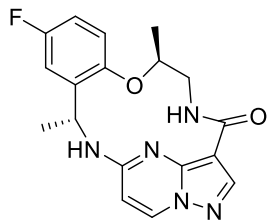
Ther. Adv. Hematol. 2013, 4(1), 15-35; LaFave, L.M. *et al.*, *Trends Pharmacol. Sci.* 2012, 33(11), 574-582. The recently collected clinical data related to ruxolitinib treatment indicated that JAK inhibitors work on both JAK2 wild-type and JAK2 mutated cases. Verstovsek, S. *et al.*, *N. Engl. J. Med.* 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.

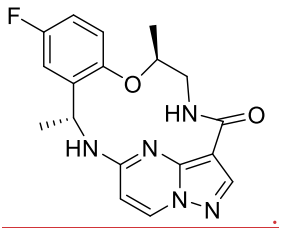
SUMMARY

[015a] In an aspect, the disclosure relates to a a compound having the formula:



or a pharmaceutically acceptable salt thereof.

[015b] In another aspect, the disclosure relates to a compound having the formula:



.

[015c] In another aspect, the disclosure relates to a pharmaceutical composition comprising a compound as defined above, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[015d] In another aspect, the disclosure relates to a compound as defind above, or pharmaceutically acceptable salt thereof, for use in treating cancer in a human patient.

[015e] In another aspect, the disclosure relates to a use of a compound as defined above, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a human patient.

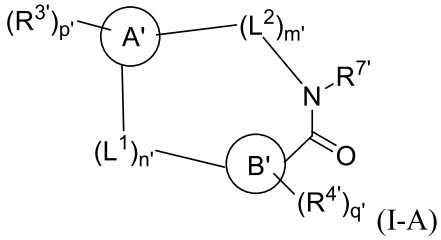
[016] In one example~~aspect~~, the ~~invention~~disclosure relates to a compound of the following Formula (I-A):

[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~~example, the ~~invention~~disclosure relates to a chemical entity of the following Formula (I-A):



(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, $-OR^{c'}$, $-OC(O)R^{c'}$, $-OC(O)NR^{c'}R^{d'}$, $-OC(=N)NR^{c'}R^{d'}$, $-OS(O)_{0-2}R^{c'}$, $-OS(O)_{0-2}NR^{c'}R^{d'}$, $-S(O)_{0-2}R^{c'}$, $-S(O)_{0-2}NR^{c'}R^{d'}$, $-NR^{c'}R^{d'}$, $-NR^{c'}C(O)R^{d'}$, $-NR^{c'}C(O)NR^{c'}R^{d'}$, $-NR^{c'}C(=N)NR^{c'}R^{d'}$, $-NR^{c'}S(O)_{0-2}R^{d'}$, $-NR^{c'}S(O)_{0-2}NR^{c'}R^{d'}$, $-C(O)R^{c'}$, $-C(O)OR^{c'}$, $-C(O)NR^{c'}R^{d'}$, $-C(=N)NR^{c'}R^{d'}$, $-P(O)_{0-2}R^{c'}R^{d'}$, $-P(O)_{0-2}NR^{c'}R^{d'}$, $-P(O)_{0-2}OR^{c'}$, -CN, $-NO_2$, 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 any two $R^{3'}$ groups or any two $R^{4'}$ groups taken together with the ring to which they are attached form a C_{5-8}cycloalkyl 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, C_{1-6}alkyl, C_{1-6}haloalkyl, $-OR^{e'}$, $-OC(O)R^{e'}$, $-OC(O)NR^{e'}R^{f'}$, $-OS(O)_{0-2}R^{e'}$, $-OS(O)_{0-2}NR^{e'}R^{f'}$, $-S(O)_{0-2}R^{e'}$, $-S(O)_{0-2}NR^{e'}R^{f'}$, $-NR^{e'}R^{f'}$, $-NR^{e'}C(O)R^{f'}$, $-NR^{e'}C(O)NR^{e'}R^{f'}$, $-NR^{e'}S(O)_{0-2}R^{f'}$, $-NR^{e'}S(O)_{0-2}NR^{e'}R^{f'}$, $-C(O)R^{e'}$, $-C(O)OR^{e'}$, $-C(O)NR^{e'}R^{f'}$, $-P(O)_{0-2}R^{e'}R^{f'}$, $-P(O)_{0-2}NR^{e'}R^{f'}$, $-P(O)_{0-2}OR^{e'}$, -CN, and $-NO_2$; and

[036] each $R^{c'}$, $R^{d'}$, $R^{e'}$, and $R^{f'}$ 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, phenyl, naphthyl, and heteroaryl;

[037] $R^{7'}$ is 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;

[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;

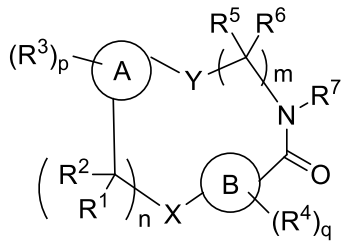
[046] n' is 2, 3, or 4;

[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~~example, the ~~invention~~ disclosure relates to a chemical entity of the following Formula (I):



