

Ther. Adv. Hematol. 2013, 4(1), 15-35; LaFave, L.M. *et al.*, *Trends Pharmacol. Sci.* 2012, 33(11), 574-582. The recently collected clinical data related to ruxolitinib treatment indicated that JAK inhibitors work on both JAK2 wild-type and JAK2 mutated cases. Verstovsek, S. *et al.*, *N. Engl. J. Med.* 2012, 366(9), 799-807; Quintas-Cardama, A. *et al.*, *Blood* 2010, 115(15), 3109-3117. The discovery of selective inhibitors of JAK2 vs JAK1/3 remains an unsolved challenge. In addition, hyperactivation of the JAK2/signal transducers and activators of transcription 3 (JAK2/STAT3) is responsible for abnormal dendritic cell differentiation leading to abnormal dendritic cell differentiation and accumulation of immunosuppressive myeloid cells in cancer (Nefedova, Y. *et al.*, *Cancer Res* 2005; 65(20): 9525-35). In Pten-null senescent tumors, activation of the Jak2/Stat3 pathway establishes an immunosuppressive tumor microenvironment that contributes to tumor growth and chemoresistance (Toso, A. *et al.*, *Cell Reports* 2014, 9, 75–89). Therefore, pharmacologic inhibition of the JAK2/STAT3 pathway can be an important new therapeutic strategy to enhance antitumor activity via the regulation of antitumor immunity.

[014] ROS1 kinase is a receptor tyrosine kinase with an unknown ligand. The normal functions of human ROS1 kinase have not been fully understood. However, it has been reported that ROS1 kinase undergoes genetic rearrangements to create constitutively active fusion proteins in a variety of human cancers including glioblastoma, non-small cell lung cancer (NSCLC), cholangiocarcinoma, ovarian cancer, gastric adenocarcinoma, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, and epithelioid hemangioendothelioma (Davies, K. D. *et al.*, *Clin Cancer Res* 2013, 19 (15): 4040-4045). Targeting ROS1 fusion proteins with crizotinib has demonstrated promising clinical efficacy in NSCLC patients whose tumors are positive for ROS1 genetic abnormalities (Shaw, A. T. *et al.*, *N Engl J Med.* 2014, 371(21):1963-1971). Acquired resistant mutations have been observed in crizotinib treatment patients (Awad, M. M. *et al.*, *N Engl J Med.* 2013, 368(25):2396-2401). It is urgent to develop the second generation of ROS1 inhibitors for overcoming crizotinib ROS1 resistance.

[015] There remains a need for small molecule inhibitors of these multiple protein or tyrosine kinase targets with desirable pharmaceutical properties. Certain diaryl macrocyclic compounds have been found in the context of this invention to have this advantageous activity profile.

SUMMARY

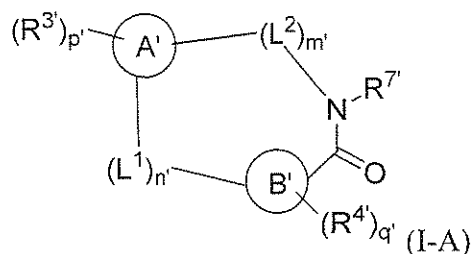
[016] In one aspect, ~~there is invention relates to provided~~ a compound of the following Formula (I-A):

[027] p' is 0, 1, 2, 3, or 4; and

[028] q' is 0, 1, 2, 3, or 4;

[029] or a pharmaceutically acceptable salt thereof.

[030] ~~In one aspect, the invention relates to~~ The invention relates to disclosure provides a chemical entity of the following Formula (I-A):



[031] wherein

[032] Ring A' and Ring B' are each independently a monocyclic or bicyclic aryl or heteroaryl;

[033] wherein one of Ring A' and Ring B' is a monocyclic aryl or heteroaryl and the other is a bicyclic heteroaryl; and at least one of Ring A' and Ring B' comprises at least one nitrogen ring member;

[034] each R^{3'} and R^{4'} is independently deuterium, halogen, -OR^{c'}, -OC(O)R^{c'}, -OC(O)NR^{c'}R^{d'}, -OC(=N)NR^{c'}R^{d'}, -OS(O)₀₋₂R^{c'}, -OS(O)₀₋₂NR^{c'}R^{d'}, -S(O)₀₋₂R^{c'}, -S(O)₀₋₂NR^{c'}R^{d'}, -NR^{c'}R^{d'}, -NR^{c'}C(O)R^{d'}, -NR^{c'}C(O)NR^{c'}R^{d'}, -NR^{c'}C(=N)NR^{c'}R^{d'}, -NR^{c'}S(O)₀₋₂R^{d'}, -NR^{c'}S(O)₀₋₂NR^{c'}R^{d'}, -C(O)R^{c'}, -C(O)OR^{c'}, -C(O)NR^{c'}R^{d'}, -C(=N)NR^{c'}R^{d'}, -P(O)₀₋₂R^{c'}R^{d'}, -P(O)₀₋₂NR^{c'}R^{d'}, -P(O)₀₋₂OR^{c'}, -CN, -NO₂, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3- to 7-membered heterocycloalkyl, phenyl, naphthyl, or mono- or bicyclic heteroaryl; or any two R^{3'} groups or any two R^{4'} groups taken together with the ring to which they are attached form a C₅₋₈cycloalkyl or a 5- to 8-membered heterocycloalkyl;

[035] wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, phenyl, naphthyl, and mono- or bicyclic heteroaryl is unsubstituted or substituted with one or more substituents selected from the group consisting of deuterium, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR^{e'}, -OC(O)R^{e'}, -OC(O)NR^{e'}R^{f'}, -OS(O)₀₋₂R^{e'}, -OS(O)₀₋₂NR^{e'}R^{f'}, -S(O)₀₋₂R^{e'}, -S(O)₀₋₂NR^{e'}R^{f'}, -NR^{e'}R^{f'}, -NR^{e'}C(O)R^{f'}, -NR^{e'}C(O)NR^{e'}R^{f'}, -NR^{e'}S(O)₀₋₂R^{f'}, -NR^{e'}S(O)₀₋₂NR^{e'}R^{f'}, -C(O)R^{e'}, -C(O)OR^{e'}, -C(O)NR^{e'}R^{f'}, -P(O)₀₋₂R^{e'}R^{f'}, -P(O)₀₋₂NR^{e'}R^{f'}, -P(O)₀₋₂OR^{e'}, -CN, and -NO₂; and

[036] each R^{c'}, R^{d'}, R^{e'}, and R^{f'} is independently selected from the group consisting of H, deuterium, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3- to 7-membered heterocycloalkyl, phenyl, naphthyl, and heteroaryl;

[037] R^{7'} is H, deuterium, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3- to 7-membered heterocycloalkyl, phenyl, naphthyl, or mono- or bicyclic heteroaryl;

[038] wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, phenyl, naphthyl, or heteroaryl is substituted or unsubstituted with one or more substituents selected from the group

consisting of deuterium, halogen, $-OR^{i'}$, $-OC(O)R^{i'}$, $-OC(O)NR^{i'}R^{j'}$, $-OS(O)_{0-2}R^{i'}$, $-OS(O)_{0-2}NR^{i'}R^{j'}$, $-S(O)_{0-2}R^{i'}$, $-S(O)_{0-2}NR^{i'}R^{j'}$, $-NR^{i'}R^{j'}$, $-NR^{i'}C(O)R^{j'}$, $-NR^{i'}C(O)NR^{i'}R^{j'}$, $-NR^{i'}S(O)_{0-2}R^{j'}$, $-NR^{i'}S(O)_{0-2}NR^{i'}R^{j'}$, $-C(O)R^{i'}$, $-C(O)OR^{i'}$, $-C(O)NR^{i'}R^{j'}$, $-P(O)_{0-2}R^{i'}R^{j'}$, $-P(O)_{0-2}NR^{i'}R^{j'}$, $-P(O)_{0-2}OR^{i'}$, $-CN$, and $-NO_2$;

[039] wherein each $R^{i'}$ and $R^{j'}$ is independently H, deuterium, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3- to 7-membered heterocycloalkyl, phenyl, naphthyl, or mono- or bicyclic heteroaryl;

[040] each L^1 and L^2 is independently $-C(R^{1'})(R^{2'})-$, $-O-$, $-N(R^{k'})-$, or $-S(O)_{0-2}$;

[041] wherein each $R^{1'}$ and $R^{2'}$ are independently H, deuterium, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3- to 7-membered heterocycloalkyl, phenyl, naphthyl, or mono- or bicyclic heteroaryl; or $R^{1'}$ and $R^{2'}$ taken together with the carbon or carbons to which they are attached form a C_{3-6} cycloalkyl or a 4- to 6-membered heterocycloalkyl;

