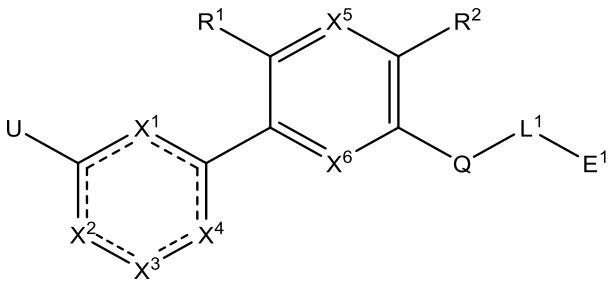
[00010] There is a need to identify RAF inhibitors that can inhibit multiple RAF isoforms. Particularly, there is a need to identify RAF inhibitors that can inhibit both BRAF and CRAF isoforms. Especially, there is a need to identify RAF inhibitors that can inhibit both RAF protomers present in signaling BRAF/BRAF homodimers and both protomers in BRAF/CRAF heterodimers. Such pan RAF inhibitors find utility in the treatment of BRAF V600X driven cancers, atypical BRAF mutated cancers, BRAF fusion cancers, CRAF fusion cancers, and RAS mutant cancers.

SUMMARY

[00010a] In a first 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:

each of X^1 and X^4 is independently selected from CR^3 and N;

X^2 is selected from the group consisting of N, CH, C=O, C-O-L^2-E^2, C-L^2-E^2, C-N(R^4)-L^2-E^2, and N-L^2-E^2;

X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, C-N(R^4)-L^3-E^3, C=O, N, and N-L^3-E^3;

provided that not more than two of X^1, X^2, X^3, and X^4 are N;

when X^2 is N, X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, C-N(R^4)-L^3-E^3, and N;

when X^3 is N, X^2 is selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^4)-L^2-E^2;

when X^2 is C=O, X^3 is N-L^3-E^3;

when X^3 is C=O, X^2 is N-L^2-E^2;

X^5 is independently selected from the group consisting of CH, CF, and N;

X^6 is independently selected from the group consisting of CH, and CF;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

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

L^3 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{31})_p$;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

E^1 is selected from the group consisting of H, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl, and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen,

hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

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

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is 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;

or wherein two occurrences of E^{21} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of hydroxy, alkoxy, alkoxylalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone,

optionally substituted heteroaryl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, alkoxyalkyl, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

U is an optionally substituted heteroaryl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, H, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, and optionally substituted heterocyclyl$(CH_2)_m$NH-; wherein the optionally substituted heterocyclyl or heterocyclyl$(CH_2)_m$NH-, at each occurrence, is independently optionally substituted with one or more occurrences of R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, haloalkoxy, cyano, and halogen;

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

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

R^4, at each occurrence, is independently selected from H and alkyl;

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

each occurrence of p is independently 0, 1, or 2; and

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

with the proviso that

when X^1 and X^2 are N, each of X^5 and X^6 is independently selected from CH and CF, X^4 is CR^3, R^3 is selected from H and alkyl, X^3 is C-L^3-E^3, and L^3 is a direct bond, E^3 is not morpholinyl; or

when X^1 and X^4 are N, each of X^5 and X^6 is independently selected from CH, and CF, X^2 is C-L^2-E^2, L^2 is a direct bond, E^2 is selected from H and alkyl, X^3 is C-L^3-E^3, and L^3 is a direct bond, E^3 is not morpholinyl; or

when X^2 is selected from C-O-L^2-E^2 and C-N(R^4)-L^2-E^2, R^4 is H, and each L^2 is a direct bond, each E^2 is not a 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O, and S; or

when X^3 is selected from C-O-L^3-E^3 and C-N(R^4)-L^3-E^3, R^4 is H, and each L^3 is a direct bond, each E^3 is not a 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O, and S; or

when L^1 is direct bond, then E^1 is not N-bound heterocyclyl;

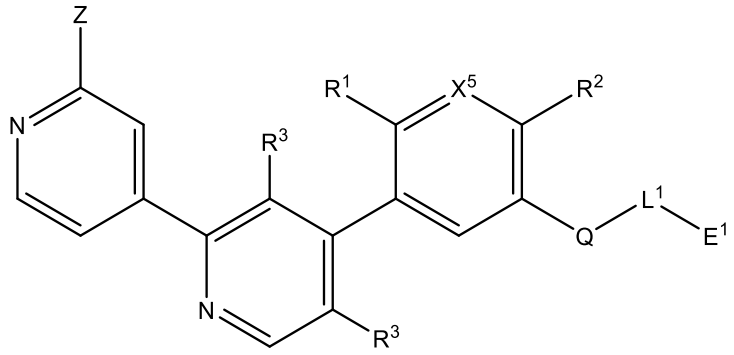
when X^6 is CH, X^5 is CH or CF, X^4 is CR^3, X^3 is N, Q is -C(O)NH-, L^1 is direct bond, and E^1 is selected from the group consisting of C_3-C_8 cycloalkyl, C_2-C_8 heterocyclyl, C_6-C_{14} aryl, and C_1-C_9 heteroaryl, X^2 is not C-N(R^4)-L^2-E^2; or

when Q is -C(O)-NH- and L^1 is direct bond, E^1 is not H; or

when Q is -NH-C(O)-, L^1-E^1 is not unsubstituted methyl; or

when X^3 is N, X^1 is CH or N, X^4 is CH, X^5 and X^6 are CH, X^2 is CH or C-NH_2, and Q is -C(O)-NH-, then L^1-E^1 is not alkyl substituted with amine.

[00010b] In another aspect of the present disclosure, there is provided a compound represented by Formula I-AA:



Formula I-AA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of

alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted

heterocyclyl, optionally substituted heterocyclyl$(CH_2)_mNH$-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

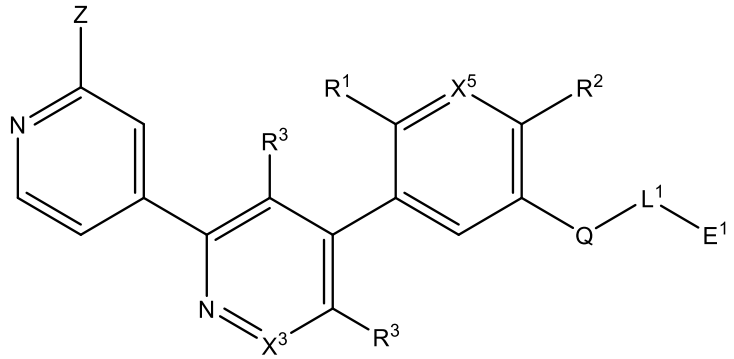
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010c] In yet another aspect of the present disclosure, there is provided a compound represented by Formula I-AB:



Formula I-AB

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

X^3 is selected from the group consisting of C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3;

X^5 is selected from the group consisting of N, CH, and CF;

L^3 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{31})_p$;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl,

haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of hydroxy, alkoxy, alkoxylalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted monocyclic heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, alkoxyalkyl, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted

heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

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

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

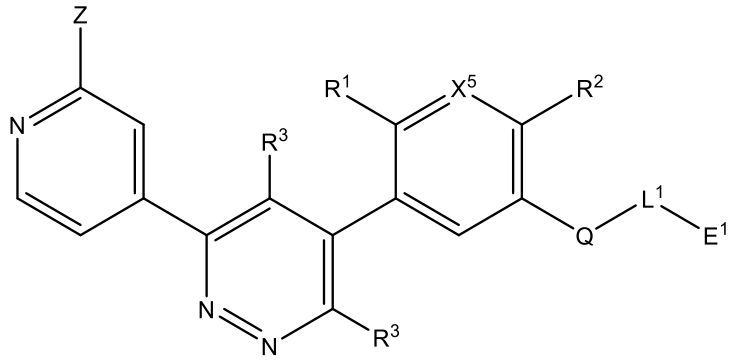
R^4, at each occurrence, is independently selected from H and alkyl;

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

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

[00010d] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-AC:



Formula I-AC

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, sulfone, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

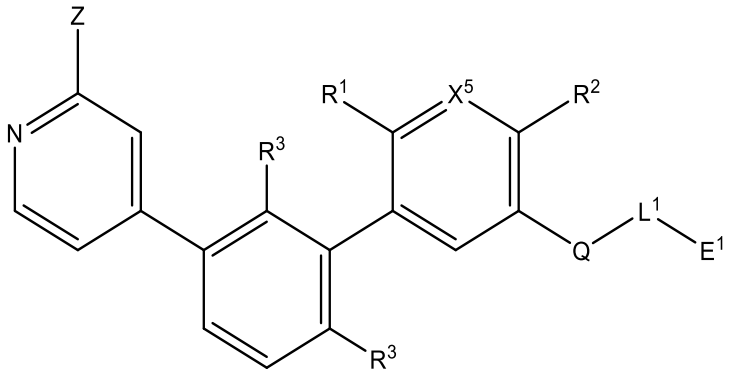
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of is selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010e] In another aspect of the present disclosure, there is provided a compound represented by Formula I-BA:



Formula I-BA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

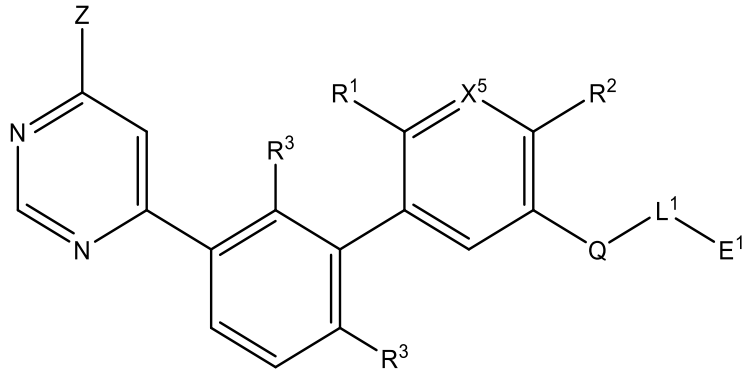
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010f] In yet another aspect of the present disclosure, there is provided a compound represented by Formula I-CA:



Formula I-CA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

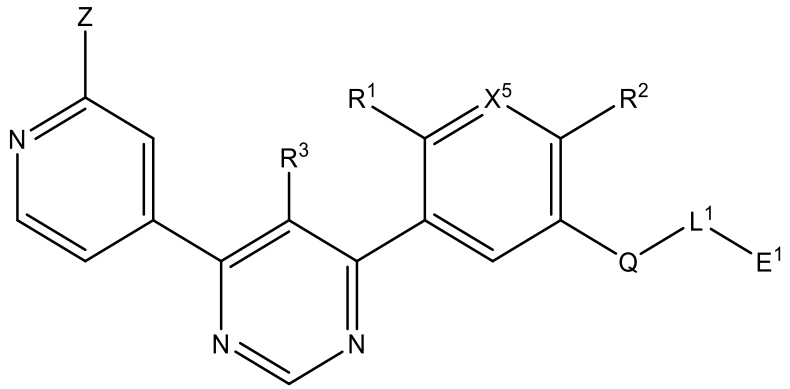
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of is selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010g] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-DA:



Formula I-DA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

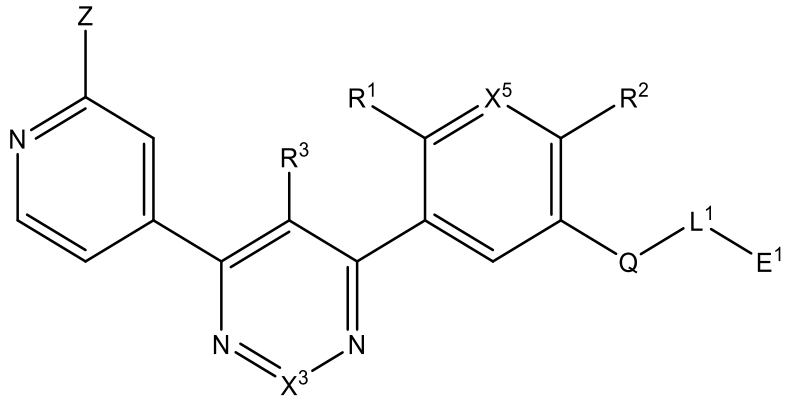
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010h] In another aspect of the present disclosure, there is provided a compound represented by Formula I-DB:



Formula I-DB

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

X^3 is selected from the group consisting of C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3;

X^5 is selected from the group consisting of N, CH, and CF;

L^3 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{31})_p$;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of hydroxy, alkoxy, alkoxylalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted monocyclic heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, alkoxyalkyl, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

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

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

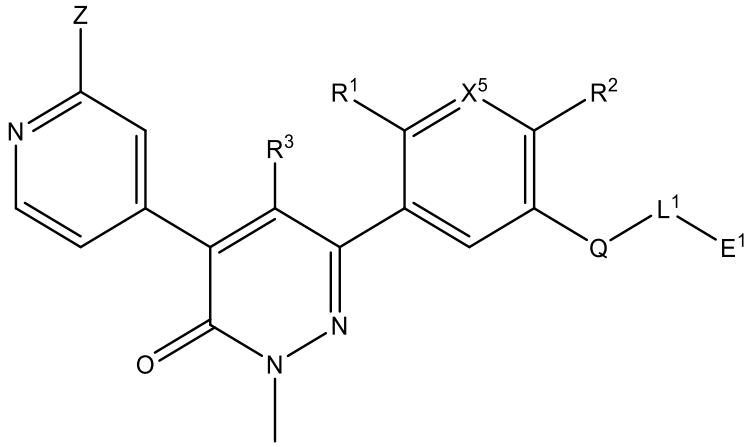
R^4, at each occurrence, is independently selected from H and alkyl;

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

each p is independently 0, 1 or 2; and

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

[00010i] In yet another aspect of the present disclosure, there is provided a compound represented by Formula I-EA:



Formula I-EA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_mNH$-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

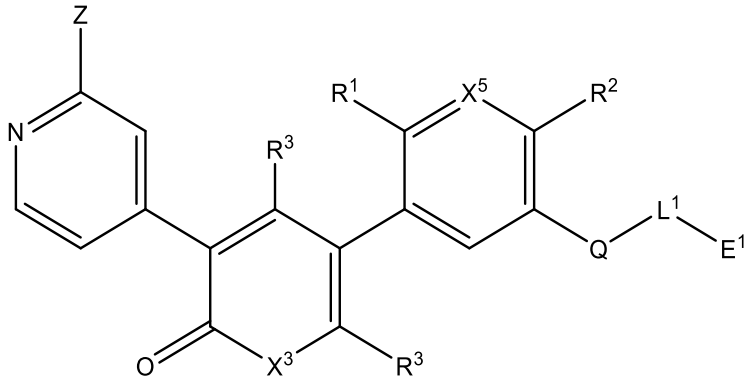
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010j] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-EB:



Formula I-EB

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

X^3 is N-L^3-E^3;

X^5 is selected from the group consisting of N, CH, and CF;

L^3 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{31})_p$;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of hydroxy, alkoxy, alkoxylalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, alkoxyalkyl, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

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

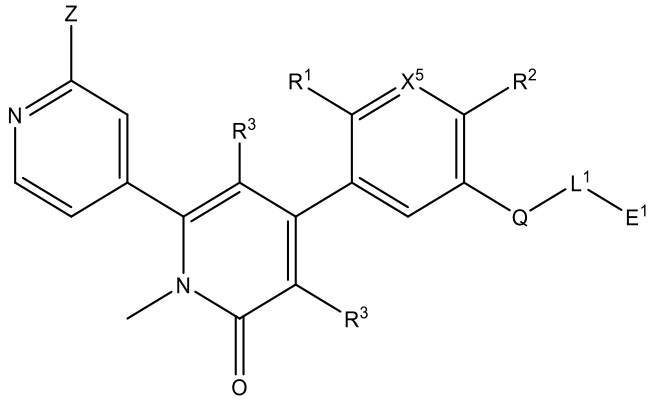
R^3, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

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

[00010k] In another aspect of the present disclosure, there is provided a compound represented by Formula I-FA:



Formula I-FA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

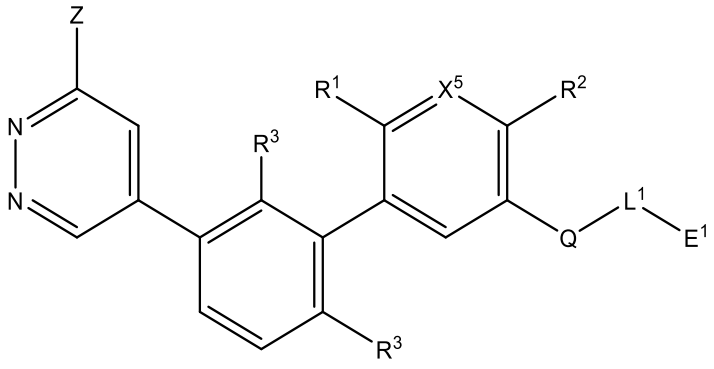
R^2 is selected from the group consisting of H and F;

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

R^9 is selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010l] In yet another aspect of the present disclosure, there is provided a compound represented by Formula I-GA:



Formula I-GA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

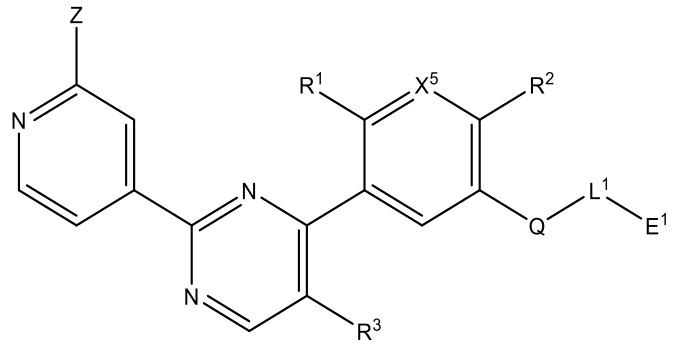
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010m] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-HA:



Formula I-HA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

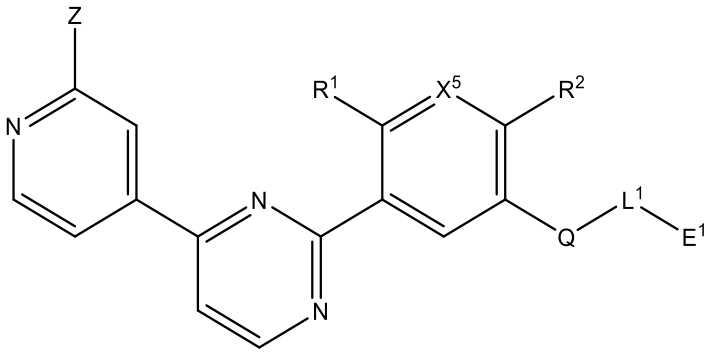
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010n] In another aspect of the present disclosure, there is provided a compound represented by Formula I-JA:



Formula I-JA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

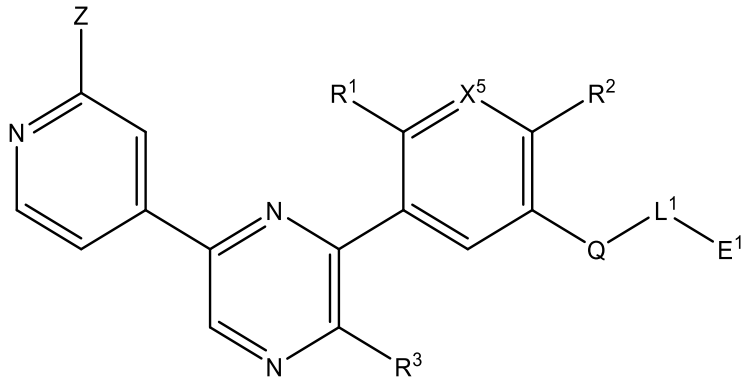
R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010o] In yet another aspect of the present disclosure, there is provided a compound represented by Formula I-KA:



Formula I-KA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent

selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted

heterocyclyl, optionally substituted heterocyclyl$(CH_2)_mNH$-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

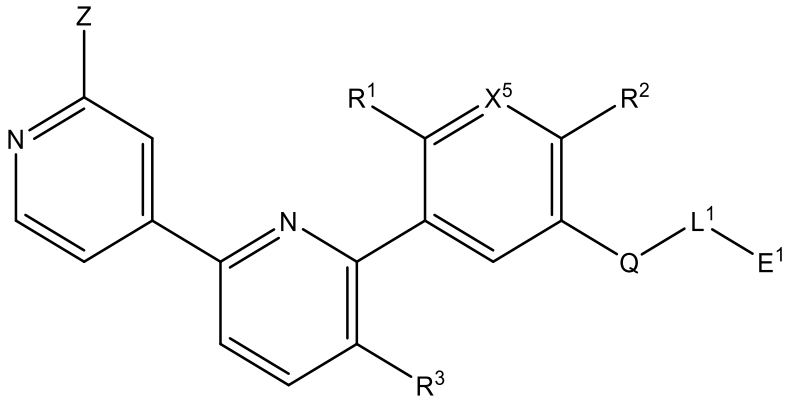
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010p] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-LA:



Formula I-LA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of

alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

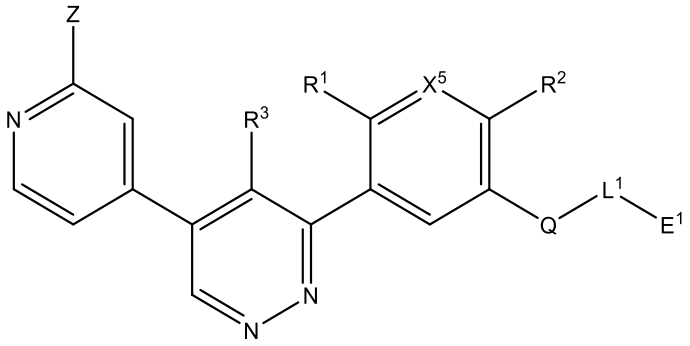
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010q] In another aspect of the present disclosure, there is provided a compound represented by Formula I-NA:



Formula I-NA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of

alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted

heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

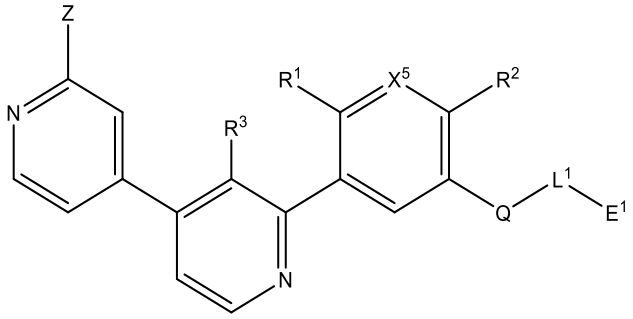
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010r] In yet another aspect of the present disclosure, there is provided a compound represented by Formula I-OA:



Formula I-OA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen,

hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

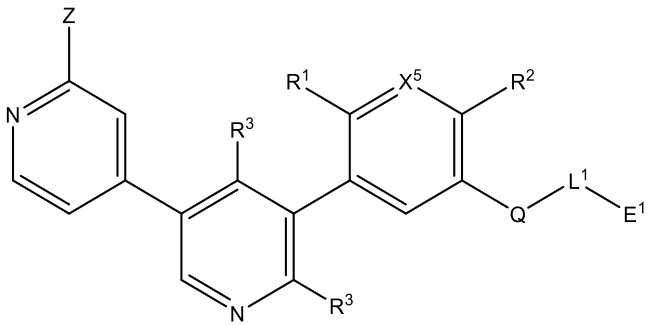
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010s] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-PA:



Formula I-PA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

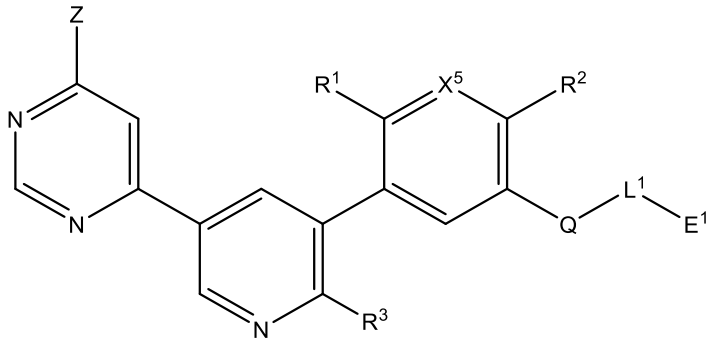
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010t] In another aspect of the present disclosure, there is provided a compound represented by Formula I-QA:



Formula I-Q

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

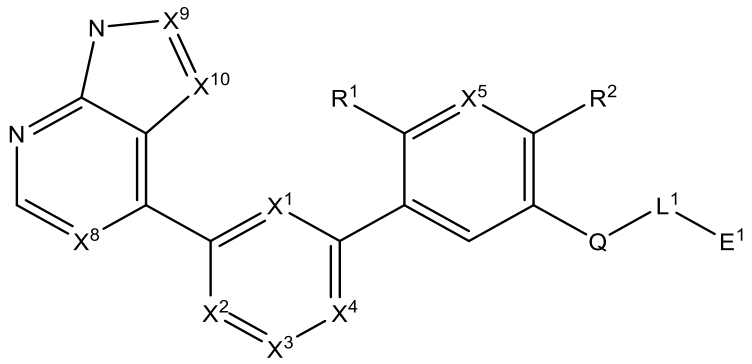
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

[00010u] In yet another aspect of the present disclosure, there is provided a compound represented by Formula I-RA:



Formula I-RA

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

each of X^1 and X^4 is independently selected from CR^3 and N;

each of X^2 and X^3 is independently selected from the group consisting of N and CH;

provided that not more than two of X^1, X^2, X^3, and X^4 are N;

each of X^8, X^9, and X^{10} is independently selected from CR^3 and N;

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

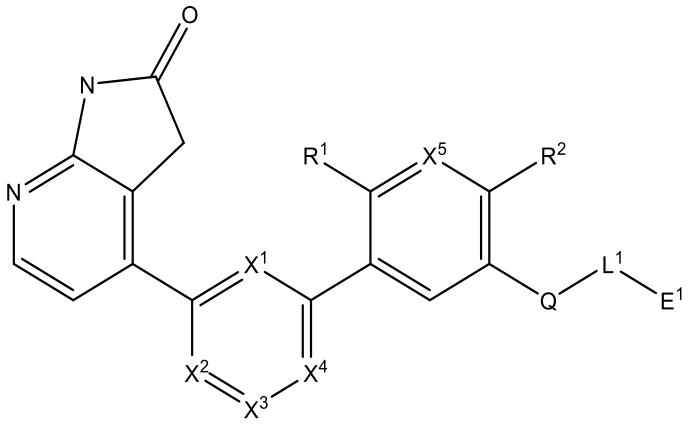
R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

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

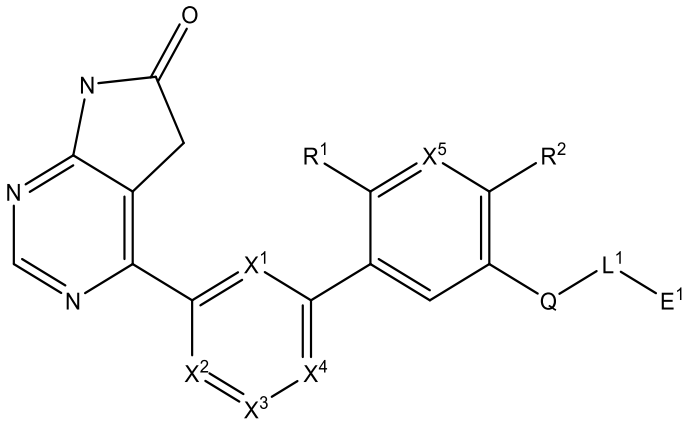
R^3, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen; and

