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.

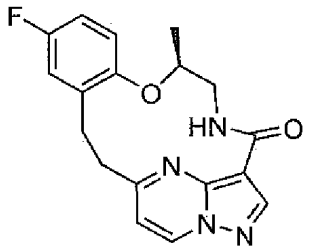
[015] There remains a need for small molecule inhibitors of these multiple protein or tyrosine kinase targets with desirable pharmaceutical properties. Certain diaryl macrocyclic compounds have been found in the context of this invention to have this advantageous activity profile.

SUMMARY

[016] There is provided a compound of the following Formula (I-A):

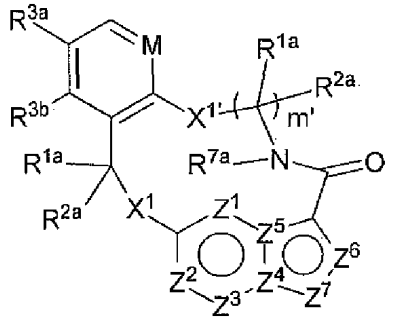
[082] or a pharmaceutically acceptable salt thereof.

[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 one aspect, there is provided a compound of the Formula (IV):



(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, $-C(O)OR^{a'}$, $-C(O)NR^{a'}R^{b'}$, $-NR^{a'}R^{b'}$, $-SR^{a'}$, $-S(O)R^{a'}$, $-S(O)NR^{a'}$, $-S(O)_2R^{a'}$, $-S(O)_2NR^{a'}$ or $-OR^{a'}$ wherein each hydrogen atom in 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), $-N(C_{1-4}alkyl)_2$, $-CO_2H$,

-CO_2C_{1-4}alkyl, -$CONH_2$, -$CONH(C_{1-4}alkyl)$, -$CON(C_{1-4}alkyl)_2$, 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 -$OR^{a'}$;

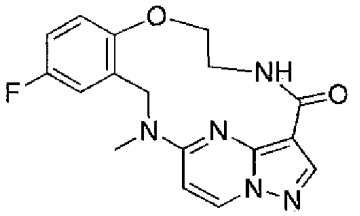
wherein each $R^{a'}$ and $R^{b'}$ is independently H, deuterium, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, or heteroaryl;

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

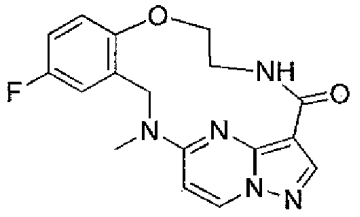
m' is 2 or 3;

or a pharmaceutically acceptable salt thereof.

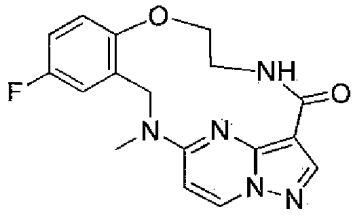
[085] The disclosure provides a crystalline form of the free base of the compound of the formula



[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

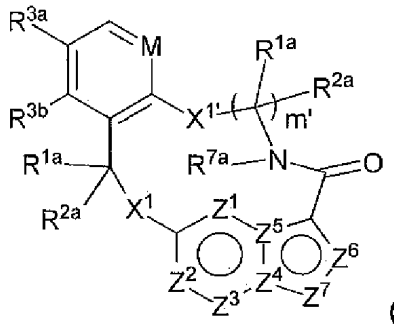


[087] wherein the powder X-ray diffraction pattern has a peak at diffraction angle (2θ) of 21.94. In some embodiments, the polymorph form 1 of the free base of the compound of the formula



[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

1. A compound of the following Formula (IV):



(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, $-C(O)OR^{a'}$, $-C(O)NR^{a'}R^{b'}$, $-NR^{a'}R^{b'}$, $-SR^{a'}$, $-S(O)R^{a'}$, $-S(O)NR^{a'}$, $-S(O)_2R^{a'}$, $-S(O)_2NR^{a'}$ or $-OR^{a'}$, wherein each hydrogen atom in 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, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, $-CO_2H$, $-CO_2C_{1-4}$alkyl, $-CONH_2$, $-CONH(C_{1-4}alkyl)$, $-CON(C_{1-4}alkyl)_2$, 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 $-OR^{a'}$;

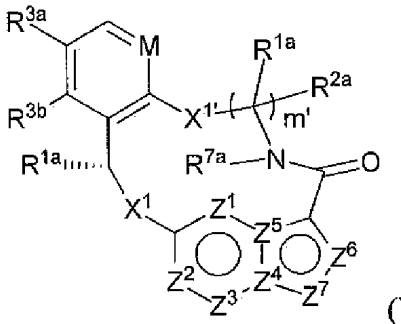
wherein each $R^{a'}$ and $R^{b'}$ is independently H, deuterium, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, or heteroaryl;