[042] each $R^{k'}$ is independently H, deuterium, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3- to 7-membered heterocycloalkyl, phenyl, naphthyl, or mono- or bicyclic heteroaryl;

[043] wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, phenyl, naphthyl, or heteroaryl in $R^{1'}$, $R^{2'}$, or $R^{k'}$ is independently unsubstituted or substituted with one or more substituents selected from the group consisting of deuterium, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^{a'}$, $-OC(O)R^{a'}$, $-OC(O)NR^{a'}R^{b'}$, $-OS(O)_{0-2}R^{a'}$, $-OS(O)_{0-2}NR^{a'}R^{b'}$, $-S(O)_{0-2}R^{a'}$, $-S(O)_{0-2}NR^{a'}R^{b'}$,

$-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}S(O)_{0-2}R^{b'}$, $-NR^{a'}S(O)_{0-2}NR^{a'}R^{b'}$, $-C(O)R^{a'}$, $-C(O)OR^{a'}$, $-C(O)NR^{a'}R^{b'}$, $-P(O)_{0-2}R^{a'}R^{b'}$, $-P(O)_{0-2}NR^{a'}R^{b'}$, $-P(O)_{0-2}OR^{a'}$, $-CN$, and $-NO_2$;

[044] wherein each $R^{a'}$ and $R^{b'}$ is independently H, deuterium, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3- to 7-membered heterocycloalkyl, phenyl, naphthyl, or heteroaryl;

[045] m' is 3, 4, or 5;

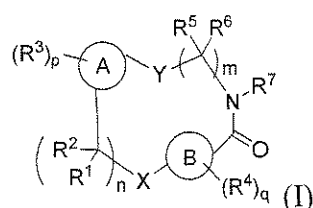
[046] n' is 2, 3, or 4;

[047] p' is 0, 1, 2, 3, or 4; and

[048] q' is 0, 1, 2, 3, or 4;

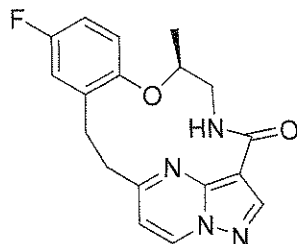
[049] or a pharmaceutically acceptable salt thereof.

[050] In another aspect, ~~the invention discloses~~ the invention discloses relates to a chemical entity of the following Formula (I):



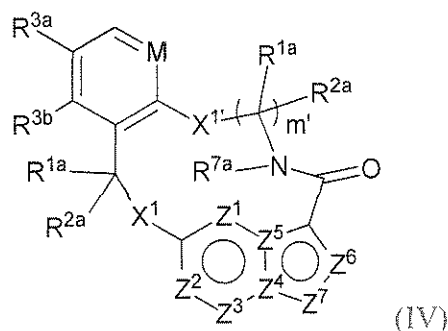
[082] or a pharmaceutically acceptable salt thereof.

[083] In certain embodiments, the compound of Formula (I) or (I-A) is a compound having the formula



[084] or a pharmaceutically acceptable salt thereof.

[084a] In another aspect, there is provided a compound of the Formula (IV):



wherein

M is CH or N;

X^1 and $X^{1'}$ are independently $-C(R^{1a})(R^{2a})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-O-$ or $-N(R^k)-$;

each R^{1a} and R^{2a} is independently H, deuterium, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-NR^aR^b$, $-SR^a$, $-S(O)R^a$, $-S(O)NR^a$, $-S(O)_2R^a$, $-S(O)_2NR^a$ or $-OR^a$ wherein each hydrogen atom in C_{1-6} alkyl is independently optionally substituted by deuterium, halogen, $-OH$, $-OC_{1-4}$ alkyl, $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl) $_2$, $NHC(O)C_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $C(O)C_{1-4}$ alkyl, $-NHC(O)NHC_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $C(O)NHC_{1-4}$ alkyl, $NHC(O)N(C_{1-4}$ alkyl) $_2$, $-N(C_{1-4}$ alkyl) $C(O)N(C_{1-4}$ alkyl) $_2$, $-NHC(O)OC_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $C(O)OC_{1-4}$ alkyl, $-CO_2H$, $-CO_2C_{1-4}$ alkyl, $-CONH_2$, $-CONH(C_{1-4}$ alkyl), $-CON(C_{1-4}$ alkyl) $_2$,

$-SC_{1-4}$ alkyl, $-S(O)C_{1-4}$ alkyl, $-S(O)_2C_{1-4}$ alkyl, $-S(O)NH(C_{1-4}$ alkyl), $-S(O)_2NH(C_{1-4}$ alkyl), $-S(O)N(C_{1-4}$ alkyl) $_2$, $-S(O)_2N(C_{1-4}$ alkyl) $_2$, C_{3-6} cycloalkyl, or 3-to 7-membered heterocycloalkyl;

R^{3a} and R^{3b} are each independently H, deuterium, fluoro, chloro, bromo, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, $-CN$, or $-CF_3$;

R^{7a} is H, C_{1-6} alkyl or 3-to 7-membered heterocycloalkyl, wherein each hydrogen atom in C_{1-6} alkyl or 3-to 7-membered heterocycloalkyl is independently optionally substituted by deuterium, halogen, $-CN$, $-OH$, $-OC_{1-4}$ alkyl, $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl) $_2$, $-CO_2H$,

-CO₂C₁₋₄alkyl, -CONH₂, -CONH(C₁₋₄alkyl), -CON(C₁₋₄alkyl)₂, cycloalkyl, or monocyclic heterocycloalkyl;

each R^k is independently H, deuterium, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3-to 7-membered heterocycloalkyl, C₆₋₁₀aryl, or mono- or bicyclic heteroaryl;
wherein each hydrogen atom in C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3-to 7-membered heterocycloalkyl, C₆₋₁₀aryl, or mono- or bicyclic heteroaryl in R^k is independently optionally substituted by deuterium, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl or -OR^a;

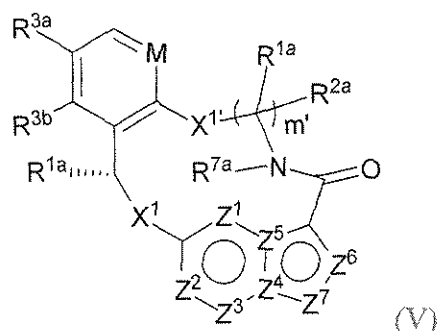
wherein each R^a and R^b is independently H, deuterium, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆₋₁₀aryl, or heteroaryl;

each Z¹, Z², Z³, Z⁴, Z⁵, Z⁶ or Z⁷ is independently N, NH, or C(R^x), wherein each R^x when present is independently H, deuterium, halogen, C₁₋₄alkyl, -O-C₁₋₄alkyl, -OH, -NH₂, -NH(C₁₋₄alkyl), -NH(phenyl), -NH(heteroaryl), CN, or -CF₃, provided that at least one of Z¹, Z², Z³, Z⁴, Z⁵, Z⁶ or Z⁷ is N or NH; and

m' is 2 or 3;

or a pharmaceutically acceptable salt thereof.

[084b] In another aspect, there is provided a compound of the Formula (V):



wherein

M is CH or N;

X¹ and X^{1'} are independently -C(R^{1a})(R^{2a})-, -S-, -S(O)-, -S(O)₂-, -O- or -N(R^k)-;

each R^{1a} and R^{2a} is independently H, deuterium, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₆₋₁₀aryl, -C(O)OR^a, -C(O)NR^aR^b, -NR^aR^b, -SR^a, -S(O)R^a, -S(O)NR^a, -S(O)₂R^a, -S(O)₂NR^a or -OR^a wherein each hydrogen atom in C₁₋₆alkyl is independently optionally substituted by deuterium, halogen, -OH, -OC₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, NHC(O)C₁₋₄alkyl, -N(C₁₋₄alkyl)C(O)C₁₋₄alkyl, -NHC(O)NHC₁₋₄alkyl, -N(C₁₋₄alkyl)C(O)NHC₁₋₄alkyl, NHC(O)N(C₁₋₄alkyl)₂, -N(C₁₋₄alkyl)C(O)N(C₁₋₄alkyl)₂, -NHC(O)OC₁₋₄alkyl, -N(C₁₋₄alkyl)C(O)OC₁₋₄alkyl, -CO₂H, -CO₂C₁₋₄alkyl, -CONH₂, -CONH(C₁₋₄alkyl), -CON(C₁₋₄alkyl)₂, -SC₁₋₄alkyl, -S(O)C₁₋₄alkyl, -S(O)₂C₁₋₄alkyl, -S(O)NH(C₁₋₄alkyl), -S(O)₂NH(C₁₋₄alkyl), -S(O)N(C₁₋₄alkyl)₂, -S(O)₂N(C₁₋₄alkyl)₂, C₃₋₆cycloalkyl, or 3-to 7-membered heterocycloalkyl;

