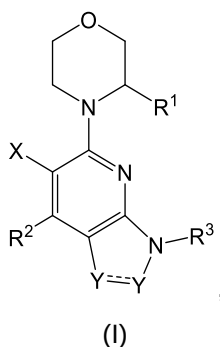


other DNA repair pathways (e.g., ATM) or that are subject to the effects of DNA damaging agents, e.g., radiation therapy or chemotherapeutic agents, are therefore more dependent on ATR for DNA repair and survival. Together, these results highlight a rationale for the selective sensitivity of proliferating tumor cells to ATR inhibition and the potential for a therapeutic window over healthy proliferating cells.

There is a need for new anti-cancer therapies and, in particular, for ATR inhibitor-based anti-cancer therapies.

Summary of the ~~Disclosure~~Invention

In one ~~example~~aspect, the ~~disclosure~~invention provides a compound of formula (I):



or a pharmaceutically acceptable salt thereof,

where

===== is a double bond, and each Y is independently N or CR⁴; or ----- is a single bond, and each Y is independently NR^Y, carbonyl, or C(R^Y)₂; where each R^Y is independently H or optionally substituted C₁₋₆ alkyl;

R¹ is optionally substituted C₁₋₆ alkyl or H;

R² is optionally substituted C₂₋₉ heterocyclyl, optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted C₂₋₉ heterocyclyl C₁₋₆ alkyl, optionally substituted C₆₋₁₀ aryl, optionally substituted C₁₋₉ heteroaryl, optionally substituted C₁₋₉ heteroaryl C₁₋₆ alkyl, halogen, -N(R⁵)₂, -OR⁵, -CON(R⁶)₂, -SO₂N(R⁶)₂, -SO₂R^{5A}, or -Q-R^{5B};

R³ is optionally substituted C₁₋₉ heteroaryl or optionally substituted C₁₋₉ heteroaryl C₁₋₆ alkyl;

each R⁴ is independently hydrogen, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, or optionally substituted C₂₋₆ alkynyl;

each R⁵ is independently hydrogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₆₋₁₀ aryl C₁₋₆ alkyl, optionally substituted C₆₋₁₀ aryl, optionally substituted C₁₋₉ heteroaryl, or -SO₂R^{5A}; or both R⁵, together with the atom to which they are attached, combine to form an optionally substituted C₂₋₉ heterocyclyl;

each R^{5A} is independently optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₈ cycloalkyl, or optionally substituted C₆₋₁₀ aryl;

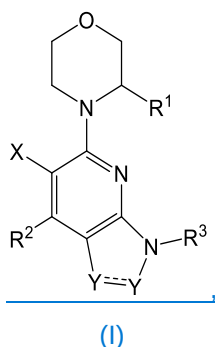
R^{5B} is hydroxyl, optionally substituted C₁₋₆ alkyl, optionally substituted C₆₋₁₀ aryl, optionally substituted C₁₋₉ heteroaryl, -N(R⁵)₂, -CON(R⁶)₂, -SO₂N(R⁶)₂, -SO₂R^{5A}, or optionally substituted alkoxy;

- each R⁶ is independently hydrogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkoxyalkyl, optionally substituted C₆₋₁₀ aryl C₁₋₆ alkyl, optionally substituted C₆₋₁₀ aryl, optionally substituted C₃₋₈ cycloalkyl, or optionally substituted C₁₋₉ heteroaryl; or both R⁶, together with the atom to which they are attached, combine to form an optionally substituted C₂₋₉ heterocyclyl;

- Q is optionally substituted C₂₋₉ heterocyclylene, optionally substituted C₃₋₈ cycloalkylene, optionally substituted C₁₋₉ heteroarylene, or optionally substituted C₆₋₁₀ arylene; and

X is hydrogen or halogen.