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;

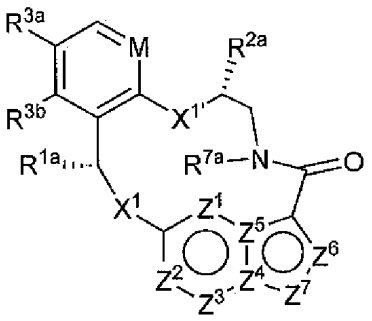
or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the formula



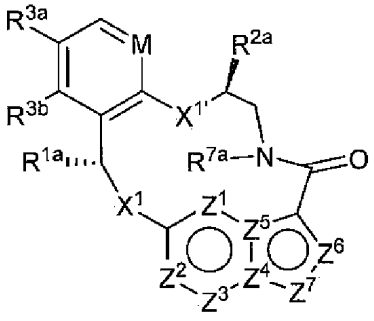
(V).

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the formula



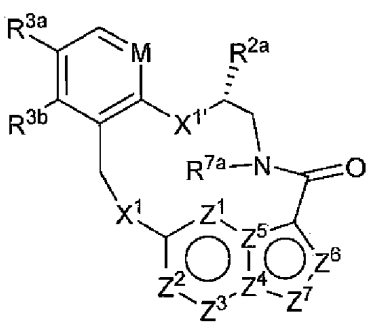
VI

or



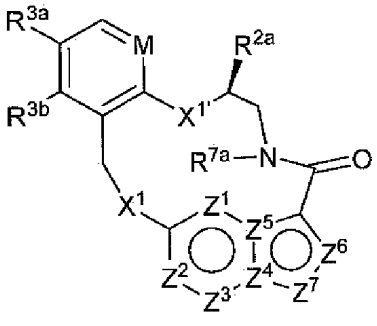
VII

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the formula



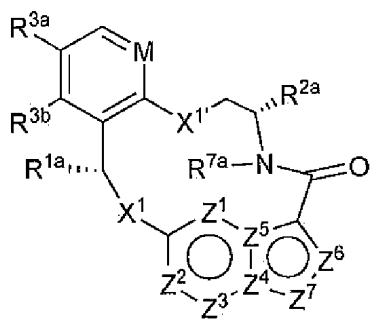
VIII

or

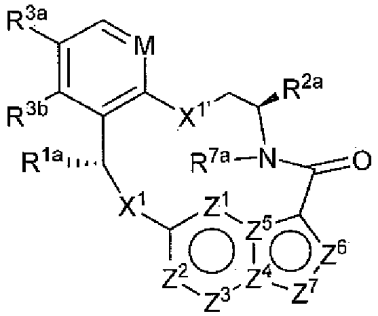


IX

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the formula

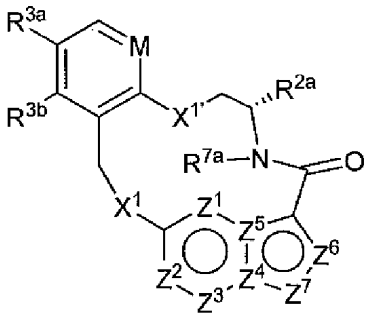


or

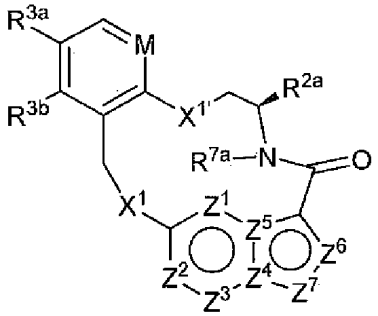


X XI

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the formula

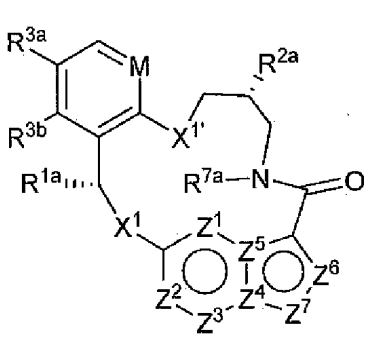


or

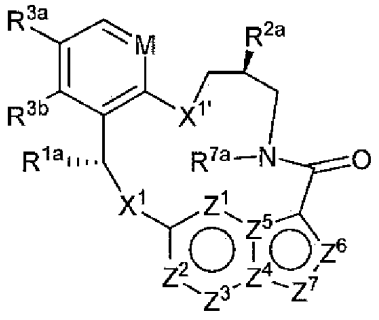


XII XIII

7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having the formula

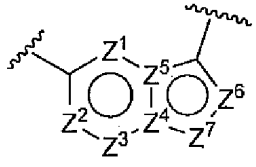


or

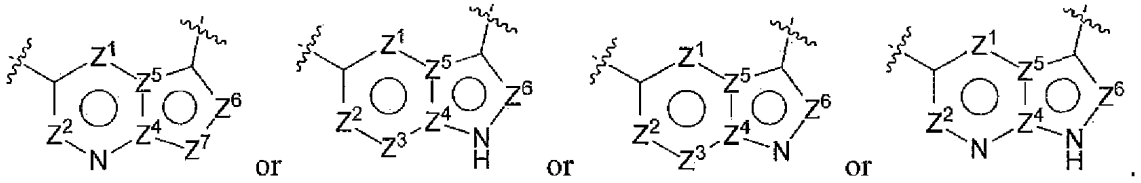


XIV or XV