(I)

[060] 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, C_{1-6}alkyl, C_{1-6}haloalkyl, $-OR^g$, $-OC(O)R^g$, $-OC(O)NR^gR^h$, $-OS(O)_{0-2}R^g$, $-OS(O)_{0-2}NR^gR^h$, $-NR^gR^h$, $-NR^gC(O)R^h$, $-NR^gC(O)NR^gR^h$, $-NR^gS(O)_{0-2}R^h$, $-NR^gS(O)_{0-2}NR^gR^h$, $-C(O)R^g$, $-C(O)OR^g$, $-C(O)NR^gR^h$, $-P(O)_{0-2}R^gR^h$, $-P(O)_{0-2}NR^gR^h$, $-P(O)_{0-2}OR^g$, -CN, and $-NO_2$;

[061] wherein each R^g and R^h 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;

[062] R^7 is 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;

[063] 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, $-OR^i$, $-OC(O)R^i$, $-OC(O)NR^iR^j$, $-OS(O)_{0-2}R^i$, $-OS(O)_{0-2}NR^iR^j$, $-NR^iR^j$, $-NR^iC(O)R^j$, $-NR^iC(O)NR^iR^j$, $-NR^iS(O)_{0-2}R^j$, $-NR^iS(O)_{0-2}NR^iR^j$, $-C(O)R^i$, $-C(O)OR^i$, $-C(O)NR^iR^j$, $-P(O)_{0-2}R^iR^j$, $-P(O)_{0-2}NR^iR^j$, $-P(O)_{0-2}OR^i$, -CN, and $-NO_2$;

[064] 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;

[065] X and Y are each independently $-C(R^k)(R^k)$-, -O-, or $-N(R^k)$-;

[066] wherein 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;

[067] m is 2, 3, or 4;

[068] n is 1, 2, or 3;

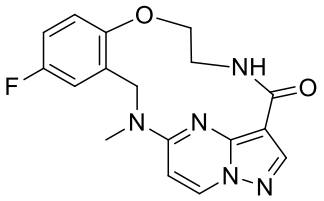
[069] p is 0, 1, 2, 3, or 4; and

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

[071] or a pharmaceutically acceptable salt thereof.

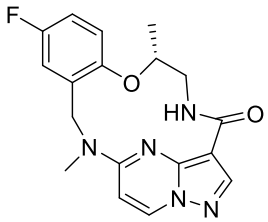
[072] In certain ~~embodiments~~examples, the compound of Formula (I) or (I-A) is a compound selected from those species described or exemplified in the detailed description below.

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



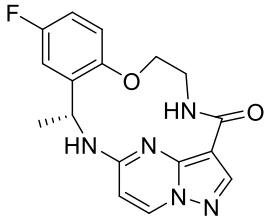
[074] or a pharmaceutically acceptable salt thereof.

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



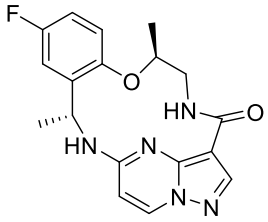
[076] or a pharmaceutically acceptable salt thereof

[077] In certain ~~embodiments~~examples, the compound of Formula (I) or (I-A) is a compound the formula



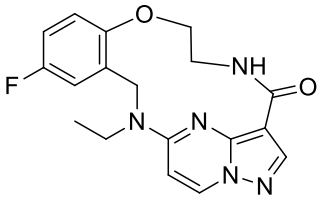
[078] or a pharmaceutically acceptable salt thereof.

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



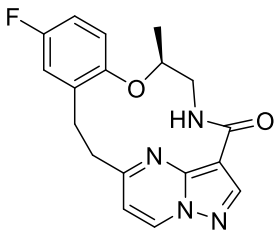
[080] or a pharmaceutically acceptable salt thereof.

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



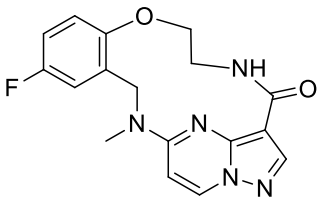
[082] or a pharmaceutically acceptable salt thereof.

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

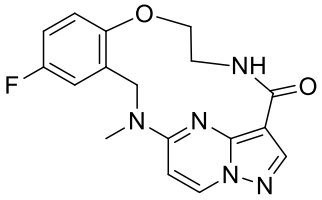


[084] or a pharmaceutically acceptable salt thereof.

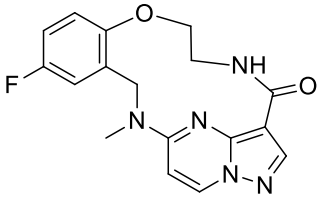
[085] In a further ~~aspect~~example, the ~~invention~~ disclosure relates to a crystalline form of the free base of the compound of the formula



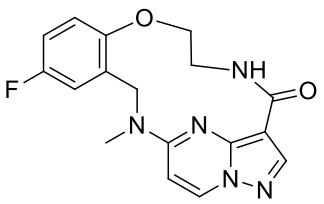
[086] having a powder X-ray diffraction pattern substantially the same as Fig. XX. In some embodiments, the crystalline polymorph form 1 of the free base of the compound of the formula



[087] wherein the powder X-ray diffraction pattern has a peak at diffraction angle (2θ) of 21.94. In some ~~embodiments~~examples, 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~~examples, 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~~example, the invention relates to 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 is also a compound of Formula (I) or (I-A) or a pharmaceutically acceptable salt thereof for use as a medicament.

