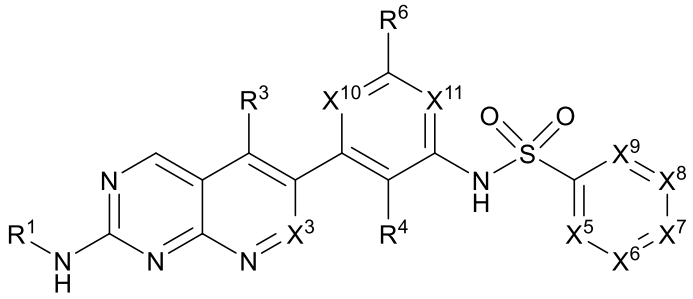
E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2; provided that the compound is not:



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2. A compound represented by Formula I-A:



Formula I-A

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^5 is selected from the group consisting of CR^8 and N;

X^6 is selected from the group consisting of CR^9 and N;

X^7 is selected from the group consisting of CR^{10} and N;

X^8 is selected from the group consisting of CR^{11} and N;

X^9 is selected from the group consisting of CR^8 and N,

provided that not more than three of X^5, X^6, X^7, X^8, and X^9 is N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

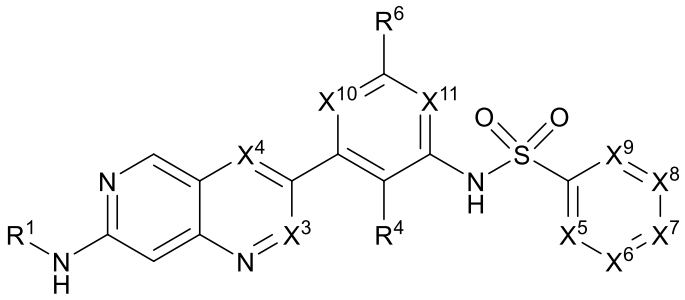
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

3. A compound represented by Formula I-B:



Formula I-B

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^4 is selected from the group consisting of CR^3 and N;

X^5 is selected from the group consisting of CR^8 and N;

X^6 is selected from the group consisting of CR^9 and N;

X^7 is selected from the group consisting of CR^{10} and N;

X^8 is selected from the group consisting of CR^{11} and N;

X^9 is selected from the group consisting of CR^8 and N,

provided that not more than three of X^5, X^6, X^7, X^8, and X^9 is N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

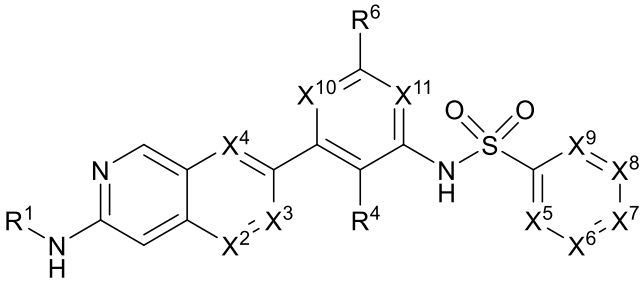
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

4. A compound represented by Formula I-C:



Formula I-C

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^5 is selected from the group consisting of CR^8 and N;

X^6 is selected from the group consisting of CR^9 and N;

X^7 is selected from the group consisting of CR^{10} and N;

X^8 is selected from the group consisting of CR^{11} and N;

X^9 is selected from the group consisting of CR^8 and N,

provided that not more than three of X^5, X^6, X^7, X^8, and X^9 is N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

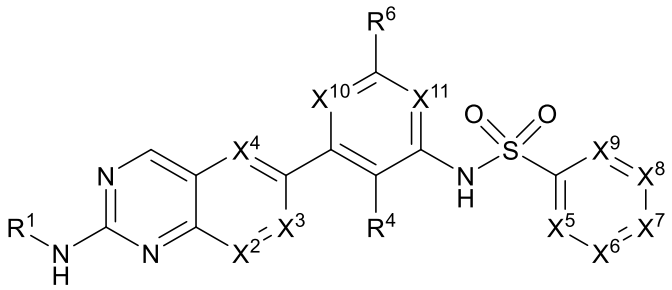
wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl,

cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

5. A compound represented by Formula I-D:



Formula I-D

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^5 is selected from the group consisting of CR^8 and N;

X^6 is selected from the group consisting of CR^9 and N;

X^7 is selected from the group consisting of CR^{10} and N;

X^8 is selected from the group consisting of CR^{11} and N;

X^9 is selected from the group consisting of CR^8 and N,

provided that not more than three of X^5, X^6, X^7, X^8, and X^9 is N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,

alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

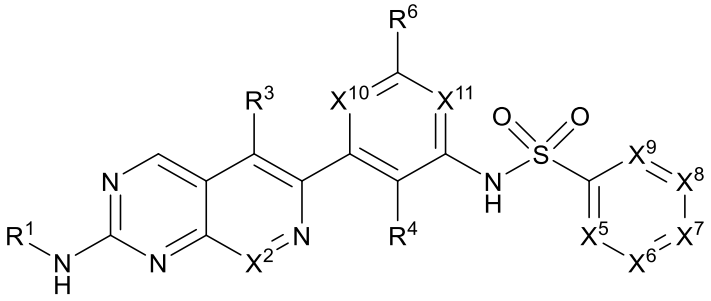
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

6. A compound represented by Formula I-E:



Formula I-E

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^5 is selected from the group consisting of CR^8 and N;

X^6 is selected from the group consisting of CR^9 and N;

X^7 is selected from the group consisting of CR^{10} and N;

X^8 is selected from the group consisting of CR^{11} and N;

X^9 is selected from the group consisting of CR^8 and N,

provided that not more than three of X^5, X^6, X^7, X^8, and X^9 is N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

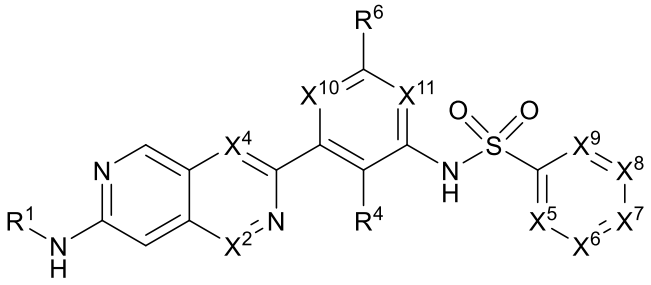
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

7. A compound represented by Formula I-F:



Formula I-F

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^4 is selected from the group consisting of CR^3 and N;

X^5 is selected from the group consisting of CR^8 and N;

X^6 is selected from the group consisting of CR^9 and N;

X^7 is selected from the group consisting of CR^{10} and N;

X^8 is selected from the group consisting of CR^{11} and N;

X^9 is selected from the group consisting of CR^8 and N,

provided that not more than three of X^5, X^6, X^7, X^8, and X^9 is N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxy, and CN;

R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

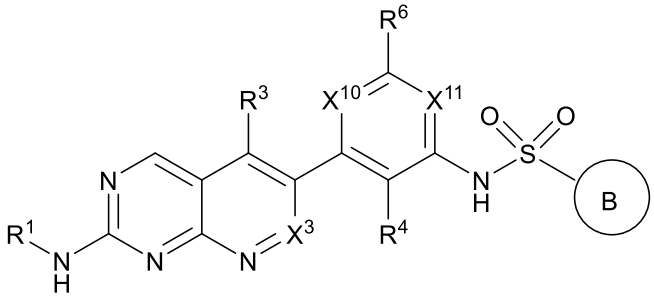
wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl,

cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

8. A compound represented by Formula I-G:



Formula I-G

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl,

aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

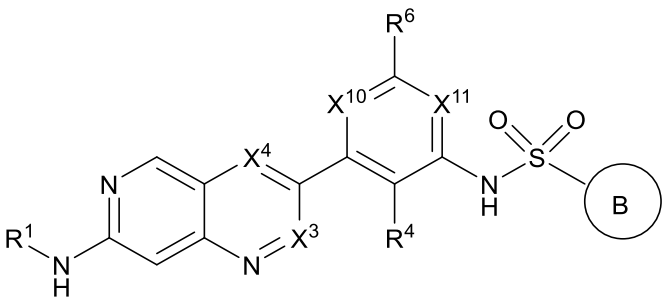
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

and each p is independently 0, 1 or 2.

9. A compound represented by Formula I-H:



Formula I-H

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

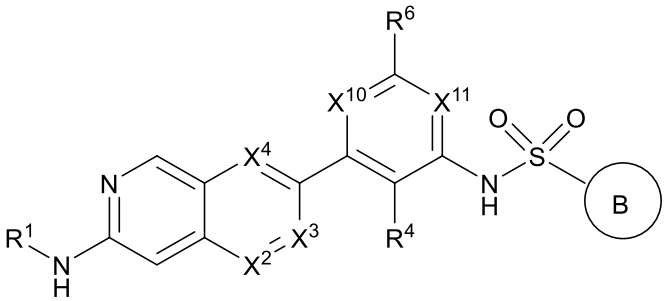
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

10. A compound represented by Formula I-J:



Formula I-J

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

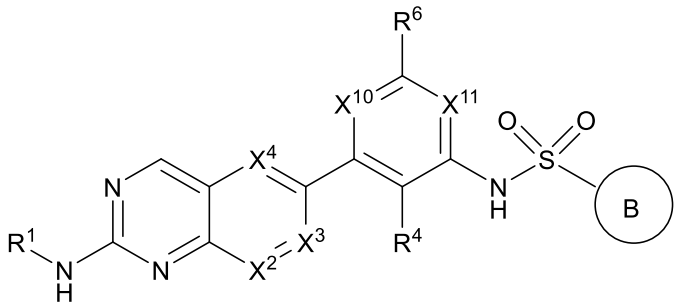
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

11. A compound represented by Formula I-K:



Formula I-K

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

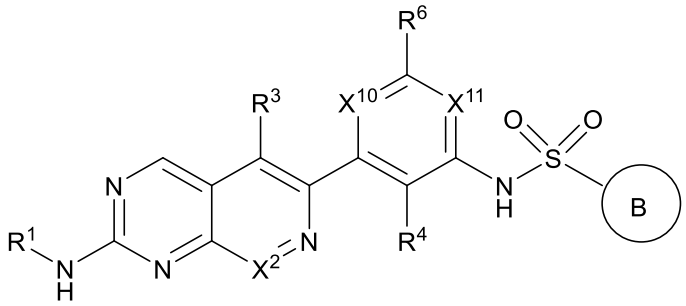
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

12. A compound represented by Formula I-L:



Formula I-L

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

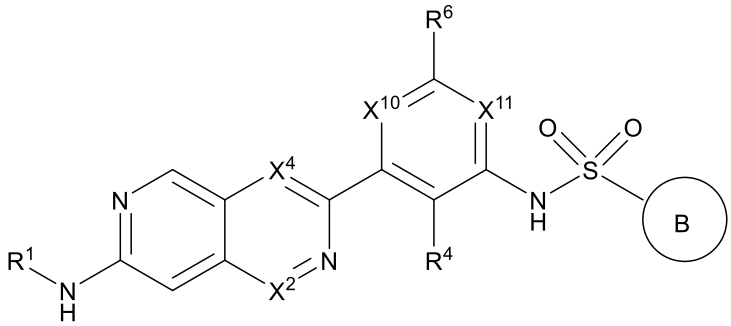
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

13. A compound represented by Formula I-M:



Formula I-M

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{12} is individually and independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, haloalkyl, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

B is selected from the group consisting of a five-membered heteroaryl, a six-membered heteroaryl, and a pyridone, wherein the five- or six-membered heteroaryl ring, or the pyridone, is optionally substituted by R^{12} at each substitutable position;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

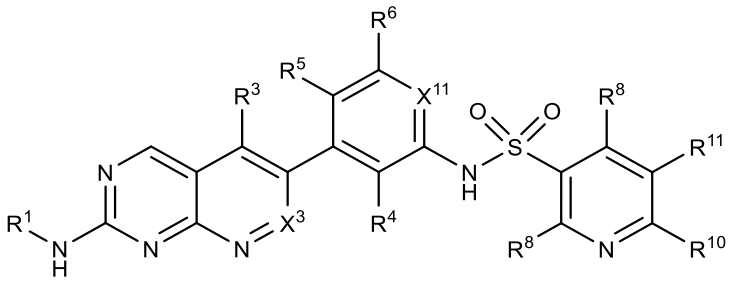
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

14. A compound represented by Formula I-N:



Formula I-N

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F; R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl; R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

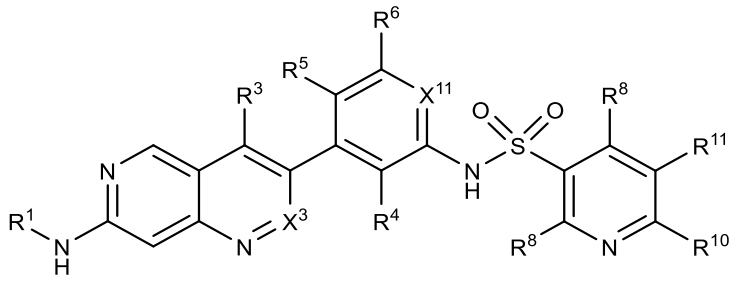
E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

~~15. The compound of claim 14, wherein X^{11} is CR^7.~~

~~16. The compound of claim 14, wherein X^{11} is N.~~

~~17~~15. A compound represented by Formula I-O:



Formula I-O

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,

alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl; R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl; R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

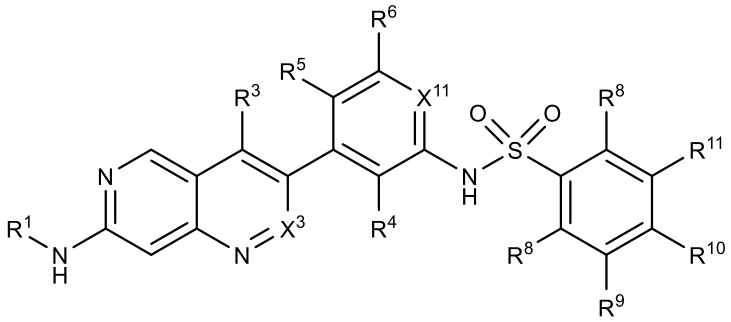
E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

~~18. The compound of claim 17, wherein X^{11} is CR^7.~~

~~19. The compound of claim 17, wherein X^{11} is N.~~

~~20~~16. A compound represented by Formula I-P:



Formula I-P

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^9, R^{10}, and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