In one aspect, the disclosure refers to a compound of formula (I):

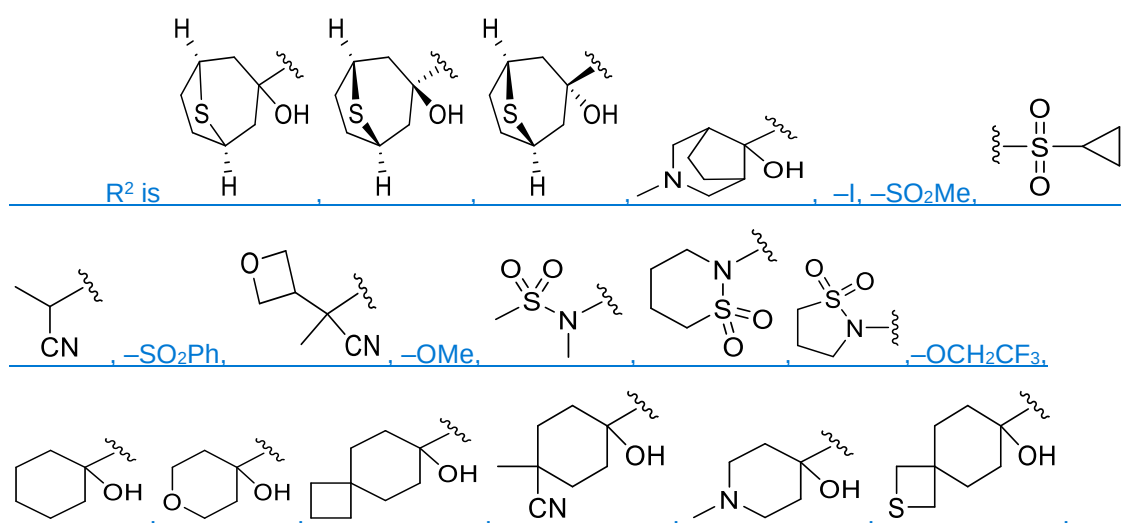


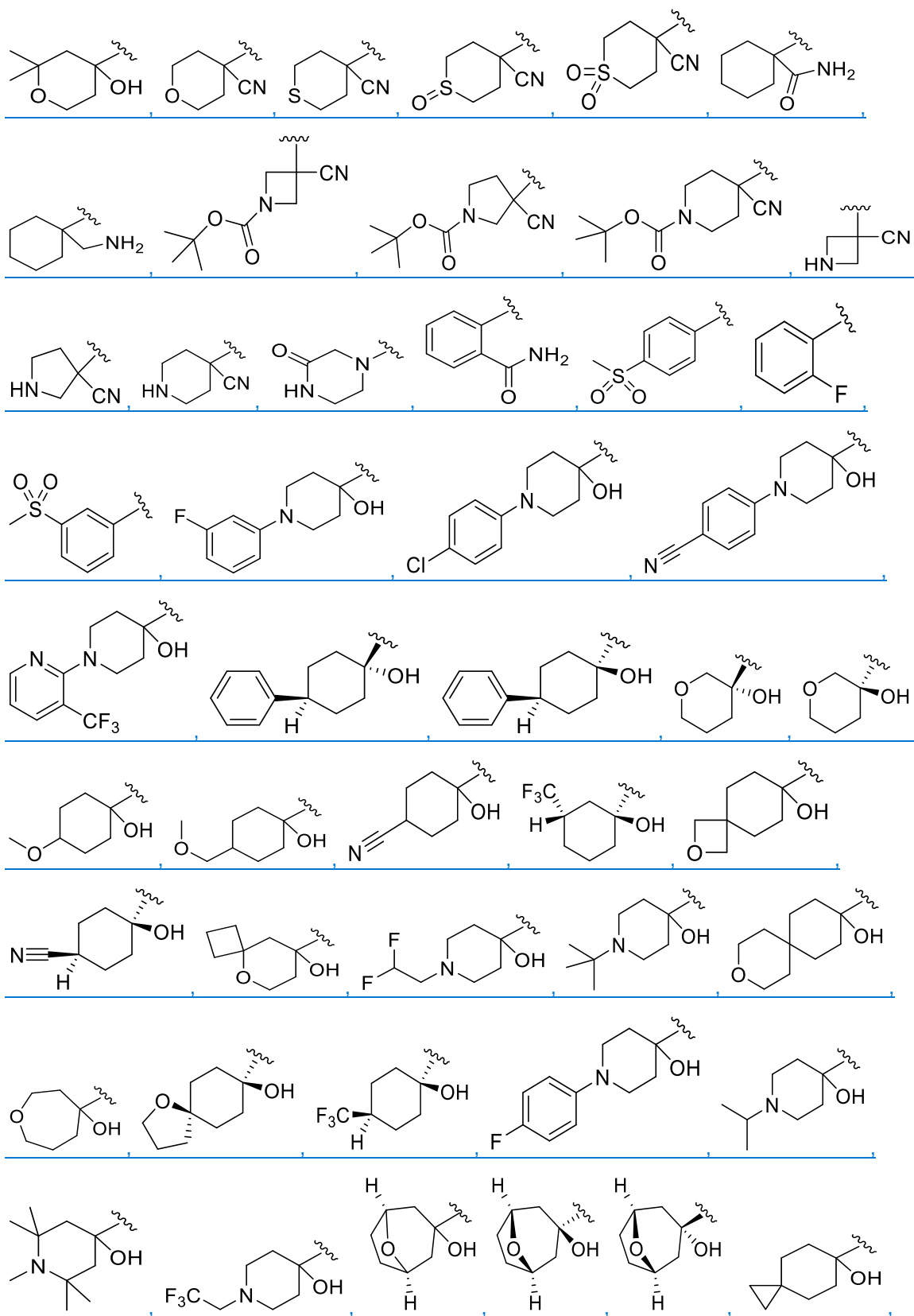
or a pharmaceutically acceptable salt thereof,