[091] In another ~~aspect~~example, 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.

[092] In another ~~aspect~~example, 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~~example, 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~~examples, features, and advantages of the ~~invention~~ disclosure will be apparent from the following detailed description and through practice of the ~~invention~~disclosure.

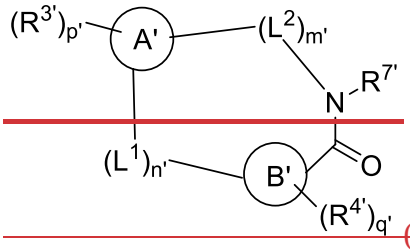
[095] For the sake of brevity, the disclosures of the publications cited in this specification, including patents, are herein incorporated by reference.

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).

WHAT IS CLAIMED IS:

1. A compound of the following Formula (I-A):



(I-A)

wherein

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

each L^1 and L^2 is independently $-C(R^{1'})(R^{2'})-$, $-O-$, $-N(R^{k'})-$, $-S-$, $-S(O)-$ or $-S(O)_2-$;

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, C_{6-10} aryl, or mono- or bicyclic heteroaryl, $-OR^{a'}$, $-OC(O)R^{a'}$, $-OC(O)NR^{a'}R^{b'}$, $-OS(O)R^{a'}$, $-OS(O)_2R^{a'}$, $-SR^{a'}$, $-S(O)R^{a'}$, $-S(O)_2R^{a'}$, $-S(O)NR^{a'}R^{b'}$, $-S(O)_2NR^{a'}R^{b'}$, $-OS(O)NR^{a'}R^{b'}$, $-OS(O)_2NR^{a'}R^{b'}$, $-NR^{a'}R^{b'}$, $-NR^{a'}C(O)R^{b'}$, $-NR^{a'}C(O)OR^{b'}$, $-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}S(O)R^{b'}$, $-NR^{a'}S(O)_2R^{b'}$, $-NR^{a'}S(O)NR^{a'}R^{b'}$, $-NR^{a'}S(O)_2NR^{a'}R^{b'}$, $-C(O)R^{a'}$, $-C(O)OR^{a'}$, $-C(O)NR^{a'}R^{b'}$, $-PR^{a'}R^{b'}$, $-P(O)R^{a'}R^{b'}$, $-P(O)_2R^{a'}R^{b'}$, $-P(O)NR^{a'}R^{b'}$, $-P(O)_2NR^{a'}R^{b'}$, $-P(O)OR^{a'}$, $-P(O)_2OR^{a'}$, $-CN$, or $-NO_2$, 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, 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, mono- or bicyclic heteroaryl, 4- to 6-membered heterocycloalkyl is independently optionally substituted by deuterium, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, $-OR^{e'}$, $-OC(O)R^{e'}$, $-OC(O)NR^{e'}R^{f'}$, $-OS(O)R^{e'}$, $-OS(O)_2R^{e'}$, $-OS(O)NR^{e'}R^{f'}$, $-OS(O)_2NR^{e'}R^{f'}$, $-SR^{e'}$, $-S(O)R^{e'}$, $-S(O)_2R^{e'}$, $-S(O)NR^{e'}R^{f'}$, $-S(O)_2NR^{e'}R^{f'}$, $-NR^{e'}R^{f'}$, $-NR^{e'}C(O)R^{f'}$, $-NR^{e'}C(O)OR^{f'}$, $-NR^{e'}C(O)NR^{e'}R^{f'}$, $-NR^{e'}S(O)R^{f'}$, $-NR^{e'}S(O)_2R^{f'}$, $-NR^{e'}S(O)NR^{e'}R^{f'}$, $-NR^{e'}S(O)_2NR^{e'}R^{f'}$, $-C(O)R^{e'}$, $-C(O)OR^{e'}$, $-C(O)NR^{e'}R^{f'}$, $-PR^{e'}R^{f'}$, $-P(O)R^{e'}R^{f'}$, $-P(O)_2R^{e'}R^{f'}$, $-P(O)NR^{e'}R^{f'}$, $-P(O)_2NR^{e'}R^{f'}$, $-P(O)OR^{e'}$, $-P(O)_2OR^{e'}$, $-CN$, or $-NO_2$;