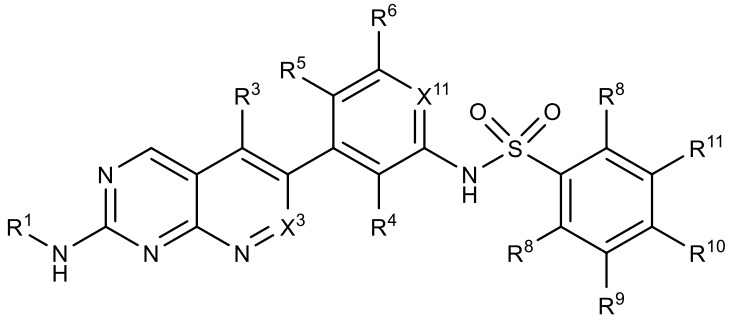
E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

~~21. The compound of claim 20, wherein X^{11} is CR^7.~~

~~22. The compound of claim 20, wherein X^{11} is N.~~

~~23~~17. A compound represented by Formula I-Q:



Formula I-Q

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^9, R^{10}, and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

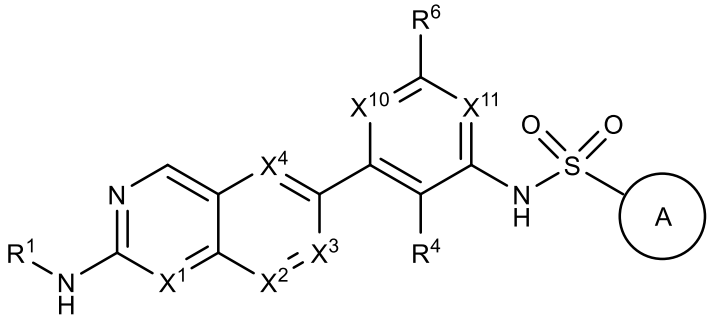
E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

~~24. The compound of claim 23, wherein X^{11} is CR^7.~~

~~25. The compound of claim 23, wherein X^{11} is N.~~

~~26~~18. A compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring;

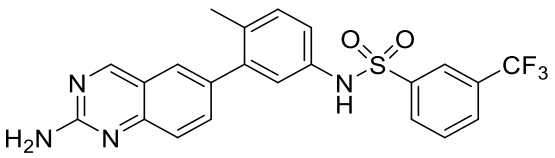
L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

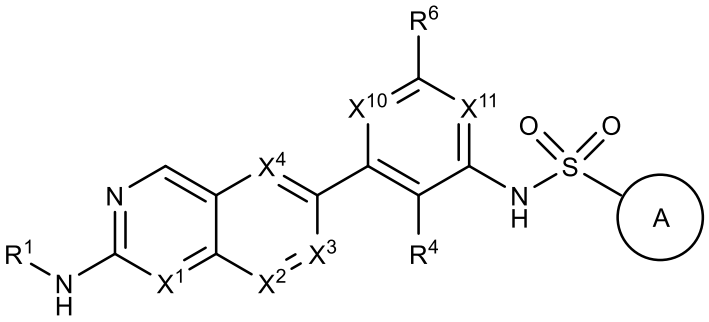
E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2; provided that the compound is not:



.

~~27~~19. A compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^2 is selected from the group consisting of N, CH, C-O-L^2-E^2, and C-L^2-E^2;

X^3 is C-N(R^2)-L^2-E^2;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

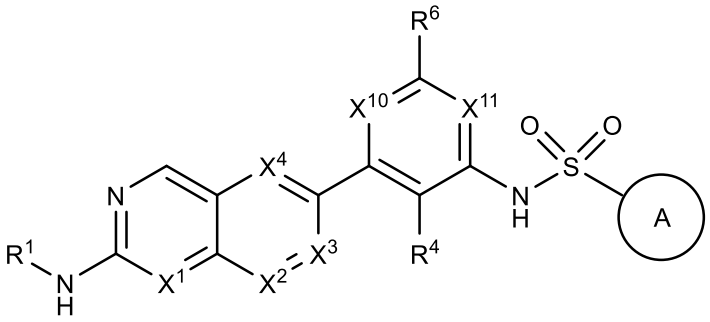
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

~~28~~20. A compound represented by Formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is CH;

X^2 and X^3 are each independently selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2,

provided that X^2 is selected from the group consisting of CH and N, and X^3 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2;

provided that X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2 and X^3 is selected from the group consisting of CH and N;

X^4 is selected from the group consisting of CR^3 and N;

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of H, alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 and R^7 are each independently selected from the group consisting of halogen, H, and alkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

A is selected from the group consisting of a substituted 5-membered heteroaryl, a substituted 6-membered heteroaryl, a pyridone, and a substituted aryl ring;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

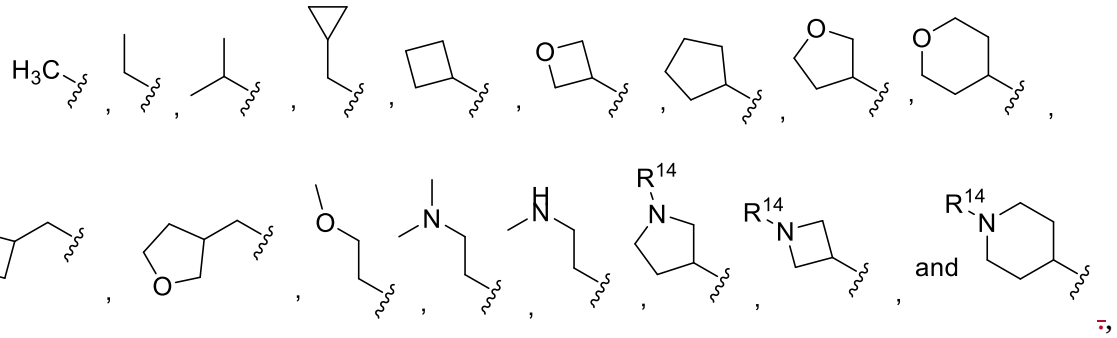
wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen; and

each p is independently 0, 1 or 2.

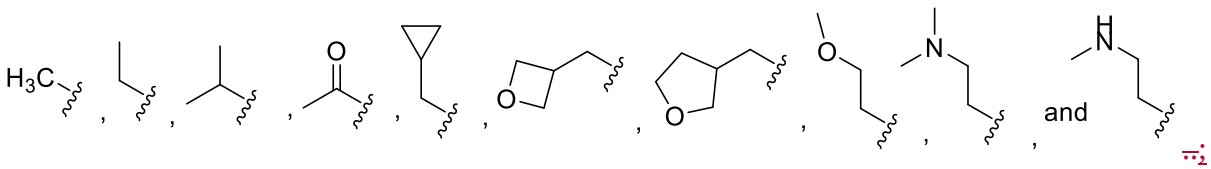
~~29~~21. The compound of any one of claims 1-20~~28~~, wherein

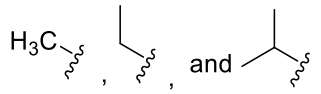
a) R^1 is selected from the group consisting of



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl;~~.~~

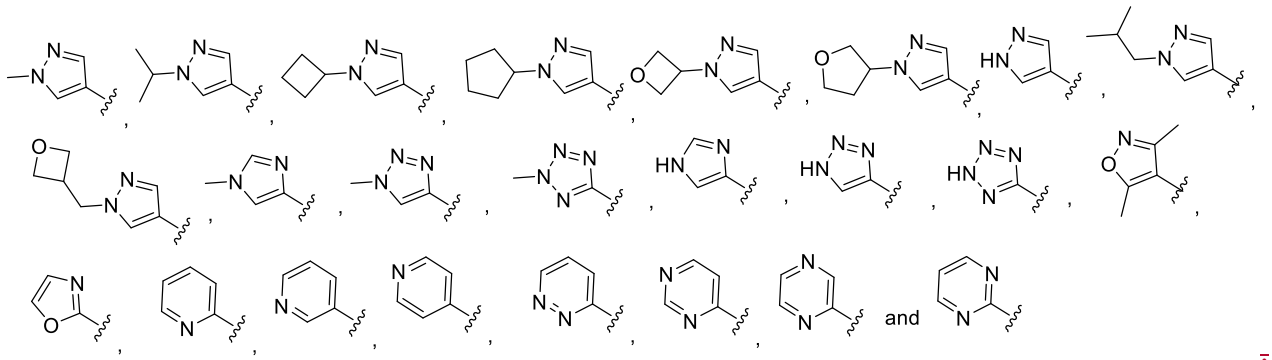
~~30. The compound of any of claims 1-28, wherein~~ b) R^1 is selected from the group consisting of



~~31. The compound of any one of claims 1-28, wherein~~ c) R^1 is selected from the group consisting of H, 

~~.~~;

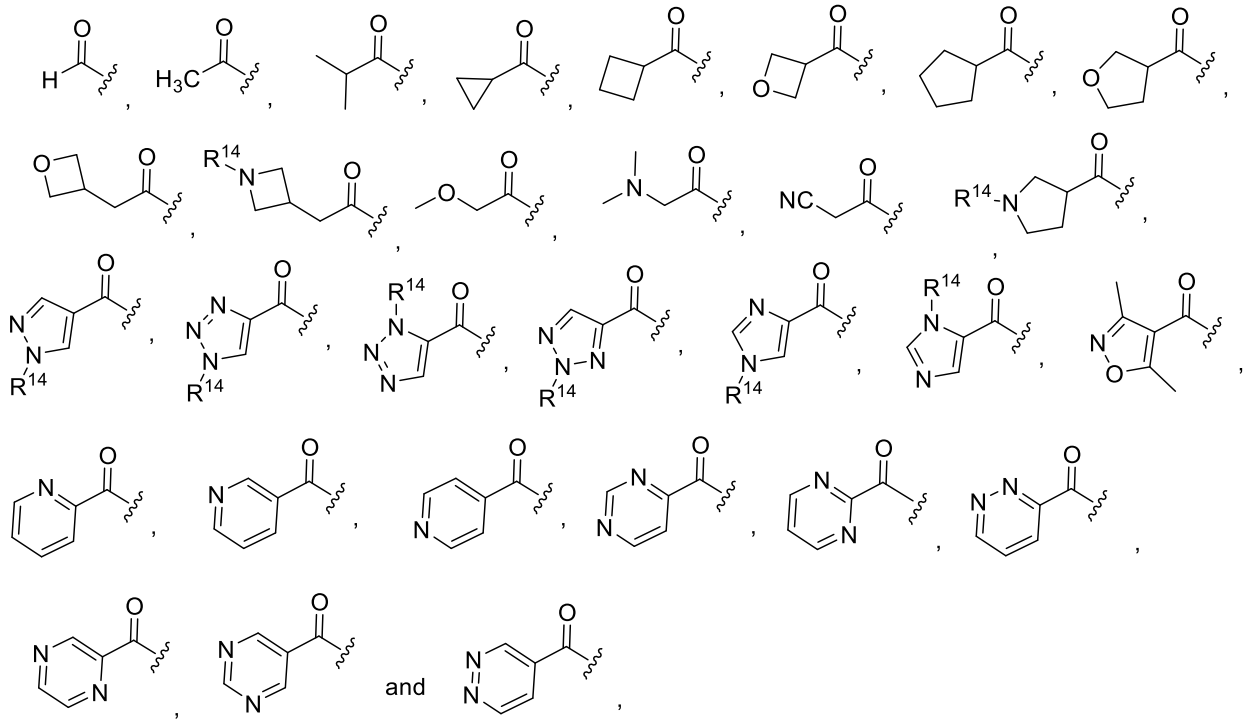
~~32. The compound of any one of claims 1-28, wherein~~ d) R^1 is selected from the group consisting of



~~.~~

; or

~~33. The compound of any one of claims 1-28, wherein~~ e) R^1 is selected from the group consisting of



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

~~34~~22. The compound of ~~any one of~~ claim~~s~~ 1~~, 26, or 27~~, wherein

a) X^1 is N; or.

~~35. The compound of any one of claims 1, 26, or 27, wherein~~b) X^1 is CH; and/or.

~~36. The compound of any one of claims 1-5, 8-11, or 14-20, wherein:~~

c) X^2 is selected from the group consisting of N and CH; and

X^3 is C-N(R^2)-L^2-E^2.

~~37. The compound of any one of claims 1-5, 8-11, 14-28, or 36, wherein X^3 is C-N(R^2)-L^2-E^2.~~

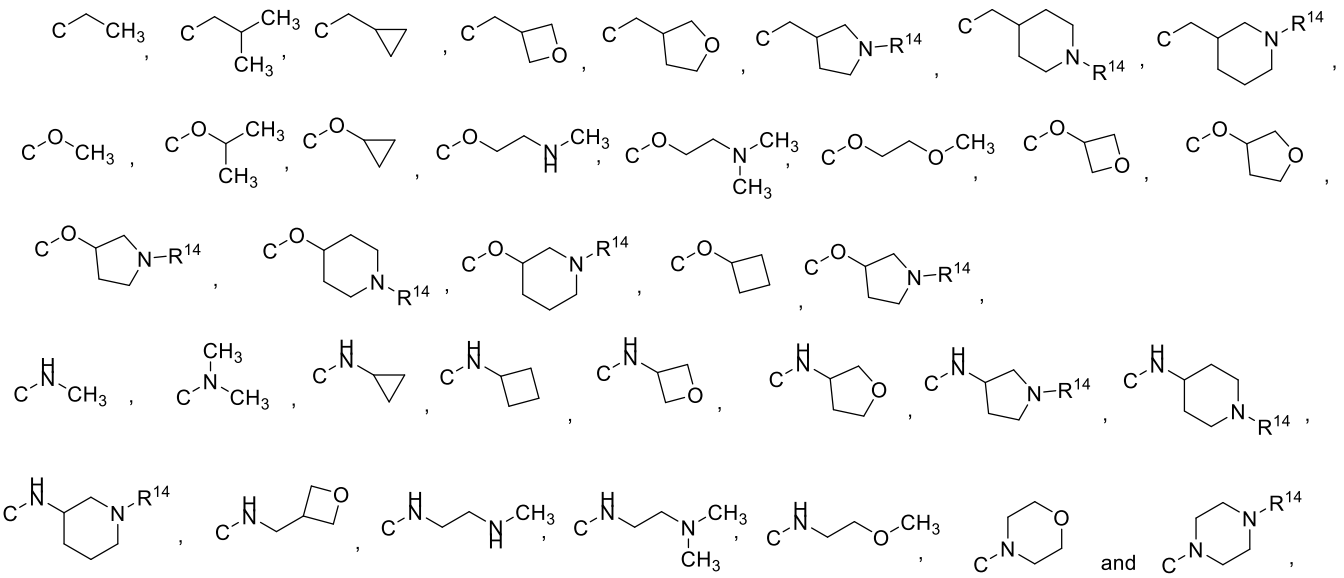
~~38. The compound of claim 37,~~ optionally wherein

X^3 is $CN(H)CH_3$; or.