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

[00010v] In a further aspect of the present disclosure, there is provided a compound represented by Formula I-SA-i or Formula I-SA-ii:



Formula I-SA-i



Formula I-SA-ii

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

each of X^1 and X^4 is independently selected from CR^3 and N;

X^2 and X^3 are each independently selected from the group consisting of N and CH;

provided that not more than two of X^1, X^2, X^3, and X^4 are N;

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

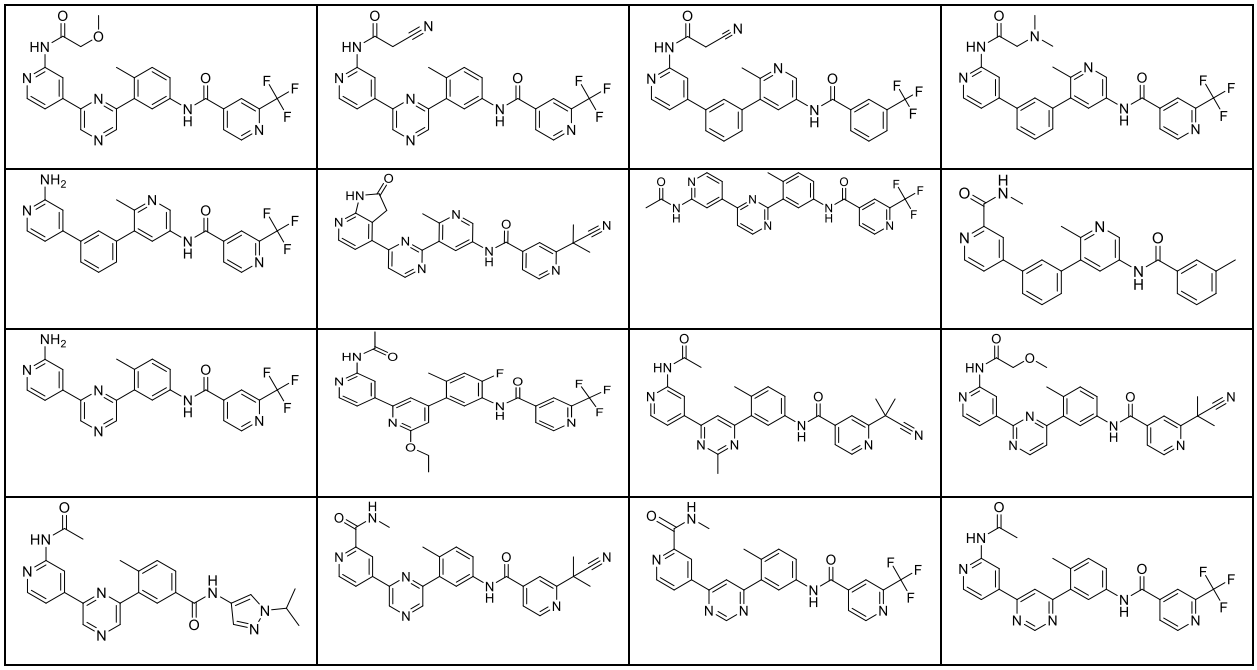
R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

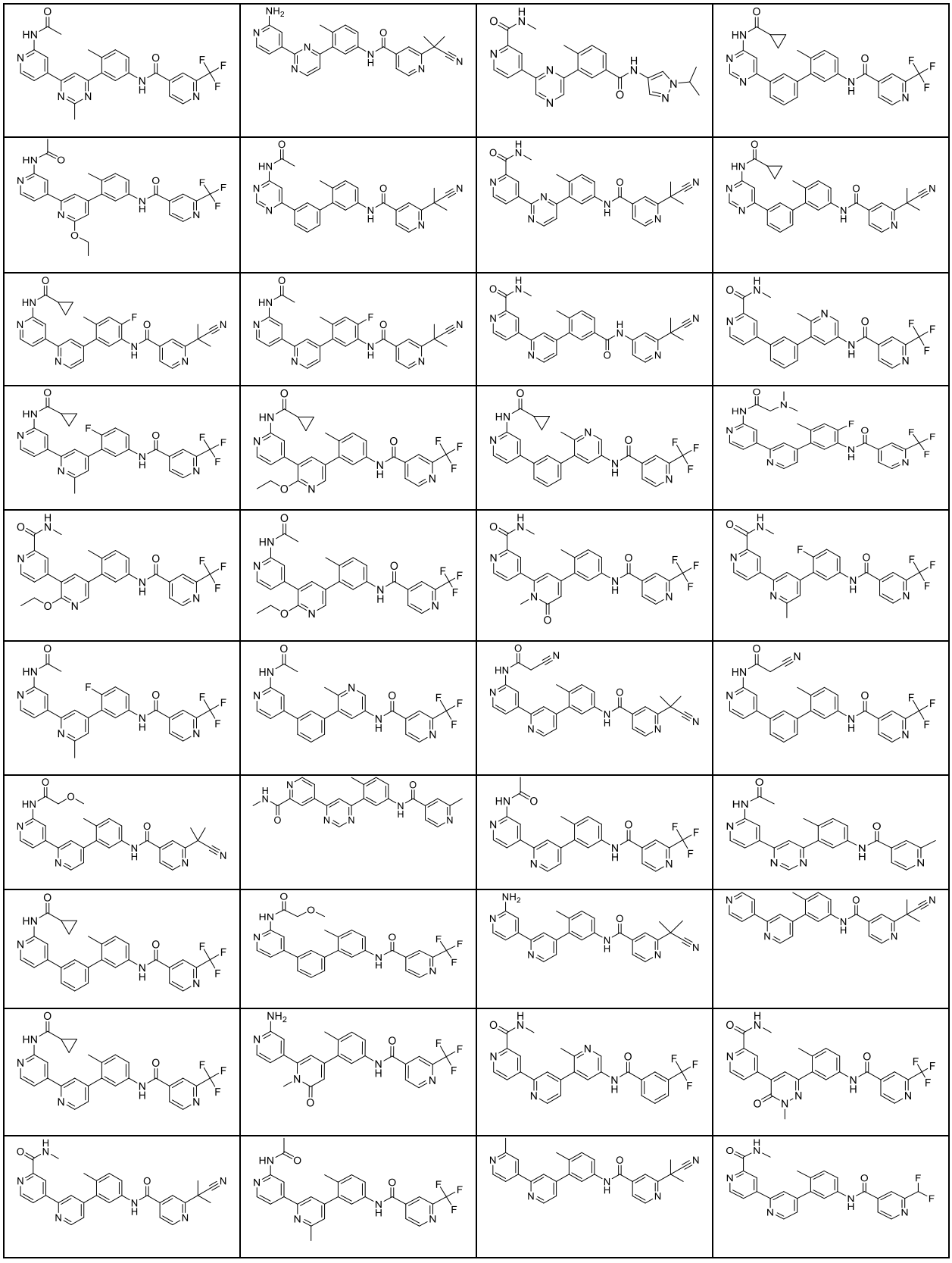
R^2 is selected from the group consisting of H and F;

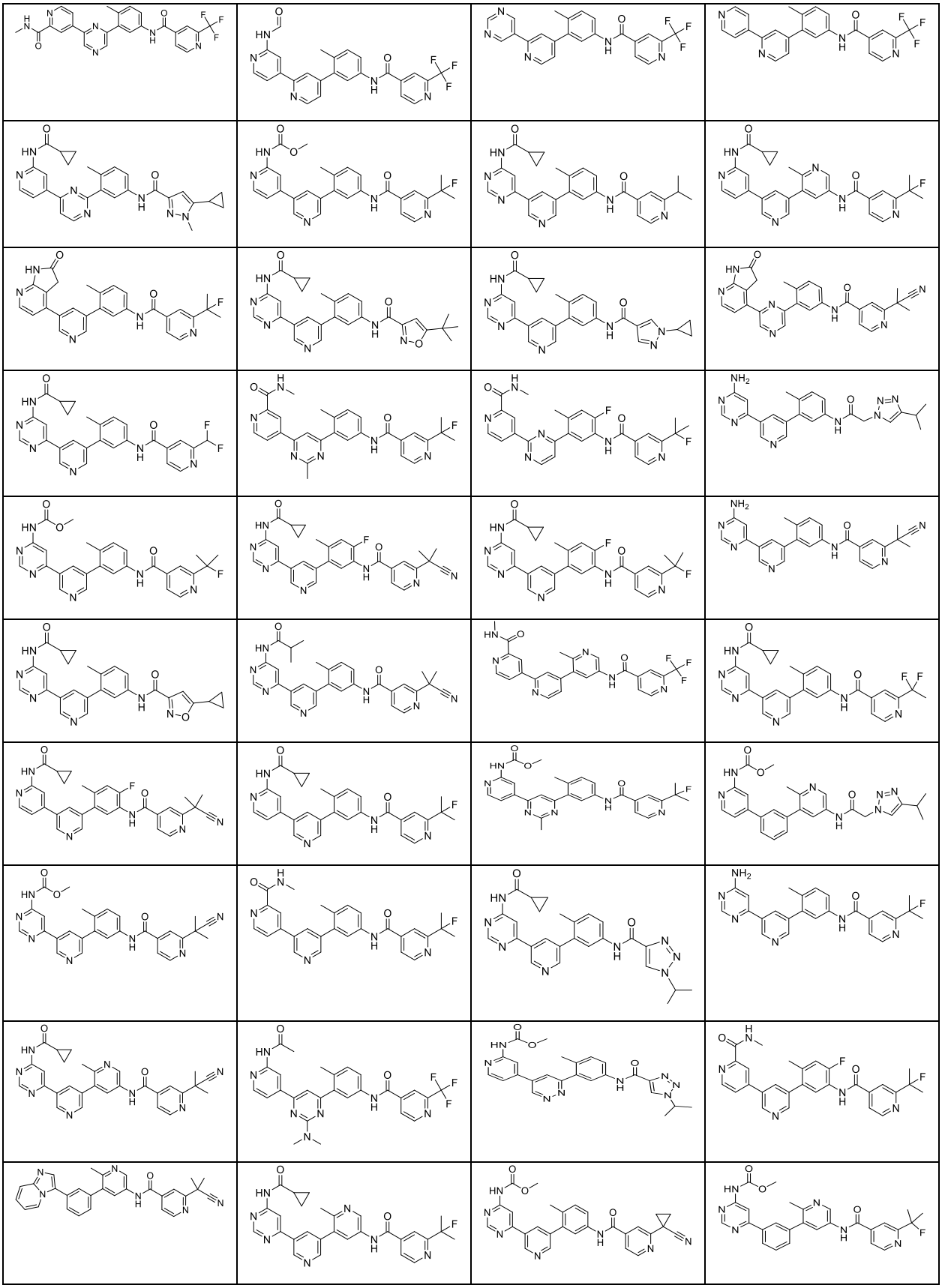
R^3, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen; and

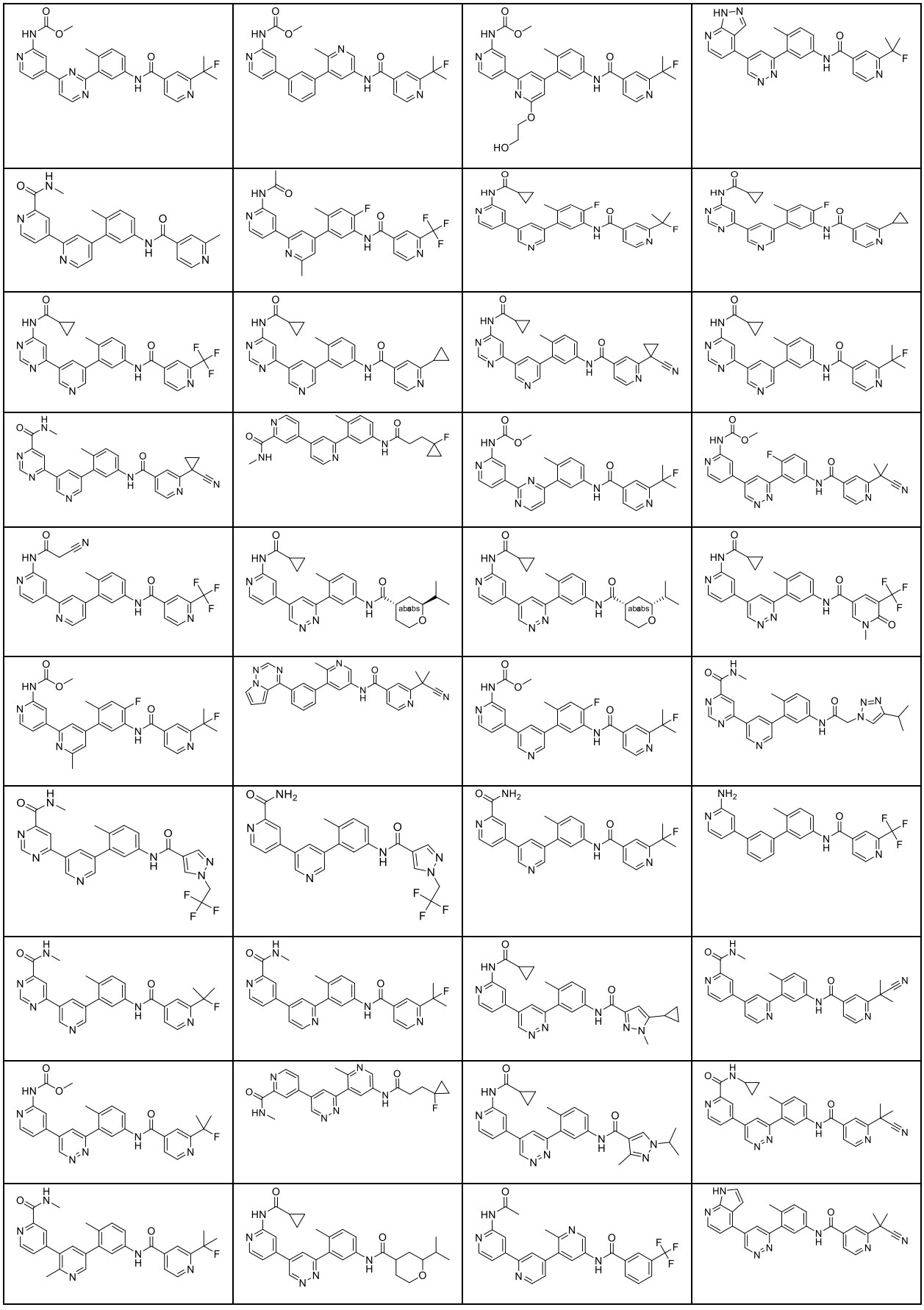
each m is independently 0, 1, 2, 3, or 4.

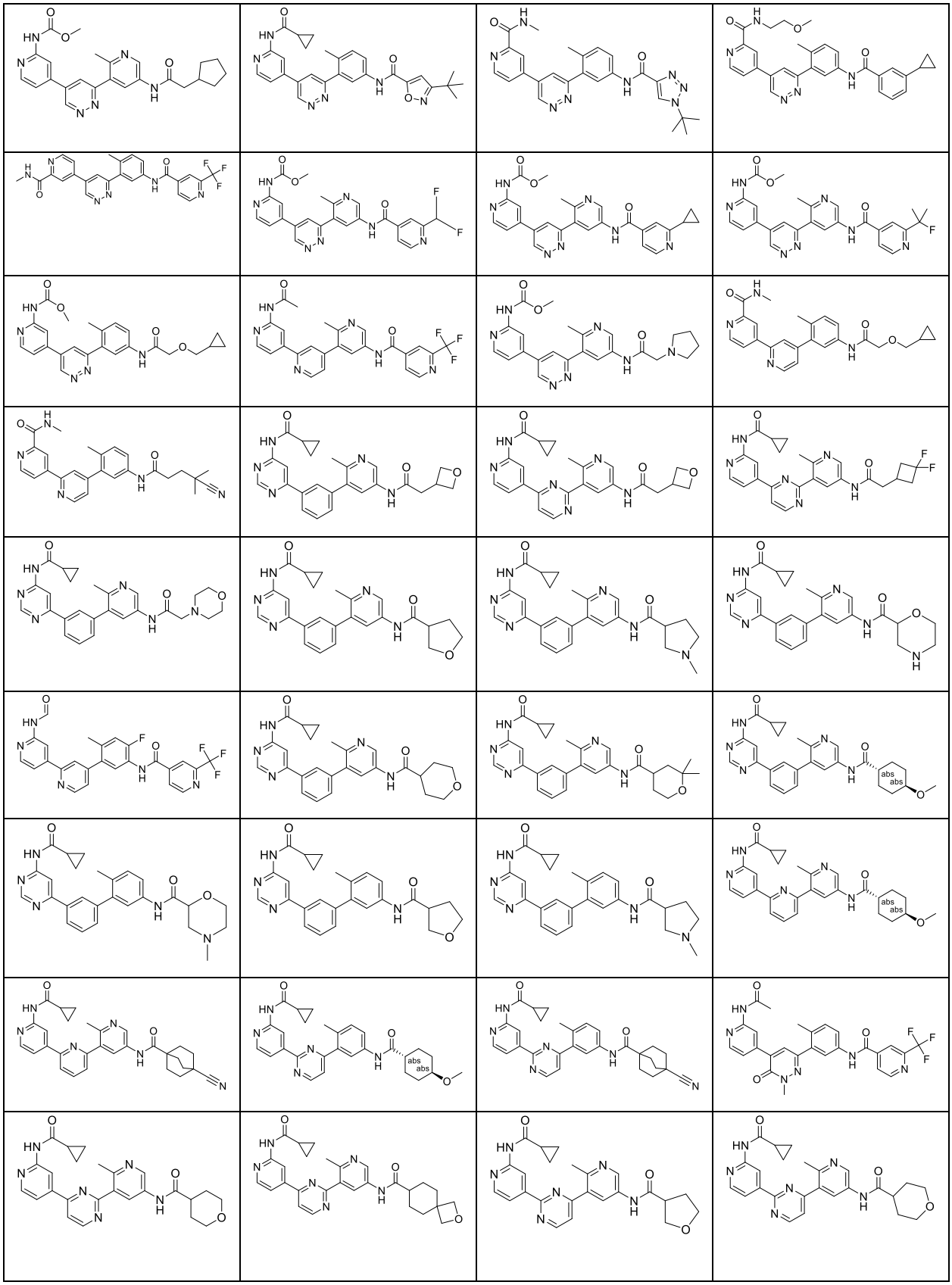
[00010w] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of:

