pathway, mTOR, the Tec family kinases, and the Rho family GTPases. The class II and III PI3-Ks play a key role in intracellular trafficking through the synthesis of PI(3)P and PI(3,4)P2. The PIKKs are protein kinases that control cell growth (mTORC1) or monitor genomic integrity (ATM, ATR, DNA-PK, and hSmg-1).

[0007] The production of PIP_3 initiates potent growth and survival signals. In some epithelial cancers the PI3K pathway is activated by direct genetic mutation. As PI3K signaling pathway plays a pivotal role in cell proliferation and differentiation, inhibition of this pathway is believed to be beneficial in hyperproliferative diseases.

[0008] Downstream mediators of the PI3K signal transduction pathway include Akt and mammalian target of rapamycin (mTOR). Akt posseses a plckstrin homology (PH) domain that bind PIP3, leading to Akt kinase activation. Akt phosphorylates many substrates and is a central downstream effector of PI3K for diverse cellular responses. Full activation of Akt typically requires phosphorylation of T308 in the activation loop and S473 in a hydrophobic motif. One important function of Akt is to augment the activity of mTOR, through phosphorylation of TSC2 and other mechanisms.

[0009] mTOR is a serine-threonine kinase related to the lipid kinases of the PI3K family. mTOR has been implicated in a wide range of biological processes including cell growth, cell proliferation, cell motility and survival. Disregulation of the mTOR pathway has been reported in various types of cancer. mTOR is a multifunctional kinase that integrates growth factor and nutrient signals to regulate protein translation, nutrient uptake, autophagy, and mitochondrial function.

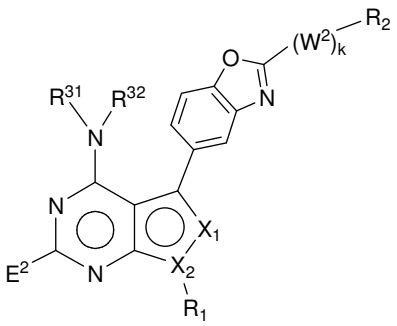
[0010] mTOR exists in two complexes, mTORC1 and mTORC2. mTORC1 contains the raptor subunit and mTORC2 contains rictor. These complexes are differentially regulated, and have distinct substrate specificities and rapamycin sensitivity. For example, mTORC1 phosphorylates S6 kinase (S6K) and 4EBP1, promoting increased translation and ribosome biogenesis to facilitate cell growth and cell cycle progression. S6K also acts in a feedback pathway to attenuate PI3K/Akt activation. mTORC2 is generaly insensitive to rapamycin. mTORC2 is though to modulate growth factor signaling by phosphorylating the C-terminal hydrophobic motif of some AGC kinases such as Akt. In many cellular contexts, mTORC2 is required for phosphorylation of the S473 site of Akt.

[0011] Over the past decade, mTOR has drawn considerable attention due to its role in cell growth control and its involvement in human diseases. mTor has been implicated in a wide range of disorders including but not limited to cancer, diabetes, obesity, cardiovascular diseases and neurological disorders. It has been shown that mTOR modulates many fundamental biological processes including transcription, translation, autophagy, actin organization and ribosome biogenesis by integrating intracellular and extracellular signals, such as signals mediated by growth factors, nutrients, energy levels and cellular stress.

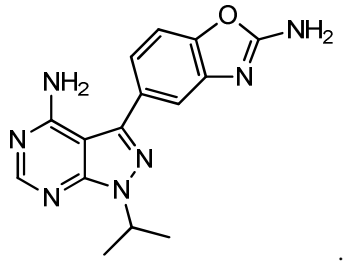
[0012] As such, kinases particularly protein kinases such as mTor and Akt, as well as lipid kinases such as PI3Ks are prime targets for drug development. The present invention addresses this need in the art by providing a new class of kinase inhibitors.

SUMMARY OF THE INVENTION

[0012a] In one aspect, the present invention refers to a compound of formula II-A-1:

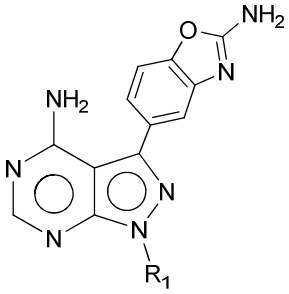


or a pharmaceutically acceptable salt thereof, wherein:X_1 is N;X_2 is N;R_1 is hydrogen, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L-C_{1-10}alkylheterocylyl, -L-heteroalkyl, or -L-heterocyclyl, each of which is unsubstituted or substituted by one or more independent R^3 substituents;L is a bond, C=O, -C(=O)O-, -C(=O)N(R^{31})-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$N(R^{31})-, or -N(R^{31})-;k is 1;E^2 is H;W^2 is –NR^7–, C(O)N(R^7)–, or –N(R^7)C(O);R^3 is halogen, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, or –CO_2R^{31};R^2 is hydrogen, C_{1-10}alkyl, or C_{3-8}cycloalkyl;each of R^{31} and R^{32} is independently H or unsubstituted C_{1-10}alkyl;R^{34} and R^{35} in –$NR^{34}R^{35}$ are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more –$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, hetaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom; andR^7 is hydrogen or C_{1-10}alkyl. In another aspect, the present invention refers to a compound of Formula:

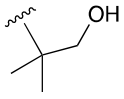


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In yet another aspect, the present invention refers to a compound of Formula:

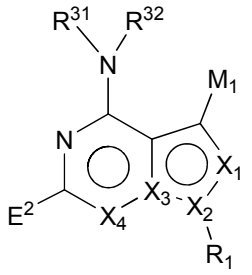


, or pharmaceutically acceptable salt thereof, wherein R_1 is-



. In yet another aspect, the present invention refers to a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of the present invention and a pharmaceutically acceptable carrier. In another aspect, the present invention refers to the use of the compound or pharmaceutically acceptable salt of the present invention for the manufacture of a medicament for inhibiting activity of mTor in a cell from a subject suffering from a disorder selected from the group consisting of cancer, diabetes, obesity, cardiovascular disease, neurological disorders, kidney diseases, bone disorder, inflammatory disease, immune disease, nervous system disease, metabolic disease, and respiratory disease.

[0013] In one example of the disclosure, compounds are provided of the Formula I'-A'



Formula I'-A'

[0014] or a pharmaceutically acceptable salt thereof, wherein:

[0015] X_1 is N or C-E^1, X_2 is N, X_3 is C, and X_4 is C-R^9 or N; or X_1 is N or C-E^1, X_2 is C, X_3 is N, and X_4 is C-R^9 or N;

[0016] R_1 is H, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L-C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[0017] L is absent, -(C=O)-, -C(=O)O-, -C(=O) N(R^{31})-,-S-, -S(O)-, -$S(O)_2$-, -$S(O)_2N(R^{31})$-, or -N(R^{31})-;

[0018] M_1 is benzoxazolyl substituted with –$(W^2)_k$ –R^2 or benzisoxazolyl substituted with –$(W^2)_k$ –R^2;

[0019] k is 0 or 1;

[0020] E^1 and E^2 are independently –$(W^1)_j$ -R^4;

[0021] j in E^1 or j in E^2, is independently 0 or 1;

[0022] W^1 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)S(O)–,–N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, -CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[0023] W^2 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)C(O)N(R^8)–,–N(R^7)S(O)–, –N(R^7)$S(O)_2$–,–C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[0024] R^3 and R^4 are independently hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –N$R^{31}R^{32}$, –N$R^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)N$R^{31}R^{32}$, –C(=O)N$R^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2N R^{31}R^{32}$, –$SO_2N R^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)N$R^{32}R^{33}$, –NR^{31}S(O)$_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})N$R^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)N$R^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)OR^{31}OR^{32}, –SC(=O)N$R^{31}R^{32}$, aryl, heteroaryl, C_{1-4}alkyl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl

or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or –$C(=O)NR^{31}R^{32}$;

[0025] R^2 is hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, –$SC(=O)NR^{31}R^{32}$, aryl (e.g. bicyclic aryl, unsubstituted aryl, or substituted monocyclic aryl), heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl (e.g. C_{2-10}alkyl-monocyclic aryl, C_{1-10}alkyl-substituted monocyclic aryl, or C_{1-10}alkylbicycloaryl), C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heteroalkyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl (e.g. monocyclic aryl-C_{2-10}alkyl, substituted monocyclic aryl- C_{1-10}alkyl, or bicycloaryl-–C_{1-10}alkyl), aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said bicyclic aryl or heteroaryl moiety is unsubstituted, or wherein each of bicyclic aryl, heteroaryl moiety or monocyclic aryl moiety is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, -OH, -R^{31}, -CF_3, -OCF_3, -OR^{31}, -O-aryl, -$NR^{31}R^{32}$, -$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or -$C(=O)NR^{31}R^{32}$;

[0026] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-10}alkyl, –CF_3, -O-aryl, –OCF_3, –OC_{1-10}alkyl, -NH_2, – N(C_{1-10}alkyl)(C_{1-10}alkyl), – NH(C_{1-10}alkyl), – NH(aryl), –$NR^{34}R^{35}$, –C(O)(C_{1-10}alkyl), –C(O)(C_{1-10}alkyl-aryl), –C(O)(aryl), –CO_2-C_{1-10}alkyl, –CO_2-C_{1-10}alkylaryl, –CO_2-aryl, –C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl), –C(=O)NH(C_{1-10}alkyl), –$C(=O)NR^{34}R^{35}$, –$C(=O)NH_2$, -OCF_3, –O(C_{1-10}alkyl), -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, –$S(O)_{0-2}$ C_{1-10}alkyl, –$S(O)_{0-2}$ C_{1-10}alkylaryl, –$S(O)_{0-2}$ aryl, –SO_2N(aryl), –SO_2 N(C_{1-10}alkyl)(C_{1-10}alkyl), –SO_2 NH(C_{1-10}alkyl) or –$SO_2NR^{34}R^{35}$;

[0027] R^{34} and R^{35} in $-NR^{34}R^{35}$, $-C(=O)NR^{34}R^{35}$, or $-SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

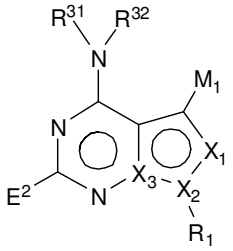
[0028] each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6;

[0029] R^6 is halo, $-OR^{31}$, –SH, $-NH_2$, $-NR^{34}R^{35}$, $-NR^{31}R^{32}$, $-CO_2R^{31}$, $-CO_2$aryl, $-C(=O)NR^{31}R^{32}$, $C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $-S(O)_{0-2}C_{1-10}$alkyl, $-S(O)_{0-2}$aryl, $-SO_2NR^{34}R^{35}$, $-SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl; aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, heteroaryl-C_{2-10}alkynyl, wherein each of said alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more independent halo, cyano, nitro, $-OC_{1-10}$alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, $-C(=O)NR^{31}R^{32}$, $-C(=O)NR^{34}R^{35}$, $-SO_2NR^{34}R^{35}$, $-SO_2NR^{31}R^{32}$, $-NR^{31}R^{32}$, or $-NR^{34}R^{35}$; and

[0030] R^9 is H, halo, $-OR^{31}$, –SH, $-NH_2$, $-NR^{34}R^{35}$, $-NR^{31}R^{32}$, $-CO_2R^{31}$, $-CO_2$aryl, $-C(=O)NR^{31}R^{32}$, $C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $-S(O)_{0-2}C_{1-10}$alkyl, $-S(O)_{0-2}$aryl, $-SO_2NR^{34}R^{35}$, $-SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl; aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, heteroaryl-C_{2-10}alkynyl, wherein each of said alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more independent halo, cyano, nitro, $-OC_{1-10}$alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, $-C(=O)NR^{31}R^{32}$, $-C(=O)NR^{34}R^{35}$, $-SO_2NR^{34}R^{35}$, $-SO_2NR^{31}R^{32}$, $-NR^{31}R^{32}$, or $-NR^{34}R^{35}$.

[0031] In some examples, X_4 is C-R^9. In other examples, X_4 is N.

[0032] The disclosure also provides a compound as defined above, wherein the compound is of Formula I-A:

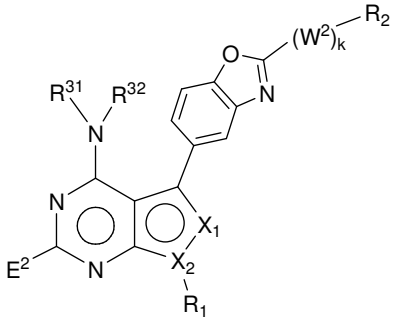


Formula I-A

or a pharnaceutically acceptable salt thereof, and wherein the substituents are as defined above.

[0033] In some examples of the compounds of Formula I'-A' or I-A, X_3 is N.

[0034] In a second example, the disclosure provides a compound of Formula II-A-1:



Formula II-A-1

[0035] or a pharmaceutically acceptable salt thereof, wherein:

[0036] X_1 is N or C-E^1 and X_2 is N; or X_1 is NH or CH-E^1 and X_2 is C;

[0037] R_1 is H, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3; and L is absent, -(C=O)-, -C(=O)O-, -C(=O) $N(R^{31})$-,-S-, -S(O)-, -$S(O)_2$-, -$S(O)_2N(R^{31})$-, or -$N(R^{31})$;

[0038] k is 0 or 1;

[0039] E^1 and E^2 are independently –$(W^1)_j$ -R^4;

[0040] j in E^1 or j in E^2, is independently 0 or 1;

[0041] W^1 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)$N(R^7)$–, –$N(R^7)C(O)$–, –$N(R^7)S(O)$–, –$N(R^7)S(O)_2$–, –C(O)O–, –$CH(R^7)N(C(O)OR^8)$–, –$CH(R^7)N(C(O)R^8)$–, –$CH(R^7)N(SO_2R^8)$–, –$CH(R^7)N(R^8)$–, –$CH(R^7)C(O)N(R^8)$–, –$CH(R^7)N(R^8)C(O)$–, –$CH(R^7)N(R^8)S(O)$–, or –$CH(R^7)N(R^8)S(O)_2$–;

[0042] W^2 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)$N(R^7)$–, –$N(R^7)C(O)$–, –$N(R^7)C(O)N(R^8)$–, –$N(R^7)S(O)$–, –$N(R^7)S(O)_2$–, –C(O)O–, –$CH(R^7)N(C(O)OR^8)$–, –$CH(R^7)N(C(O)R^8)$–, –$CH(R^7)N(SO_2R^8)$–, –$CH(R^7)N(R^8)$–, –$CH(R^7)C(O)N(R^8)$–, –$CH(R^7)N(R^8)C(O)$–, –$CH(R^7)N(R^8)S(O)$–, or –$CH(R^7)N(R^8)S(O)_2$–;

[0043] R^2 is hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, –$SC(=O)NR^{31}R^{32}$, aryl (e.g. bicyclic aryl, unsubstituted aryl, or substituted monocyclic aryl), heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl (e.g. C_{2-10}alkyl-monocyclic aryl, C_{1-10}alkyl-substituted monocyclic aryl, or C_{1-10}alkylbicycloaryl), C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heteroalkyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl (e.g. monocyclic aryl-C_{2-10}alkyl, substituted monocyclic aryl- C_{1-10}alkyl, or bicycloaryl-–C_{1-10}alkyl), aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said bicyclic aryl or heteroaryl moiety is unsubstituted, or wherein each of bicyclic aryl, heteroaryl moiety or monocyclic aryl moiety is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or

is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$;

[0044] R^3 and R^4 are independently hydrogen, halogen, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, $–SC(=O)NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or$–SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$;

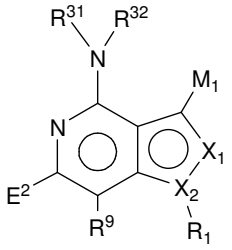
[0045] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-10}alkyl, $–CF_3$, -O-aryl, $–OCF_3$, $–OC_{1-10}$alkyl, $-NH_2$, – N(C_{1-10}alkyl)(C_{1-10}alkyl), – NH(C_{1-10}alkyl), – NH(aryl), $–NR^{34}R^{35}$, –C(O)(C_{1-10}alkyl), –C(O)(C_{1-10}alkyl-aryl), –C(O)(aryl), $–CO_2$-C_{1-10}alkyl, $–CO_2$-C_{1-10}alkylaryl, $–CO_2$-aryl, –C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl), –C(=O)NH(C_{1-10}alkyl), $–C(=O)NR^{34}R^{35}$, $–C(=O)NH_2$, $-OCF_3$, –O(C_{1-10}alkyl), -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, $–S(O)_{0–2}$ C_{1-10}alkyl, $–S(O)_{0–2}$ C_{1-10}alkylaryl, $–S(O)_{0–2}$ aryl, $–SO_2$N(aryl), $–SO_2$ N(C_{1-10}alkyl)(C_{1-10}alkyl), $–SO_2$ NH(C_{1-10}alkyl) or $–SO_2NR^{34}R^{35}$;

[0046] R^{34} and R^{35} in $–NR^{34}R^{35}$, $–C(=O)NR^{34}R^{35}$, or $–SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

[0047] each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6; and

[0048] R^6 is halo, $–OR^{31}$, –SH, NH_2, $–NR^{34}R^{35}$, $– NR^{31}R^{32}$, $–CO_2R^{31}$, $–CO_2$aryl, $–C(=O)NR^{31}R^{32}$, $C(=O) NR^{34}R^{35}$, $–NO_2$, –CN, $–S(O)_{0–2}$ C_{1-10}alkyl, $–S(O)_{0–2}$aryl, $–SO_2NR^{34}R^{35}$, $–SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl; or R^6 is aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, heteroaryl-C_{2-10}alkynyl, each of which is unsubstituted or is substituted with one or more independent halo, cyano, nitro, $–OC_{1-10}$alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, $–C(=O)NR^{31}R^{32}$, $–C(=O) NR^{34}R^{35}$, $–SO_2NR^{34}R^{35}$, $–SO_2 NR^{31}R^{32}$, $-NR^{31}R^{32}$, or $– NR^{34}R^{35}$.

[0049] In a third example, the disclosure provides a compound of Formula III:



Formula III

[0050] or a pharmaceutically acceptable salt thereof, wherein:

[0051] X_1 is N or C-E^1 and X_2 is N; or X_1 is NH or CH-$E^1$and X_2 is C;

[0052] R_1 is –H, $–L-C_{1-10}$alkyl, $-L-C_{3-8}$cycloalkyl, $-L-C_{1-10}$alkyl $-C_{3-8}$cycloalkyl, -L- aryl, -L-heteroaryl, $-L-C_{1-10}$alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, $-L-C_{2-10}$alkenyl, $-L-C_{2-10}$alkynyl, $-L-C_{2-10}$alkenyl-C_{3-8}cycloalkyl, $-L-C_{2-10}$alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[0053] L is absent, -(C=O)-, -C(=O)O-, -C(=O) $N(R^{31})$-,-S-, -S(O)-, $-S(O)_2$-, $-S(O)_2N(R^{31})$-, or $-N(R^{31})$-;

[0054] M_1 is benzoxazolyl substituted with $–(W^2)_k –R^2$;

[0055] k is 0 or 1;

[0056] E^1 and E^2 are independently $–(W^1)_j -R^4$;

[0057] j in E^1 or j in E^2, is independently 0 or 1;

[0058] W^1 is –O–, $–NR^7–$, $–S(O)_{0-2}–$,–C(O)–,–C(O)N(R^7)–, $–N(R^7)C(O)–$, $–N(R^7)S(O)–$,$–N(R^7)S(O)_2–$, –C(O)O–, $–CH(R^7)N(C(O)OR^8)–$, $–CH(R^7)N(C(O)R^8)–$, $–CH(R^7)N(SO_2R^8)–$, $–CH(R^7)N(R^8)–$, $–CH(R^7)C(O)N(R^8)–$, $-CH(R^7)N(R^8)C(O)–$, $–CH(R^7)N(R^8)S(O)–$, or $–CH(R^7)N(R^8)S(O)_2–$;

[0059] W^2 is –O–, $–NR^7–$, $–S(O)_{0-2}–$,–C(O)–,–C(O)N(R^7)–, $–N(R^7)C(O)–$, $–N(R^7)C(O)N(R^8)–$,$–N(R^7)S(O)–$, $–N(R^7)S(O)_2–$,–C(O)O–, $–CH(R^7)N(C(O)OR^8)–$, $–CH(R^7)N(C(O)R^8)–$, $–CH(R^7)N(SO_2R^8)–$, $–CH(R^7)N(R^8)–$, $–CH(R^7)C(O)N(R^8)–$, $–CH(R^7)N(R^8)C(O)–$, $–CH(R^7)N(R^8)S(O)–$, or $–CH(R^7)N(R^8)S(O)_2–$;

[0060] R^2 is hydrogen, halogen, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, $–SC(=O)NR^{31}R^{32}$, aryl (e.g. bicyclic aryl, unsubstituted aryl, or substituted monocyclic aryl), heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl (e.g. C_{2-10}alkyl-monocyclic aryl, C_{1-10}alkyl-substituted monocyclic aryl, or C_{1-10}alkylbicycloaryl), C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-}

$_{10}$alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heteroalkyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl (e.g. monocyclic aryl-C_{2-10}alkyl, substituted monocyclic aryl- C_{1-10}alkyl, or bicycloaryl-–C_{1-10}alkyl), aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said bicyclic aryl, heteroaryl moiety or monocyclic aryl moiety is unsubstituted, or wherein each of bicyclic aryl, heteroaryl moiety or monocyclic aryl moiety is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$;