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 is independently optionally substituted by deuterium, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, $-OR^{e'}$, $-OC(O)R^{e'}$, $-OC(O)NR^{e'}R^{f'}$, $-OS(O)R^{e'}$, $-OS(O)_2R^{e'}$, $-OS(O)NR^{e'}R^{f'}$, $-OS(O)_2NR^{e'}R^{f'}$, $-SR^{e'}$, $-S(O)R^{e'}$, $-S(O)_2R^{e'}$, $-S(O)NR^{e'}R^{f'}$, $-S(O)_2NR^{e'}R^{f'}$, $-NR^{e'}R^{f'}$, $-NR^{e'}C(O)R^{f'}$, $-NR^{e'}C(O)OR^{f'}$, $-NR^{e'}C(O)NR^{e'}R^{f'}$, $-NR^{e'}S(O)R^{f'}$, $-NR^{e'}S(O)_2R^{f'}$, $-NR^{e'}S(O)NR^{e'}R^{f'}$, $-NR^{e'}S(O)_2NR^{e'}R^{f'}$, $-C(O)R^{e'}$, $-C(O)OR^{e'}$, $-C(O)NR^{e'}R^{f'}$, $-PR^{e'}R^{f'}$, $-P(O)R^{e'}R^{f'}$, $-P(O)_2R^{e'}R^{f'}$, $-P(O)NR^{e'}R^{f'}$, $-P(O)_2NR^{e'}R^{f'}$, $-P(O)OR^{e'}$, $-P(O)_2OR^{e'}$, $-CN$, or $-NO_2$;

each $R^{3'}$ and $R^{4'}$ is independently deuterium, halogen, $-OR^{e'}$, $-OC(O)R^{e'}$, $-OC(O)NR^{e'}R^{d'}$, $-OC(=N)NR^{e'}R^{d'}$, $-OS(O)R^{e'}$, $-OS(O)_2R^{e'}$, $-OS(O)NR^{e'}R^{d'}$, $-OS(O)_2NR^{e'}R^{d'}$, $-SR^{e'}$, $-S(O)R^{e'}$, $-S(O)_2R^{e'}$, $-S(O)NR^{e'}R^{d'}$, $-S(O)_2NR^{e'}R^{d'}$, $-NR^{e'}R^{d'}$, $-NR^{e'}C(O)R^{d'}$, $-NR^{e'}C(O)OR^{d'}$, $-NR^{e'}C(O)NR^{e'}R^{d'}$, $-NR^{e'}C(=N)NR^{e'}R^{d'}$, $-NR^{e'}S(O)R^{d'}$, $-NR^{e'}S(O)_2R^{d'}$, $-NR^{e'}S(O)NR^{e'}R^{d'}$, $-NR^{e'}S(O)_2NR^{e'}R^{d'}$, $-C(O)R^{e'}$, $-C(O)OR^{e'}$, $-C(O)NR^{e'}R^{d'}$, $-C(=N)NR^{e'}R^{d'}$, $-PR^{e'}R^{d'}$, $-P(O)R^{e'}R^{d'}$, $-P(O)_2R^{e'}R^{d'}$, $-P(O)NR^{e'}R^{d'}$, $-P(O)_2NR^{e'}R^{d'}$, $-P(O)OR^{e'}$, $-P(O)_2OR^{e'}$, $-CN$, $-NO_2$, 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, or any two $R^{3'}$ groups or any two $R^{4'}$ groups taken together with the ring to which they are attached form a C_{5-8}cycloalkyl or a 5- to 8-membered heterocycloalkyl, 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, mono- or bicyclic heteroaryl C_{5-8}cycloalkyl or a 5- to 8-membered heterocycloalkyl is independently optionally substituted by deuterium, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, $-OR^{e'}$, $-OC(O)R^{e'}$, $-OC(O)NR^{e'}R^{f'}$, $-OS(O)R^{e'}$, $-OS(O)_2R^{e'}$, $-OS(O)NR^{e'}R^{f'}$, $-OS(O)_2NR^{e'}R^{f'}$, $-SR^{e'}$, $-S(O)R^{e'}$, $-S(O)_2R^{e'}$, $-S(O)NR^{e'}R^{f'}$, $-S(O)_2NR^{e'}R^{f'}$, $-NR^{e'}R^{f'}$, $-NR^{e'}C(O)R^{f'}$, $-NR^{e'}C(O)OR^{f'}$, $-NR^{e'}C(O)NR^{e'}R^{f'}$, $-NR^{e'}S(O)R^{f'}$, $-NR^{e'}S(O)_2R^{f'}$, $-NR^{e'}S(O)NR^{e'}R^{f'}$, $-NR^{e'}S(O)_2NR^{e'}R^{f'}$, $-C(O)R^{e'}$, $-C(O)OR^{e'}$, $-C(O)NR^{e'}R^{f'}$, $-PR^{e'}R^{f'}$, $-P(O)R^{e'}R^{f'}$, $-P(O)_2R^{e'}R^{f'}$, $-P(O)NR^{e'}R^{f'}$, $-P(O)_2NR^{e'}R^{f'}$, $-P(O)OR^{e'}$, $-P(O)_2OR^{e'}$, $-CN$, or $-NO_2$;

