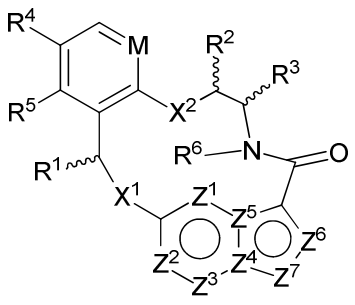
selected from the group consisting of F1174C/I/L/S/V, F1245C/I/L/V, R1275L/Q, T1151M, L1152R, C1156Y, G1202R, S1206Y, G1269A, G1269S, R1275Q, I1170N, I1170S and L1196M.

[028e] In another aspect, there is provided use of (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, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by a TPM3-TRKA fusion protein comprising at least one resistance mutation.

[028f] In another aspect, there is provided use of (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, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by JAK1 or JAK3.

[029] The present disclosure provides a method of treating cancer in a patient previously shown to express a genetically altered tyrosine or serine/throenine kinase comprising, administering to the patient a therapeutically effective amount of a compound of the formula I



I

[052] each R^7 and R^8 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl or heteroaryl;

[053] each R^9 is independently H, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl or -OR^7;

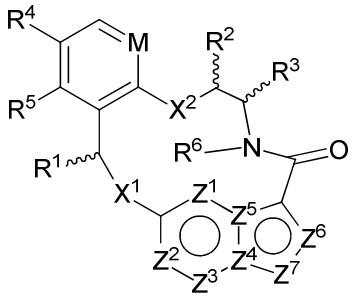
[054] each Z^1, Z^2, Z^3, Z^4, Z^5, Z^6 or Z^7 is independently N, NH, or C(R^{10}), wherein each R^{10} is independently H, deuterium, halogen, C_1-C_6 alkyl, -OC_1-C_6 alkyl, -OH, -NH_2, -NH(C_1-C_6 alkyl), -NH(phenyl), -NH(heteroaryl), -CN, or –CF_3, and

[055] 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;

[056] or a pharmaceutically acceptable salt thereof.

[056a] In another aspect, there is provided use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriaza-cyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein a genetically altered tyrosine or serine/threonine kinase selected from the group consisting of ROS1, TRKB, TRKC, SRC, FYN, LYN, YES, FGR, FAK, ARK5, and combinations thereof, in the patient is to be identified, and a therapeutically effective amount of the medicament is to be administered if the genetically altered tyrosine or serine/threonine kinase in the patient is identified by subjecting a patient sample to a test selected from the group consisting of FISH, IHC, PCR and gene sequencing.

[057] The present disclosure provides a method of identifying a patient for treatment with a compound of the formula I



I

[058] wherein

[059] M is CR^{4a} or N;

[060] X^1 and X^2 are independently S, S(O), $S(O)_2$, O or N(R^9);

wherein each hydrogen atom in C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl or -OR^7;

[067] each Z^1, Z^2, Z^3, Z^4, Z^5, Z^6 or Z^7 is independently N, NH, or C(R^{10}), wherein each R^{10} is independently H, deuterium, halogen, C_1-C_6 alkyl, -OC_1-C_6 alkyl, -OH, -NH_2, -NH(C_1-C_6 alkyl), -NH(phenyl), -NH(heteroaryl), -CN, or –CF_3, and

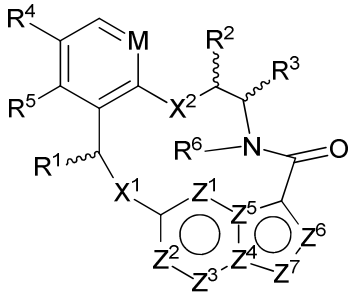
[068] provided that at least one of Z^1, Z^2, Z^3, Z^4, Z^5, Z^6 or Z^7 is N or NH;

[069] or a pharmaceutically acceptable salt thereof,

[070] comprising diagnosing the patient with a cancer mediated by a genetically altered tyrosine or serine/threonine kinase.

[070a] In another aspect, there is provided a method of identifying a patient for treatment with (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriaza-cyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof, comprising subjecting a patient sample to a test selected from the group consisting of FISH, IHC, PCR and gene sequencing to identify the patient as having a cancer mediated by a genetically altered tyrosine or serine/threonine kinase selected from the group consisting of ROS1, TRKB, TRKC, SRC, FYN, LYN, YES, FGR, FAK, ARK5, and combinations thereof.

