(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
04 May 2023 (04.05.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/076485 A1

(51) International Patent Classification:
A61K 31/437 (2006.01) *A61K 31/519* (2006.01)
A61K 31/497 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US2022/048037

(22) International Filing Date:
27 October 2022 (27.10.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/263,224 28 October 2021 (28.10.2021) US

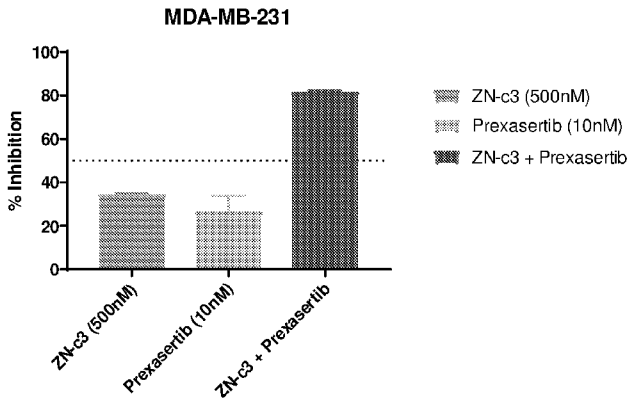
(71) Applicant: **RECURIUM IP HOLDINGS, LLC** [US/US]; 10275 Science Center Drive, Suite 200, San Diego, California 92121 (US).

(72) Inventors: **DONATE, Fernando**; 10275 Science Center Drive, Suite 200, San Diego, California 92121 (US). **ESCOUBET, Laure**; 10275 Science Center Drive, Suite 200, San Diego, California 92121 (US). **DE JONG, Petrus, Rudolf**; 10275 Science Center Drive, Suite 200, San Diego, California 92121 (US). **IZADI, Hooman**; 10275 Science Center Drive, Suite 200, San Diego, California 92121 (US). **SAMATAR, Ahmed, Abdi**; 10275 Science Center Drive, Suite 200, San Diego, California 92121 (US). **BOREN, Brant, Clayton**; 10275 Science Center Drive, Suite 200, San Diego, California 92121 (US). **BUNKER, Kevin, Duane**; 10275 Science Center Drive, Suite 200, San Diego, California 92121 (US). **HUANG, Peter, Qinhua**; 10275 Science Center Drive, Suite 200, San Diego, California 92121 (US).

(74) Agent: **MILLER, Kimberly, J.**; KNOBBE, MARTENS, OLSON & BEAR, LLP , 2040 Main Street , 14th Floor, Irvine, California 92614 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(54) Title: COMBINATION THERAPIES COMPRISING WEE1 INHIBITORS AND DNA DAMAGE RESPONSE (DDR) INHIBITORS



Cell line	MDA-MB-231
	% inhibition
ZN-c3	35
Prexasertib	26
Prexasertib + ZN-c3	81

FIG. 1

(57) Abstract: Disclosed herein are combinations of compounds for treating diseases or conditions such as cancer. The combinations include a WEE1 inhibitor and a DDR inhibitor such as an ATR, ATM or CHK1 inhibitor.

WO 2023/076485 A1

[Continued on next page]

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

COMBINATION THERAPIES COMPRISING WEE1 INHIBITORS AND DNA DAMAGE RESPONSE (DDR) INHIBITORS

INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] Any and all applications for which a foreign or domestic priority claim is identified, for example, in the Application Data Sheet or Request as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57, and Rules 4.18 and 20.6, including U.S. Provisional Application No. 63/263,224, filed October 28, 2021, which is incorporated by reference in its entirety.

Field

[0002] The present application relates to the fields of chemistry, biochemistry and medicine. More particularly, disclosed herein are combination therapies, and methods of treating diseases and/or conditions with combination therapies described herein.

Description

[0003] Cancers are a family of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body. Cancer treatments today include surgery, hormone therapy, radiation, chemotherapy, immunotherapy, targeted therapy and combinations thereof. Survival rates vary by cancer type and by the stage at which the cancer is diagnosed. In 2021, roughly 1.9 million people will be diagnosed with cancer, and an estimated 600,000 people will die of cancer in the United States. Thus, there still exists a need for effective cancer treatments.

SUMMARY

[0004] Some embodiments described herein relate to a combination of compounds that can include an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof, and an effective amount of Compound (B), or a pharmaceutically acceptable salt of any of the foregoing. Other embodiments described herein relate to a combination of compounds that can include an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof, an effective amount of Compound (B), or a

pharmaceutically acceptable salt thereof, and an effective amount of Compound (C), or a pharmaceutically acceptable salt thereof.

[0005] Some embodiments described herein relate to the use of a combination of compounds for treating a disease or condition, wherein the combination includes an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof, and an effective amount of Compound (B), or a pharmaceutically acceptable salt of thereof. Other embodiments described herein relate to the use of a combination of compounds in the manufacture of a medicament for treating a disease or condition, wherein the combination includes an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof, and an effective amount of Compound (B), or a pharmaceutically acceptable salt thereof. Still other embodiments described herein relate to the use of a combination of compounds in a method for treating a disease or condition, wherein the combination includes an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof, and an effective amount of Compound (B), or a pharmaceutically acceptable salt thereof.

[0006] Some embodiments described herein relate to the use of a combination of compounds for treating a disease or condition, wherein the combination includes an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof, an effective amount of Compound (B), or a pharmaceutically acceptable salt of thereof, and an effective amount of Compound (C), or a pharmaceutically acceptable salt of thereof. Other embodiments described herein relate to the use of a combination of compounds in the manufacture of a medicament for treating a disease or condition, wherein the combination includes an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof, an effective amount of Compound (B), or a pharmaceutically acceptable salt thereof, and an effective amount of Compound (C), or a pharmaceutically acceptable salt of thereof. Still other embodiments described herein relate to the use of a combination of compounds in a method for treating a disease or condition, wherein the combination includes an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof, an effective amount of Compound (B), or a pharmaceutically acceptable salt thereof, and an effective amount of Compound (C), or a pharmaceutically acceptable salt of thereof.

[0007] In some embodiments, the disease or condition can be a cancer described herein.

DRAWINGS

[0008] FIG. 1 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3) and a CHK1 inhibitor (Prexasertib) in a MDA-MB-231 (TNBC) cell line. The results show that single agent activity was observed with both ZN-c3 and Prexasertib, and that, surprisingly, the combination resulted in synergistic activity.

[0009] FIG. 2 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3) and an ATR inhibitor (Berzosertib) in a MDA-MB-231 (TNBC) cell line. The results show that single agent activity was observed with both ZN-c3 and Berzosertib, and that, surprisingly, the combination resulted in synergistic activity.

[0010] FIG. 3 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3) and a CHK1 inhibitor (Prexasertib) in a H23 (NSCLC) cell line. The results show that single agent activity was observed with ZN-c3 and practically no activity with Prexasertib, and that, surprisingly, the combination resulted in synergistic activity.

[0011] FIG. 4 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3) and an ATR inhibitor (Berzosertib) in a H23 (NSCLC) cell line. The results show that single agent activity was observed with both ZN-c3 and Berzosertib, and that, surprisingly, the combination resulted in synergistic activity.

[0012] FIG. 5 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3) and a CHK1 inhibitor (Prexasertib) in a MV4-11 (AML) cell line. The results show that single agent activity was observed with ZN-c3 and no activity with Prexasertib, and that, surprisingly, the combination resulted in synergistic activity.

[0013] FIG. 6 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3) and an ATM inhibitor (AZD0156) in a MV4-11 (AML) cell line. The results show that single agent activity was observed with both ZN-c3 and AZD0156, and that, surprisingly, the combination resulted in synergistic activity.