R^{3a} and R^{3b} are each independently H, fluoro, chloro, bromo, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, -CN, or -CF₃;

R^{7a} is H, C₁₋₆alkyl or 3-to 7-membered heterocycloalkyl, wherein each hydrogen atom in C₁₋₆alkyl or 3-to 7-membered heterocycloalkyl is independently optionally substituted by halogen, -OH, -OC₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CO₂H, -CO₂C₁₋₄alkyl, -CONH₂, -CONH(C₁₋₄alkyl), -CON(C₁₋₄alkyl)₂, cycloalkyl, or monocyclic heterocycloalkyl;

each $R^{k'}$ is independently H, deuterium, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3-to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3-to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or mono- or bicyclic heteroaryl in $R^{k'}$ is independently optionally substituted by deuterium, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl or -OR^u;

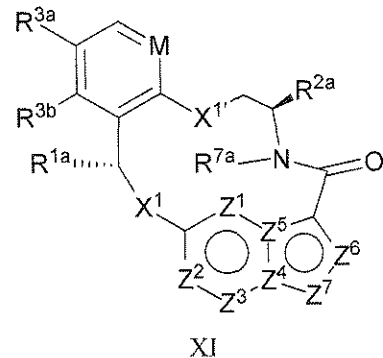
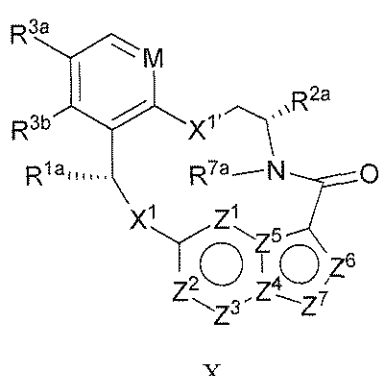
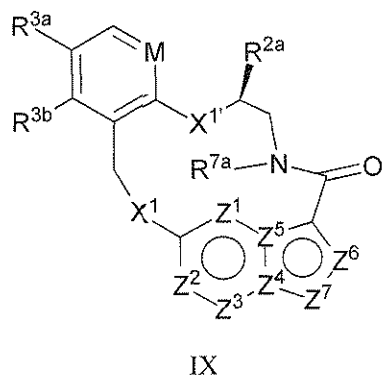
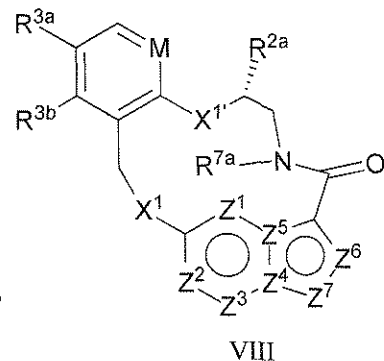
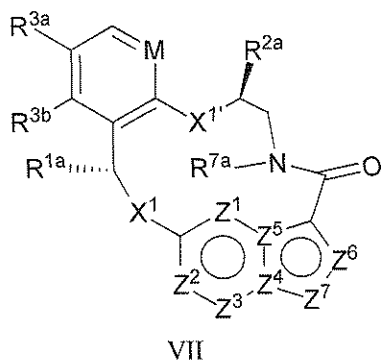
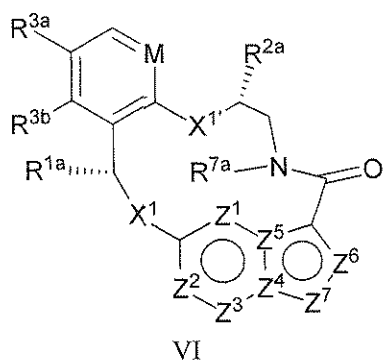
wherein each R^a and R^b is independently H, deuterium, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or heteroaryl;

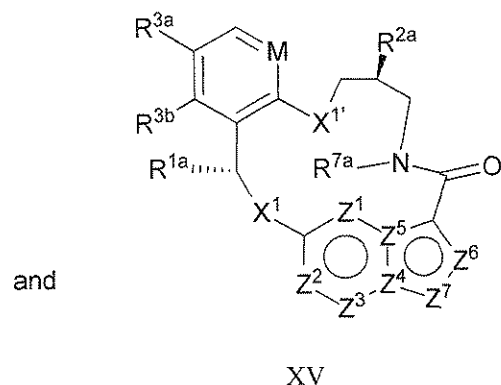
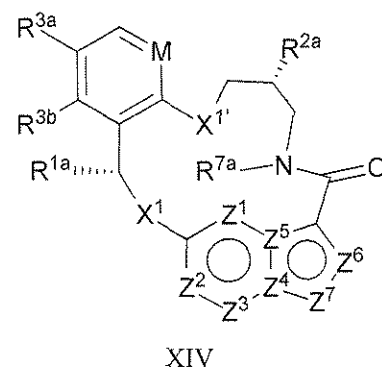
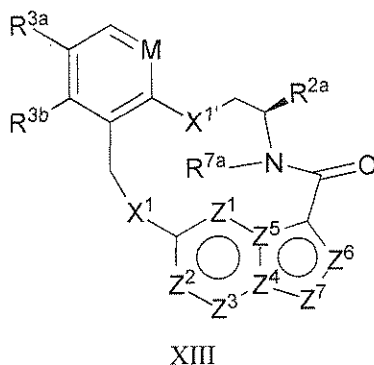
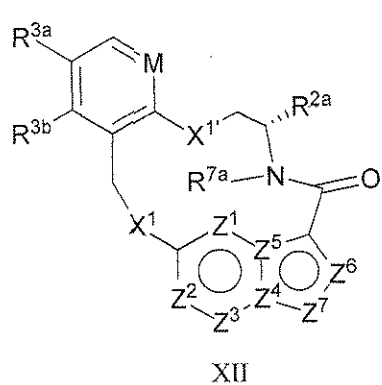
each $Z^1, Z^2, Z^3, Z^4, Z^5, Z^6$ or Z^7 is independently N, NH, or C(R^x), wherein each R^x when present is independently H, deuterium, halogen, C₁₋₄alkyl, -O-C₁₋₄alkyl, -OH, -NH₂, -NH(C₁₋₄alkyl), -NH(phenyl), -NH(heteroaryl), CN, or -CF₃, provided that at least one of $Z^1, Z^2, Z^3, Z^4, Z^5, Z^6$ or Z^7 is N or NH; and

m^* is 2 or 3;

or a pharmaceutically acceptable salt thereof.

[084c] In another aspect, there is provided a compound selected from the group consisting of





wherein

M is CH or N;

X¹ and X^{1'} are independently -C(R^{1a})(R^{2a})-, -S-, -S(O)-, -S(O)₂-, -O- or -N(R^k)-;

each R^{1a} and R^{2a} is independently H, deuterium, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₆₋₁₀ aryl, -C(O)OR^a, -C(O)NR^aR^b, -NR^aR^b, -SR^a, -S(O)R^a, -S(O)NR^a, -S(O)₂R^a, -S(O)₂NR^a or -OR^a wherein each hydrogen atom in C₁₋₆alkyl is independently optionally substituted by deuterium, halogen, -OH, -OC₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, NHC(O)C₁₋₄alkyl, -N(C₁₋₄alkyl)C(O)C₁₋₄alkyl, -NHC(O)NHC₁₋₄alkyl, -N(C₁₋₄alkyl)C(O)NHC₁₋₄alkyl, -NHC(O)N(C₁₋₄alkyl)₂, -N(C₁₋₄alkyl)C(O)N(C₁₋₄alkyl)₂, -NHC(O)OC₁₋₄alkyl, -N(C₁₋₄alkyl)C(O)OC₁₋₄alkyl, -CO₂H, -CO₂C₁₋₄alkyl, -CONH₂, -CONH(C₁₋₄alkyl), -CON(C₁₋₄alkyl)₂, -SC₁₋₄alkyl, -S(O)C₁₋₄alkyl, -S(O)₂C₁₋₄alkyl, -S(O)NH(C₁₋₄alkyl), -S(O)₂NH(C₁₋₄alkyl), -S(O)N(C₁₋₄alkyl)₂, -S(O)₂N(C₁₋₄alkyl)₂, C₃₋₆cycloalkyl, or 3-to 7-membered heterocycloalkyl;

R^{3a} and R^{3b} are each independently H, fluoro, chloro, bromo, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, -CN, or -CF₃;