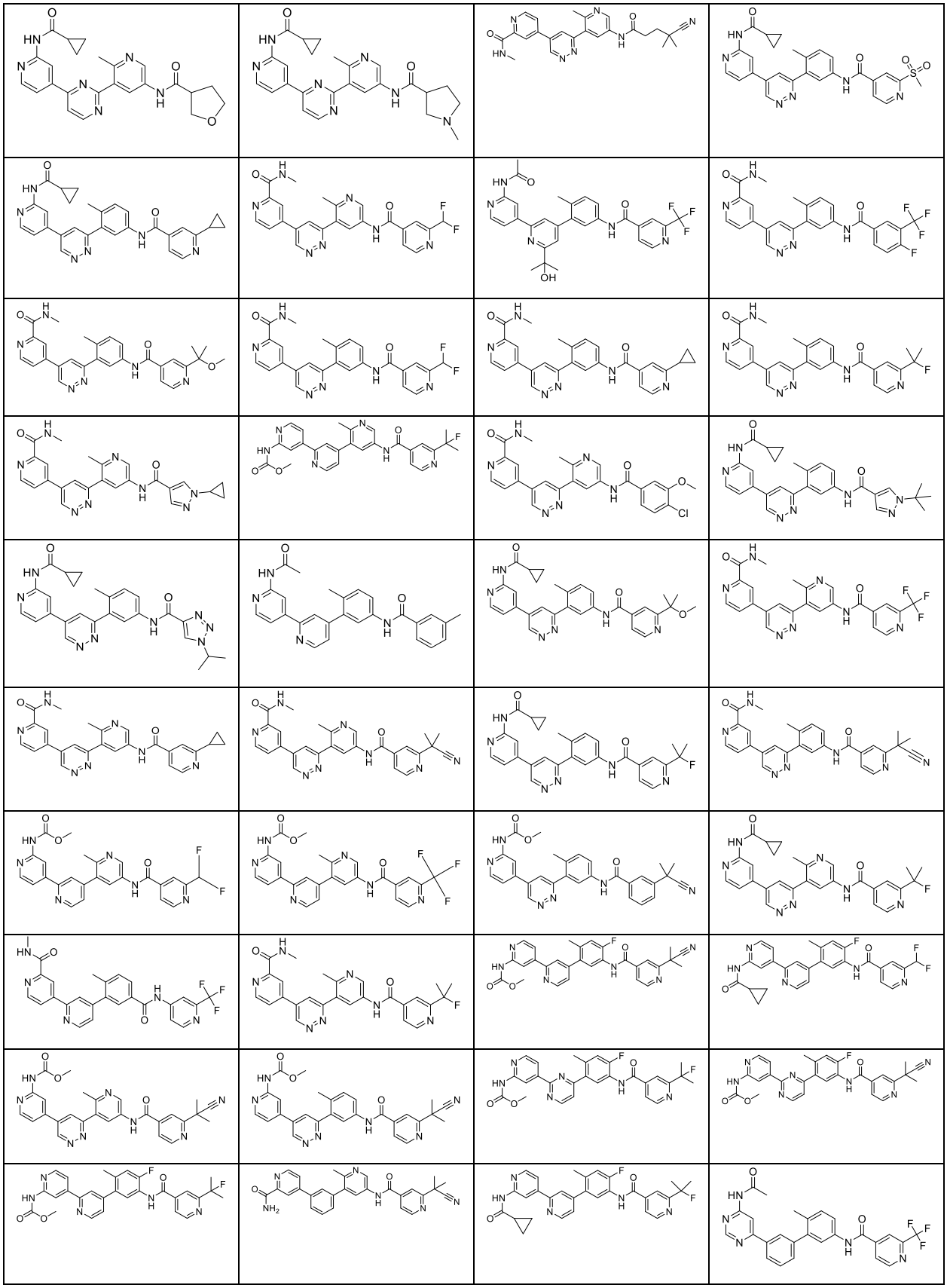


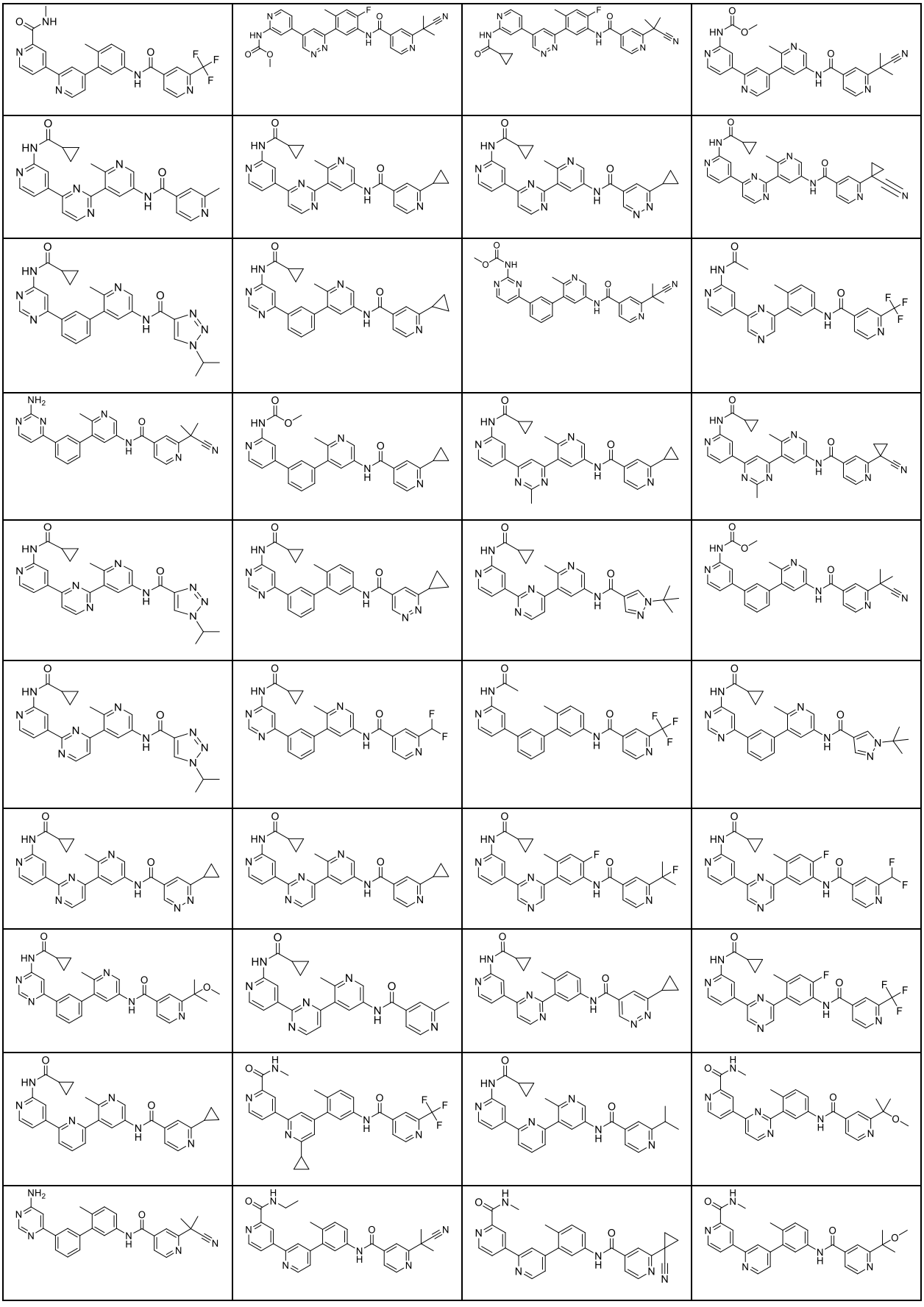


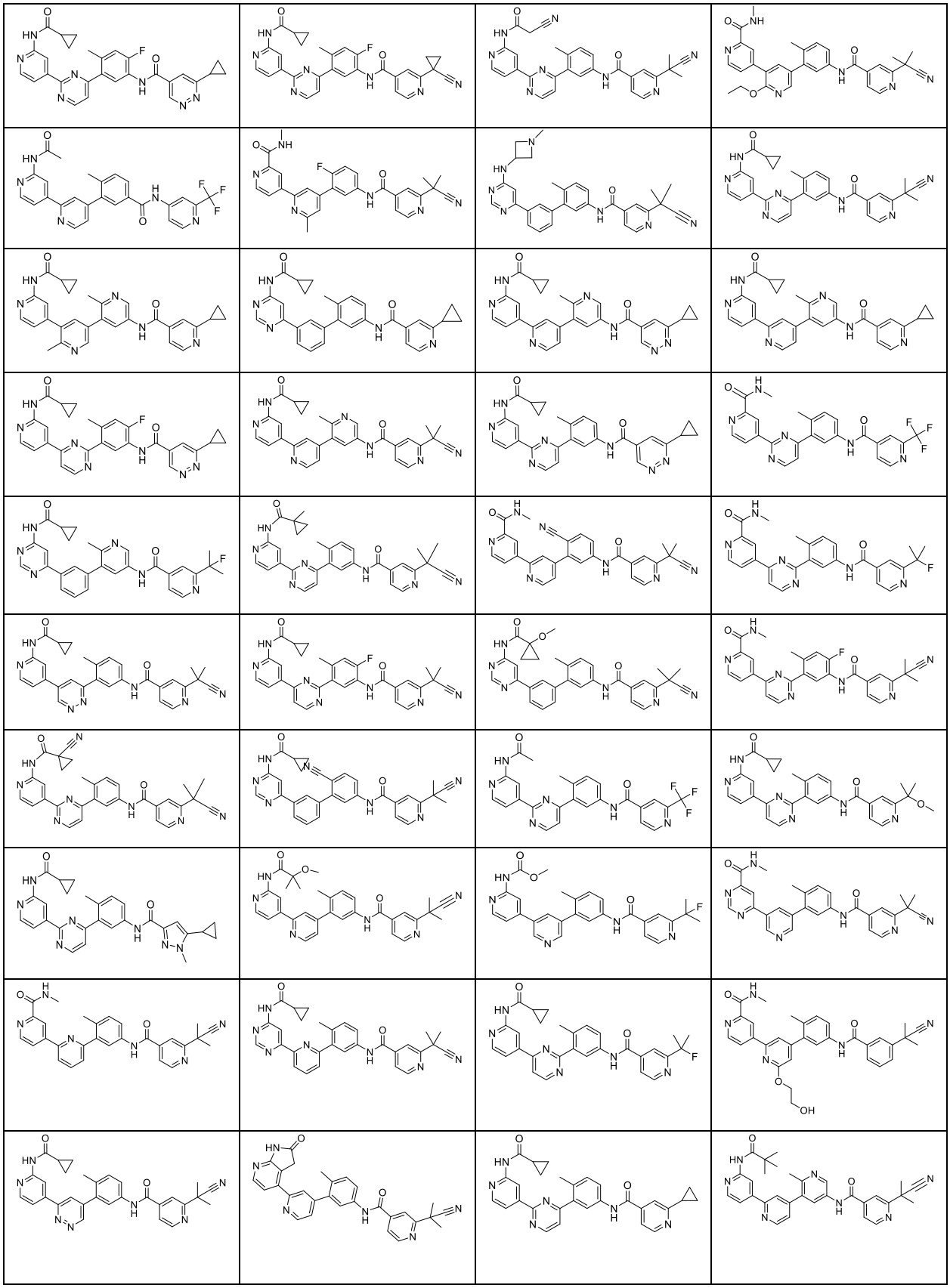


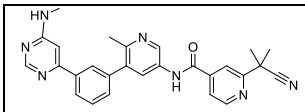
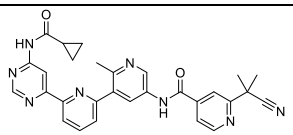
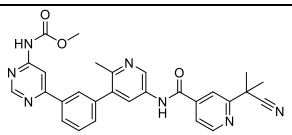
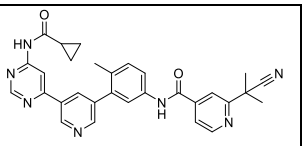
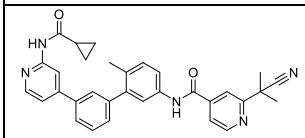
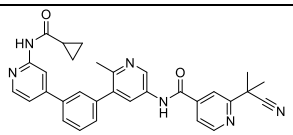
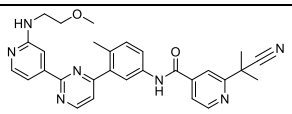
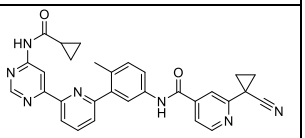
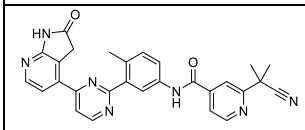
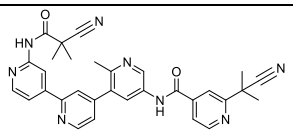
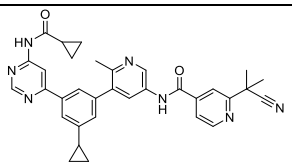
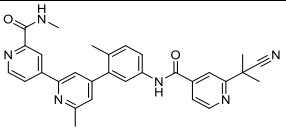
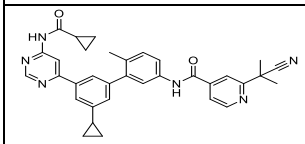
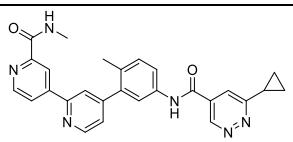
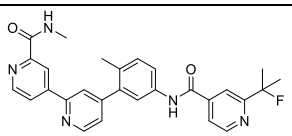
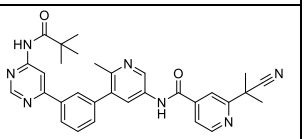
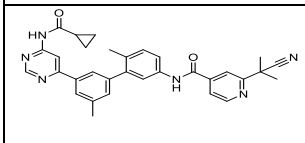
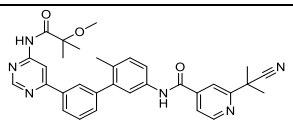
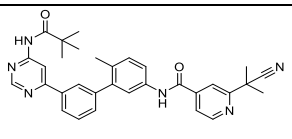
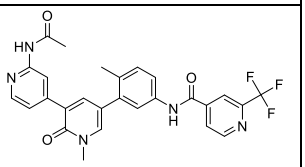
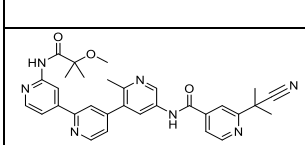
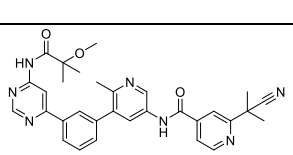
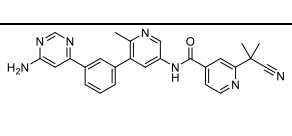
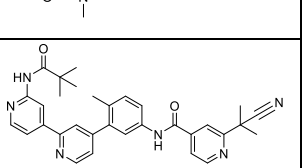
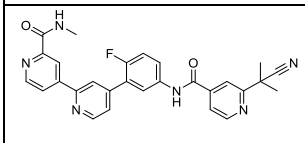
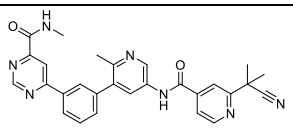
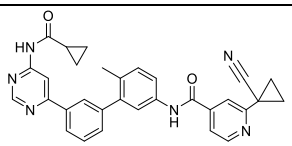
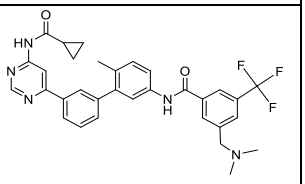
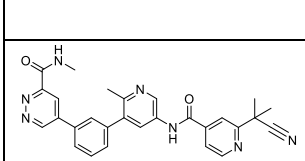
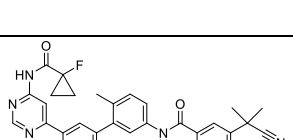
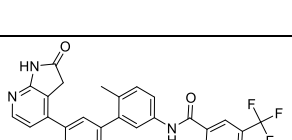
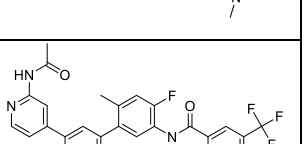
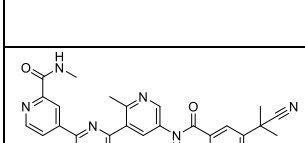
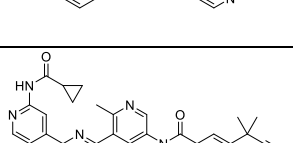
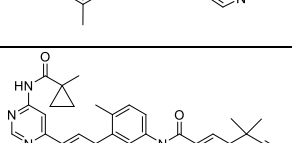
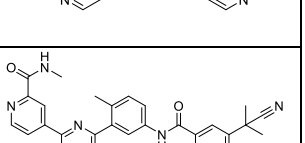


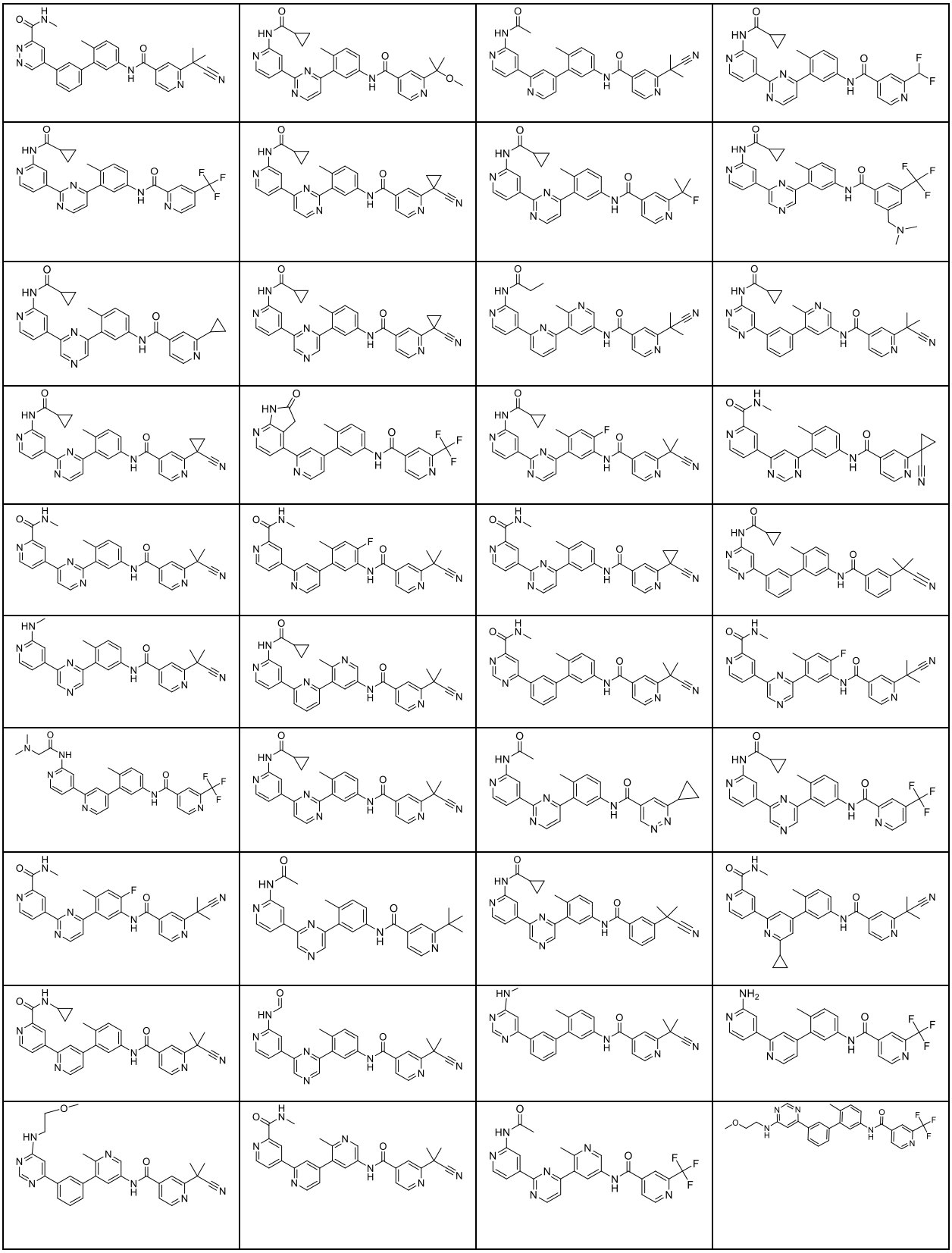


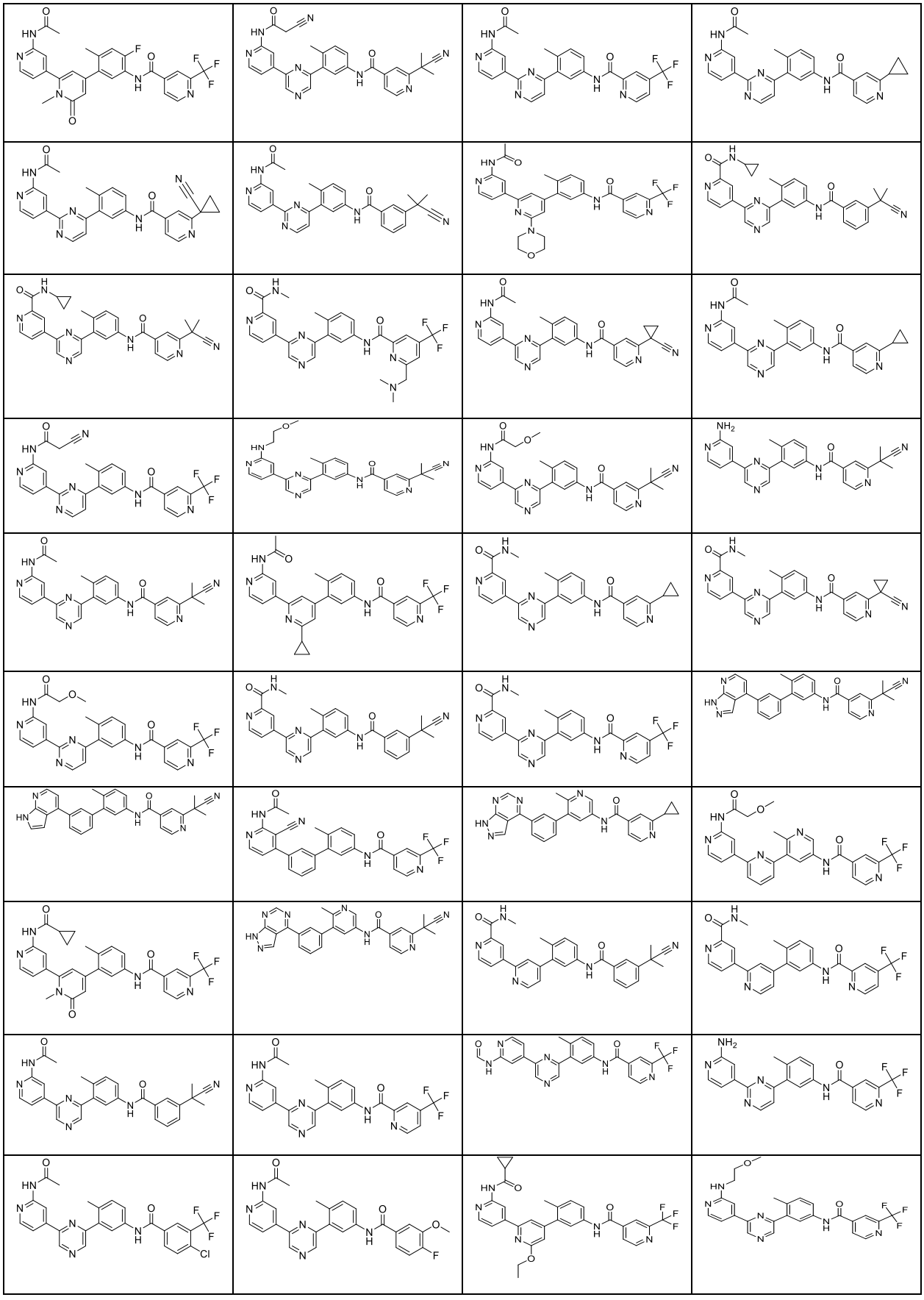


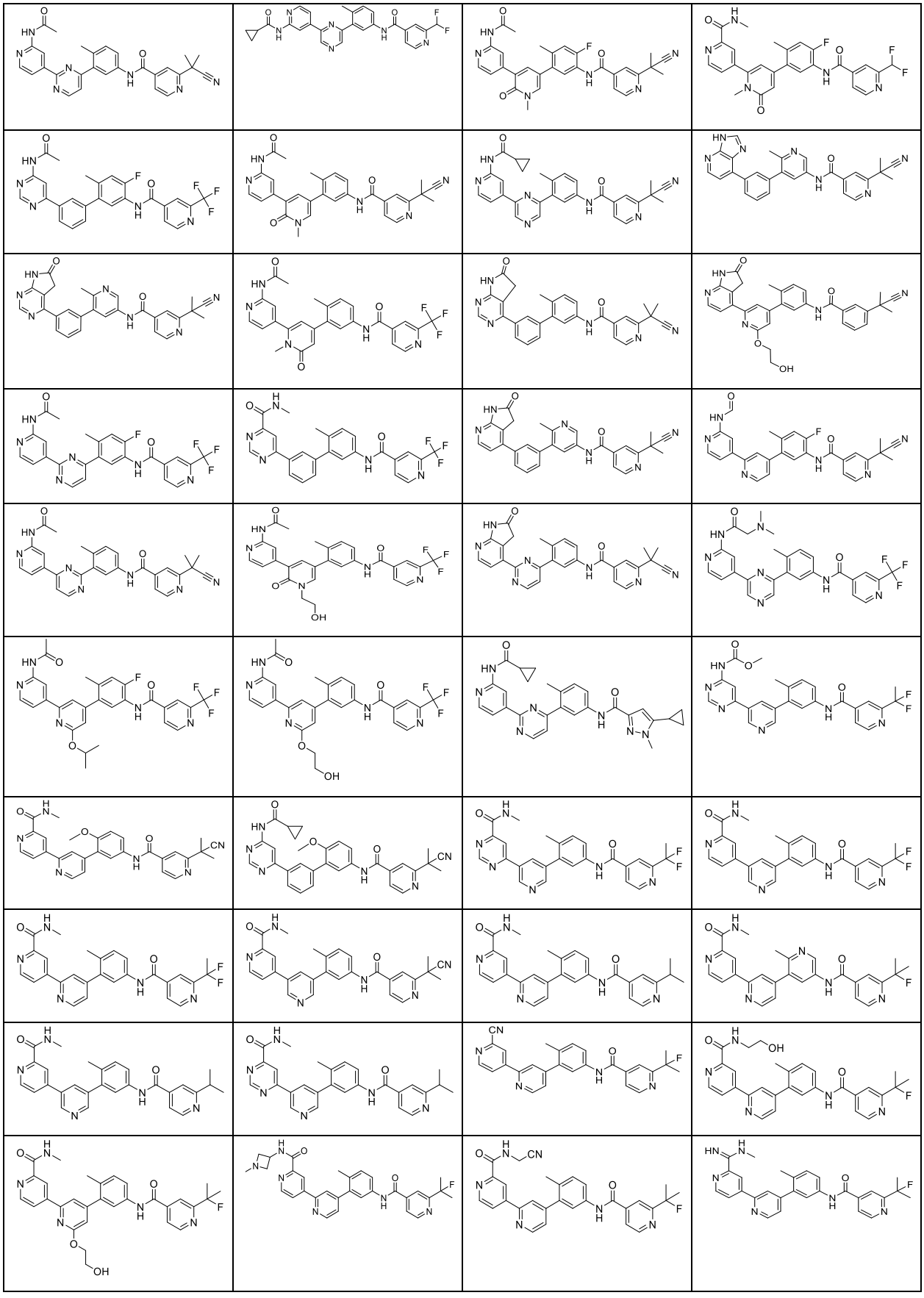


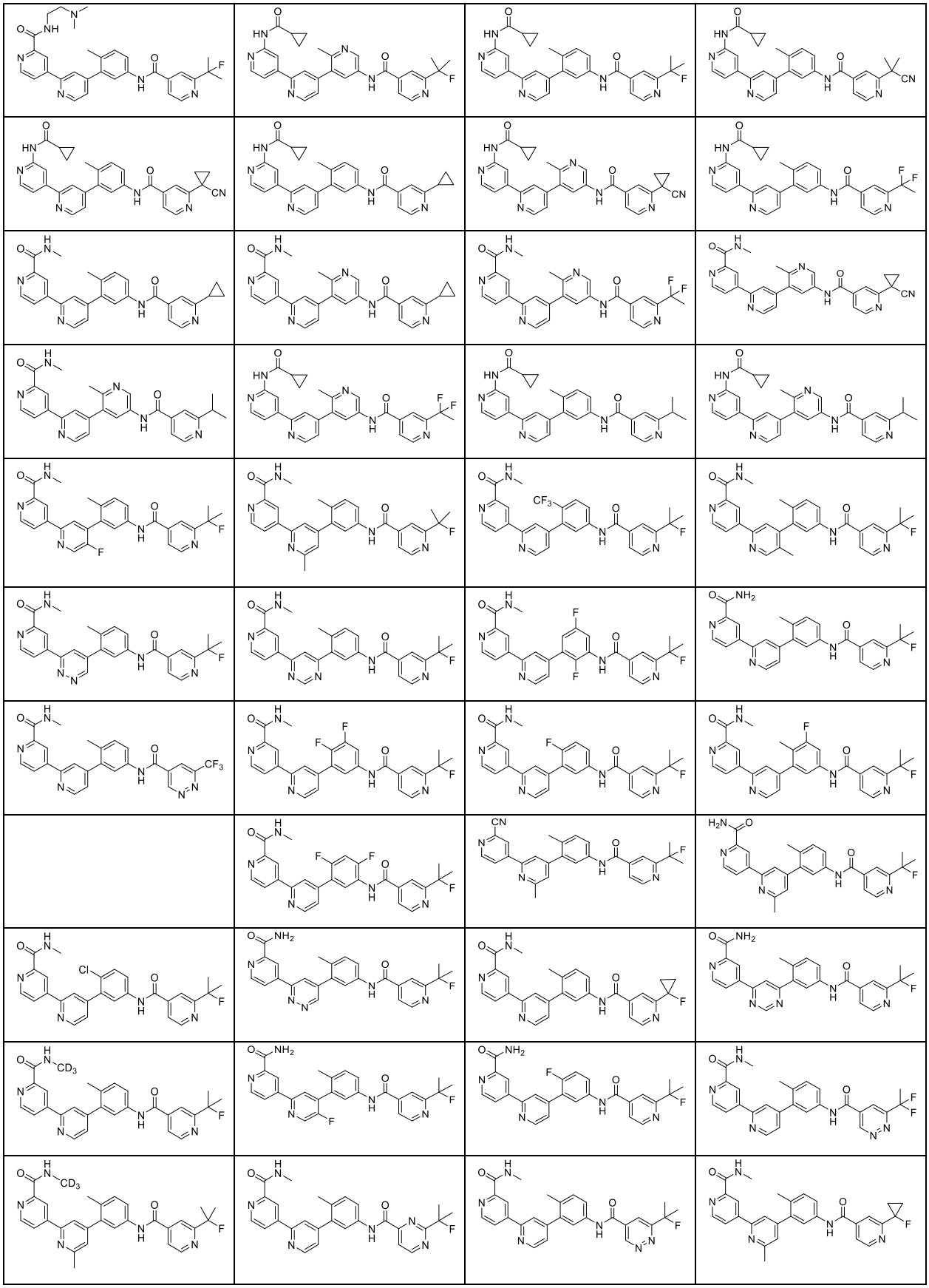


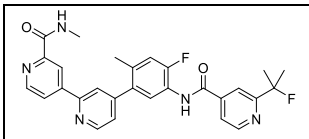
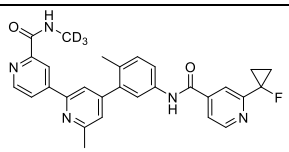
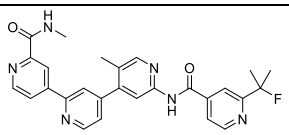
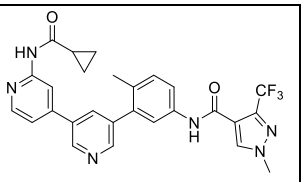
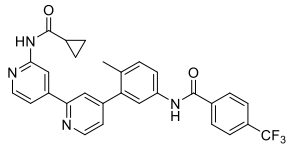
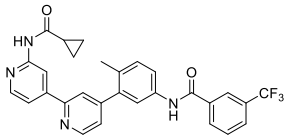
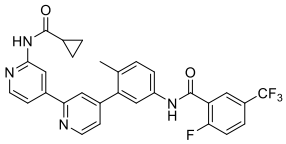
			
			
			
			
			
			
			
			
			









and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

[00010x] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

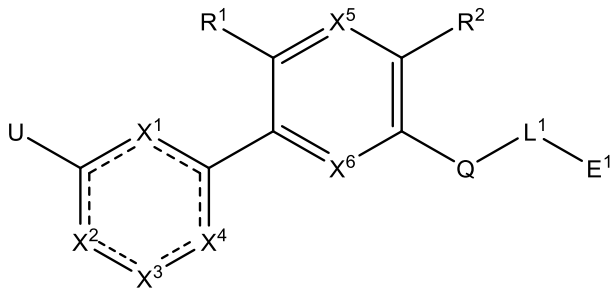
[00010y] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or of a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a cancer in a patient in need thereof.

[00010z] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or of a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a disorder selected from the group consisting of melanoma, multiple myeloma, thyroid cancer, ovarian cancer, colorectal cancer, colon cancer, pancreatic cancer, lung cancer, bladder cancer, gastrointestinal stromal tumors, solid tumors, brain cancers, gliomas, glioblastomas, astrocytomas, blood-borne cancers, hairy cell leukemia, acute myelogenous leukemia (AML), other cancers caused by activation of the RAS→RAF→MEK→ ERK signaling pathway in a patient in need thereof.

[00010aa] In yet another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutical composition disclosed herein, for use in therapy.

[00011] Described herein, are compounds that are RAF inhibitors. and methods of use thereof. In some examples, the compounds are BRAF or CRAF inhibitors. In some examples, the compounds are useful for the treatment of cancers driven by oncogenic forms of RAS or BRAF. In some examples, the compounds inhibit both BRAF and CRAF isoforms. In some other examples, the compounds inhibit both RAF protomers present in signaling BRAF/BRAF homodimers and both protomers present in signaling BRAF/CRAF heterodimers. In some other examples, the compounds inhibit ARAF, BRAF, and CRAF present in signaling homodimers or heterodimers.

[00012] In an example, the present disclosure provides a compound represented by Formula I:



Formula I

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

each of X^1 and X^4 is independently selected from CR^3 and N;

X^2 is selected from the group consisting of N, CH, C=O, C-O-L^2-E^2, C-L^2-E^2, C-N(R^4)-L^2-E^2, and N-L^2-E^2;

X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, C-N(R^4)-L^3-E^3, C=O, N, and N-L^3-E^3;

provided that not more than two of X^1, X^2, X^3, and X^4 are N;

[00013] In another example, described herein is a pharmaceutical composition comprising a compound described herein (e.g., a compound of the disclosure as described herein) and a pharmaceutically acceptable carrier or excipient.

[00014] In another example, 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 the disclosure as described herein).

[00015] In another example, described herein is a method of treating a disorder selected from the group consisting of histiocytosis, melanoma, multiple myeloma, thyroid cancer, ovarian cancer, colorectal cancer, colon cancer, pancreatic cancer, lung cancer, bladder cancer, gastrointestinal stromal tumors, solid tumors, brain cancers, gliomas, glioblastomas, astrocytomas, blood-borne cancers, hairy cell leukemia, acute myelogenous leukemia (AML), and other cancers caused by activation of the RAS→RAF→MEK→ERK 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 the disclosure as described herein).