[0014] FIG. 7 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3) and a CHK1 inhibitor (Prexasertib) in a THP-1 (AML) cell line. The results show that single agent activity was observed with both ZN-c3 and AZD0156, and that, surprisingly, the combination resulted in synergistic activity.

[0015] FIG. 8 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3) and an ATR inhibitor (Berzosertib) in a THP-1 (AML) cell line. The results show that single agent activity was observed with both ZN-c3 and AZD0156, and that, surprisingly, the combination resulted in synergistic activity.

[0016] FIG. 9 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3) and a CHK1 inhibitor (Prexasertib) in an HL-60 (AML) cell line. The results show that single agent activity was observed with ZN-c3 and no activity with Prexasertib, and that, surprisingly, the combination resulted in synergistic activity.

[0017] FIG. 10 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3) and an ATM inhibitor (AZD0156) in an HL-60 (AML) cell line. The results show that single agent activity was observed with ZN-c3 and practically no activity with AZD0156, and that, surprisingly, the combination resulted in synergistic activity.

[0018] FIG. 11 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3) and an ATR inhibitor (Berzosertib) in an HL-60 (AML) cell line. The results show that single agent activity was observed with both ZN-c3 and Berzosertib, and that, surprisingly, the combination resulted in synergistic activity.

[0019] FIG. 12 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3) and a CHK1 inhibitor (Prexasertib) in a LNCaP (Prostate) cell line. The results show that single agent activity was observed with both ZN-c3 and Prexasertib, and that, surprisingly, the combination resulted in synergistic activity.

[0020] FIG. 13 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3) and an ATM inhibitor (AZD0156) in a LNCaP (Prostate) cell line. The results show that single agent activity was observed with both ZN-c3 and AZD0156, and that, surprisingly, the combination resulted in synergistic activity.

[0021] FIG. 14 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3), a Bcl-2 inhibitor (Zn-d5) and a CHK1 inhibitor (Prexasertib) in a MV4-11 (AML) cell line.

[0022] FIG. 15 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3), a Bcl-2 inhibitor (Zn-d5) and an ATM inhibitor (AZD0156) in a MV4-11 (AML) cell line.

[0023] FIG. 16 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3), a Bcl-2 inhibitor (Zn-d5) and an ATR inhibitor (Berzosertib) in a MV4-11 (AML) cell line.

[0024] FIG. 17 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3), a Bcl-2 inhibitor (Zn-d5) and a CHK1 inhibitor (Prexasertib) in a THP-1 (AML) cell line.

[0025] FIG. 18 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3), a Bcl-2 inhibitor (Zn-d5) and an ATM inhibitor (AZD0156) in a THP-1 (AML) cell line.

[0026] FIG. 19 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3), a Bcl-2 inhibitor (Zn-d5) and an ATR inhibitor (Berzosertib) in a THP-1 (AML) cell line.

[0027] FIG. 20 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3), a Bcl-2 inhibitor (Zn-d5) and a CHK1 inhibitor (Prexasertib) in an HL-60 (AML) cell line.

[0028] FIG. 21 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3), a Bcl-2 inhibitor (Zn-d5) and an ATM inhibitor (AZD0156) in an HL-60 (AML) cell line.

[0029] FIG. 22 illustrates representative assay data obtained for a WEE1 inhibitor (ZN-c3), a Bcl-2 inhibitor (Zn-d5) and an ATR inhibitor (Berzosertib) in an HL-60 (AML) cell line.

[0030] FIG. 23 illustrates chemical structures of examples of WEE1 inhibitors.

DETAILED DESCRIPTION

Definitions

[0031] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0032] The term "pharmaceutically acceptable salt" refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), a sulfuric acid, a nitric acid and a phosphoric acid (such as 2,3-dihydroxypropyl dihydrogen phosphate). Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluensulfonic, trifluoroacetic, benzoic, salicylic, 2-oxopentanedioic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium, a potassium or a lithium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of a carbonate, a salt of a bicarbonate, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine and salts with amino acids such as arginine and lysine. Those skilled in the art understand that when a salt is formed by protonation of a nitrogen-based group (for example, NH_2), the nitrogen-based group can be associated with a positive charge (for example, NH_2 can become NH_3^+) and the positive charge can be balanced by a negatively charged counterion (such as Cl^-).

[0033] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched or a stereoisomeric mixture. In addition, it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof. Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included.

[0034] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

[0035] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0036] It is understood that the methods and combinations described herein include crystalline forms (also known as polymorphs, which include the different crystal packing arrangements of the same elemental composition of a compound), amorphous phases, salts, solvates and hydrates. In some embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol or the like. In other embodiments, the compounds described herein exist in unsolvated form. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol or the like. Hydrates are formed when the solvent is water or alcoholates are formed when the solvent is alcohol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[0037] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

[0038] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as

open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' 'including but not limited to,' or the like; the term 'comprising' as used herein is synonymous with 'including,' 'containing,' or 'characterized by,' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term 'having' should be interpreted as 'having at least;' the term 'includes' should be interpreted as 'includes but is not limited to;' the term 'example' is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof; and use of terms like 'preferably,' 'preferred,' 'desired,' or 'desirable,' and words of similar meaning should not be understood as implying that certain features are critical, essential, or even important to the structure or function, but instead as merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment. In addition, the term "comprising" is to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a compound, composition or device, the term "comprising" means that the compound, composition or device includes at least the recited features or components but may also include additional features or components.

[0039] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article "a" or "an" does not exclude a plurality. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

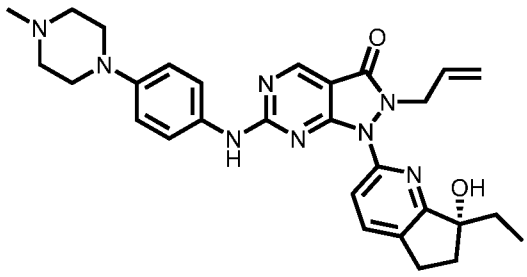
Compounds

[0040] Some embodiments disclosed herein relate to the use of a combination of compounds for treating a disease or condition, wherein the combination can include an effective amount of Compound (A), or a pharmaceutically acceptable salt thereof, and an effective amount of Compound (B), or a pharmaceutically acceptable salt of any of the foregoing, wherein Compound (A) is a WEE1 inhibitor; and Compound (B) is a DNA

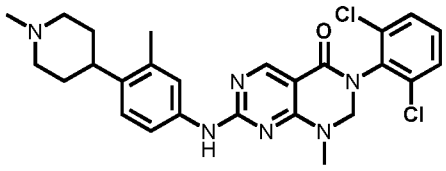
damage response (DDR) inhibitor selected from an inhibitor of ataxia telangiectasia and Rad3-related protein kinase ("ATR inhibitor" or "ATRi"), an inhibitor of ataxia telangiectasia mutated kinase ("ATM inhibitor" or "ATMi"), and an inhibitor of Checkpoint Kinase 1 ("CHK1 inhibitor" or "CHKi").