~~39. The compound of any one of claims 1-5, 8-11, or 14-28, wherein~~ d) X^2 is N and X^3 is CCH_3; or.

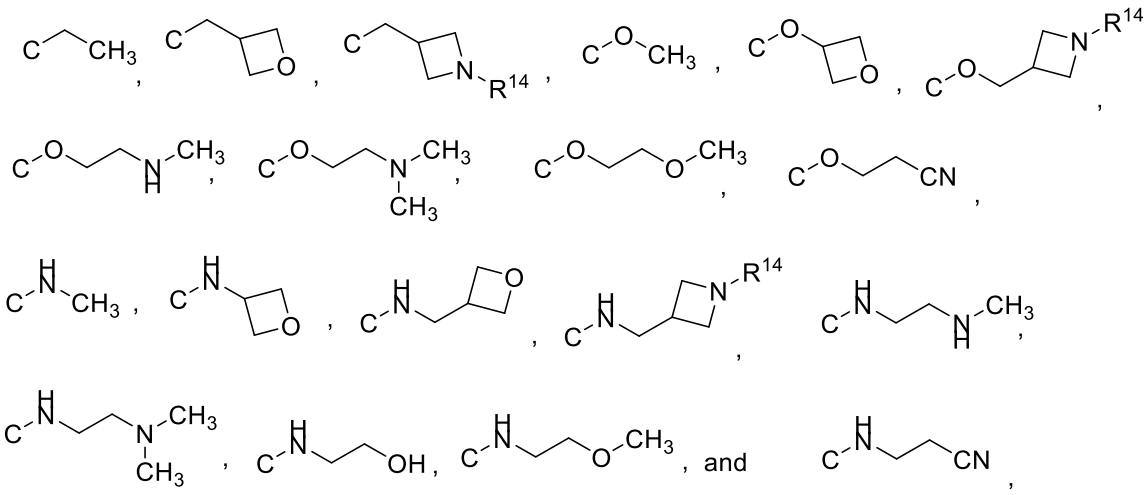
~~40. The compound of any one of claims 1, 4-7, 10-13, or 26-28, wherein~~ e) X^2 is CH and X^3 is N; or.

~~41. The compounds of any one of claims 1, 4-7, 10-13, 26-35, wherein~~ f) X^2 is selected from the group consisting of:



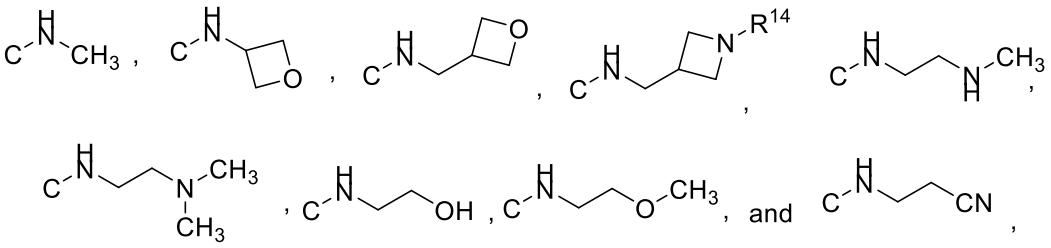
wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl; and/or.

~~42. The compound of any one of claims 1-5, 8-11, 14-35, wherein~~ g) X^3 is selected from the group consisting of:



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl; or~~.~~

~~43. The compound of any one of claims 1-5, 8-11, 14-37, wherein~~h) X^3 is selected from the group consisting of



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

~~44~~23. The compound of any one of claims 1-~~43~~22, wherein X^4 is CR^3, optionally wherein R^3 is selected from the group consisting of H, methyl, and F.

~~45~~24. The compound of any one of claims 1-~~44~~23, wherein

a) X^{10} is CR^5 and X^{11} is CR^7;~~.~~

~~46. The compound of any one of claims 1-44, wherein~~ b) X^{10} and X^{11} are N; or~~.~~

~~47. The compound of any one of claims 1-44, wherein~~ c) X^{10} is CR^5 and X^{11} is N.

~~48. The compound of claim 44, wherein R^3 is selected from the group consisting of H, methyl, and F.~~

~~49~~25. The compound of any one of claims 1-~~48~~24, wherein

a) R^4 and R^5 are each independently selected from the group consisting of H, F, Cl, Me, OMe, CF_3, and CN; and/or~~.~~

~~50. The compound of any one of claims 1-49, wherein~~b) R^6 and R^7 are each independently selected from the group consisting of H, F, Cl, Me; or~~.~~

~~51. The compound of any one of claims 1-49, wherein~~ c) R^4, R^5, R^6, and R^7 are each independently H or F, and wherein at least one of R^4, R^5, R^6, and R^7 is F; or~~.~~

~~52. The compound of any one of claims 1-51, wherein:~~

d) R^6 is F; and

R^4, R^5, and R^7 are each H;~~.~~

~~53. The compound of any one of claims 1-51, wherein:~~

e) R^4 is F; and

R^5, R^6, and R^7 are each H;~~.~~

~~54. The compound of any one of claims 1-51, wherein:~~

f) R^4 and R^6 are each F; and

R^5 and R^7 are each H;~~.~~

~~55. The compound of any one of claims 1-51, wherein:~~

g) R^4 and R^5 are each F; and

R^6 and R^7 are each H; or~~.~~

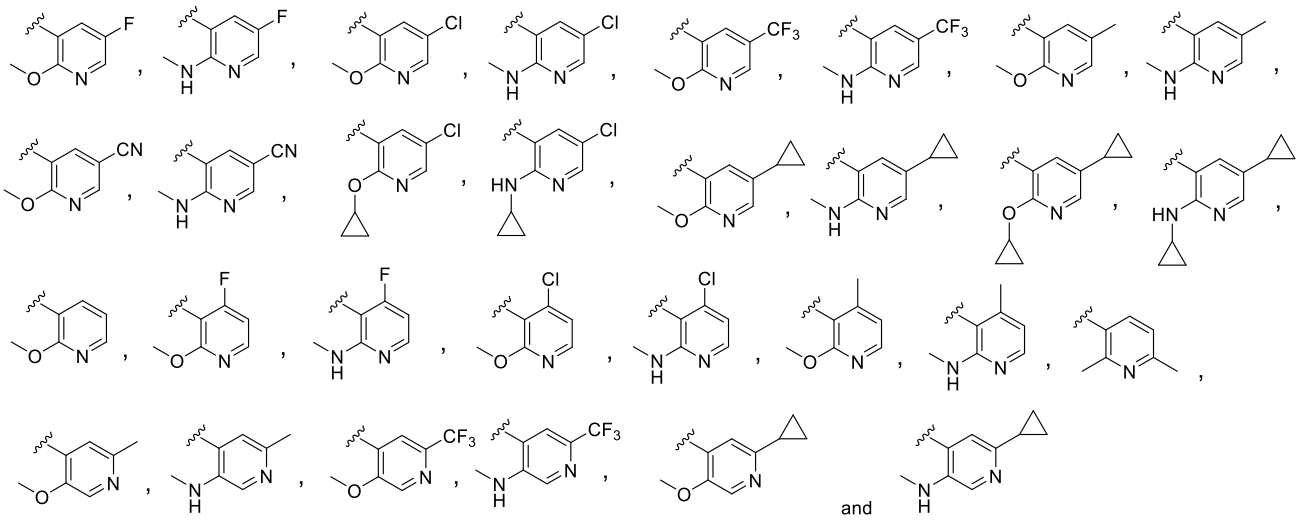
~~56. The compound of any one of claims 1-51, wherein:~~

h) R^5 and R^6 are each F; and

R^4 and R^7 are each H.

~~57~~26. The compound of any one of claims 1, 8-13, ~~or 26-56~~and 18-25, wherein

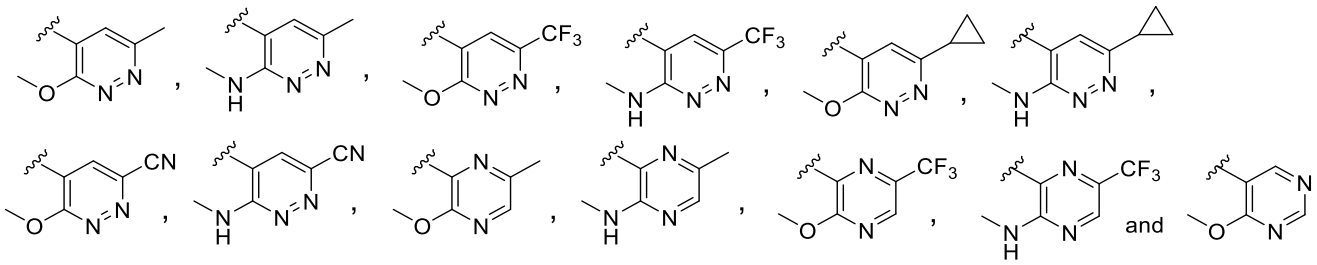
a) A or B is selected from the group consisting of:



~~.~~

;

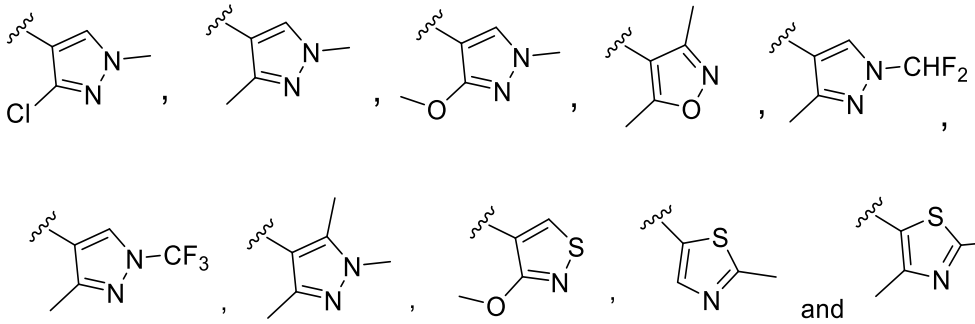
~~58. The compound of any one of claims 1, 8-13, or 26-56, wherein~~ b) A or B is selected from the group consisting of:



~~.~~

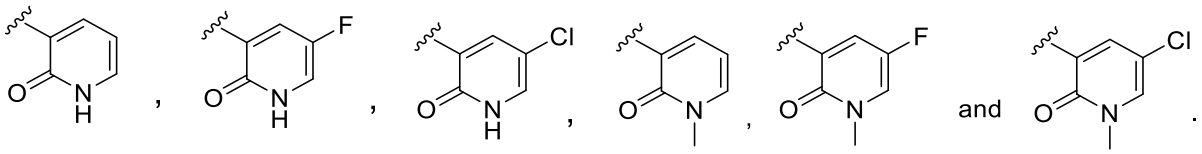
;

c) A or B is selected from the group consisting of:



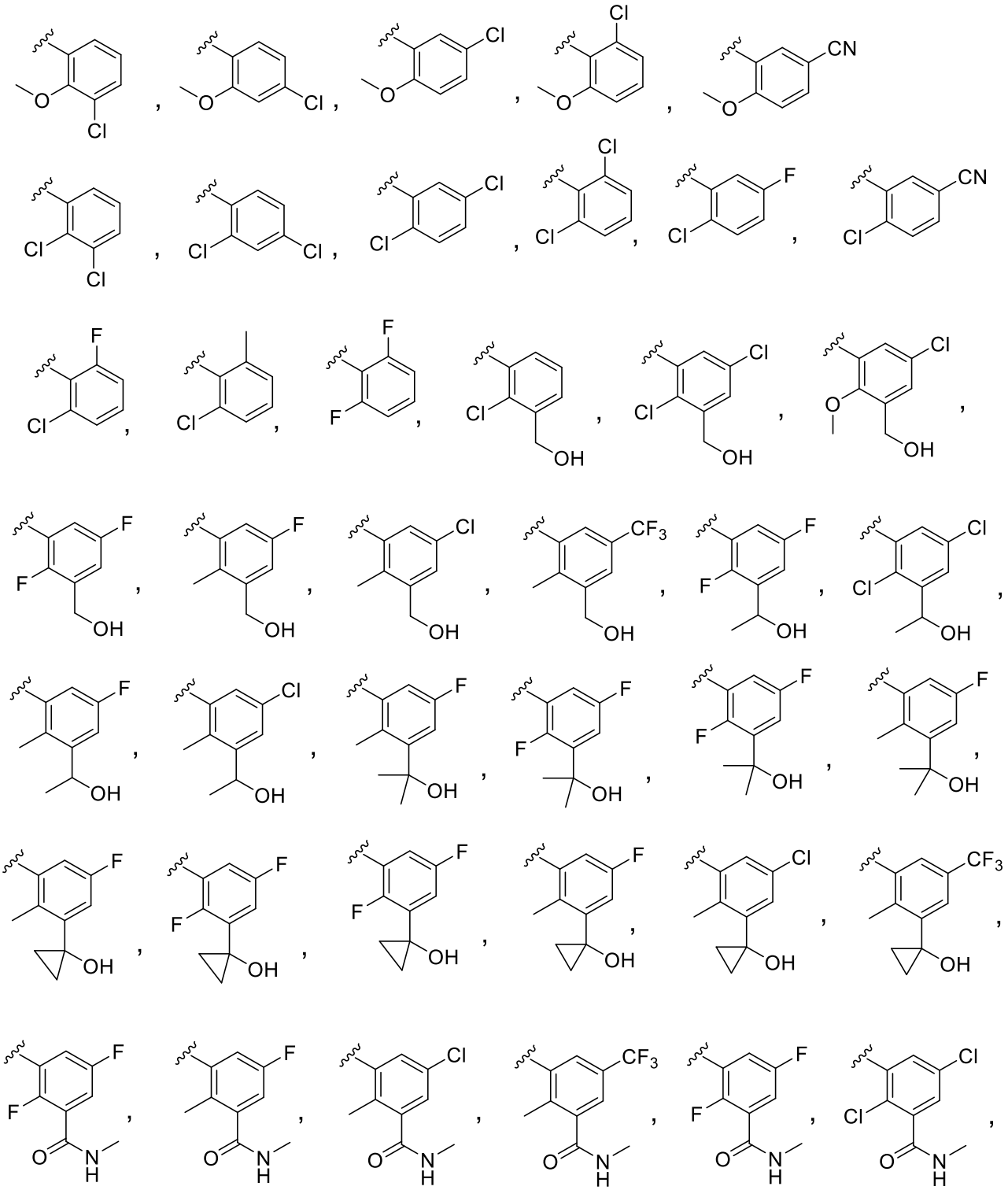
; or

d) A or B is selected from the group consisting of:



