DUAL ATM AND DNA-PK INHIBITORS FOR USE IN ANTI-TUMOR THERAPY

FIELD OF THE INVENTION

The invention relates to compounds and pharmaceutically acceptable salts thereof and methods of their use for the treatment of cancer as a monotherapy or in combination with radiotherapy, chemotherapy, and/or immunotherapy.

BACKGROUND OF THE INVENTION

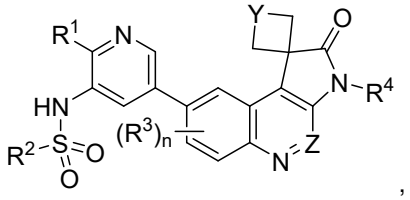
Several members of the PIKK (PI-3K-like Kinase) family of serine-threonine kinases are known mediators of DNA damage signaling.

Radiation therapy (RT) is used to treat >50% of all cancer patients at some point during their illness. Despite significant effort, previous approaches to develop clinical radiosensitizers have not been highly effective, primarily as a result of targeting non-specific pathways which are not direct regulators of the cellular response to radiation.

There is a need for new therapies for oncological diseases.

SUMMARY ~~OF THE INVENTION~~

In general, the ~~invention~~disclosure provides a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

where

Z is CH, CR^3, or N;

Y is CHR^5 or NR^6;

n is 0, 1, 2, or 3;

R^1 is –O–L–$N(R^7)_2$ or optionally substituted, four-memberred, saturated *N*-heterocyclyl;

R^2 is $C_{1\text{-}3}$ alkyl;

each R^3 is independently halogen;

R^4 is optionally substituted alkyl;

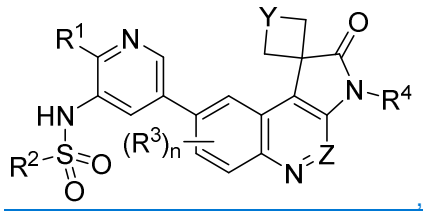
R^5 is hydrogen, optionally substituted $C_{1\text{-}3}$ alkyl, or benzyloxy;

R^6 is optionally substituted $C_{1\text{-}3}$ alkyl;

each R^7 is independently H or optionally substituted $C_{1\text{-}3}$ alkyl; and

L is optionally substituted ethylene.

In one aspect, the disclosure provides a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

Y is CHR^5 or NR^6;

Z is CH, CR^3, or N;

n is 0, 1, 2, or 3;

R^1 is $–O–L–N(R^7)_2$ or optionally substituted, four-membered, saturated *N*-heterocyclyl;

R^2 is $C_{1\text{-}3}$ alkyl;

each R^3 is independently halogen or optionally substituted $C_{1\text{-}3}$ alkyl;

R^4 is optionally substituted alkyl;

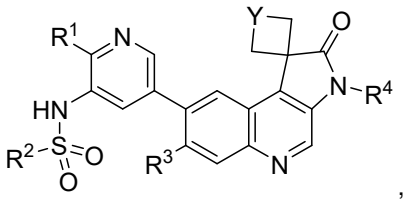
R^5 is hydrogen, optionally substituted $C_{1\text{-}3}$ alkyl, or benzyloxy;

R^6 is optionally substituted $C_{1\text{-}3}$ alkyl;

each R^7 is independently H or optionally substituted $C_{1\text{-}3}$ alkyl; and

L is optionally substituted ethylene.

In some ~~embodiment~~examples, n is 1. In certain ~~embodiment~~examples, the compound is a compound of formula (IA):

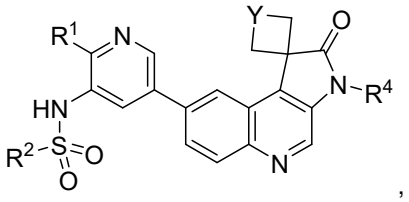


(IA)

or a pharmaceutically acceptable salt thereof.

In particular ~~embodiment~~examples, R^3 is halogen (e.g., fluorine). In further ~~embodiment~~examples, n is 0.