[071] The present disclosure provides a use of compound of the formula I



I

[072] wherein

[073] M is CR^{4a} or N;

[074] X^1 and X^2 are independently S, S(O), $S(O)_2$, O or N(R^9);

WHAT IS CLAIMED IS:

1. Use of (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, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer or pain in a patient, wherein the cancer is mediated by a tyrosine kinase selected from the group consisting of ROS1, TRKB, TRKC, SRC, FYN, LYN, YES, FGR, FAK, ARK5, and combinations thereof, or pain mediated by TRKA, TRKB, or TRKC.

2. The use of claim 1, wherein the cancer or pain is mediated by a receptor tyrosine kinase.

3. The use of claim 2, wherein the receptor tyrosine kinase is selected from the group consisting of ROS1, TRKA, TRKB and TRKC.

4. The use of claim 1, wherein the cancer is mediated by a non-receptor kinase.

5. The use of claim 4, wherein the non-receptor kinase is FYN, LYN, YES, FGR, SRC, FAK or ARK5.

6. Use of (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, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by an EML4-ALK fusion protein comprising at least one resistance mutation.

7. The use of claim 6, wherein the EML4-ALK fusion protein comprises at least one mutation selected from the group consisting of L1196M, G1202R, D1203R, L1152P/R, F1174C/L/V, C1156Y, I1171N, G1123S, S1206Y, G1269S/A, and a 1151T insertion.

8. The use of claim 7, wherein the mutation is L1196M.

9. The use of claim 7, wherein the mutation is G1202R.

10. The use of claim 7, wherein the mutation is L1152P.

11. The use of claim 7, wherein the mutation is F1174C.

12. The use of claim 7, wherein the mutation is C1156Y.

13. The use of claim 7, wherein the mutation is I1171N.

14. The use of claim 7, wherein the mutation is G1269S.

15. The use of claim 7, wherein the mutation is 1151T insertion.

16. Use of (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, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by a fusion protein comprising a fragment of a protein encoded by an ALK gene and a fragment of a protein encoded by a TPR gene.

17. The use of claim 16, wherein the genetically altered ALK is a TPR-ALK fusion protein.

18. The use of claim 17, wherein the TPR-ALK fusion protein is a wild-type protein.

19. The use of claim 17, wherein the TPR-ALK fusion protein comprises at least one resistance mutation.

20. The use of claim 17, wherein the TPR-ALK fusion protein comprises a L1196M point mutation.

21. Use of (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, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by ALK having one or more point mutations selected from the group consisting of F1174C/I/L/S/V, F1245C/I/L/V, R1275L/Q, T1151M, L1152R, C1156Y, G1202R, S1206Y, G1269A, G1269S, R1275Q, I1170N, I1170S and L1196M.

22. The use of claim 21, wherein the point mutation is a mutation of ALK at F1174.

23. The use of claim 21, wherein the point mutation is a mutation of ALK at F1245.

24. The use of claim 21, wherein the point mutation is a mutation of ALK at R1275.

25. The use of any one of claims 6 to 24, wherein the cancer is selected from the group consisting of ALCL, NSCLC, neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme and anaplastic thyroid cancer.

26. The use of any one of claims 6 to 25, wherein the cancer is NSCLC.

27. The use of any one of claims 1 to 3, wherein the cancer is mediated by ROS1.

28. The use of any one of claims 1 to 3, wherein the cancer is mediated by a genetically altered ROS1.

29. The use of any one of claims 1 to 3, wherein the cancer is mediated by a fusion protein comprising a fragment of a protein encoded by an ROS1 gene and a fragment of a protein encoded by a gene selected from the group consisting of TPM3, SDC4, SLC34A2 and CD74.

30. The use of claim 29, wherein the fusion protein comprises a fragment of a protein encoded by an ROS1 gene and a fragment of a protein encoded by a CD74 gene.