$R^{7'}$ is 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 is independently optionally substituted by deuterium, halogen, $-OR^{i'}$, $-OC(O)R^{i'}$, $-OC(O)NR^{i'}R^{j'}$, $-OS(O)R^{i'}$, $-OS(O)_2R^{i'}$, $-OS(O)NR^{i'}R^{j'}$, $-OS(O)_2NR^{i'}R^{j'}$, $-SR^{i'}$, $-S(O)R^{i'}$, $-S(O)_2R^{i'}$, $-S(O)NR^{i'}R^{j'}$, $-S(O)_2NR^{i'}R^{j'}$, $-NR^{i'}R^{j'}$, $-NR^{i'}C(O)R^{j'}$, $-NR^{i'}C(O)OR^{j'}$, $-NR^{i'}C(O)NR^{i'}R^{j'}$, $-NR^{i'}S(O)R^{j'}$, $-NR^{i'}S(O)_2R^{j'}$, $-NR^{i'}S(O)NR^{i'}R^{j'}$, $-NR^{i'}S(O)_2NR^{i'}R^{j'}$, $-C(O)R^{i'}$, $-C(O)OR^{i'}$, $-C(O)NR^{i'}R^{j'}$, $-PR^{i'}R^{j'}$, $-P(O)R^{i'}R^{j'}$, $-P(O)_2R^{i'}R^{j'}$, $-P(O)NR^{i'}R^{j'}$, $-P(O)_2NR^{i'}R^{j'}$, $-P(O)OR^{i'}$, $-P(O)_2OR^{i'}$, $-CN$, or $-NO_2$;

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.

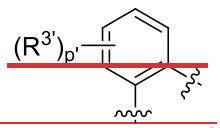
3. The compound of claim 1, wherein Ring A' is bicyclic heteroaryl and Ring B' is monocyclic aryl or heteroaryl, or a pharmaceutically acceptable salt thereof.

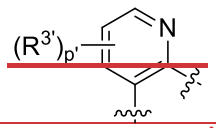
4. The compound of claim 1, wherein Ring A' is phenyl or a 6-membered heteroaryl, or a pharmaceutically acceptable salt thereof.

5. 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.

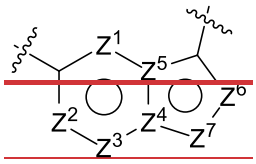
6. The compound of claim 1, wherein Ring A' is phenyl or pyridyl, or a pharmaceutically acceptable salt thereof.

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

8. The compound of claim 1, wherein Ring A' substituted with $(R^{3'})_{p'}$ is , or a pharmaceutically acceptable salt thereof.

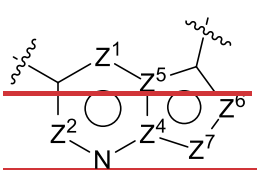
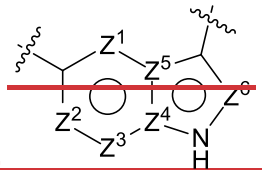
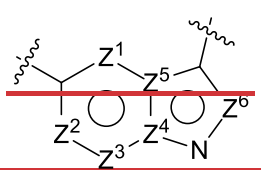
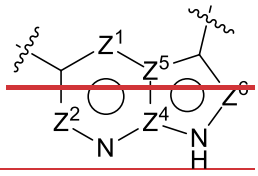
9. The compound of claim 1, wherein Ring A' substituted with $(R^{3'})_{p'}$ is , or a pharmaceutically acceptable salt thereof.

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



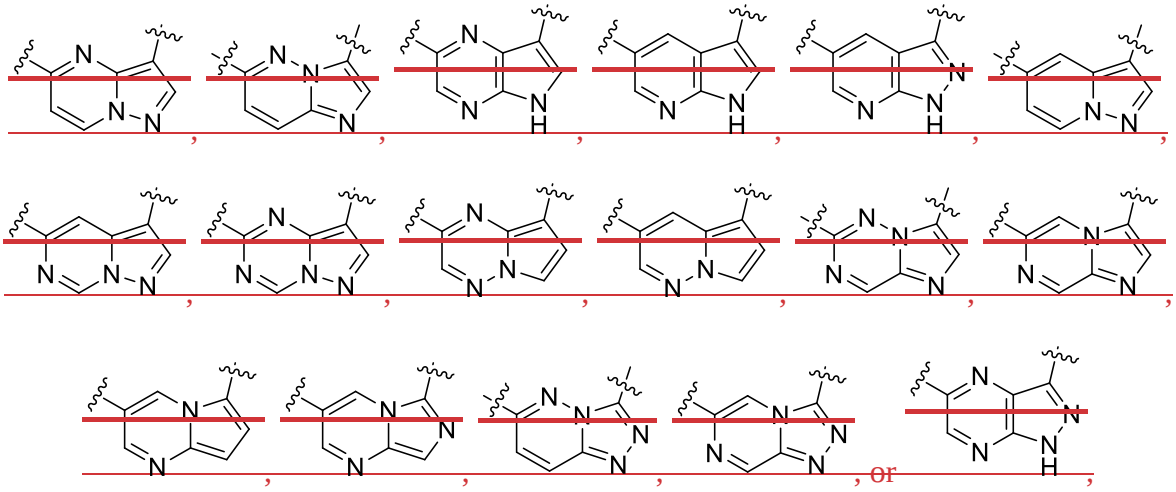
wherein Z^1-Z^7 are defined as described herein, or a pharmaceutically acceptable salt thereof.