R^{7a} is H, C₁₋₆alkyl or 3-to 7-membered heterocycloalkyl, wherein each hydrogen atom in C₁₋₆alkyl or 3-to 7-membered heterocycloalkyl is independently optionally substituted by halogen, -OH, -OC₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CO₂H, -CO₂C₁₋₄alkyl, -CONH₂, -CONH(C₁₋₄alkyl), -CON(C₁₋₄alkyl)₂, cycloalkyl, or monocyclic heterocycloalkyl;

each $R^{k'}$ is independently H, deuterium, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3-to 7-membered heterocycloalkyl, C_{6-10} aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3-to 7-membered heterocycloalkyl, C_{6-10} aryl, or mono- or bicyclic heteroaryl in $R^{k'}$ is independently optionally substituted by deuterium, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl or $-OR^{a'}$;

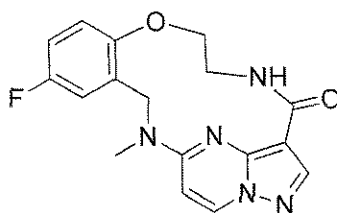
wherein each $R^{a'}$ and $R^{b'}$ is independently H, deuterium, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, or heteroaryl;

each $Z^1, Z^2, Z^3, Z^4, Z^5, Z^6$ or Z^7 is independently N, NH, or $C(R^x)$, wherein each R^x when present is independently H, deuterium, halogen, C_{1-4} alkyl, $-O-C_{1-4}$ alkyl, $-OH$, $-NH_2$, $-NH(C_{1-4}$ alkyl), $-NH(phenyl)$, $-NH(heteroaryl)$, CN, or $-CF_3$, provided that at least one of $Z^1, Z^2, Z^3, Z^4, Z^5, Z^6$ or Z^7 is N or NH; and

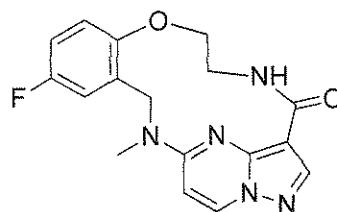
m' is 2 or 3;

or a pharmaceutically acceptable salt thereof.

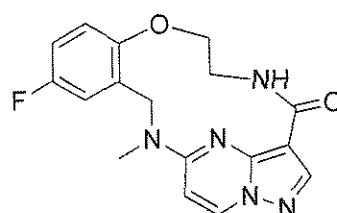
[085] ~~In a further aspect, the invention relates to~~ disclosure provides a crystalline form of the free base of the compound of the formula



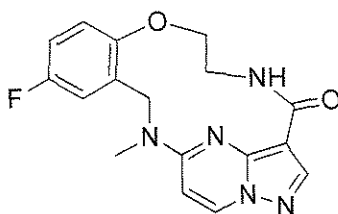
[086] having a powder X-ray diffraction pattern substantially the same as Fig. XX. In another aspect, there is provided a crystalline form of the free base of the compound as defined herein, having a powder X-ray diffraction pattern substantially the same as Fig. 1. In some embodiments, the crystalline polymorph form 1 of the free base of the compound of the formula



[087] wherein the powder X-ray diffraction pattern has a peak at diffraction angle (2θ) of 21.94. In some embodiments, the polymorph form 1 of the free base of the compound of the formula



[088] wherein the powder X-ray diffraction pattern has peaks at diffraction angles (2θ) of 21.94 and 23.96. In some embodiments, the polymorph form 1 of the free base of the compound of the formula



[089] wherein the powder X-ray diffraction pattern has peaks at diffraction angles (2θ) of 21.94, 23.96 and 19.64.

[090] ~~In a further aspect, the invention relates to~~ disclosure provides a pharmaceutical composition comprising at least one compound of Formula (I) or (I-A) or a pharmaceutically acceptable salt thereof. Pharmaceutical compositions according to the ~~invention~~ disclosure may further comprise a pharmaceutically acceptable excipient. The ~~invention~~ disclosure also provides a compound of Formula (I) or (I-A) or a pharmaceutically acceptable salt thereof for use as a medicament. In another aspect, there is provided a pharmaceutical composition comprising (a) at least one compound as defined herein, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable excipient.

[091] ~~In another aspect, the invention~~ disclosure is directed to a method of treating cancer, pain, neurological diseases, autoimmune diseases, or inflammation comprising administering to a subject in need of such treatment an effective amount of at least one compound of Formula (I) or (I-A) or a pharmaceutically acceptable salt thereof. In another aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof for use in treating cancer, pain, neurological diseases, autoimmune diseases, and inflammation.

[091a] In another aspect, there is provided use of the compound as defined herein in the manufacture of a medicament for treating cancer, pain, neurological diseases, autoimmune diseases, and inflammation.

[092] ~~In another aspect, the invention~~ disclosure is directed to use of a compound of Formula (I) or (I-A) in the preparation of a medicament for the treatment of such diseases and medical conditions, and the use of such compounds and salts for treatment of such diseases and medical conditions.

[093] ~~In yet another aspect, the invention~~ disclosure relates to a method of inhibiting protein or tyrosine kinases, including one or more of MET, ALK, ROS1, AXL, TRKs, and JAKs, comprising contacting a cell comprising one or more of such kinases with an effective amount of at least one compound of Formula (I) or (I-A) or a salt thereof, and/or with at least one pharmaceutical composition of the ~~invention~~ disclosure, wherein the contacting is *in vitro*, *ex vivo*, or *in vivo*.

[094] Additional embodiments, features, and advantages of the invention will be apparent from the following detailed description and through practice of the ~~invention~~disclosure.

[095] For the sake of brevity, the disclosures of the publications cited in this specification, including patents, are herein incorporated by reference.

DESCRIPTION OF THE DRAWINGS

[096] Fig. 1 shows a powder X-ray diffraction pattern of the crystalline polymorph form 1 of the free base of 11-fluoro-14-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclo-tridecin-4(5H)-one (Example 20).

each R^a , R^b , R^c , R^d , R^e , R^f , R^i and R^j is independently selected from the group consisting of H, deuterium, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, and heteroaryl;

m' is 2, 3, 4, or 5;

n' is 2, 3, or 4;

p' is 0, 1, 2, 3, or 4; and

q' is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein Ring A' is monocyclic aryl or heteroaryl and Ring B' is bicyclic heteroaryl, or a pharmaceutically acceptable salt thereof.

~~3. The compound of claim 1, wherein Ring A' is bicyclic heteroaryl and Ring B' is monocyclic aryl or heteroaryl, or a pharmaceutically acceptable salt thereof.~~

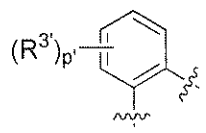
~~43. The compound of claim 1, wherein Ring A' is phenyl or a 6-membered heteroaryl, or a pharmaceutically acceptable salt thereof.~~

~~54. The compound of claim 1, wherein Ring B' is bicyclic heteroaryl containing 1, 2, or 3 nitrogen ring atoms, or a pharmaceutically acceptable salt thereof.~~

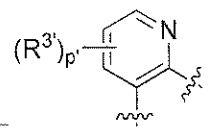
~~65. The compound of claim 1, wherein Ring A' is phenyl or pyridyl, or a pharmaceutically acceptable salt thereof.~~

~~7. The compound of claim 1, wherein Ring A' is phenyl, or a pharmaceutically acceptable salt thereof.~~

86. The compound of claim 1, wherein Ring A' substituted with $-(R^{3'})_{p'}$ is



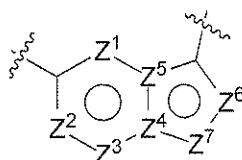
or a pharmaceutically acceptable salt thereof.



~~9. The compound of claim 1, wherein Ring A' substituted with $-(R^{3'})_{p'}$ is~~

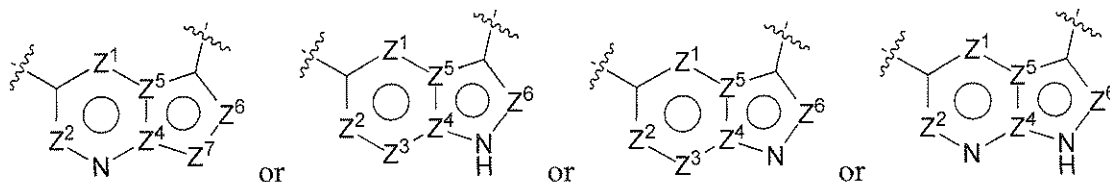
or a pharmaceutically acceptable salt thereof.