[0041] Examples of suitable WEE1 inhibitors for Compound (A) include those described in the following publications: WO 2019/074979, WO 2020/210383, WO 2020/210375, WO 2020/210377, WO 2020/210380, WO 2020/210381, WO 2022/082174, U.S. 2022/0162229, U.S. 2022/0168313, U.S. 2022/0169646, U.S. 2022/0220115, U.S. 11,332,473, WO 2019/173082, WO 2019/011228, WO 2019/138227, WO 2018/162932, WO 2018/011570, WO 2018/011569, US 2022/0194947, WO 2018/090939, WO 2015/092431, WO 2015/019037, WO 2014/167347, WO 2007/126122, WO 2011/034743, U.S. 2007/0254892, WO 2008/133866, U.S. 2016/0060258, U.S. 2019/0308984, U.S. 2020/0131192, WO 2021/073491, US 11,345,710, US 11,345,711 WO 2019/085933, WO 2020/221358, EP 3712150, WO 2018/133829, WO 2021/047627, US 2021/0403451, WO 2020/083404, WO 2019/037678, WO 2018/171633, CN 113387962, WO 2019/165204, WO 2012/161812, WO 2013/012681, WO 2013/013031, WO 2013/059485, WO 2013/126656, U.S. 2012/0220572, U.S. 2013/0018045, KR 2016035878, KR 2020016567, WO 2018/056621, WO 2017/075629, WO 2019/169065, WO 2019/134539, WO 2020/028814, US 2021/0309630, WO 2020/069105, WO 2020/192581, U.S. 2022/0194960, CN 114831993, CN 111718348, WO 2022/188802, WO 96/34867, WO 2008/153207, WO 2010/067888, WO 2009/054332, WO 2021/073491, WO 2021/074251, CN 112142763, WO 2020/259724, U.S. 2022/0259210, WO 2019/096322, CN 112142747, CN 112142747, WO 2021/043152, WO2021/254389, WO 2022/171088, WO 2022/171126, WO 2022/171128, WO 2022/174765, WO 2022/174796, CN 112442049, CN 114072411, CN 113402520, CN113387962, KR 2022081171, WO 2022/124748, WO 2022/155202, CN 114591334 and WO 2021/074251..

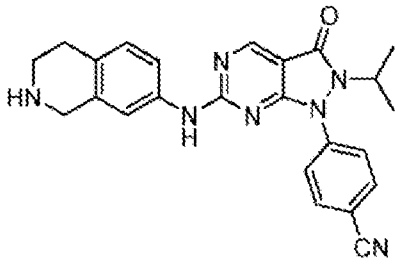
[0042] In some embodiments, the WEE1 inhibitor can be selected from AZD1775, SC0191, PD0166285, NUV-569, SDR-7995, SDR-7778, IMP7068, Debio 0123, SY-4835, SPH-6162 and ATRN-W1051, or any combination thereof. Further details regarding WEE1 inhibitors are provided in Figure 23. In other embodiments, the WEE1



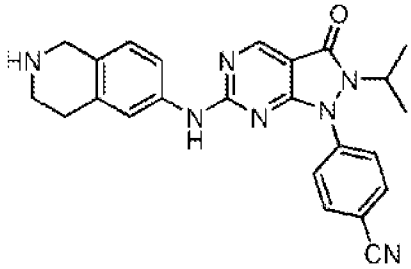
inhibitor can be (ZN-c3), or a pharmaceutically acceptable salt thereof. In still other embodiments, the WEE1 inhibitor can be



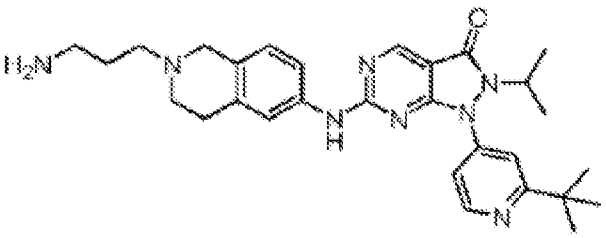
, or a pharmaceutically acceptable salt or N-oxide thereof. In yet still other embodiments, the WEE1 inhibitor can be selected from



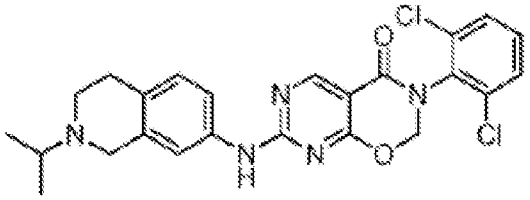
,



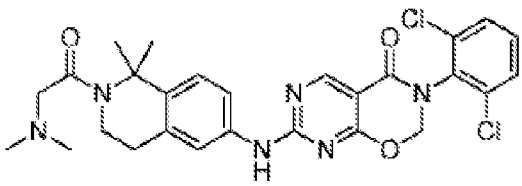
and



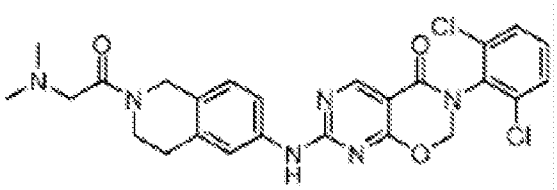
, or a pharmaceutically acceptable salt thereof of any of the foregoing. In some embodiments, the WEE1 inhibitor can be selected from



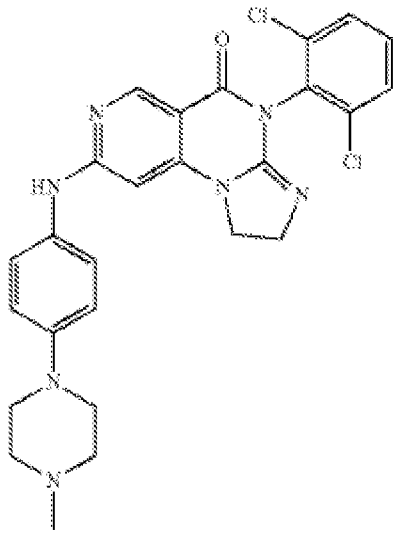
,



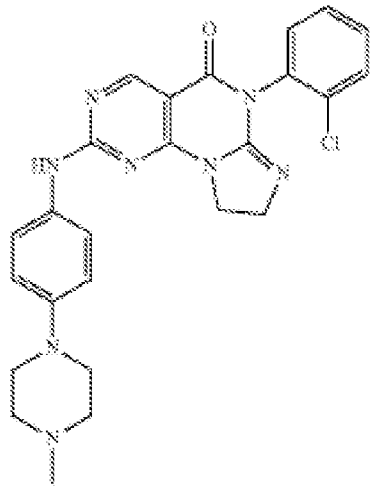
and



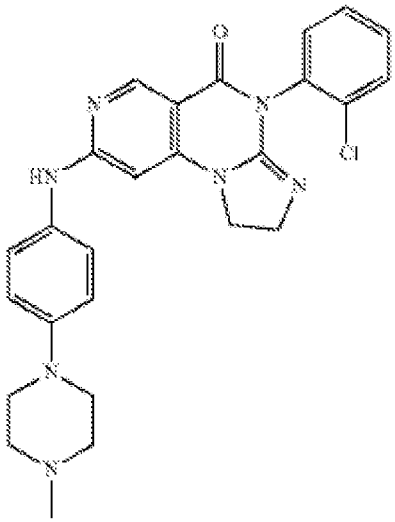
, or a pharmaceutically acceptable salt thereof of any of the foregoing. In other embodiments, the WEE1 inhibitor can be



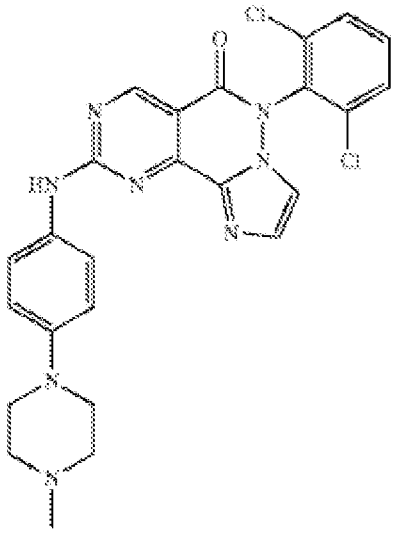
, or a pharmaceutically acceptable salt thereof. In still other embodiments, the WEE1 inhibitor can be selected from



,



and

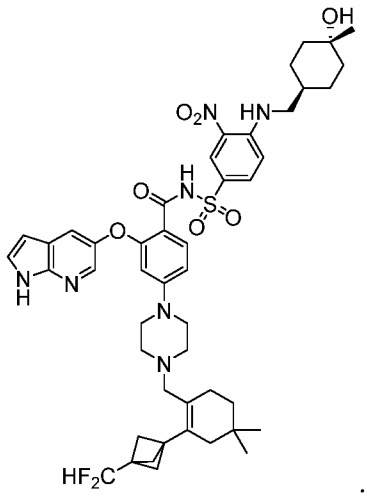


, or a pharmaceutically acceptable salt thereof of any of the foregoing.