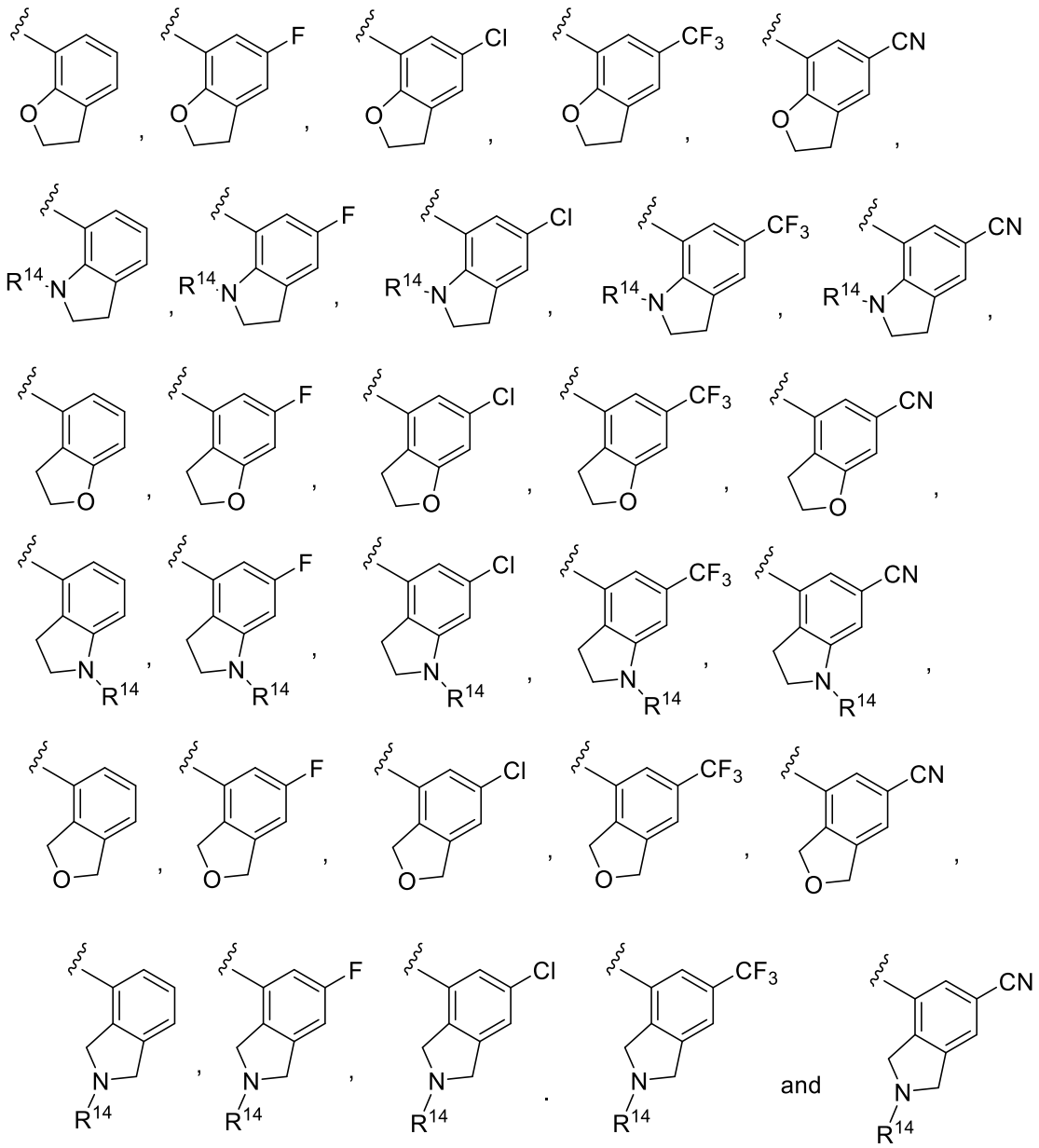
5927. The compound of any one of claims 1, or 26-56and 18-25, wherein

a) A is selected from the group consisting of:



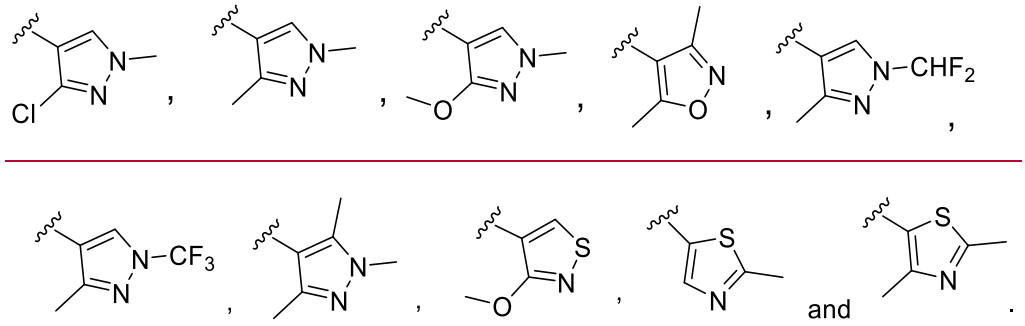
; or

~~60. The compound of any one of claims 1, or 26-56, wherein~~ b) A is selected from the group consisting of:

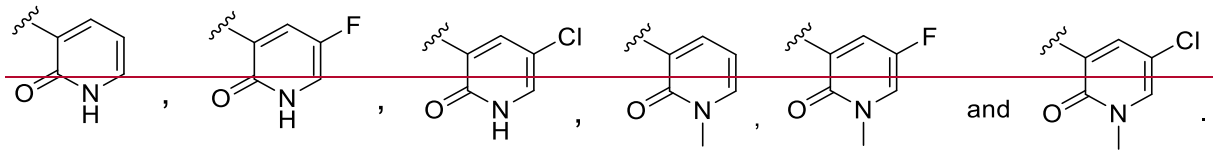


wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

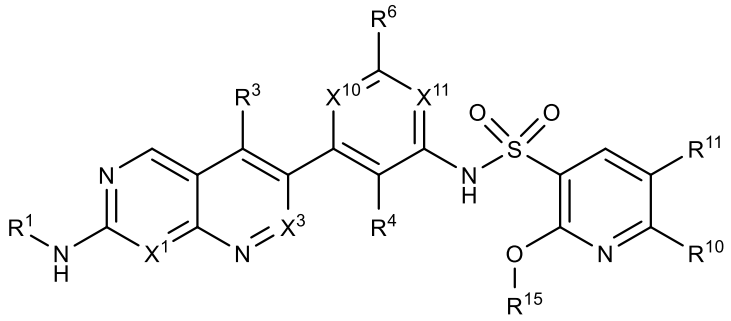
~~61. The compound of any one of claims 1, 8-13, or 26-56, wherein A or B is selected from the group consisting of:~~



~~62. The compound of any one of claims 1, 8-13, or 26-56, wherein A or B is selected from the group consisting of:~~



~~63~~28. A compound represented by Formula I-R, Formula I-S, Formula I-T, Formula I-U, Formula I-V, Formula I-W, Formula I-X, or Formula I-Y:



Formula I-R

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

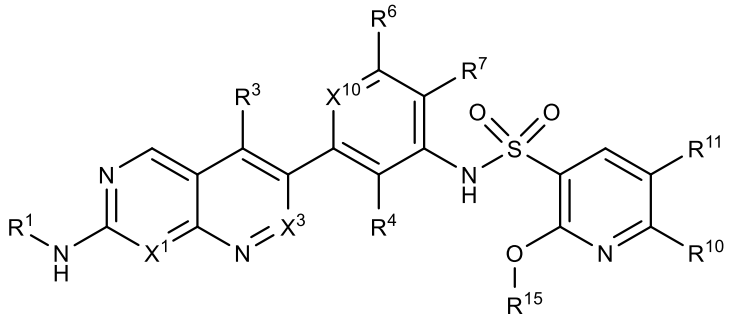
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2~~.~~;

~~64. A compound represented by Formula I-S:~~



Formula ~~1~~I-S

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

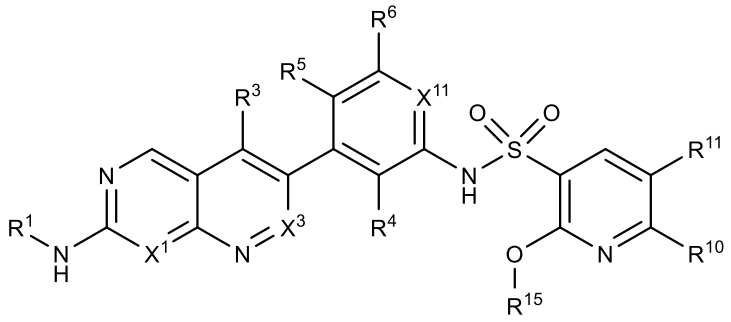
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2~~.~~;

~~65. A compound represented by Formula I-T:~~



Formula ~~I~~I-T

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

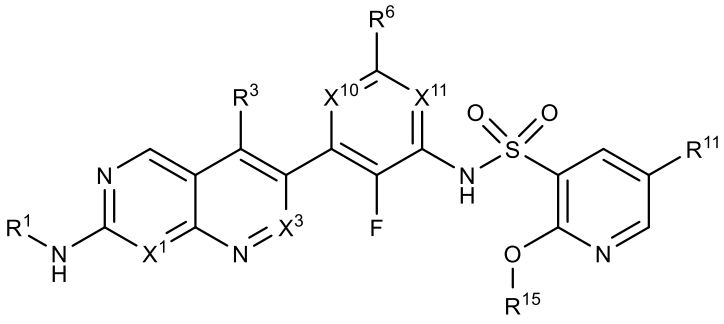
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;.

~~66. A compound represented by Formula I-U:~~



Formula ~~1~~I-U

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

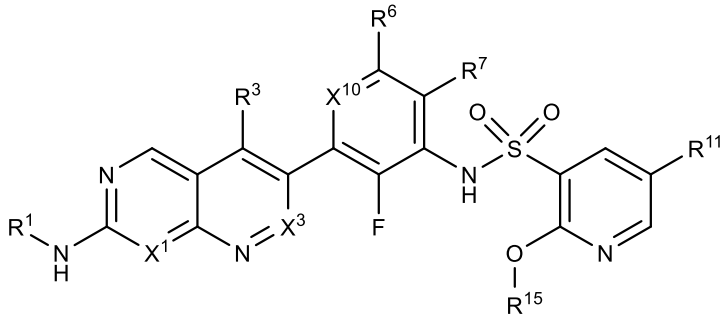
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;~~.~~

~~67. A compound represented by Formula I-V:~~



Formula ~~1~~I-V

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

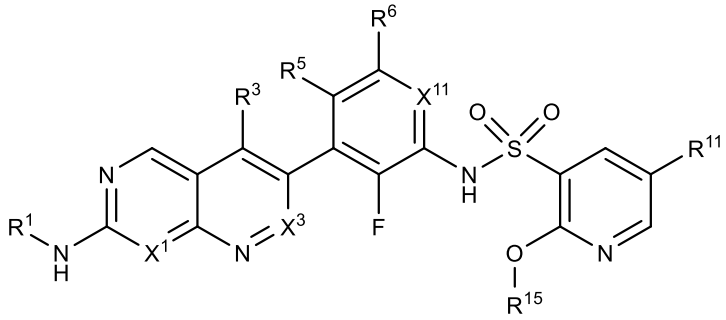
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;

~~68. A compound represented by Formula I-W:~~



Formula ~~I~~I-W

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

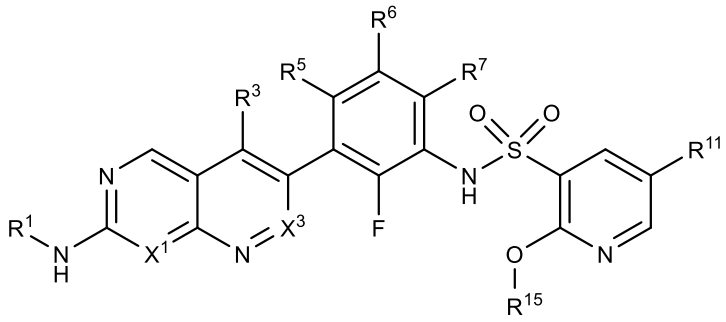
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;.

~~69. A compound represented by Formula I-X:~~



Formula ~~I~~I-X

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

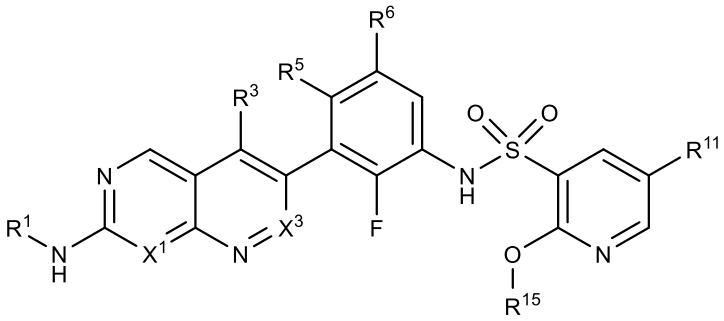
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2; or.

~~70. A compound represented by Formula I-Y:~~



Formula ~~1~~I-Y

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^{15} is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

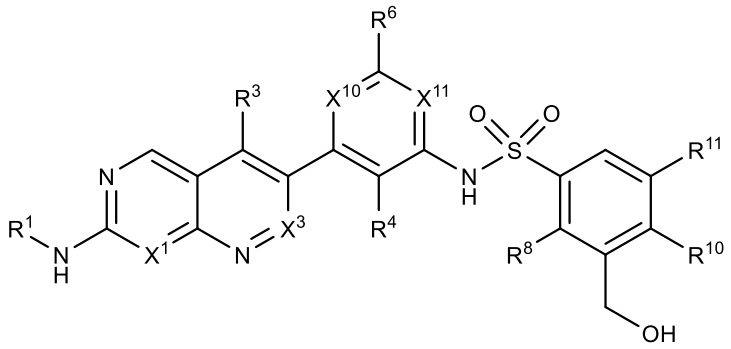
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2.