~~107. The compound of claim 1, wherein Ring B' is:~~



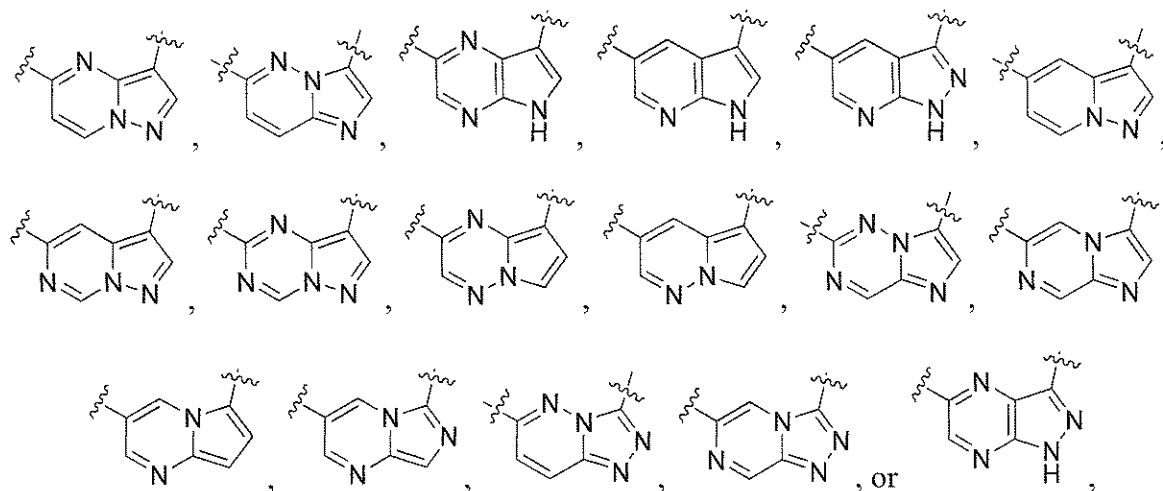
wherein Z^1 - Z^7 are defined as described herein, or a pharmaceutically acceptable salt thereof.

~~118. The compound of claim 1, wherein Ring B' is:~~



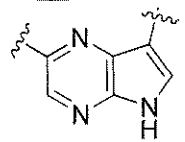
wherein Z^{1-7} are otherwise defined as described herein, or a pharmaceutically acceptable salt thereof.

129. The compound of claim 1, wherein Ring B' is:

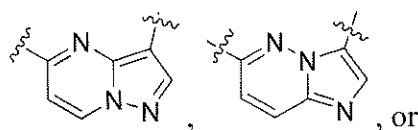


or a pharmaceutically acceptable salt thereof.

130. The compound of claim 1, wherein Ring B' is



, or a pharmaceutically acceptable salt thereof.



141. The compound of any one of claims 1-130, wherein each $R^{3'}$ is independently deuterium, fluoro, chloro, bromo, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, -CN, -CF₃, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CO₂C₁₋₄alkyl, -CO₂H, -NHC(O)C₁₋₄alkyl, -SO₂C₁₋₄alkyl, -C(O)NH₂, -C(O)NH(C₁₋₄alkyl), -C(O)N(C₁₋₄alkyl)₂, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, or a pharmaceutically acceptable salt thereof.

~~15. The compound of any one of claims 1-14, wherein each $R^{3'}$ is independently fluoro, chloro, bromo, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, -CN, or -CF₃, or a pharmaceutically acceptable salt thereof.~~

~~16. The compound of any one of claims 1-15, wherein each $R^{3'}$ is fluoro or chloro, or a pharmaceutically acceptable salt thereof.~~

~~17~~12. The compound of any one of claims 1-~~16~~11, wherein R⁷ is H, deuterium, optionally substituted methyl, optionally substituted ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidinyl, furanyl, thiofuranyl, piperidinyl, piperazinyl, morpholinyl, phenyl, or monocyclic heteroaryl, or a pharmaceutically acceptable salt thereof, wherein said optionally substituted methyl or optionally substituted ethyl is:

~~18. The compound of any one of claims 1-17, wherein R⁷ is H, or is methyl, ethyl, propyl, isopropyl, or cyclopropyl, or a pharmaceutically acceptable salt thereof.~~

~~19. The compound of any one of claims 1-18, wherein R⁷ is H or is methyl or ethyl, each unsubstituted or substituted with halogen, -OH, -OC₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CO₂H, -CO₂C₁₋₄alkyl, -CONH₂, cycloalkyl, or monocyclic heterocycloalkyl, or a pharmaceutically acceptable salt thereof.~~

~~20. The compound of any one of claims 1-19, wherein R⁷ is H, methyl, hydroxyethyl, -CH₂CONH₂, or 3-pyrrolidinylmethyl, or a pharmaceutically acceptable salt thereof.~~

~~21. The compound of any one of claims 1-20, wherein R⁷ is H or methyl, or a pharmaceutically acceptable salt thereof.~~

~~22~~13. The compound of any one of claims 1-~~21~~12, wherein R^{1'} and R^{2'} are each independently H, deuterium, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidinyl, furanyl, thiofuranyl, piperidinyl, piperazinyl, morpholinyl, phenyl, or monocyclic heteroaryl, or a pharmaceutically acceptable salt thereof.

~~23~~14. The compound of any one of claims 1-~~22~~13, wherein R^{1'} is H, or a pharmaceutically acceptable salt thereof.

~~24~~15. The compound of any one of claims 1-~~23~~14, wherein R^{2'} is deuterium, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidinyl, furanyl, thiofuranyl, piperidinyl, piperazinyl, morpholinyl, phenyl, or monocyclic heteroaryl, or a pharmaceutically acceptable salt thereof.

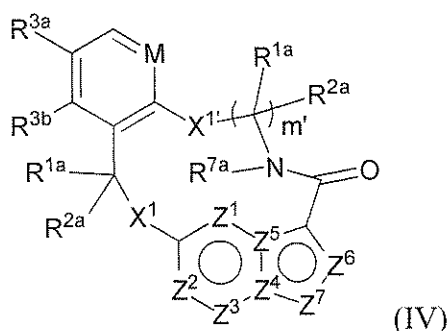
~~25~~16. The compound of any one of claims 1-~~24~~15, wherein R^{2'} is H or is methyl or ethyl, each unsubstituted or substituted with halogen, -OH, -OC₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CO₂H, -CO₂C₁₋₄alkyl, -CONH₂, cycloalkyl, or monocyclic heterocycloalkyl, or a pharmaceutically acceptable salt thereof.

~~26~~17. The compound of any one of claims 1-~~25~~16, wherein R^{2'} is H, methyl, fluoromethyl, hydroxymethyl or cyclopropyl, or a pharmaceutically acceptable salt thereof.

~~27~~18. The compound of any one of claims 1-~~26~~17, wherein each R^k is independently H, methyl, ethyl, propyl, isopropyl, or cyclopropyl, or a pharmaceutically acceptable salt thereof.

~~28~~19. The compound of any one of claims 1-~~27~~18, wherein each L¹ and L² is independently -CH₂-, -CH(methyl)-, -CH(substituted methyl)-, -CH(C₃₋₆cycloalkyl)-, -O-, -NH-, -N(C₁₋₄alkyl), -N(C₃₋₆cycloalkyl), -S-, -S(O)-, or -SO₂-, or a pharmaceutically acceptable salt thereof.

3526. A compound of the Formula (IV):



each R^{1a} and R^{2a} is independently H, deuterium, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₆₋₁₀ aryl, -C(O)OR^{a'}, -C(O)NR^{a'}R^{b'}, -NR^{a'}R^{b'}, -SR^{a'}, -S(O)R^{a'}, -S(O)NR^{a'}, -S(O)₂R^{a'}, -S(O)₂NR^{a'} or -OR^{a'} wherein each hydrogen atom in C₁₋₆alkyl is independently optionally substituted by deuterium, halogen, -OH, -OC₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, NHC(O)C₁₋₄alkyl, -N(C₁₋₄alkyl)C(O)C₁₋₄alkyl, -NHC(O)NHC₁₋₄alkyl, -N(C₁₋₄alkyl)C(O)NHC₁₋₄alkyl, NHC(O)N(C₁₋₄alkyl)₂, -N(C₁₋₄alkyl)C(O)N(C₁₋₄alkyl)₂, -NHC(O)OC₁₋₄alkyl, -N(C₁₋₄alkyl)C(O)OC₁₋₄alkyl, -CO₂H, -CO₂C₁₋₄alkyl, -CONH₂, -CONH(C₁₋₄alkyl), -CON(C₁₋₄alkyl)₂,

-SC₁₋₄alkyl, -S(O)C₁₋₄alkyl, -S(O)₂C₁₋₄alkyl, -S(O)NH(C₁₋₄alkyl), -S(O)₂NH(C₁₋₄alkyl), -S(O)N(C₁₋₄alkyl)₂, -S(O)₂N(C₁₋₄alkyl)₂, C₃₋₆cycloalkyl, or 3-to 7-membered heterocycloalkyl;

R^{3a} and R^{3b} are each independently H, deuterium, fluoro, chloro, bromo, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, -CN, or -CF₃;