31. The use of claim 28, wherein the genetically altered ROS1 is a CD74-ROS1 fusion protein.

32. The use of claim 31, wherein the CD74-ROS1 fusion protein is a wild-type protein.

33. The use of claim 31, wherein the CD74-ROS1 fusion protein comprises at least one resistance mutation.

34. The use of claim 31, wherein the CD74-ROS1 fusion protein comprises a G2032R, L2026M or D2033N point mutation.

35. The use of claim 28, wherein the genetically altered ROS1 is a SDC4-ROS1 fusion protein.

36. The use of claim 35, wherein the SDC4-ROS1 fusion protein is a wild-type protein.

37. The use of claim 35, wherein the SDC4-ROS1 fusion protein comprises at least one resistance mutation.

38. The use of claim 35, wherein the SDC4-ROS1 fusion protein comprises a G2032R point mutation.

39. The use of claim 28, wherein the genetically altered ROS1 is a SLC34A2-ROS1 fusion protein.

40. The use of claim 39, wherein the SLC34A2-ROS1 fusion protein is a wild-type protein.

41. The use of claim 39, wherein the SLC34A2-ROS1 fusion protein comprises at least one resistance mutation.

42. The use of claim 39, wherein the SLC34A2-ROS1 fusion protein comprises a G2032R point mutation.

43. The use of any one of claims 27 to 42, wherein the cancer is selected from the group consisting of glioblastoma, glioblastoma multiforme, NSCLC, cholangiocarcinoma, ovarian cancer, gastric adenocarcinoma, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, and epithelioid hemangioendothelioma.

44. The use of any one of claims 27 to 43, wherein the cancer is NSCLC.

45. Use of (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, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by a TPM3-TRKA fusion protein comprising at least one resistance mutation.

46. The use of any one of claims 1 to 3, wherein the cancer is mediated by TRKB.

47. The use of any one of claims 1 to 3, wherein the cancer is mediated by a genetically altered TRKB.

48. The use of any one of claims 1 to 3, wherein the cancer is mediated by TRKC.

49. The use of any one of claims 1 to 3, wherein the cancer is mediated by a genetically altered TRKC.

50. The use of any one of claims 45 to 49, wherein the cancer is selected from the group consisting of glioblastoma, glioblastoma multiforme, NSCLC, cholangiocarcinoma, intrahepatic cholangiocarcinoma, colorectal cancer, thyroid papillary cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, breast cancer, acute myeloid leukemia, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, colon adenocarcinoma, thyroid carcinoma, skin cutaneous melanoma, head and neck squamous cell carcinoma and pediatric glioma.

51. The use of any one of claims 45 to 50, wherein the cancer is NSCLC.

52. The use of any one of claims 45 to 50, wherein the cancer is colorectal cancer.

53. Use of (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, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein the cancer is mediated by JAK1 or JAK3.

54. The use of any one of claims 1 to 3, wherein the cancer is mediated by SRC.

55. The use of claim 54, wherein the cancer is selected from the group consisting of glioblastoma, glioblastoma multiforme, NSCLC, cholangiocarcinoma, intrahepatic cholangiocarcinoma, colorectal cancer, thyroid papillary cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, breast cancer, acute myeloid leukemia, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, colon adenocarcinoma, thyroid carcinoma, skin cutaneous melanoma, head and neck squamous cell carcinoma and pediatric glioma.

56. The use of any one of claims 1 to 3, wherein the medicament is for treating pain.

57. The use of any one of claims 1 to 3, wherein the medicament is for treating pain mediated by TRKA, TRKB or TRKC.

58. The use of claim 57, wherein the pain is mediated by TRKA.

59. The use of claim 57, wherein the pain is mediated by TRKB.

60. The use of claim 57, wherein the pain is mediated by TRKC.

61. The use of any one of claims 1, 4 or 5, wherein the cancer is a cancer exhibiting bypass resistance.

62. Use of (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, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient previously shown to express a genetically altered tyrosine or serine/threonine kinase, wherein the cancer is mediated by a tyrosine kinase selected from the group consisting of ROS1, TRKB, TRKC, SRC, FYN, LYN, YES, FGR, FAK, ARK5, and combinations thereof.

63. The use of claim 62, wherein the genetically altered tyrosine kinase is genetically altered ROS1.

64. Use of (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, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient previously shown to express a protein encoded by an ALK gene and a fragment of a protein encoded by a TPR gene.

65. Use of (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, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient previously shown to express an EML4-ALK fusion protein comprising at least one resistance mutation.