In yet further ~~embodiment~~examples, the compound is a compound of formula (IB):

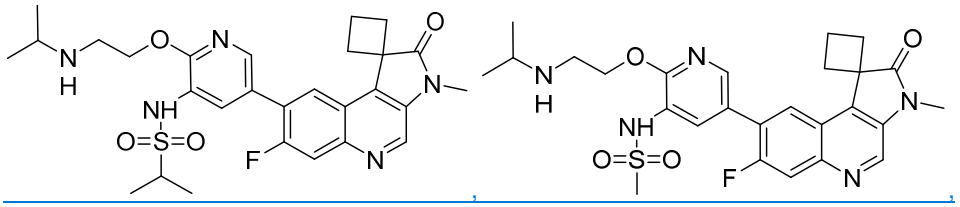


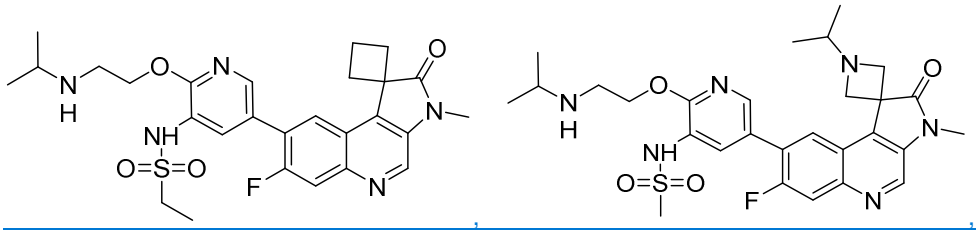
(IB)

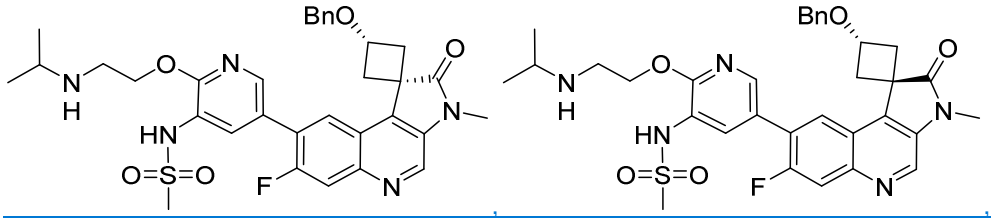
or a pharmaceutically acceptable salt thereof.

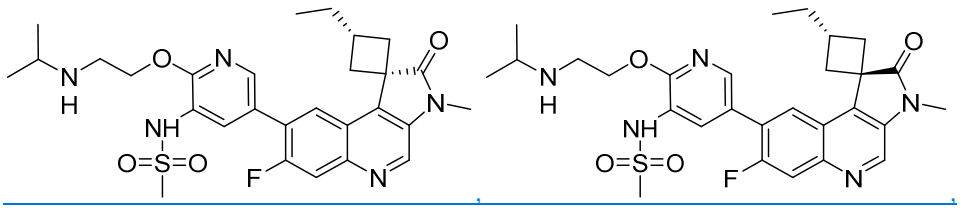
In still further ~~embodiment~~examples, R^1 is –O–L–N(R^7)$_2$. In some ~~embodiment~~examples, one R^7 is H, and the remaining R^7 is optionally C_{1-3} alkyl. In certain ~~embodiment~~examples, at least one R^7 is isopropyl. In particular ~~embodiment~~examples, R^2 is methyl, ethyl, or isopropyl. In further ~~embodiment~~examples, R^2 is methyl. In yet further ~~embodiment~~examples, R^4 is methyl. In yet further ~~embodiment~~examples, Y is CHR^5. In still further ~~embodiment~~examples, R^5 is hydrogen. In other ~~embodiment~~examples, R^5 is optionally substituted C_{1-3} alkyl. In yet other ~~embodiment~~examples, R^5 is benzyloxy. In still other ~~embodiment~~examples, Y is NR^6. In some ~~embodiment~~examples, R^6 is optionally substituted C_3 alkyl. In certain ~~embodiment~~examples, R^6 is isopropyl.

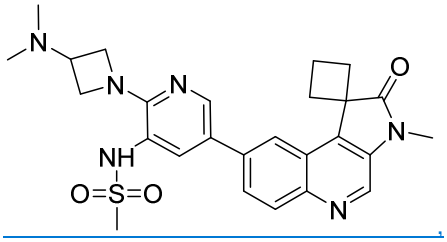
In another aspect, the present disclosure provides a compound selected from the group consisting of:



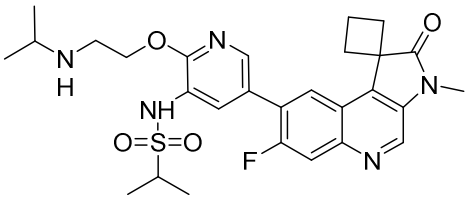
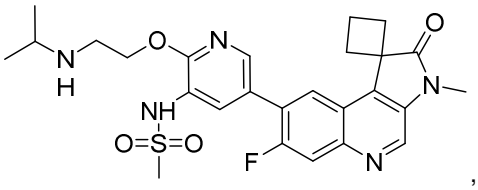
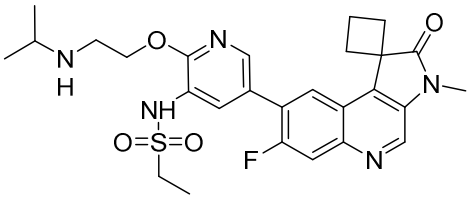
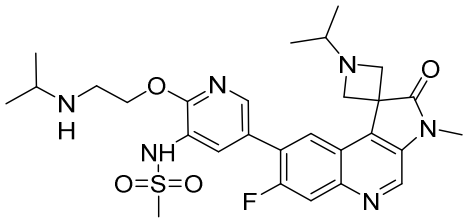


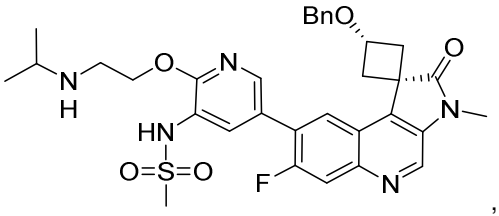
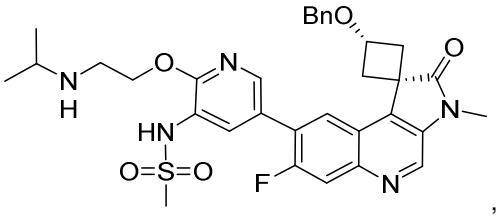
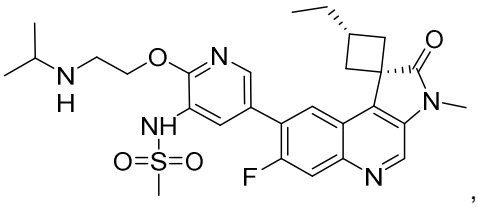
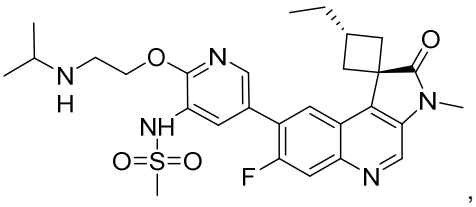
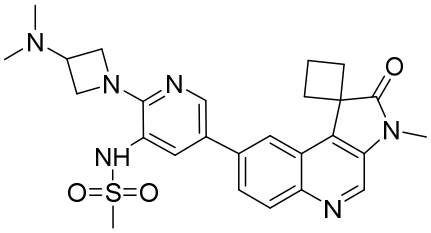






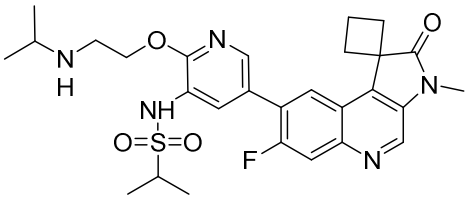
and pharmaceutically acceptable salts thereof. In particular ~~embodiment~~examples, the compound is selected from the group consisting of:


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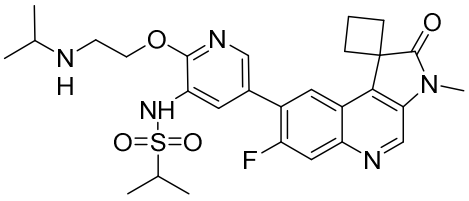






and pharmaceutically acceptable salts thereof.