DETAILED DESCRIPTION

[00016] The features and other details of the disclosure will now be more particularly described. Certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

Definitions

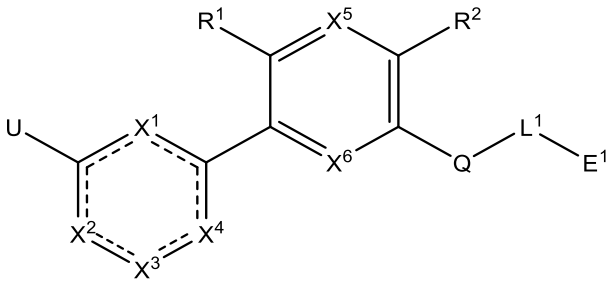
[00017] The definitions set forth in this application are intended to clarify terms used throughout this application.

[00018] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the subject matter herein belongs. As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated in order to facilitate the understanding of the present disclosure.

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:

each of X^1 and X^4 is independently selected from CR^3 and N;

X^2 is selected from the group consisting of N, CH, C=O, C-O-L^2-E^2, C-L^2-E^2, C-N(R^4)-L^2-E^2, and N-L^2-E^2;

X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, C-N(R^4)-L^3-E^3, C=O, N, and N-L^3-E^3;

provided that not more than two of X^1, X^2, X^3, and X^4 are N;

when X^2 is N, X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, C-N(R^4)-L^3-E^3, and N;

when X^3 is N, X^2 is selected from the group consisting of N, CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^4)-L^2-E^2;

when X^2 is C=O, X^3 is N-L^3-E^3;

when X^3 is C=O, X^2 is N-L^2-E^2;

X^5 is independently selected from the group consisting of CH, CF, and N;

X^6 is independently selected from the group consisting of CH, and CF;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

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

L^3 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{31})_p$;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

E^1 is selected from the group consisting of H, alkoxy, cyano, haloalkoxy, halogen,

optionally substituted alkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl, and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

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

optionally substituted heterocyclyl wherein the optionally substituted substituent, at each occurrence, is 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;

or wherein two occurrences of E^{21} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of hydroxy, alkoxy, alkoxylalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone,

optionally substituted heteroaryl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, cyano, cyanoalkyl, and heterocyclyl, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, alkoxyalkyl, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

U is an optionally substituted heteroaryl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, H, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, and optionally substituted heterocyclyl$(CH_2)_m$NH-; wherein the optionally substituted heterocyclyl or heterocyclyl$(CH_2)_m$NH-, at each occurrence, is independently optionally substituted with one or more occurrences of R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, haloalkoxy, cyano, and halogen;

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

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

R^4, at each occurrence, is independently selected from H and alkyl;

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

each occurrence of p is independently 0, 1, or 2; and

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

with the proviso that

when X^1 and X^2 are N, each of X^5 and X^6 is independently selected from CH and CF, X^4 is CR^3, R^3 is selected from H and alkyl, X^3 is C-L^3-E^3, and L^3 is a direct bond, E^3 is not morpholinyl; or

when X^1 and X^4 are N, each of X^5 and X^6 is independently selected from CH, and CF, X^2 is C-L^2-E^2, L^2 is a direct bond, E^2 is selected from H and alkyl, X^3 is C-L^3-E^3, and L^3 is a direct bond, E^3 is not morpholinyl; or

when X^2 is selected from C-O-L^2-E^2 and C-N(R^4)-L^2-E^2, R^4 is H, and each L^2 is a direct bond, each E^2 is not a 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O, and S; or

when X^3 is selected from C-O-L^3-E^3 and C-N(R^4)-L^3-E^3, R^4 is H, and each L^3 is a direct bond, each E^3 is not a 6-, 7-, 8-, 9-, 10- or 11-membered bicyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O, and S; or

when L^1 is direct bond, then E^1 is not N-bound heterocyclyl;

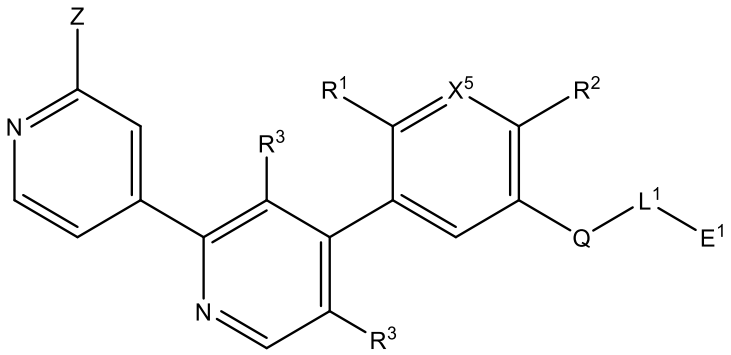
when X^6 is CH, X^5 is CH or CF, X^4 is CR^3, X^3 is N, Q is -C(O)NH-, L^1 is direct bond, and E^1 is selected from the group consisting of C_3-C_8 cycloalkyl, C_2-C_8 heterocyclyl, C_6-C_{14} aryl, and C_1-C_9 heteroaryl, X^2 is not C-N(R^4)-L^2-E^2; or

when Q is -C(O)-NH- and L^1 is direct bond, E^1 is not H; or

when Q is -NH-C(O)-, L^1-E^1 is not unsubstituted methyl; or

when X^3 is N, X^1 is CH or N, X^4 is CH, X^5 and X^6 are CH, X^2 is CH or C-NH_2, and Q is -C(O)-NH-, then L^1-E^1 is not alkyl substituted with amine.

2. A compound represented by Formula I-AA:



Formula I-AA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl,

haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally

substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

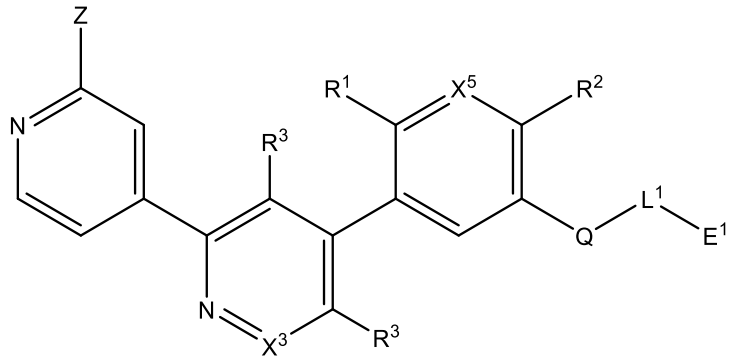
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

3. A compound represented by Formula I-AB:



Formula I-AB

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

X^3 is selected from the group consisting of C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3;

X^5 is selected from the group consisting of N, CH, and CF;

L^3 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{31})_p$;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of hydroxy, alkoxy, alkoxylalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted monocyclic heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, alkoxyalkyl, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally

substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

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

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

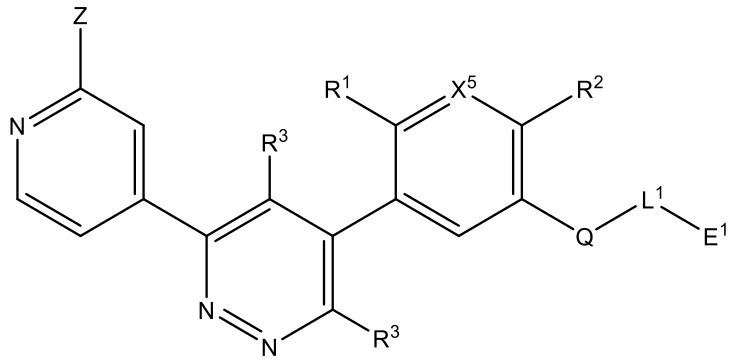
R^4, at each occurrence, is independently selected from H and alkyl;

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

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

4. A compound represented by Formula I-AC:



Formula I-AC

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, sulfone, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of

alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

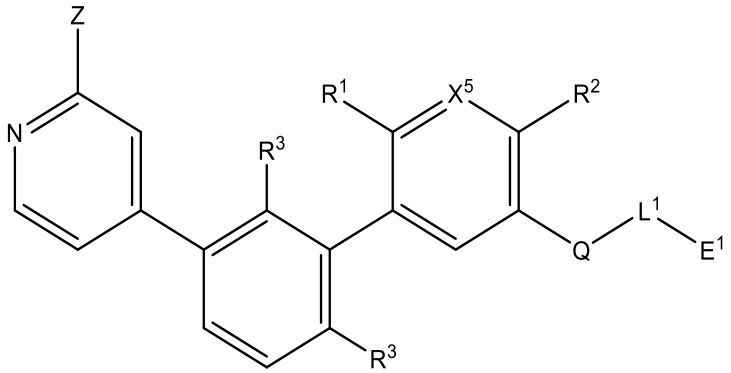
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

5. A compound represented by Formula I-BA:



Formula I-BA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl,

haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally

substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

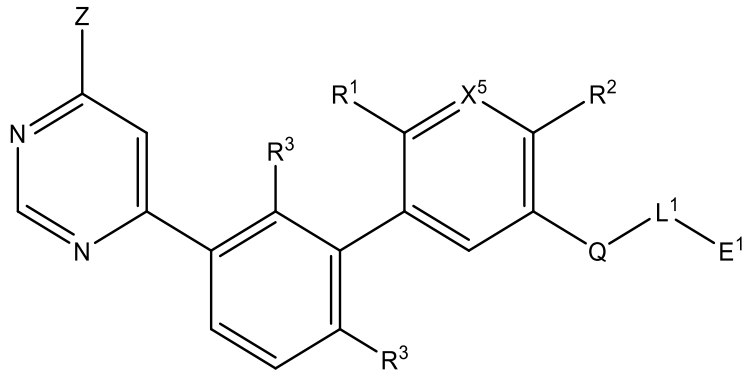
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

6. A compound represented by Formula I-CA:



Formula I-CA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl,

alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

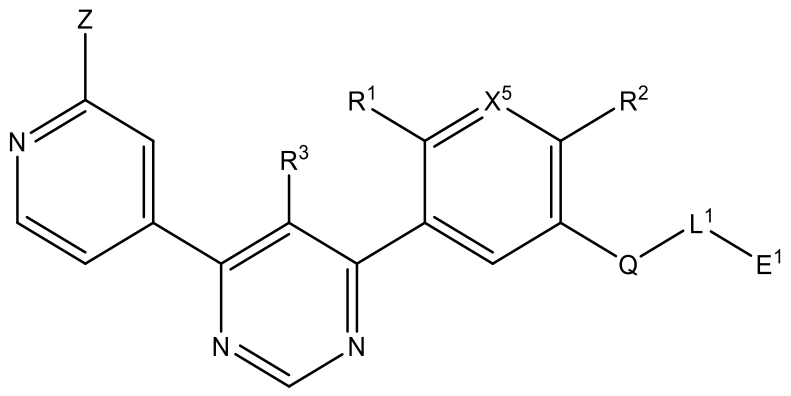
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of is selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

7. A compound represented by Formula I-DA:



Formula I-DA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_mNH$-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

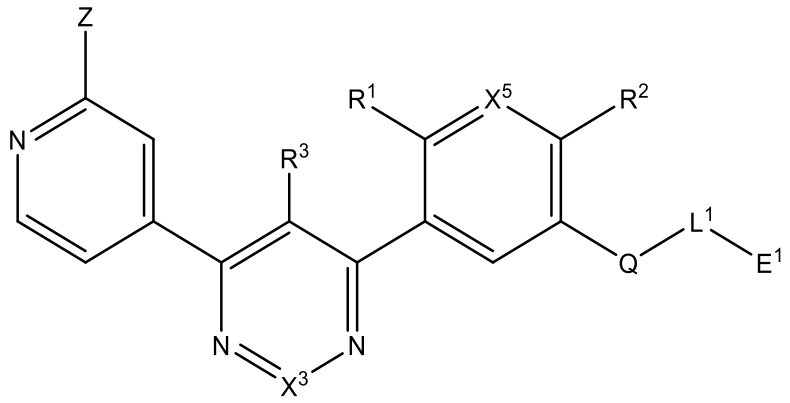
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

8. A compound represented by Formula I-DB:



Formula I-DB

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

X^3 is selected from the group consisting of C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3;

X^5 is selected from the group consisting of N, CH, and CF;

L^3 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{31})_p$;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of

alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of hydroxy, alkoxy, alkoxylalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted monocyclic heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, alkoxyalkyl, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

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

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

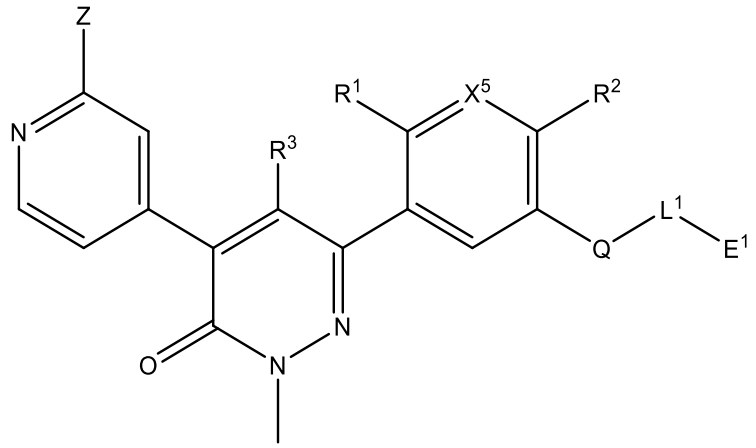
R^4, at each occurrence, is independently selected from H and alkyl;

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

each p is independently 0, 1 or 2; and

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

9. A compound represented by Formula I-EA:



Formula I-EA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of

alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

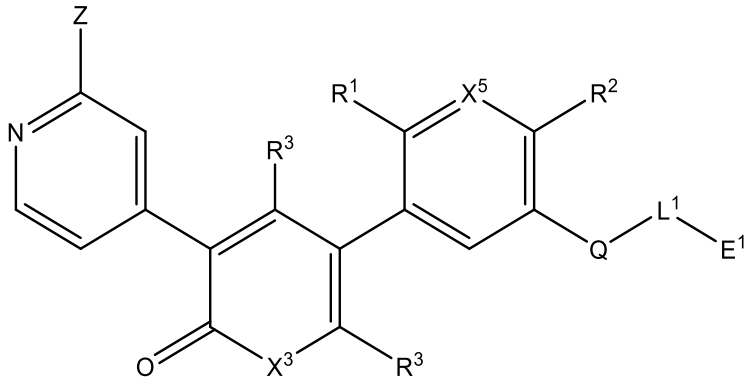
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

10. A compound represented by Formula I-EB:



Formula I-EB

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

X^3 is N-L^3-E^3;

X^5 is selected from the group consisting of N, CH, and CF;

L^3 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{31})_p$;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

E^3 is selected from the group consisting of hydroxy, alkoxy, alkoxylalkyl, cyano, sulfonyl, haloalkoxy, H, alkyl, acyl, amine, aminoalkyl, amide, haloalkyl, cyano, sulfone,

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, or sulfone, and

optionally substituted cycloalkyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano;

E^{31}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, alkoxyalkyl, cyano, cyanoalkyl, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{31} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

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

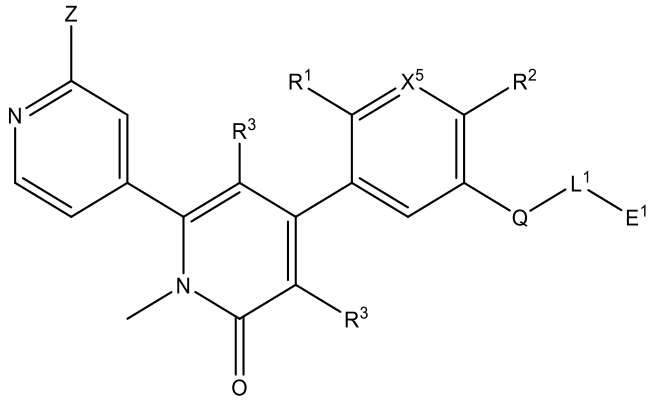
R^3, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen;

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl;

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

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

11. A compound represented by Formula I-FA:



Formula I-FA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

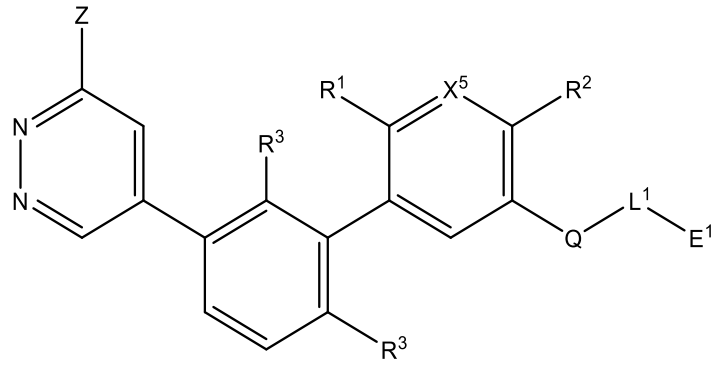
R^2 is selected from the group consisting of H and F;

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

R^9 is selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

12. A compound represented by Formula I-GA:



Formula I-GA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

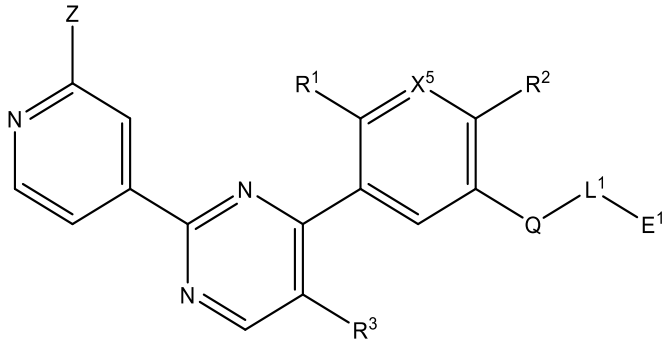
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

13. A compound represented by Formula I-HA:



Formula I-HA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl,

haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally

substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

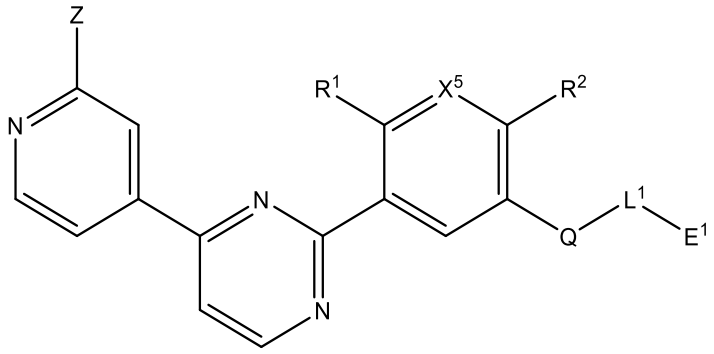
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

14. A compound represented by Formula I-JA:



Formula I-JA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl,

alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

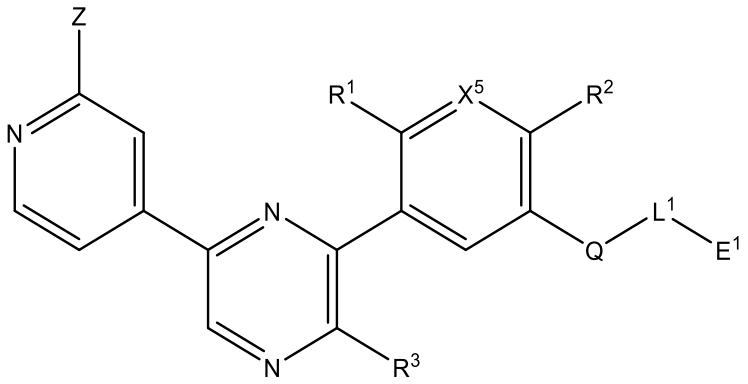
R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

15. A compound represented by Formula I-KA:



Formula I-KA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

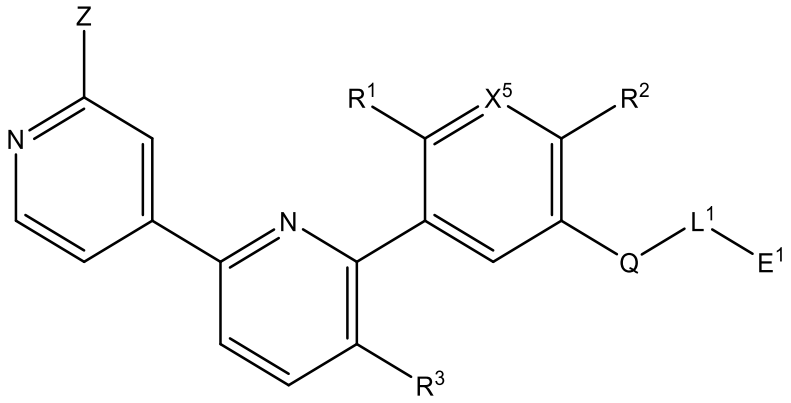
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

16. A compound represented by Formula I-LA:



Formula I-LA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

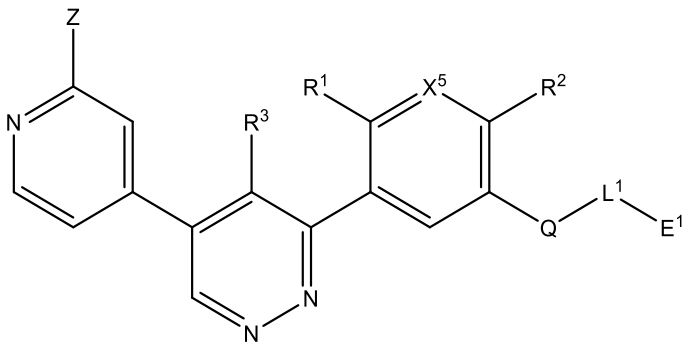
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

17. A compound represented by Formula I-NA:



Formula I-NA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_mNH$-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

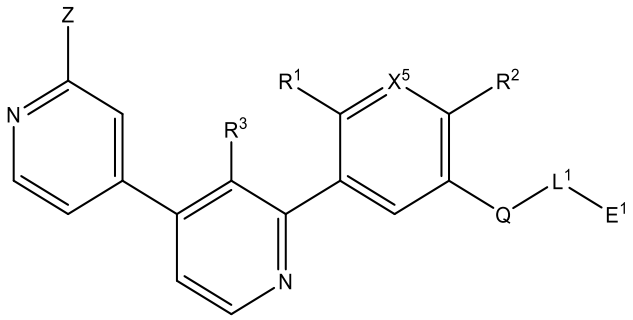
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

18. A compound represented by Formula I-OA:



Formula I-OA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_mNH$-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

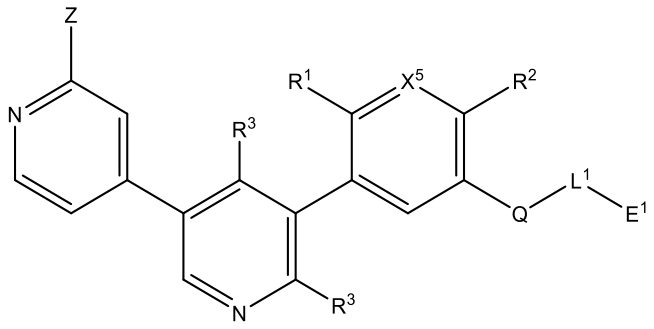
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

19. A compound represented by Formula I-PA:



Formula I-PA

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_m$NH-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

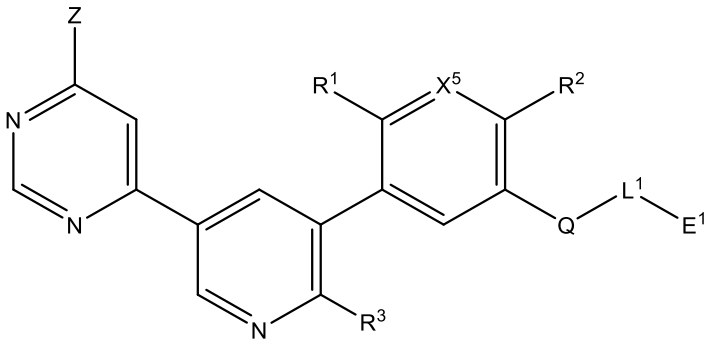
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

20. A compound represented by Formula I-QA:



Formula I-Q

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

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

Z is selected from the group consisting of acyl, carbamoyl, formyl, amide, alkoxy, alkoxyalkyl, urea, amine, amidine, alkyl, cycloalkyl, cyano, cyanoalkyl, sulfonamide, hydroxy, hydroxyalkyl, halogen, sulfone, optionally substituted heterocyclyl, optionally substituted heterocyclyl$(CH_2)_mNH$-, wherein the optionally substituted substituent on the heterocyclyl ring, at each occurrence, is independently R^9;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

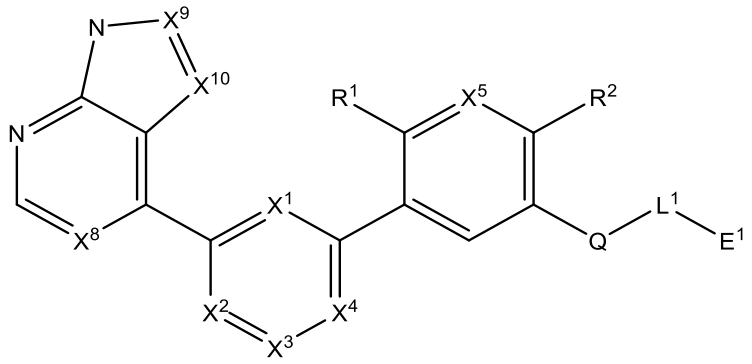
R^2 is selected from the group consisting of H and F;

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

R^9, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl; and

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

21. A compound represented by Formula I-RA:



Formula I-RA

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

each of X^1 and X^4 is independently selected from CR^3 and N;

each of X^2 and X^3 is independently selected from the group consisting of N and CH;

provided that not more than two of X^1, X^2, X^3, and X^4 are N;

each of X^8, X^9, and X^{10} is independently selected from CR^3 and N;

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

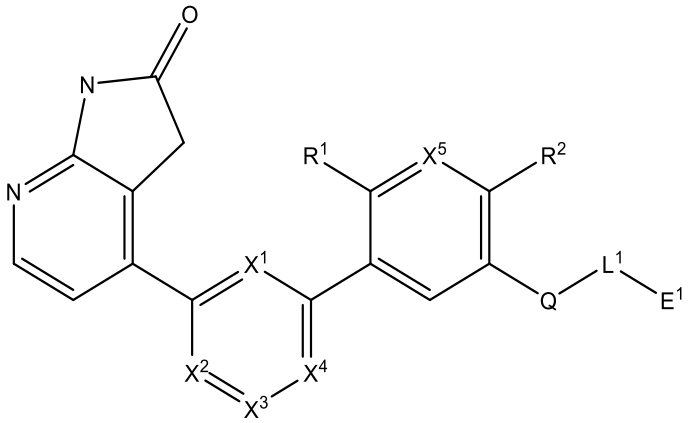
R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

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

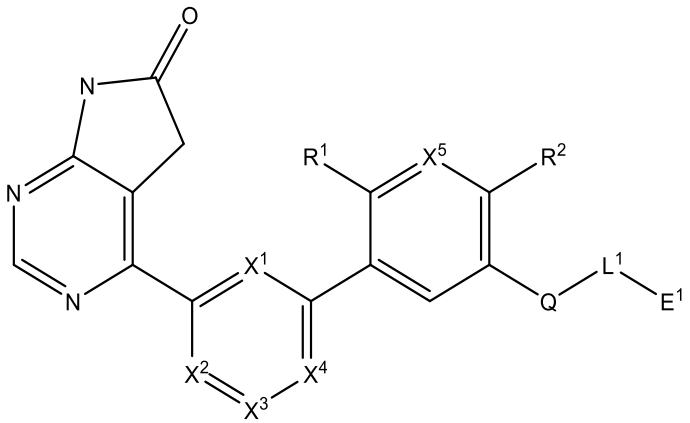
R^3, at each occurrence, is independently selected from the group consisting of H, alkyl, and halogen; and

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

22. A compound represented by Formula I-SA-i or Formula I-SA-ii:



Formula I-SA-i



Formula I-SA-ii

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

each of X^1 and X^4 is independently selected from CR^3 and N;

X^2 and X^3 are each independently selected from the group consisting of N and CH;

provided that not more than two of X^1, X^2, X^3, and X^4 are N;

X^5 is selected from the group consisting of N, CH, and CF;

Q is selected from the group consisting of -NH-C(O)- and -C(O)-NH-;

L^1 is selected from the group consisting of a direct bond and optionally substituted C_1-C_6alkyl, wherein the optionally substituted substituent, at each occurrence, is $(E^{11})_m$;

E^1 is selected from the group consisting of

optionally substituted cycloalkyl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano,

optionally substituted heteroaryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, sulfone, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

optionally substituted aryl wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, amine, amide, acyl, alkoxyalkyl, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, hydroxyalkyl, cyanoalkyl, aminoalkyl, cycloalkyl and heterocyclyl, wherein

the alkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl,

the cycloalkyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of cycloalkyl, cyano, alkoxy, and aminoalkyl, and

the heterocyclyl substituent is independently optionally substituted, at each occurrence, with a substituent selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone, and

optionally substituted heterocyclyl, wherein the optionally substituted substituent, at each occurrence, is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfone,

wherein when L^1 is a direct bond and E^1 is an optionally substituted heterocyclyl or optionally substituted heteroaryl, the heterocyclyl or heteroaryl is C-bound;

E^{11}, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, alkoxy, cyano, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, and halogen;

or wherein two occurrences of E^{11} taken together with the carbon atom to which they are attached form a cycloalkyl or a heterocyclyl ring having from 3 to 6 atoms in the ring structure;

R^1 is selected from the group consisting of H, alkyl, alkoxy, haloalkyl, cyano, and halogen;

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

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

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

23. The compound of any one of claims 2-20, wherein Z is $-NHC(O)R^6$, $-NHC(O)OR^6$, or $-C(O)NHR^7$, wherein

R^6, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, wherein

each of alkyl and cycloalkyl is optionally substituted with one or more independent occurrences of R^8, and

the 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 sulfone; and

R^7 is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, wherein

each of alkyl and cycloalkyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, cyano, amino, hydroxy, alkoxy, and heterocyclyl, and

the 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 sulfone; and

R^8 is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl, wherein

each of alkyl and cycloalkyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, cyano, amino, hydroxy, alkoxy, and heterocyclyl, and

the 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 sulfone.