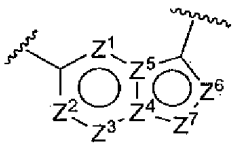
8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein



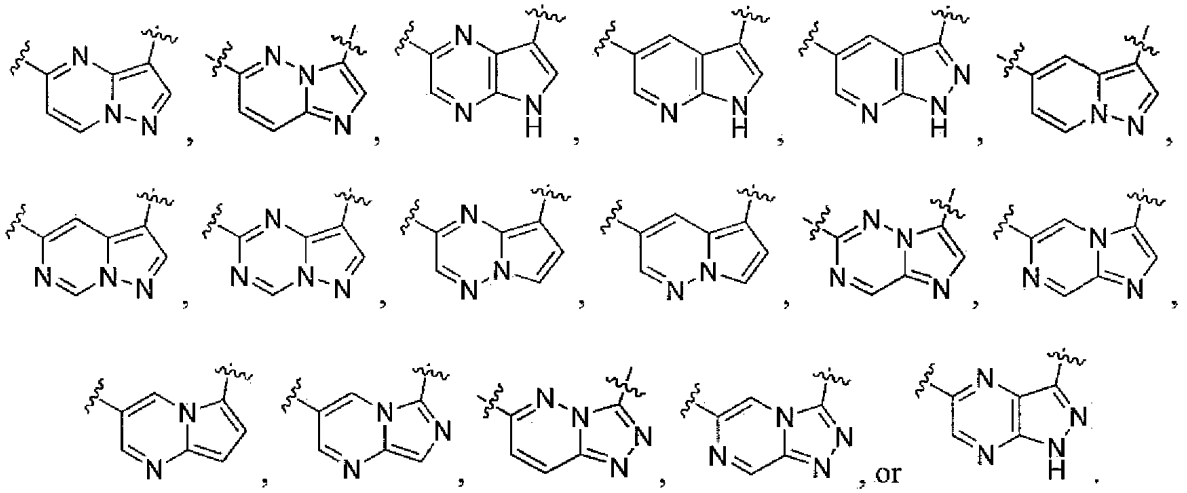
is:



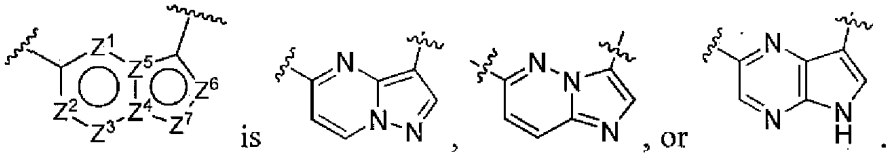
9. The compound of claim 1, wherein



is selected from



10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein



11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^{3a} and R^{3b} are independently H, fluoro, or chloro.

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^{7a} is H, methyl, hydroxyethyl, $-CH_2CONH_2$, or 3-pyrrolidinylmethyl.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt thereof, wherein R^{1a} and R^{2a} are each independently H, deuterium, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidinyl, furanyl, thiofuranyl, piperidinyl, piperazinyl, morpholinyl, phenyl, or monocyclic heteroaryl, wherein each hydrogen atom in methyl, ethyl, propyl or isopropyl 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)$_2$NH(C_{1-4}alkyl), -S(O)N(C_{1-4}alkyl)$_2$, -S(O)$_2$N(C_{1-4}alkyl)$_2$, C_{3-6}cycloalkyl, or 3-to 7-membered heterocycloalkyl.

