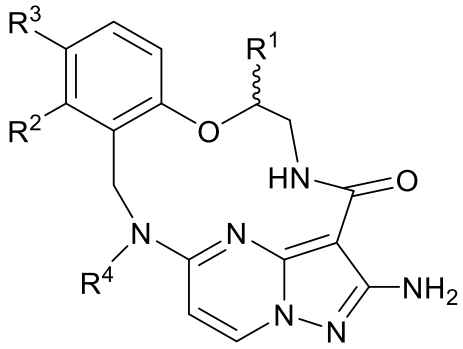
lymphocytes under normal physiological conditions. Activation of Fyn is observed in various cancers, including melanoma, glioblastoma, squamous cell carcinoma, prostate and breast cancers. (Elias D., et al. *Pharmacological Research* **2015**, *100*, 250-254) Fyn was upregulated in tamoxifen-resistant breast cancer cell lines and plays a key role in the resistance mechanism. Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of aggressive non Hodgkin lymphomas with poor prognosis. FYN activating mutations were found in PTCL, and promoted the growth of cells transformed via expression of activated FYN mutant alleles. SRC kinase inhibitors may play important roles in the treatment of PTCLs. (Couronne L, et al. *Blood* 2013, 122, 811).

[007] It is desirable to prepare compounds that have activity against disease-driving kinase inhibitors, especially compounds that have activity against genetically altered MET, SCR and CSF1R. New compounds with polypharmacology profiles are also desired for targeting the primary oncogene drivers and their acquired resistance mechanisms including secondary mutations, bypass signaling, EMT, cancer stemness, and metastasis.

SUMMARY

[007a] In an aspect, there is provided a use of a compound in the preparation of a medicament for treating cancer in a patient, wherein the compound is of formula



wherein

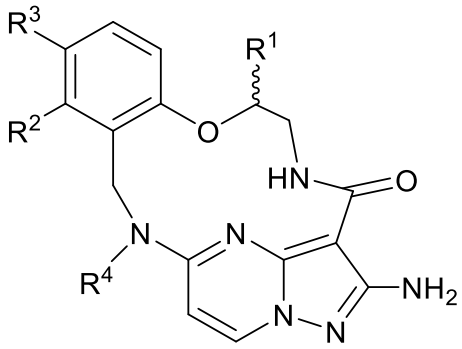
R^1 is H, deuterium, or C_1-C_6 alkyl;

R^2 is chloro or -CN;

R^3 is H, deuterium, or fluoro;

R^4 is H or C_1-C_6 alkyl, wherein each hydrogen atom in C_1-C_6 alkyl is independently optionally substituted by deuterium, fluoro, chloro, bromo, -OH, -CN, -OC_1-C_6 alkyl, -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, or C_3-C_7 cycloalkyl, or a pharmaceutically acceptable salt thereof.

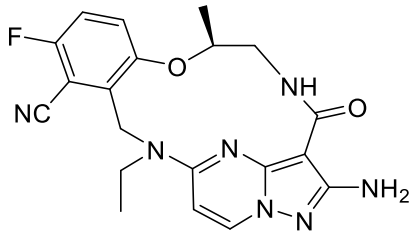
[008] Compounds that inhibit MET, SRC, and CSF1R gene products have been discovered. Compounds of the formula I



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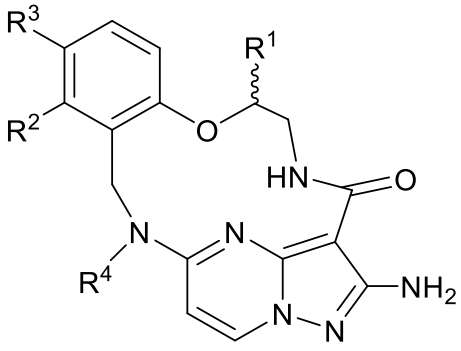
wherein R^1, R^2, R^3, and R^4 are defined as described herein have been shown to have activity against wild-type and mutant MET, SRC, and CSF1R.