~~71~~29. A compound represented by Formula I-Z, Formula I-AA, Formula I-AB, Formula I-AC, Formula I-AD, Formula I-AE, Formula I-AF, or Formula I-AG:



Formula I-Z

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

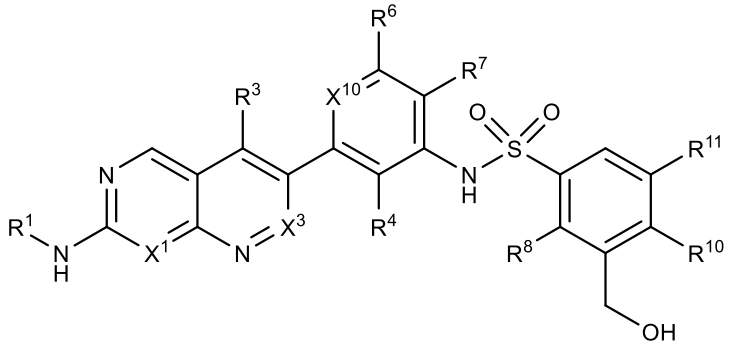
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;~~.~~

~~72. A compound represented by Formula I-AA:~~



Formula I-AA

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

R^{10} and R^{11} are each independently selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

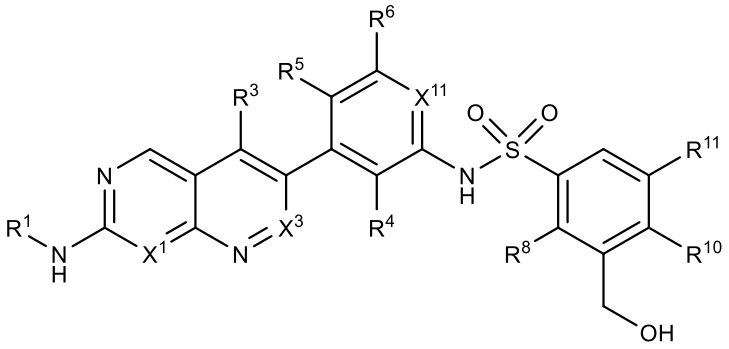
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;~~.~~

~~73. A compound represented by Formula I-AB:~~



Formula I-AB

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, $(C=O)R^{13}$, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy,

alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^4 and R^5 are each independently selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

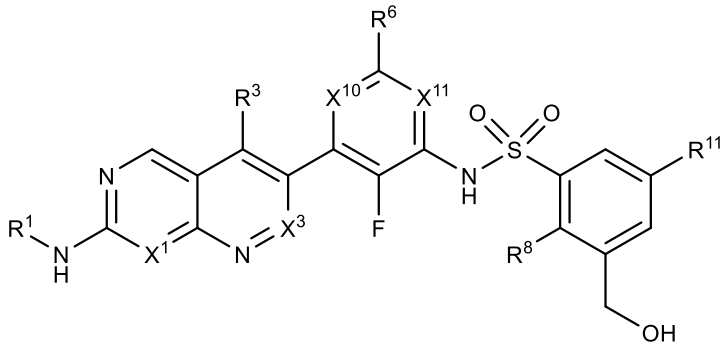
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;.

~~74. A compound represented by Formula I-AC:~~



Formula ~~I~~I-AC

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

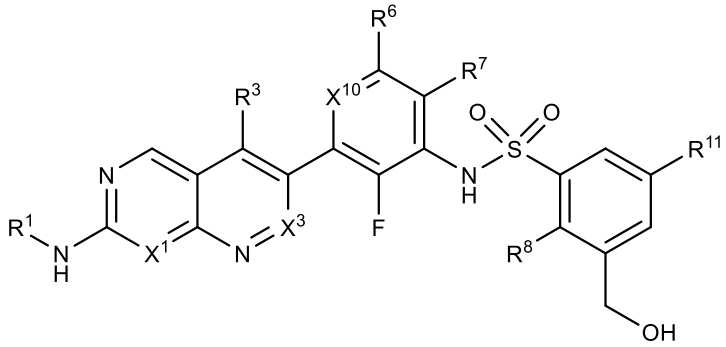
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2~~;~~.

~~75. A compound represented by Formula I-AD:~~



Formula ~~1~~I-AD

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{10} is selected from the group consisting of CR^5 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano,

alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

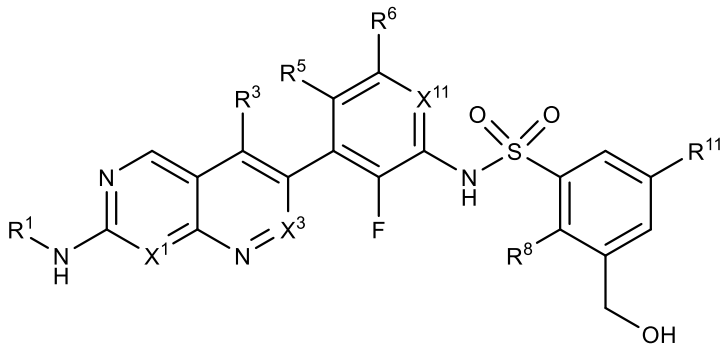
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;~~.~~

~~76. A compound represented by Formula I-AE:~~



Formula I~~1~~-AE

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

X^{11} is selected from the group consisting of CR^7 and N;

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

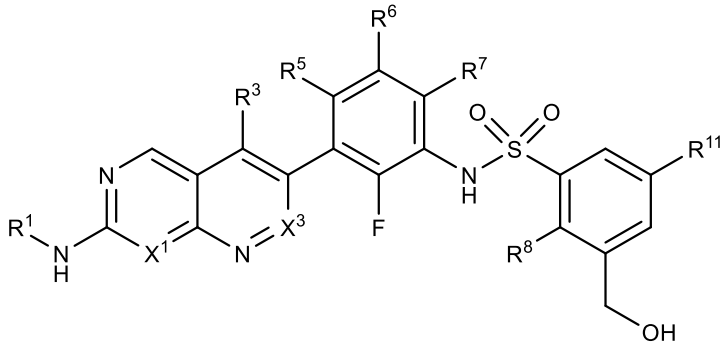
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2;~~.~~

~~77. A compound represented by Formula I-AF:~~



Formula ~~I~~I-AF

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine,

aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^7 is selected from the group consisting of H and F;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN;

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

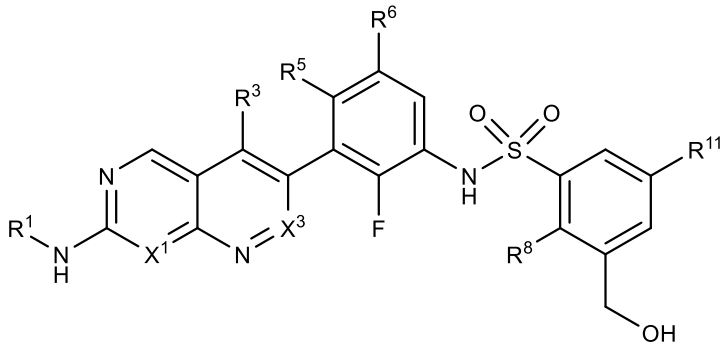
E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2; or.

~~78. A compound represented by Formula I-AG:~~



Formula ~~I~~I-AG

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

X^1 is selected from the group consisting of CH and N;

X^3 is selected from the group consisting of C-O-L^2-E^2, C-L^2-E^2, and C-N(R^2)-L^2-E^2

R^1 is selected from the group consisting of alkyl, (C=O)R^{13}, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

R^2 is selected from the group consisting of H and alkyl;

R^3 is selected from the group consisting of H, alkyl, and halogen;

R^5 is selected from the group consisting of halogen, H, alkoxy, alkylamino, amino, alkyl, haloalkyl and CN;

R^6 is selected from the group consisting of halogen, H, and alkyl;

R^8 is selected from the group consisting of alkoxy, alkylamino, cycloalkoxy, cycloalkylamino, halogen, H, alkyl, haloalkoxy, haloalkyl, amide, alkoxycarbonyl, hydroxyalkyl, hydroxycycloalkyl, hydroxy, and CN

R^{11} is selected from the group consisting of hydroxyalkyl, hydroxycycloalkyl, alkoxyalkyl, alkoxycycloalkyl, amino, aminoalkyl, aminocycloalkyl, aminocarbonyl, acylamino, halogen, cyano, alkoxy, alkylamino, H, cyanoalkyl, alkyl, cycloalkyl, haloalkyl, cycloalkoxy, cycloalkylamino, heterocyclyl, alkoxycarbonyl, and heterocyclylalkyl;

R^{13} is selected from the group consisting of H, alkyl, cycloalkyl, alkoxyalkyl, cycloalkoxyalkyl, aminoalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl, and heteroarylalkyl,

wherein each of aryl and heteroaryl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of haloalkyl, alkyl, haloalkoxy, alkoxy, halogen, amine, amide, acyl, alkoxyalkyl, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

L^2 is selected from the group consisting of a direct bond and C_1-C_6alkyl, wherein C_1-C_6alkyl is optionally substituted with $(E^{21})_p$;

E^2 is selected from the group consisting of hydroxy, alkoxy, alkoxyalkyl, cyano, halogen, sulfonyl, H, alkyl, amine, amide, acyl, haloalkoxy, haloalkyl, and heterocyclyl,

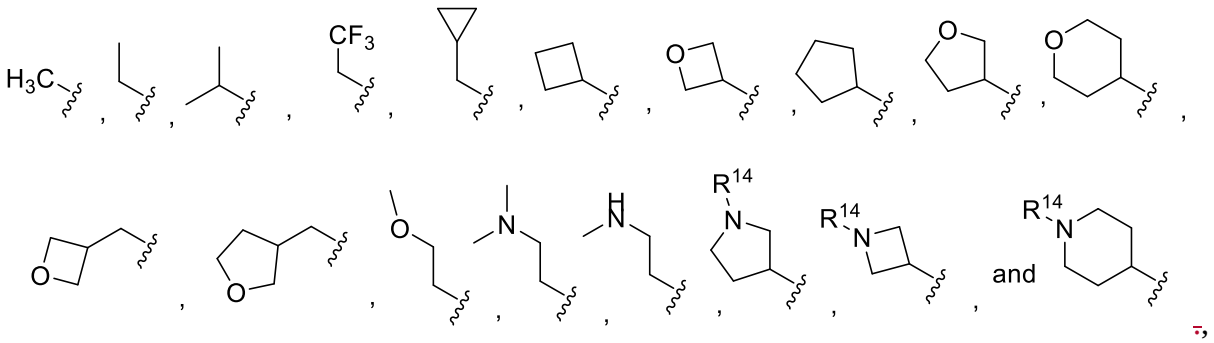
wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl;

E^{21}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen, and

each p is independently 0, 1 or 2.

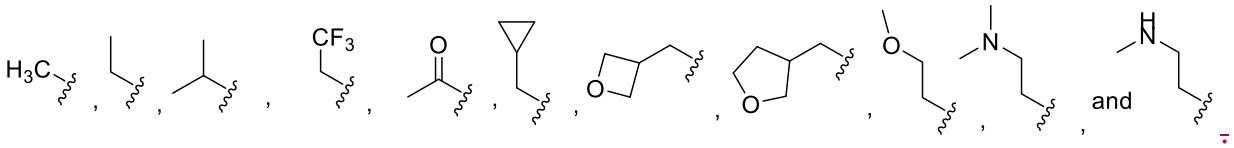
~~79~~30. The compound of ~~any one of claims 63-78~~claim 28 or 29, wherein

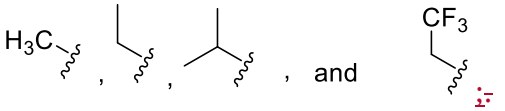
a) R^1 is selected from the group consisting of



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl;.

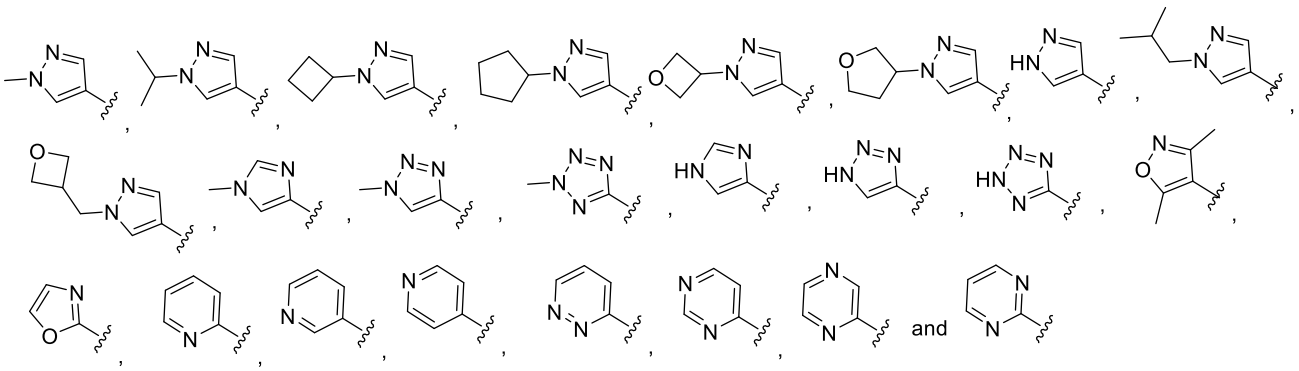
~~80. The compound of any of claims 63-78, wherein~~ b) R^1 is selected from the group consisting of



~~81. The compound of any one of claims 63-78, wherein~~ c) R^1 is selected from the group consisting of H, 

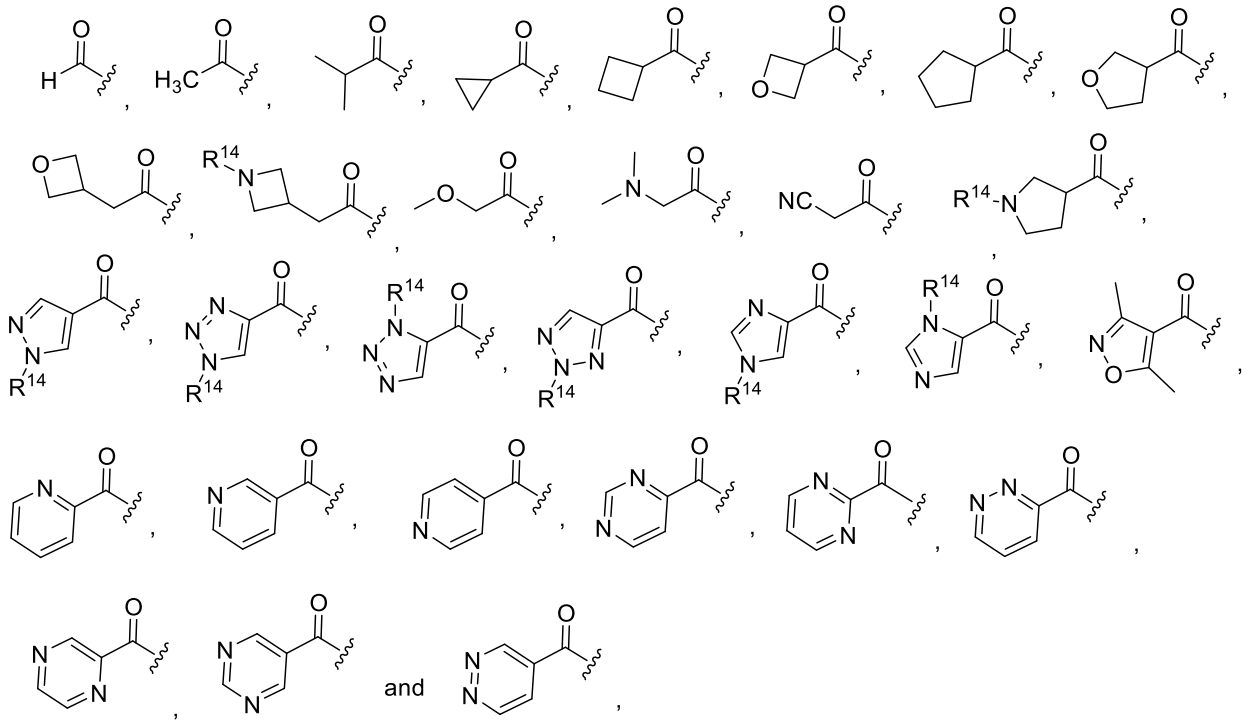
;.