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

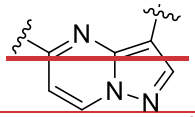
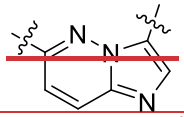
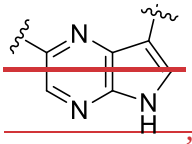





wherein Z^{1-7} are otherwise defined as described herein, or a pharmaceutically acceptable salt thereof.

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



or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1, wherein Ring B' is , , or , or a pharmaceutically acceptable salt thereof.

14. The compound of any one of claims 1-14, wherein each $R^{3'}$ is independently deuterium, fluoro, chloro, bromo, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, $-CO_2C_{1-4}alkyl$, $-CO_2H$, $-NHC(O)C_{1-4}alkyl$, $-SO_2C_{1-4}alkyl$, $-C(O)NH_2$, $-C(O)NH(C_{1-4}alkyl)$, $-C(O)N(C_{1-4}alkyl)_2$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, or a pharmaceutically acceptable salt thereof.

15. The compound of any one of claims 1-15, wherein each $R^{3'}$ is independently fluoro, chloro, bromo, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, isopropoxy, -CN, or $-CF_3$, or a pharmaceutically acceptable salt thereof.

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

17. The compound of any one of claims 1-17, wherein $R^{7'}$ is 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.

18. The compound of any one of claims 1-18, wherein $R^{7'}$ is H, or is methyl, ethyl, propyl, isopropyl, or cyclopropyl, or a pharmaceutically acceptable salt thereof.

19. The compound of any one of claims 1-19, wherein $R^{7'}$ is H 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.

20. The compound of any one of claims 1-20, wherein $R^{7'}$ is H, methyl, hydroxyethyl, $-CH_2CONH_2$, or 3-pyrrolidinylmethyl, or a pharmaceutically acceptable salt thereof.

21. The compound of any one of claims 1-21, wherein $R^{7'}$ is H or methyl, or a pharmaceutically acceptable salt thereof.

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

24. The compound of any one of claims 1-24, 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. The compound of any one of claims 1-25, wherein $R^{2'}$ is H 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.

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

27. The compound of any one of claims 1-27, wherein each $R^{k'}$ is independently H, methyl, ethyl, propyl, isopropyl, or cyclopropyl, or a pharmaceutically acceptable salt thereof.

28. The compound of any one of claims 1-28, wherein each L^1 and L^2 is independently $-CH_2-$, -CH(methyl)-, -CH(substituted methyl)-, $-CH(C_{3-6}$cycloalkyl)-, -O-, -NH-, $-N(C_{1-4}$alkyl), $-N(C_{3-6}$cycloalkyl), -S-, -S(O)-, or $-SO_2-$, or a pharmaceutically acceptable salt thereof.

29. The compound of any one of claims 1-29, wherein $(L^1)_{n'}$ is CH_2O, $CH(C_{1-4}alkyl)O$, $CH(C_{3-6}cycloalkyl)O$; or $CH(H$ or optionally substituted $C_{1-4}alkyl)N(H$ or optionally substituted $C_{1-4}alkyl)$, $CH(CO_2C_{1-4}alkyl$ or $C(O)N(H$ or $C_{1-4}alkyl)_2)N(H$ or optionally substituted $C_{1-4}alkyl)$, or a pharmaceutically acceptable salt thereof.

30. The compound of any one of claims 1-30, wherein $(L^2)_{m'}$ is $O(C(R^{1'})(R^{2'}))_{2-3}$, $O(CH_2)_{2-3}$, $N(R^{k'})(C(R^{1'})(R^{2'}))_{2-3}$, $N(H$ or $C_{1-4}alkyl)(CH_2)_{2-3}$, $S(C(R^{1'})(R^{2'}))_{2-3}$, $SO_2(C(R^{1'})(R^{2'}))_{2-3}$, $SO_2N(R^{k'})(C(R^{1'})(R^{2'}))_2$ or $(C(R^{1'})(R^{2'}))_3$, or a pharmaceutically acceptable salt thereof.

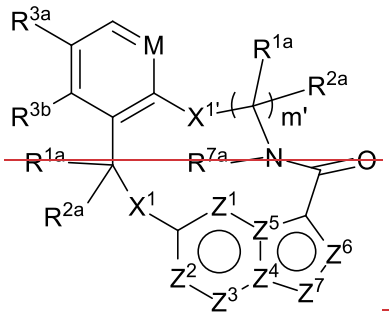
31. The compound of any one of claims 1-31, wherein m' is 3; or 4; or 5, or a pharmaceutically acceptable salt thereof.

32. The compound of any one of claim 1-32, wherein n' is 2; or 3; or 4, or a pharmaceutically acceptable salt thereof.

33. The compound of any one of claims 1-33, wherein p' is 0, 1, or 2, or a pharmaceutically acceptable salt thereof.

34. The compound of any one of claims 1-34, wherein q' is 0; or is 1; or is 2, or a pharmaceutically acceptable salt thereof.