R^{7a} is H, C₁₋₆alkyl or 3-to 7-membered heterocycloalkyl, wherein each hydrogen atom in C₁₋₆alkyl or 3-to 7-membered heterocycloalkyl is independently optionally substituted by deuterium, halogen, -CN, -OH, -OC₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CO₂H, -CO₂C₁₋₄alkyl, -CONH₂, -CONH(C₁₋₄alkyl), -CON(C₁₋₄alkyl)₂, cycloalkyl, or monocyclic heterocycloalkyl;

each R^k is independently H, deuterium, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3-to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3-to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or mono- or bicyclic heteroaryl in R^k is independently optionally substituted by deuterium, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl or -OR^a;

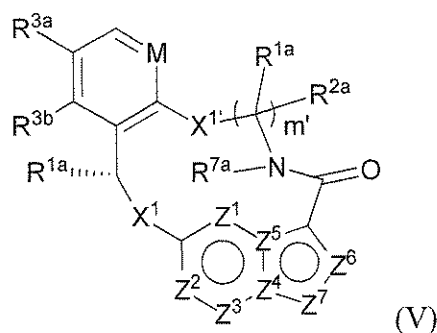
wherein each R^a and R^b is independently H, deuterium, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or heteroaryl;

each Z¹, Z², Z³, Z⁴, Z⁵, Z⁶ or Z⁷ is independently N, NH, or C(R^x), wherein each R^x when present is independently H, deuterium, halogen, C₁₋₄alkyl, -O-C₁₋₄alkyl, -OH, -NH₂, -NH(C₁₋₄alkyl), -NH(phenyl), -NH(heteroaryl), CN, or -CF₃, provided that at least one of Z¹, Z², Z³, Z⁴, Z⁵, Z⁶ or Z⁷ is N or NH; and

m' is 2 or 3;

or a pharmaceutically acceptable salt thereof.

3627. A compound of the Formula (V):



wherein

M is CH or N;

X¹ and X^{1'} are independently -C(R^{1a})(R^{2a})-, -S-, -S(O)-, -S(O)₂-, -O- or -N(R^k)-;

each R^{1a} and R^{2a} is independently H, deuterium, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₆₋₁₀ aryl, -C(O)OR^a, -C(O)NR^aR^b, -NR^aR^b, -SR^a, -S(O)R^a, -S(O)NR^a, -S(O)₂R^a, -S(O)₂NR^a or

-OR^{a'} wherein each hydrogen atom in C₁₋₆alkyl is independently optionally substituted by deuterium, halogen, -OH, -OC₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, NHC(O)C₁₋₄alkyl, -N(C₁₋₄alkyl)C(O)C₁₋₄alkyl, -NHC(O)NHC₁₋₄alkyl, -N(C₁₋₄alkyl)C(O)NHC₁₋₄alkyl, NHC(O)N(C₁₋₄alkyl)₂, -N(C₁₋₄alkyl)C(O)N(C₁₋₄alkyl)₂, -NHC(O)OC₁₋₄alkyl, -N(C₁₋₄alkyl)C(O)OC₁₋₄alkyl, -CO₂H, -CO₂C₁₋₄alkyl, -CONH₂, -CONH(C₁₋₄alkyl), -CON(C₁₋₄alkyl)₂, -SC₁₋₄alkyl, -S(O)C₁₋₄alkyl, -S(O)₂C₁₋₄alkyl, -S(O)NH(C₁₋₄alkyl), -S(O)₂NH(C₁₋₄alkyl), -S(O)N(C₁₋₄alkyl)₂, -S(O)₂N(C₁₋₄alkyl)₂, C₃₋₆cycloalkyl, or 3-to 7-membered heterocycloalkyl;

R^{3a} and R^{3b} are each independently H, fluoro, chloro, bromo, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, -CN, or -CF₃;

R^{7a} is H, C₁₋₆alkyl or 3-to 7-membered heterocycloalkyl, wherein each hydrogen atom in C₁₋₆alkyl or 3-to 7-membered heterocycloalkyl is independently optionally substituted by halogen, -OH, -OC₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CO₂H, -CO₂C₁₋₄alkyl, -CONH₂, -CONH(C₁₋₄alkyl), -CON(C₁₋₄alkyl)₂, cycloalkyl, or monocyclic heterocycloalkyl;

each R^{k'} is independently H, deuterium, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3-to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3-to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or mono- or bicyclic heteroaryl in R^{k'} is independently optionally substituted by deuterium, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl or -OR^{a'};

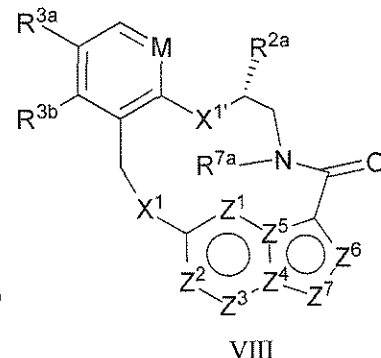
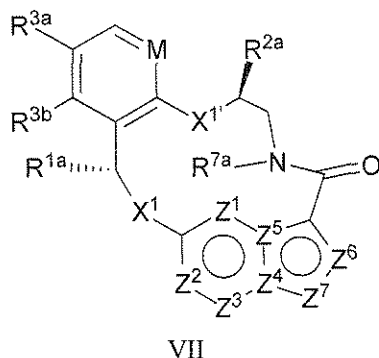
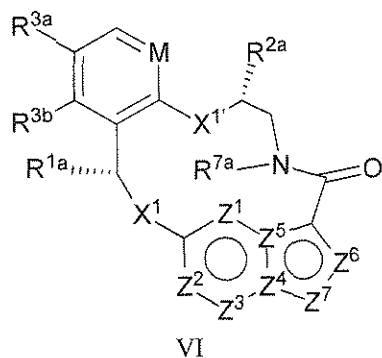
wherein each R^{a'} and R^{b'} is independently H, deuterium, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or heteroaryl;

each Z¹, Z², Z³, Z⁴, Z⁵, Z⁶ or Z⁷ is independently N, NH, or C(R^x), wherein each R^x when present is independently H, deuterium, halogen, C₁₋₄alkyl, -O-C₁₋₄alkyl, -OH, -NH₂, -NH(C₁₋₄alkyl), -NH(phenyl), -NH(heteroaryl), CN, or -CF₃, provided that at least one of Z¹, Z², Z³, Z⁴, Z⁵, Z⁶ or Z⁷ is N or NH; and

m' is 2 or 3;

or a pharmaceutically acceptable salt thereof.

3728. A compound selected from the group consisting of



-S(O)N(C₁₋₄alkyl)₂, -S(O)₂N(C₁₋₄alkyl)₂, C₃₋₆cycloalkyl, or 3-to 7-membered heterocycloalkyl;

R^{3a} and R^{3b} are each independently H, fluoro, chloro, bromo, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, -CN, or -CF₃;

R^{7a} is H, C₁₋₆alkyl or 3-to 7-membered heterocycloalkyl, wherein each hydrogen atom in C₁₋₆alkyl or 3-to 7-membered heterocycloalkyl is independently optionally substituted by halogen, -OH, -OC₁₋₄alkyl, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -CO₂H, -CO₂C₁₋₄alkyl, -CONH₂, -CONH(C₁₋₄alkyl), -CON(C₁₋₄alkyl)₂, cycloalkyl, or monocyclic heterocycloalkyl;

each R^{k'} is independently H, deuterium, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3-to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3-to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or mono- or bicyclic heteroaryl in R^{k'} is independently optionally substituted by deuterium, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl or -OR^{a'};

wherein each R^{a'} and R^{b'} is independently H, deuterium, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or heteroaryl;

each Z¹, Z², Z³, Z⁴, Z⁵, Z⁶ or Z⁷ is independently N, NH, or C(R^x), wherein each R^x when present is independently H, deuterium, halogen, C₁₋₄alkyl, -O-C₁₋₄alkyl, -OH, -NH₂, -NH(C₁₋₄alkyl), -NH(phenyl), -NH(heteroaryl), CN, or -CF₃, provided that at least one of Z¹, Z², Z³, Z⁴, Z⁵, Z⁶ or Z⁷ is N or NH; and

m' is 2 or 3;

or a pharmaceutically acceptable salt thereof.

3829. The compound of any one of claims ~~3526-3728~~, wherein Z¹, Z⁴ and Z⁷ are N, and Z², Z³, Z⁵ and Z⁶ are C(R^x), wherein each R^x when present is H, or a ~~pharmaceutically acceptable salt thereof~~.