~~82. The compound of any one of claims 63-78, wherein~~ d) R^1 is selected from the group consisting of



; or.

~~83. The compound of any one of claims 63-78, wherein~~ e) R^1 is selected from the group consisting of



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

~~84~~31. The compound of any one of claims ~~63-83~~28-30, wherein

a) X^1 is N; or~~.~~

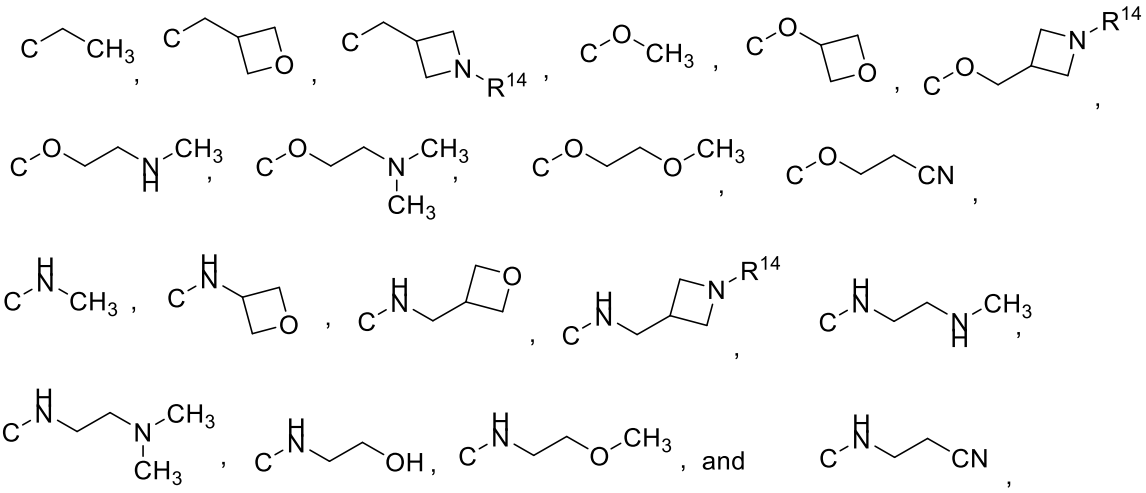
~~85. The compound of any one of claims 63-83, wherein~~ b) X^1 is CH; and/or~~.~~

~~86. The compound of any one of claims 63-85, wherein~~ c) X^3 is C-N(R^2)-L^2-E^2, optionally wherein ~~.~~

~~87. The compound of claim 86, wherein~~ X^3 is CN(H)CH_3; or.

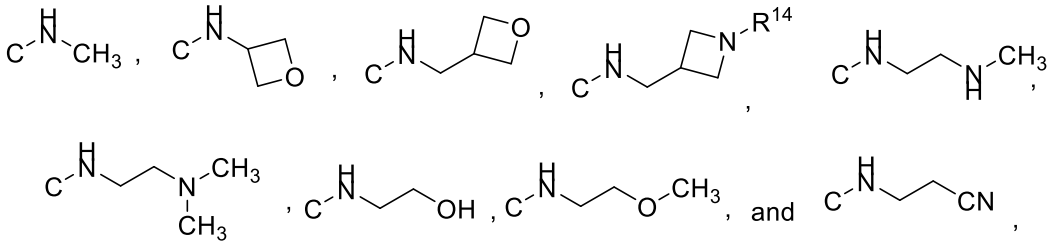
~~88. The compound of any one of claims 63-85, wherein~~ d) X^3 is CCH_3~~.~~; or

~~89. The compound of any one of claims 63-85, wherein~~ e) X^3 is selected from the group consisting of:



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl; or.

90. The compound of any one of claims 63-85, wherein f) X^3 is selected from the group consisting of



wherein each occurrence of R^{14} is independently selected from the group consisting of H, alkyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, and cyanoalkyl.

91. The compound of any one of claims 63-68 and 71-76, wherein X^{10} is N and X^{11} is CR^7.

92. The compound of any one of claims 63-68 and 71-76, wherein X^{10} and X^{11} are N.

93. The compound of any one of claims 63-68 and 71-76, wherein X^{10} is CR^5 and X^{11} is N.

94. The compound of any one of claims 63, 68, and 71-76, wherein R^3 is H, C_1-C_6 alkyl, and halogen.

95. The compound of any one of claims 63, 68, 71-76, and 94, wherein R^3 is H.

96. The compound of any one of claims 63, 68, 71-76, and 94, wherein R^3 is Me.

97. The compound of any one of claims 63, 68, 71-76, and 94, wherein R^3 is F.

98. The compound of any one of claims 63, 68, 71-76, and 94, wherein R^3 is Cl.

99. The compound of any one of claims 63-65, 71-73, and 79-98, wherein R^4 is selected from the group consisting of H, F, Cl, Me, OMe, CF_3, and CN.

100. The compound of any one of claims 63-99, wherein R^5 is selected from the group consisting of H, F, Cl, Me, OMe, CF_3, and CN.

101. The compound of any one of claims 63-100, wherein R^6 and R^7 are each independently selected from the group consisting of H, F, Cl, Me.

102. The compound of any one of claims 63-101, wherein R^4, R^5, R^6, and R^7 are each independently H or F, and wherein at least one of R^4, R^5, R^6, and R^7 is F.

103. The compound of any one of claims 63-65, 71-73, and 79-102, wherein:

R^6 is F; and

R^4, R^5, and R^7 are each H.

104. The compound of any one of claims 63-102, wherein:

R^4 is F; and

R^5, R^6, and R^7 are each H.

105. The compound of any one of claims 63-102, wherein:

R^4 and R^6 are each F; and

R^5 and R^7 are each H.

106. The compound of any one of claims 63-102, wherein:

R^4 and R^5 are each F; and

R^6 and R^7 are each H.

~~107. The compound of any one of claims 63-65, 71-73, and 79-102, wherein:~~

~~R^5 and R^6 are each F; and~~

~~R^4 and R^7 are each H.~~

~~10832~~. The compound of any one of claims ~~63-107~~28-31, wherein

a) R^{15} is selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and C_3-C_6 heterocyclyl;~~.~~

~~109. The compound of any one of claims 63-108, wherein~~b) ~~R^{15}~~ is cyclopropyl;~~.~~

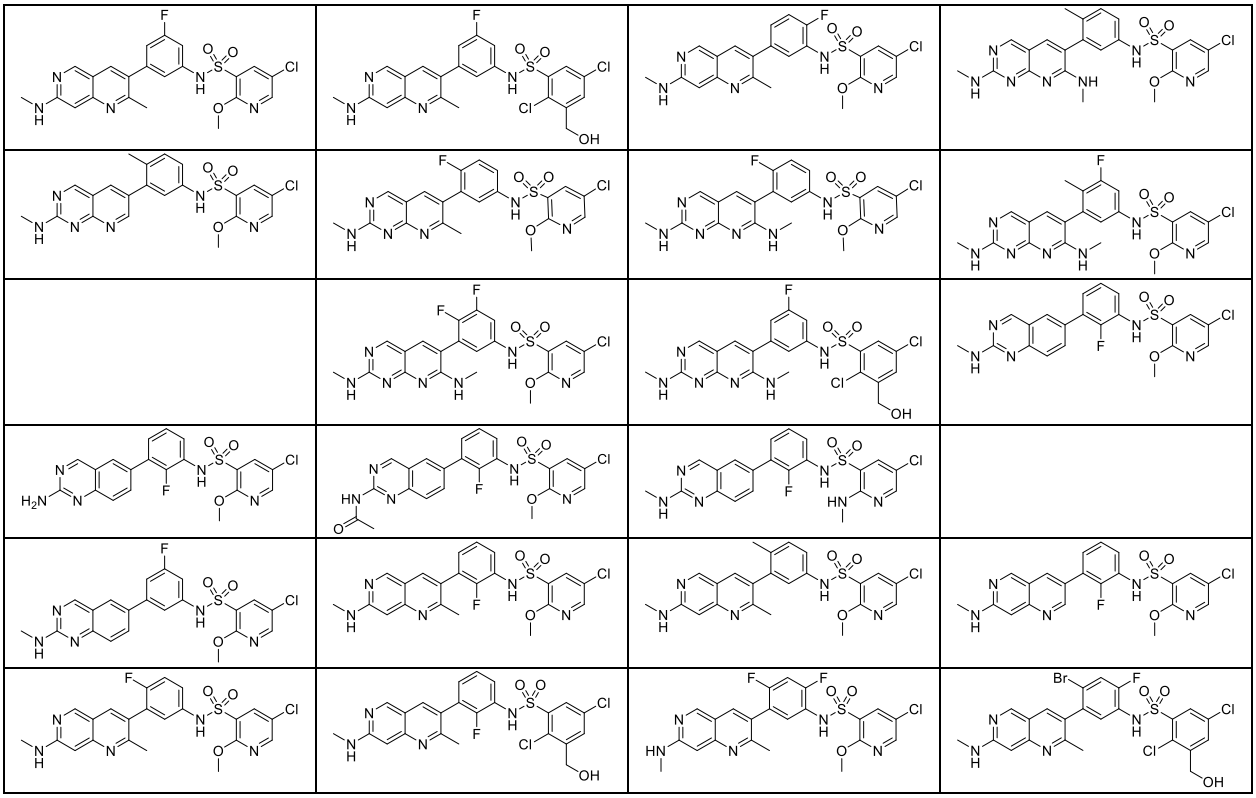
~~110. The compound of any one of claims 63-108, wherein~~ c) R^{15} is Me;~~.~~

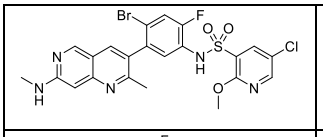
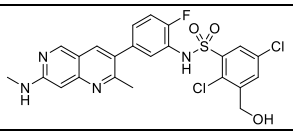
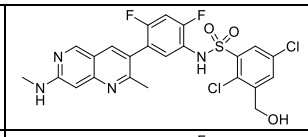
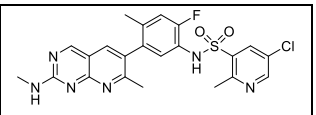
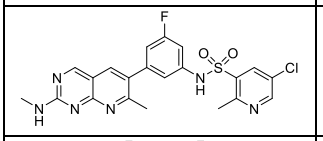
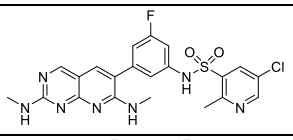
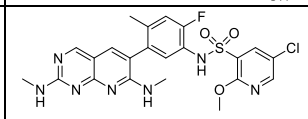
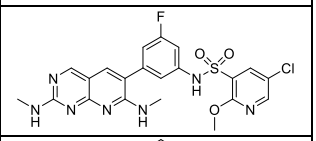
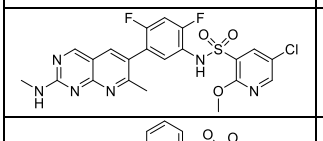
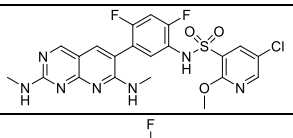
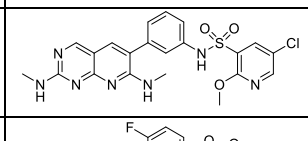
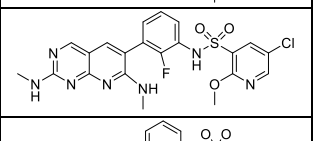
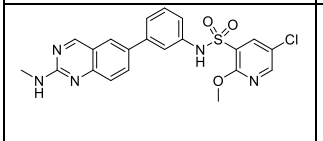
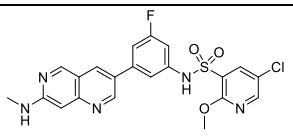
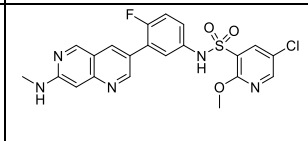
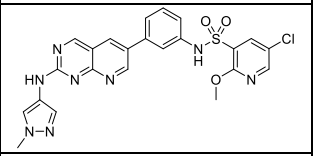
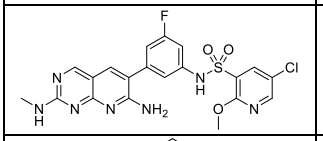
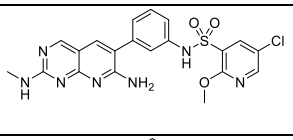
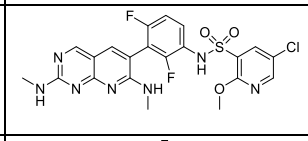
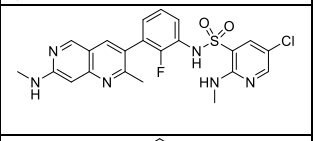
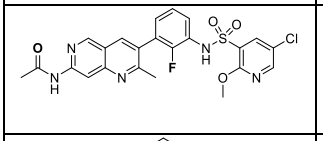
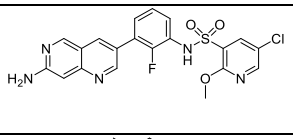
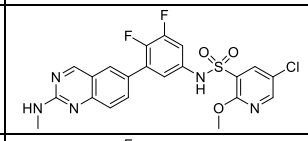
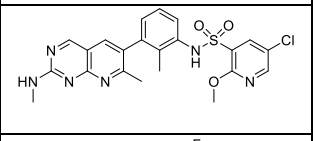
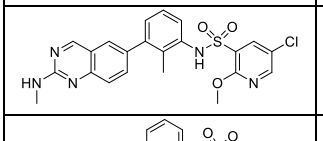
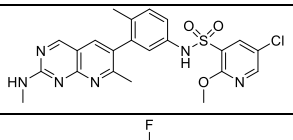
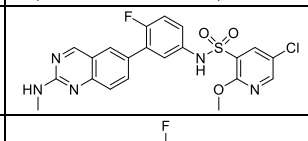
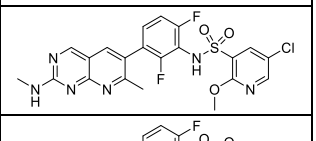
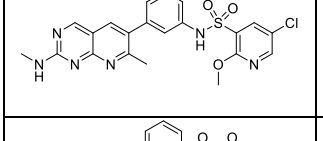
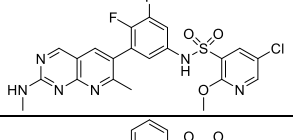
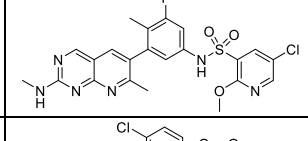
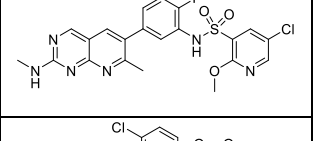
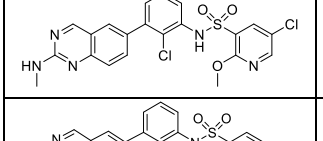
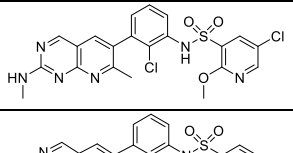
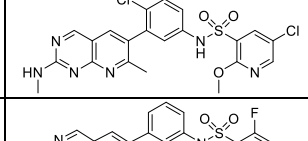
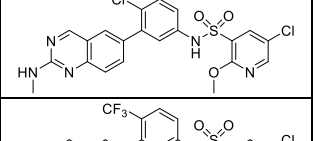
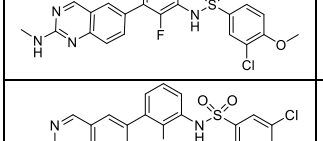
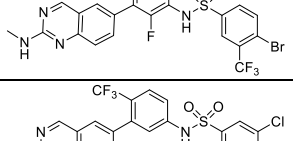
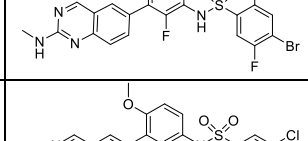
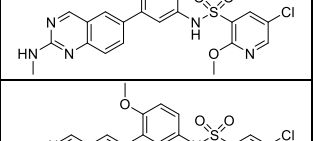
~~111. The compound of any one of claims 63-108, wherein~~ d) R^{15} is oxetanyl;~~.~~