24. The compound of any one of claims 2-20 and 23, wherein Z is $-NHC(O)R^6$, wherein:

R^6, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, wherein

each of alkyl and cycloalkyl is optionally substituted with one or more independent occurrences of R^8, and

the 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 sulfone; and

R^8 is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl, wherein

each of alkyl and cycloalkyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, cyano, amino, hydroxy, alkoxy, and heterocyclyl, and

the 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 sulfone.

25. The compound of any one of claims 2-20 and 23, wherein Z is $-C(O)NHR^7$, wherein:

R^7 is selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, wherein

each of alkyl and cycloalkyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, cyano, amino, hydroxy, alkoxy, and heterocyclyl, and

the 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 sulfone.

26. The compound of any one of claims 2-20 and 23, wherein Z is $-NHC(O)OR^6$, wherein

R^6, at each occurrence, is independently selected from the group consisting of H, alkyl, cycloalkyl, and heterocyclyl, wherein

each of alkyl and cycloalkyl is optionally substituted with one or more independent occurrences of R^8, and

the 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 sulfone; and

R^8 is selected from the group consisting of alkyl, cycloalkyl, and heterocyclyl, wherein

each of alkyl and cycloalkyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, cyano, amino, hydroxy, alkoxy, and heterocyclyl, and

the 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 sulfone.

27. The compound of any one of claims 1-26, wherein Q is -NH-C(O)-.

28. The compound of any one of claims 1-26, wherein Q is -C(O)-NH-.

29. The compound of claim 1, wherein X^1, X^4, X^5, and X^6 are each CH; X^2 is N; and X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, C-N(R^4)-L^3-E^3 and N.

30. The compound of claim 1, wherein X^1, X^4, X^5, and X^6 are each CH; X^2 is CH; and X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, C-N(R^4)-L^3-E^3 and N.

31. The compound of claim 21, wherein X^1, X^4, and X^5 are each CH; X^2 is CH; X^8 is N; and X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, C-N(R^4)-L^3-E^3 and N.

32. The compound of claim 1, wherein X^1 is CR^3; X^2 and X^4 are each N; X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3; X^5 is CH or N; and X^6 is CH.

33. The compound of claim 21, wherein X^1 and X^4 are each CR^3; X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, C-N(R^4)-L^3-E^3, and N; X^8 is N; and X^2, X^5, and X^6 are CH.

34. The compound of claim 1, wherein X^1 and X^4 are each CR^3; X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, C-N(R^4)-L^3-E^3, and N; X^5 is N; and X^2 and X^6 are CH.

35. The compound of claim 21, wherein X^1 and X^4 are each CR^3; X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, C-N(R^4)-L^3-E^3, and N; X^5 and X^8 are N; and X^2 and X^6 are CH.

36. The compound of claim 1, wherein X^1 is CR^3 and X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3; X^2 and X^4 are N; and X^5 and X^6 are CH.

37. The compound of claim 1, wherein X^1 is CR^3; X^4 is CR^3 or N; X^3 is N-L^3-E^3; X^2 is C=O; and X^5 and X^6 are CH.

38. The compound of claim 1, wherein X^1 and X^4 are CR^3; X^3 is C=O; X^2 is N-L^2-E^2; and X^5 and X^6 are CH.

39. The compound of claim 1, wherein X^1 and X^4 are CR^3; X^2 is N; X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, C-N(R^4)-L^3-E^3 and N; and X^5 and X^6 are CH.

40. The compound of claim 1, wherein X^1 and X^2 are N; X^4 is CR^3; X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3; and X^5 and X^6 are CH.

41. The compound of claim 1, wherein X^1 and X^4 are N; X^5, and X^6 are each CH; X^2 is selected from the group consisting of CH, C-L^2-E^2, C-O-L^2-E^2, C-N(R^4)-L^2-E^2; and X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3.

42. The compound of claim 1, wherein X^1 and X^3 are N; X^4 is CR^3, X^5 and X^6 are each CH; and X^2 is selected from the group consisting of CH, C-L^2-E^2, C-O-L^2-E^2, and C-N(R^4)-L^2-E^2.

43. The compound of claim 1, wherein X^1 is N; X^4 is CR^3; X^5 and X^6 are each CH; X^2 is selected from the group constating of CH, C-L^2-E^2, C-O-L^2-E^2, and C-N(R^4)-L^2-E^2; and X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3.

44. The compound of claim 1, wherein X^1 is CR^3; X^2 and X^6 are CH; and X^3, X^4, and X^5 are N.

45. The compound of claim 1, wherein X^1 is CR^3; X^2, X^5, and X^6 are CH; and X^3 and X^4 are N.

46. The compound of claim 21, wherein X^1 is CR^3; X^2, X^5, and X^6 are CH; and X^3, X^4 and X^8 are N.

47. The compound of any one of claims 1, 3, 8, 29-37, 39-41, and 43, wherein E^3 is selected from the group consisting of H, alkyl, and cycloalkyl, wherein cycloalkyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, and cyano.

48. The compound of any one of claims 1, 3, 8, 29-37, 39-41, and 43, wherein E^3 is selected from the group consisting of hydroxy, alkoxy, and cyano.

49. The compound of any one of claims 1, 3, 8, 29-37, 39-41, and 43, wherein E^3 is heterocyclyl, 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.

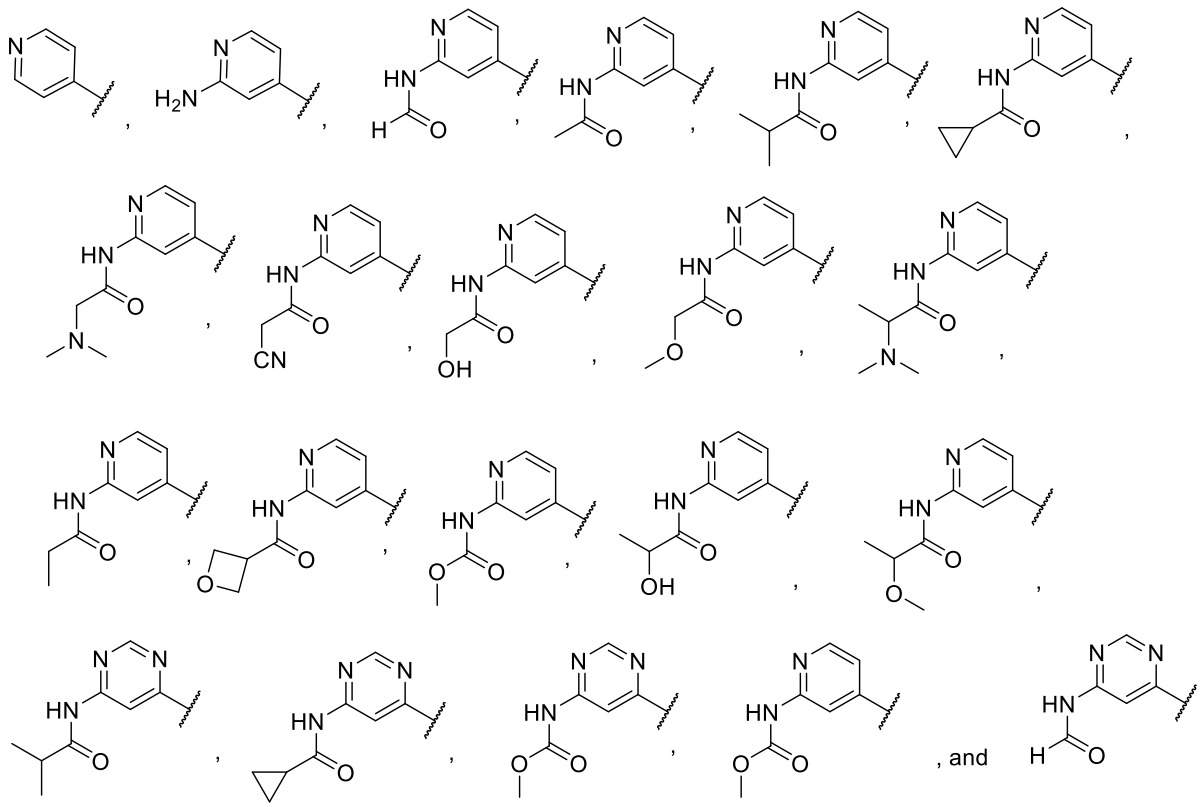
50. The compound of any one of claims 1, 38, and 41-43, wherein E^2 is selected from the group consisting of H, hydroxy, alkoxy, alkoxyalkyl, cyano, sulfonyl, and heterocyclyl, wherein heterocyclyl is optionally substituted with one or more occurrences of a substituent independently selected from the group consisting of alkyl, alkoxy, amide, amine, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, and cyanoalkyl, alkyl, amine, haloalkoxy, haloalkyl, and sulfonyl.

51. The compound of any one of claims 1-50, wherein R^1 is selected from the group consisting of H, alkyl, haloalkyl, and halogen.

52. The compound of any one of claims 1-51, wherein R^1 is selected from the group consisting of methyl and fluorine.

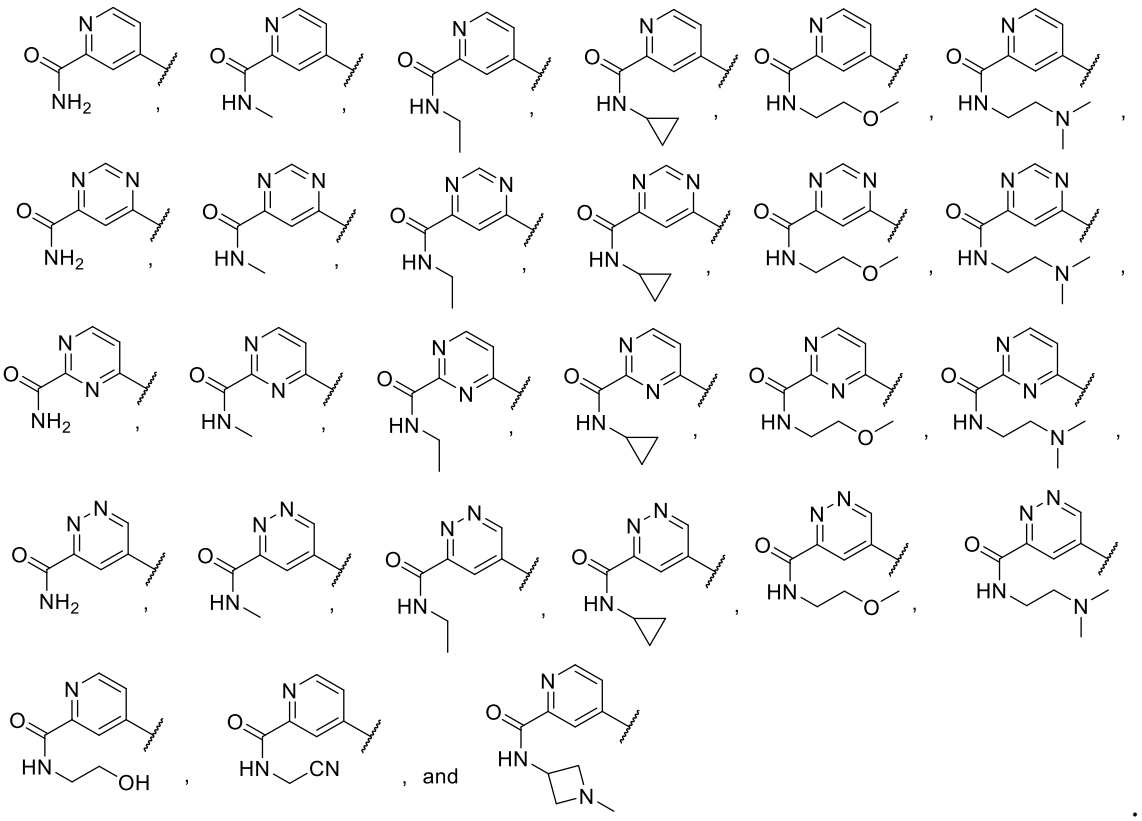
53. The compound of any one of claims 1-52, wherein R^2 is selected from H and F.

54. The compound of any one of claims 2-20 and 23-53, wherein the Z-substituted ring is selected from the group consisting of



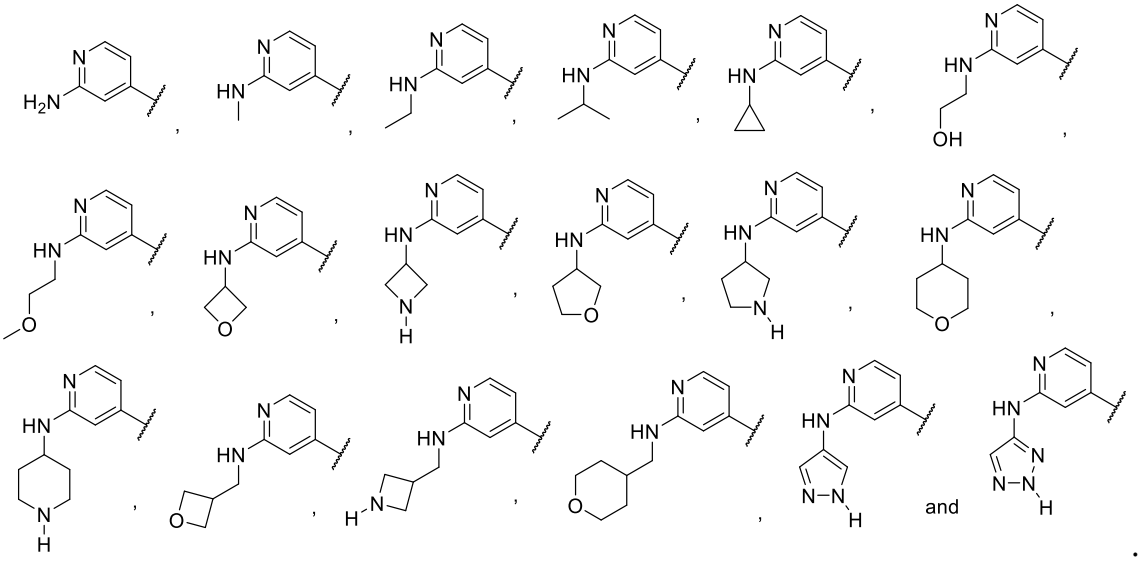
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55. The compound of any one of claims 2-20 and 23-53, wherein the Z-substituted ring is selected from the group consisting of



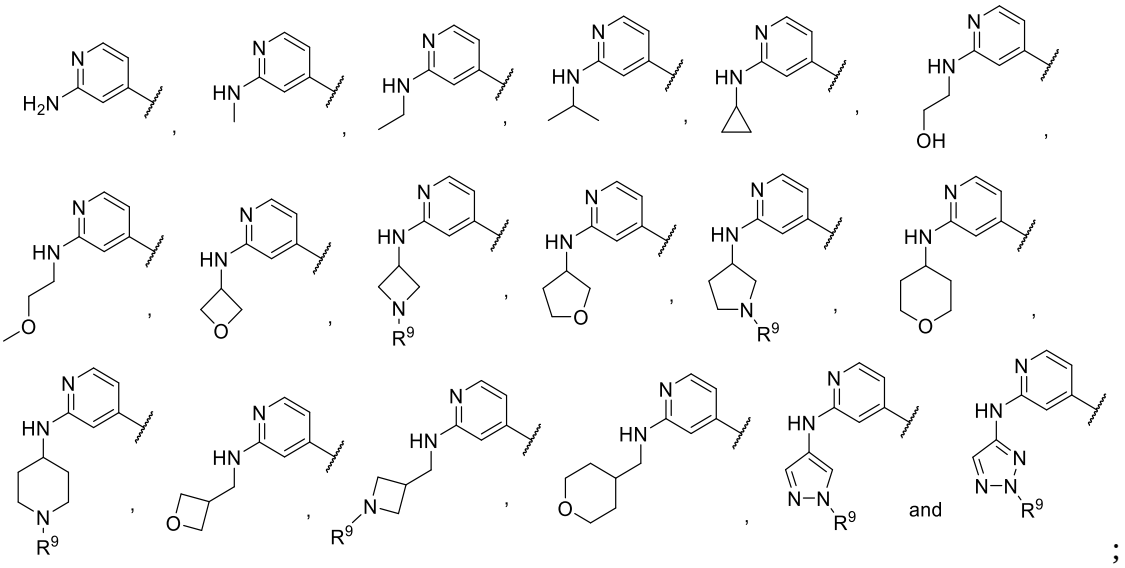
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56. The compound of any one of claims 2-20 and 23-53, wherein the Z-substituted ring is selected from the group consisting of



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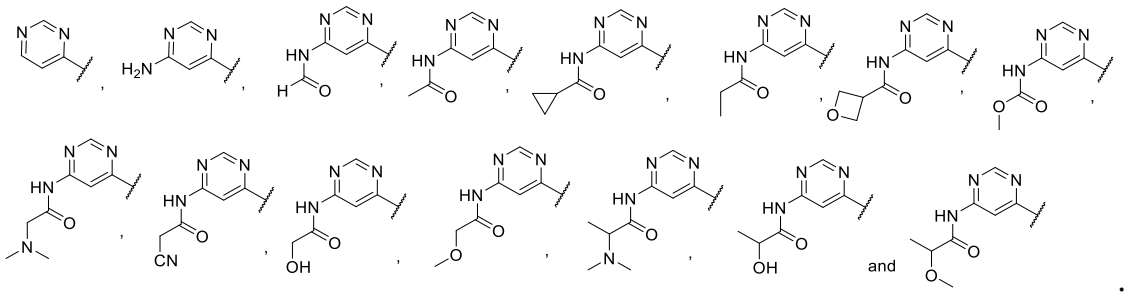
57. The compound of any one of claims 2-20 and 23-53, wherein the Z-substituted ring is selected from the group consisting of



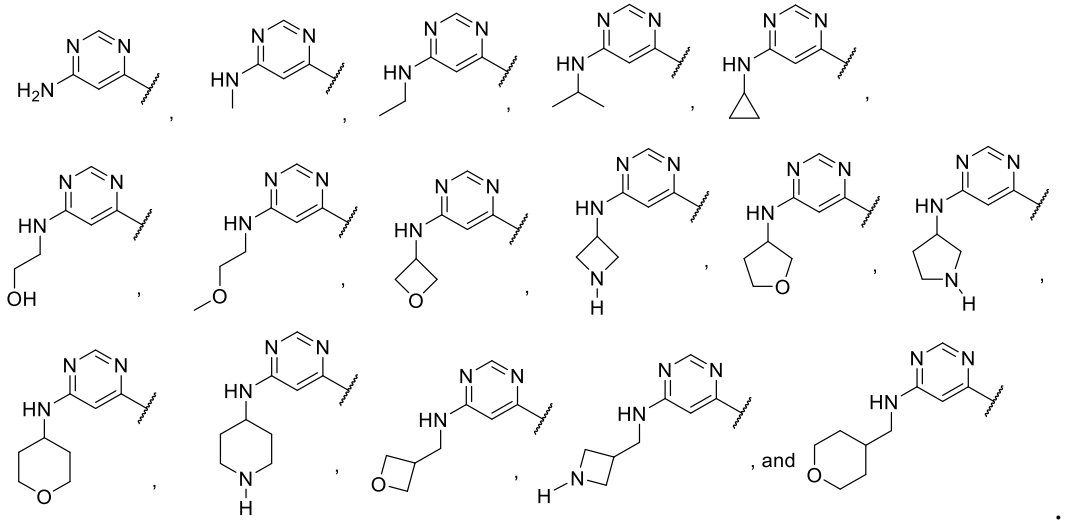
;

wherein each occurrence of R^9 is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl.

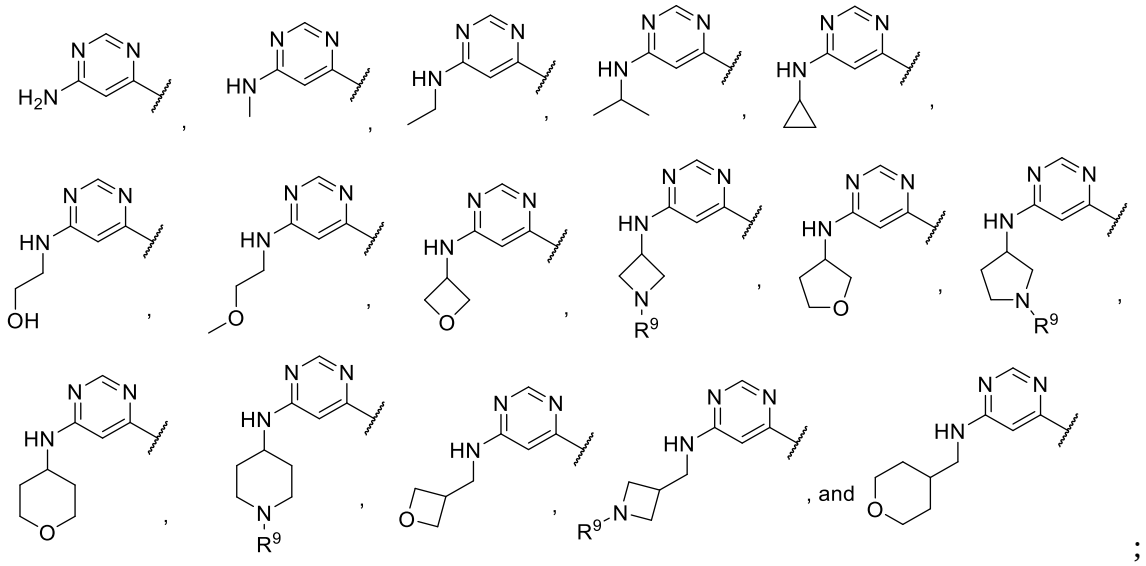
58. The compound of any one of claims 2-20 and 23-53, wherein the Z-substituted containing ring is selected from the group consisting of



59. The compound of any one of claims 2-20 and 23-53, wherein the Z-substituted ring is selected from the group consisting of

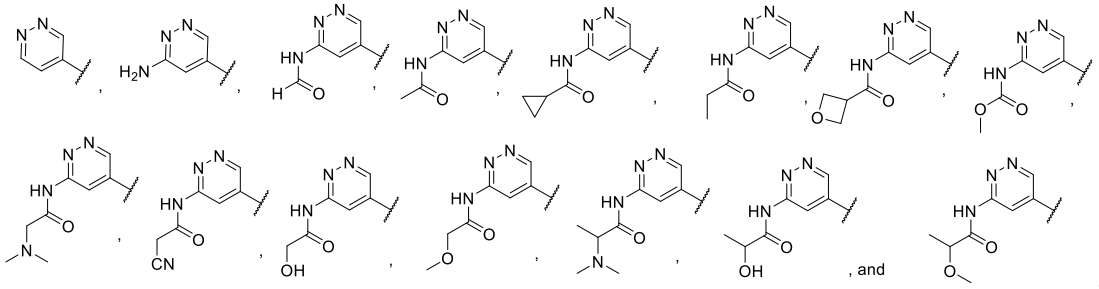


60. The compound of any one of claims 2-20 and 23-53, wherein the Z-substituted ring is selected from the group consisting of

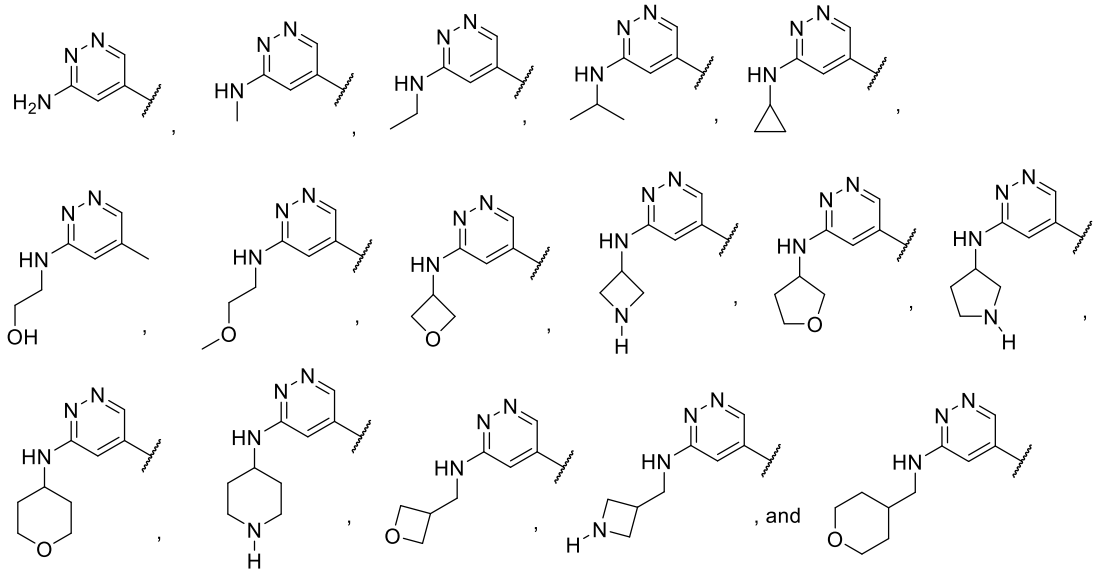


wherein each occurrence of R^9 is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl.