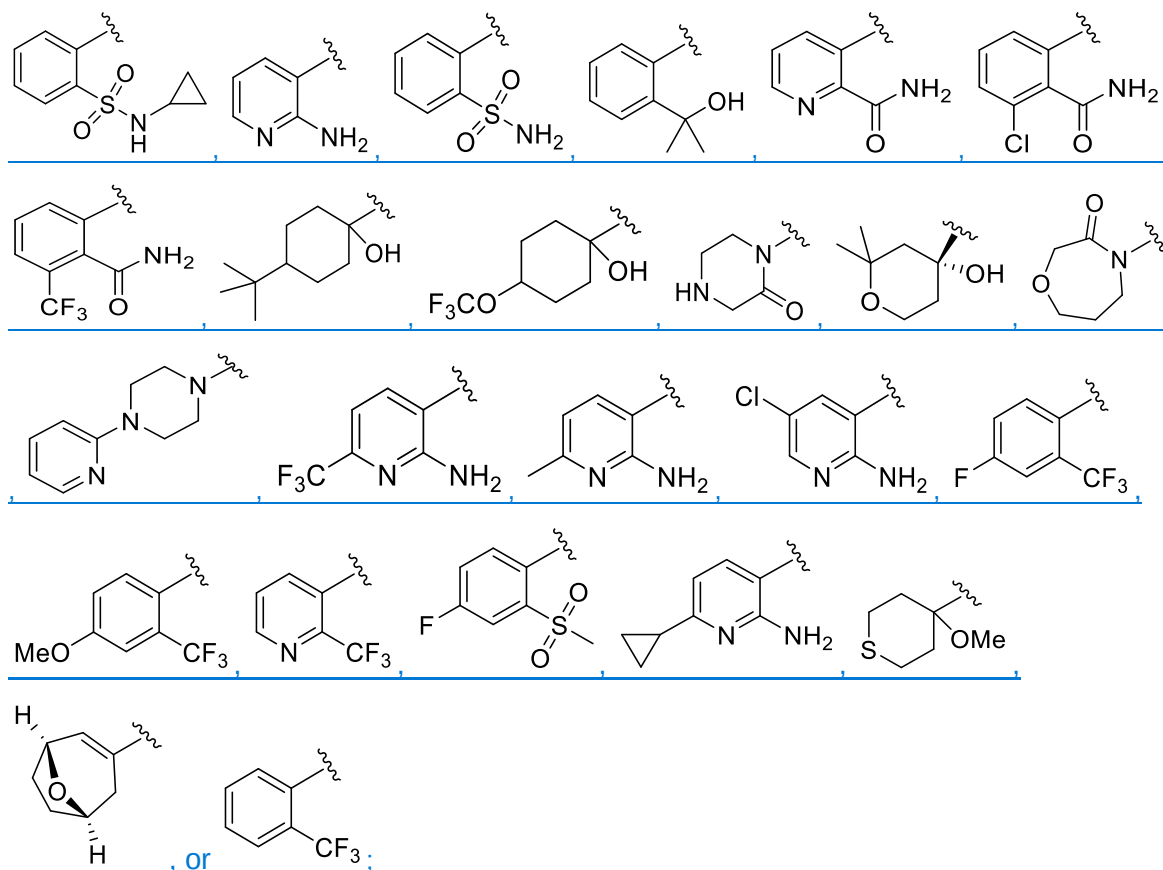
wherein

===== is a double bond, and each Y is independently N or CR⁴; or ----- is a single bond, and each Y is independently NR^Y, carbonyl, or C(R^Y)₂; wherein each R^Y is independently H or optionally substituted C₁₋₆ alkyl;