[0061] R^3 and R^4 are independently hydrogen, halogen, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, $–SC(=O)NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$;

[0062] each of R^{31}, R^{32}, and R^{33} is are independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-}

$_{10}$alkyl, –CF_3, -O-aryl, –OCF_3, –OC_{1-10}alkyl, -NH_2, – N(C_{1-10}alkyl)(C_{1-10}alkyl), – NH(C_{1-10}alkyl), – NH(aryl), – $NR^{34}R^{35}$, –C(O)(C_{1-10}alkyl), –C(O)(C_{1-10}alkyl-aryl), –C(O)(aryl), –CO_2-C_{1-10}alkyl, –CO_2-C_{1-10}alkylaryl, –CO_2-aryl, –C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl), –C(=O)NH(C_{1-10}alkyl), –$C(=O)NR^{34}R^{35}$, –$C(=O)NH_2$, -OCF_3, –O(C_{1-10}alkyl), -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, –$S(O)_{0–2}$ C_{1-10}alkyl, –$S(O)_{0–2}$ C_{1-10}alkylaryl, –$S(O)_{0–2}$ aryl, –SO_2N(aryl), – SO_2 N(C_{1-10}alkyl)(C_{1-10}alkyl), –SO_2 NH(C_{1-10}alkyl) or –$SO_2NR^{34}R^{35}$;

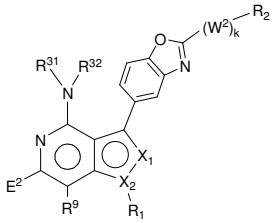
[0063] R^{34} and R^{35} in –$NR^{34}R^{35}$, –$C(=O)NR^{34}R^{35}$, or –$SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

[0064] each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6;

[0065] R^6 is halo, –OR^{31}, –SH, -NH_2, –$NR^{34}R^{35}$, – $NR^{31}R^{32}$, –CO_2R^{31}, –CO_2aryl, –$C(=O)NR^{31}R^{32}$, $C(=O)NR^{34}R^{35}$, –NO_2, –CN, –$S(O)_{0–2}$ C_{1-10}alkyl, –$S(O)_{0–2}$aryl, –$SO_2NR^{34}R^{35}$, –$SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl; aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, heteroaryl-C_{2-10}alkynyl, wherein each of said alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more independent halo, cyano, nitro, –OC_{1-10}alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, –$SO_2NR^{34}R^{35}$, –SO_2 $NR^{31}R^{32}$, -$NR^{31}R^{32}$, or –$NR^{34}R^{35}$; and

[0066] R^9 is H, halo, –OR^{31}, –SH, -NH_2, –$NR^{34}R^{35}$, – $NR^{31}R^{32}$, –CO_2R^{31}, –CO_2aryl, –$C(=O)NR^{31}R^{32}$, $C(=O)NR^{34}R^{35}$, –NO_2, –CN, –$S(O)_{0–2}$ C_{1-10}alkyl, –$S(O)_{0–2}$aryl, –$SO_2NR^{34}R^{35}$, –$SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl; aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, heteroaryl-C_{2-10}alkynyl, wherein each of said alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more independent halo, cyano, nitro, –OC_{1-10}alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, –$SO_2NR^{34}R^{35}$, –SO_2 $NR^{31}R^{32}$, -$NR^{31}R^{32}$, or –$NR^{34}R^{35}$.

[0067] In yet another example, the disclosure provides a compound of Formula IV-A-1:



Formula IV-A-1

[0068] or a pharmaceutically acceptable salt thereof wherein:

[0069] X_1 is N or C-E^1 and X_2 is N; or X_1 is NH or CH-$E^1$and X_2 is C;

[0070] R_1 is –H, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[0071] L is absent, -(C=O)-, -C(=O)O-, -C(=O) $N(R^{31})$-,-S-, -S(O)-, $-S(O)_2$-, $-S(O)_2N(R^{31})$-, or $-N(R^{31})$-;

[0072] E^1 and E^2 are independently $-(W^1)_j-R^4$;

[0073] j in E^1 or j in E^2, is independently 0 or 1;

[0074] W^1 is $-O-$, $-NR^7-$, $-S(O)_{0-2}-$,$-C(O)-$,$-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)S(O)-$, $-N(R^7)S(O)_2-$, $-C(O)O-$, $-CH(R^7)N(C(O)OR^8)-$, $-CH(R^7)N(C(O)R^8)-$, $-CH(R^7)N(SO_2R^8)-$, $-CH(R^7)N(R^8)-$, $-CH(R^7)C(O)N(R^8)-$, $-CH(R^7)N(R^8)C(O)-$, $-CH(R^7)N(R^8)S(O)-$, or $-CH(R^7)N(R^8)S(O)_2-$;

[0075] W^2 is $-O-$, $-NR^7-$, $-S(O)_{0-2}-$,$-C(O)-$,$-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)C(O)N(R^8)-$, $-N(R^7)S(O)-$, $-N(R^7)S(O)_2-$, $-C(O)O-$, $-CH(R^7)N(C(O)OR^8)-$, $-CH(R^7)N(C(O)R^8)-$, $-CH(R^7)N(SO_2R^8)-$, $-CH(R^7)N(R^8)-$, $-CH(R^7)C(O)N(R^8)-$, $-CH(R^7)N(R^8)C(O)-$, $-CH(R^7)N(R^8)S(O)-$, or $-CH(R^7)N(R^8)S(O)_2-$;

[0076] k is 0 or 1;

[0077] R^2, R^3 and R^4 are independently hydrogen, halogen, –OH, $-R^{31}$, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-NR^{34}R^{35}$, $-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}R^{32}$, $-C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $-S(O)_{0-2}R^{31}$, $-SO_2NR^{31}R^{32}$, $-SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{32}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{33}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, $-P(O)OR^{31}OR^{32}$, $-SC(=O)NR^{31}R^{32}$, aryl (e.g. bicyclic aryl, unsubstituted aryl, or substituted monocyclic aryl), heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl (e.g. C_{2-10}alkyl-monocyclic aryl, C_{1-10}alkyl-substituted monocyclic aryl, or C_{1-10}alkylbicycloaryl), C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heteroalkyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl (e.g. monocyclic aryl-C_{2-10}alkyl, substituted monocyclic aryl- C_{1-10}alkyl, or bicycloaryl-–C_{1-10}alkyl), aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $-R^{31}$, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-NR^{34}R^{35}$, $-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}R^{32}$, $-C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $-S(O)_{0-2}R^{31}$, $-SO_2NR^{31}R^{32}$, $-SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{32}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{33}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, $-P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $-R^{31}$, $-CF_3$, $-OCF_3$, $-OR^{31}$, –O-aryl, $-NR^{31}R^{32}$, $-NR^{34}R^{35}$,$-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{34}R^{35}$, or $-C(=O)NR^{31}R^{32}$;

[0078] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-10}alkyl, $-CF_3$, -O-aryl, $-OCF_3$, $-OC_{1-10}$alkyl, $-NH_2$, – $N(C_{1-10}alkyl)(C_{1-10}alkyl)$, – $NH(C_{1-10}alkyl)$, – NH(aryl), – $NR^{34}R^{35}$, $-C(O)(C_{1-10}alkyl)$, $-C(O)(C_{1-10}alkyl\text{-}aryl)$, –C(O)(aryl), $-CO_2-C_{1-10}$alkyl, $-CO_2-C_{1-10}$alkylaryl, $-CO_2$-aryl, $-C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $-C(=O)NH(C_{1-10}alkyl)$, $-C(=O)NR^{34}R^{35}$, $-C(=O)NH_2$, $-OCF_3$, $-O(C_{1-10}alkyl)$, -O-

aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, –$S(O)_{0–2}$ C_{1-10}alkyl, –$S(O)_{0–2}$ C_{1-10}alkylaryl, –$S(O)_{0–2}$ aryl, –SO_2N(aryl), –SO_2 N(C_{1-10}alkyl)(C_{1-10}alkyl), –SO_2 NH(C_{1-10}alkyl) or –$SO_2NR^{34}R^{35}$;

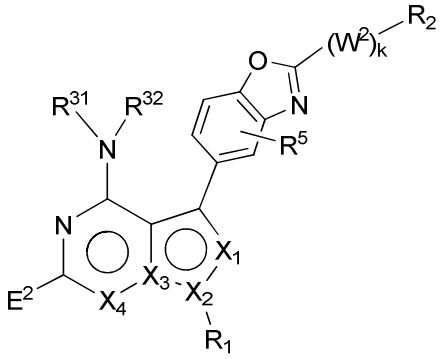
[0079] R^{34} and R^{35} in –$NR^{34}R^{35}$, –C(=O)$NR^{34}R^{35}$, or –$SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

[0080] each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6;

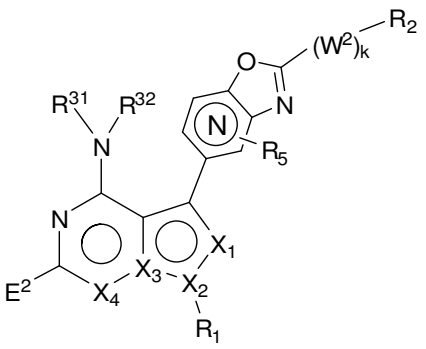
[0081] R^6 is halo, –OR^{31}, –SH, -NH_2, –$NR^{34}R^{35}$, – $NR^{31}R^{32}$, –CO_2R^{31}, –CO_2aryl, –C(=O)$NR^{31}R^{32}$, C(=O)$NR^{34}R^{35}$, –NO_2, –CN, –$S(O)_{0–2}$ C_{1-10}alkyl, –$S(O)_{0–2}$aryl, –$SO_2NR^{34}R^{35}$, –$SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl; aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, heteroaryl-C_{2-10}alkynyl, wherein each of said alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more independent halo, cyano, nitro, –OC_{1-10}alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, –$SO_2NR^{34}R^{35}$, –SO_2 $NR^{31}R^{32}$, -$NR^{31}R^{32}$, or –$NR^{34}R^{35}$; and

[0082] R^9 is H, halo, –OR^{31}, –SH, -NH_2, –$NR^{34}R^{35}$, – $NR^{31}R^{32}$, –CO_2R^{31}, –CO_2aryl, –C(=O)$NR^{31}R^{32}$, C(=O)$NR^{34}R^{35}$, –NO_2, –CN, –$S(O)_{0–2}$ C_{1-10}alkyl, –$S(O)_{0–2}$aryl, –$SO_2NR^{34}R^{35}$, –$SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl; aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, heteroaryl-C_{2-10}alkynyl, wherein each of said alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more independent halo, cyano, nitro, –OC_{1-10}alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, –$SO_2NR^{34}R^{35}$, –SO_2 $NR^{31}R^{32}$, -$NR^{31}R^{32}$, or –$NR^{34}R^{35}$.

[0083] In another example, the disclosure provides a compound of Formula IV-A or Formula IV-B:



Formula IV-A



Formula IV-B;

or pharmaceutically acceptable salt thereof, wherein:

[0084] X_1 is N or C-E^1, X_2 is N, X_3 is C, and X_4 is CR^9 or N; or X_1 is N or C-E^1, X_2 is C, X_3 is N, and X_4 is CR^9 or N;

[0085] R_1 is –H, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L-C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-}8cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-

heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[0086] L is absent, -(C=O)-, -C(=O)O-, -C(=O) $N(R^{31})$-,-S-, -S(O)-, $-S(O)_2$-, $-S(O)_2N(R^{31})$-, or $-N(R^{31})$-;

[0087] k is 0 or 1;

[0088] E^1 and E^2 are independently $-(W^1)_j$ $-R^4$;

[0089] j in E^1 or j in E^2, is independently 0 or 1;

[0090] W^1 is $-O-$, $-NR^7-$, $-S(O)_{0-2}-$,$-C(O)-$,$-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)S(O)-$,$-N(R^7)S(O)_2-$, $-C(O)O-$, $-CH(R^7)N(C(O)OR^8)-$, $-CH(R^7)N(C(O)R^8)-$, $-CH(R^7)N(SO_2R^8)-$, $-CH(R^7)N(R^8)-$, $-CH(R^7)C(O)N(R^8)-$, $-CH(R^7)N(R^8)C(O)-$, $-CH(R^7)N(R^8)S(O)-$, or $-CH(R^7)N(R^8)S(O)_2-$;

[0091] W^2 is $-O-$, $-NR^7-$, $-S(O)_{0-2}-$,$-C(O)-$,$-C(O)N(R^7)-$, $-N(R^7)C(O)-$, $-N(R^7)C(O)N(R^8)-$,$-N(R^7)S(O)-$, $-N(R^7)S(O)_2-$,$-C(O)O-$, $-CH(R^7)N(C(O)OR^8)-$, $-CH(R^7)N(C(O)R^8)-$, $-CH(R^7)N(SO_2R^8)-$, $-CH(R^7)N(R^8)-$, $-CH(R^7)C(O)N(R^8)-$, $-CH(R^7)N(R^8)C(O)-$, $-CH(R^7)N(R^8)S(O)-$, or $-CH(R^7)N(R^8)S(O)_2-$;

[0092] R^3 and R^4 are independently hydrogen, halogen, –OH, $-R^{31}$, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-NR^{34}R^{35}$, $-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}R^{32}$, $-C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $-S(O)_{0-2}R^{31}$, $-SO_2NR^{31}R^{32}$, $-SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{32}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{33}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, $-P(O)OR^{31}OR^{32}$, $-SC(=O)NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, $-R^{31}$, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-NR^{34}R^{35}$, $-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}R^{32}$, $-C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $-S(O)_{0-2}R^{31}$, $-SO_2NR^{31}R^{32}$, $-SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{32}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{33}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, $-P(O)OR^{31}OR^{32}$, or$-SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, $-R^{31}$, $-CF_3$, $-OCF_3$, $-OR^{31}$, –O-aryl, $-NR^{31}R^{32}$, $-NR^{34}R^{35}$,$-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{34}R^{35}$, or $-C(=O)NR^{31}R^{32}$;

[0093] R^2 is hydrogen, halogen, –OH, $-R^{31}$, $-CF_3$, $-OCF_3$, $-OR^{31}$, $-NR^{31}R^{32}$, $-NR^{34}R^{35}$, $-C(O)R^{31}$, $-CO_2R^{31}$, $-C(=O)NR^{31}R^{32}$, $-C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $-S(O)_{0-2}R^{31}$, $-SO_2NR^{31}R^{32}$, $-SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $-NR^{31}C(=O)OR^{32}$, $-NR^{31}C(=O)NR^{32}R^{33}$, $-NR^{31}S(O)_{0-2}R^{32}$, $-C(=S)OR^{31}$, $-C(=O)SR^{31}$, $-NR^{31}C(=NR^{32})NR^{33}R^{32}$, $-NR^{31}C(=NR^{32})OR^{33}$, $-NR^{31}C(=NR^{32})SR^{33}$, $-OC(=O)OR^{33}$, $-OC(=O)NR^{31}R^{32}$, $-OC(=O)SR^{31}$, $-SC(=O)OR^{31}$, $-P(O)OR^{31}OR^{32}$, $-SC(=O)NR^{31}R^{32}$, aryl (e.g. bicyclic aryl, unsubstituted aryl, or substituted monocyclic aryl), heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl (e.g. C_{2-10}alkyl-monocyclic aryl, C_{1-10}alkyl-substituted monocyclic aryl, or C_{1-10}alkylbicycloaryl), C_{1-10}alkylheteroaryl, C_{1-}

$_{10}$alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heteroalkyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl (e.g. monocyclic aryl-C_{2-10}alkyl, substituted monocyclic aryl- C_{1-10}alkyl, or bicycloaryl-–C_{1-10}alkyl), aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said bicyclic aryl or heteroaryl moiety is unsubstituted, or wherein each of bicyclic aryl, heteroaryl moiety or monocyclic aryl moiety is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or– $SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$;

[0094] R^5 is hydrogen, halogen, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$,or $–SC(=O)NR^{31}R^{32}$;

[0095] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said alkyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-10}alkyl, $–CF_3$, -O-aryl, $–OCF_3$, $–OC_{1-10}$alkyl, $-NH_2$, – $N(C_{1-10}alkyl)(C_{1-10}alkyl)$, – $NH(C_{1-10}alkyl)$, – NH(aryl), – $NR^{34}R^{35}$, $–C(O)(C_{1-10}alkyl)$, $–C(O)(C_{1-10}alkyl\text{-}aryl)$, –C(O)(aryl), $–CO_2$-C_{1-10}alkyl, $–CO_2$-C_{1-10}alkylaryl, $–CO_2$-aryl, $–C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $–C(=O)NH(C_{1-10}alkyl)$, $–C(=O)NR^{34}R^{35}$, $–C(=O)NH_2$, $-OCF_3$, $–O(C_{1-10}alkyl)$, -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, $–S(O)_{0–2}$ C_{1-10}alkyl, $–S(O)_{0–2}$ C_{1-10}alkylaryl, $–S(O)_{0–2}$ aryl, $–SO_2N$(aryl), $–SO_2N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $–SO_2NH(C_{1-10}alkyl)$ or $–SO_2NR^{34}R^{35}$;

[0096] R^{34} and R^{35} in $–NR^{34}R^{35}$, $–C(=O)NR^{34}R^{35}$, or $–SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

[0097] each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6;

[0098] R^6 is halo, $–OR^{31}$, –SH, $-NH_2$, $–NR^{34}R^{35}$, – $NR^{31}R^{32}$, $–CO_2R^{31}$, $–CO_2$aryl, $–C(=O)NR^{31}R^{32}$, $C(=O)NR^{34}R^{35}$, $–NO_2$, –CN, $–S(O)_{0–2}$ C_{1-10}alkyl, $–S(O)_{0–2}$aryl, $–SO_2NR^{34}R^{35}$, $–SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl; aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, heteroaryl-C_{2-}

$_{10}$alkynyl, wherein each of said alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more independent halo, cyano, nitro, –OC$_{1-10}$alkyl, C$_{1-10}$alkyl, C$_{2-10}$alkenyl, C$_{2-10}$alkynyl, haloC$_{1-10}$alkyl, haloC$_{2-10}$alkenyl, haloC$_{2-10}$alkynyl, –COOH, –C(=O)NR^{31}R^{32}, –C(=O) NR^{34}R^{35} , –SO$_2$NR^{34}R^{35}, –SO$_2$ NR^{31}R^{32}, -NR^{31}R^{32}, or –NR^{34}R^{35}; and

[0099] R^9 is H, halo, –OR^{31}, –SH, -NH$_2$, –NR^{34}R^{35} , – NR^{31}R^{32}, –CO$_2$R^{31}, –CO$_2$aryl, –C(=O)NR^{31}R^{32}, C(=O)NR^{34}R^{35} , –NO$_2$, –CN, –S(O) $_{0–2}$ C$_{1-10}$alkyl, –S(O) $_{0–2}$aryl, –SO$_2$NR^{34}R^{35}, –SO$_2$NR^{31}R^{32}, C$_{1-10}$alkyl, C$_{2-10}$alkenyl, C$_{2-10}$alkynyl; aryl-C$_{1-10}$alkyl, aryl-C$_{2-10}$alkenyl, aryl-C$_{2-10}$alkynyl, heteroaryl-C$_{1-10}$alkyl, heteroaryl-C$_{2-10}$alkenyl, heteroaryl-C$_{2-10}$alkynyl, wherein each of said alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more independent halo, cyano, nitro, –OC$_{1-10}$alkyl, C$_{1-10}$alkyl, C$_{2-10}$alkenyl, C$_{2-10}$alkynyl, haloC$_{1-10}$alkyl, haloC$_{2-10}$alkenyl, haloC$_{2-10}$alkynyl, –COOH, –C(=O)NR^{31}R^{32}, –C(=O) NR^{34}R^{35} , –SO$_2$NR^{34}R^{35}, –SO$_2$ NR^{31}R^{32}, -NR^{31}R^{32}, or –NR^{34}R^{35}.

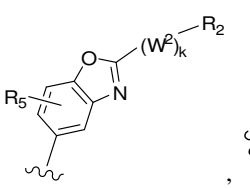
[00100] In one example of the compounds of the disclosure, X$_4$ is CR^9. In another example, X$_4$ is N.

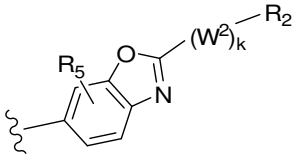
[00101] In some examples of the compounds of the disclosure, E^2 is –H. In some examples of the compounds of the disclosure, X$_1$ is N and X$_2$ is N. In other examples of the compounds of the disclosure, X$_1$ is C-E^1 and X$_2$ is N. In one example of the compounds of the disclosure, X$_1$ is NH and X$_2$ is C.

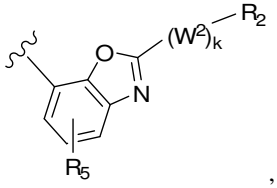
[00102] In some examples of the compounds of the disclosure, R$_{31}$ and R$_{32}$ are –H.