~~39. The compound of any one of claim 35-37, wherein M is CH, Z¹, Z⁴ and Z⁷ are N, and Z², Z³, Z⁵ and Z⁶ are C(R^x), wherein each R^x when present is H, or a pharmaceutically acceptable salt thereof.~~

~~40. The compound of any one of claims 35-37, wherein M is CH, Z¹, Z⁴ and Z⁷ are N, Z², Z³, Z⁵ and Z⁶ are C(R^x), wherein each R^x when present is H, and X¹ is -N(R^{k'})-, or a pharmaceutically acceptable salt thereof.~~

~~41. The compound of any one of claims 35-37, wherein M is CH, Z¹, Z⁴ and Z⁷ are N, Z², Z³, Z⁵ and Z⁶ are C(R^x), wherein each R^x when present is H, X¹ is -N(R^{k'})-, and X^{1'} is -O-, or a pharmaceutically acceptable salt thereof.~~

~~42. The compound of any one of claims 35-37, wherein M is CH, Z¹, Z⁴ and Z⁷ are N, Z², Z³, Z⁵ and Z⁶ are C(R^x), wherein each R^x when present is H, X¹ is -C(R^{1a})(R^{2a})-, and X^{1'} is -O-, or a pharmaceutically acceptable salt thereof.~~

~~43~~30. The compound of any one of claims ~~35-43~~26-4229, wherein R^k is selected from the group consisting of H, methyl, ethyl, propyl, iso-propyl, cyclopropyl, 2-hydroxyethyl, 2-hydroxy-2-methyl-propyl, and N-methyl-pyrrol-3-yl, or a pharmaceutically acceptable salt thereof.

~~44. The compound of claims 35-43, wherein R^k is H or methyl, or a pharmaceutically acceptable salt thereof.~~

~~45~~31. The compound of claim 1 selected from the group consisting of (13R)-5,13-dimethyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; 5,13-dimethyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; (13R)-11-fluoro-5,13-dimethyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; 11-fluoro-5,13-dimethyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; (13R)-12-chloro-11-fluoro-5,13-dimethyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-5,13-dimethyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; (13R)-12-chloro-11-fluoro-5-(2-hydroxyethyl)-13-methyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-5-(2-hydroxyethyl)-13-methyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; 2-[(13R)-12-chloro-11-fluoro-13-methyl-4-oxo-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-5(4H)-yl]acetamide; 2-[12-chloro-11-fluoro-13-methyl-4-oxo-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-5(4H)-yl]acetamide; (13R)-12-chloro-11-fluoro-13-methyl-5-(pyrrolidin-2-ylmethyl)-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-13-methyl-5-(pyrrolidin-2-ylmethyl)-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; (13R)-12-chloro-11-fluoro-7-(hydroxymethyl)-5,13-dimethyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-7-(hydroxymethyl)-5,13-dimethyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; (13S)-11-fluoro-13-(fluoromethyl)-5-methyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; 11-fluoro-13-(fluoromethyl)-5-methyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-

ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-13,14-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-5,14-dimethyl-6,7,13,14-tetrahydro-15,1-(azenometheno)pyrazolo[4,3-f][1,4,10]benzoxadiazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-14-methyl-6,7,13,14-tetrahydro-15,1-(azenometheno)pyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-14-methyl-6,7,13,14-tetrahydro-1,15-(azenometheno)pyrrolo[3,2-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-14-methyl-6,7,13,14-tetrahydro-1,15-(azenometheno)pyrrolo[3,2-f][1,4,10]benzoxadiazacyclotridecin-4(5H)-one; 9-chloro-10-fluoro-7-methyl-7,8,15,16-tetrahydro-3,6-ethenoimidazo[5,1-f][1,4,7,8,10]benzoxatetraazacyclotridecin-17(14H)-one; 9-chloro-10-fluoro-7-methyl-7,8,15,16-tetrahydro-6,3-(azenometheno)imidazo[5,1-f][1,4,7,8,10]benzoxatetraazacyclotridecin-17(14H)-one; 9-chloro-10-fluoro-7-methyl-7,8,15,16-tetrahydro-6,3-(azenometheno)imidazo[5,1-f][1,4,7,10]benzoxatriazacyclotridecin-17(14H)-one; 9-chloro-10-fluoro-7-methyl-7,8,15,16-tetrahydro-3,6-(azenometheno)pyrrolo[2,1-f][1,4,7,10]benzoxatriazacyclotridecin-17(14H)-one; 9-chloro-10-fluoro-7-methyl-7,8,15,16-tetrahydro-3,6-(azenometheno)imidazo[2,1-f][1,4,7,10]benzoxatriazacyclotridecin-17(14H)-one; 9-chloro-10-fluoro-7-methyl-7,8,15,16-tetrahydro-3,6-etheno[1,2,4]triazolo[3,4-f][1,4,7,8,10]benzoxatetraazacyclotridecin-17(14H)-one; 9-chloro-10-fluoro-7-methyl-7,8,15,16-tetrahydro-6,3-(azenometheno)[1,2,4]triazolo[3,4-f][1,4,7,10]benzoxatriazacyclotridecin-17(14H)-one; 8-chloro-9-fluoro-6-methyl-6,7,14,15-tetrahydro-2H-3,5-(azenometheno)pyrrolo[3,4-f][1,4,8,10]benzoxatriazacyclotridecin-16(13H)-one; 8-chloro-9-fluoro-6-methyl-6,7,14,15-tetrahydro-2H-3,5-(azenometheno)pyrazolo[3,4-f][1,4,8,10]benzoxatriazacyclotridecin-16(13H)-one; 8-chloro-9-fluoro-6-methyl-6,7,14,15-tetrahydro-2H-3,5-(azenometheno)pyrazolo[3,4-f][1,4,10]benzoxadiazacyclotridecin-16(13H)-one; 12-chloro-11-fluoro-5,14-dimethyl-6,7,13,14-tetrahydro-2H-1,15-(azenometheno)pyrrolo[3,4-f][1,4,10]benzoxadiazacyclotridecin-4(5H)-one; (8R)-10-fluoro-8,16-dimethyl-15,16-dihydro-8H-3,6-ethenoimidazo[5,1-f][1,10,4,7,8]benzodioxatriazacyclotridecin-17(14H)-one; 10-fluoro-8,16-dimethyl-15,16-dihydro-8H-3,6-ethenoimidazo[5,1-f][1,10,4,7,8]benzodioxatriazacyclotridecin-17(14H)-one; (7R)-9-fluoro-7,15-dimethyl-14,15-dihydro-2H,7H-3,5-(azenometheno)pyrrolo[3,4-f][1,10,4,8]benzodioxadiazacyclotridecin-16(13H)-one; and 9-fluoro-7,15-dimethyl-14,15-dihydro-2H,7H-3,5-(azenometheno)pyrrolo[3,4-f][1,10,4,8]benzodioxadiazacyclotridecin-16(13H)-one; or a pharmaceutically acceptable salt thereof.

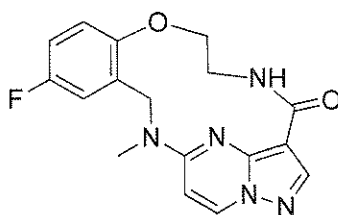
46. The compound of claim 1 selected from the group consisting of 12-chloro-11-fluoro-14-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 11-fluoro-3,14-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 10-fluoro-8-methyl-15,16-dihydro-8H-3,6-ethenoimidazo[5,1-f][1,10,4,7,8]benzodioxatriazacyclotridecin-17(14H)-one; 10-fluoro-7-methyl-7,8,15,16-tetrahydro-3,6-ethenoimidazo[5,1-f][1,4,7,8,10]benzoxatetraazacyclotridecin-17(14H)-one; 14-ethyl-11-fluoro-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 11-fluoro-14-propyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 11-fluoro-14-(propan-2-yl)-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 14-cyclopropyl-11-fluoro-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 11-fluoro-14-(2-hydroxyethyl)-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 11-fluoro-6,14-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 14-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 11-fluoro-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 11-fluoro-13-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; (13*R*)-11-fluoro-13-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-13-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 11-fluoro-14-methyl-4-oxo-4,5,6,7,13,14-hexahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-7-carboxamide; 11-fluoro-7-(hydroxymethyl)-14-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 11-fluoro-13-methyl-4-oxo-4,5,6,7,13,14-hexahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-7-carboxamide; 11-fluoro-7-(hydroxymethyl)-13-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 11-fluoro-4-oxo-4,5,6,7,13,14-hexahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-7-carboxamide; 11-fluoro-7-(hydroxymethyl)-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; methyl 11-fluoro-4-oxo-4,5,6,7,13,14-hexahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-13-carboxylate; 11-fluoro-4-oxo-4,5,6,7,13,14-hexahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-13-carboxamide; 11-fluoro-14-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f]pyrido[3,2-