14. The compound of any one of claims 1-3, 5 and 7-13, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is H, methyl, fluoromethyl, hydroxymethyl or cyclopropyl.

15. The compound of any one of claims 1-3, 5 and 7-13, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is deuterium, -$CONH_2$, -CO_2C_{1-4}alkyl, methyl, hydroxymethyl, fluoromethyl, methylcyclopropyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, pyrrolidinyl, furanyl, thiofuranyl, piperidinyl, piperazinyl, morpholinyl, phenyl, or monocyclic heteroaryl.

16. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is H, deuterium, -OH, -$CONH_2$, or is methyl or ethyl, each unsubstituted or substituted with halogen, -OH, -OC_{1-4}alkyl, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$, -CO_2H, -CO_2C_{1-4}alkyl, -$CONH_2$, cycloalkyl, or monocyclic heterocycloalkyl, or a pharmaceutically acceptable salt thereof.

17. The compound of any one of claims 1-3, 5 and 7-14, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is H or methyl.

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

19. The compound of any one of claims 1-7, wherein Z^1, Z^4 and Z^7 are N, and Z^2, Z^3, Z^5 and Z^6 are C(R^x), wherein each R^x when present is H, or
M is CH, Z^1, Z^4 and Z^7 are N, and Z^2, Z^3, Z^5 and Z^6 are C(R^x), wherein each R^x when present is H, or
M is CH, Z^1, Z^4 and Z^7 are N, Z^2, Z^3, Z^5 and Z^6 are C(R^x), wherein each R^x when present is H, and X^1 is –N($R^{k'}$)-, or
M is CH, Z^1, Z^4 and Z^7 are N, Z^2, Z^3, Z^5 and Z^6 are C(R^x), wherein each R^x when present is H, X^1 is –N($R^{k'}$)-, and $X^{1'}$ is -O-, or

M is CH, Z^1, Z^4 and Z^7 are N, Z^2, Z^3, Z^5 and Z^6 are $C(R^x)$, wherein each R^x when present is H, X^1 is $-C(R^{1a})(R^{2a})-$, and $X^{1'}$ is -O-, or a pharmaceutically acceptable salt thereof.

20. The compound of any one of claims 1-17, 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.

21. 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-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; (13R)-13-cyclopropyl-11-fluoro-5-

methyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; 13-cyclopropyl-11-fluoro-5-methyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; (13R)-11-fluoro-13-methyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; 11-fluoro-13-methyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; (13R)-12-chloro-11-fluoro-13-methyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-13-methyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-6-methyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-7-methyl-6,7-dihydro-13H-1,15-ethenopyrazolo[4,3-f][1,10,4,8]benzodioxadiazacyclotridecin-4(5H)-one; (8R)-9-chloro-10-fluoro-8-methyl-15,16-dihydro-8H-3,6-ethenoimidazo[5,1-f][1,10,4,7,8]benzodioxatriazacyclotridecin-17(14H)-one; 9-chloro-10-fluoro-8-methyl-15,16-dihydro-8H-3,6-ethenoimidazo[5,1-f][1,10,4,7,8]benzodioxatriazacyclotridecin-17(14H)-one; (7R)-8-chloro-9-fluoro-7-methyl-14,15-dihydro-2H,7H-3,5-(azenometheno)pyrrolo[3,4-f][1,10,4,8]benzodioxadiazacyclotridecin-16(13H)-one; 8-chloro-9-fluoro-7-methyl-14,15-dihydro-2H,7H-3,5-(azenometheno)pyrrolo[3,4-f][1,10,4,8]benzodioxadiazacyclotridecin-16(13H)-one; (5R)-3-fluoro-5-methyl-14,15-dihydro-5H,10H-9,7-(azenometheno)pyrido[2,3-k]pyrrolo[3,4-d][1,10,3,7]dioxadiazacyclotridecin-12(13H)-one; 3-fluoro-5-methyl-14,15-dihydro-5H,10H-9,7-(azenometheno)pyrido[2,3-k]pyrrolo[3,4-d][1,10,3,7]dioxadiazacyclotridecin-12(13H)-one; (5R)-3-fluoro-5,16-dimethyl-13,14,15,16-tetrahydro-5H-9,7-(azenometheno)pyrido[2,3-k]pyrrolo[3,4-d][1,3,7,10]oxatriazacyclotridecin-12(10H)-one; 3-fluoro-5,16-dimethyl-13,14,15,16-tetrahydro-5H-9,7-(azenometheno)pyrido[2,3-k]pyrrolo[3,4-d][1,3,7,10]oxatriazacyclotridecin-12(10H)-one; (13R)-12-chloro-11-fluoro-5,13-dimethyl-6,7-dihydro-2H,13H-1,15-(azenometheno)pyrrolo[3,4-f][1,10,4]benzodioxazacyclotridecin-4(5H)-one; 12-chloro-11-fluoro-5,13-dimethyl-6,7-dihydro-2H,13H-1,15-(azenometheno)pyrrolo[3,4-f][1,10,4]benzodioxazacyclotridecin-4(5H)-one; (7R)-8-chloro-9-fluoro-7,15-dimethyl-14,15-dihydro-2H,7H-3,5-(azenometheno)pyrazolo[3,4-f][1,10,4]benzodioxazacyclotridecin-16(13H)-one; 8-chloro-9-fluoro-7,15-dimethyl-14,15-dihydro-2H,7H-3,5-(azenometheno)pyrazolo[3,4-f][1,10,4]benzodioxazacyclotridecin-16(13H)-one; 11-fluoro-14-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; (13R)-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-