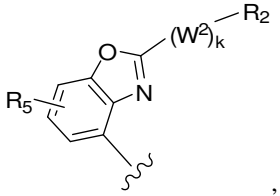
[00103] In some examples of the compounds of Formula I'-A', I-A, I-B, III (including III-A and III-B) , C, or C", M$_1$ is a benzoxazolyl moiety, substituted at the 2-position with –(W$_2$)$_k$-R$_2$. In some examples, M$_1$ is either a 5-benzoxazolyl or a 6- benzoxazolyl moiety, optionally substituted with –(W$_2$)$_k$-R$_2$. In some examples, M$_1$ is either a 5- benzoxazolyl or a 6- benzoxazolyl moiety, optionally substituted at its 2-position with –(W$_2$)$_k$-R$_2$.

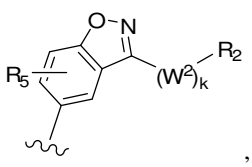
[00104] In some examples of the compounds of the disclosure, M$_1$ is a moiety having one of the following structures:

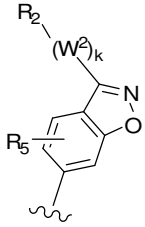


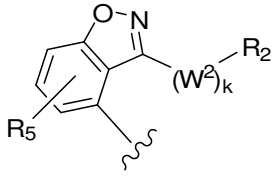
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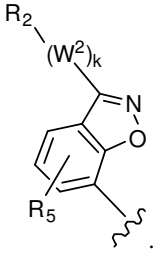
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, or


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[00105] In some examples of the compounds of the disclosure, –(W^2)k– is –NR^7–, –N(R^7)C(O)–, –N(R^7)C(O)N(R^8)–, or –N(R^7)S(O)$_2$–. In other examples of the compounds of the disclosure, –(W^2)$_k$ – is –NH–. In

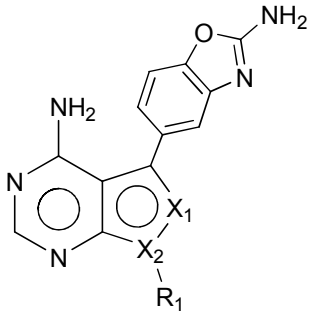
another example of the compounds of the disclosure, $-(W^2)_k-$ is $-(CH)_2-$. In yet another example of the compounds of the disclosure, $-(W^2)_k-$ is –NHC(O)–. In yet another example of the compounds of the disclosure, $-(W^2)_k-$ is —$N(R^7)C(O)N(R^8)$–. In a further example of the compounds of the disclosure, $-(W^2)_k-$ is $-NHS(O)_2-$.

[00106] In some examples of the compounds of the disclosure, R_1 is -L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3, wherein R^3 is hydrogen, –OH, $–OR^{31}$, $–C(O)R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl, heteroaryl, alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl or –OH. In some examples of the compounds of the disclosure, R_1 is unsubstituted or is substituted with C_{1-10}alkyl or cycloC_{3-10}alkyl.

[00107] In some examples of the compounds of the disclosure, R^2 is –H. In other examples of the compounds of the disclosure, R^2 is alkyl. In yet other examples of the compounds of the disclosure, R^2 is methyl. In other examples of the compounds of the disclosure, R^2 is isopropyl. In some examples of the compounds of the disclosure, R^2 is cycloalkyl. In other examples of the compounds of the disclosure, R^2 is cyclopropyl.

[00108] In some examples of the compounds of the disclosure, E^2 is –H; X_1 and X_2 are N; R_1 is –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3; R^3 is hydrogen, –OH, $–OR^{31}$, $–NR^{31}R^{32}$, $–C(O)R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, aryl, heteroaryl, C_{1-4}alkyl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0-2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0-2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$; and wherein $-(W^2)_k-$ is $–NR^7–$, $–N(R^7)C(O)–$ or $–N(R^7)S(O)_2–$.

[00109] In another example, the disclosure provides a compound of formula:



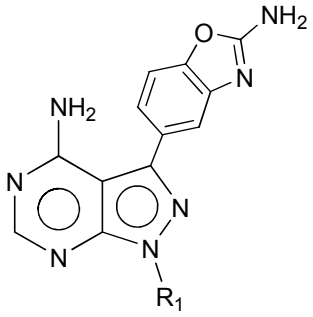
[00110] wherein X_1 is N or C-E^1 and X_2 is N;

[00111] R_1 is –L–C_{1-10}alkyl, -L–C_{3-8}cycloalkyl, -L-C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or substituted by one or more independent R^3 substituents; and

[00112] R^3 is hydrogen, –OH, $–OR^{31}$, $–NR^{31}R^{32}$, $–C(O)R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is

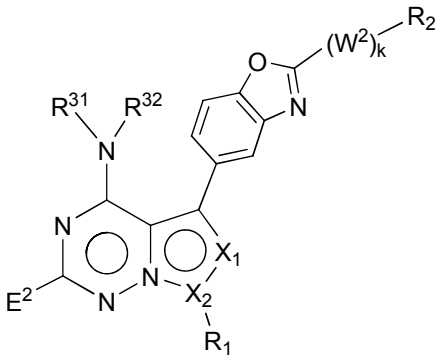
substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or$–SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$.

[00113] In one example, the compound is:



[00114] or a pharmaceutically acceptable salt thereof, wherein R_1 is $–C_{1-10}$alkyl, $–C_{3-8}$cycloalkyl, or $–C_{1-10}$alkylheterocyclyl. For example, R_1 is isopropyl.

[00115] The disclosure further provides a compound of Formula:



[00116] or a pharmaceutically acceptable salt thereof, wherein:

[00117] X_1 is N or C-E^1 and X_2 is N; or X_1 is NH or CH-E^1 and X_2 is C;

[00118] R_1 is hydrogen, $–L-C_{1-10}$alkyl, $-L-C_{3-8}$cycloalkyl, -L- C_{1-10}alkyl $-C_{3-8}$cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, $-L-C_{2-10}$alkenyl, $-L-C_{2-10}$alkynyl, $-L-C_{2-10}$alkenyl-C_{3-8}cycloalkyl, $-L-C_{2-10}$alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or substituted by one or more independent R^3 substituents;

[00119] L is absent, C=O, -C(=O)O-, -C(=O) $N(R^{31})$-,-S-, -S(O)-, $-S(O)_2$-, $-S(O)_2N(R^{31})$-, or $-N(R^{31})$-;

[00120] k is 0 or 1;

[00121] E^1 and E^2 are independently $–(W^1)_j$ $-R^4$;

[00122] j in E^1 or j in E^2, is independently 0 or 1;

[00123] W^1 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)S(O)–, –N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00124] W^2 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)C(O)N(R^8)–, –N(R^7)S(O)–, –N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00125] R^3 and R^4 are independently hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)$OR^{31}OR^{32}$, –SC(=O)$NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)$OR^{31}OR^{32}$, or–SC(=O)$NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{34}R^{35}$, or –C(=O)$NR^{31}R^{32}$;

[00126] R^2 is hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)$OR^{31}OR^{32}$, –SC(=O)$NR^{31}R^{32}$, bicyclic aryl, substituted monocyclic aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl- C_{1-10}alkyl, C_{3-8}cycloalkyl- C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{2-10}alkyl-monocyclic aryl, monocyclic aryl-C_{2-10}alkyl, C_{1-10}alkylbicycloaryl, bicycloaryl-–C_{1-10}alkyl, substituted C_{1-10}alkylaryl, substituted aryl-C_{1-10}alkyl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, heterocyclylC_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said bicyclic aryl, monocyclic aryl, or heteroaryl

moiety is unsubstituted or is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or –$C(=O)NR^{31}R^{32}$;

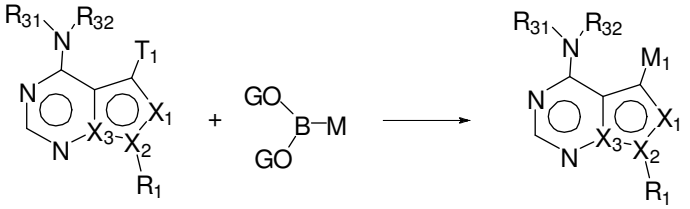
[00127] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl substituent, wherein each of said aryl, heteroalkyl, heterocyclyl, or heteroaryl substituent is unsubstituted or is substituted with one or more halo, –OH, –C_{1-10}alkyl, –CF_3, -O-aryl, –OCF_3, –OC_{1-10}alkyl, -NH_2, – $N(C_{1-10}alkyl)(C_{1-10}alkyl)$, – $NH(C_{1-10}alkyl)$, – NH(aryl), –$NR^{34}R^{35}$, –$C(O)(C_{1-10}alkyl)$, –$C(O)(C_{1-10}alkyl\text{-}aryl)$, –C(O)(aryl), –$CO_2$-$C_{1-10}$alkyl, –$CO_2$-$C_{1-10}$alkylaryl, –$CO_2$-aryl, –$C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl)$, –$C(=O)NH(C_{1-10}alkyl)$, –$C(=O)NR^{34}R^{35}$, –$C(=O)NH_2$, -$OCF_3$, –$O(C_{1-10}alkyl)$, -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, –$S(O)_{0-2}$ C_{1-10}alkyl, –$S(O)_{0-2}$ C_{1-10}alkylaryl, –$S(O)_{0-2}$ aryl, –SO_2N(aryl), –SO_2 $N(C_{1-10}alkyl)(C_{1-10}alkyl)$, –$SO_2$ NH(C_{1-10}alkyl) or –$SO_2NR^{34}R^{35}$;

[00128] R^{34} and R^{35} in –$NR^{34}R^{35}$, –$C(=O)NR^{34}R^{35}$, or –$SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

[00129] each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6 substituents; and

[00130] R^6 is halo, –OR^{31}, –SH, NH_2, –$NR^{34}R^{35}$, – $NR^{31}R^{32}$, –CO_2R^{31}, –CO_2aryl, –$C(=O)NR^{31}R^{32}$, C(=O) $NR^{34}R^{35}$, –NO_2, –CN, –$S(O)_{0-2}$ C_{1-10}alkyl, –$S(O)_{0-2}$aryl, –$SO_2NR^{34}R^{35}$, –$SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, or heteroaryl-C_{2-10}alkynyl, each of which is unsubstituted or is substituted with one or more independent halo, cyano, nitro, –OC_{1-10}alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, –$C(=O)NR^{31}R^{32}$, –C(=O) $NR^{34}R^{35}$, –$SO_2NR^{34}R^{35}$, –SO_2 $NR^{31}R^{32}$, -$NR^{31}R^{32}$, or – $NR^{34}R^{35}$.

[00131] The disclosure also provides a process for synthesizing a compound of Formula C:



Formula A Formula B Formula C

[00132] comprising the step of allowing a compound of Formula A to react with a compound of Formula B under conditions that are effective for synthesizing a compound of Formula C; wherein:

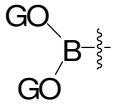
[00133] T_1 is halo;

[00134] X_1 is N or C-E^1, X_2 is N, and X_3 is C; or X_1 is N or C-E^1, X_2 is C, and X_3 is N;

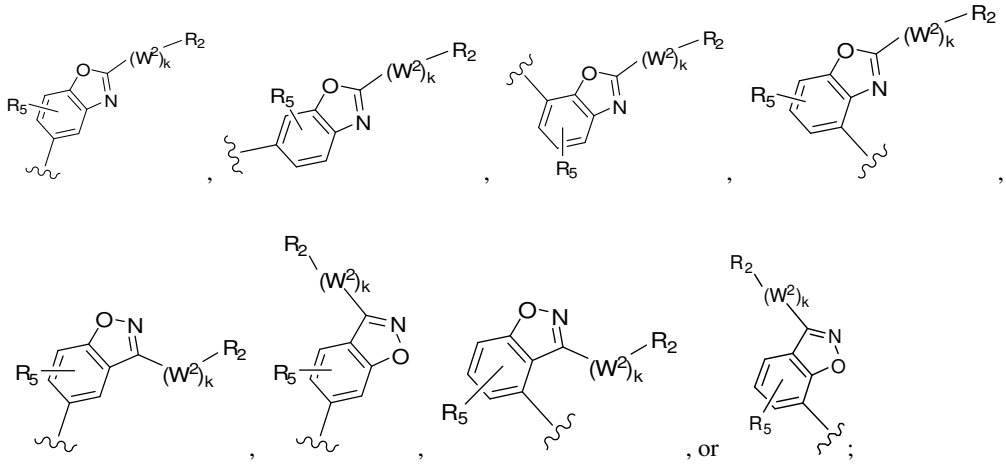
[00135] R_1 is hydrogen, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[00136] L is absent, -(C=O)-, -C(=O)O-, -C(=O) N(R^{31})-,-S-, -S(O)-, -$S(O)_2$-, -$S(O)_2N(R^{31})$-, or -N(R^{31})-;

each of G is independently H or R_{G1}; and R_{G1} is alkyl, alkenyl, or aryl;

or the G groups of  join together to form a 5- or 6- membered cyclic moiety;

[00137] M of Formula B is a M_1 moiety, and wherein M_1 moiety of Formula B and M_1 moiety of Formula C are identical, having one of the following structures:



[00138] E^1 is $–(W^1)_j$ -R^4 wherein j is 0 or 1;

[00139] W^1 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)S(O)–, –N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00140] k is 0 or 1;

[00141] W^2 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)C(O)N(R^8)–, –N(R^7)S(O)–, –N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00142] R^2 is hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)OR^{31}OR^{32}, –SC(=O)$NR^{31}R^{32}$, bicyclic aryl, substituted monocyclic aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl- C_{1-10}alkyl, C_{3-8}cycloalkyl- C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{2-10}alkyl-monocyclic aryl, monocyclic aryl-C_{2-10}alkyl, C_{1-10}alkylbicycloaryl, bicycloaryl-–C_{1-10}alkyl, substituted C_{1-10}alkylaryl, substituted aryl-C_{1-10}alkyl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl,

C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, heterocyclyl, heteroalkyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, or heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said bicyclic aryl or heteroaryl moiety is unsubstituted, or wherein each of bicyclic aryl, heteroaryl moiety or monocyclic aryl moiety is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or –$C(=O)NR^{31}R^{32}$;

[00143] R^3 and R^4 are independently hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, –$SC(=O)NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or –$C(=O)NR^{31}R^{32}$;

[00144] R^5 is hydrogen;

[00145] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-10}alkyl, –CF_3, -O-aryl, –OCF_3, –OC_{1-10}alkyl, -NH_2, – $N(C_{1-10}alkyl)(C_{1-10}alkyl)$, – $NH(C_{1-10}alkyl)$, – NH(aryl), –$NR^{34}R^{35}$, –$C(O)(C_{1-10}alkyl)$, –$C(O)(C_{1-10}alkyl\text{-}aryl)$, –C(O)(aryl), –$CO_2$-$C_{1-10}$alkyl, –$CO_2$-$C_{1-10}$alkylaryl, –$CO_2$-aryl, –

$C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $–C(=O)NH(C_{1-10}alkyl)$, $–C(=O)NR^{34}R^{35}$, $–C(=O)NH_2$, $-OCF_3$, $–O(C_{1-10}alkyl)$, -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, $–S(O)_{0–2}\ C_{1-10}$alkyl, $–S(O)_{0–2}\ C_{1-10}$alkylaryl, $–S(O)_{0–2}$ aryl, $–SO_2N$(aryl), $–SO_2\ N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $–SO_2\ NH(C_{1-10}alkyl)$ or $–SO_2NR^{34}R^{35}$;

[00146] R^{34} and R^{35} in $–NR^{34}R^{35}$, $–C(=O)NR^{34}R^{35}$, or $–SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

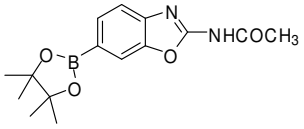
each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6; and

[00147] R^6 is halo, $–OR^{31}$, –SH, NH_2, $–NR^{34}R^{35}$, $–NR^{31}R^{32}$, $–CO_2R^{31}$, $–CO_2$aryl, $–C(=O)NR^{31}R^{32}$, $C(=O)\ NR^{34}R^{35}$, $–NO_2$, –CN, $–S(O)_{0–2}\ C_{1-10}$alkyl, $–S(O)_{0–2}$aryl, $–SO_2NR^{34}R^{35}$, $–SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, or heteroaryl-C_{2-10}alkynyl, each of which is unsubstituted or is substituted with one or more independent halo, cyano, nitro, $–OC_{1-10}$alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, $–C(=O)NR^{31}R^{32}$, $–C(=O)\ NR^{34}R^{35}$, $–SO_2NR^{34}R^{35}$, $–SO_2\ NR^{31}R^{32}$, $-NR^{31}R^{32}$, or $–\ NR^{34}R^{35}$; and

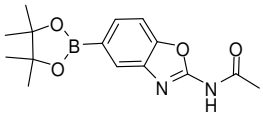
[00148] M_1 of Formula B and M_1 of Formula C are the same; R_1 of Formula A and R_1 of Formula C are the same; R_{31} of Formula A and R_{31} of Formula C are the same; R_{32} of Formula A and R_{32} of Formula C are the same; X_1 of Formula A and X_1 of Formula C are the same; X_2 of Formula A and X_2 of Formula C are the same; and X_3 of Formula A and X_3 of Formula C are the same.

[00149] In some examples of the process for synthesizing a compound of Formula C, T_1 is iodo or bromo.

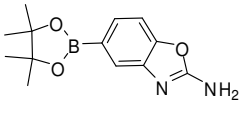
[00150] In other examples of the process for synthesizing a compound of Formula C, the compound of Formula B is a compound having one of the following formulae:



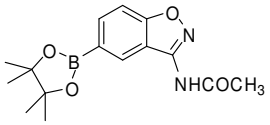
H-7



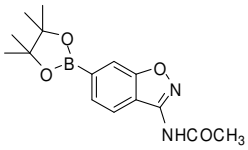
F-7



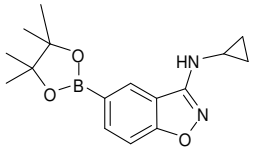
G-6



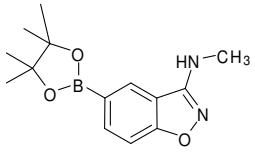
I-4



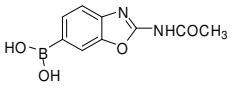
J-4



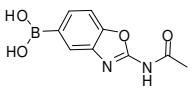
K-6



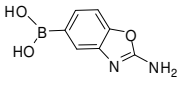
L-6



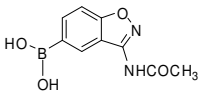
H-7-B



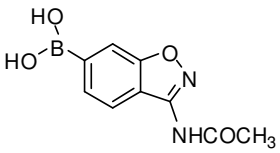
F-7-B



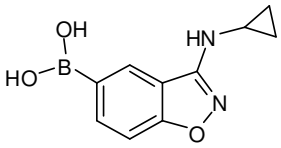
G-6-B



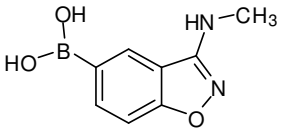
I-4-B



J-4-B



K-6-B



L-6-B .

[00151] In some examples of the process for synthesizing a compound of Formula C, each of the compound of Formula B and the compound of Formula C is the compound wherein:

[00152] X_1 and X_2 are N and X_3 is C;

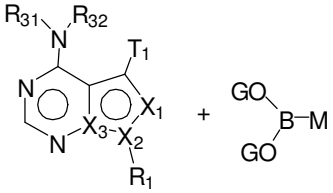
[00153] R_1 is –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3 substituents;

[00154] R^3 is hydrogen, –OH, $–OR^{31}$, $–NR^{31}R^{32}$, $–C(O)R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0-2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0-2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or$–SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$; and wherein

$–(W^2)_k–$ is $–NR^7–$, $–N(R^7)C(O)–$ or $–N(R^7)S(O)_2–$.

[00155] In some examples, the compound of Formula A reacts with the compound of Formula B in the presence of palladium tetrakis (triphenylphosphine). In some examples, when the compound of Formula A reacts with the compound of Formula B in the presence of palladium tetrakis (triphenylphosphine), the palladium tetrakis (triphenylphosphine) is present in an amount from about 0.05 molar equivalents to about 0.20 molar equivalents, or from about 0.07 molar equivalents to about 0.15 molar equivalents of the compound of Formula A.