[009] One such compound is (7*S*)-3-amino-14-ethyl-11-fluoro-7-methyl-4-oxo-4,5,6,7,13,14-hexahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecine-12-carbonitrile (also herein referred to as "Compound 1"), represented by the formula



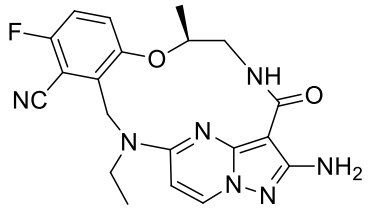
has been shown to be a potent small-molecule kinase inhibitor showing activity against wild-type and mutant wild-type and mutant MET, SRC, and CSF1R. Compound 1 has properties, including anti-tumor properties, which are pharmacologically mediated through inhibition of receptor and non-receptor tyrosine kinases. Compounds of the formula I, in particular, Compound 1, are disclosed in International Patent Publication No. WO2019/023417, which is incorporated herein by reference in its entirety.

[010] In one example, the present disclosure provide a method of treating disease, such as cancer, in a mammal, in particular a human patient comprising, administering to the mammal, in particular a human patient, a therapeutically effective amount of a compound that inhibits MET, SRC, and CSF1R, wherein the disease is mediated by a genetically altered MET. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula I



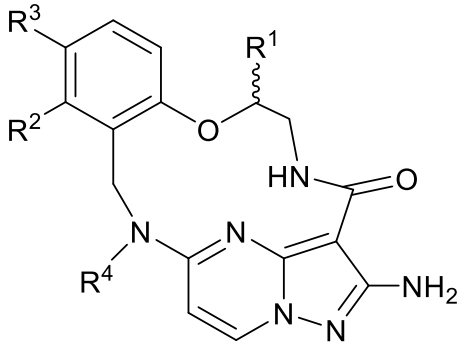
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or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and R^4 are defined as described herein. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula



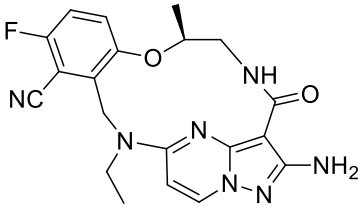
or a pharmaceutically acceptable salt thereof. In some examples, the mammal, in particular a human patient, has received prior treatment with one or more therapeutic agents.

[011] In another example, the present disclosure provides a method of treating cancer in a patient previously shown to express a genetically altered MET comprising, administering to the patient a therapeutically effective amount of a compound that inhibits MET, SRC, and CSF1R. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula I



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or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and R^4 are defined as described herein. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula

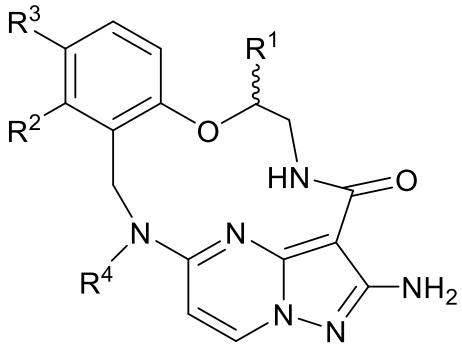


or a pharmaceutically acceptable salt thereof. In some examples, the patient, has received prior treatment with one or more therapeutic agents.

[012] In another example, the present disclosure provides a method of treating cancer in a patient comprising;

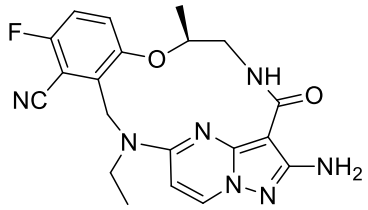
i. identifying a genetically altered MET in the patient, and

ii. administering to the patient a therapeutically effective amount of a compound that inhibits MET, SRC, and CSF1R. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula I



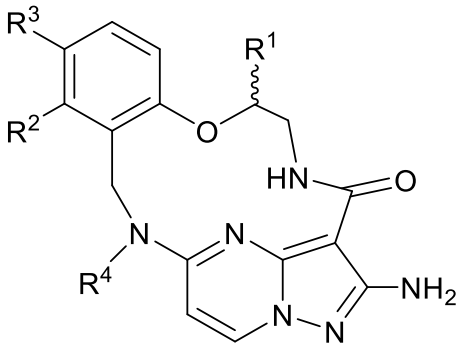
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or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and R^4 are defined as described herein. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula



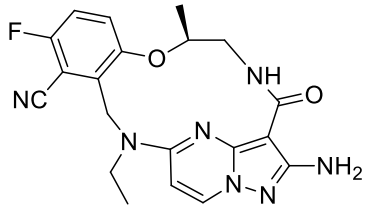
or a pharmaceutically acceptable salt thereof. In some examples, the patient, has received prior treatment with one or more therapeutic agents.