[0043] Examples of ATR inhibitors include Gartisertib, Berzosertib, Ceralasertib, SchisandrinB, Elimusertib, NU6027, Dactolisib, ETP-46464, Torin 2, VE-821, AZ20, Camonsertib, CGK733, ART-0380, ATRN-119 and ATRN-212.

[0044] Examples of ATM inhibitors include AZD7648, AZD0156, AZ31, AZ32, AZD1390, KU55933, KU59403, KU60019, CP-466722, CGK733, NVP-BEZ235, SJ573017, AZ31, AZ32, AZD1390, SKLB-197, CGK733, M4076, M3541 and M4076.

[0045] Examples of CHK1 inhibitors include Prexasertib, AZD7762, Rabusertib, MK-8776, CCT245737, CCT244747, CHIR-124, PD 407824, PD-321852, PF-00477736, GDC-0425, GDC-0575, SB-218078, V158411, SAR-020106, XL-844, UCN-01, SOL-578, IMP 10 and CBP501.

[0046] A combination described herein can further include Compound (C), including pharmaceutically acceptable salts thereof, wherein Compound (C) can be a Bcl-2 inhibitor such as 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide. 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide, or a pharmaceutically acceptable salt thereof, can be prepared as provided in WO 2019/139899 and have the structure 

.

[0047] The order of administration of compounds in a combination described herein can vary. In some embodiments, Compound (A), including pharmaceutically acceptable salts thereof, can be administered prior to Compound (B), or a pharmaceutically

acceptable salt thereof. In other embodiments, Compound (A), including pharmaceutically acceptable salts thereof, can be administered concomitantly with Compound (B), or a pharmaceutically acceptable salt thereof. In still other embodiments, Compound (A), including pharmaceutically acceptable salts thereof, can be administered subsequent to the administration of Compound (B), or a pharmaceutically acceptable salt thereof. In some embodiments, when Compound (C), including pharmaceutically acceptable salts thereof, can be administered prior to both Compound (A) and Compound (B), including pharmaceutically acceptable salts of any of the foregoing. In other embodiments, when Compound (C), including pharmaceutically acceptable salts thereof, can be administered subsequent to both Compound (A) and Compound (B), including pharmaceutically acceptable salts of any of the foregoing. In still other embodiments, when Compound (C), including pharmaceutically acceptable salts thereof, can be administered prior to one of Compound (A), including pharmaceutically acceptable salts thereof, and subsequent to Compound (B), including pharmaceutically acceptable salts thereof. In yet still other embodiments, when Compound (C), including pharmaceutically acceptable salts thereof, can be administered prior to one of Compound (B), including pharmaceutically acceptable salts thereof, and subsequent to Compound (A), including pharmaceutically acceptable salts thereof.

[0048] There may be several advantages for using a combination of compounds described herein. For example, combining compounds that attack multiple pathways at the same time, can be more effective in treating a cancer, such as those described herein, compared to when the compounds of combination are used as monotherapy.

[0049] In some embodiments, a combination as described herein (such as Compound (A), including pharmaceutically acceptable salts thereof, and Compound (B), or pharmaceutically acceptable salts thereof, and Compound (A), including pharmaceutically acceptable salts thereof, Compound (B), or pharmaceutically acceptable salts thereof, and Compound (C), or pharmaceutically acceptable salts thereof), can decrease the number and/or severity of side effects that can be attributed to a compound described herein, such as Compound (B), or a pharmaceutically acceptable salt thereof.

[0050] Using a combination of compounds described herein can results in additive, synergistic or strongly synergistic effect. A combination of compounds described herein can result in an effect that is not antagonistic.

[0051] In some embodiments, a combination as described herein (such as Compound (A), including pharmaceutically acceptable salts thereof, and Compound (B), or pharmaceutically acceptable salts thereof, and Compound (A), including pharmaceutically acceptable salts thereof, Compound (B), or pharmaceutically acceptable salts thereof, and Compound (C), or pharmaceutically acceptable salts thereof), can result in an additive effect. In some embodiments, a combination as described herein (for example, Compound (A), including pharmaceutically acceptable salts thereof, and Compound (B), or pharmaceutically acceptable salts thereof, and Compound (A), including pharmaceutically acceptable salts thereof, Compound (B), or pharmaceutically acceptable salts thereof, and Compound (C), or pharmaceutically acceptable salts thereof), can result in a synergistic effect. In some embodiments, a combination as described herein (for example, Compound (A), including pharmaceutically acceptable salts thereof, and Compound (B), or pharmaceutically acceptable salts thereof, and Compound (A), including pharmaceutically acceptable salts thereof, Compound (B), or pharmaceutically acceptable salts thereof, and Compound (C), or pharmaceutically acceptable salts thereof), can result in a strongly synergistic effect. In some embodiments, a combination as described herein (such as Compound (A), including pharmaceutically acceptable salts thereof, and Compound (B), or pharmaceutically acceptable salts thereof, and Compound (A), including pharmaceutically acceptable salts thereof, Compound (B), or pharmaceutically acceptable salts thereof, and Compound (C), or pharmaceutically acceptable salts thereof), is not antagonistic.

[0052] As used herein, the term "antagonistic" means that the activity of the combination of compounds is less compared to the sum of the activities of the compounds in combination when the activity of each compound is determined individually (i.e., as a single compound). As used herein, the term "synergistic effect" means that the activity of the combination of compounds is greater than the sum of the individual activities of the compounds in the combination when the activity of each compound is determined individually. As used herein, the term "additive effect" means that the activity of the combination of compounds is about equal to the sum of the individual activities of the compounds in the combination when the activity of each compound is determined individually.

[0053] A potential advantage of utilizing a combination as described herein may be a reduction in the required amount(s) of the compound(s) that is effective in treating a disease condition disclosed herein compared to when each compound is administered as a monotherapy. For example, the amount of Compound (B), or a pharmaceutically acceptable salt thereof, used in a combination described herein can be less compared to the amount of Compound (B), or a pharmaceutically acceptable salt thereof, needed to achieve the same reduction in a disease marker (for example, tumor size) when administered as a monotherapy. Another potential advantage of utilizing a combination as described herein is that the use of two or more compounds having different mechanisms of action can create a higher barrier to the development of resistance compared to when a compound is administered as monotherapy. Additional advantages of utilizing a combination as described herein may include little to no cross resistance between the compounds of a combination described herein; different routes for elimination of the compounds of a combination described herein; and/or little to no overlapping toxicities between the compounds of a combination described herein.

Pharmaceutical Compositions

[0054] Compound (A), including pharmaceutically acceptable salts thereof, can be provided in a pharmaceutical composition. Likewise, Compound (B) and Compound (C), including pharmaceutically acceptable salts of any of the foregoing, can be provided in a pharmaceutical composition(s).

[0055] The term "pharmaceutical composition" refers to a mixture of one or more compounds and/or salts disclosed herein with other chemical components, such as diluents, carriers and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicylic acid. Pharmaceutical compositions will generally be tailored to the specific intended route of administration.

[0056] As used herein, a "carrier" refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl

sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

[0057] As used herein, a "diluent" refers to an ingredient in a pharmaceutical composition that lacks appreciable pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture and/or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the pH and isotonicity of human blood.