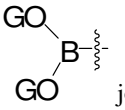
[00156] In another example, the disclosure provides a composition comprising a compound of Formula A and a compound of Formula B:



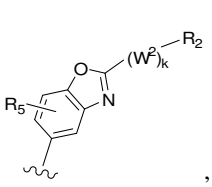
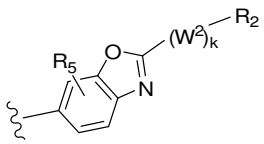
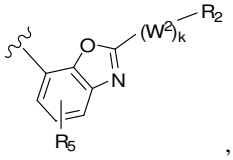
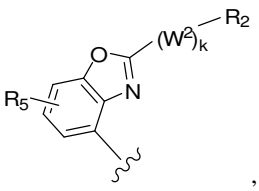
` Formula A Formula B

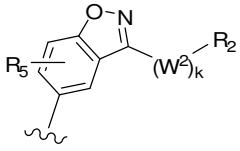
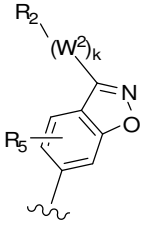
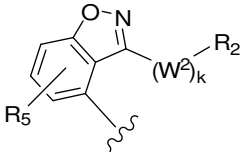
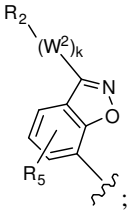
[00157] or a salt thereof, wherein: T is halo; X_1 is N or C-E^1, X_2 is N, and X_3 is C; or X_1 is N or C-E^1, X_2 is C, and X_3 is N; wherein no more than two ring nitrogen atoms of the compound of Formula A are adjacent; and wherein no more than two ring nitrogen atoms of the compound of Formula C are adjacent;

[00158] each of G is independently H or R_{G1}; and R_{G1} is alkyl, alkenyl, or aryl;

[00159] or the G groups of  join together to form a 5- or 6- membered cyclic moiety;

[00160] M of Formula B is a M_1 moiety, and wherein M_1 of Formula B has one of the following structures:

, , , ,

, , , or ;

[00161] E^1 is $-(W^1)_j$ -R^4 wherein j is 0 or 1;

[00162] W^1 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)S(O)–, –N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00163] k is 0 or 1;

[00164] W^2 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)C(O)N(R^8)–, –N(R^7)S(O)–, –N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00165] R_1 is hydrogen, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[00166] L is absent, -(C=O)-, -C(=O)O-, -C(=O) N(R^{31})-,-S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$N(R^{31})-, or -N(R^{31})-;

[00167] R^2 is hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)$OR^{31}OR^{32}$, –SC(=O)$NR^{31}R^{32}$, bicyclic aryl, substituted monocyclic aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl- C_{1-10}alkyl, C_{3-8}cycloalkyl- C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{2-10}alkyl-monocyclic aryl, monocyclic aryl-C_{2-10}alkyl, C_{1-10}alkylbicycloaryl, bicycloaryl-–C_{1-10}alkyl, substituted C_{1-10}alkylaryl, substituted aryl-C_{1-10}alkyl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-

C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, heterocyclyl, heteroalkyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, or heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said bicyclic aryl or heteroaryl moiety is unsubstituted, or wherein each of bicyclic aryl, heteroaryl moiety or monocyclic aryl moiety is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or –$C(=O)NR^{31}R^{32}$;

[00168] R^3 and R^4 are independently hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, –$SC(=O)NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or –$C(=O)NR^{31}R^{32}$;

[00169] R^5 is hydrogen;

[00170] each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6;

[00171] R^6 is halo, –OR^{31}, –SH, NH_2, –$NR^{34}R^{35}$, – $NR^{31}R^{32}$, –CO_2R^{31}, –CO_2aryl, –$C(=O)NR^{31}R^{32}$, C(=O) $NR^{34}R^{35}$, –NO_2, –CN, –$S(O)_{0-2}$ C_{1-10}alkyl, –$S(O)_{0-2}$aryl, –$SO_2NR^{34}R^{35}$, –$SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, or heteroaryl-C_{2-10}alkynyl, each of which is unsubstituted or is substituted with one or more independent halo, cyano, nitro, –OC_{1-}

$_{10}$alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, –C(=O)$NR^{31}R^{32}$, –C(=O) $NR^{34}R^{35}$, $–SO_2NR^{34}R^{35}$, $–SO_2$ $NR^{31}R^{32}$, $-NR^{31}R^{32}$, or – $NR^{34}R^{35}$;

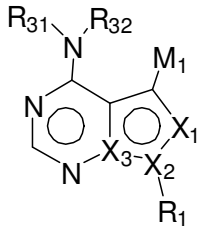
[00172] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said alkyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-10}alkyl, $–CF_3$, -O-aryl, $–OCF_3$, $–OC_{1-10}$alkyl, $-NH_2$, – N(C_{1-10}alkyl)(C_{1-10}alkyl), – NH(C_{1-10}alkyl), – NH(aryl), – $NR^{34}R^{35}$, –C(O)(C_{1-10}alkyl), –C(O)(C_{1-10}alkyl-aryl), –C(O)(aryl), $–CO_2$-C_{1-10}alkyl, $–CO_2$-C_{1-10}alkylaryl, $–CO_2$-aryl, –C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl), –C(=O)NH(C_{1-10}alkyl), –C(=O)$NR^{34}R^{35}$, $–C(=O)NH_2$, $-OCF_3$, –O(C_{1-10}alkyl), -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, $–S(O)_{0–2}$ C_{1-10}alkyl, $–S(O)_{0–2}$ C_{1-10}alkylaryl, $–S(O)_{0–2}$ aryl, $–SO_2$N(aryl), – SO_2 N(C_{1-10}alkyl)(C_{1-10}alkyl), $–SO_2$ NH(C_{1-10}alkyl) or $–SO_2NR^{34}R^{35}$; and

[00173] R^{34} and R^{35} in $–NR^{34}R^{35}$, –C(=O)$NR^{34}R^{35}$, or $–SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom.

[00174] In some examples of the compositions of the disclosure, each of the compound of Formula A and the compound of Formula B is the compound wherein:

[00175] X_1 and X_2 are N and X_3 is C; R_1 is –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3 substituents; R^3 is hydrogen, –OH, $–OR^{31}$, $–NR^{31}R^{32}$, –C(O)R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, –C(O)R^{31}, $–CO_2R^{31}$, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}$C(=O)R^{32}, $–NR^{31}$C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –OC(=O)$OR^{33}$, –OC(=O)$NR^{31}R^{32}$, –OC(=O)$SR^{31}$, –SC(=O)$OR^{31}$, $–P(O)OR^{31}OR^{32}$, or–SC(=O)$NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,–C(O)R^{31}, $–CO_2R^{31}$, –C(=O)$NR^{34}R^{35}$, or –C(=O)$NR^{31}R^{32}$; and wherein $–(W^2)_k–$ is $–NR^7–$, –N(R^7)C(O)– or –N(R^7)S(O)$_2$–.

[00176] In some examples of the compositions of the disclosure, the composition further comprises a compound of Formula C:



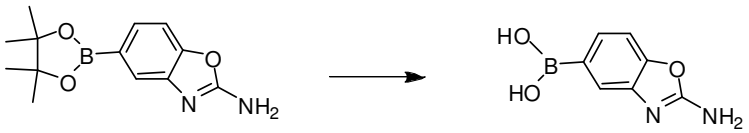
Formula C

or a salt thereof, wherein:

[00177] M_1 of Formula B and M_1 of Formula C are the same; R_1 of Formula A and R_1 of Formula C are the same; R_{31} of Formula A and R_{31} of Formula C are the same; R_{32} of Formula A and R_{32} of Formula C are the same; X_1 of Formula A and X_1 of Formula C are the same; X_2 of Formula A and X_2 of Formula C are the same; and X_3 of Formula A and X_3 of Formula C are the same.

[00178] In some examples of the compositions of the disclosure, the composition further comprises an organic solvent.

[00179] In another example, the disclosure provides a process for synthesizing a compound of Formula G-6-B:

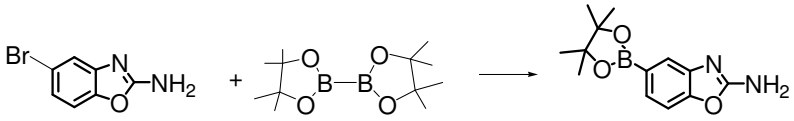


G-6 G-6-B

comprising the step of allowing a compound of Formula G-6 to react with an acid under conditions effective for synthesizing a compound of Formula G-6-B.

[00180] In some examples of the process for synthesizing a compound of Formula G-6-B,the acid is hydrochloric acid.

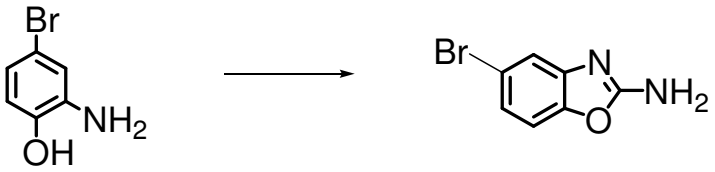
[00181] In another example, the disclosure provides a process for synthesizing a compound of Formula G-6:



Formula 1-2 Formula G-6

comprising the step of allowing a compound of Formula 1-2 to react with bis(pinacolato)diboron under conditions effective for synthesis of the compound of Formula G-6.

[00182] In yet another example, the disclosure provides a process for synthesizing a compound of Formula 1-2:

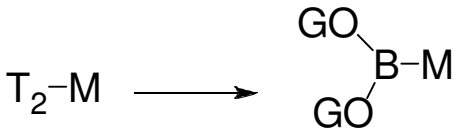


Formula 1-1 Formula 1-2

comprising the step of allowing a compound of Formula 1-1 to react with a cyanogen halide under conditions effective to synthesize the compound of Formula 1-2.

[00183] In some examples of the process for synthesizing a compound of Formula 1-2, the cyanogen halide is cyanogen bromide.

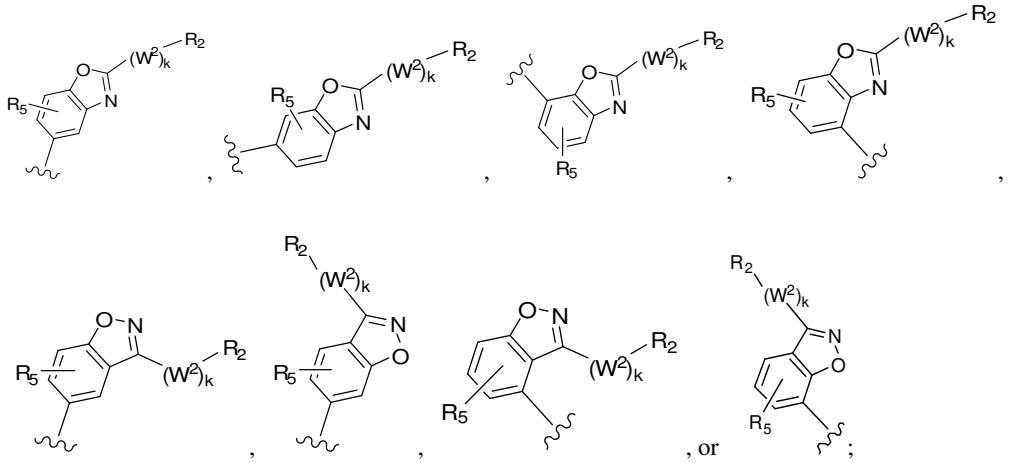
[00184] In a further example, the disclosure provides a process for synthesizing a compound of Formula B:



Formula D Formula B

comprising the step of allowing a compound of Formula D to react with a base and a trialkyl borate under conditions effective to synthesize a compound of Formula B; wherein: G is alkyl; T_2 is halo, triflate, tosylate or mesylate; each

of M of Formula D and M of Formula B is a M_1 moiety, and wherein M_1 moiety of Formula D and M_1 moiety of Formula B are identical, having one of the following structures:



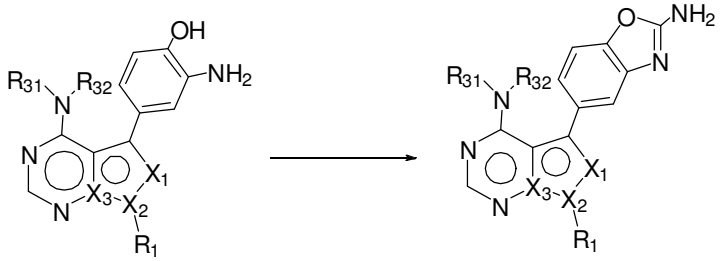
[00185] R^5 is hydrogen; k is 1; $-W^2-R^2$ is –NH- G_p;

[00186] G_p is acetyl, tert-butyl carbamate (Boc), carbobenzyloxy (Cbz), benzyl (Bz), fluorenylmethyloxycarbonyl (FMOC), or p-methoxybenzyl (PMB); and wherein G_p of Formula D and G_p of Formula B are the same.

[00187] In other examples of the process for synthesizing a compound of Formula B, the base is n-butyllithium. In yet other examples, the trialkyl borate is triisopropyl borate. In some examples of the process for synthesizing a compound of Formula B, each of the compound of Formula D and the compound of Formula B is the compound wherein $–(W^2)_k–$ is $–NR^7–$, $–N(R^7)C(O)–$ or $–N(R^7)S(O)_2–$.

[00188] In some examples, the process further comprises the step of allowing the compound of Formula B wherein $-W^2-R^2$ is –NH- G_p and G_p is tert-butyl carbamate to react with a reagent under conditions effective to yield a compound of Formula B, wherein $-W^2-R^2$ is $–NH_2$. In some examples, the reagent is hydrochloric acid.

[00189] In yet another example, the disclosure provides a process for synthesizing a compound of Formula 3-4:



Formula 3-3 Formula 3-4

[00190] comprising the step of allowing a compound of Formula 3-3 to react with a cyanogen halide under conditions effective for synthesizing a compound of Formula 3-4; wherein:

[00191] X_1 is N or C-E^1, X_2 is N, and X_3 is C; or X_1 is N or C-E^1, X_2 is C, and X_3 is N; wherein no more than two ring nitrogen atoms of the compound of Formula 3-3 are adjacent; and wherein no more than two ring nitrogen atoms of the compound of Formula 3-4 are adjacent;

[00192] E^1 is $–(W^1)_j$ -R^4 wherein j is 0 or 1;

[00193] W^1 is $–O–$, $–NR^7–$, $–S(O)_{0-2}–$, $–C(O)–$, $–C(O)N(R^7)–$, $–N(R^7)C(O)–$, $–N(R^7)S(O)–$, $–N(R^7)S(O)_2–$, $–C(O)O–$, $–CH(R^7)N(C(O)OR^8)–$, $–CH(R^7)N(C(O)R^8)–$, $–CH(R^7)N(SO_2R^8)–$, $–CH(R^7)N(R^8)–$, $–CH(R^7)C(O)N(R^8)–$, $–CH(R^7)N(R^8)C(O)–$, $–CH(R^7)N(R^8)S(O)–$, or $–CH(R^7)N(R^8)S(O)_2–$;

[00194] R_1 is hydrogen, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[00195] L is absent, -(C=O)-, -C(=O)O-, -C(=O) N(R^{31})-,-S-, -S(O)-, -$S(O)_2$-, -$S(O)_2N(R^{31})$-, or -N(R^{31})-;

[00196] R^3 and R^4 are independently hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, –$SC(=O)NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or –$C(=O)NR^{31}R^{32}$;

[00197] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said alkyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-10}alkyl, –CF_3, -O-aryl, –OCF_3, –OC_{1-10}alkyl, -NH_2, – N(C_{1-10}alkyl)(C_{1-10}alkyl), – NH(C_{1-10}alkyl), – NH(aryl), –$NR^{34}R^{35}$, –C(O)(C_{1-10}alkyl), –C(O)(C_{1-10}alkyl-aryl), –C(O)(aryl), –CO_2-C_{1-10}alkyl, –CO_2-C_{1-10}alkylaryl, –CO_2-aryl, –C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl), –C(=O)NH(C_{1-10}alkyl), –$C(=O)NR^{34}R^{35}$, –$C(=O)NH_2$, -OCF_3, –O(C_{1-10}alkyl), -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, –$S(O)_{0-2}$ C_{1-10}alkyl, –$S(O)_{0-2}$ C_{1-10}alkylaryl, –$S(O)_{0-2}$ aryl, –SO_2N(aryl), –SO_2 N(C_{1-10}alkyl)(C_{1-10}alkyl), –SO_2 NH(C_{1-10}alkyl) or –$SO_2NR^{34}R^{35}$;

[00198] R^{34} and R^{35} in –$NR^{34}R^{35}$, –$C(=O)NR^{34}R^{35}$, or –$SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6; and

[00199] R^6 is halo, $–OR^{31}$, –SH, NH_2, $–NR^{34}R^{35}$, $–NR^{31}R^{32}$, $–CO_2R^{31}$, $–CO_2$aryl, $–C(=O)NR^{31}R^{32}$, $C(=O)NR^{34}R^{35}$, $–NO_2$, –CN, $–S(O)_{0–2}C_{1-10}$alkyl, $–S(O)_{0–2}$aryl, $–SO_2NR^{34}R^{35}$, $–SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, or heteroaryl-C_{2-10}alkynyl, each of which is unsubstituted or is substituted with one or more independent halo, cyano, nitro, $–OC_{1-10}$alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $–SO_2NR^{34}R^{35}$, $–SO_2NR^{31}R^{32}$, $-NR^{31}R^{32}$, or $–NR^{34}R^{35}$; and

[00200] wherein R_1 of Formula 3-3 and R_1 of Formula 3-4 are the same; R_{31} of Formula 3-3 and R_{31} of Formula 3-4 are the same; R_{32} of Formula 3-3 and R_{32} of Formula 3-4 are the same; X_1 of Formula 3-3 and X_1 of Formula 3-4 are the same; X_2 of Formula 3-3 and X_2 of Formula 3-4 are the same; and X_3 of Formula 3-3 and X_3 of Formula 3-4 are the same.

[00201] In some examples of the process of the disclosure, each of the compound of Formula 3-3 and the compound of Formula 3-4 is the compound wherein:

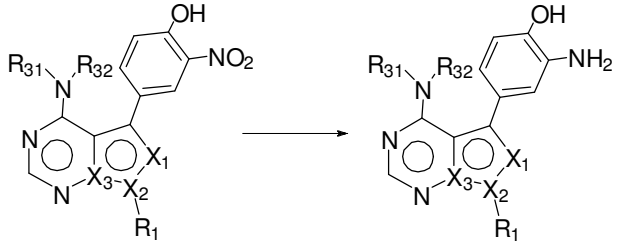
[00202] X_1 and X_2 are N;

[00203] R_1 is $–L-C_{1-10}$alkyl, $-L-C_{3-8}$cycloalkyl, -L- C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3 substituents; and wherein

R^3 is hydrogen, –OH, $–OR^{31}$, $–NR^{31}R^{32}$, $–C(O)R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or $–SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$.

[00204] In some examples for synthesizing a compound of Formula 3-4, the cyanogen halide is cyanogen bromide.

[00205] In another example, the disclosure provides a process for synthesizing a compound of Formula 3-3:



Formula 3-2 Formula 3-3

[00206] comprising the step of allowing a compound of Formula 3-2 to react with a reagent under conditions effective to synthesize a compound of Formula 3-3; wherein;

[00207] X_1 is N or C-E^1, X_2 is N, and X_3 is C; or X_1 is N or C-E^1, X_2 is C, and X_3 is N; wherein no more than two ring nitrogen atoms of the compound of Formula 3-3 are adjacent; and wherein no more than two ring nitrogen atoms of the compound of Formula 3-4 are adjacent;

[00208] E^1 is $–(W^1)_j$ -R^4 wherein j is 0 or 1;

[00209] W^1 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)$N(R^7)$–, –$N(R^7)C(O)$–, –$N(R^7)S(O)$–, –$N(R^7)S(O)_2$–, –C(O)O–, –$CH(R^7)N(C(O)OR^8)$–, –$CH(R^7)N(C(O)R^8)$–, –$CH(R^7)N(SO_2R^8)$–, –$CH(R^7)N(R^8)$–, –$CH(R^7)C(O)N(R^8)$–, –$CH(R^7)N(R^8)C(O)$–, –$CH(R^7)N(R^8)S(O)$–, or –$CH(R^7)N(R^8)S(O)_2$–;

[00210] R_1 is hydrogen, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[00211] L is absent, -(C=O)-, -C(=O)O-, -C(=O) $N(R^{31})$-,-S-, -S(O)-, -$S(O)_2$-, -$S(O)_2N(R^{31})$-, or -$N(R^{31})$-;

[00212] R^3 and R^4 are independently hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)$OR^{31}$, –C(=O)$SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –OC(=O)$OR^{33}$, –OC(=O)$NR^{31}R^{32}$, –OC(=O)$SR^{31}$, –SC(=O)$OR^{31}$, –P(O)$OR^{31}OR^{32}$, –SC(=O)$NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)$OR^{31}$, –C(=O)$SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –OC(=O)$OR^{33}$, –OC(=O)$NR^{31}R^{32}$, –OC(=O)$SR^{31}$, –SC(=O)$OR^{31}$, –P(O)$OR^{31}OR^{32}$, or–SC(=O)$NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{34}R^{35}$, or –C(=O)$NR^{31}R^{32}$;

[00213] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said alkyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-10}alkyl, –CF_3, -O-aryl, –OCF_3, –OC_{1-10}alkyl, -NH_2, – N(C_{1-10}alkyl)(C_{1-10}alkyl), – NH(C_{1-10}alkyl), – NH(aryl), –$NR^{34}R^{35}$, –C(O)(C_{1-10}alkyl), –C(O)(C_{1-10}alkyl-aryl), –C(O)(aryl), –CO_2-C_{1-10}alkyl, –CO_2-C_{1-10}alkylaryl, –CO_2-aryl, –C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl), –C(=O)NH(C_{1-10}alkyl), –C(=O)$NR^{34}R^{35}$, –C(=O)NH_2, -OCF_3, –O(C_{1-10}alkyl), -O-

aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, –$S(O)_{0–2}$ C_{1-10}alkyl, –$S(O)_{0–2}$ C_{1-10}alkylaryl, –$S(O)_{0–2}$ aryl, –SO_2N(aryl), –SO_2 N(C_{1-10}alkyl)(C_{1-10}alkyl), –SO_2 NH(C_{1-10}alkyl) or –$SO_2NR^{34}R^{35}$;

[00214] R^{34} and R^{35} in –$NR^{34}R^{35}$, –C(=O)$NR^{34}R^{35}$, or –$SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6; and

[00215] R^6 is halo, –OR^{31}, –SH, NH_2, –$NR^{34}R^{35}$, – $NR^{31}R^{32}$, –CO_2R^{31}, –CO_2aryl, –C(=O)$NR^{31}R^{32}$, C(=O) $NR^{34}R^{35}$, –NO_2, –CN, –$S(O)_{0–2}$ C_{1-10}alkyl, –$S(O)_{0–2}$aryl, –$SO_2NR^{34}R^{35}$, –$SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, or heteroaryl-C_{2-10}alkynyl, each of which is unsubstituted or is substituted with one or more independent halo, cyano, nitro, –OC_{1-10}alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, –C(=O)$NR^{31}R^{32}$, –C(=O) $NR^{34}R^{35}$, –$SO_2NR^{34}R^{35}$, –SO_2 $NR^{31}R^{32}$, -$NR^{31}R^{32}$, or – $NR^{34}R^{35}$; and

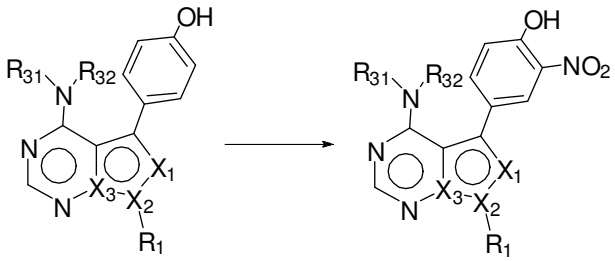
[00216] wherein R_1 of Formula 3-2 and R_1 of Formula 3-3 are the same; R_{31} of Formula 3-2 and R_{31} of Formula 3-3 are the same; R_{32} of Formula 3-2 and R_{32} of Formula 3-3 are the same; X_1 of Formula 3-2 and X_1 of Formula 3-3 are the same; X_2 of Formula 3-2 and X_2 of Formula 3-3 are the same; and X_3 of Formula 3-2 and X_3 of Formula 3-3 are the same.