[013] In another example, the present disclosure provides a method of identifying a patient for treatment with a compound that inhibits MET, SRC, and CSF1R. comprising diagnosing the patient with a cancer mediated by a genetically altered MET. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula I



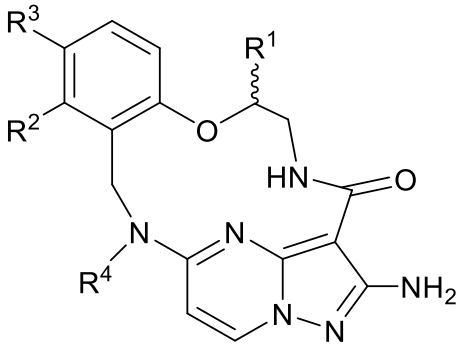
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or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and R^4 are defined as described herein. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula



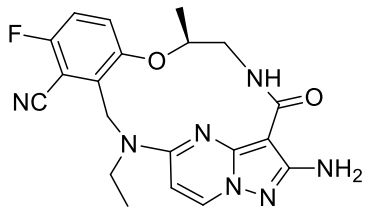
or a pharmaceutically acceptable salt thereof. In some examples, the patient, has received prior treatment with one or more therapeutic agents.

[014] In another example, the present disclosure provides a use of compound that inhibits MET, SRC, and CSF1R in the preparation of a medicament for the treatment of a disease in a patient. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula I



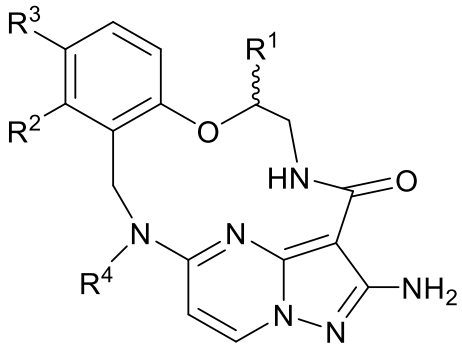
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or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and R^4 are defined as described herein. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula



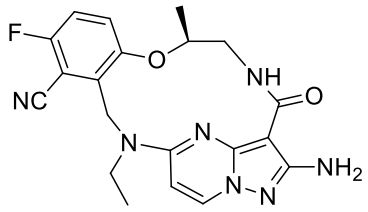
or a pharmaceutically acceptable salt thereof. In some examples, the patient, has received prior treatment with one or more therapeutic agents.

[015] In another example, the present disclosure provides a compound inhibits MET, SRC, and CSF1R for treating cancer in a patient. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula I



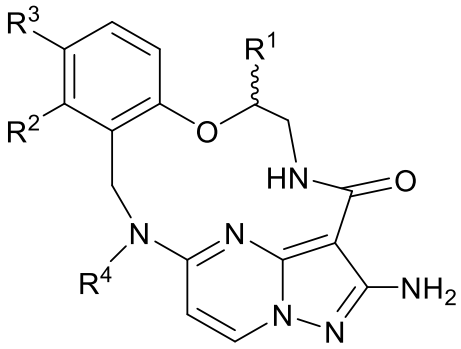
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or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and R^4 are defined as described herein. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula



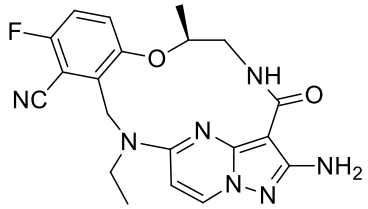
or a pharmaceutically acceptable salt thereof. In some examples, the patient, has received prior treatment with one or more therapeutic agents.