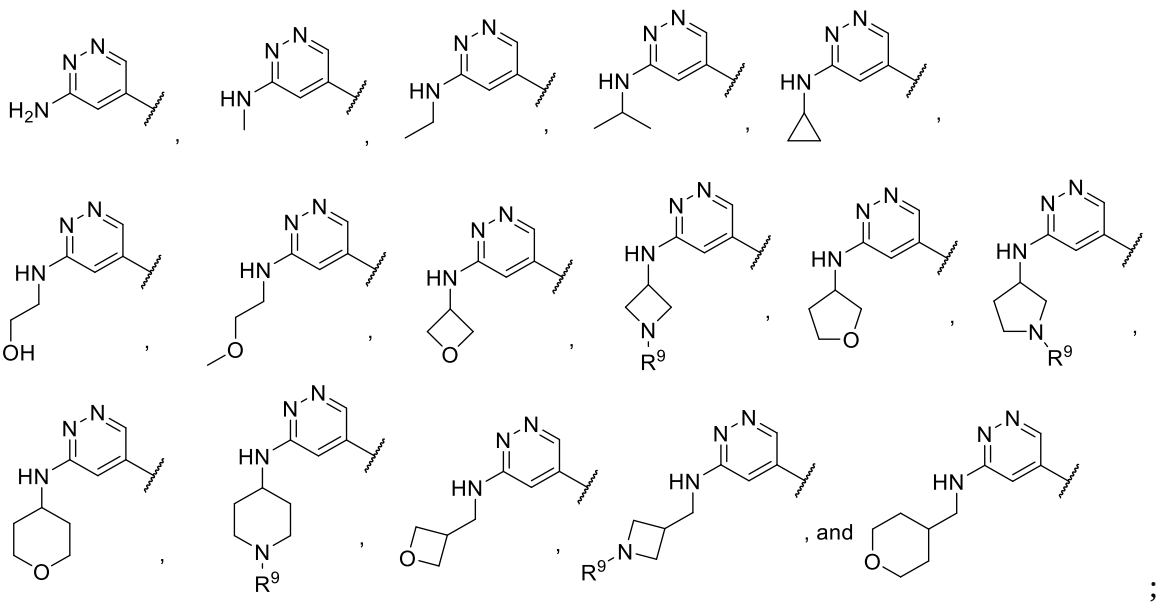
61. The compound of any one of claims 2-20 and 23-53, wherein the Z-substituted ring is selected from the group consisting of



62. The compound of any one of claims 2-20 and 23-53, wherein the Z-substituted ring is selected from the group consisting of



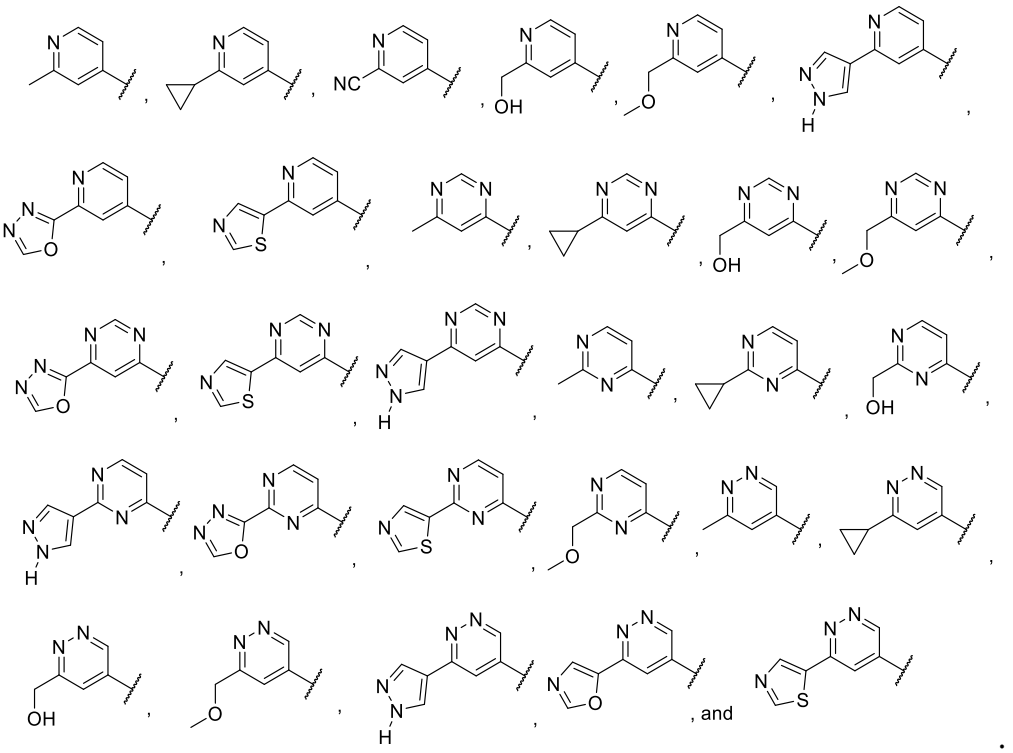
63. The compound of any one of claims 2-20 and 23-53, wherein the Z-substituted ring is selected from the group consisting of



;

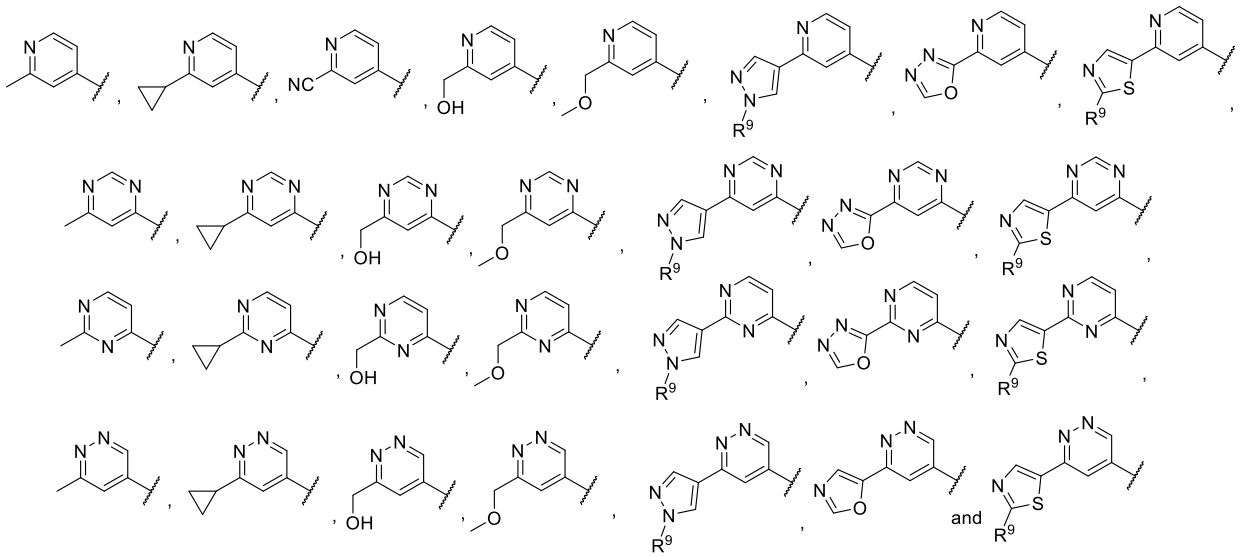
wherein each occurrence of R^9 is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl.

64. The compound of any one of claims 2-20 and 23-53, wherein the Z-substituted ring is selected from the group consisting of



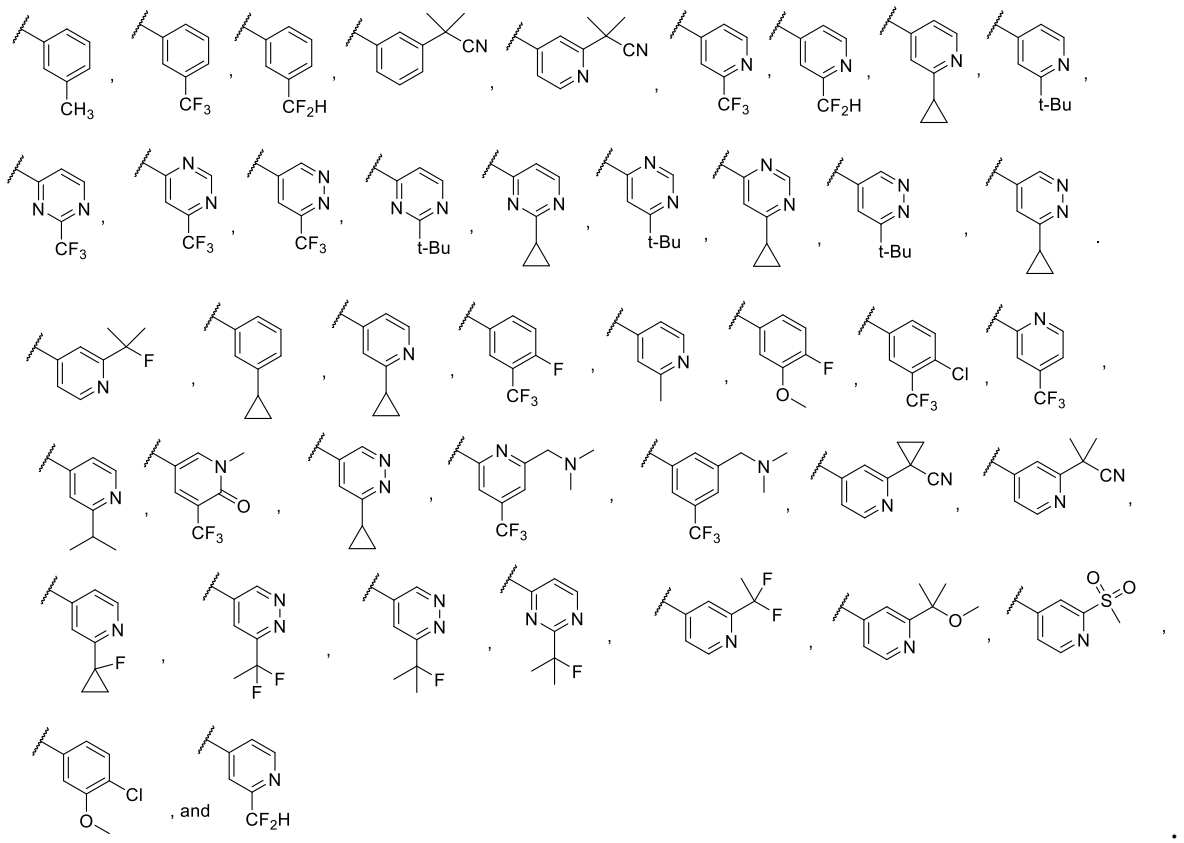
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65. The compound of any one of claims 2-20 and 23-53, wherein the Z-substituted ring is selected from the group consisting of

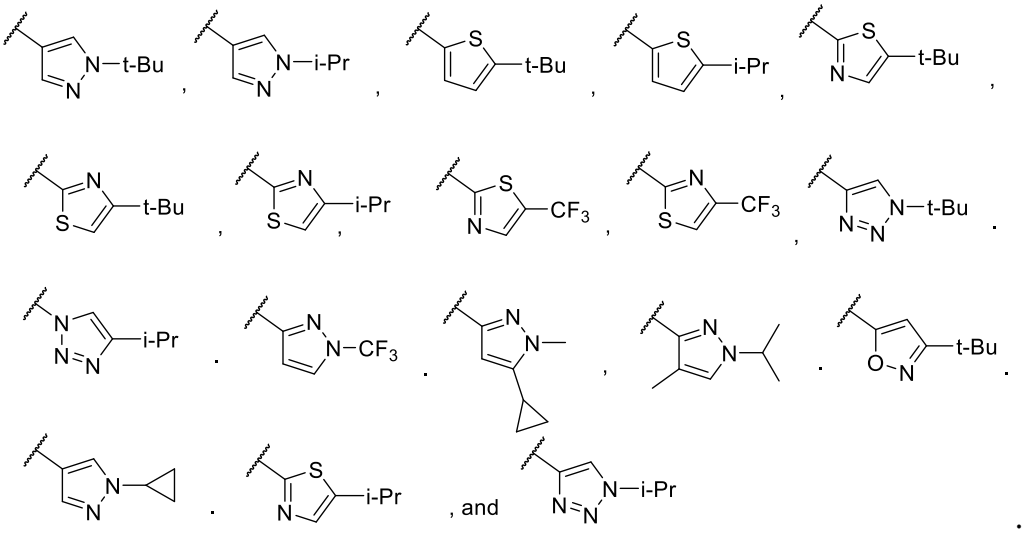


; wherein each occurrence of R^9 is independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, amide, amine, aminoalkyl, acyl, haloalkyl, haloalkoxy, halogen, hydroxy, hydroxyalkyl, oxo, cyano, cyanoalkyl, and sulfonyl.

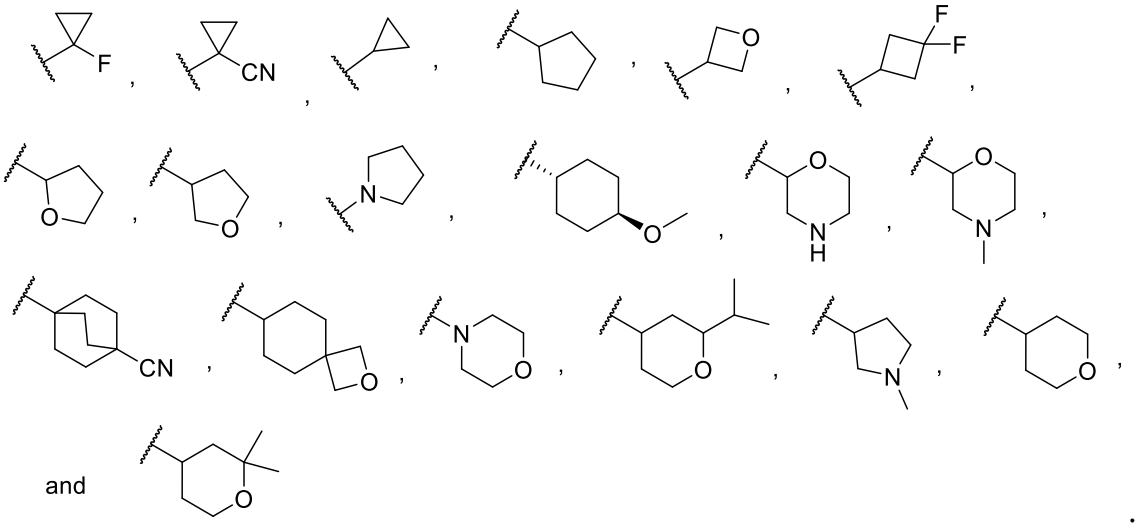
66. The compound of any one of claims 1-65, wherein E^1 is selected from the group consisting of:



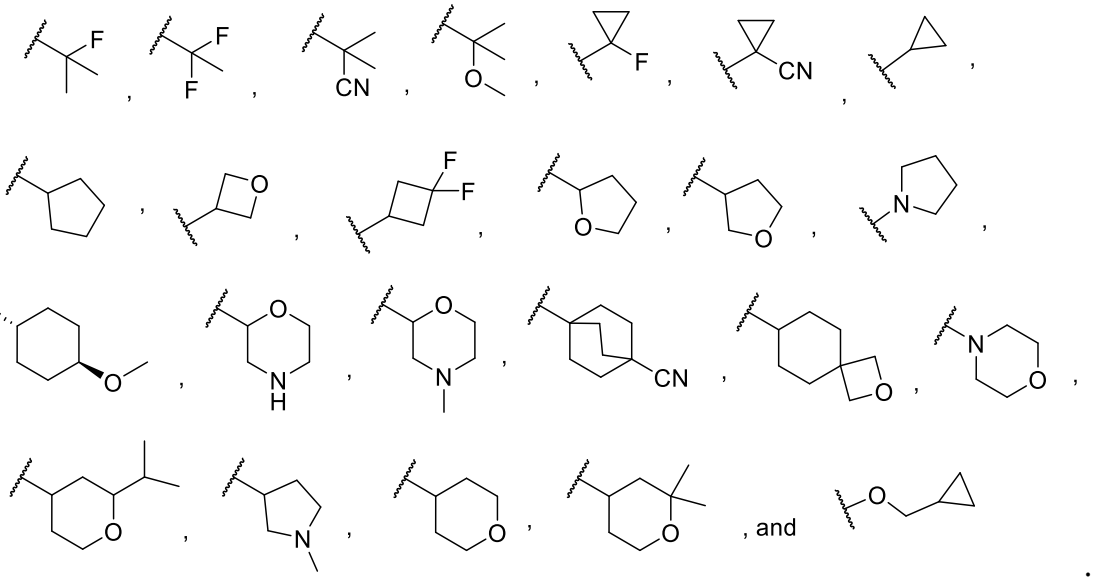
67. The compound of any one of claims 1-65, wherein E^1 is selected from the group consisting of:



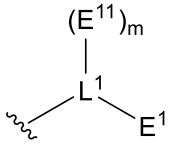
68. The compound of any one of claims 1-65, wherein E^1 is selected from the group consisting of

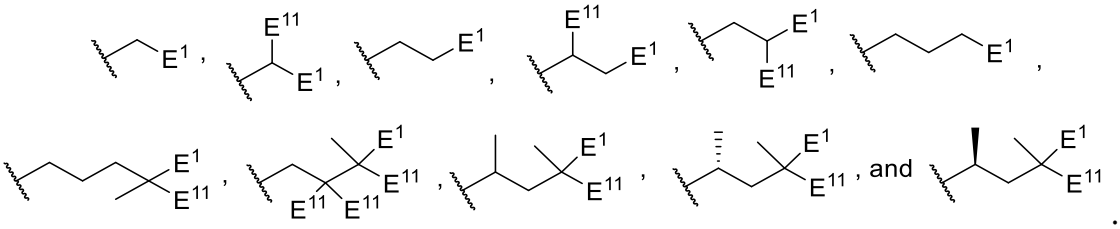


69. The compound of claim 1, wherein E^1 is selected from the group consisting of

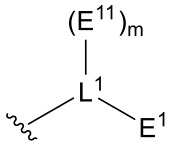


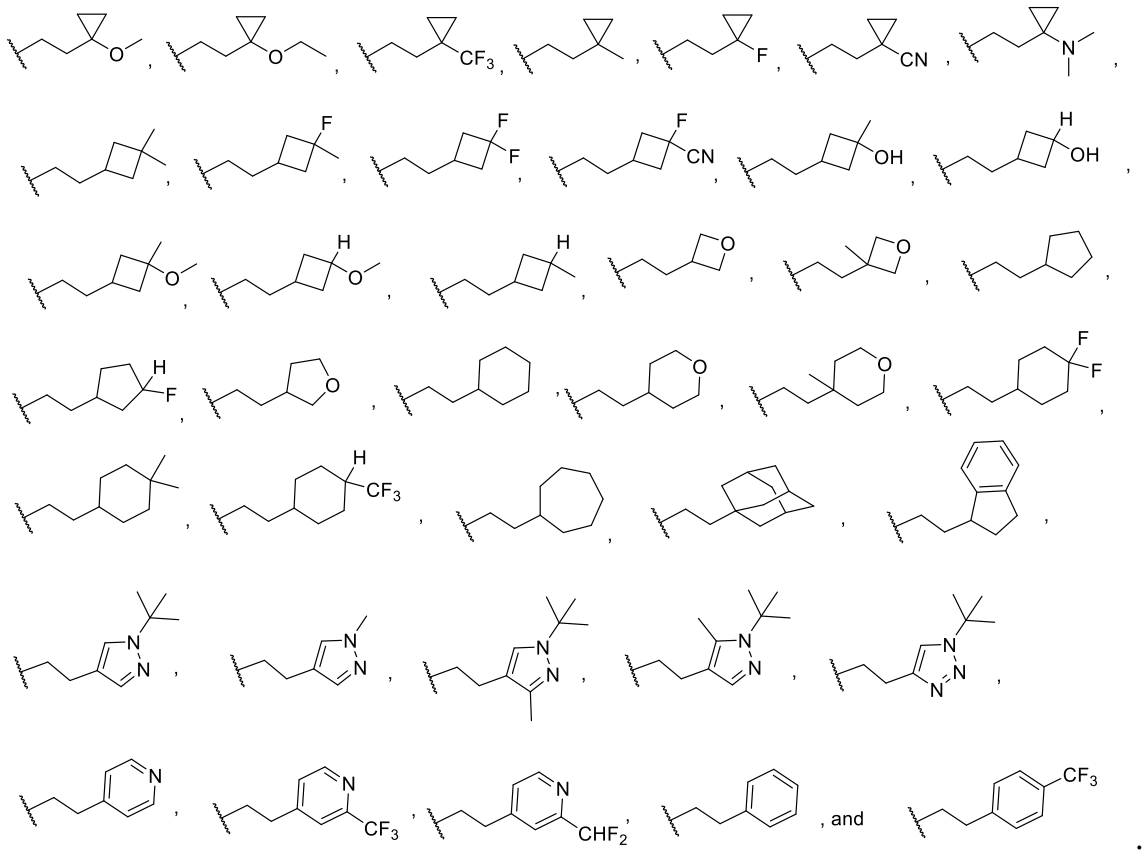
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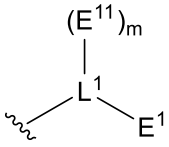
70. The compound of any one of claims 1-69, wherein  is selected from the group consisting of

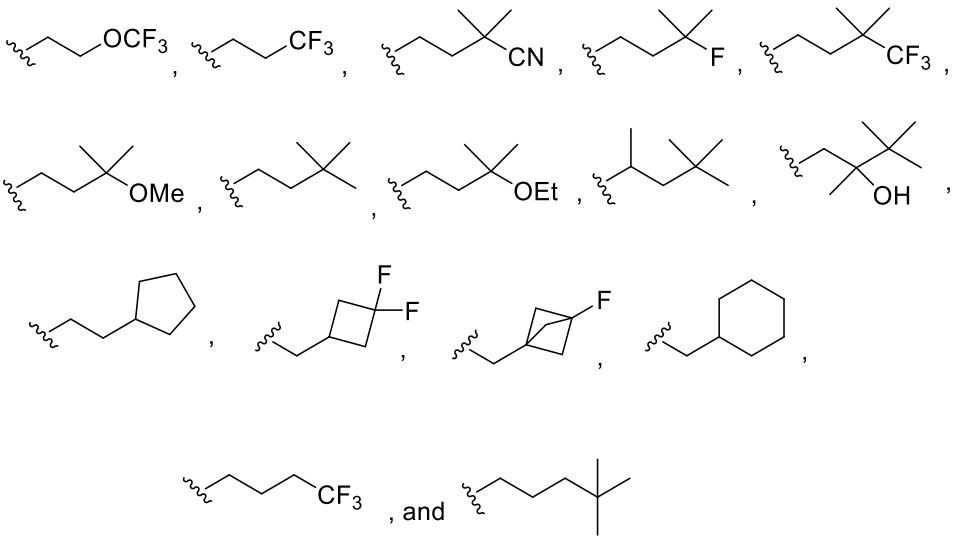


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71. The compound of any one of claims 1-65, wherein  is selected from the group consisting of

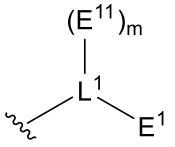


72. The compound of claim 1, wherein  is selected from the group consisting of:

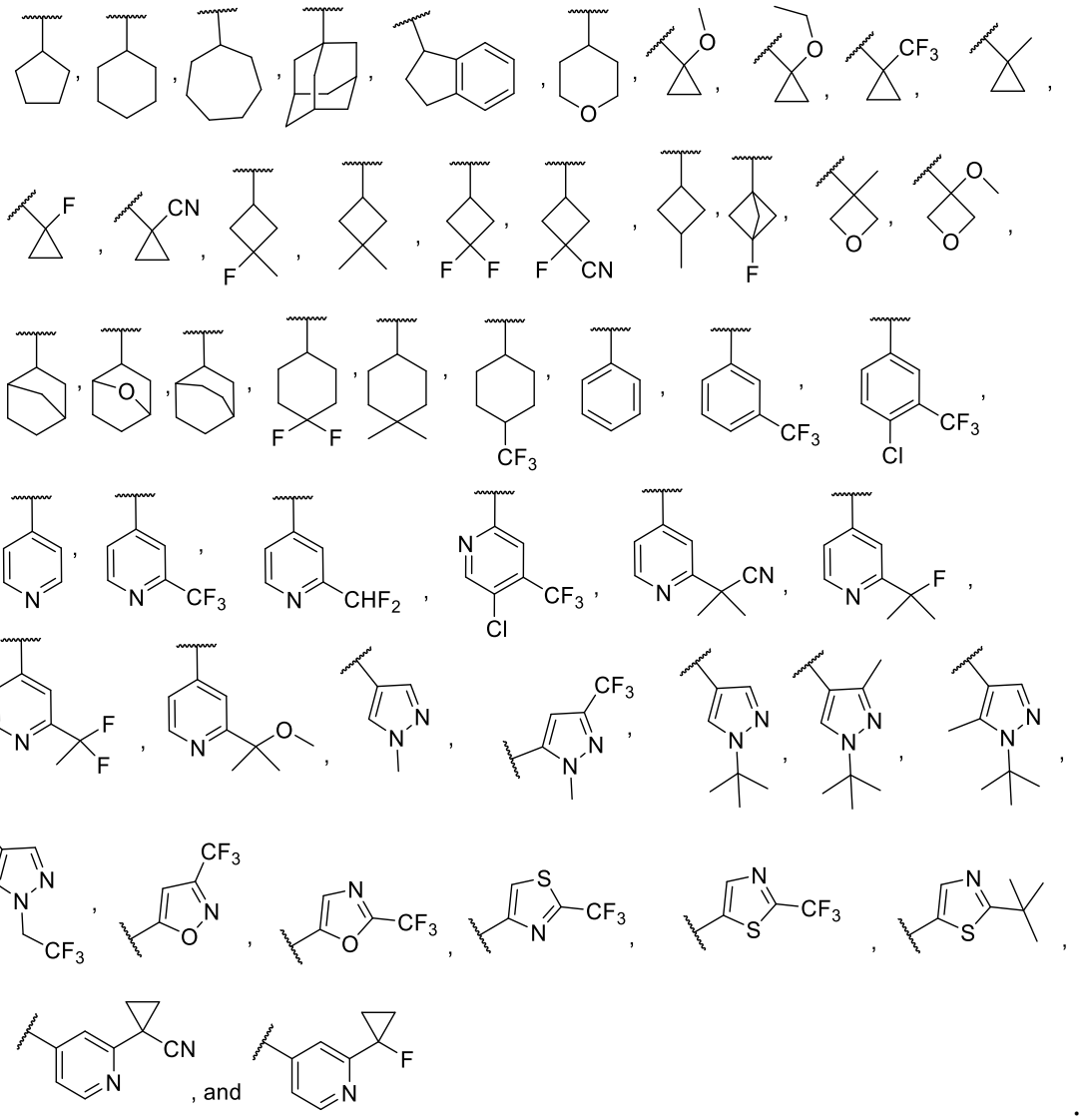

OCF3
CF3
CN
F
CF3
OMe
OEt
OH
F
F
F
CF3
, and

.