[00217] In some examples of the process for synthesizing a compound of Formula 3-3, the reagent is (a) sodium dithionite or (b) palladium on carbon in the presence of hydrogen gas.

[00218] In some examples of the process for synthesizing a compound of Formula 3-3, each of the compound of Formula 3-2 and the compound of Formula 3-3 is a compound wherein: X_1 and X_2 are N and X_3 is C; R_1 is –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3 substituents; and wherein

[00219] R^3 is hydrogen, –OH, –OR^{31}, –$NR^{31}R^{32}$, –C(O)R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0–2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0–2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)$OR^{31}OR^{32}$, or–SC(=O)$NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{34}R^{35}$, or –C(=O)$NR^{31}R^{32}$.

[00220] In another example, the disclosure provides a process for synthesizing a compound of Formula 3-2:



Formula 3-1 Formula 3-2

[00221] comprising the step of allowing a compound of Formula 3-1 to react with a reagent under conditions effective to synthesize the compound of Formula 3-2; wherein:

[00222] X_1 is N or C-E^1, X_2 is N, and X_3 is C; or X_1 is N or C-E^1, X_2 is C, and X_3 is N; wherein no more than two ring nitrogen atoms of the compound of Formula 3-1 are adjacent; and wherein no more than two ring nitrogen atoms of the compound of Formula 3-2 are adjacent;

[00223] E^1 is $–(W^1)_j$ -R^4 wherein j is 0 or 1;

[00224] W^1 is –O–, $–NR^7–$, $–S(O)_{0-2}–$,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)S(O)–, –N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00225] R_1 is hydrogen, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[00226] L is absent, -(C=O)-, -C(=O)O-, -C(=O) N(R^{31})-,-S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$N(R^{31})-, or -N(R^{31})-;

[00227] R^3 and R^4 are independently hydrogen, halogen, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, –C(O)R^{31}, $–CO_2R^{31}$, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0-2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, $–NR^{31}$C(=O)OR^{32}, $–NR^{31}$C(=O)$NR^{32}R^{33}$, $–NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, $–NR^{31}$C(=NR^{32})OR^{33}, $–NR^{31}$C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)OR^{31}OR^{32}, –SC(=O)$NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, –C(O)R^{31}, $–CO_2R^{31}$, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0-2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, $–NR^{31}$C(=O)OR^{32}, $–NR^{31}$C(=O)$NR^{32}R^{33}$, $–NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, $–NR^{31}$C(=NR^{32})OR^{33}, $–NR^{31}$C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)OR^{31}OR^{32}, or–SC(=O)$NR^{31}R^{32}$, and wherein each of said

alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$;

[00228] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said alkyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-10}alkyl, $–CF_3$, -O-aryl, $–OCF_3$, $–OC_{1-10}$alkyl, $-NH_2$, – $N(C_{1-10}alkyl)(C_{1-10}alkyl)$, – $NH(C_{1-10}alkyl)$, – NH(aryl), – $NR^{34}R^{35}$, $–C(O)(C_{1-10}alkyl)$, $–C(O)(C_{1-10}alkyl\text{-}aryl)$, –C(O)(aryl), $–CO_2$-C_{1-10}alkyl, $–CO_2$-C_{1-10}alkylaryl, $–CO_2$-aryl, – $C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $–C(=O)NH(C_{1-10}alkyl)$, $–C(=O)NR^{34}R^{35}$, $–C(=O)NH_2$, $-OCF_3$, $–O(C_{1-10}alkyl)$, -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, $–S(O)_{0–2}$ C_{1-10}alkyl, $–S(O)_{0–2}$ C_{1-10}alkylaryl, $–S(O)_{0–2}$ aryl, $–SO_2N$(aryl), – SO_2 $N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $–SO_2$ $NH(C_{1-10}alkyl)$ or $–SO_2NR^{34}R^{35}$;

[00229] R^{34} and R^{35} in $–NR^{34}R^{35}$, $–C(=O)NR^{34}R^{35}$, or $–SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

[00230] each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6; and

[00231] R^6 is halo, $–OR^{31}$, –SH, NH_2, $–NR^{34}R^{35}$, – $NR^{31}R^{32}$, $–CO_2R^{31}$, $–CO_2$aryl, $–C(=O)NR^{31}R^{32}$, $C(=O)$ $NR^{34}R^{35}$, $–NO_2$, –CN, $–S(O)_{0–2}$ C_{1-10}alkyl, $–S(O)_{0–2}$aryl, $–SO_2NR^{34}R^{35}$, $–SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, or heteroaryl-C_{2-10}alkynyl, each of which is unsubstituted or is substituted with one or more independent halo, cyano, nitro, $–OC_{1-10}$alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, – $C(=O)NR^{31}R^{32}$, $–C(=O)$ $NR^{34}R^{35}$, $–SO_2NR^{34}R^{35}$, $–SO_2$ $NR^{31}R^{32}$, $-NR^{31}R^{32}$, or – $NR^{34}R^{35}$; and

[00232] wherein R_1 of Formula 3-1 and R_1 of Formula 3-23 are the same; R_{31} of Formula 3-1 and R_{31} of Formula 3-2 are the same; R_{32} of Formula 3-1 and R_{32} of Formula 3-2 are the same; X_1 of Formula 3-1 and X_1 of Formula 3-2 are the same; X_2 of Formula 3-1 and X_2 of Formula 3-2 are the same; and X_3 of Formula 3-1 and X_3 of Formula 3-2 are the same.

[00233] In some examples of the process for synthesizing a compound of Formula 3-2, the reagent is nitric acid.

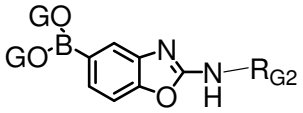
[00234] In some examples of the process for synthesizing a compound of Formula 3-2, each of the compound of Formula 3-1 and the compound of Formula 3-2 is a compound wherein:

[00235] X_1 and X_2 are N and X_3 is C; R_1 is $–L\text{-}C_{1-10}$alkyl, $-L\text{-}C_{3-8}$cycloalkyl, -L- C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3 substituents; and wherein

[00236] R^3 is hydrogen, –OH, $–OR^{31}$, $–NR^{31}R^{32}$, $–C(O)R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, –

$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,–$C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$.

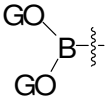
[00237] The disclosure also provides a compound of Formula E:



Formula E

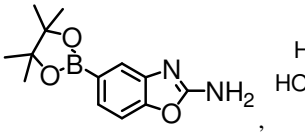
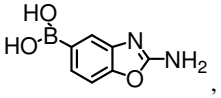
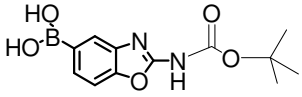
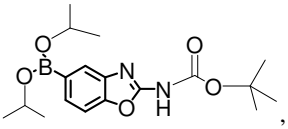
[00238] or a salt thereof, wherein:

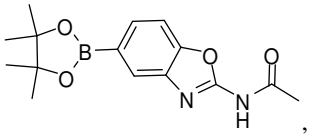
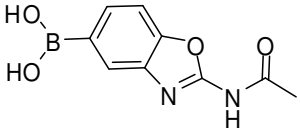
[00239] G is H or R_{G1}; and R_{G1} is alkyl, alkenyl, or aryl;

[00240] or the G groups of  join together to form a 5- or 6- membered cyclic moiety; and

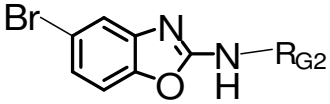
[00241] R_{G2} is H, acetyl, tert-butyl carbamate (Boc), carbobenzyloxy (Cbz), benzyl (Bz), fluorenylmethyloxycarbonyl (FMOC), or p-methoxybenzyl (PMB).

[00242] In some examples, the compound of Formula E is:

, , , or ,

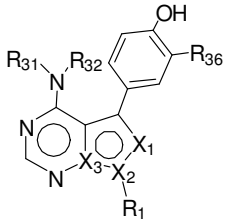
, or .

[00243] In some examples, a compound of the disclosure is a compound of Formula F:



[00244] or a salt thereof, wherein R_{G2} is H, tert- butyl carbamate,acetyl, tert-butyl carbamate (Boc), carbobenzyloxy (Cbz), benzyl (Bz), fluorenylmethyloxycarbonyl (FMOC), or p-methoxybenzyl (PMB).

[00245] In some examples, the disclosure provides a compound of Formula 3-3':



Formula 3-3'

[00246] or a salt thereof wherein:

[00247] X_1 is N or C-E^1, X_2 is N, and X_3 is C; or X_1 is N or C-E^1, X_2 is C, and X_3 is N;

wherein no more than two ring nitrogen atoms are adjacent;

[00248] E^1 is $–(W^1)_j$ -R^4 wherein j is 0 or 1;

[00249] W^1 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)S(O)–, –N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00250] R_1 is hydrogen, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[00251] L is absent, -(C=O)-, -C(=O)O-, -C(=O) N(R^{31})-,-S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$N(R^{31})-, or -N(R^{31})-;

[00252] R^3 and R^4 are independently hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)$OR^{31}OR^{32}$, –SC(=O)$NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)$OR^{31}OR^{32}$, or–SC(=O)$NR^{31}R^{32}$ and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{34}R^{35}$, or –C(=O)$NR^{31}R^{32}$;

[00253] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-10}alkyl, –CF_3, -O-aryl, –OCF_3, –OC_{1-10}alkyl, -NH_2, – N(C_{1-10}alkyl)(C_{1-10}alkyl), – NH(C_{1-10}alkyl), – NH(aryl), –$NR^{34}R^{35}$, –C(O)(C_{1-10}alkyl), –C(O)(C_{1-10}alkyl-aryl), –C(O)(aryl), –CO_2-C_{1-10}alkyl, –CO_2-C_{1-10}alkylaryl, –CO_2-aryl, –C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl), –C(=O)NH(C_{1-10}alkyl), –C(=O)$NR^{34}R^{35}$, –C(=O)NH_2, -OCF_3, –O(C_{1-10}alkyl), -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, –$S(O)_{0-2}$ C_{1-10}alkyl, –$S(O)_{0-2}$ C_{1-10}alkylaryl, –$S(O)_{0-2}$ aryl, –SO_2N(aryl), –SO_2 N(C_{1-10}alkyl)(C_{1-10}alkyl), –SO_2 NH(C_{1-10}alkyl) or –$SO_2NR^{34}R^{35}$;

[00254] R^{34} and R^{35} in –$NR^{34}R^{35}$, –C(=O)$NR^{34}R^{35}$, or –$SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-

aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6;

[00255] R^6 is halo, $–OR^{31}$, –SH, NH_2, $–NR^{34}R^{35}$, $– NR^{31}R^{32}$, $–CO_2R^{31}$, $–CO_2$aryl, $–C(=O)NR^{31}R^{32}$, $C(=O) NR^{34}R^{35}$, $–NO_2$, –CN, $–S(O)_{0–2} C_{1-10}$alkyl, $–S(O)_{0–2}$aryl, $–SO_2NR^{34}R^{35}$, $–SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, or heteroaryl-C_{2-10}alkynyl, each of which is unsubstituted or is substituted with one or more independent halo, cyano, nitro, $–OC_{1-10}$alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, $–C(=O)NR^{31}R^{32}$, $–C(=O) NR^{34}R^{35}$, $–SO_2NR^{34}R^{35}$, $–SO_2 NR^{31}R^{32}$, $-NR^{31}R^{32}$, or $– NR^{34}R^{35}$; and

[00256] R^{36} is NH_2 or NO_2.

[00257] In some examples, the compound of Formula 3-3' is a compound wherein:

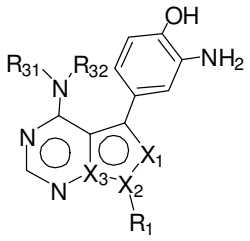
[00258] X_1 and X_2 are N and X_3 is C;

[00259] R_1 is $–L-C_{1-10}$alkyl, $-L-C_{3-8}$cycloalkyl, -L- C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3 substituents;

[00260] R^3 is hydrogen, –OH, $–OR^{31}$, $–NR^{31}R^{32}$, $–C(O)R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or$–SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$; and wherein

$–(W^2)_k–$ is $–NR^7–$, $–N(R^7)C(O)–$ or $–N(R^7)S(O)_2–$.

[00261] In another example, the disclosure provides a composition comprising a compound of Formula 3-3:



Formula 3-3

[00262] or a salt thereof, and a cyanogen halide wherein:

[00263] X_1 is N or C-E^1, X_2 is N, and X_3 is C; or X_1 is N or C-E^1, X_2 is C, and X_3 is N;

wherein no more than two nitrogen ring atoms are adjacent;

[00264] E^1 is $–(W^1)_j$ -R^4 wherein j is 0 or 1;

[00265] W^1 is –O–, $–NR^7–$, $–S(O)_{0-2}–$,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)S(O)–, –N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00266] R_1 is hydrogen, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[00267] L is absent, -(C=O)-, -C(=O)O-, -C(=O) N(R^{31})-,-S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$N(R^{31})-, or -N(R^{31})-;

[00268] R^3 and R^4 are independently hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)$OR^{31}OR^{32}$, –SC(=O)$NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)$OR^{31}OR^{32}$, or–SC(=O)$NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{34}R^{35}$, or –C(=O)$NR^{31}R^{32}$;

[00269] each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6;

[00270] R^6 is halo, –OR^{31}, –SH, NH_2, –$NR^{34}R^{35}$, – $NR^{31}R^{32}$, –CO_2R^{31}, –CO_2aryl, –C(=O)$NR^{31}R^{32}$, C(=O) $NR^{34}R^{35}$, –NO_2, –CN, –$S(O)_{0-2}$ C_{1-10}alkyl, –$S(O)_{0-2}$aryl, –$SO_2NR^{34}R^{35}$, –$SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, or heteroaryl-C_{2-10}alkynyl, each of which is unsubstituted or is substituted with one or more independent halo, cyano, nitro, –OC_{1-10}alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, –C(=O)$NR^{31}R^{32}$, –C(=O) $NR^{34}R^{35}$, –$SO_2NR^{34}R^{35}$, –SO_2 $NR^{31}R^{32}$, -$NR^{31}R^{32}$, or – $NR^{34}R^{35}$;

[00271] each of R^{31}, R^{32}, and $R^{33}$is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-}

$_{10}$alkyl, –CF_3, -O-aryl, –OCF_3, –OC_{1-10}alkyl, -NH_2, – N(C_{1-10}alkyl)(C_{1-10}alkyl), – NH(C_{1-10}alkyl), – NH(aryl), – $NR^{34}R^{35}$, –C(O)(C_{1-10}alkyl), –C(O)(C_{1-10}alkyl-aryl), –C(O)(aryl), –CO_2-C_{1-10}alkyl, –CO_2-C_{1-10}alkylaryl, –CO_2-aryl, –C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl), –C(=O)NH(C_{1-10}alkyl), –C(=O)$NR^{34}R^{35}$, –C(=O)NH_2, -OCF_3, –O(C_{1-10}alkyl), -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, –$S(O)_{0–2}$ C_{1-10}alkyl, –$S(O)_{0–2}$ C_{1-10}alkylaryl, –$S(O)_{0–2}$ aryl, –SO_2N(aryl), –SO_2 N(C_{1-10}alkyl)(C_{1-10}alkyl), –SO_2 NH(C_{1-10}alkyl) or –$SO_2NR^{34}R^{35}$; and

[00272] R^{34} and R^{35} in –$NR^{34}R^{35}$, –C(=O)$NR^{34}R^{35}$, or –$SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom.

[00273] In some examples of the composition comprisng a compound of Formula 3-3 and cyanogen halide, the cyanogen halide is cyanogen bromide.

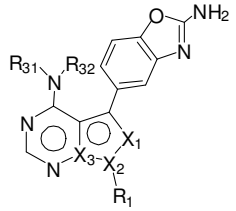
[00274] In some examples of the composition comprisng a compound of Formula 3-3 and cyanogen halide, the compound of Formula 3-3 is the compound wherein:

[00275] X_1 and X_2 are N and X_3 is C;

[00276] R_1 is –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3 substituents; and wherein

[00277] R^3 is hydrogen, –OH, –OR^{31}, –$NR^{31}R^{32}$, –C(O)R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0–2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0–2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)$OR^{31}OR^{32}$, or–SC(=O)$NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{34}R^{35}$, or –C(=O)$NR^{31}R^{32}$.

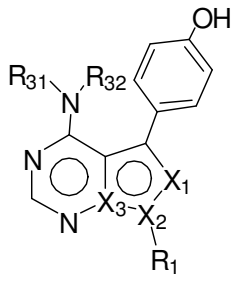
[00278] In some examples of the composition comprisng a compound of Formula 3-3 and cyanogen halide, the composition further comprises a compound of Formula 3-4:



Formula 3-4

[00279] or a salt thereof, wherein: R_1 of Formula 3-3 and R_1 of Formula 3-4 are the same; R_{31} of Formula 3-3 and R_{31} of Formula 3-4 are the same; R_{32} of Formula 3-3 and R_{32} of Formula 3-4 are the same; X_1 of Formula 3-3 and X_1 of Formula 3-4 are the same; X_2 of Formula 3-3 and X_2 of Formula 3-4 are the same; and X_3 of Formula 3-3 and X_3 of Formula 3-4 are the same.

[00280] In another example, the disclosure provides a composition comprising a compound of Formula 3-1:



Formula 3-1

[00281] or a salt thereof, and a nitrating reagent wherein:

[00282] X_1 is N or C-E^1, X_2 is N, and X_3 is C; or X_1 is N or C-E^1, X_2 is C, and X_3 is N;

wherein no more than two nitrogen ring atoms are adjacent;

[00283] E^1 is $–(W^1)_j$ -R^4 wherein j is 0 or 1;

[00284] W^1 is –O–, $–NR^7–$, $–S(O)_{0-2}–$,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)S(O)–, –N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00285] R_1 is hydrogen, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[00286] L is absent, -(C=O)-, -C(=O)O-, -C(=O) N(R^{31})-,-S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$N(R^{31})-, or -N(R^{31})-;

[00287] R^3 and R^4 are independently hydrogen, halogen, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, –C(O)R^{31}, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, $–SC(=O)NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, –C(O)R^{31}, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said

alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$;

[00288] each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6;

[00289] R^6 is halo, $–OR^{31}$, –SH, NH_2, $–NR^{34}R^{35}$, $– NR^{31}R^{32}$, $–CO_2R^{31}$, $–CO_2$aryl, $–C(=O)NR^{31}R^{32}$, $C(=O) NR^{34}R^{35}$, $–NO_2$, –CN, $–S(O)_{0–2} C_{1-10}$alkyl, $–S(O)_{0–2}$aryl, $–SO_2NR^{34}R^{35}$, $–SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, or heteroaryl-C_{2-10}alkynyl, each of which is unsubstituted or is substituted with one or more independent halo, cyano, nitro, $–OC_{1-10}$alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, $–C(=O)NR^{31}R^{32}$, $–C(=O) NR^{34}R^{35}$, $–SO_2NR^{34}R^{35}$, $–SO_2 NR^{31}R^{32}$, $-NR^{31}R^{32}$, or $– NR^{34}R^{35}$;

[00290] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, $– C_{1-10}$alkyl, $–CF_3$, -O-aryl, $–OCF_3$, $–OC_{1-10}$alkyl, $-NH_2$, $– N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $– NH(C_{1-10}alkyl)$, – NH(aryl), $–NR^{34}R^{35}$, $–C(O)(C_{1-10}alkyl)$, $–C(O)(C_{1-10}alkyl\text{-}aryl)$, –C(O)(aryl), $–CO_2\text{-}C_{1-10}$alkyl, $–CO_2\text{-}C_{1-10}$alkylaryl, $–CO_2$-aryl, $–C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $–C(=O)NH(C_{1-10}alkyl)$, $–C(=O)NR^{34}R^{35}$, $–C(=O)NH_2$, $-OCF_3$, $–O(C_{1-10}alkyl)$, -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, $–S(O)_{0–2} C_{1-10}$alkyl, $–S(O)_{0–2} C_{1-10}$alkylaryl, $–S(O)_{0–2}$ aryl, $–SO_2N$(aryl), $–SO_2 N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $–SO_2 NH(C_{1-10}alkyl)$ or $–SO_2NR^{34}R^{35}$; and

[00291] R^{34} and R^{35} in $–NR^{34}R^{35}$, $–C(=O)NR^{34}R^{35}$, or $–SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom.