R¹ is optionally substituted C₁₋₆ alkyl or H;







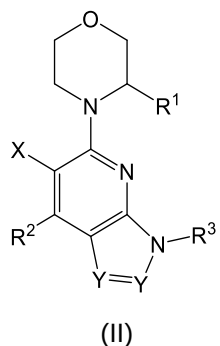
R³ is optionally substituted C₁₋₉ heteroaryl or optionally substituted C₁₋₉ heteroaryl C₁₋₆ alkyl;

each R⁴ is independently hydrogen, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, or optionally substituted C₂₋₆ alkynyl; and

X is hydrogen or halogen.

In some embodiments, ===== is a double bond. In some embodiments, ----- is a single bond.

In some embodiments, the compound is a compound of formula (II):



or a pharmaceutically acceptable salt thereof,
where

each Y is independently N or CR⁴; and the remaining variables are as described for formula (I).

In some [examples](#) ~~embodiments~~, in the compound of formula (I) or (II):

5 each Y is independently N or CR⁴;

R¹ is H or optionally substituted C₁₋₆ alkyl;

R² is optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted C₂₋₉ heterocyclyl, optionally substituted C₆₋₁₀ aryl, optionally substituted C₁₋₉ heteroaryl, optionally substituted C₁₋₉ heteroaryl C₁₋₆ alkyl, -N(R⁵)₂, -CON(R⁶)₂, -SO₂N(R⁶)₂, or -SO₂R^{5A};

10 R³ is optionally substituted C₁₋₉ heteroaryl;

each R⁴ is independently hydrogen or optionally substituted C₁₋₆ alkyl;

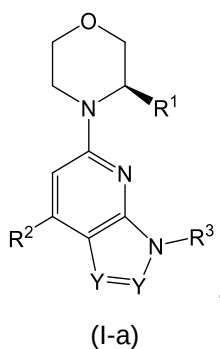
each R⁵ is independently hydrogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₆₋₁₀ aryl C₁₋₆ alkyl, optionally substituted C₆₋₁₀ aryl, optionally substituted C₁₋₉ heteroaryl, or –

SO₂R^{5A}; or both R⁵, together with the atom to which they are attached, combine to form an optionally substituted C₂₋₉ heterocyclyl;

each R^{5A} is independently optionally substituted C₁₋₆ alkyl or optionally substituted C₃₋₈ cycloalkyl; and

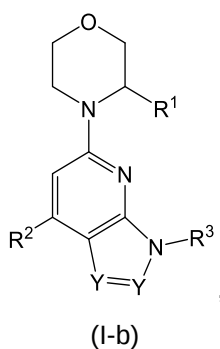
- 5 each R⁶ is independently hydrogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₆₋₁₀ aryl C₁₋₆ alkyl, optionally substituted C₆₋₁₀ aryl, or optionally substituted C₁₋₉ heteroaryl; or both R⁶, together with the atom to which they are attached, combine to form an optionally substituted C₂₋₉ heterocyclyl.

In some [example embodiments](#), the compound is a compound of formula (I-a):



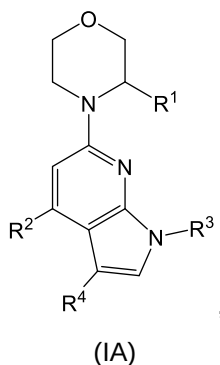
or a pharmaceutically acceptable salt thereof, where all variables are as described herein.

In some [example embodiments](#), the compound is a compound of formula (I-b):



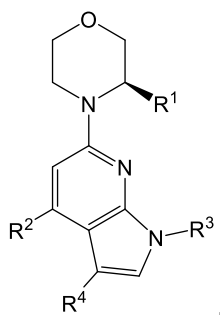
or a pharmaceutically acceptable salt thereof, where all variables are as described herein.

In some [example embodiments](#), the compound is a compound of formula (IA):



or a pharmaceutically acceptable salt thereof, where all variables are as described herein.