[016] In another example, the present disclosure provides use of a compound that inhibits MET, SRC, and CSF1R for treating cancer in a patient previously shown to express a genetically altered tyrosine or serine/threonine kinase. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula I



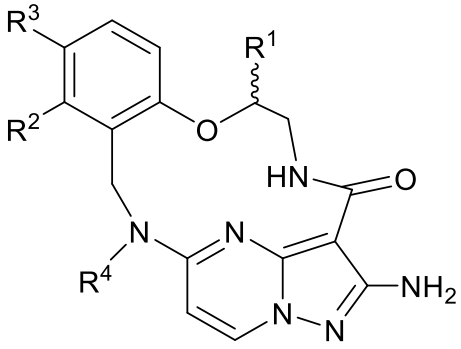
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or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and R^4 are defined as described herein. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula



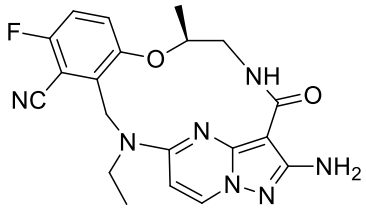
or a pharmaceutically acceptable salt thereof. In some examples, the patient, has received prior treatment with one or more therapeutic agents.

[017] In another example, the present disclosure provide a use a compound inhibits MET, SRC, and CSF1R for treating cancer in a patient, wherein the patient has been previously treated with a cancer therapeutic, and the cancer has developed resistance to the cancer therapeutic. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula I



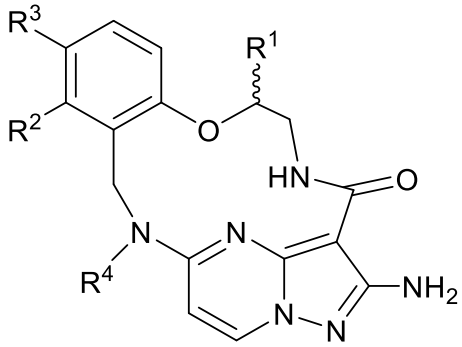
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or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and R^4 are defined as described herein. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula



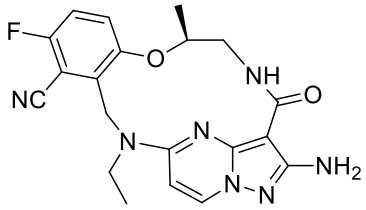
or a pharmaceutically acceptable salt thereof. In some examples, the patient, has received prior treatment with one or more therapeutic agents.

[018] In another example, the present disclosure provides the use of a compound that inhibits MET, SRC, and CSF1R for treating cancer in a patient previously shown to express a genetically altered tyrosine or serine/threonine kinase, wherein the patient has been previously treated with a cancer therapeutic, and the cancer has developed resistance to the cancer therapeutic. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula I



I

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and R^4 are defined as described herein. In some examples, the compound that inhibits MET, SRC, and CSF1R is of the formula



or a pharmaceutically acceptable salt thereof. In some examples, the patient, has received prior treatment with one or more therapeutic agents.

[019] In some examples, the genetically altered MET gene comprising a point mutation that is expressed in the c-Met protein. In some examples, the genetically altered MET comprises a point mutation expressed in the c-Met protein at one or more of positions P991, T992, D1010, V1092, H1094, G1163, T1173, H1094, N1100, Y1003, H1106, V1070, V1188, V1092, H1094, G1162, L1195, F1200, V1220, D1228, Y1230, D1231, Y1235, D1246, Y1248, M1250, and M1268. In some examples, the genetically altered MET comprises a point mutation expressed in the c-Met protein that is selected from the group consisting of P991S, T992I, D1010H, D1010Y, V1092I, H1094N, H1094R, H1094Y, N1100K, N1100S, Y1003C, Y1003F, Y1003H, H1106D, V1070A, V1092I, V1188I, T1173I, H1094Y, G1163R, L1195F, F1195I, L1195V, F1200I, V1220I, D1228N, D1228H, D1228V, Y1230A, Y1230C, Y1230D, Y1230H, Y1230H, Y1230S, D1231Y, Y1235D, D1246N, D1246H, Y1248D, Y1248H, Y1248C, M1250T, and M1268T. In some examples, the genetically altered MET comprises a point mutation expressed in the c-Met protein that is selected from the group consisting of T1173I, P991S, M1250T, T992I, V1092I, F1200I, Y1235D, Y1230H, D1246N, D1246H, Y1248D, Y1248H, Y1248C, and M1268T. In some examples, the cancer is exhibiting bypass resistance. In some examples, the bypass resistance is mediated by a SRC/CSF1R.