In one aspect, the present disclosure provides a compound of the following structure:

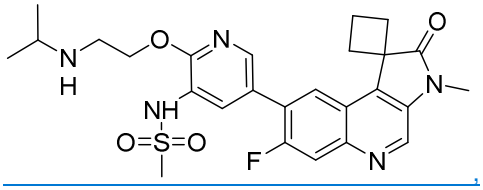


or a pharmaceutically acceptable salt thereof. In further ~~embodiment~~examples, the compound is of the following structure:

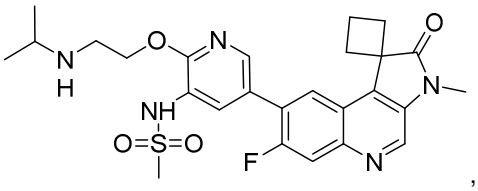


or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a compound of the following structure:



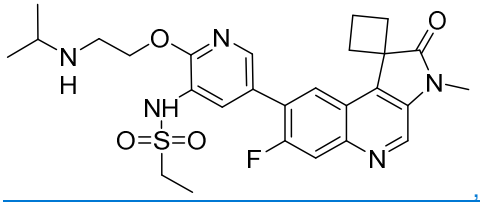
or a pharmaceutically acceptable salt thereof. In yet further ~~embodiment~~examples, the compound is of the following structure:



,

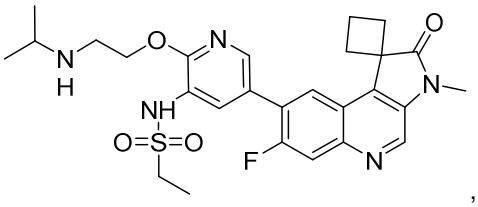
or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure provides a compound of the following structure:



,

or a pharmaceutically acceptable salt thereof. In still further ~~embodiment~~examples, the compound is of the following structure:



,

or a pharmaceutically acceptable salt thereof.

In another ~~aspect~~example, the ~~invention~~disclosure provides a pharmaceutical composition including the compound of the ~~invention~~disclosure or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient. In one aspect, the present disclosure provides a pharmaceutical composition comprising the compound disclosed herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

In yet another ~~aspect~~example, the ~~invention~~disclosure provides a method of treating an oncological disease (e.g., cancer, e.g., those cancers described herein) by administering a therapeutically effective amount of the compound of the ~~invention~~disclosure, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of the ~~invention~~disclosure to a patient in need thereof. In still another ~~aspect~~example, the ~~invention~~disclosure provides pharmaceutical compositions for use in the treatment of an oncological disease (e.g., cancer, e.g., those cancers described herein). The pharmaceutical compositions include the compound of the ~~invention~~disclosure. In a further ~~aspect~~example, the ~~invention~~disclosure provides use of the compound of the ~~invention~~disclosure in the manufacture of a medicament for the treatment of an oncological disease (e.g., cancer, e.g., those cancers described herein). In one aspect, the present disclosure provides use of a therapeutically effective amount of the compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition dislcoused herein in the manufacture of a medicament for treating an oncological disease in a patient in need thereof. In some ~~embodiment~~examples, the oncological disease is a brain cancer, bladder cancer, breast cancer, central nervous system cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, gastrointestinal stromal tumor, gastric cancer, head and neck cancer, buccal cancer, cancer of the mouth, hepatocellular cancer, lung cancer, melanoma, Merkel cell carcinoma, mesothelioma, nasopharyngeal cancer, neuroblastoma, osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, salivary gland cancer, sarcomas, testicular cancer, urothelial cancer, vulvar cancer, or Wilm's tumor. In further ~~embodiment~~examples, the oncological disease is a breast cancer, lung cancer, head and neck cancer, pancreatic cancer, rectal cancer, glioblastoma, hepatocellular carcinoma, cholangiocarcinoma, metastic liver lesions, melanoma, bone sarcoma, soft tissue sarcoma, endometrial cancer, cervical cancer, prostate cancer, or Merkel cell carcinoma.