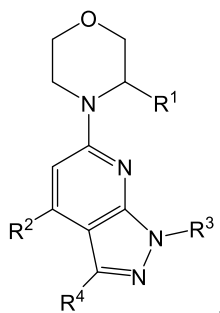
In some [example embodiments](#), the compound is a compound of formula (IA-a):



(IA-a)

or a pharmaceutically acceptable salt thereof, where all variables are as described herein.

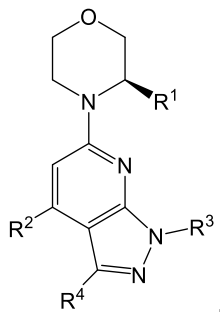
In some [example embodiments](#), the compound is a compound of formula (IB):



(IB)

or a pharmaceutically acceptable salt thereof, where all variables are as described herein.

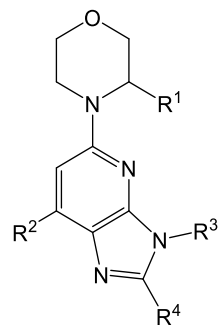
In some [example embodiments](#), the compound is a compound of formula (IB-a):



(IB-a)

or a pharmaceutically acceptable salt thereof, where all variables are as described herein.

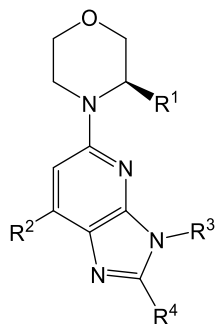
In some [example embodiments](#), the compound is a compound of formula (IC):



(IC)

or a pharmaceutically acceptable salt thereof, where all variables are as described herein.

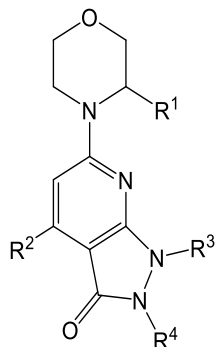
In some [example embodiments](#), the compound is a compound of formula (IC-a):



(IC-a)

5 or a pharmaceutically acceptable salt thereof, where all variables are as described herein.

In some [example embodiments](#), the compound is a compound of formula (ID):

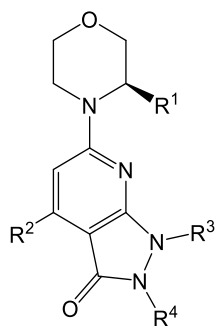


(ID)

or a pharmaceutically acceptable salt thereof, where all variables are as described herein.

10

In some [example embodiments](#), the compound is a compound of formula (ID-a):



(ID-a)

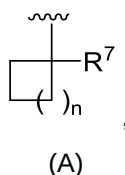
or a pharmaceutically acceptable salt thereof, where all variables are as described herein.

15 In some [example embodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R¹ is methyl.

In some [example embodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R² is optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted C₂₋₉ heterocyclyl, optionally substituted C₆₋₁₀ aryl, optionally substituted C₁₋₉

heteroaryl, optionally substituted C₁₋₉ heteroaryl C₁₋₆ alkyl, -N(R⁵)₂, -CON(R⁶)₂, -SO₂N(R⁶)₂, or -SO₂R^{5A}.

In some [examplesembodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R² is optionally substituted C₃₋₈ cycloalkyl. In some [examplesembodiments](#), R² is a group of formula (A):

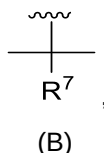


where

n is 0, 1, 2, or 3; and

R⁷ is hydrogen, alkylsulfonyl, cyano, -CON(R^A)₂, -SON(R^A)₂, optionally substituted C₁₋₉ heteroaryl, hydroxy, or alkoxy, where each R^A is independently H or alkyl; or both R^A, together with the atom to which they are attached, combine to form C₂₋₉ heterocyclyl.

In some [examplesembodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R² is a group of formula (B):



where R⁷ is hydrogen, alkylsulfonyl, cyano, -CON(R^A)₂, -SON(R^A)₂, optionally substituted C₁₋₉ heteroaryl, hydroxy, or alkoxy, where each R^A is independently H or alkyl; or both R^A, together with the atom to which they are attached, combine to form C₂₋₉ heterocyclyl.

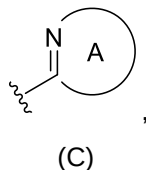
In some [examplesembodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R² is optionally substituted non-aromatic C₂₋₉ heterocyclyl. In some [examplesembodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R² is optionally substituted, non-aromatic, bridged C₂₋₉ heterocyclyl. In some [examplesembodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R² is optionally substituted, non-aromatic, spiro C₂₋₉ heterocyclyl.