[0058] As used herein, an "excipient" refers to an essentially inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability etc., to the composition. For example, stabilizers such as antioxidants and metal-chelating agents are excipients. In an embodiment, the pharmaceutical composition comprises an antioxidant and/or a metal-chelating agent. A "diluent" is a type of excipient.

[0059] In some embodiments, Compound (B), along with pharmaceutically acceptable salts thereof, can be provided in a pharmaceutical composition that includes Compound (A), including pharmaceutically acceptable salts thereof. In other embodiments, Compound (B), along with pharmaceutically acceptable salts thereof, can be administered in a pharmaceutical composition that is separate from a pharmaceutical composition that includes Compound (A), including pharmaceutically acceptable salts thereof. When Compound (C), including pharmaceutically acceptable salts thereof, is included, Compound (C), including pharmaceutically acceptable salts thereof, can be provided in a pharmaceutical composition that includes Compound (A), along with pharmaceutically acceptable salts thereof, and/or Compound (B), along with pharmaceutically acceptable salts thereof. In other instances, Compound (C), including pharmaceutically acceptable salts thereof, can be provided in a separate pharmaceutical composition from Compound (A), along with pharmaceutically acceptable salts, and Compound (B), along with pharmaceutically acceptable salts.

[0060] The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other

active ingredients, as in combination therapy, or carriers, diluents, excipients or combinations thereof. Proper formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art.

[0061] The pharmaceutical compositions disclosed herein may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes. Additionally, the active ingredients are contained in an amount effective to achieve its intended purpose. Many of the compounds used in the pharmaceutical combinations disclosed herein may be provided as salts with pharmaceutically compatible counterions.

[0062] Multiple techniques of administering a compound, salt and/or composition exist in the art including, but not limited to, oral, rectal, pulmonary, topical, aerosol, injection, infusion and parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal and intraocular injections. In some embodiments, Compound (A), including pharmaceutically acceptable salts thereof, can be administered orally. In some embodiments, Compound (A), including pharmaceutically acceptable salts thereof, can be provided to a subject by the same route of administration as Compound (B), along with pharmaceutically acceptable salts thereof, and/or Compound (C), along with pharmaceutically acceptable salts thereof. In other embodiments, Compound (A), including pharmaceutically acceptable salts thereof, can be provided to a subject by a different route of administration as Compound (B), along with pharmaceutically acceptable salts thereof, and/or Compound (C), along with pharmaceutically acceptable salts thereof.

[0063] One may also administer the compound, salt and/or composition in a local rather than systemic manner, for example, via injection or implantation of the compound directly into the affected area, often in a depot or sustained release formulation. Furthermore, one may administer the compound in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ. For example, intranasal or pulmonary delivery to target a respiratory disease or condition may be desirable.

[0064] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions that can include a compound and/or salt described herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Uses and Methods of Treatment

[0065] As provided herein, in some embodiments, a combination of compounds that includes an effective amount of Compound (A), including pharmaceutically acceptable salts thereof, and an effective amount of Compound (B), or a pharmaceutically acceptable salt of any of the foregoing, can be used to treat a disease or condition. In some embodiments, a combination of compounds that includes an effective amount of Compound (A), including pharmaceutically acceptable salts thereof, an effective amount of Compound (B), including pharmaceutically acceptable salts thereof, and an effective amount of Compound (C), including pharmaceutically acceptable salts thereof, can be used to treat a disease or condition.

[0066] In some embodiments, the disease or condition can be selected from glioblastoma, astrocytoma, meningioma, craniopharyngioma, medulloblastoma, other brain cancers, head and neck cancer, leukemia, AML (Acute Myeloid Leukemia), CLL (Chronic lymphocytic leukemia), ALL (Acute Lymphocytic Leukemia), myelodysplastic syndromes (MDS), skin cancer, adrenal cancer, anal cancer, bile duct cancer, bladder cancer, bone cancer, breast cancer (for example, triple negative breast cancer), cervical cancer, colorectal cancer (such as colon adenocarcinoma), prostate cancer, endometrial cancer, esophagus cancer, eye cancer, gallbladder cancer, gastric cancer, gastrointestinal cancer, Hodgkin

lymphoma, Non-Hodgkin lymphoma, hematological tumor, Kaposi sarcoma, kidney cancer, laryngeal and hypopharyngeal cancer, liver cancer, lung cancer, non-small cell lung cancer, small cell, lung cancer, lymphoma, mesothelioma, melanoma, multiple myeloma, neuroblastoma, nasopharyngeal cancer, ovarian cancer, osteosarcoma, sarcomas, gastrointestinal stromal tumor (GIST), pancreatic cancer, pituitary cancer, retinoblastoma, salivary gland cancer, stomach cancer, small intestine cancer, testicular cancer, thymus cancer, thyroid cancer, uterine cancer, uterine sarcoma, uterine serous carcinoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, Wilms tumor, solid tumor and a liquid tumor. In some embodiments, the disease or condition can be leukemia, AML (Acute Myeloid Leukemia), CLL (Chronic lymphocytic leukemia) and/or ALL (Acute Lymphocytic Leukemia). In some embodiments, the disease or condition can be breast cancer such as triple negative breast cancer. In some embodiments, the disease or condition can be prostate cancer. In some embodiments, the disease or condition can be non-small cell lung cancer.

[0067] In some cases, following cancer treatment, a subject can relapse or have reoccurrence of the cancer. As used herein, the terms "relapse" and "reoccurrence" are used in their normal sense as understood by those skilled in the art. Thus, the cancer can be a recurrent cancer.

[0068] As used herein, a "subject" refers to an animal that is the object of treatment, observation or experiment. "Animal" includes cold- and warm-blooded vertebrates and invertebrates such as fish, shellfish, reptiles and, in particular, mammals. "Mammal" includes, without limitation, mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, horses, primates, such as monkeys, chimpanzees, and apes, and, in particular, humans. In some embodiments, the subject can be human. In some embodiments, the subject can be a child and/or an infant. In other embodiments, the subject can be an adult.

[0069] As used herein, the terms "treat," "treating," "treatment," "therapeutic," and "therapy" do not necessarily mean total cure or abolition of the disease or condition. Any alleviation of any undesired signs or symptoms of the disease or condition, to any extent can be considered treatment and/or therapy. Furthermore, treatment may include acts that may worsen the subject's overall feeling of well-being or appearance.

[0070] The term "effective amount" is used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response

indicated. For example, an effective amount of compound, salt or composition can be the amount needed to prevent, alleviate or ameliorate symptoms of the disease or condition, or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease or condition being treated. Determination of an effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0071] For example, an effective amount of a compound, or radiation, is the amount that results in: (a) the reduction, alleviation or disappearance of one or more symptoms caused by the cancer, (b) the reduction of tumor size, (c) the elimination of the tumor, and/or (d) long-term disease stabilization (growth arrest) of the tumor.

[0072] The amount of compound, salt and/or composition required for use in treatment will vary not only with the particular compound or salt selected but also with the route of administration, the nature and/or symptoms of the disease or condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician. In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free base. As will be understood by those of skill in the art, in certain situations it may be necessary to administer the compounds disclosed herein in amounts that exceed, or even far exceed, the dosage ranges described herein in order to effectively and aggressively treat particularly aggressive diseases or conditions.

[0073] As will be readily apparent to one skilled in the art, the useful *in vivo* dosage to be administered and the particular mode of administration will vary depending upon the age, weight, the severity of the affliction, the mammalian species treated, the particular compounds employed and the specific use for which these compounds are employed. The determination of effective dosage levels, that is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine methods, for example, human clinical trials, *in vivo* studies and *in vitro* studies. For example,

useful dosages of Compounds (A) and/or (B), or pharmaceutically acceptable salts of the foregoing, can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Such comparison can be done by comparison against an established drug, such as cisplatin and/or gemcitabine.