[00292] In some examples of the composition comprising a compound of Formula 3-1 and a nitrating agent, the compound of Formula 3-1 is the compound wherein:

[00293] X_1 and X_2 are N and X_3 is C;

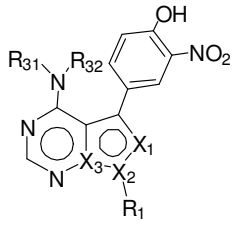
[00294] R_1 is $–L\text{-}C_{1-10}$alkyl, $-L\text{-}C_{3-8}$cycloalkyl, -L- C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3 substituents;

[00295] R^3 is hydrogen, –OH, $–OR^{31}$, $–NR^{31}R^{32}$, $–C(O)R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$; and wherein

$–(W^2)_k–$ is $–NR^7–$, $–N(R^7)C(O)–$ or $–N(R^7)S(O)_2–$.

[00296] In some examples, the nitrating agent is nitric acid.

[00297] In some examples of the composition comprising a compound of Formula 3-1 and a nitrating agent, the compostion further comprises a compound of Formula 3-2:

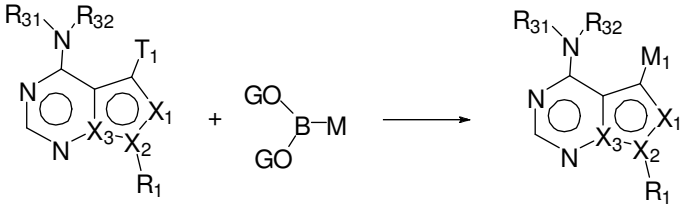


Formula 3-2

[00298] or a salt thereof, wherein:

[00299] R_1 of Formula 3-1 and R_1 of Formula 3-2 are the same; R_{31} of Formula 3-1 and R_{31} of Formula 3-2 are the same; R_{32} of Formula 3-1 and R_{32} of Formula 3-2 are the same; X_1 of Formula 3-1 and X_1 of Formula 3-2 are the same; X_2 of Formula 3-1 and X_2 of Formula 3-2 are the same, and X_3 of Formula 3-1 and X_3 of Formula 3-2 are the same.

[00300] In another example, the disclosure provides a process for synthesizing a compound of Formula C:



Formula A Formula B Formula C

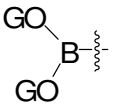
[00301] comprising the step of allowing a compound of Formula A to react with a compound of Formula B under conditions that are effective for synthesizing a compound of Formula C; wherein;

[00302] T_1 is halo;

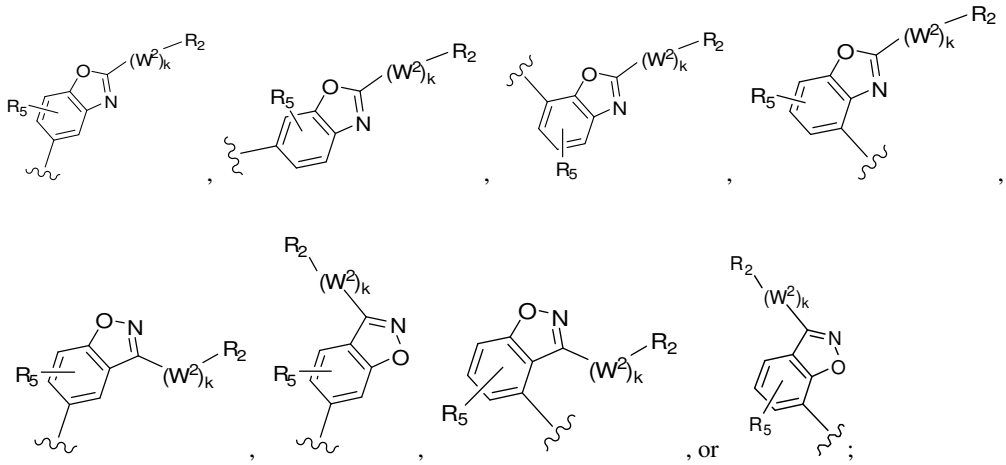
[00303] X_1 is N or C-E^1, X_2 is N, and X_3 is C; or X_1 is N or C-E^1, X_2 is C, and X_3 is N; wherein no more than two ring nitrogen atoms of the compound of Formula A are adjacent; and wherein no more than two ring nitrogen atoms of the compound of Formula C are adjacent;

[00304] R_1 is hydrogen, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[00305] L is absent, -(C=O)-, -C(=O)O-, -C(=O) N(R^{31})-,-S-, -S(O)-, -S$(O)_2$-, -S$(O)_2$N(R^{31})-, or -N(R^{31})-;
each of G is independently H or R_{G1}; and R_{G1} is alkyl, alkenyl, or aryl;

[00306] or the G groups of  join together to form a 5- or 6- membered cyclic moiety;

[00307] M of Formula B is a M_1 moiety, and wherein M_1 moiety of Formula B and M_1 moiety of Formula C are identical, having one of the following structures:



[00308] E^1 is $–(W^1)_j$ -R^4 wherein j is 0 or 1;

[00309] W^1 is –O–, $–NR^7–$, $–S(O)_{0-2}–$,–C(O)–,–C(O)N(R^7)–, $–N(R^7)C(O)–$, $–N(R^7)S(O)–$, $–N(R^7)S(O)_2–$, –C(O)O–, $–CH(R^7)N(C(O)OR^8)–$, $–CH(R^7)N(C(O)R^8)–$, $–CH(R^7)N(SO_2R^8)–$, $–CH(R^7)N(R^8)–$, $–CH(R^7)C(O)N(R^8)–$, $–CH(R^7)N(R^8)C(O)–$, $–CH(R^7)N(R^8)S(O)–$, or $–CH(R^7)N(R^8)S(O)_2–$;

[00310] k is 0 or 1;

[00311] W^2 is –O–, $–NR^7–$, $–S(O)_{0-2}–$,–C(O)–,–C(O)N(R^7)–, $–N(R^7)C(O)–$, $–N(R^7)C(O)N(R^8)–$, $–N(R^7)S(O)–$, $–N(R^7)S(O)_2–$, –C(O)O–, $–CH(R^7)N(C(O)OR^8)–$, $–CH(R^7)N(C(O)R^8)–$, $–CH(R^7)N(SO_2R^8)–$, $–CH(R^7)N(R^8)–$, $–CH(R^7)C(O)N(R^8)–$, $–CH(R^7)N(R^8)C(O)–$, $–CH(R^7)N(R^8)S(O)–$, or $–CH(R^7)N(R^8)S(O)_2–$;

[00312] R^2 is hydrogen, halogen, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0-2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0-2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, $–SC(=O)NR^{31}R^{32}$, bicyclic aryl, substituted monocyclic aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl- C_{1-10}alkyl, C_{3-8}cycloalkyl- C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{2-10}alkyl-monocyclic aryl, monocyclic aryl-C_{2-10}alkyl, C_{1-10}alkylbicycloaryl, bicycloaryl-–C_{1-10}alkyl, substituted C_{1-10}alkylaryl, substituted aryl-C_{1-10}alkyl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, heterocyclyl, heteroalkyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, or heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said bicyclic aryl or heteroaryl moiety is unsubstituted, or wherein each of bicyclic aryl, heteroaryl moiety or monocyclic aryl moiety is substituted with one or more independent halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0-2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0-2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety

is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or –$C(=O)NR^{31}R^{32}$;

[00313] R^3 and R^4 are independently hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, –$SC(=O)NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or –$C(=O)NR^{31}R^{32}$;

[00314] R^5 is halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$,or –$SC(=O)NR^{31}R^{32}$;

[00315] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-10}alkyl, –CF_3, -O-aryl, –OCF_3, –OC_{1-10}alkyl, -NH_2, – N(C_{1-10}alkyl)(C_{1-10}alkyl), – NH(C_{1-10}alkyl), – NH(aryl), –$NR^{34}R^{35}$, –C(O)(C_{1-10}alkyl), –C(O)(C_{1-10}alkyl-aryl), –C(O)(aryl), –CO_2-C_{1-10}alkyl, –CO_2-C_{1-10}alkylaryl, –CO_2-aryl, –C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl), –C(=O)NH(C_{1-10}alkyl), –$C(=O)NR^{34}R^{35}$, –$C(=O)NH_2$, -OCF_3, –O(C_{1-10}alkyl), -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, –$S(O)_{0-2}$ C_{1-10}alkyl, –$S(O)_{0-2}$ C_{1-10}alkylaryl, –$S(O)_{0-2}$ aryl, –SO_2N(aryl), –SO_2 N(C_{1-10}alkyl)(C_{1-10}alkyl), –SO_2 NH(C_{1-10}alkyl) or –$SO_2NR^{34}R^{35}$;

[00316] R^{34} and R^{35} in –$NR^{34}R^{35}$, –$C(=O)NR^{34}R^{35}$, or –$SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6; and

[00317] R^6 is halo, $–OR^{31}$, –SH, NH_2, $–NR^{34}R^{35}$, $–NR^{31}R^{32}$, $–CO_2R^{31}$, $–CO_2$aryl, $–C(=O)NR^{31}R^{32}$, $C(=O)NR^{34}R^{35}$, $–NO_2$, –CN, $–S(O)_{0–2}C_{1-10}$alkyl, $–S(O)_{0–2}$aryl, $–SO_2NR^{34}R^{35}$, $–SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, or heteroaryl-C_{2-10}alkynyl, each of which is unsubstituted or is substituted with one or more independent halo, cyano, nitro, $–OC_{1-10}$alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $–SO_2NR^{34}R^{35}$, $–SO_2NR^{31}R^{32}$, $-NR^{31}R^{32}$, or $–NR^{34}R^{35}$; and

[00318] M_1 of Formula B and M_1 of Formula C are the same; R_5 of Formula B and R_5 of Formula C are the same; R_1 of Formula A and R_1 of Formula C are the same; R_{31} of Formula A and R_{31} of Formula C are the same; R_{32} of Formula A and R_{32} of Formula C are the same; X_1 of Formula A and X_1 of Formula C are the same; X_2 of Formula A and X_2 of Formula C are the same; and X_3 of Formula A and X_3 of Formula C are the same.

[00319] In some of the examples of the process for synthesizing a compound of Formula C, each of the compound of Formula A and the compound of Fornula C is the compound wherein:

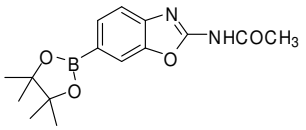
[00320] X_1 and X_2 are N and X_3 is C;

[00321] R_1 is $–L-C_{1-10}$alkyl, $-L-C_{3-8}$cycloalkyl, -L- C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3 substituents;

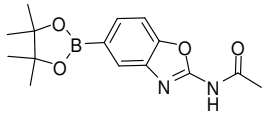
[00322] R^3 is hydrogen, –OH, $–OR^{31}$, $–NR^{31}R^{32}$, $–C(O)R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or$–SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$; and wherein

[00323] $–(W^2)_k–$ is $–NR^7–$, $–N(R^7)C(O)–$ or $–N(R^7)S(O)_2–$.

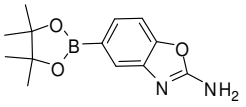
[00324] In some of the examples of the process for synthesizing a compound of Formula C, the compound of Formula B has one of the following structures:



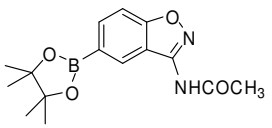
H-7



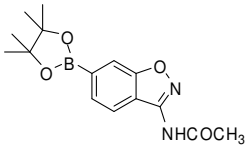
F-7



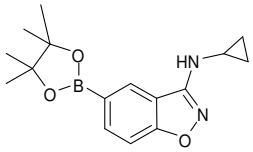
G-6



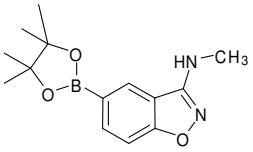
I-4



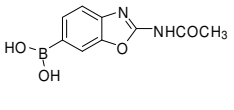
J-4



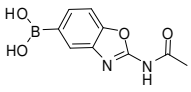
K-6



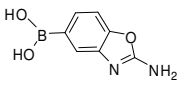
L-6



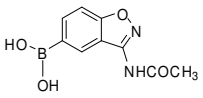
H-7-B



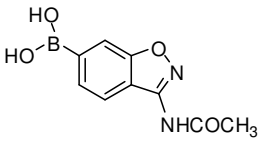
F-7-B



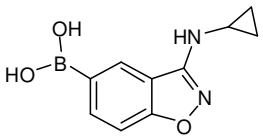
G-6-B



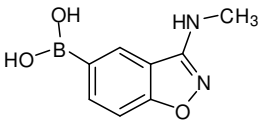
I-4-B



J-4-B

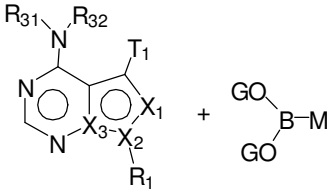


K-6-B



L-6-B .

[00325] In another example, the disclosure provides a composition comprising a compound of Formula A and a compound of Formula B:



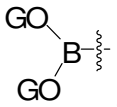
` Formula A Formula B

[00326] or a salt thereof, wherein:

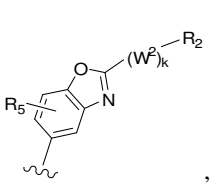
[00327] T is halo;

[00328] X_1 is N or C-E^1, X_2 is N, and X_3 is C; or X_1 is N or C-E^1, X_2 is C, and X_3 is N; wherein no more than two ring nitrogen atoms of the compound of Formula A are adjacent; and wherein no more than two ring nitrogen atoms of the compound of Formula C are adjacent;

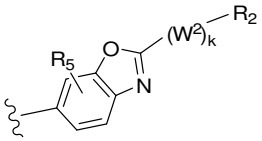
[00329] each of G is independently H or R_{G1}; and R_{G1} is alkyl, alkenyl, or aryl;

[00330] or the G groups of  join together to form a 5- or 6- membered cyclic moiety;

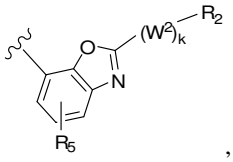
[00331] M of Formula B is a M_1 moiety, and wherein M_1 moiety of Formula B has one of the following structures:



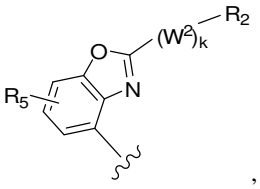
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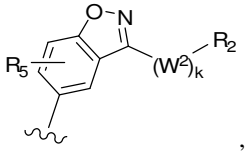
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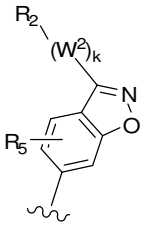
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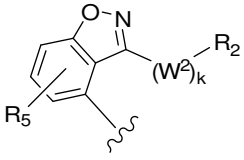
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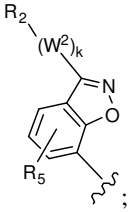
,



,



, or



;

[00332] E^1 is $-(W^1)_j$ -R^4 wherein j is 0 or 1;

[00333] W^1 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)S(O)–, –N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00334] k is 0 or 1;

[00335] W^2 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)C(O)N(R^8)–, –N(R^7)S(O)–, –N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00336] R_1 is hydrogen, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[00337] L is absent, -(C=O)-, -C(=O)O-, -C(=O) N(R^{31})-,-S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$N(R^{31})-, or -N(R^{31})-;

[00338] R^2 is hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)$OR^{31}OR^{32}$, –SC(=O)$NR^{31}R^{32}$, bicyclic aryl, substituted monocyclic aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl- C_{1-10}alkyl, C_{3-8}cycloalkyl- C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{2-10}alkyl-monocyclic aryl, monocyclic aryl-C_{2-10}alkyl, C_{1-10}alkylbicycloaryl, bicycloaryl-–C_{1-10}alkyl, substituted C_{1-10}alkylaryl, substituted aryl-C_{1-10}alkyl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, heterocyclyl, heteroalkyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, or heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said bicyclic aryl or heteroaryl moiety is unsubstituted, or wherein each of bicyclic aryl, heteroaryl moiety or monocyclic aryl moiety is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)$OR^{31}OR^{32}$, or–SC(=O)$NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{34}R^{35}$, or –C(=O)$NR^{31}R^{32}$;

[00339] R^3 and R^4 are independently hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)$OR^{31}OR^{32}$, –SC(=O)$NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-}

$_{10}$alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or –$C(=O)NR^{31}R^{32}$;

[00340] R^5 is halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$,or –$SC(=O)NR^{31}R^{32}$;

each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6;

[00341] R^6 is halo, –OR^{31}, –SH, NH_2, –$NR^{34}R^{35}$, – $NR^{31}R^{32}$, –CO_2R^{31}, –CO_2aryl, –$C(=O)NR^{31}R^{32}$, C(=O) $NR^{34}R^{35}$, –NO_2, –CN, –$S(O)_{0-2}$ C_{1-10}alkyl, –$S(O)_{0-2}$aryl, –$SO_2NR^{34}R^{35}$, –$SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, or heteroaryl-C_{2-10}alkynyl, each of which is unsubstituted or is substituted with one or more independent halo, cyano, nitro, –OC_{1-10}alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, –$C(=O)NR^{31}R^{32}$, –C(=O) $NR^{34}R^{35}$, –$SO_2NR^{34}R^{35}$, –SO_2 $NR^{31}R^{32}$, -$NR^{31}R^{32}$, or – $NR^{34}R^{35}$;

[00342] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said alkyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-10}alkyl, –CF_3, -O-aryl, –OCF_3, –OC_{1-10}alkyl, -NH_2, – N(C_{1-10}alkyl)(C_{1-10}alkyl), – NH(C_{1-10}alkyl), – NH(aryl), –$NR^{34}R^{35}$, –C(O)(C_{1-10}alkyl), –C(O)(C_{1-10}alkyl-aryl), –C(O)(aryl), –CO_2-C_{1-10}alkyl, –CO_2-C_{1-10}alkylaryl, –CO_2-aryl, –C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl), –C(=O)NH(C_{1-10}alkyl), –$C(=O)NR^{34}R^{35}$, –$C(=O)NH_2$, -OCF_3, –O(C_{1-10}alkyl), -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, –$S(O)_{0-2}$ C_{1-10}alkyl, –$S(O)_{0-2}$ C_{1-10}alkylaryl, –$S(O)_{0-2}$ aryl, –SO_2N(aryl), –SO_2 N(C_{1-10}alkyl)(C_{1-10}alkyl), –SO_2 NH(C_{1-10}alkyl) or –$SO_2NR^{34}R^{35}$; and

[00343] R^{34} and R^{35} in –$NR^{34}R^{35}$, –$C(=O)NR^{34}R^{35}$, or –$SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-

aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom.

[00344] In some examples of the composition comprising a compound of Formula A and a compound of Formula B, the compound of Formula A is the compound wherein:

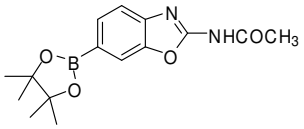
[00345] X_1 and X_2 are N and X_3 is C;

[00346] R_1 is –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3 substituents;

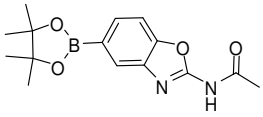
[00347] R^3 is hydrogen, –OH, $–OR^{31}$, $–NR^{31}R^{32}$, $–C(O)R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or$–SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$; and wherein

$–(W^2)_k–$ is $–NR^7–$, $–N(R^7)C(O)–$ or $–N(R^7)S(O)_2–$.