In some [examplesembodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R² is -Q-R^{5B}. In some [examplesembodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), Q is optionally substituted C₂₋₉ heterocyclylene. In some [examplesembodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R^{5B} is hydroxyl.

In some [examplesembodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R² is:

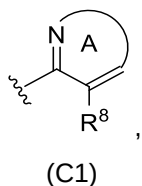
(IB-a), (IC), (IC-a), (ID), and (ID-a), R³ is optionally substituted, monocyclic C₁₋₉ heteroaryl including two nitrogen atoms. In

some [example embodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R³ is a group of formula (C):



5 where A is optionally substituted, monocyclic C₁₋₉ heteroaryl ring.

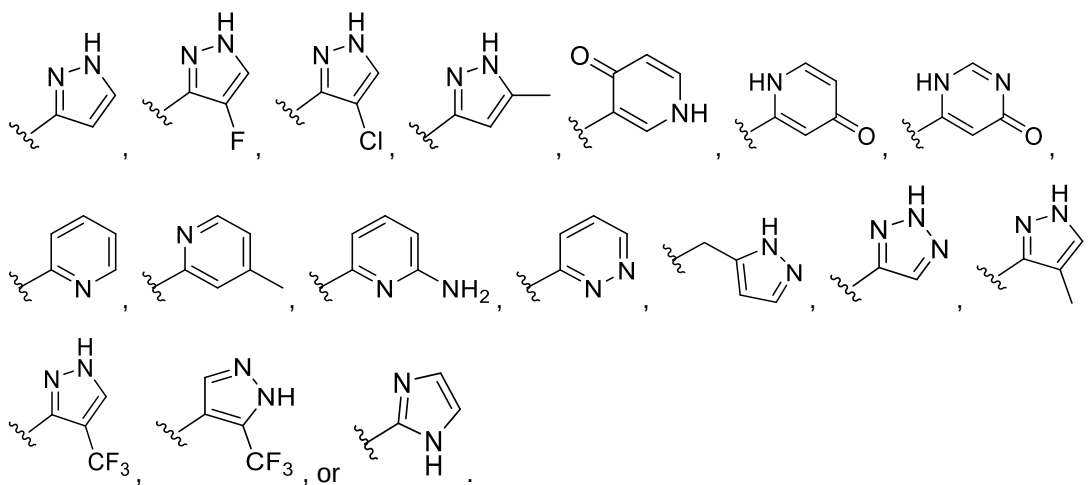
In some [example embodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R³ is a group of formula (C1):



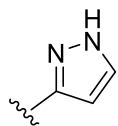
10 where R⁸ is hydrogen, halogen, or optionally substituted C₁₋₆ alkyl.

In some [example embodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), A is optionally substituted, monocyclic C₁₋₉ heteroaryl ring including two nitrogen atoms.

In some [example embodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R³ is:



In some [example embodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R³ is:



In some [example embodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), R⁴ is hydrogen.

In some [example embodiments](#) of any of formulas (I), (II), (IA), (IA-a), (IB), (IB-a), (IC), (IC-a), (ID), and (ID-a), X is hydrogen.

In some [example embodiments](#), the compound is selected from the group consisting of compounds 1-152 (e.g., compounds 1-140) and pharmaceutically acceptable salts thereof (e.g., the compound is selected from the group consisting of: 1, 2, 3, 4, 5, 6, 7, 8, 43, 45, 47, 48, 49, 52, 53, 55, 57, 58, 59, 61, 62, 63, 73, 74, 77, 80, 81, 82, 84, 86, 87, 92, 93, 94, 95, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 118, 119, 120, 121, 122, 123, 125, 126, 127, 128, 129, 130, 131, 132, 133, 135, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 150, 151, and pharmaceutically acceptable salts thereof).

[In yet another aspect, the disclosure refers to a compound selected from the group consisting of compounds 42-152 and pharmaceutically acceptable salts thereof.](#)

In another [example aspect](#), the [disclosure invention](#) provides a pharmaceutical composition including the compound of the [disclosure invention](#) and a pharmaceutically acceptable excipient. [In yet another aspect, the disclosure refers to a pharmaceutical composition comprising the compound as defined above and a pharmaceutically acceptable excipient.](#) In some [example embodiments](#), the compound of the [disclosure invention](#) is isotopically enriched in deuterium.