[020] In some examples, the cancer is a carcinoma, a sarcoma, a lymphoma, Hodgekin's disease, a melanoma, a mesothelioma, Burkitt's lymphoma, a nasopharyngeal carcinoma, a leukemia, a lung cancer, a breast cancer, a hereditary human papillary renal carcinoma, a sporadic human papillary renal carcinoma, a childhood hepatocellular carcinoma, or a myeloma. In some examples, the cancer is selected from the group consisting of ALCL, NSCLC, neuroblastoma, inflammatory myofibroblastic tumor, renal cancer, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, triple negative breast cancer, triple positive breast cancer, HER^+ breast cancer, mouth cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, bladder cancer, colon cancer, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, thyroid cancer, anaplastic thyroid cancer, endocrine cancer, bone cancer, cholangiocarcinoma, ovarian cancer, cervical cancer, uterine cancer, testicular cancer, gastric cancer, gastric adenocarcinoma, colorectal cancer, rectal cancer, liver cancer, kidney cancer, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid papillary cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, acute myeloid leukemia, congenital mesoblastic nephroma, congenital

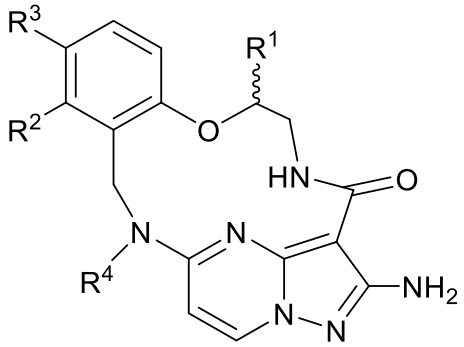
fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, skin cancer, head and neck squamous cell carcinoma, pediatric glioma CML, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, metastatic castration-resistant prostate cancer, Hodgkin lymphoma, neuroendocrine tumors, serous and clear cell endometrial cancer.

[021] In some examples, the patient has been previously treated with a cancer therapeutic. In some examples, the patient has been previously treated with a cancer therapeutic, and the cancer has developed resistance to the cancer therapeutic. In some examples, the resistance is a primary intrinsic resistance. In some examples, the resistance is an acquired resistance from mutation(s). In some examples, the resistance is a bypass resistance. In some examples, the resistance is an EMT-based resistance.

[022] Additional examples, features, and advantages of the disclosure will be apparent from the following detailed description and through practice of the disclosure. The compounds of the present disclosure can be described as examples in any of the following enumerated clauses. It will be understood that any of the examples described herein can be used in connection with any other examples described herein to the extent that the examples do not contradict one another.

[023] 1. A method of treating cancer in a patient comprising, administering to the patient a therapeutically effective amount of a compound that inhibits MET, SRC and CSF1R, wherein the cancer is mediated by a genetically altered MET.

[024] 2. The method of clause 1, wherein the compound of the formula



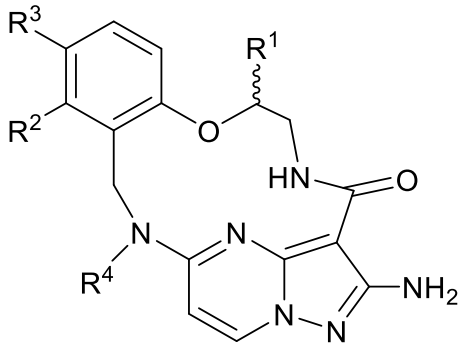
wherein

R^1 is H, deuterium, or C_1-C_6 alkyl;

R^2 is chloro or -CN;

WHAT IS CLAIMED IS:

1. Use of a compound in the preparation of a medicament for treating cancer in a patient, wherein the compound is of formula



wherein

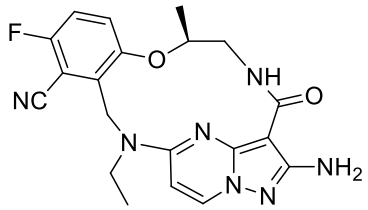
R^1 is H, deuterium, or C_1-C_6 alkyl;