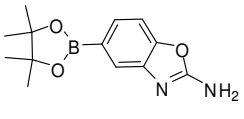
[00348] In some examples of the composition comprising a compound of Formula A and a compound of Formula B, the compound of Formula B is a compound having one of the following formulae:



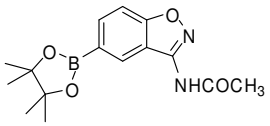
H-7



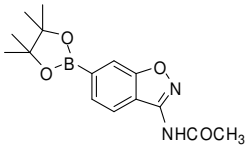
F-7



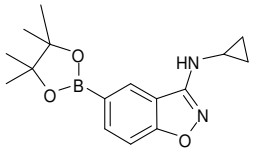
G-6



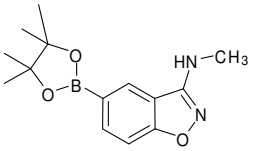
I-4



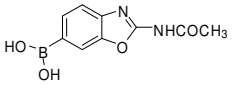
J-4



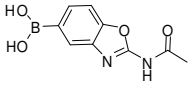
K-6



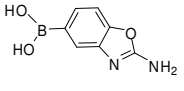
L-6



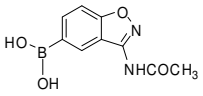
H-7-B



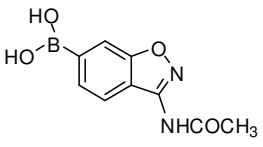
F-7-B



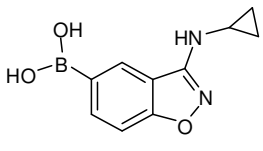
G-6-B



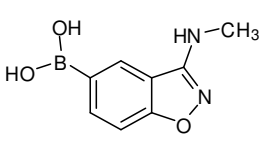
I-4-B



J-4-B

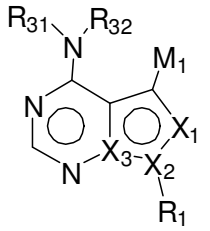


K-6-B



L-6-B .

[00349] In some examples of the composition comprising a compound of Formula A and a compound of Formula B, the composition further comprises a compound of Formula C:

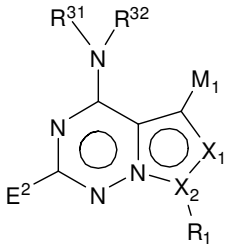


Formula C

[00350] or a salt thereof, wherein:

[00351] M_1 of Formula B and M_1 of Formula C are the same; R_5 of Formula B and R_5 of Formula C are the same; R_1 of Formula A and R_1 of Formula C are the same; R_1 of Formula A and R_1 of Formula C are the same; R_{31} of Formula A and R_{31} of Formula C are the same; R_{32} of Formula A and R_{32} of Formula C are the same; X_1 of Formula A and X_1 of Formula C are the same; X_2 of Formula A and X_2 of Formula C are the same; and X_3 of Formula A and X_3 of Formula C are the same.

[00352] In a further example the disclosure provides a compound of Formula I-B:



Formula I-B;

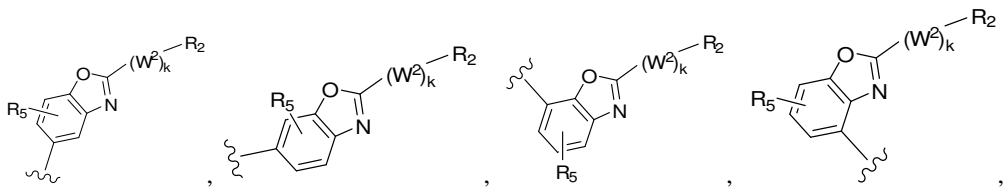
[00353] or a pharmaceutically acceptable salt thereof, wherein:

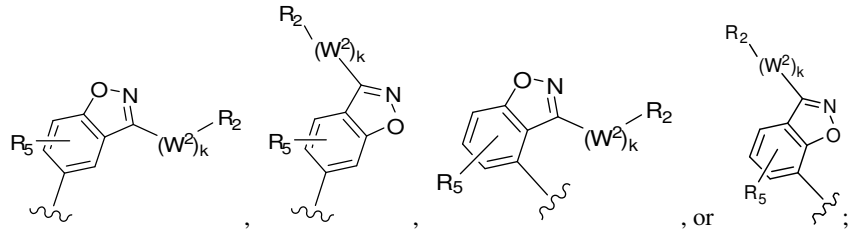
[00354] X_1 is N and X_2 is C, or X_1 is C-E^1 and X_2 is C;

[00355] R_1 is hydrogen, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[00356] L is absent, -(C=O)-, -C(=O)O-, -C(=O) N(R^{31})-,-S-, -S(O)-, -S$(O)_2$-, -S$(O)_2$N(R^{31})-, or -N(R^{31})-;

[00357] M_1 is a moiety having one of the following structures:





[00358] k is 0 or 1;

[00359] E^1 and E^2 are independently $–(W^1)_j$ -R^4;

[00360] j in E^1 or j in E^2, is independently 0 or 1;

[00361] W^1 is –O–, $–NR^7–$, $–S(O)_{0-2}–$,–C(O)–,–C(O)N(R^7)–, $–N(R^7)C(O)–$, $–N(R^7)S(O)–$,$–N(R^7)S(O)_2–$, –C(O)O–, $–CH(R^7)N(C(O)OR^8)–$, $–CH(R^7)N(C(O)R^8)–$, $–CH(R^7)N(SO_2R^8)–$, $–CH(R^7)N(R^8)–$, $–CH(R^7)C(O)N(R^8)–$, - $CH(R^7)N(R^8)C(O)–$, $–CH(R^7)N(R^8)S(O)–$, or $–CH(R^7)N(R^8)S(O)_2–$;

[00362] W^2 is –O–, $–NR^7–$, $–S(O)_{0-2}–$,–C(O)–,–C(O)N(R^7)–, $–N(R^7)C(O)–$, $–N(R^7)C(O)N(R^8)–$,$–N(R^7)S(O)–$, – $N(R^7)S(O)_2–$,–C(O)O–, $–CH(R^7)N(C(O)OR^8)–$, $–CH(R^7)N(C(O)R^8)–$, $–CH(R^7)N(SO_2R^8)–$, $–CH(R^7)N(R^8)–$, – $CH(R^7)C(O)N(R^8)–$, $–CH(R^7)N(R^8)C(O)–$, $–CH(R^7)N(R^8)S(O)–$, or $–CH(R^7)N(R^8)S(O)_2–$;

[00363] R^3 and R^4 are independently hydrogen, halogen, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, – $C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0-2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, - $NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0-2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, – $NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, – $OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, $–SC(=O)NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl - C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, – $NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0-2}R^{31}$, $–SO_2NR^{31}R^{32}$, – $SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0-2}R^{32}$, $–C(=S)OR^{31}$, – $C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, – $OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$;

[00364] R^5 is hydrogen, halogen, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, – $C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0-2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, – $NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0-2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, – $NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, – $P(O)OR^{31}OR^{32}$,or $–SC(=O)NR^{31}R^{32}$;

[00365] R^2 is hydrogen, halogen, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, $–SC(=O)NR^{31}R^{32}$, bicyclic aryl, substituted monocyclic aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl- C_{1-10}alkyl, C_{3-8}cycloalkyl- C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{2-10}alkyl-monocyclic aryl, monocyclic aryl-C_{2-10}alkyl, C_{1-10}alkylbicycloaryl, bicycloaryl-–C_{1-10}alkyl, substituted C_{1-10}alkylaryl, substituted aryl-C_{1-10}alkyl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, heterocyclyl, heteroalkyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, or heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said bicyclic aryl or heteroaryl moiety is unsubstituted, or wherein each of bicyclic aryl, heteroaryl moiety or monocyclic aryl moiety is substituted with one or more independent halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$;

[00366] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said alkyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, – C_{1-10}alkyl, $–CF_3$, -O-aryl, $–OCF_3$, $–OC_{1-10}$alkyl, $-NH_2$, – $N(C_{1-10}alkyl)(C_{1-10}alkyl)$, – $NH(C_{1-10}alkyl)$, – NH(aryl), – $NR^{34}R^{35}$, $–C(O)(C_{1-10}alkyl)$, $–C(O)(C_{1-10}alkyl\text{-}aryl)$, –C(O)(aryl), $–CO_2$-C_{1-10}alkyl, $–CO_2$-C_{1-10}alkylaryl, $–CO_2$-aryl, $–C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $–C(=O)NH(C_{1-10}alkyl)$, $–C(=O)NR^{34}R^{35}$, $–C(=O)NH_2$, $-OCF_3$, $–O(C_{1-10}alkyl)$, -O-aryl, –N(aryl)(C_{1-10}alkyl), —NO_2, –CN, $–S(O)_{0–2}$ C_{1-10}alkyl, $–S(O)_{0–2}$ C_{1-10}alkylaryl, $–S(O)_{0–2}$ aryl, $–SO_2N$(aryl), $–SO_2$ $N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $–SO_2$ $NH(C_{1-10}alkyl)$ or $–SO_2NR^{34}R^{35}$ s;

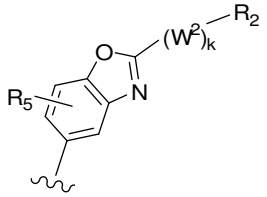
R^{34} and R^{35} in $–NR^{34}R^{35}$, $–C(=O)NR^{34}R^{35}$, or $–SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

[00367] each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6; and

[00368] R^6 is halo, $–OR^{31}$, –SH, NH_2, $–NR^{34}R^{35}$, – $NR^{31}R^{32}$, $–CO_2R^{31}$, $–CO_2$aryl, $–C(=O)NR^{31}R^{32}$, C(=O) $NR^{34}R^{35}$, $–NO_2$, –CN, $–S(O)_{0–2}$ C_{1-10}alkyl, $–S(O)_{0–2}$aryl, $–SO_2NR^{34}R^{35}$, $–SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl,

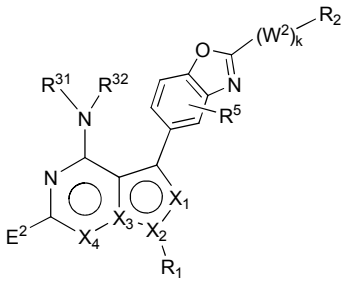
aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, or heteroaryl-C_{2-10}alkynyl, each of which is unsubstituted or is substituted with one or more independent halo, cyano, nitro, –OC_{1-10}alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, –C(=O)$NR^{31}R^{32}$, –C(=O) $NR^{34}R^{35}$, –$SO_2NR^{34}R^{35}$, –SO_2 $NR^{31}R^{32}$, -$NR^{31}R^{32}$, or – $NR^{34}R^{35}$.

[00369] In some examples the compound Formula I-B, is the compound wherein M_1 is:

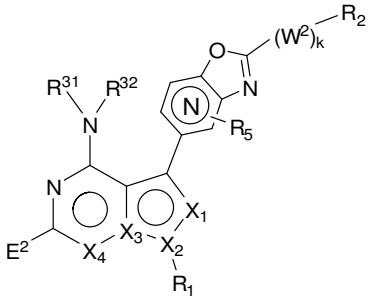


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[00370] In yet another example, the disclosure provides a compound of Formula IV-A or Formula IV-B:



Formula IV-A



Formula IV-B;

[00371] or a pharmaceutically acceptable salt thereof, wherein:

[00372] X_1 is N or C-E^1, X_2 is N, and X_3 is C; or X_1 is N or C-E^1, X_2 is C, X_3 is N, and X_4 is CR^9 or N;

[00373] R_1 is –H, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L-C_{1-10}alkyl -C_{3-8}cycloalkyl, -L- aryl, -L-heteroaryl, -L-C_{1-10}alkylaryl, -L- C_{1-10}alkylheteroaryl, -L- C_{1-10}alkylheterocyclyl, -L-C_{2-10}alkenyl, -L-C_{2-10}alkynyl, -L-C_{2-10}alkenyl-C_{3-8}cycloalkyl, -L-C_{2-10}alkynyl-C_{3-8}cycloalkyl, -L-heteroalkyl, -L-heteroalkylaryl, -L-heteroalkylheteroaryl, -L-heteroalkyl-heterocyclyl, -L-heteroalkyl-C_{3-8}cycloalkyl, -L-aralkyl, -L-heteroaralkyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3;

[00374] L is absent, -(C=O)-, -C(=O)O-, -C(=O) $N(R^{31})$-,-S-, -S(O)-, -$S(O)_2$-, -$S(O)_2N(R^{31})$-, or -$N(R^{31})$-;

[00375] k is 0 or 1;

[00376] E^1 and E^2 are independently –$(W^1)_j$ -R^4;

[00377] j in E^1 or j in E^2, is independently 0 or 11;

[00378] W^1 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)S(O)–,–N(R^7)$S(O)_2$–, –C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, -CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00379] W^2 is –O–, –NR^7–, –$S(O)_{0-2}$–,–C(O)–,–C(O)N(R^7)–, –N(R^7)C(O)–, –N(R^7)C(O)N(R^8)–,–N(R^7)S(O)–, –N(R^7)$S(O)_2$–,–C(O)O–, –CH(R^7)N(C(O)OR^8)–, –CH(R^7)N(C(O)R^8)–, –CH(R^7)N(SO_2R^8)–, –CH(R^7)N(R^8)–, –CH(R^7)C(O)N(R^8)–, –CH(R^7)N(R^8)C(O)–, –CH(R^7)N(R^8)S(O)–, or –CH(R^7)N(R^8)$S(O)_2$–;

[00380] R^3 and R^4 are independently hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, –CO_2R^{31}, –C(=O)$NR^{31}R^{32}$, –C(=O)$NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -NR^{31}C(=O)R^{32}, –NR^{31}C(=O)OR^{32}, –NR^{31}C(=O)$NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –C(=S)OR^{31}, –C(=O)SR^{31}, –NR^{31}C(=NR^{32})$NR^{33}R^{32}$, –NR^{31}C(=NR^{32})OR^{33}, –NR^{31}C(=NR^{32})SR^{33}, –OC(=O)OR^{33}, –OC(=O)$NR^{31}R^{32}$, –OC(=O)SR^{31}, –SC(=O)OR^{31}, –P(O)OR^{31}OR^{32}, –SC(=O)$NR^{31}R^{32}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-}

$_{10}$alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl -C_{1-10}alkyl, C_{3-8}cycloalkyl -C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{1-10}alkylaryl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxy-C_{2-10}alkenyl, C_{1-10}alkoxy-C_{2-10}alkynyl, heterocyclyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl- C_{1-10}alkyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or –$C(=O)NR^{31}R^{32}$;

[00381] R^2 is hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, –$SC(=O)NR^{31}R^{32}$, bicyclic aryl, substituted monocyclic aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, C_{1-10}alkyl–C_{3-8}cycloalkyl, C_{3-8}cycloalkyl- C_{1-10}alkyl, C_{3-8}cycloalkyl- C_{2-10}alkenyl, C_{3-8}cycloalkyl- C_{2-10}alkynyl, C_{1-10}alkyl- C_{2-10}alkenyl, C_{1-10}alkyl- C_{2-10}alkynyl, C_{2-10}alkyl-monocyclic aryl, monocyclic aryl-C_{2-10}alkyl, C_{1-10}alkylbicycloaryl, bicycloaryl-–C_{1-10}alkyl, substituted C_{1-10}alkylaryl, substituted aryl-C_{1-10}alkyl, C_{1-10}alkylheteroaryl, C_{1-10}alkylheterocyclyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{2-10}alkenyl -C_{1-10}alkyl, C_{2-10}alkynyl -C_{1-10}alkyl, C_{2-10}alkenylaryl, C_{2-10}alkenylheteroaryl, C_{2-10}alkenylheteroalkyl, C_{2-10}alkenylheterocyclcyl, C_{2-10}alkenyl-C_{3-8}cycloalkyl, C_{2-10}alkynylaryl, C_{2-10}alkynylheteroaryl, C_{2-10}alkynylheteroalkyl, C_{2-10}alkynylheterocyclyl, C_{2-10}alkynyl-C_{3-8}cycloalkenyl, C_{1-10}alkoxy C_{1-10}alkyl, C_{1-10}alkoxyC_{2-10}alkenyl, C_{1-10}alkoxyC_{2-10}alkynyl, heterocyclyl, heteroalkyl, heterocyclyl -C_{1-10}alkyl, heterocyclyl-C_{2-10}alkenyl, heterocyclyl-C_{2-10}alkynyl, aryl–C_{2-10}alkenyl, aryl–C_{2-10}alkynyl, aryl-heterocyclyl, or heteroaryl–C_{1-10}alkyl, heteroaryl–C_{2-10}alkenyl, heteroaryl–C_{2-10}alkynyl, heteroaryl–C_{3-8}cycloalkyl, heteroaryl–heteroalkyl, or heteroaryl–heterocyclyl, wherein each of said bicyclic aryl or heteroaryl moiety is unsubstituted, or wherein each of bicyclic aryl, heteroaryl moiety or monocyclic aryl moiety is substituted with one or more independent halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$, and wherein each of said alkyl, cycloalkyl, heterocyclyl, or heteroalkyl moiety is unsubstituted or is substituted with one or more halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or –$C(=O)NR^{31}R^{32}$;

[00382] R^5 is hydrogen, halogen, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –

$NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$,or $–SC(=O)NR^{31}R^{32}$;

[00383] each of R^{31}, R^{32}, and R^{33} is independently H or C_{1-10}alkyl , wherein the C_{1-10}alkyl is unsubstituted or is substituted with one or more aryl, heteroalkyl, heterocyclyl, or heteroaryl group, wherein each of said aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more halo, –OH, $– C_{1-10}$alkyl, $–CF_3$, -O-aryl, $–OCF_3$, $–OC_{1-10}$alkyl, $-NH_2$, $– N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $– NH(C_{1-10}alkyl)$, – NH(aryl), $–NR^{34}R^{35}$, $–C(O)(C_{1-10}alkyl)$, $–C(O)(C_{1-10}alkyl\text{-}aryl)$, –C(O)(aryl), $–CO_2\text{-}C_{1-10}alkyl$, $–CO_2\text{-}C_{1-10}alkylaryl$, $–CO_2$-aryl, $–C(=O)N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $–C(=O)NH(C_{1-10}alkyl)$, $–C(=O)NR^{34}R^{35}$, $–C(=O)NH_2$, $-OCF_3$, $–O(C_{1-10}alkyl)$, -O-aryl, $–N(aryl)(C_{1-10}alkyl)$, —NO_2, –CN, $–S(O)_{0–2} C_{1-10}alkyl$, $–S(O)_{0–2} C_{1-10}alkylaryl$, $–S(O)_{0–2}$ aryl, $–SO_2N(aryl)$, $–SO_2 N(C_{1-10}alkyl)(C_{1-10}alkyl)$, $–SO_2 NH(C_{1-10}alkyl)$ or $–SO_2NR^{34}R^{35}$;

[00384] R^{34} and R^{35} in $–NR^{34}R^{35}$, $–C(=O)NR^{34}R^{35}$, or $–SO_2NR^{34}R^{35}$, are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more —$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, heteroaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom;

[00385] each of R^7 and R^8 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, aryl, heteroaryl, heterocyclyl or C_{3-10}cycloalkyl, each of which except for hydrogen is unsubstituted or is substituted by one or more independent R^6;

[00386] R^6 is halo, $–OR^{31}$, –SH, $-NH_2$, $–NR^{34}R^{35}$, $– NR^{31}R^{32}$, $–CO_2R^{31}$, $–CO_2$aryl, $–C(=O)NR^{31}R^{32}$, $C(=O)NR^{34}R^{35}$, $–NO_2$, –CN, $–S(O)_{0–2} C_{1-10}$alkyl, $–S(O)_{0–2}$aryl, $–SO_2NR^{34}R^{35}$, $–SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl; aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, heteroaryl-C_{2-10}alkynyl, wherein each of said alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more independent halo, cyano, nitro, $–OC_{1-10}$alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $–SO_2NR^{34}R^{35}$, $–SO_2 NR^{31}R^{32}$, $-NR^{31}R^{32}$, or $–NR^{34}R^{35}$; and

[00387] R^9 is H, halo, $–OR^{31}$, –SH, $-NH_2$, $–NR^{34}R^{35}$, $– NR^{31}R^{32}$, $–CO_2R^{31}$, $–CO_2$aryl, $–C(=O)NR^{31}R^{32}$, $C(=O)NR^{34}R^{35}$, $–NO_2$, –CN, $–S(O)_{0–2} C_{1-10}$alkyl, $–S(O)_{0–2}$aryl, $–SO_2NR^{34}R^{35}$, $–SO_2NR^{31}R^{32}$, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl; aryl-C_{1-10}alkyl, aryl-C_{2-10}alkenyl, aryl-C_{2-10}alkynyl, heteroaryl-C_{1-10}alkyl, heteroaryl-C_{2-10}alkenyl, heteroaryl-C_{2-10}alkynyl, wherein each of said alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heterocyclyl, or heteroaryl group is unsubstituted or is substituted with one or more independent halo, cyano, nitro, $–OC_{1-10}$alkyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, haloC_{1-10}alkyl, haloC_{2-10}alkenyl, haloC_{2-10}alkynyl, –COOH, $–C(=O)NR^{31}R^{32}$, $–C(=O) NR^{34}R^{35}$, $–SO_2NR^{34}R^{35}$, $–SO_2 NR^{31}R^{32}$, $-NR^{31}R^{32}$, or $–NR^{34}R^{35}$.

[00388] In some examples of the compound of Formula IV-A or Formula IV-B, X_4 is CR^9. In other examples, X_4 is N.

[00389] The compounds of the disclosure inhibit a protein kinase. In some examples of the compounds of the disclosure, the compound inhibits a lipid kinase. In other examples of the compounds of the disclosure, the compound inhibits a protein kinase and a lipid kinase. In some examples of the compounds of the disclosure, the compound inhibits a kinase selected from the group consisting of PI3 kinase α, PI3 kinase β, PI3 kinase γ, PI3 kinase δ, DNA-PK, mTorC (including mTorC1 and mTorC2), Abl. VEGFR, EphB4, Tie2, Flt3, PDGFR, RET, InsR, ATM, ATR, hSmg-1, and IGFR.

