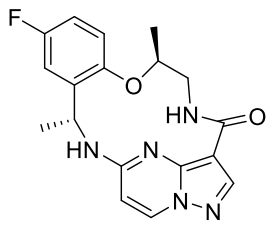
Ther. Adv. Hematol. 2013, 4(1), 15-35; LaFave, L.M. *et al.*, *Trends Pharmacol. Sci.* 2012, 33(11), 574-582. The recently collected clinical data related to ruxolitinib treatment indicated that JAK inhibitors work on both JAK2 wild-type and JAK2 mutated cases. Verstovsek, S. *et al.*, *N. Engl. J. Med.*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

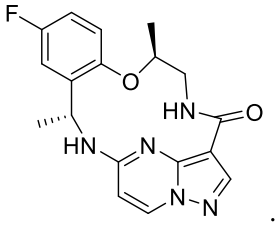
SUMMARY

[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.

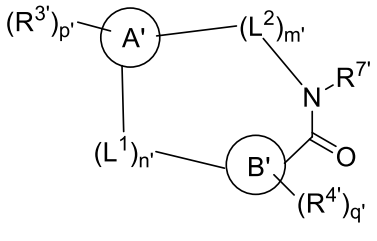
[016] In one example, the disclosure relates to a compound of the following Formula (I-A):

[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 example, the 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;

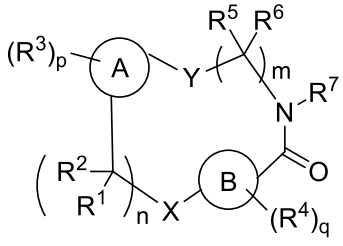
[046] n' is 2, 3, or 4;

[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 example, the 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;

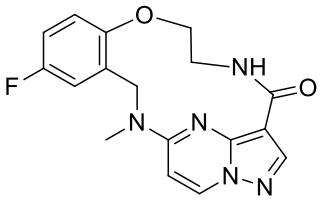
[069] p is 0, 1, 2, 3, or 4; and

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

[071] or a pharmaceutically acceptable salt thereof.

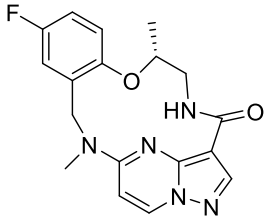
[072] In certain examples, the compound of Formula (I) or (I-A) is a compound selected from those species described or exemplified in the detailed description below.

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



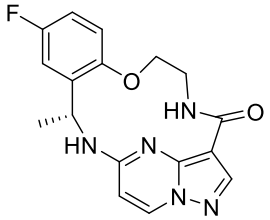
[074] or a pharmaceutically acceptable salt thereof.

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



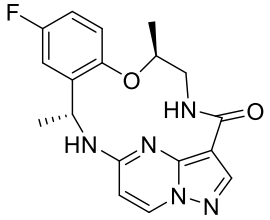
[076] or a pharmaceutically acceptable salt thereof

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



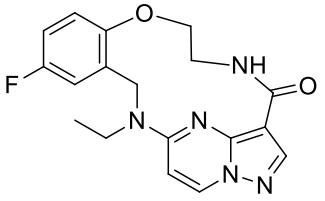
[078] or a pharmaceutically acceptable salt thereof.

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



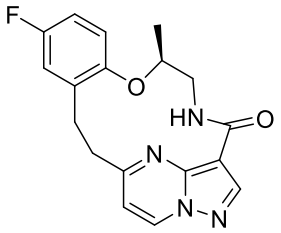
[080] or a pharmaceutically acceptable salt thereof.

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



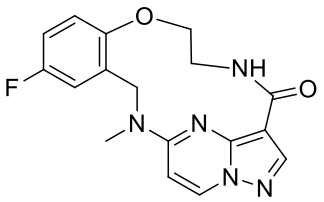
[082] or a pharmaceutically acceptable salt thereof.

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

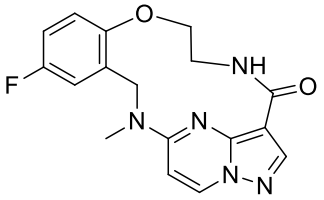


[084] or a pharmaceutically acceptable salt thereof.

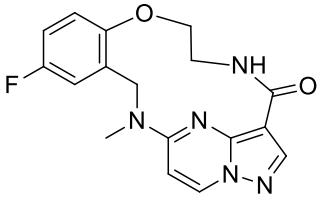
[085] In a further example, the disclosure relates to a crystalline form of the free base of the compound of the formula



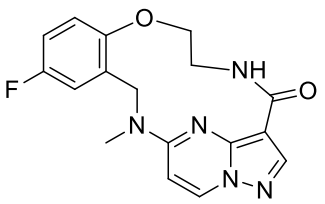
[086] having a powder X-ray diffraction pattern substantially the same as Fig. XX. In some embodiments, the crystalline polymorph form 1 of the free base of the compound of the formula



[087] wherein the powder X-ray diffraction pattern has a peak at diffraction angle (2θ) of 21.94. In some 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 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 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 disclosure may further comprise a pharmaceutically acceptable excipient. The 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 example, the 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 example, the 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 example, the 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 disclosure, wherein the contacting is *in vitro, ex vivo,* or *in vivo*.

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

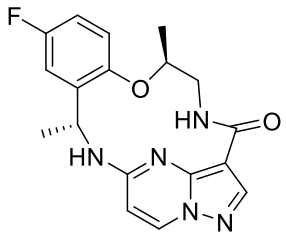
[095] For the sake of brevity, the disclosures of the publications cited in this specification, including patents, are herein incorporated by reference.

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).

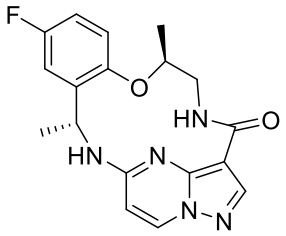
WHAT IS CLAIMED IS:

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof.

2. A compound having the formula:



.

3. A pharmaceutical composition comprising a compound of claim 1 or 2, or pharmaceutically acceptable salt thereof, and 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.