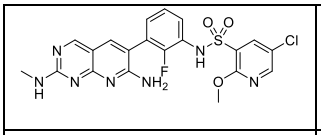
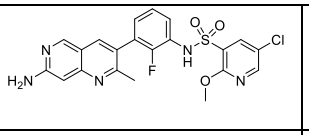
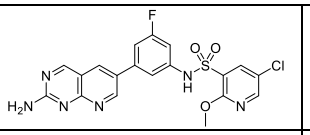
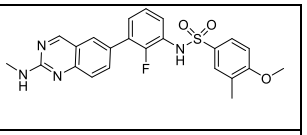
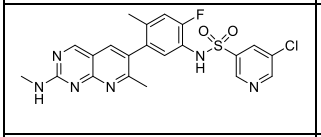
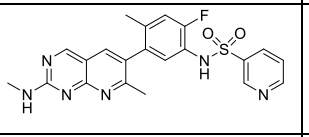
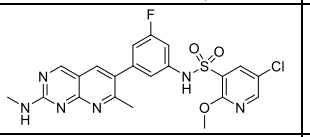
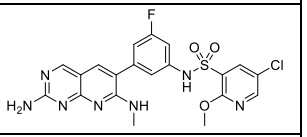
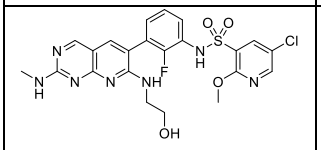
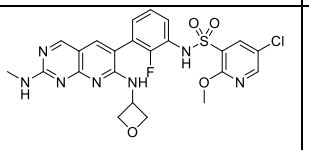
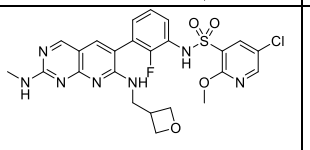
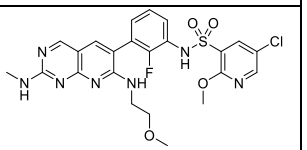
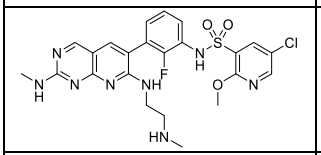
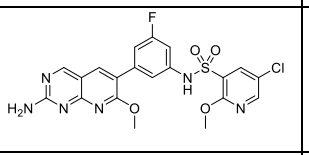
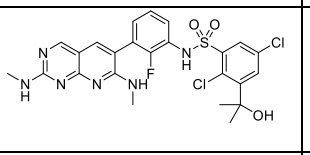
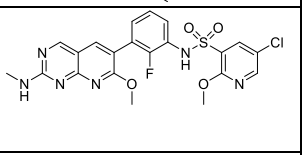
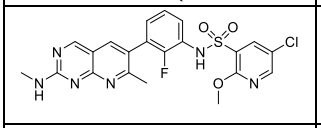
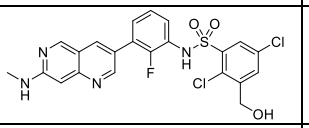
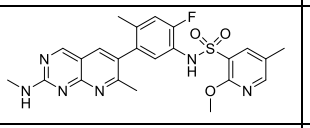
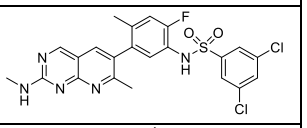
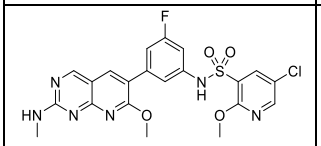
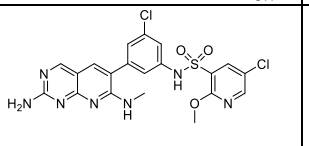
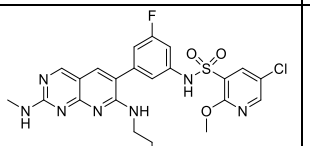
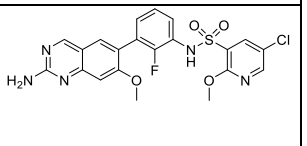
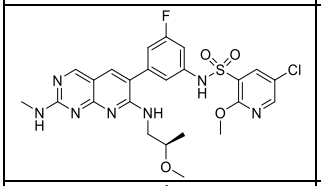
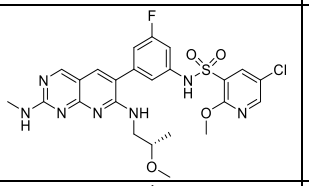
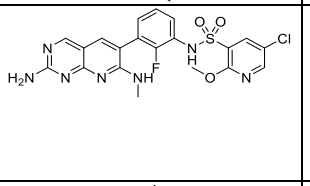
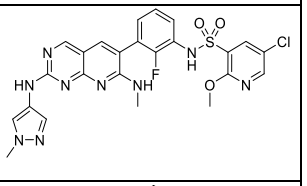
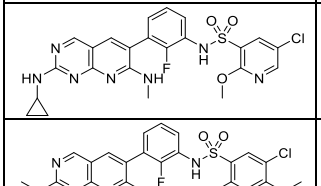
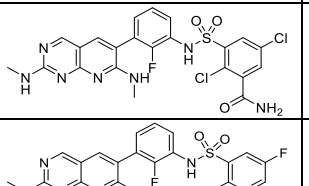
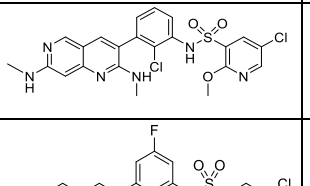
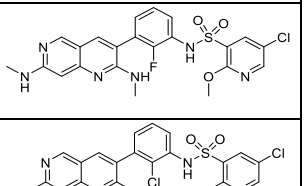
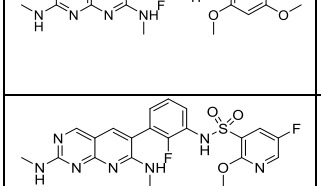
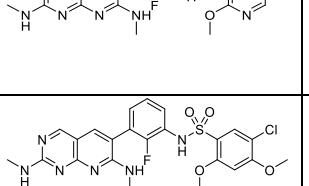
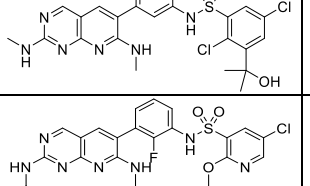
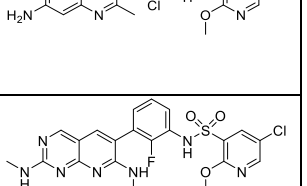
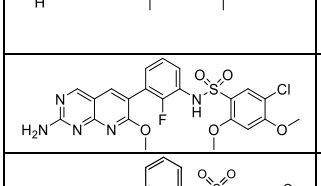
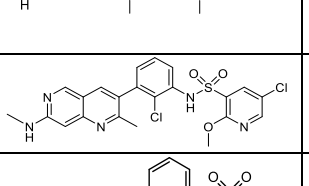
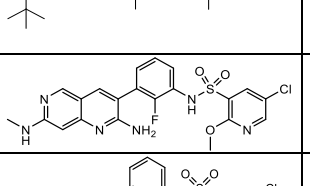
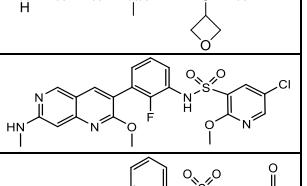
~~112. The compound of any one of claims 63-108, wherein~~ e) R^{15} is oxetan-2-yl; or~~.~~

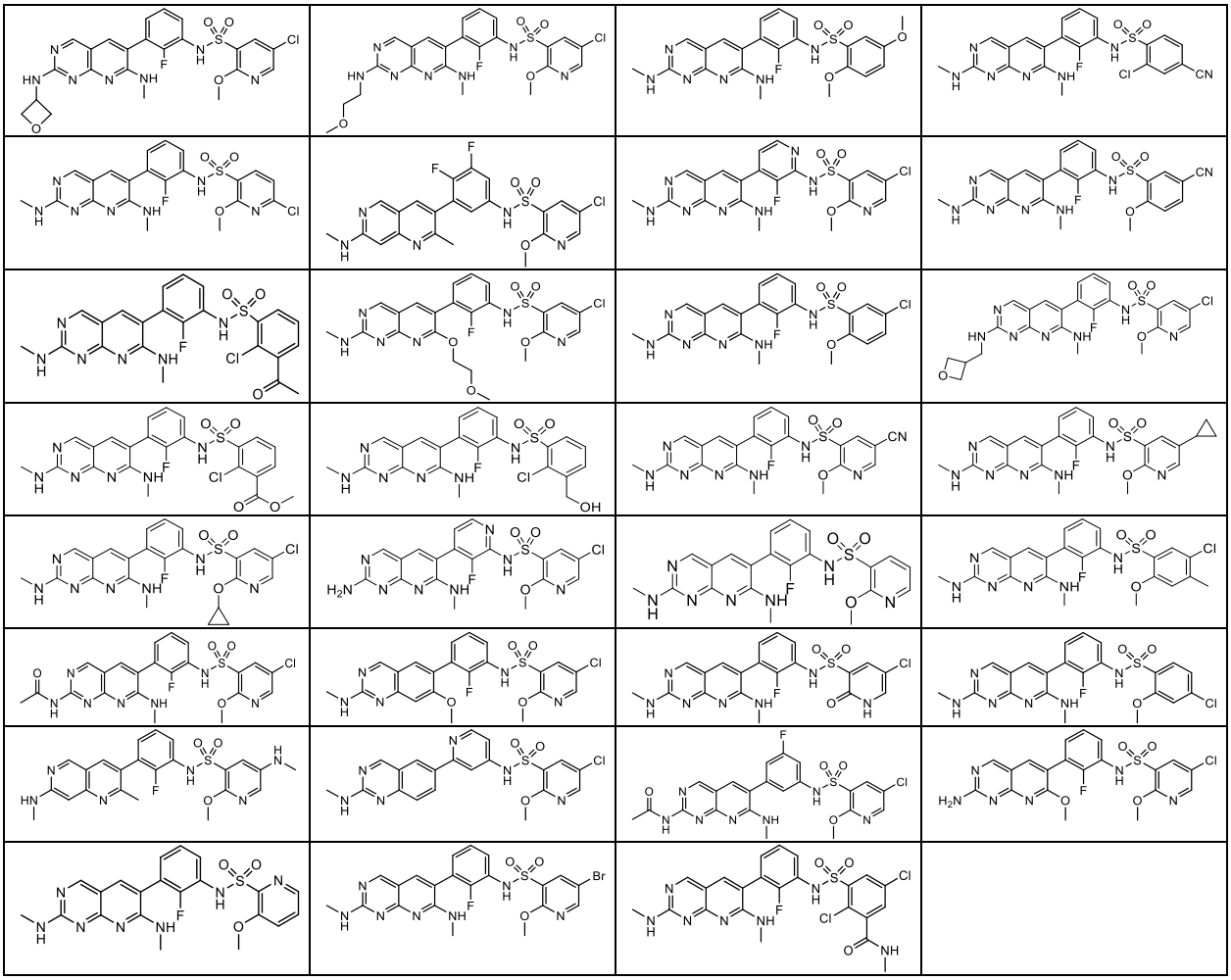
~~113. The compound of any one of claims 63-108, wherein~~ f) R^{15} is oxetan-3-yl.