[0074] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vivo* and/or *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations. Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0075] It should be noted that the attending physician would know how to and when to terminate, interrupt or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administrated dose in the management of the disorder of interest will vary with the severity of the disease or condition to be treated and to the route of administration. The severity of the disease or condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0076] Compounds, salts and compositions disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset of the compounds, sharing certain chemical moieties, may be established by determining *in vitro* toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, rabbits, dogs or monkeys, may

be determined using known methods. The efficacy of a particular compound may be established using several recognized methods, such as *in vitro* methods, animal models, or human clinical trials. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, route of administration and/or regime.

EXAMPLES

[0077] Additional embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims.

[0078] 20,000 MDA-MB-231 cells were incubated in a 96 well plate as a triplicate with 500 nM of ZN-c3 and 10 nM of CHK inhibitor or 700 nM of ATR inhibitor as a single agent or the combination of both for 72 h. 20,000 H23 cells were incubated in a 96 well plate as a triplicate with 150 nM of ZN-c3 and 5 nM of CHK inhibitor or 500 nM of ATR inhibitor as a single agent or the combination of both for 72 h. 10,000 MV4-11 cells were incubated in a 96 well plate as a triplicate with 400 nM of ZN-c3 and 2 nM of CHK inhibitor or 2000 nM of ATM inhibitor as a single agent or the combination of both for 72 h. 20,000 THP-1 cells were incubated in a 96 well plate as a triplicate with 600 nM of ZN-c3 and 4 nM of CHK inhibitor or 1000 nM of ATR inhibitor as a single agent or the combination of both for 72 h. 10,000 HL-60 cells were incubated in a 96 well plate as a triplicate with 750 nM of ZN-c3 and 15 nM of CHK inhibitor or 2000 nM of ATM inhibitor as a single agent or the combination of both for 72 h. 10,000 LNCaP cells were incubated in a 96 well plate as a triplicate with 500 nM of ZN-c3 and 10 nM of CHK inhibitor or 1000 nM of ATM inhibitor as a single agent or the combination of both for 72 h. For each cell line, the cell viability was assessed using a CellTiter-Glo® (CTG) assay.

[0079] Table 1, Table 2 and Table 3 provide representative data and shows that the tested combinations of ZN-c3 (WEE1 inhibitor) and DNA damage response (DDR) inhibitors demonstrated synergistic effects in all the cell lines tested. Data is also summarized in FIGS. 1-13.

Table 1

Cell line	MDA-MB-231	H23	HL60	THP	MV4;11	LNCaP
	% Inhibition	% Inhibition	% Inhibition	% Inhibition	% Inhibition	% Inhibition
ZN-c3	35	22	25	18	49	24
CHKi	26	1	0	32	0	14
ZN-c3 + CHKi	81	78	94	97	99	70

Table 2

Cell line	MDA-MB-231	H23	THP	HL60
	% Inhibition	% Inhibition	% Inhibition	% Inhibition
ZN-c3	35	22	18	25
ATRi	33	35	37	15
ZN-c3 + ATRi	80	82	94	81

Table 3

Cell line	MV4;11	HL60	LNCaP
	% Inhibition	% Inhibition	% Inhibition
ZN-c3	49	25	24
ATMi	18	3	14
ZN-c3 + ATMi	76	45	50

[0080] 10,000 MV4-11 cells were incubated in a 96 well plate as a triplicate with 2 nM of ZN-d5, 400 nM of ZN-c3 and 2 nM of CHK inhibitor or 2000 nM of ATM inhibitor or 150 nM of ATR inhibitor as a single, double or triple combination for 72 h. 20,000 THP-1 cells were incubated in a 96 well plate as a triplicate with 100 nM of ZN-d5, 600 nM of ZN-c3 and 4 nM of CHK inhibitor or 1000 nM of ATM inhibitor or 1000 nM of ATR inhibitor as a single, double or triple combination for 72 h. 10,000 HL-60 cells were incubated in a 96 well plate as a triplicate with 75 nM of ZN-d5, 750 nM of ZN-c3 and 15 nM of CHK inhibitor or 2000 nM of ATM inhibitor or 1000 nM of ATR inhibitor as a single, double or triple combination for 72 h. For each cell line, the cell viability was assessed using a CellTiter-Glo® (CTG) assay.

[0081] Table 4 provides representative data and shows that the tested combinations of ZN-c3 (WEE1 inhibitor), ZN-d5 (Bcl-2 inhibitor) and DNA damage

response (DDR) inhibitors are effective in all the cell lines tested. Data is also summarized in FIGS. 14-22.

Table 4

Cell line	MV4;11	THP	HL60
	% Inhibition	% Inhibition	% Inhibition
ZN-c3	49.18	18.08	25.46
ZN-d5	8.44	2.60	37.56
CHEKi	0	32.29	0
ZN-c3 + ZN-d5	79.84	33.32	79.17
ZN-c3 + CHEKi	98.73	96.88	93.97
ZN-d5 + CHEKi	17.79	71.28	38.55
ZN-c3 + ZN-d5 + CHEKi	99.84	98.40	96.16
ATMi	18.48	19.52	2.95
ZN-c3 + ATMi	75.50	40.82	48.83
ZN-d5 + ATMi	70.71	35.78	77.29
ZN-c3 + ZN-d5 + ATMi	98.46	60.09	87.56
ATRi	13.99	36.93	15.91
ZN-c3 + ATRi	87.94	93.72	81.05
ZN-d5 + ATRi	61	94.63	74.91
ZN-c3 + ZN-d5 + ATRi	98.91	98.76	91.14

[0082] In Examples and Tables 1-4:

CHK: Checkpoint kinases

ATM: Ataxia-telangiectasia mutated

ATR: Ataxia telangiectasia and Rad3-related protein

ZN-c3 (WEE1 inhibitor)

Prexasertib (CHKi inhibitor)

AZD0156 (ATMi inhibitor)

Berzosertib (ATRi inhibitor)

[0083] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly

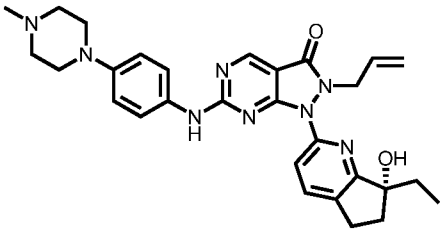
understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the present disclosure.

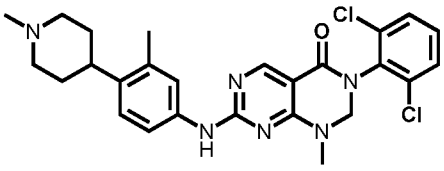
WHAT IS CLAIMED IS:

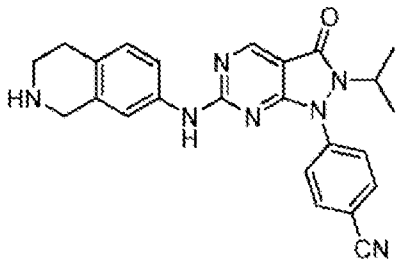
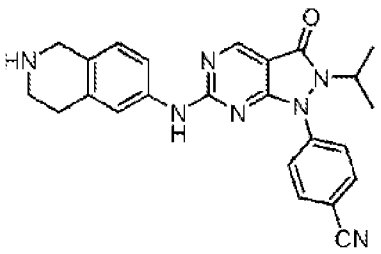
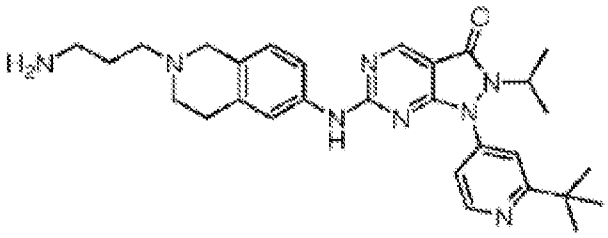
1. Use of a combination of compounds for treating a disease or condition, wherein the combination includes an effective amount of Compound (A) and an effective amount of Compound (B), or a pharmaceutically acceptable salt of any of the foregoing, wherein Compound (A) is a WEE1 inhibitor; and Compound (B) is a DNA damage response (DDR) inhibitor selected from an ATR inhibitor, an ATM inhibitor or a CHK1 inhibitor.