In some ~~embodiment~~examples, the patient is receiving radiotherapy. In certain ~~embodiment~~examples, the compound or the pharmaceutical composition is administered to the patient concomitantly with the radiotherapy. In particular ~~embodiment~~examples, the compound or the pharmaceutical composition is administered to the patient before radiotherapy. In further ~~embodiment~~examples, the compound or the pharmaceutical composition is administered to the patient after radiotherapy. In yet further ~~embodiment~~examples, the radiotherapy comprises external, internal, brachytherapy, or systemic exposure, e.g., with a radionuclide (e.g., a β-emitting radionuclide (e.g., ^{32}Phosphorus, ^{67}Copper, ^{77}Bromine, ^{89}Strontium, ^{90}Yttrium, ^{105}Rhodium, ^{131}Iodine, ^{137}Cesium, ^{149}Prometheum, ^{153}Samarium, ^{166}Holmium, ^{177}Lutetium, ^{186}Rhenium, ^{188}Rhenium, or ^{199}Gold), α-emitting radionuclide (e.g., ^{211}Astatine, ^{213}Bismuth, ^{223}Radium, ^{225}Actinium, or ^{227}Thorium), γ-ray emitting radionuclide (e.g., ^{192}Iridium), or electron capturing radionuclides (e.g., ^{67}Gallium, ^{103}Palladium, or ^{125}Iodine)), antibody radionuclide conjugate (e.g., ^{90}Y-ibritumomab tiuxetane, ^{131}I-tositumomab, ^{225}Ac-lintuzumab satetraxetan, ^{227}Th-anetumab corixetan, ^{90}Y-epitumomab cituxetan, ^{90}Y-clivatuzumab tetraxetan, ^{177}Lu-lilotomab satetraxetan, ^{90}Y-rosopatamab tetraxetan, ^{90}Y-tabituximab barzuxetan, or ^{90}Y-tacatuzumab tetraxetan), or another targeted radionuclide conjugate (e.g., ^{131}I-PSMA, ^{90}Y-PSMA, ^{177}Lu-PSMA, or ^{177}Lu-satoreotide tetraxetan). Preferably, the radiotherapy comprises administering an antibody radionuclide conjugate. In still further ~~embodiment~~examples, the patient is receiving an anti-tumor agent. In other ~~embodiment~~examples, the anti-tumor agent is one or more of cisplatin, oxaliplatin, carboplatin, valrubicin, idarubicin, calicheamicin, or a PARP inhibitor. In yet other ~~embodiment~~examples, the anti-tumor agent is an anti-tumor biological agent and/or anti-tumor immunotherapeutic agent. In still other ~~embodiment~~examples, the compound or the pharmaceutical composition is administered to the patient concomitantly with the anti-

tumor agent. In some ~~embodiment~~examples, the compound or the pharmaceutical composition is administered to the patient before the anti-tumor agent. In certain embodiments, the compound or the pharmaceutical composition is administered to the patient after the anti-tumor agent.

DETAILED DESCRIPTION

DEFINITIONS

It is to be understood that the terminology employed herein is for the purpose of describing particular embodiments, and is not intended to be limiting. Further, although any methods, devices and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods, devices and materials are now described. In addition to the foregoing, as used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated:

"Amino" refers to the $-NH_2$ radical.

"Cyano" refers to the -CN radical.

"Hydroxyl" refers to the -OH radical.

"Imino" refers to the = NH substituent.

"Nitro" refers to the $-NO_2$ radical.

"Oxo" refers to the = O substituent.

"Thioxo" refers to the = S substituent.

"Trifluoromethyl" refers to the $-CF_3$ radical.

"Alkyl" refers to a linear, saturated, acyclic, monovalent hydrocarbon radical or branched, saturated, acyclic, monovalent hydrocarbon radical, having from one to twelve carbon atoms, preferably one to eight carbon atoms or one to six carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl and the like. An optionally substituted alkyl radical is an alkyl radical that is optionally substituted, valence permitting, by one, two, three, four, or five substituents independently selected from the group consisting of halo, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilanyl, $-OR^{14}$, $-OC(O)-R^{14}$, $-N(R^{14})_2$, $-C(O)R^{15}$, $-C(O)OR^{14}$, $-C(O)N(R^{14})_2$, $-N(R^{14})C(O)OR^{16}$, $-N(R^{14})C(O)R^{16}$, $-N(R^{14})S(O)_tR^{16}$ (where t is 1 or 2), $-S(O)_tOR^{16}$ (where t is 1 or 2), $-S(O)_pR^{16}$ (where p is 0, 1, or 2) and $-S(O)_tN(R^{14})_2$ (where t is 1 or 2), where each R^{14} is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, or heteroaryl; each R^{15} is independently hydrogen, cycloalkyl, aryl, heterocyclyl, or heteroaryl; and each R^{16} is independently alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl.

"Alkenyl" refers to a linear, acyclic, monovalent hydrocarbon radical or branched, acyclic, monovalent hydrocarbon radical, containing one, two, or three carbon-carbon double bonds, having from two to twelve carbon atoms, preferably two to eight carbon atoms and which is attached to the rest of the molecule by a single bond, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl and the like. An optionally substituted alkenyl radical is an alkenyl radical that is optionally substituted, valence permitting, by one, two, three, four, or five substituents independently selected from the group consisting