35. 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)$_2$C$_{1-4}$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;

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$_2$H, -CO$_2$C$_{1-4}$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$^{a'}$;

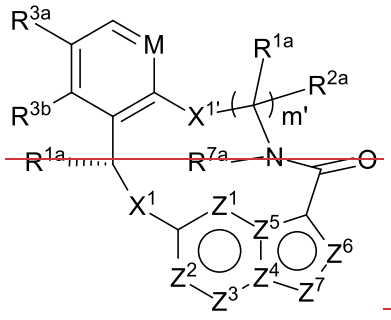
wherein each R$^{a'}$ and R$^{b'}$ is independently H, deuterium, C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, C$_{3-6}$cycloalkyl, 3- to 7-membered heterocycloalkyl, C$_{6-10}$ aryl, or heteroaryl;

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.

36. A compound of the Formula (V):



(V)

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

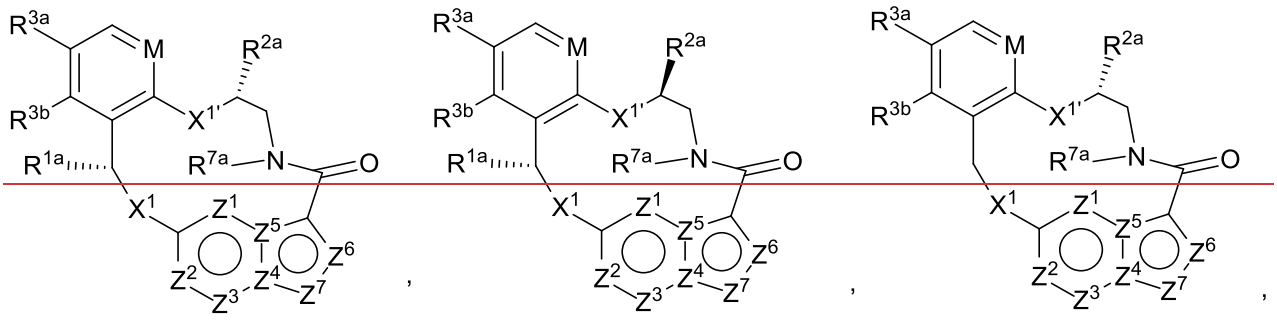
wherein each $R^{a'}$ and $R^{b'}$ is independently H, deuterium, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, or heteroaryl;

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

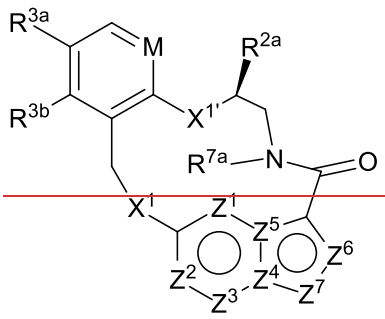
m' is 2 or 3;

or a pharmaceutically acceptable salt thereof.

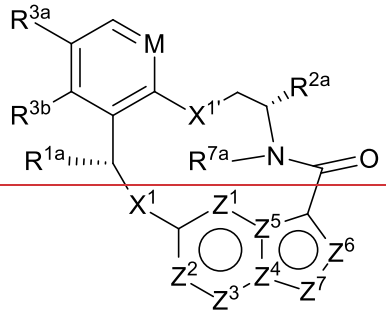
37. A compound selected from the group consisting of



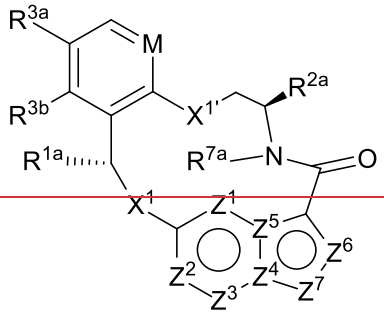
VI , VII , VIII ,



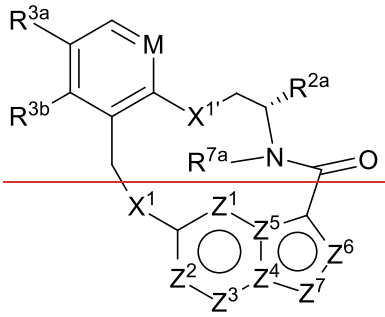
IX



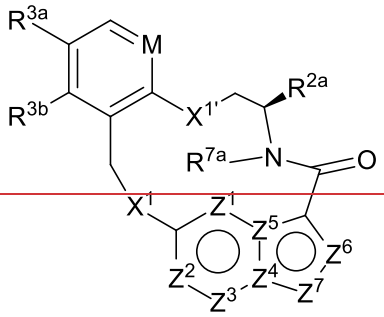
X



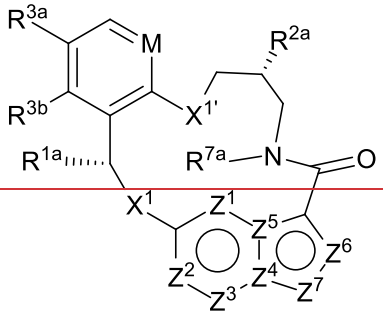
XI



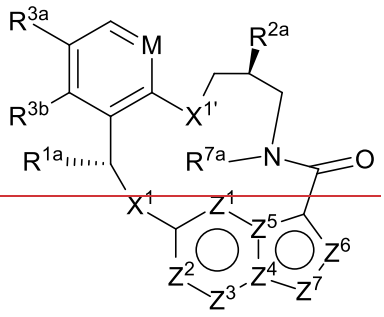
XII



XIII



XIV



and

XV

~~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, 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 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, -$CONH_2$, -$CONH(C_{1-4}$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.