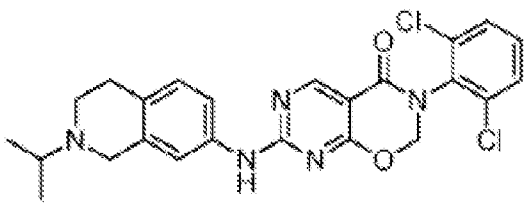
2. The use of Claim 1, wherein the WEE1 inhibitor is provided in any one or more of the following publications: WO 2019/074979, WO 2020/210383, WO 2020/210375, WO 2020/210377, WO 2020/210380, WO 2020/210381, WO 2022/082174, U.S. 2022/0162229, U.S. 2022/0168313, U.S. 2022/0169646, U.S. 2022/0220115, U.S. 11,332,473, WO 2019/173082, WO 2019/011228, WO 2019/138227, WO 2018/162932, WO 2018/011570, WO 2018/011569, US 2022/0194947, WO 2018/090939, WO 2015/092431, WO 2015/019037, WO 2014/167347, WO 2007/126122, WO 2011/034743, U.S. 2007/0254892, WO 2008/133866, U.S. 2016/0060258, U.S. 2019/0308984, U.S. 2020/0131192, WO 2021/073491, US 11,345,710, US 11,345,711 WO 2019/085933, WO 2020/221358, EP 3712150, WO 2018/133829, WO 2021/047627, US 2021/0403451, WO 2020/083404, WO 2019/037678, WO 2018/171633, CN 113387962, WO 2019/165204, WO 2012/161812, WO 2013/012681, WO 2013/013031, WO 2013/059485, WO 2013/126656, U.S. 2012/0220572, U.S. 2013/0018045, KR 2016035878, KR 2020016567, WO 2018/056621, WO 2017/075629, WO 2019/169065, WO 2019/134539, WO 2020/028814, US 2021/0309630, WO 2020/069105, WO 2020/192581, U.S. 2022/0194960, CN 114831993, CN 111718348, WO 2022/188802, WO 96/34867, WO 2008/153207, WO 2010/067888, WO 2009/054332, WO 2021/073491, WO 2021/074251, CN 112142763, WO 2020/259724, U.S. 2022/0259210, WO 2019/096322, CN 112142747, CN 112142747, WO 2021/043152, WO2021/254389, WO 2022/171088, WO 2022/171126, WO 2022/171128, WO 2022/174765, WO 2022/174796, CN 112442049, CN 114072411, CN 113402520, CN113387962, KR 2022081171, WO 2022/124748, WO 2022/155202, CN 114591334 and WO 2021/074251.

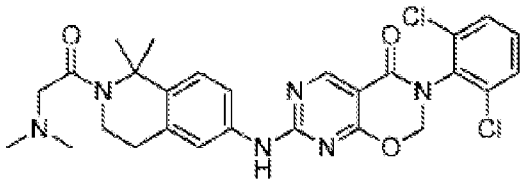
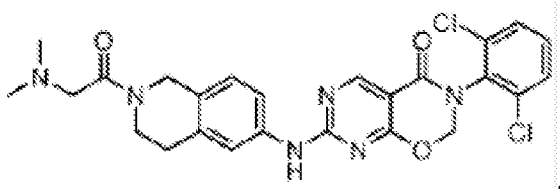
3. The use of claim 1 or 2, wherein the WEE1 inhibitor is selected from the group consisting of AZD1775, SC0191, PD0166285, NUV-569, SDR-7995, SDR-7778, IMP7068, Debio 0123, SY-4835, SPH-6162 and ATRN-W1051, or any combination thereof.

4. The use of any one of claims 1-3, wherein the WEE1 inhibitor is  (ZN-c3), or a pharmaceutically acceptable salt thereof.

5. The use of any one of claims 1-3, wherein the WEE1 inhibitor is  , or a pharmaceutically acceptable salt or N-oxide thereof.

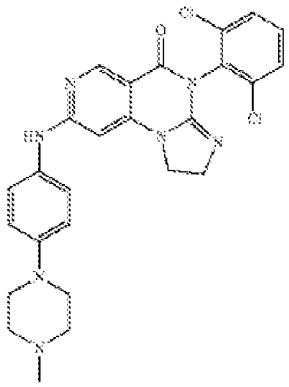
6. The use of any one of claims 1-3, wherein the WEE1 inhibitor is selected from the group consisting of:  ,  and  , or a pharmaceutically acceptable salt thereof of any of the foregoing.

7. The use of any one of claims 1-3, wherein the WEE1 inhibitor is selected from the group consisting of:  ,

 and  ,

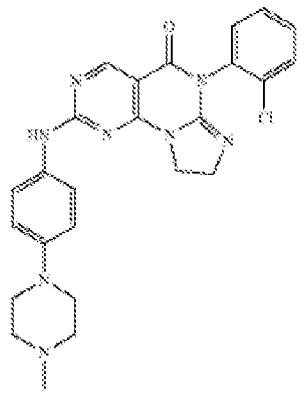
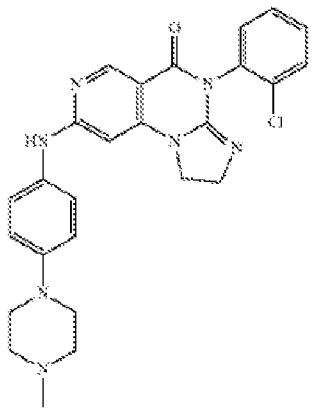
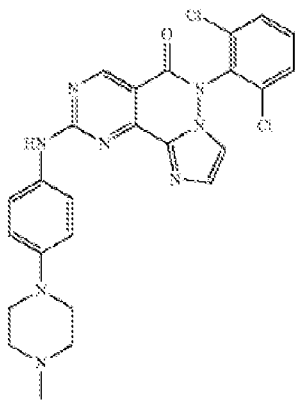
or a pharmaceutically acceptable salt thereof of any of the foregoing.

8. The use of any one of claims 1-3, wherein the WEE1 inhibitor is



, or a pharmaceutically acceptable salt thereof.

9. The use of any one of claims 1-3, wherein the WEE1 inhibitor is selected from the group consisting of:

 ,  and  , or a pharmaceutically acceptable salt thereof of any of the foregoing.

10. The use of any one of claims 1-9, wherein the ATR inhibitor is selected from the group consisting of Gartisertib, Berzosertib, Ceralasertib, SchisandrinB, Elimusertib, NU6027, Dactolisib, ETP-46464, Torin 2, VE-821, AZ20, Camonsertib, CGK733, ART-0380, ATRN-119 and ATRN-212.

11. The use of any one of claims 1-9, wherein the ATM inhibitor is selected from the group consisting of AZD7648, AZD0156, AZ31, AZ32, AZD1390, KU55933, KU59403,

KU60019, CP-466722, CGK733, NVP-BEZ235, SJ573017, AZ31, AZ32, AZD1390, SKLB-197, CGK733, M4076, M3541 and M4076.