66. The use of claim 65, wherein the EML4-ALK fusion protein comprises at least one mutation selected from the group consisting of L1196M, G1202R, D1203R, L1152P/R, F1174C/L/V, C1156Y, I1171N, G1123S, S1206Y, G1269S/A, and a 1151T insertion.

67. The use of claim 64, wherein the protein is a TPR-ALK fusion protein.

68. The use of claim 67, wherein the TPR-ALK fusion protein is a wild-type protein.

69. The use of claim 67, wherein the TPR-ALK fusion protein comprises at least one resistance mutation.

70. The use of claim 69, wherein the TPR-ALK fusion protein comprises a L1196M point mutation.

71. The use of any one of claims 62 to 70, wherein the cancer exhibits a bypass resistance mechanism.

72. The use of claim 71, wherein the bypass resistance mechanism is mediated by SRC.

73. The use of any one of claims 62 to 72, wherein the cancer is selected from the group consisting of ALCL, NSCLC, neuroblastoma, inflammatory myofibroblastic tumor, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme and anaplastic thyroid cancer.

74. The use of any one of claims 62 to 73, wherein the cancer is NSCLC.

75. The use of claim 63, wherein the genetically altered ROS1 is a fusion protein comprising a fragment of a protein encoded by an ROS1 gene and a fragment of a protein encoded by a gene selected from the group consisting of TPM3, SDC4, SLC34A2 and CD74.

76. The use of claim 75, wherein the fusion protein comprises a fragment of a protein encoded by an ROS1 gene and a fragment of a protein encoded by a CD74 gene.

77. The use of claim 75, wherein the genetically altered ROS1 is a CD74-ROS1 fusion protein.

78. The use of claim 77, wherein the CD74-ROS1 fusion protein is a wild-type protein.

79. The use of claim 77, wherein the CD74-ROS1 fusion protein comprises at least one resistance mutation.

80. The use of claim 77, wherein the CD74-ROS1 fusion protein comprises a G2032R, L2026M or D2033N point mutation.

81. The use of claim 75, wherein the genetically altered ROS1 is a SDC4-ROS1 fusion protein.

82. The use of claim 81, wherein the SDC4-ROS1 fusion protein is a wild-type protein.

83. The use of claim 81, wherein the SDC4-ROS1 fusion protein comprises at least one resistance mutation.

84. The use of claim 81, wherein the SDC4-ROS1 fusion protein comprises a G2032R point mutation.

85. The use of claim 75, wherein the genetically altered ROS1 is a SLC34A2-ROS1 fusion protein.

86. The use of claim 85, wherein the SLC34A2-ROS1 fusion protein is a wild-type protein.

87. The use of claim 85, wherein the SLC34A2-ROS1 fusion protein comprises at least one resistance mutation.

88. The use of claim 84, wherein the SLC34A2-ROS1 fusion protein comprises a G2032R point mutation.

89. The use of any one of claims 62, 63 or 75 to 88, wherein the cancer is selected from the group consisting of glioblastoma, glioblastoma multiforme, NSCLC, cholangiocarcinoma, ovarian cancer, gastric adenocarcinoma, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, and epithelioid hemangioendothelioma.

90. The use of any one of claims 62, 63 or 75 to 89, wherein the cancer is NSCLC.

91. Use of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriaza-cyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a patient, wherein a genetically altered tyrosine or serine/threonine kinase selected from the group consisting of ROS1, TRKB, TRKC, SRC, FYN, LYN, YES, FGR, FAK, ARK5, and combinations thereof, in the patient is to be identified, and a therapeutically effective amount of the medicament is to be administered if the genetically altered tyrosine or serine/threonine kinase in the patient is identified by subjecting a patient sample to a test selected from the group consisting of FISH, IHC, PCR and gene sequencing.

92. A method of identifying a patient for treatment with (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriaza-cyclotridecin-4(5*H*)-one, or a pharmaceutically acceptable salt thereof, comprising subjecting a patient sample to a test selected from the group consisting of FISH, IHC, PCR and gene sequencing to identify the patient as having a cancer mediated by a genetically altered tyrosine or serine/threonine kinase selected from the group consisting of ROS1, TRKB, TRKC, SRC, FYN, LYN, YES, FGR, FAK, ARK5, and combinations thereof.