[00390] In some examples, a compound of the disclosure or a pharmaceutically acceptable salt thereof inhibits mTor at an IC_{50} value of less than about 100 nM. In other examples, a compound of the disclosure or a pharmaceutically acceptable salt thereof inhibits mTor at an IC_{50} value of less than about 10 nM.

[00391] In a further example, the disclosure provides a composition comprising a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3 , or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[00392] In some examples of the compositions of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically acceptable salt thereof, is a compound wherein E^2 is –H; X_1 and X_2 are N; R_1 is –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L-C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3; R^3 is hydrogen, –OH, $–OR^{31}$, $–NR^{31}R^{32}$, $–C(O)R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, aryl, heteroaryl, C_{1-4}alkyl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$, $–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{31}R^{32}$, $–C(=O)NR^{34}R^{35}$, $-NO_2$, –CN, $–S(O)_{0–2}R^{31}$, $–SO_2NR^{31}R^{32}$, $–SO_2NR^{34}R^{35}$, $-NR^{31}C(=O)R^{32}$, $–NR^{31}C(=O)OR^{32}$, $–NR^{31}C(=O)NR^{32}R^{33}$, $–NR^{31}S(O)_{0–2}R^{32}$, $–C(=S)OR^{31}$, $–C(=O)SR^{31}$, $–NR^{31}C(=NR^{32})NR^{33}R^{32}$, $–NR^{31}C(=NR^{32})OR^{33}$, $–NR^{31}C(=NR^{32})SR^{33}$, $–OC(=O)OR^{33}$, $–OC(=O)NR^{31}R^{32}$, $–OC(=O)SR^{31}$, $–SC(=O)OR^{31}$, $–P(O)OR^{31}OR^{32}$, or$–SC(=O)NR^{31}R^{32}$ s, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, $–R^{31}$, $–CF_3$, $–OCF_3$, $–OR^{31}$, –O-aryl, $–NR^{31}R^{32}$, $–NR^{34}R^{35}$,$–C(O)R^{31}$, $–CO_2R^{31}$, $–C(=O)NR^{34}R^{35}$, or $–C(=O)NR^{31}R^{32}$; and wherein $–(W^2)_k–$ is $–NR^7–$, $–N(R^7)C(O)–$ or $–N(R^7)S(O)_2–$.

[00393] In some examples of the compositions of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically acceptable salt thereof, is a compound wherein X_4 is CR^9. In another example, X_4 is N.

[00394] In some examples of the compositions of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically acceptable salt thereof, is a compound wherein E^2 is –H. In some examples of the compounds of the disclosure, X_1 is N and X_2 is N. In other examples of the compounds of the disclosure, X_1 is C-E^1 and X_2 is N. In one example of the compounds of the disclosure, X_1 is NH and X_2 is C.

[00395] In some examples of the compositions of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically acceptable salt thereof, is a compound wherein R_{31} and R_{32} are –H.

[00396] In some examples of the compositions of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically

acceptable salt thereof, is a compound wherein –(W^2)k– is –NR^7–, –$N(R^7)C(O)$–, –$N(R^7)C(O)N(R^8)$–, or –$N(R^7)S(O)_2$–. In other examples, –$(W^2)_k$ – is –NH–. In another example, –$(W^2)_k$ – is –$(CH)_2$–. In yet another example, –$(W^2)_k$ – is –NHC(O)–. In a further example of the compounds of the disclosure, –$(W^2)_k$ – is —$N(R^7)C(O)N(R^8)$–. In another example of the compounds of the disclosure, –$(W^2)_k$ – is –$NHS(O)_2$–.

[00397] In some examples of the compositions of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically acceptable salt thereof, is a compound wherein R_1 is –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L- C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3, wherein R^3 is hydrogen, –OH, –OR^{31}, –$C(O)R^{31}$, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, aryl, heteroaryl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl, heteroaryl, alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl or –OH. In some examples of the compounds of the disclosure, R_1 is unsubstituted or is substituted with C_{1-10}alkyl or cycloC_{3-10}alkyl.

[00398] In some examples of the compositions of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically acceptable salt thereof, is a compound wherein R^2 is alkyl. In yet other examples, R^2 is methyl. In other examples of the compounds of the disclosure, R^2 is isopropyl. In some examples , R^2 is cycloalkyl. In other examples, R^2 is cyclopropyl.

[00399] In another example of the disclosure, a method is provided of inhibiting activity of a protein kinase and/or a lipid kinase present in a cell, comprising contacting said cell with an effective amount of a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3.

[00400] In some examples of the methods of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically acceptable salt thereof, is a compound wherein E^2 is –H; X_1 and X_2 are N; R_1 is –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L-C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3; R^3 is hydrogen, –OH, –OR^{31}, –$NR^{31}R^{32}$, –$C(O)R^{31}$, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, aryl, heteroaryl, C_{1-4}alkyl, C_{1-10}alkyl, C_{3-8}cycloalkyl, or heterocyclyl, wherein each of said aryl or heteroaryl moiety is unsubstituted or is substituted with one or more independent alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, -NO_2, –CN, –$S(O)_{0-2}R^{31}$, –$SO_2NR^{31}R^{32}$, –$SO_2NR^{34}R^{35}$, -$NR^{31}C(=O)R^{32}$, –$NR^{31}C(=O)OR^{32}$, –$NR^{31}C(=O)NR^{32}R^{33}$, –$NR^{31}S(O)_{0-2}R^{32}$, –$C(=S)OR^{31}$, –$C(=O)SR^{31}$, –$NR^{31}C(=NR^{32})NR^{33}R^{32}$, –$NR^{31}C(=NR^{32})OR^{33}$, –$NR^{31}C(=NR^{32})SR^{33}$, –$OC(=O)OR^{33}$, –$OC(=O)NR^{31}R^{32}$, –$OC(=O)SR^{31}$, –$SC(=O)OR^{31}$, –$P(O)OR^{31}OR^{32}$, or–$SC(=O)NR^{31}R^{32}$ s, and wherein each of said alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, halo, –OH, –R^{31}, –CF_3, –OCF_3, –OR^{31}, –O-aryl, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$,–$C(O)R^{31}$, –CO_2R^{31}, –$C(=O)NR^{34}R^{35}$, or –$C(=O)NR^{31}R^{32}$; and wherein –$(W^2)_k$– is –NR^7–, –$N(R^7)C(O)$– or –$N(R^7)S(O)_2$–.

[00401] In some examples of the methods of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically acceptable salt thereof, is a compound wherein X_4 is CR^9. In another example, X_4 is N.

[00402] In some examples of the methods of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically acceptable salt thereof, is a compound wherein E^2 is –H. In some examples of the compounds of the disclosure, X_1 is N and X_2 is N. In other examples of the compounds of the disclosure, X_1 is C-E^1 and X_2 is N. In one example of the compounds of the disclosure, X_1 is NH and X_2 is C.

[00403] In some examples of the methods of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically acceptable salt thereof, is a compound wherein R_{31} and R_{32} are –H.

[00404] In some examples of the methods of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically acceptable salt thereof, is a compound wherein –(W^2)k– is –NR^7–, –$N(R^7)C(O)$–, –$N(R^7)C(O)N(R^8)$–, or –$N(R^7)S(O)_2$–. In other examples, –$(W^2)_k$ – is –NH–. In another example, –$(W^2)_k$ – is –$(CH)_2$–. In yet another example, –$(W^2)_k$ – is –NHC(O)–. In a further example of the compounds of the disclosure, –$(W^2)_k$ – is —$N(R^7)C(O)N(R^8)$–. In another example of the compounds of the disclosure, –$(W^2)_k$ – is –$NHS(O)_2$–.

[00405] In some examples of the methods of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically acceptable salt thereof, is a compound wherein R_1 is –L-$C_{1\text{-}10}$alkyl, -L-$C_{3\text{-}8}$cycloalkyl, -L- $C_{1\text{-}10}$alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3, wherein R^3 is hydrogen, –OH, –OR^{31}, –$C(O)R^{31}$, –$C(=O)NR^{31}R^{32}$, –$C(=O)NR^{34}R^{35}$, aryl, heteroaryl, $C_{1\text{-}10}$alkyl, $C_{3\text{-}8}$cycloalkyl, or heterocyclyl, wherein each of said aryl, heteroaryl, alkyl, cycloalkyl, or heterocyclyl moiety is unsubstituted or is substituted with one or more alkyl or –OH. In some examples of the compounds of the disclosure, R_1 is unsubstituted or is substituted with $C_{1\text{-}10}$alkyl or cyclo$C_{3\text{-}10}$alkyl.

[00406] In some examples of the compositions of the disclosure, a compound of Formula I'-A', I (including I-A and I-B), II-A (including II-A-1, II-A-1a, and II-A-2), II-B (including II-B-1 and II-B-2), III (including III-A and III-B), IV-A (including IV-A-1 and IV-A-2) , IV-B (including IV-B-1 and IV-B-2), C, 3-6, or N-3, or a pharmaceutically acceptable salt thereof, is a compound wherein R^2 is alkyl. In yet other examples, R^2 is methyl. In other examples of the compounds of the disclosure, R^2 is isopropyl. In some examples , R^2 is cycloalkyl. In other examples, R^2 is cyclopropyl.

[00407] In some of the examples of the methods of the disclosure, the inhibiting takes place in a subject suffering from a disorder selected from the group consisting of cancer, kidney disease, bone disorder, inflammatory disease, immune disease, nervous system disease, metabolic disease, respiratory disease, cardiac disease, and any other conditions disclosed herein. Further, in some examples of the method of the disclosure a second therapeutic agent is administered.

[00408] In some examples, one or more compounds of the disclosure yield selective inhibition of mTor-mediated signal transduction as compared to PI3K. In some other examples, the compounds provided herein can inhibit mTor-mediated activity more effectively than rapamycin, hence providing an alternative treatment for rapamycin-resistant conditions.

[00409] In some examples, one or more compounds of the disclosure selectively inhibits both mTorC1 and mTorC2 activity relative to all type I phosphatidylinositol 3-kinases (PI3-kinase) consisting of PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ. In some examples, one or more compounds of the disclosure selectively inhibits both mTor activity with an IC_{50} value of about 100 nM, 50 nM, 10 nM, 5 nM, 100 pM, 10 pM or even 1 pM, or less as ascertained in an *in vitro* kinase assay. In some examples, one or more compounds of the disclosure is substantially ineffective in inhibiting a type I PI3-kinase at a concentration of 100nM, 200nM, 500nM, or 1uM, 5 uM or 10uM, or higher in an *in vitro* kinase assay.

[00410] In some examples, one or more compounds of the disclosure inhibits phosphorylation of Akt (S473) and Akt (T308) more effectively than rapamycin when tested at a comparable molar concentration in an *in vitro* kinase assay.

[00411] In some examples, one or more compounds of the disclosure competes with ATP for binding to ATP-binding site on mTorC1 and/or mTorC2.

[00412] In some examples, one or more compounds of the disclosure causes apoptosis of said cell or cell cycle arrest.

[00413] The present disclosure provides methods and composition for inhibiting cell proliferation. In one example, the method comprises contacting a cell with one or more compounds of the disclosure that selectively inhibits mTorC1 and/or mTorC2 activity relative to one or more type I phosphatidylinositol 3-kinases (PI3-kinase) ascertained by an *in vitro* kinase assay, wherein the one or more type I PI3-kinase is selected from the group consisting of PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ. In some example, the inhibition of cell-proliferation is evidenced by an assay selected from the group consisting of an MTS cell proliferation assay, a resazurin assay, a colony formation assay, flow cytometry, and a cell division tracker dye assay.

[00414] In a separate and related example, the present disclosure provides a method of inhibiting phosphorylation of both Akt (S473) and Akt (T308) in a cell, comprising contacting a cell with an effective amount of one or more compounds of the disclosure that selectively inhibits both mTorC1 and mTorC2 activity relative to one or more type I phosphatidylinositol 3-kinases (PI3-kinase) as ascertained by a cell-based assay or an *in vitro* kinase assay, wherein the one or more type I PI3-kinase is selected from the group consisting of PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ, thereby Akt phosphorylation at residues S473 and T308 is simultaneously inhibited.

[00415] In another example, the present disclosure provies a method of substantially inhibiting proliferation of a neoplastic cell comprising contacting the cell with an effective amount of one or more compounds of the disclosure that inhibits full activation of Akt in a cell and an anti-cancer agent, wherein said inhibition of cell proliferation is enhanced through a synergistic effect of said compound and said anti-cancer agent.

[00416] In yet another example, the present disclosure provides a method of ameliorating a medical condition mediated by mTorC1 and/or mTorC2, comprising administering to a subject in need thereof a therapeutically effective amount of one or more compounds of the disclosure that selectively inhibits mTorC1 and/or mTorC2 activity relative to one or more type I phosphatidylinositol 3-kinases (PI3-kinase) as ascertained in a cell-based assay or an *in vitro* kinase assay, wherein the one or more type I PI3-kinase is selected from the group consisting of PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ.

[00417] Also provided in the present disclosure is a combination treatment for a subject diagnosed with or at risk of a neoplastic condition, comprising administering to said subject a therapeutically effective amount of one or more compounds of the disclosure that substantially inhibits full activation of Akt in a cell and an anti-cancer agent, wherein the efficacy of said treatment is enhanced through a synergistic effect of said compound and said anti-cancer agent.

[00418] In some example, the compound utilized in the subject methods is a compound that selectively inhibits both mTorC1 and mTORC2 activity relative to all type I phosphatidylinositol 3-kinases (PI3-kinase) consisting of PI3-kinase α, PI3-kinase β, PI3-kinase γ, and PI3-kinase δ.

[00419] In some other examples, the anti-cancer agent utlized in the subject methods can include but are not limited to rapamycin, Gleevec, or derivative thereof, which inhibits a mammalian target of rapamycin or Gleevec.

[00420] A wide variety of neoplastic conditions can be treated using one or more of the subject compositions. Such conditions include but are not limited to neoplastic condition such as restenosis, cancer selected from B cell lymphoma, T cell lymphoma, non small cell lung carcinoma, and leukemia, or an autoimmune disorder.

[00421] The compound of the disclosure and/or the anti-cancer agent can be administered parenterally, orally, intraperitoneally, intravenously, intraarterially, transdermally, intramuscularly, liposomally, via local delivery by catheter or stent, subcutaneously, intraadiposally, or intrathecally.

INCORPORATION BY REFERENCE

[00422] All publications and patent applications mentioned in this specification are herein incorporated by reference in their entirety as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

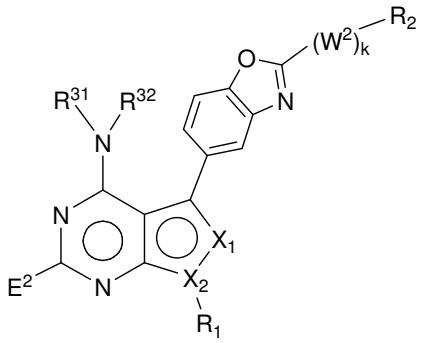
BRIEF DESCRIPTION OF THE DRAWINGS

[00423] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[00424] Figure 1A-1B summarizes the results of cell proliferation inhibition assays performed with a wide range of neoplastic cell lines *in vitro* using conventional anti-cancer drugs or a compound of the present invention such as a compound of Table 1. The experimental procedure is described herein, e.g., in Example 17. The degree of inhibition is reported in the Figure herein as +, ++, +++, ++++, or +++++ in the order of increased magnitude in

CLAIMS:

1. A compound of Formula II-A-1:



Formula II-A-1

or a pharmaceutically acceptable salt thereof, wherein:

X_1 is N;

X_2 is N;

R_1 is hydrogen, –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L-C_{1-10}alkylheterocylyl, -L-heteroalkyl, or -L-heterocyclyl, each of which is unsubstituted or substituted by one or more independent R^3 substituents;

L is a bond, C=O, -C(=O)O-, -C(=O)N(R^{31})-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$N(R^{31})-, or -N(R^{31})-;

k is 1;

E^2 is H;

W^2 is –NR^7–, C(O)N(R^7)–, or –N(R^7)C(O);

R^3 is halogen, –CF_3, –OCF_3, –OR^{31}, –$NR^{31}R^{32}$, –$NR^{34}R^{35}$, –C(O)R^{31}, or –CO_2R^{31};

R^2 is hydrogen, C_{1-10}alkyl, or C_{3-8}cycloalkyl;

each of R^{31} and R^{32} is independently H or unsubstituted C_{1-10}alkyl;

R^{34} and R^{35} in –$NR^{34}R^{35}$ are taken together with the nitrogen atom to which they are attached to form a 3-10 membered saturated or unsaturated ring; wherein said ring is independently unsubstituted or is substituted by one or more –$NR^{31}R^{32}$, hydroxyl, halogen, oxo, aryl, hetaryl, C_{1-6}alkyl, or O-aryl, and wherein said 3-10 membered saturated or unsaturated ring independently contains 0, 1, or 2 more heteroatoms in addition to the nitrogen atom; and

R^7 is hydrogen or C_{1-10}alkyl.

2. The compound or pharmaceutically acceptable salt of claim 1, wherein

R_1 is –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, -L-C_{1-10}alkylheterocylyl, or -L-heterocyclyl, each of which is unsubstituted or is substituted by one or more independent R^3 substituents; and
R^3 is $–OR^{31}$, $–NR^{31}R^{32}$, or $–C(O)R^{31}$.

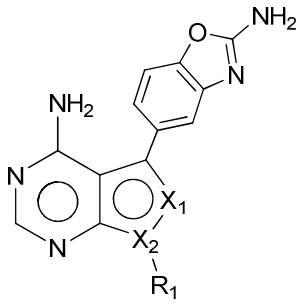
3. The compound or pharmaceutically acceptable salt of claims 1 or 2, wherein $–(W^2)_k–$ is $–NR^7–$, or $–N(R^7)C(O)–$; wherein R^7 is H.

4. The compound or pharmaceutically acceptable salt of any one of claims 1-3, wherein R_2 is H.

5. The compound or pharmaceutically acceptable salt of any one of claims 1-4, wherein R_1 is –L-C_{1-10}alkyl, -L-C_{3-8}cycloalkyl, each of which is unsubstituted or is substituted by one or more independent R^3 substituents, wherein R^3 is $–OR^{31}$, or $–C(O)R^{31}$.

6. The compound or pharmaceutically acceptable salt of any one of claims 1-5, wherein R^{31} and R^{32} are each H.

7. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound is:

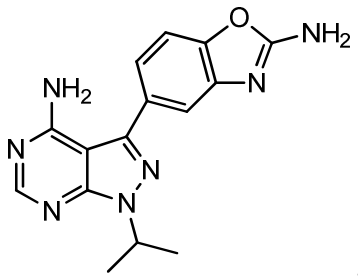


wherein
X_1 is N; X_2 is N;
R_1 is –L–C_{1-10}alkyl, -L–C_{3-8}cycloalkyl, -L-C_{1-10}alkylheterocyclyl, or -L-heterocyclyl, each of which is unsubstituted or substituted by one or more independent R^3 substituents; and
R^3 is $–OR^{31}$, $–NR^{31}R^{32}$, or $–C(O)R^{31}$.

8. The compound or pharmaceutically acceptable salt of claim 7, wherein R_1 is unsubstituted –C_{3-8}cycloalkyl, or R_1 is -C_{1-10}alkylheterocyclyl that is unsubstituted or substituted with R_3.

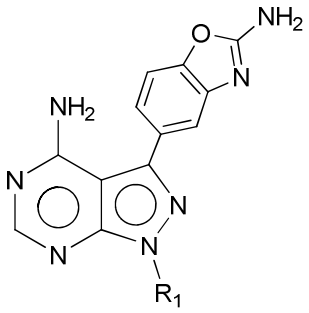
9. The compound or pharmaceutically acceptable salt of claim 7, wherein R_1 is unsubstituted –C_{1-10}alkyl.

10. A compound of Formula:



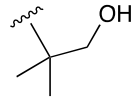
.

11. A compound of Formula:



,

or pharmaceutically acceptable salt thereof, wherein R_1 is



.

12. A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt of any one of claims 1- 11 and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition of claim 12, wherein the pharmaceutical composition is a formulation for oral administration.

14. The pharmaceutical composition of claim 12, wherein the pharmaceutical composition is a solid dosage form.

15. Use of the compound or pharmaceutically acceptable salt of any one of claims 1-11 for the manufacture of a medicament for inhibiting activity of mTor in a cell from a subject suffering from a disorder selected from the group consisting of cancer, diabetes, obesity, cardiovascular disease, neurological disorders, kidney diseases, bone disorder, inflammatory disease, immune disease, nervous system disease, metabolic disease, and respiratory disease.

16. Use of claim 15, wherein the disorder is cancer.

17. Use of claim 16, wherein the cancer is selected from the group consisting of kidney cancer, breast cancer, prostate cancer, colorectal cancer, lung cancer, endometrial cancer, renal cancer, or gynecological cancer.

18. The use of claim 16 wherein the cancer is lung cancer.

19. Use of claim 18, wherein the lung cancer is small cell lung cancer.

20. Use of claim 18, wherein the lung cancer is non-small cell lung cancer.