73. The compound of any one of claims 1-65, wherein when L^1 is a direct bond,

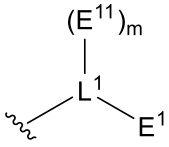


is selected from the group consisting of

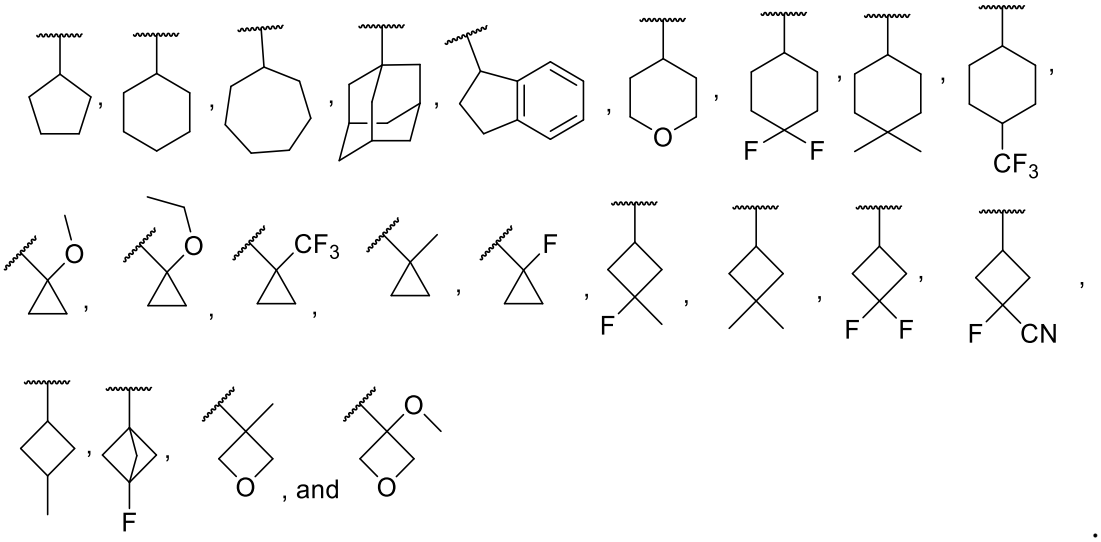


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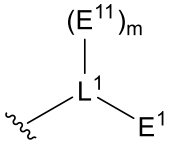
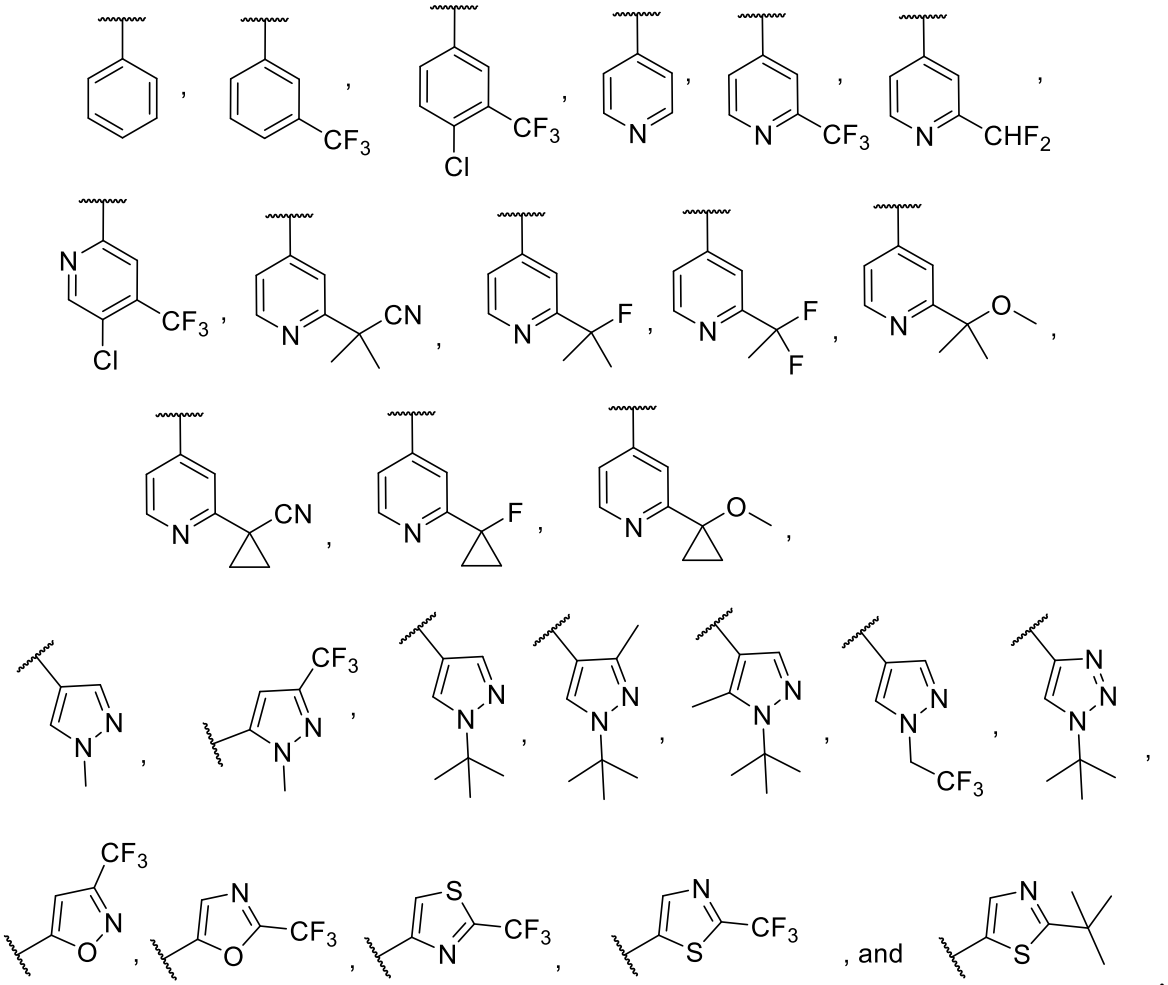
74. The compound of any one of claims 1-65, wherein when L^1 is a direct bond,

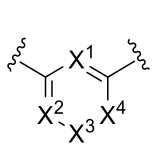
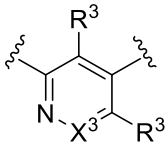


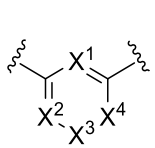
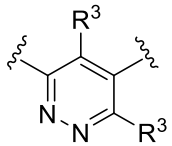
is selected from the group consisting of

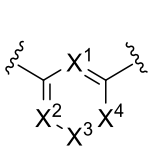
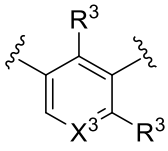


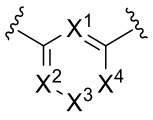
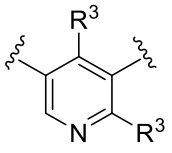
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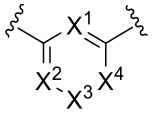
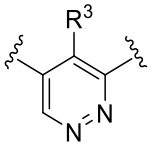
75. The compound of any one of claims 1-65, wherein when L^1 is a direct bond,  is selected from the group consisting of .

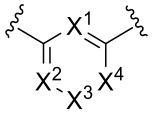
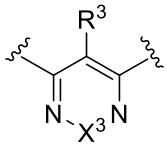
76. The compound of claim 1, wherein  is , wherein X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3.

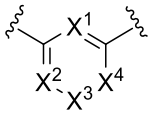
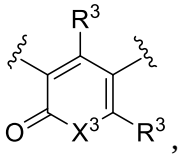
77. The compound of claim 1, wherein  is .

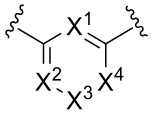
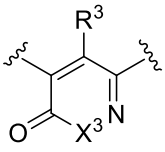
78. The compound of claim 1, wherein  is , wherein X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3.

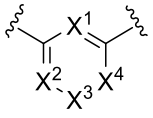
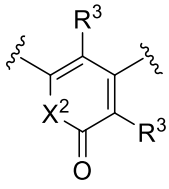
79. The compound of claim 1, wherein  is .

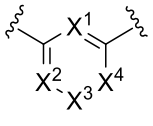
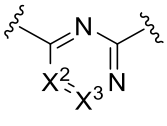
80. The compound of claim 1, wherein  is .

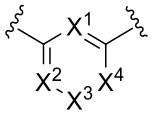
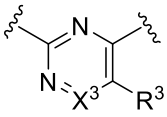
81. The compound of claim 1, wherein  is ,wherein X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3.

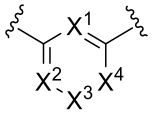
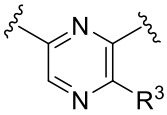
82. The compound of claim 1, wherein  is , wherein X^3 is N-L^3-E^3.

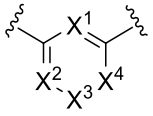
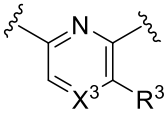
83. The compound of claim 1, wherein  is , wherein X^3 is N-L^3-E^3.

84. The compound of claim 1, wherein  is , wherein X^2 is N-L^2-E^2.

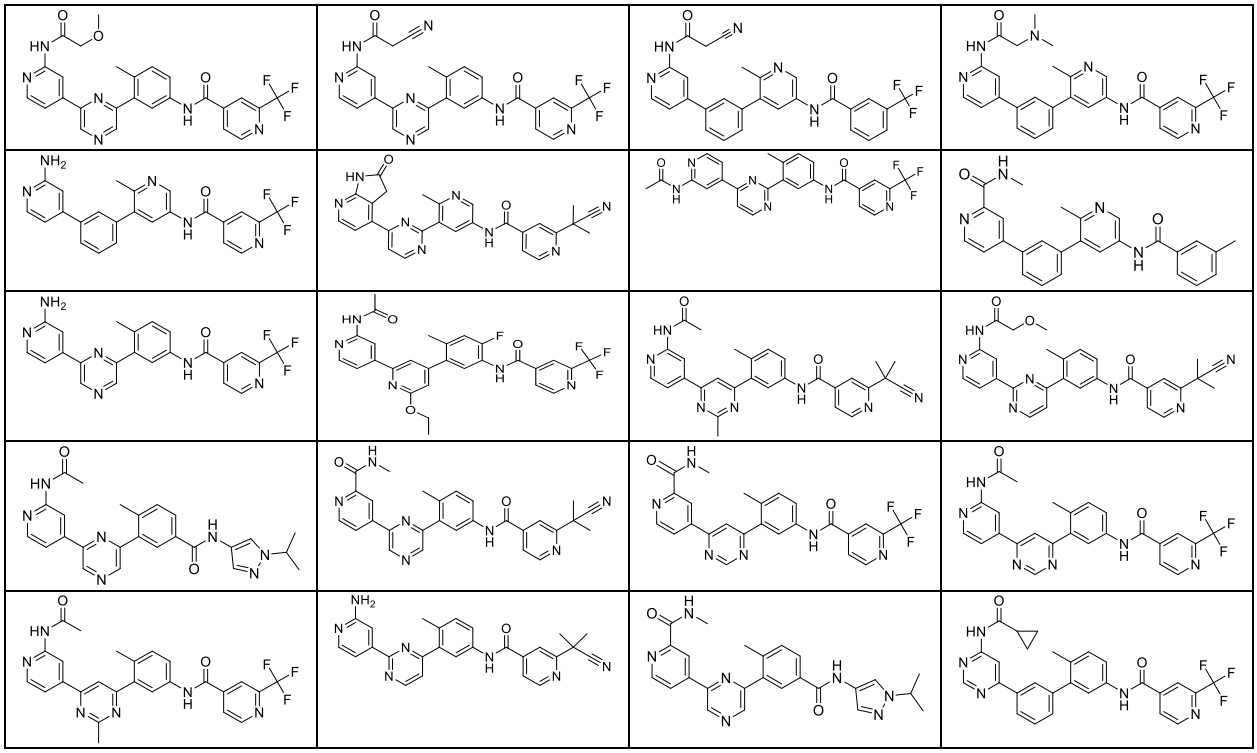
85. The compound of claim 1, wherein  is , wherein X^2 is selected from the group consisting of CH, C-O-L^2-E^2, C-L^2-E^2, and C-N(R^4)-L^2-E^2; and wherein X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3.

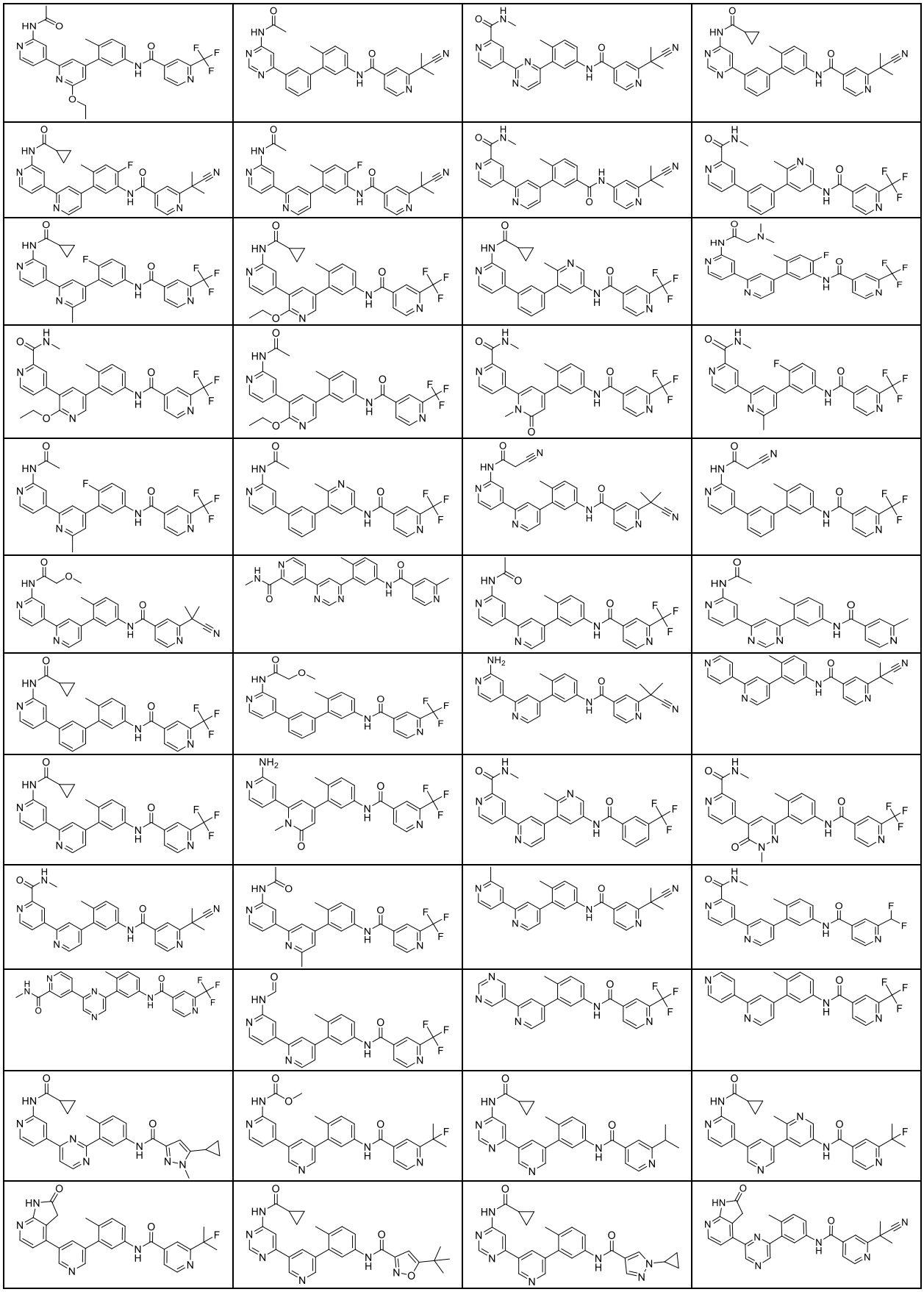
86. The compound of claim 1, wherein  is , wherein X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3.

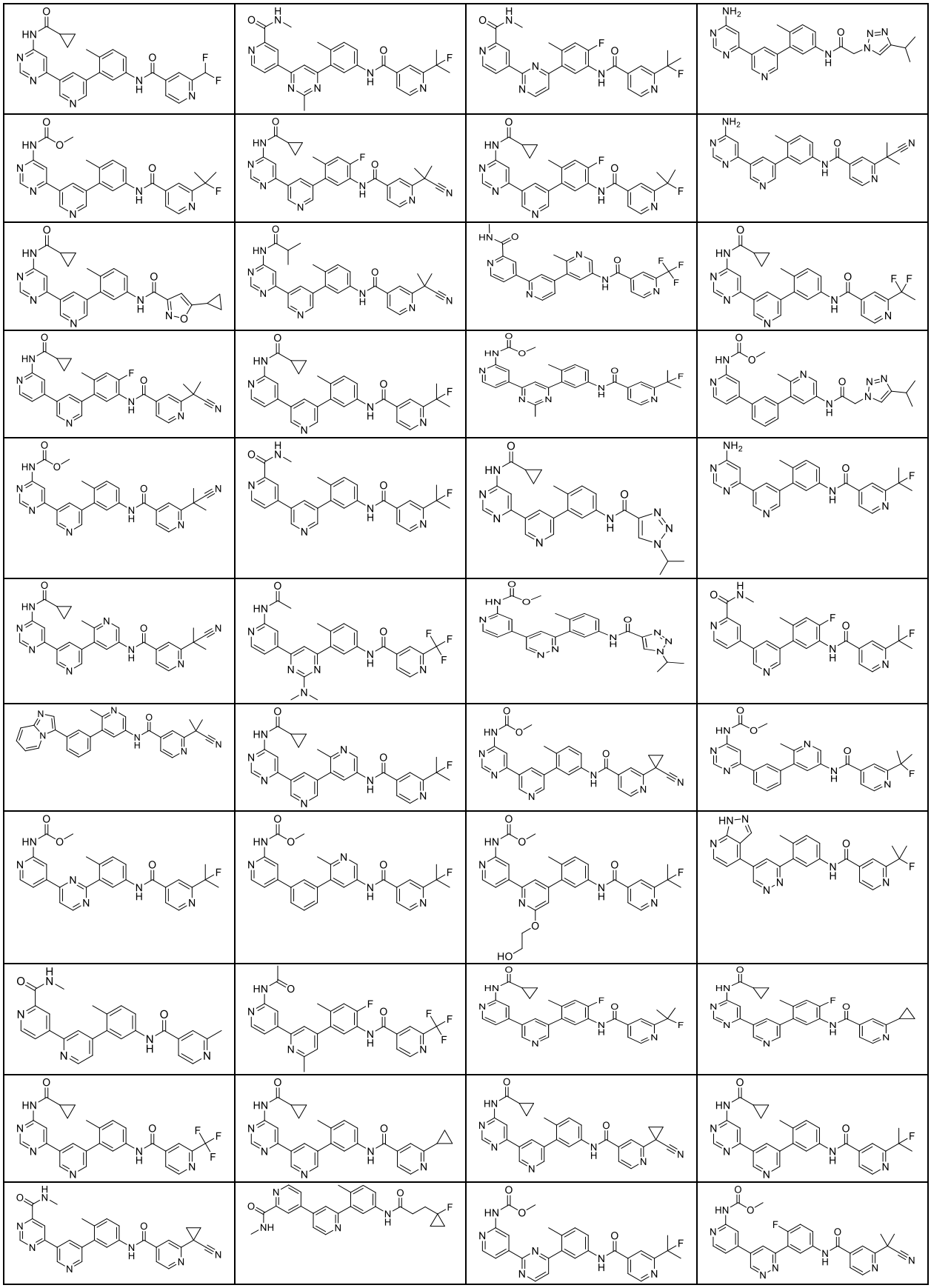
87. The compound of claim 1, wherein  is .

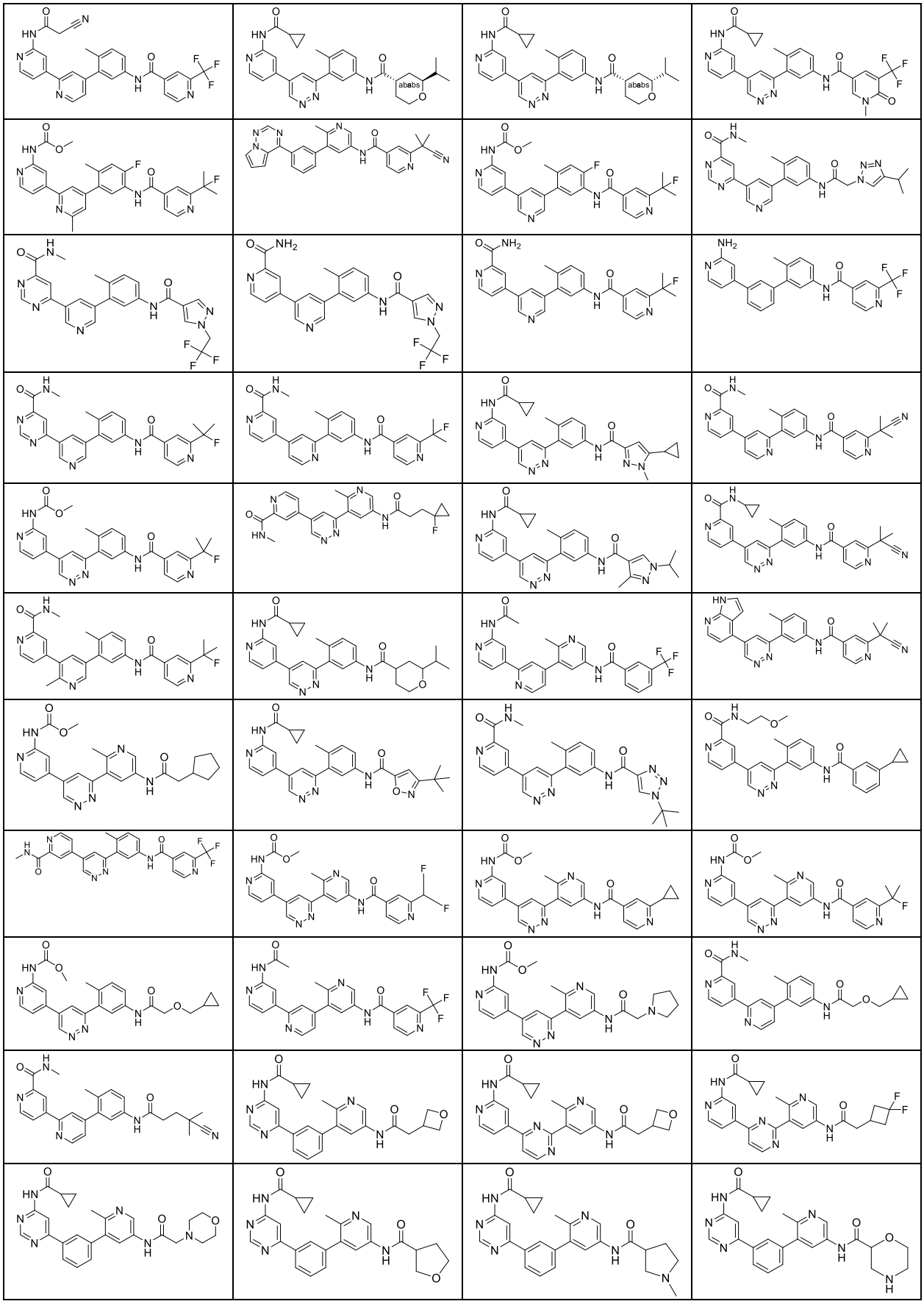
88. The compound of claim 1, wherein  is , wherein X^3 is selected from the group consisting of CH, C-L^3-E^3, C-O-L^3-E^3, and C-N(R^4)-L^3-E^3.