11-[1,4,8,10]oxatriazacyclotridecin-4(5H)-one; 11-fluoro-13-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f]pyrido[3,2-l][1,4,8,10]oxatriazacyclotridecin-4(5H)-one; 11-fluoro-13-(propan-2-yl)-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f]pyrido[3,2-l][1,4,8,10]oxatriazacyclotridecin-4(5H)-one; 13-cyclopropyl-11-fluoro-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f]pyrido[3,2-l][1,4,8,10]oxatriazacyclotridecin-4(5H)-one; 13-cyclopropyl-11-fluoro-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 11-fluoro-13-(propan-2-yl)-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 11-fluoro-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzoxathiadiazacyclotridecin-4(5H)-one; 11-fluoro-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzoxathiadiazacyclotridecin-4(5H)-one 14,14-dioxide; 6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][10,1,4,8]benzoxathiadiazacyclotridecin-4(5H)-one; 14-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzothiatiazacyclotridecin-4(5H)-one; 13-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzothiatiazacyclotridecin-4(5H)-one; 11-fluoro-6,7-dihydro-5H-1,15-ethenopyrazolo[3,4-e][11,1,2,4,8]benzoxathiatriazacyclotridecin-4(14H)-one 13,13-dioxide; 11-fluoro-14-methyl-6,7-dihydro-5H-1,15-ethenopyrazolo[3,4-e][11,1,2,4,8]benzoxathiatriazacyclotridecin-4(14H)-one 13,13-dioxide; 12-fluoro-15-methyl-5,6,7,8,14,15-hexahydro-4H-1,16-ethenopyrazolo[4,3-g][1,5,9,11]benzoxatriazacyclotetradecin-4-one; 12-fluoro-14-methyl-5,6,7,8,14,15-hexahydro-4H-1,16-ethenopyrazolo[4,3-g][1,5,9,11]benzoxatriazacyclotetradecin-4-one; (14*R*)-12-fluoro-14-methyl-5,6,7,8,14,15-hexahydro-4*H*-1,16-ethenopyrazolo[4,3-g][1,5,9,11]benzoxatriazacyclotetradecin-4-one; 11-fluoro-7,14-dimethyl-4,5,6,7,13,14-hexahydro-8H-1,15-ethenopyrazolo[3,4-e][2,4,10]benzotriazacyclotridecin-8-one; 11-fluoro-7,14-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[3,4-e][7,2,4,10]benzoxatriazacyclotridecin-8(5H)-one; 11-fluoro-7,14-dimethyl-4,5,6,7,13,14-hexahydro-8H-1,15-ethenopyrazolo[3,4-e][2,4,7,10]benzotetraazacyclotridecin-8-one; 11-fluoro-4,7,14-trimethyl-4,5,6,7,13,14-hexahydro-8H-1,15-ethenopyrazolo[3,4-e][2,4,7,10]benzotetraazacyclotridecin-8-one; 11-fluoro-7,14-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[3,4-e][7,2,4,10]benzothiatiazacyclotridecin-8(5H)-one; 11-fluoro-7,14-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[3,4-e][7,2,4,10]benzothiatiazacyclotridecin-8(5H)-one 4,4-dioxide; and 12-fluoro-8,15-dimethyl-5,6,7,8,14,15-hexahydro-9H-1,16-ethenopyrazolo[3,4-e][7,2,4,8,11]benzothiatetraazacyclotetradecin-9-one 4,4-dioxide; or a pharmaceutically acceptable salt thereof.

47. — The compound of claim 1 selected from the group consisting of 11-chloro-13-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; 13-ethyl-11-fluoro-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; 13-cyclobutyl-11-fluoro-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; 11-fluoro-14-methyl(6,6,7,7-²H₄)-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; 11-fluoro-13-phenyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; 13-(cyclopropylmethyl)-11-fluoro-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; (7*R*,14*R*)-12-fluoro-7-hydroxy-14-methyl-5,6,7,8,14,15-hexahydro-4*H*-1,16-ethenopyrazolo[4,3-*g*][1,5,9,11]benzoxatriazacyclotetradecin-4-one; (7*S*,14*R*)-12-fluoro-7-hydroxy-14-methyl-5,6,7,8,14,15-hexahydro-4*H*-1,16-ethenopyrazolo[4,3-*g*][1,5,9,11]benzoxatriazacyclotetradecin-4-one; (7*R*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; (7*R*)-11-fluoro-7,14-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; (6*R*)-11-fluoro-6,14-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; 12-fluoro-7-hydroxy-15-methyl-5,6,7,8,14,15-hexahydro-4*H*-1,16-ethenopyrazolo[4,3-*g*][1,5,9,11]benzoxatriazacyclotetradecin-4-one; (7*S*)-11-fluoro-7,14-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; 11-fluoro-13-(hydroxymethyl)-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; 12-fluoro-14-(hydroxymethyl)-5,6,7,8,14,15-hexahydro-4*H*-1,16-ethenopyrazolo[4,3-*g*][1,5,9,11]benzoxatriazacyclotetradecin-4-one; 11-fluoro-13,14-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; 11-fluoro-14-(2-hydroxy-2-methylpropyl)-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; 12-fluoro-5,6,7,8,14,15-hexahydro-4*H*-1,16-ethenopyrazolo[4,3-*g*][1,5,9]benzoxadiazacyclotetradecin-4-one; 11-fluoro-14-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzothiatiazacyclotridecin-4(5*H*)-one; 11-fluoro-14-(1-methylpyrrolidin-3-yl)-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; 11-fluoro-14-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzothiatiazacyclotridecin-4(5*H*)-one 8-oxide; 11-fluoro-

14-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzothiazacyclotridecin-4(5*H*)-one 8,8-dioxide; (7*S*)-11-fluoro-7-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8]benzoxadiazacyclotridecin-4(5*H*)-one; (6*S*,13*R*)-11-fluoro-6,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; (6*R*,13*R*)-11-fluoro-6,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; (7*S*,13*S*)-11-fluoro-13-(hydroxymethyl)-7-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one; and 11-fluoro-6,7-dihydro-13*H*-1,15-ethenopyrazolo[4,3-*f*][1,10,4,8]benzoxathiadiazacyclotridecin-4(5*H*)-one; or a pharmaceutically acceptable salt thereof.

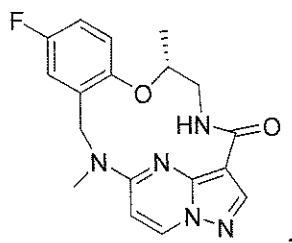
4832. The compound of claim 1 having the formula



or a pharmaceutically acceptable salt thereof.

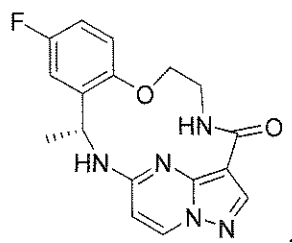
4933. A crystalline form of the free base of the compound of claim 4832, having a powder X-ray diffraction pattern substantially the same as Fig. 1.

5034. The compound of claim 1 having the formula



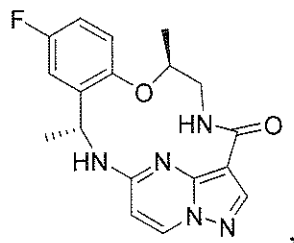
or a pharmaceutically acceptable salt thereof.

51. The compound of claim 1 having the formula



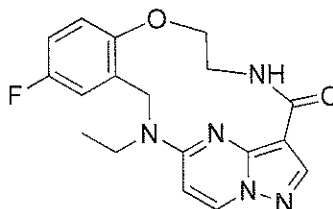
or a pharmaceutically acceptable salt thereof.

52. The compound of claim 1 having the formula



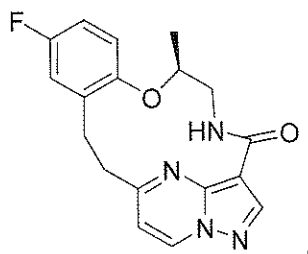
or a pharmaceutically acceptable salt thereof.

53. The compound of claim 1 having the formula



or a pharmaceutically acceptable salt thereof.

54. The compound of claim 1 having the formula



or a pharmaceutically acceptable salt thereof.

5535. A pharmaceutical composition comprising (a) at least one compound of any one of claims 1-5434, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable excipient.

5636. A method of treating cancer, pain, neurological diseases, autoimmune diseases, and inflammation, comprising administering to a subject in need of such treatment an effective amount of at least one compound of any one of claims 1-5434, or a pharmaceutically acceptable salt thereof for use in treating cancer, pain, neurological diseases, autoimmune diseases, and inflammation.

37. Use of the compound of any one of claims 1-34 in the manufacture of a medicament for treating cancer, pain, neurological diseases, autoimmune diseases, and inflammation.