~~11433~~. A compound selected from the group consisting of:





and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

~~115~~34. A pharmaceutical composition comprising a compound according to any one of claims 1-~~114~~33, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

~~116~~35. ~~A~~Use of a compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 34, in the manufacture of a medicament for ~~method of~~ treating a disease caused by a dysregulation of an integrated stress response and/or an unfolded protein response in a patient in need thereof, ~~comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115~~.

~~117. The method of claim 116, wherein the dysregulation of the integrated stress response and/or an unfolded protein response is caused by a kinase selected from the group consisting of PERK kinase and GCN2 kinase.~~

~~118. The method of claim 116 or 117, wherein the dysregulation of the integrated stress response and/or the unfolded protein response is caused by GCN2 kinase.~~

~~119. The method of claim 116 or 117, wherein the dysregulation of the integrated stress response and/or the unfolded protein response is caused by PERK kinase.~~

~~120. A method of modulating the activity of GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.~~

~~121. A method of activating GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.~~

~~122. A method of modulating the activity of PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.~~

~~123. A method of activating PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.~~

~~124. A method of inhibiting GCN2 kinase and inhibiting PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.~~

~~125. A method of inhibiting the activity of GCN2 kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.~~

~~126. A method of inhibiting the activity of PERK kinase in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.~~

~~127~~36. ~~A~~ Use of a compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 34, in the manufacture of a medicament for ~~method of~~ treating a cancer in a patient in need thereof, ~~optionally comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.~~

~~128. The method of claim 126,~~ wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocyctic lymphoma, waldenstrom macroglobulinemia, light chain amyloidosis, and malignant lymphoma.

~~129. The method of claim 127 or 128, wherein the cancer is leukemia.~~

~~130. The method of claim 127 or 128, wherein the cancer is acute myeloid leukemia.~~

~~131. The method of claim 127 or 128, wherein the cancer is acute lymphoblastic leukemia.~~

~~132. The method of claim 127 or 128, wherein the cancer is fibrosarcoma.~~

~~133. The method of claim 127 or 128, wherein the cancer is multiple myeloma.~~

~~134. The method of claim 127 or 128, wherein the cancer is lymphoma.~~

~~135. The method of claim 127 or 128, wherein the cancer is B-cell lymphoma.~~

~~136. The method of claim 127 or 128, wherein the cancer is T cell lymphoma.~~

~~137~~37. ~~A method of~~Use of a compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 34, in the manufacture of a medicament for treating amyloidosis in a patient in need thereof, ~~comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115~~.

~~138. A method of treating light chain amyloidosis in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.~~

~~139. A method of treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 115.~~

~~140. The method of claim 139, wherein the disease is a GCN2 associated disease.~~

~~141. The method of claim 139, wherein the disease is a PERK associated disease.~~

~~142. The method of any one of claims 139-141, wherein the disease is a cancer.~~

~~143. The method of claim 142, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian~~

~~cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, Mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocyctic lymphoma, waldenstrom macroglobulinemia, and malignant lymphoma.~~

~~144. The method of claim 142 or 143, wherein the cancer is leukemia.~~

~~145. The method of claim 142 or 143, wherein the cancer is acute myeloid leukemia.~~

~~146. The method of claim 142 or 143, wherein the cancer is acute lymphoblastic leukemia.~~

~~147. The method of claim 142 or 143, wherein the cancer is fibrosarcoma.~~

~~148. The method of claim 142 or 143, wherein the cancer is multiple myeloma.~~

~~149. The method of claim 142 or 143, wherein the cancer is lymphoma.~~

~~150. The method of claim 142 or 143, wherein the cancer is B-cell lymphoma.~~

~~151. The method of claim 142 or 143, wherein the cancer is T-cell lymphoma.~~

~~152. The method of claim 139, wherein the disease is amyloidosis.~~

~~153. The method of claim 139, wherein the disease is light chain amyloidosis.~~

~~154. A method of treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound according to any one of claims 1-114, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of one or more therapeutic agents.~~

~~155. The method of claim 154, wherein the disease is a GCN2 associated disease.~~

156. The method of claim 154, wherein the disease is a PERK-associated disease.

157. The method of any one of claims 154-156, wherein the disease is a cancer.

158. The method of claim 157, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocyctic lymphoma, waldenstrom macroglobulinemia, light chain amyloidosis, and malignant lymphoma.

159. The method of claim 157 or 158, wherein the cancer is leukemia.

160. The method of claim 157 or 158, wherein leukemia is acute myeloid leukemia.

161. The method of claim 157 or 158, wherein leukemia is acute lymphoblastic leukemia.

162. The method of claim 157 or 158, wherein the cancer is fibrosarcoma.

163. The method of claim 157 or 158, wherein the cancer is multiple myeloma.

164. The method of claim 157 or 158, wherein the cancer is lymphoma.

165. The method of claim 157 or 158, wherein the cancer is B-cell lymphoma.

166. The method of claim 157 or 158, wherein the cancer is T-cell lymphoma.

167. The method of claim 154, wherein the disease is amyloidosis.

~~168. The method of claim 154, wherein the disease is light chain amyloidosis.~~

~~169~~38. The ~~method of any one of claims 154-168~~ use of any one of claims 35-37, wherein the medicament is to be administered to the patient, and wherein one or more therapeutic agents are to be further administered to the patient, optionally~~,~~ wherein

a) the one or more therapeutic agents is selected from the group consisting of an IMiD agent, a proteasome inhibitor, a steroid, an anti-CD38 agent, an anti-CD20 agent, a Bcl-2 inhibitor, a PI3K inhibitor, a bi-specific antibody, a nucleoside analog, a BTK inhibitor, a DNA alkylating agent, an EZH2 inhibitor, an anthracycline, a topoisomerase inhibitor, a platin, a tyrosine kinase inhibitor, an HDAC inhibitor, a nuclear export inhibitor, an anti-microtubule agent, L-asparaginase, pegylated asparaginase, a PERK inhibitor, a mTOR inhibitor, an immunomodulatory agent, a MAPK pathway inhibitor, a MEK inhibitor, an ERK inhibitor, and a Ras inhibitor; or~~.~~

~~170. The method of any one of claims 154-168, wherein~~ b) the one or more therapeutic agents is selected from the group consisting of L-asparaginase, pegaspargase, calaspargase pegol – mnkl, bortezomib, carfilzomib, ixazomib, thalidomide, pomalidomide, lenalidomide, dexamethasone, prednisone, daratumumab, daratumumab / hyaluronidase, isatuximab, rituximab, obinutuzumab, venetoclax, idelalisib, copanlisib, duvelisib, umbralisib, gemcitabine, cytarabine, ibrutinib, acalabrutinib, zanubrutinib, bendamustine, cyclophosphamide, tazemetostat, doxorubicin, daunorubicin, etoposide, oxaloplatin, carboplatin, cisplatinbosutinib, dasatinib, imatinib, nilotinib, ponatinib, panobinostat, selinexor, vincristine, JZP-458, eryaspase, PF745 (JZP-341), asparaginase *Erwinia chrysanthemi* (crisantaspase), *Escherichia coli* asparaginase (colaspase), an anti-PD1 agent, an anti-PDL1 agent, and an anti-CTLA4 agent.

39. A compound of any one of claims 1-33, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 34, for use in therapy.

~~171. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in treating a disease caused by a dysregulation of an integrated stress response and/or the unfolded protein response in a patient in need thereof.~~

~~172. The use of claim 171, wherein the dysregulation of the integrated stress response and/or the unfolded protein response is caused by a kinase selected from the group consisting of PERK kinase and GCN2 kinase.~~

~~173. The use of claim 171 or 172, wherein the dysregulation of the integrated stress response and/or the unfolded protein response is caused by GCN2 kinase.~~

~~174. The use of claim 171 or 172, wherein the dysregulation of the integrated stress response and/or the unfolded protein response is caused by PERK kinase.~~

~~175. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in modulating the activity of GCN2 kinase in a patient in need thereof.~~

~~176. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in activating GCN2 kinase in a patient in need thereof.~~

~~177. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in modulating the activity of PERK kinase in a patient in need thereof.~~

~~178. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in activating PERK kinase in a patient in need thereof.~~

~~179. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in inhibiting GCN2 kinase and inhibiting PERK kinase in a patient in need thereof.~~

~~180. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in modulating the activity of GCN2 kinase in a patient in need thereof.~~

~~181. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in inhibiting the activity of PERK kinase in a patient in need thereof.~~

~~182. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in treating a cancer in a patient in need thereof.~~

~~183. The use of claim 182, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocyctic lymphoma, waldenstrom macroglobulinemia, and malignant lymphoma.~~

~~184. The use of claim 182 or 183, wherein the cancer is leukemia.~~

~~185. The use of claim 182 or 183, wherein the cancer is acute myeloid leukemia.~~

~~186. The use of claim 182 or 183, wherein the cancer is acute lymphoblastic leukemia.~~

~~187. The use of claim 182 or 183, wherein the cancer is fibrosarcoma.~~

~~188. The use of claim 182 or 183, wherein the cancer is multiple myeloma.~~

~~189. The use of claim 182 or 183, wherein the cancer is lymphoma.~~

~~190. The use of claim 182 or 183, wherein the cancer is B-cell lymphoma.~~

~~191. The use of claim 182 or 183, wherein the cancer is T-cell lymphoma.~~

~~192. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in treating amyloidosis in a patient in need thereof.~~

~~193. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in treating light chain amyloidosis in a patient in need thereof.~~

~~194. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in treating a disease selected from a GCN2 associated disease and a PERK associated disease, in a patient in need thereof.~~

~~195. The use of claim 194, wherein the disease is a GCN2 associated disease.~~

~~196. The use of claim 194, wherein the disease is a PERK associated disease.~~

~~197. The use of any one of claims 194-196, wherein the disease is a cancer.~~

~~198. The use of claim 197, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocyctic lymphoma, waldenstrom macroglobulinemia, and malignant lymphoma.~~

~~199. The use of claim 197 or 198, wherein the cancer is leukemia.~~

~~200. The use of claim 197 or 198, wherein the cancer is acute myeloid leukemia.~~

~~201. The use of claim 197 or 198, wherein the cancer is acute lymphoblastic leukemia.~~

~~202. The use of claim 197 or 198, wherein the cancer is fibrosarcoma.~~

~~203. The method of claim 197 or 198, wherein the cancer is multiple myeloma.~~

~~204. The method of claim 197 or 198, wherein the cancer is lymphoma.~~

~~205. The method of claim 197 or 198, wherein the cancer is B-cell lymphoma.~~

~~206. The method of claim 197 or 198, wherein the cancer is T-cell lymphoma.~~

~~207. The use of claim 194, wherein the disease is amyloidosis.~~

~~208. The use of claim 194, wherein the disease is light chain amyloidosis.~~

~~209. The compound of any one of claims 1-114, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 115, for use in treating a disease selected from a GCN2 associated disease and a PERK-associated disease, in a patient in need thereof.~~

~~210. The use of claim 209, wherein the disease is a GCN2-associated disease.~~

~~211. The use of claim 209, wherein the disease is a PERK-associated disease.~~

~~212. The use of any one of claims 209-211, wherein the disease is a cancer.~~

~~213. The use of claim 212, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, mesothelioma, pancreatic cancer, pharyngeal cancer, laryngeal cancer, esophagus cancer, gastric, duodenal cancer, small intestinal cancer, breast cancer, ovarian cancer, testis tumor, prostate, liver cancer, thyroid cancer, renal cancer, uterine cancer, gestational choriocarcinoma, brain tumor, retinoblastoma, skin cancer, melanoma, sarcoma, fibrosarcoma, malignant bone tumor, urinary bladder cancer, hematologic cancer, leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, B-cell lymphoma, Follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, T-cell lymphoma, erythroleukemia, histocyctic lymphoma, waldenstrom macroglobulinemia, and malignant lymphoma.~~

~~214. The use of claim 212 or 213, wherein the cancer is leukemia.~~

~~215. The use of claim 212 or 213, wherein leukemia is acute myeloid leukemia.~~

~~216. The use of claim 212 or 213, wherein leukemia is acute lymphoblastic leukemia.~~

~~217. The use of claim 212 or 213, wherein the cancer is fibrosarcoma.~~

~~218. The method of claim 212 or 213, wherein the cancer is multiple myeloma.~~

~~219. The method of claim 212 or 213, wherein the cancer is lymphoma.~~

~~220. The method of claim 212 or 213, wherein the cancer is B-cell lymphoma.~~

~~221. The method of claim 212 or 213, wherein the cancer is T cell lymphoma.~~

~~222. The use of claim 209, wherein the disease is amyloidosis.~~

~~223. The method of claim 209, wherein the disease is light chain amyloidosis.~~

~~224. The use of any one of claims 209-223, wherein the one or more therapeutic agents is selected from the group consisting of an IMiD agent, a proteasome inhibitor, a steroid, an anti-CD38 agent, an anti-CD20 agent, a Bcl-2 inhibitor, a PI3K inhibitor, a Bi-specific antibody, a nucleoside analog, a BTK inhibitor, a DNA alkylating agent, an EZH2 inhibitor, an anthracycline, a topoisomerase inhibitor, a platin, a tyrosine kinase inhibitor, a HDAC inhibitor, a nuclear export inhibitor, an anti-microtubule agent, L-asparaginase, pegylated asparaginase, a PERK inhibitor, a mTOR inhibitor, an immunomodulatory agent, a MAPK pathway inhibitor, a MEK inhibitor, an ERK inhibitor, and a Ras inhibitor.~~

~~225. The use of any one of claims 209-223, wherein the one or more therapeutic agents is selected from the group consisting of L-asparaginase, pegaspargase, calaspargase pegol – mnkl, bortezomib, carfilzomib, ixazomib, thalidomide, pomalidomide, lenalidomide, dexamethasone, prednisone, daratumumab, daratumumab / hyaluronidase, isatuximab, rituximab, obinutuzumab, venetoclax, idelalisib, copanlisib, duvelisib, umbralisib, gemcitabine, cytarabine, ibrutinib, acalabrutinib, zanubrutinib, bendamustine, cyclophosphamide, tazemetostat, doxorubicin, daunorubicin, etoposide, oxaloplatin, carboplatin, cisplatinbosutinib, dasatinib, imatinib, nilotinib, ponatinib, panobinostat, selinexor, vincristine, JZP-458, eryaspase, PF745 (JZP-341), asparaginase *Erwinia chrysanthemi*~~

~~(crisantaspase), *Escherichia coli* asparaginase (colaspase), an anti-PD1 agent, an anti-PDL1 agent, and an anti-CTLA4 agent.~~