38. The compound of any one of claims 36-38, 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 a pharmaceutically acceptable salt thereof.

39. The compound of any one of claim claims 36-38, wherein 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 a pharmaceutically acceptable salt thereof.

40. The compound of any one of claims claims 36-38, wherein 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 a pharmaceutically acceptable salt thereof.

41. The compound of any one of claims claims 36-38, wherein 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 a pharmaceutically acceptable salt thereof.

42. The compound of any one of claims claims 36-38, wherein 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.

43. The compound of any one of claims 36-43, 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 36-44, wherein $R^{k'}$ is H or methyl, or a pharmaceutically acceptable salt thereof.

45. 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; 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(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-

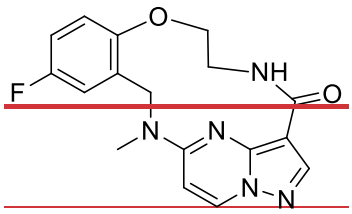
~~(propan-2-yl)-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f]pyrido[3,2-l][1,4,8,10]oxatriazacyclotridecin-4(5H)-one; 13-cyclopropyl-11-fluoro-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f]pyrido[3,2-l][1,4,8,10]oxatriazacyclotridecin-4(5H)-one; 13-cyclopropyl-11-fluoro-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-f][1,4,8,10]benzoxatriazacyclotridecin-4(5H)-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; 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-$^{2}H_{4}$)-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.~~

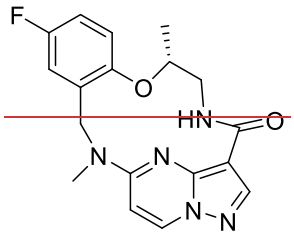
~~48. The compound of claim 1 having the formula~~



~~or a pharmaceutically acceptable salt thereof.~~

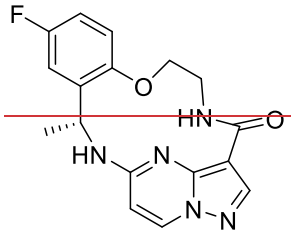
~~49. A crystalline form of the free base of the compound of claim 49, having a powder X-ray diffraction pattern substantially the same as Fig. 1.~~

~~50. The compound of claim 1 having the formula~~



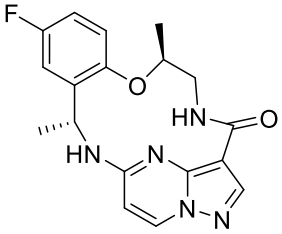
~~or a pharmaceutically acceptable salt thereof.~~

~~51. The compound of claim 1 having the formula~~



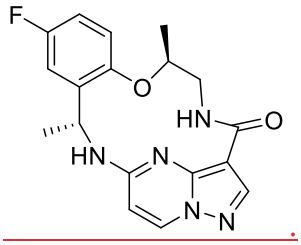
~~or a pharmaceutically acceptable salt thereof.~~

~~52~~1. ~~The~~ A compound ~~of claim 1~~ having the formula:



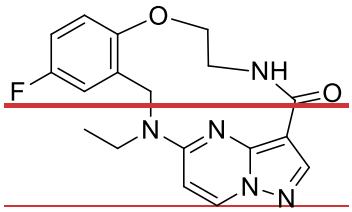
or a pharmaceutically acceptable salt thereof.

2. A compound having the formula:



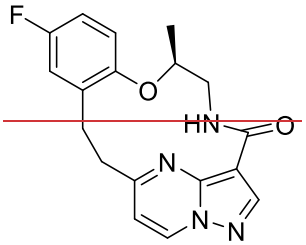
.

~~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.~~

~~55~~3. A pharmaceutical composition comprising ~~(a) at least one~~a compound of ~~any one of~~ claim~~s 1-55~~1 or 2, or ~~a~~ pharmaceutically acceptable salt thereof, and ~~(b)~~ a pharmaceutically acceptable excipient.

4. A compound of claim 1 or 2, or pharmaceutically acceptable salt thereof, for use in treating cancer in a human patient.

5. Use of a compound of claim 1 or 2, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a human patient.

6. The compound of claim 4 or use of claim 5, wherein the cancer is selected from lung cancer, colon cancer, breast cancer, prostate cancer, hepatocellular carcinoma, renal cell carcinoma, gastric and esophago-gastric cancers, glioblastoma, head and neck cancers, inflammatory myofibroblastic tumors, and anaplastic large cell lymphoma.

~~56. 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 1-55 or a pharmaceutically acceptable salt thereof.~~