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; 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; 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-

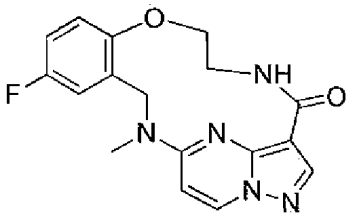
fluoro-8-methyl-15,16-dihydro-8H-3,6-ethenoimidazo[5,1-f][1,10,4,7,8]benzodioxatriazacyclotridecin-17(14H)-one; 10-fluoro-7-methyl-7,8,15,16-tetrahydro-3,6-ethenoimidazo[5,1-f][1,4,7,8,10]benzoxatetraazacyclotridecin-17(14H)-one; 14-ethyl-11-fluoro-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-one; 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(5*H*)-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]benzoxatriazacyclotridecine-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]benzoxatriazacyclotridecine-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]benzoxatriazacyclotridecine-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]benzoxatriazacyclotridecine-13-carboxylate; 11-fluoro-4-oxo-4,5,6,7,13,14-hexahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecine-13-carboxamide; 11-fluoro-14-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-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]benzothiatriazacyclotridecin-4(5H)-one; 13-methyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzothiatriazacyclotridecin-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]benzothiatriazacyclotridecin-8(5H)-one; 11-fluoro-7,14-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[3,4-e][7,2,4,10]benzothiatriazacyclotridecin-8(5H)-one 4,4-dioxide; 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; 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-$^{2}H_4$)-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]benzothiatriazacyclotridecin-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]benzothiatriazacyclotridecin-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]benzothiatriazacyclotridecin-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.

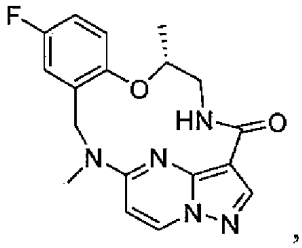
22. The compound of claim 1 having the formula



or a pharmaceutically acceptable salt thereof.

23. A crystalline form of the free base of the compound of claim 22, having a powder X-ray diffraction pattern substantially the same as Fig. 1.

24. The compound of claim 1 having the formula



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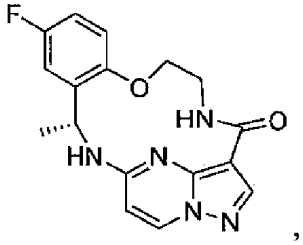

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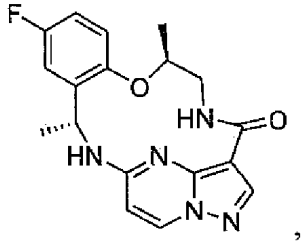

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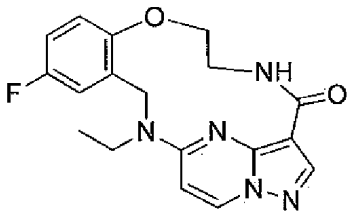

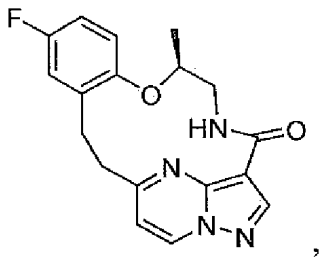

or a pharmaceutically acceptable salt thereof.

25. A pharmaceutical composition comprising (a) at least one compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable excipient.

26. A compound of any one of claims 1-24, or a pharmaceutically acceptable salt thereof for use in treating cancer, pain, neurological diseases, autoimmune diseases, and inflammation.

27. Use of the compound of any one of claims 1-24, in the manufacture of a medicament for treating cancer, pain, neurological diseases, autoimmune diseases, and inflammation.