R^2 is chloro or -CN;

R^3 is H, deuterium, or fluoro;

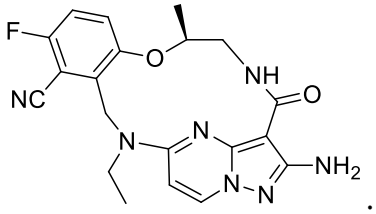
R^4 is H or C_1-C_6 alkyl, wherein each hydrogen atom in C_1-C_6 alkyl is independently optionally substituted by deuterium, fluoro, chloro, bromo, -OH, -CN, -OC_1-C_6 alkyl, -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, or C_3-C_7 cycloalkyl, or a pharmaceutically acceptable salt thereof.

2. The use of claim 1, wherein the compound is of formula



or a pharmaceutically acceptable salt thereof.

3. The use of claim 1, wherein the compound is of formula



.

4. The use of any one of claims 1 to 3, wherein the cancer is a carcinoma, a sarcoma, a lymphoma, Hodgekin's disease, a melanoma, a mesothelioma, Burkitt's lymphoma, a nasopharyngeal carcinoma, a leukemia, a lung cancer, a breast cancer, a hereditary human papillary renal carcinoma, a sporadic human papillary renal carcinoma, a childhood hepatocellular carcinoma, or a myeloma.

5. The use of any one of claims 1 to 3, wherein the cancer is selected from the group consisting of ALCL, NSCLC, neuroblastoma, inflammatory myofibroblastic tumor, renal cancer, adult renal cell carcinoma, pediatric renal cell carcinoma, breast cancer, triple negative breast cancer, triple positive breast cancer, HER^+ breast cancer, mouth cancer, esophageal cancer, laryngeal cancer, pancreatic cancer, bladder cancer, colon cancer, colonic adenocarcinoma, glioblastoma, glioblastoma multiforme, thyroid cancer, anaplastic thyroid cancer, endocrine cancer, bone cancer, cholangiocarcinoma, ovarian cancer, cervical cancer, uterine cancer, testicular cancer, gastric cancer, gastric adenocarcinoma, colorectal cancer, rectal cancer, liver cancer, kidney cancer, angiosarcoma, epithelioid hemangioendothelioma, intrahepatic cholangiocarcinoma, thyroid papillary cancer, spitzoid neoplasms, sarcoma, astrocytoma, brain lower grade glioma, secretory breast carcinoma, mammary analogue carcinoma, acute myeloid leukemia, congenital mesoblastic nephroma, congenital fibrosarcomas, Ph-like acute lymphoblastic leukemia, thyroid carcinoma, skin cancer, head and neck squamous cell carcinoma, pediatric glioma CML, prostate cancer, lung squamous carcinoma, ovarian serous cystadenocarcinoma, skin cutaneous melanoma, metastatic castration-resistant prostate cancer, Hodgkin lymphoma, neuroendocrine tumors, and serous and clear cell endometrial cancer.

6. The use of any one of claims 1 to 5, wherein the patient has received prior treatment with one or more therapeutic agents.

7. The use of any one of claims 1 to 6, wherein the cancer is mediated by a genetically altered MET.

8. The use of claim 7, wherein the genetically altered MET encodes a point mutation that is expressed in the c-Met protein.

9. The use of any one of claims 7 to 8, wherein the genetically altered MET encodes a point mutation expressed in the c-Met protein at one or more of positions P991, T992, V1092, H1094, G1163, T1173, L1195, F1200, D1228, Y1230, Y1235, D1246, Y1248, M1250, and M1268.

10. The use of any one of claims 7 to 9, wherein the genetically altered MET encodes a point mutation expressed in the c-Met protein that is selected from the group consisting of T1173I, P991S, M1250T, T992I, V1092I, F1200I, Y1235D, Y1230H, D1246N, D1246H, Y1248D, Y1248H, Y1248C, and M1268T.

11. The use of any one of claims 7 to 10, wherein the cancer is exhibiting bypass resistance mediated by a SRC/CSF1R.