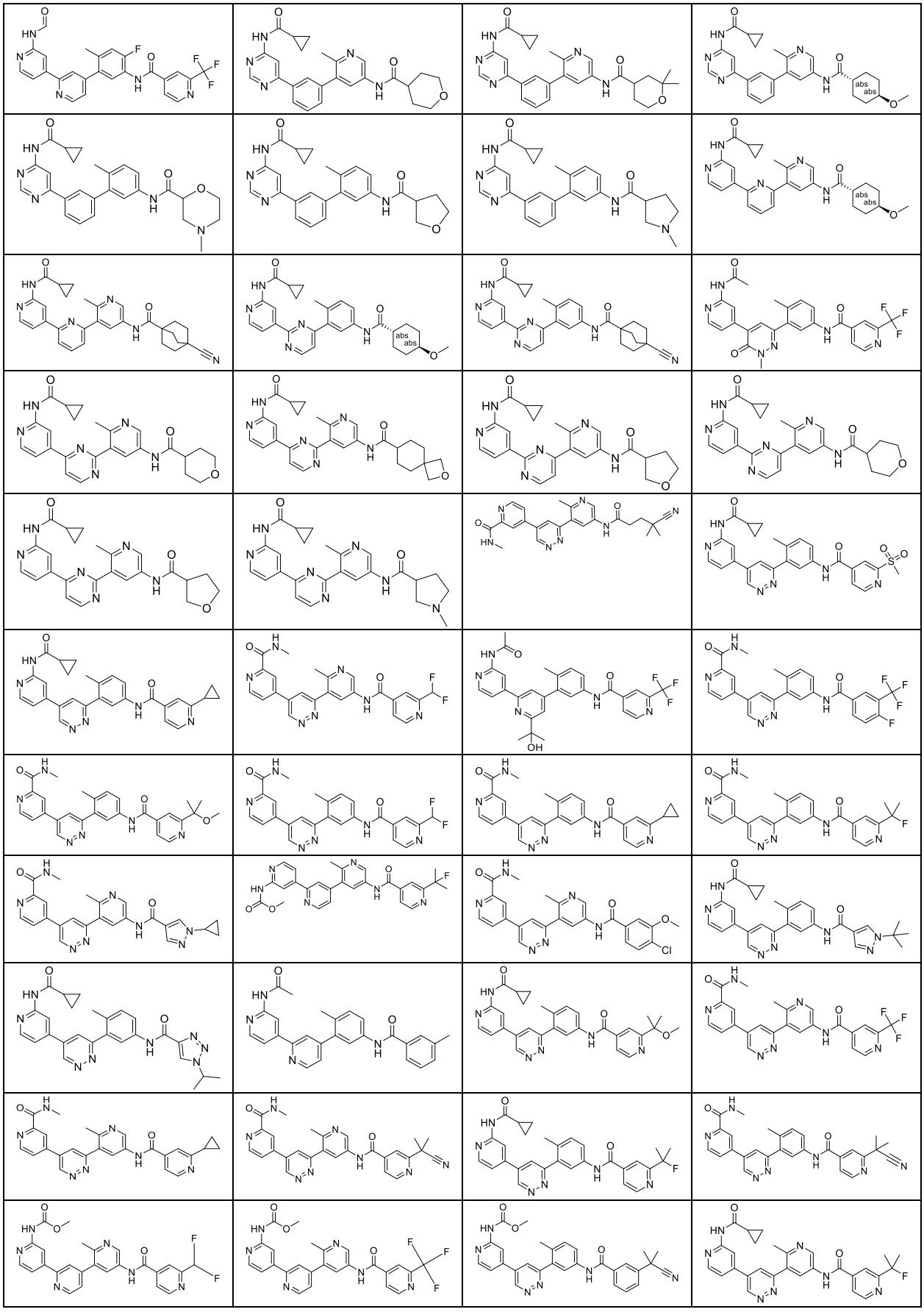
89. A compound selected from the group consisting of:

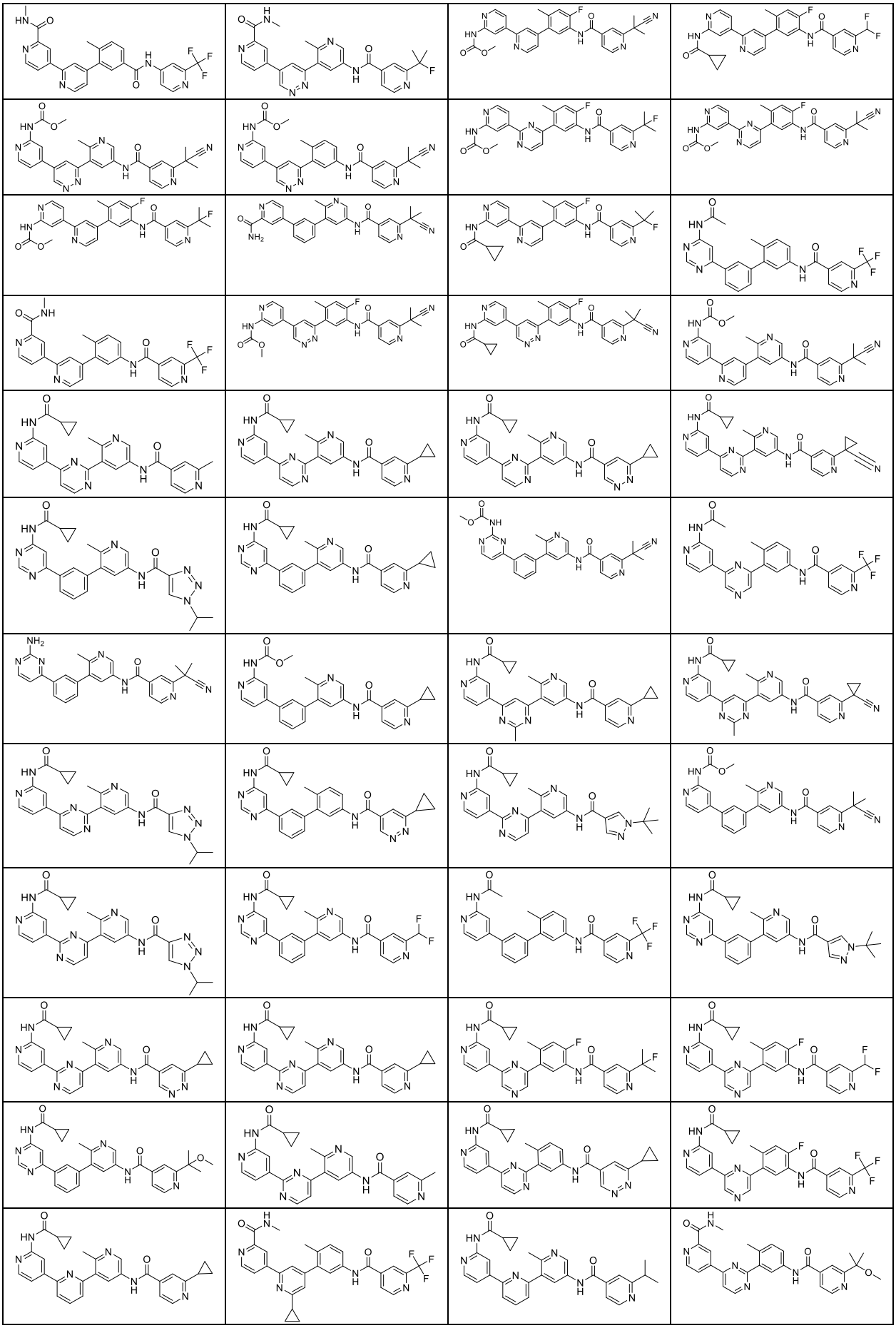


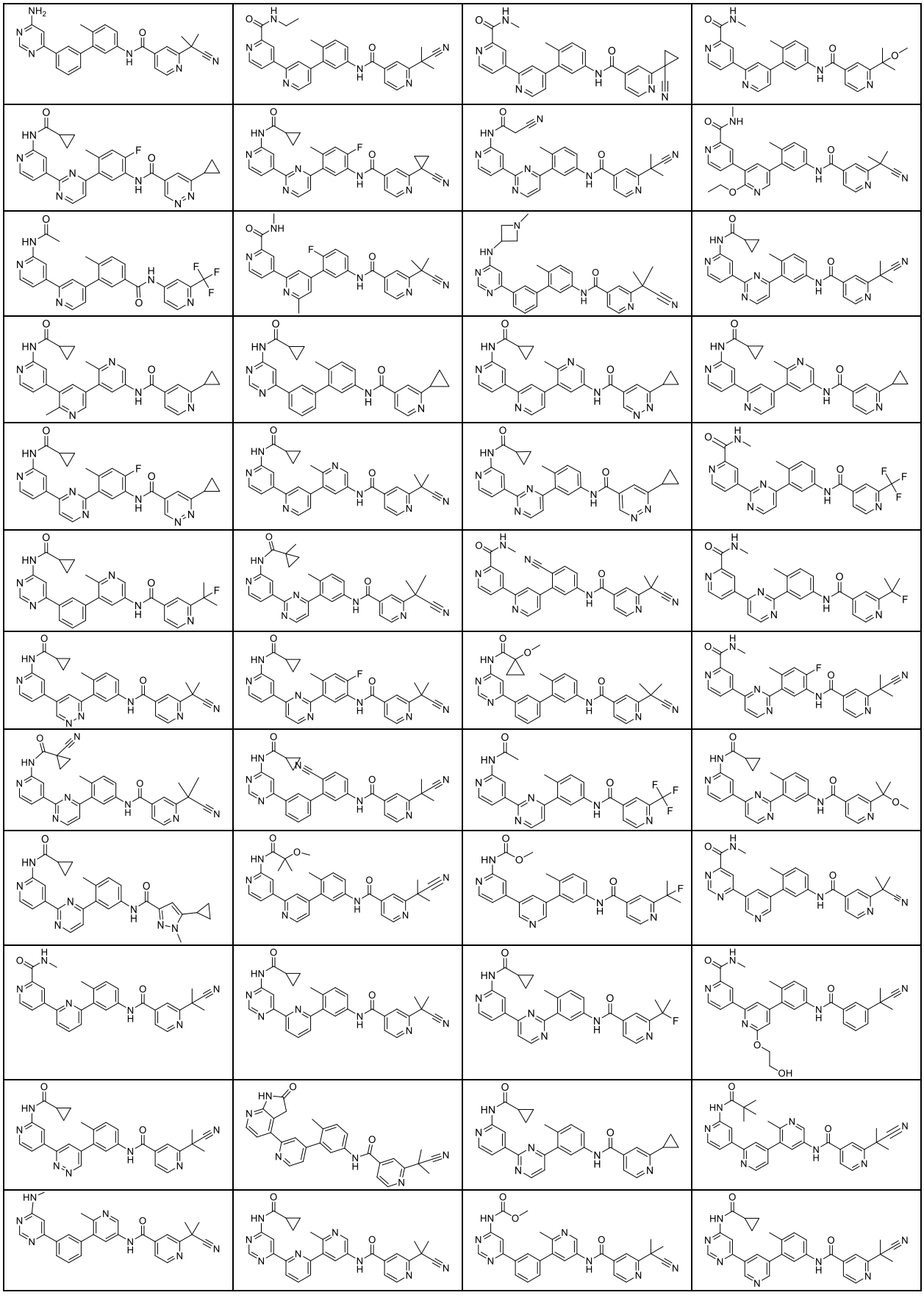


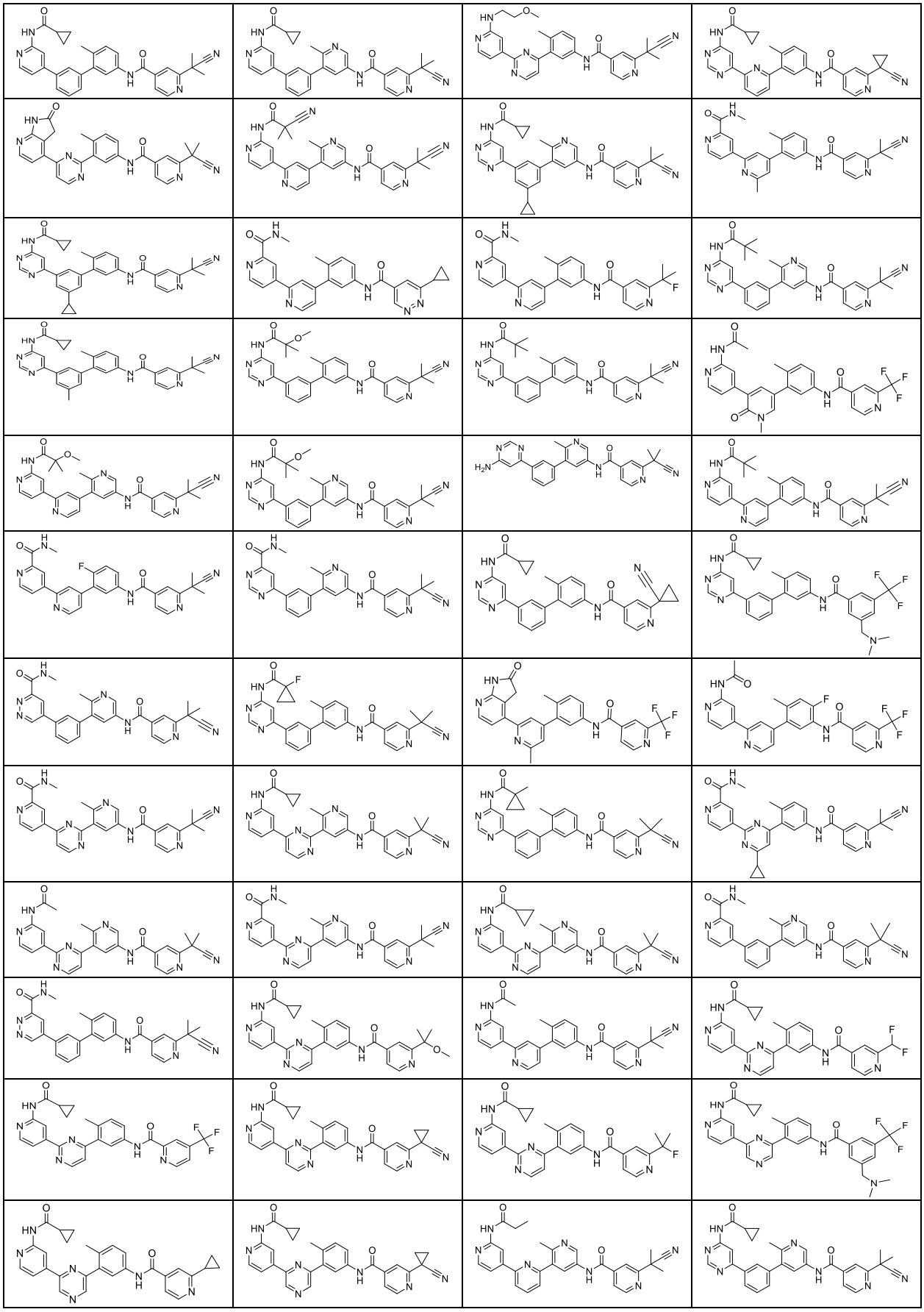


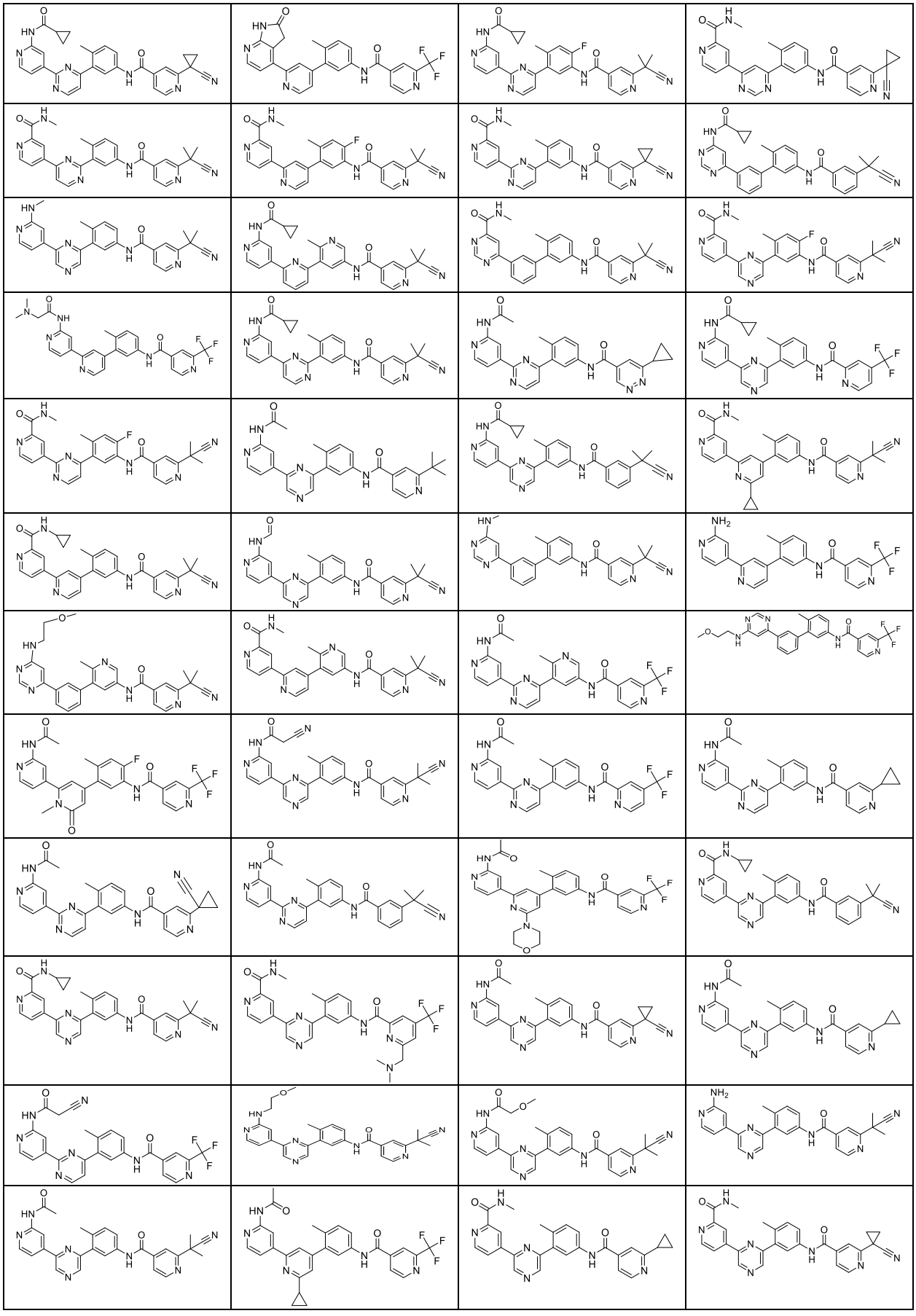


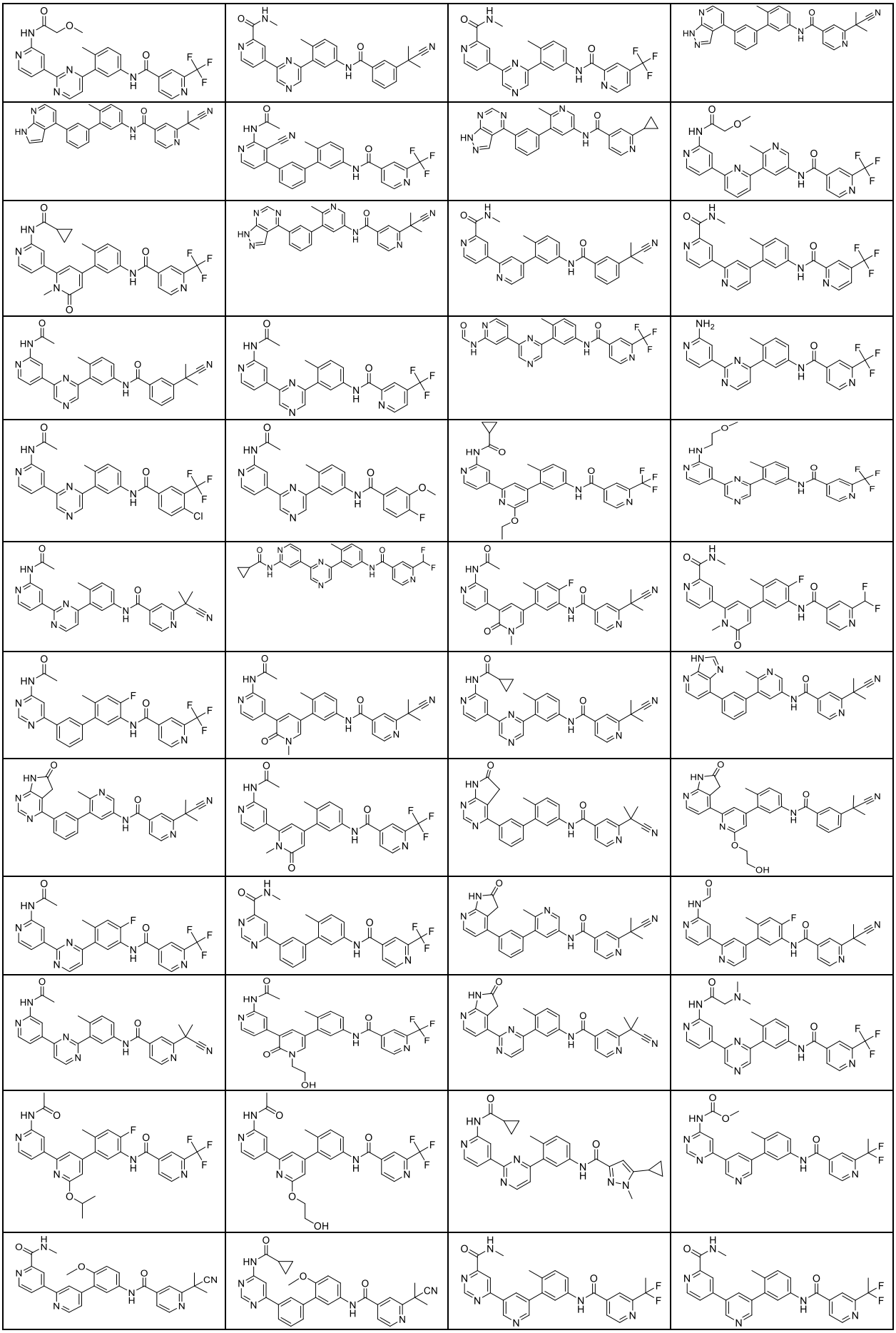


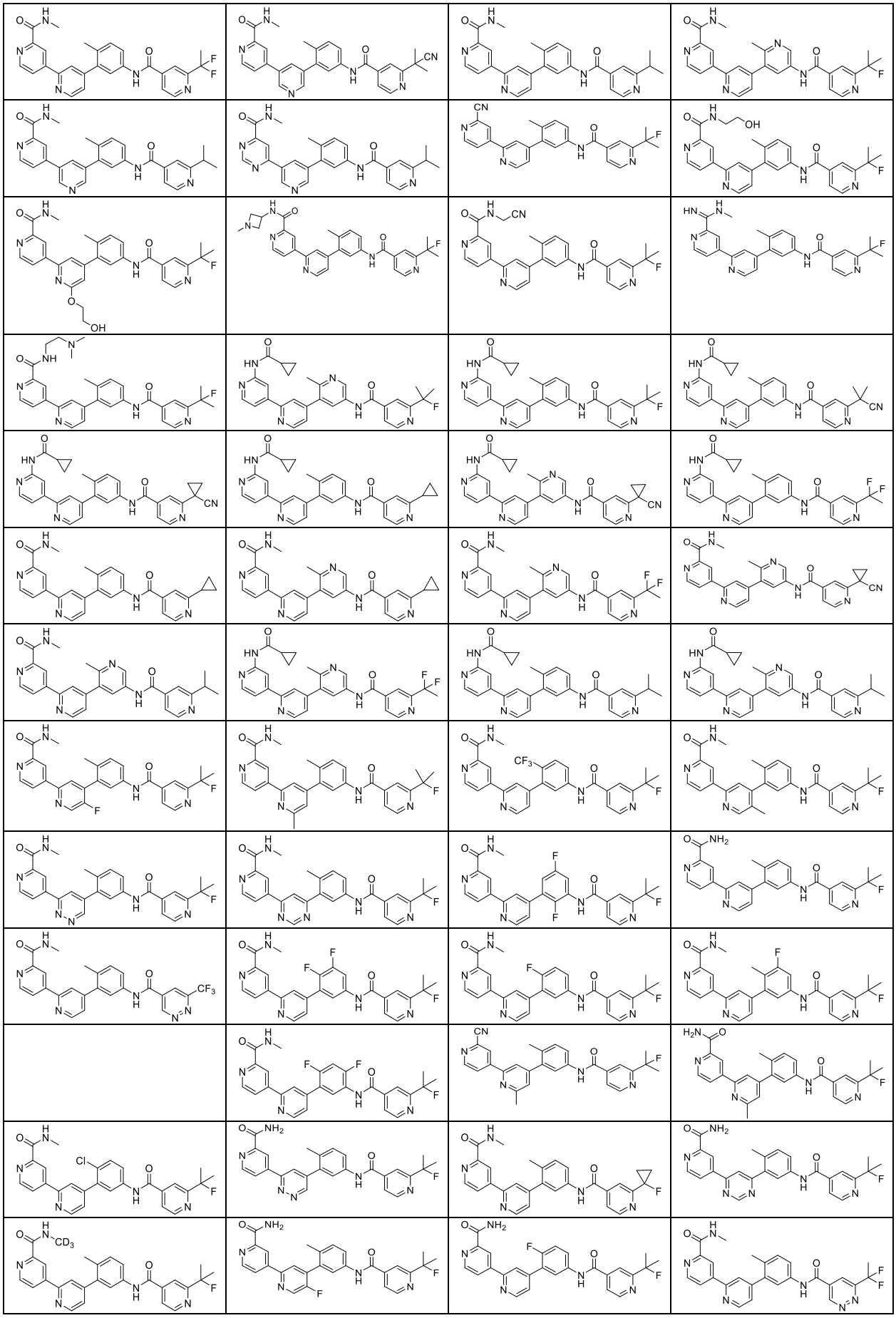


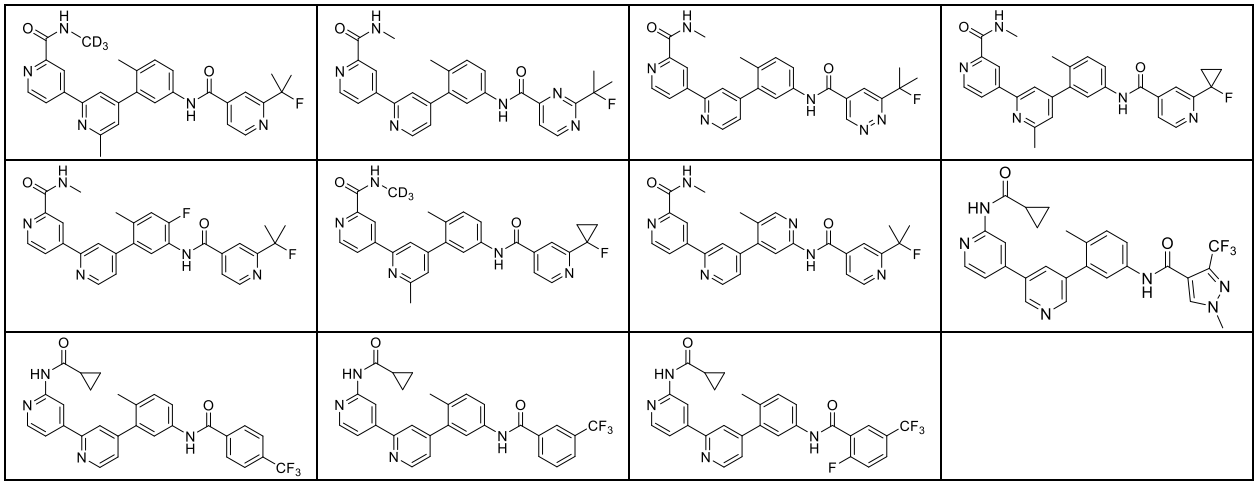












and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

90. A pharmaceutical composition comprising the compound according to any one of claims 1-89, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

91. Use of a compound of any one of claims 1-89, or of a pharmaceutical composition of claim 90, in the manufacture of a medicament for treating a cancer in a patient in need thereof.

92. The use of claim 91, wherein the cancer is selected from the group consisting of melanoma, multiple myeloma, thyroid cancer, ovarian cancer, colorectal cancer, colon cancer, pancreatic cancer, lung cancer, bladder cancer, gastrointestinal stromal tumors, solid tumors, brain cancers, gliomas, glioblastomas, astrocytomas, blood-borne cancers, hairy cell leukemia, acute myelogenous leukemia (AML), or other cancers caused by activation of the RAS→RAF→MEK→ ERK signaling pathway.

93. The use of claim 91 or 92, wherein the cancer has a BRAF oncogenic mutation.

94. The use of any one of claims 91-93, wherein the cancer has a RAS oncogenic mutation.

95. The use of claim 94, wherein the RAS oncogenic mutation is RAS Q61R or Q61K mutation.

96. The uses of any one of claims 91-95, wherein the cancer has a NF1 oncogenic mutation.

97. Use of a compound of any one of claims 1-89, or of a pharmaceutical composition of claim 90, in the manufacture of a medicament for treating a disorder selected from the group consisting of melanoma, multiple myeloma, thyroid cancer, ovarian cancer, colorectal cancer, colon cancer, pancreatic cancer, lung cancer, bladder cancer, gastrointestinal stromal tumors,

solid tumors, brain cancers, gliomas, glioblastomas, astrocytomas, blood-borne cancers, hairy cell leukemia, acute myelogenous leukemia (AML), other cancers caused by activation of the RAS→RAF→MEK→ ERK signaling pathway in a patient in need thereof.

98. A compound of any one of claims 1-89, or a pharmaceutical composition of claim 90, for use in therapy.