In a further [example aspect](#), the [disclosure invention](#) provides a method of inhibiting ATR kinase in a cell expressing ATR kinase by contacting the cell with the compound of the [disclosure invention](#). [In yet another aspect, the disclosure refers to a method of inhibiting ATR kinase in a cell expressing ATR kinase, the method comprising contacting the cell with the compound as defined above.](#)

In some [example embodiments](#), the cell is *in vitro*. In some [example embodiments](#), the cell is in a subject.

In a yet further [example aspect](#), the [disclosure invention](#) provides a method of treating a subject in need thereof including administering to the subject an effective amount of the compound of the [disclosure invention](#) or the pharmaceutical composition of the [disclosure invention](#). [In yet another aspect, the disclosure refers to a compound as defined above for use as a medicament.](#)

In some [example embodiments](#), the subject is suffering from, and is in need of a treatment for, a disease or condition having the symptom of cell hyperproliferation (e.g., the disease or condition is a cancer or pre-malignant or pre-cancerous condition). [In yet another aspect, the disclosure refers to use of the compound as defined above in the manufacture of a medicament for a treatment, a disease or condition having the symptom of cell hyperproliferation.](#) In some [example embodiments](#), the cancer is a carcinoma, sarcoma, adenocarcinoma, leukemia, or melanoma.

In some [example embodiments](#), the cancer is a carcinoma selected from the group consisting of medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatousum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma,

cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniformi carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma

myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhus carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberos carcinoma, verrucous carcinoma, and carcinoma villosum.

10 In some [examples](#), the cancer is a sarcoma selected from the group consisting of chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abernethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial
15 sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, and telangiectatic
20 sarcoma.

In some [examples](#), the cancer is a leukemia selected from the group consisting of nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemetic leukemia, basophilic leukemia, blast cell leukemia, bovine
25 leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia,
30 myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, and undifferentiated cell leukemia.

In some [examples](#), the cancer is a melanoma selected from the group
35 consisting of acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungual melanoma, and superficial spreading melanoma.

In some [exampleembeddings](#), the cancer is prostate cancer, thyroid cancer, endocrine system cancer, brain cancer, breast cancer, cervix cancer, colon cancer, head & neck cancer, liver cancer,

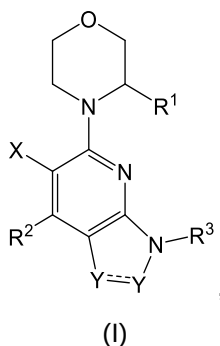
kidney cancer, lung cancer, non-small cell lung cancer, melanoma, mesothelioma, ovarian cancer, sarcoma, stomach cancer, uterus cancer, medulloblastoma, ampullary cancer, colorectal cancer, or pancreatic cancer.

In some [examples](#), the cancer is Hodgkin's disease, Non-Hodgkin's lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulinoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphoma, thyroid cancer, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

In some [examples](#), the subject is suffering from, and is in need of a treatment for, a pre-malignant condition.

The invention is also described by the following enumerated items.

1. A compound of formula (I):



or a pharmaceutically acceptable salt thereof,

where

===== is a double bond, and each Y is independently N or CR⁴; or ===== is a single bond, and each Y is independently NR^Y, carbonyl, or C(R^Y)₂; where each R^Y is independently H or optionally substituted C₁₋₆ alkyl;

R¹ is optionally substituted C₁₋₆ alkyl or H;

R² is optionally substituted C₂₋₉ heterocyclyl, optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted C₂₋₉ heterocyclyl C₁₋₆ alkyl, optionally substituted C₆₋₁₀ aryl, optionally substituted C₁₋₉ heteroaryl, optionally substituted C₁₋₉ heteroaryl C₁₋₆ alkyl, halogen, -N(R⁵)₂, -OR⁵, -CON(R⁶)₂, -SO₂N(R⁶)₂, -SO₂R^{5A}, or -Q-R^{5B};

R³ is optionally substituted C₁₋₉ heteroaryl or optionally substituted C₁₋₉ heteroaryl C₁₋₆ alkyl;

each R⁴ is independently hydrogen, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, or optionally substituted C₂₋₆ alkynyl;