12. The use of any one of claims 1-9, wherein the CHK1 inhibitor is selected from the group consisting of Prexasertib, AZD7762, Rabusertib, MK-8776, CCT245737, CCT244747, CHIR-124, PD 407824, PD-321852, PF-00477736, GDC-0425, GDC-0575, SB-218078, V158411, SAR-020106, XL-844, UCN-01, SOL-578, IMP 10 and CBP501.

13. The use of any one of claims 1-12, wherein the use further comprises the use of 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((2-(3-(difluoromethyl)bicyclo[1.1.1]pentan-1-yl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((4-((((1r,4r)-4-hydroxy-4-methylcyclohexyl)methyl)amino)-3-nitrophenyl)sulfonyl)benzamide.

14. The use of any one of Claims 1-13, wherein the disease or condition is selected from the group consisting of glioblastoma, astrocytoma, meningioma, craniopharyngioma, medulloblastoma, other brain cancers, head and neck cancer, leukemia, AML (Acute Myeloid Leukemia), CLL (Chronic lymphocytic leukemia), ALL (Acute Lymphocytic Leukemia), myelodysplastic syndromes (MDS), skin cancer, adrenal cancer, anal cancer, bile duct cancer, bladder cancer, bone cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, esophagus cancer, eye cancer, gallbladder cancer, gastric cancer, gastrointestinal cancer, Hodgkin lymphoma, Non-Hodgkin lymphoma, hematological tumor, Kaposi sarcoma, kidney cancer, laryngeal and hypopharyngeal cancer, liver cancer, lung cancer, non-small cell lung cancer, small cell, lung cancer, lymphoma, mesothelioma, melanoma, multiple myeloma, neuroblastoma, nasopharyngeal cancer, ovarian cancer, osteosarcoma, sarcomas, gastrointestinal stromal tumor (GIST), pancreatic cancer, pituitary cancer, retinoblastoma, salivary gland cancer, stomach cancer, small intestine cancer, testicular cancer, thymus cancer, thyroid cancer, uterine cancer, uterine sarcoma, uterine serous carcinoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, Wilms tumor, solid tumor and a liquid tumor.

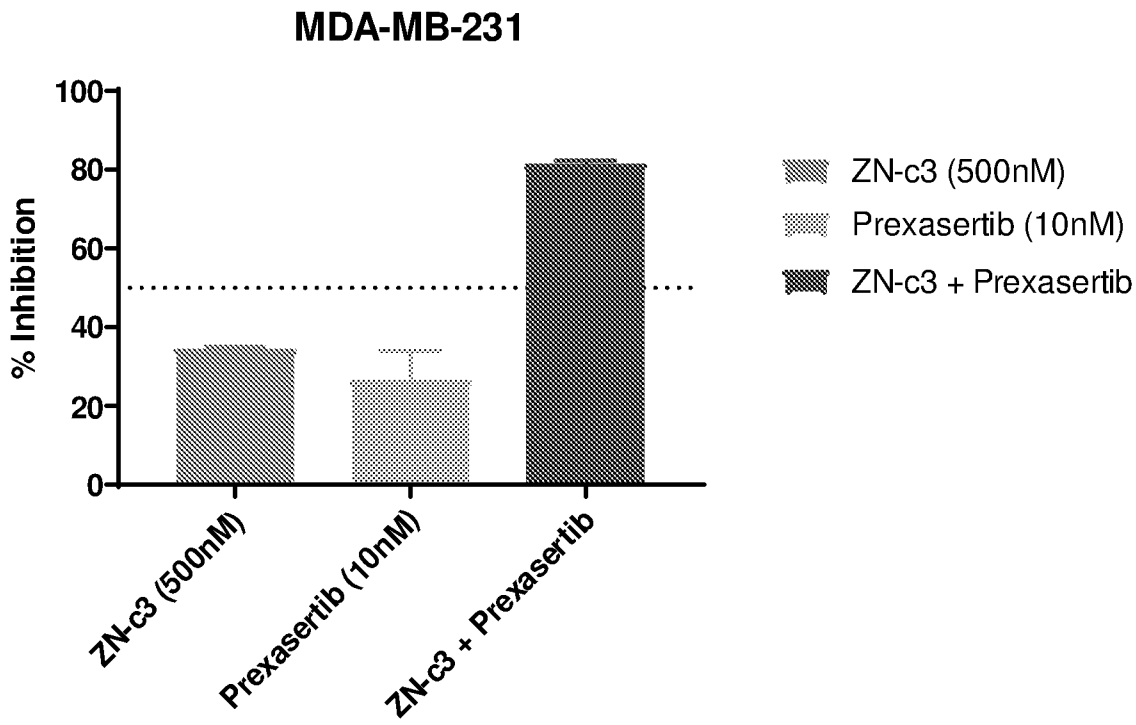
15. The use of Claim 14, wherein the disease or condition is selected from the group consisting of leukemia, AML (Acute Myeloid Leukemia), CLL (Chronic lymphocytic leukemia) and ALL (Acute Lymphocytic Leukemia).

16. The use of Claim 14, wherein the disease or condition is breast cancer.

17. The use of Claim 16, wherein the breast cancer is triple negative breast cancer.

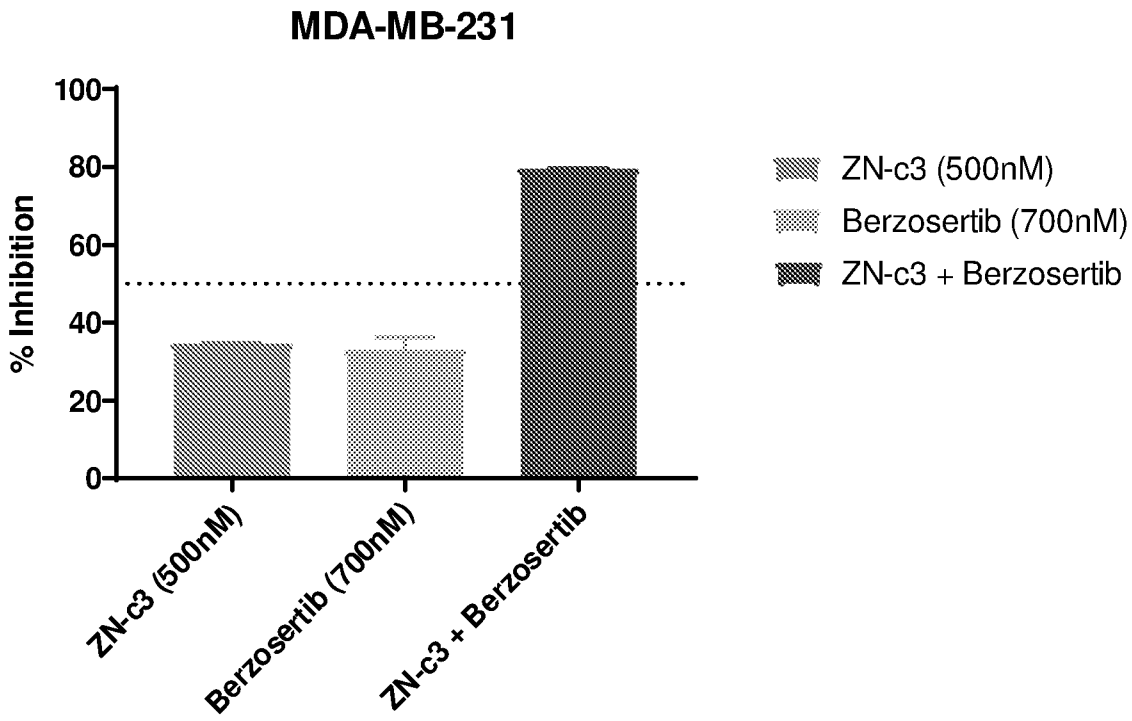
18. The use of Claim 14, wherein the disease or condition is prostate cancer.

19. The use of Claim 14, wherein the disease or condition is non-small cell lung cancer.



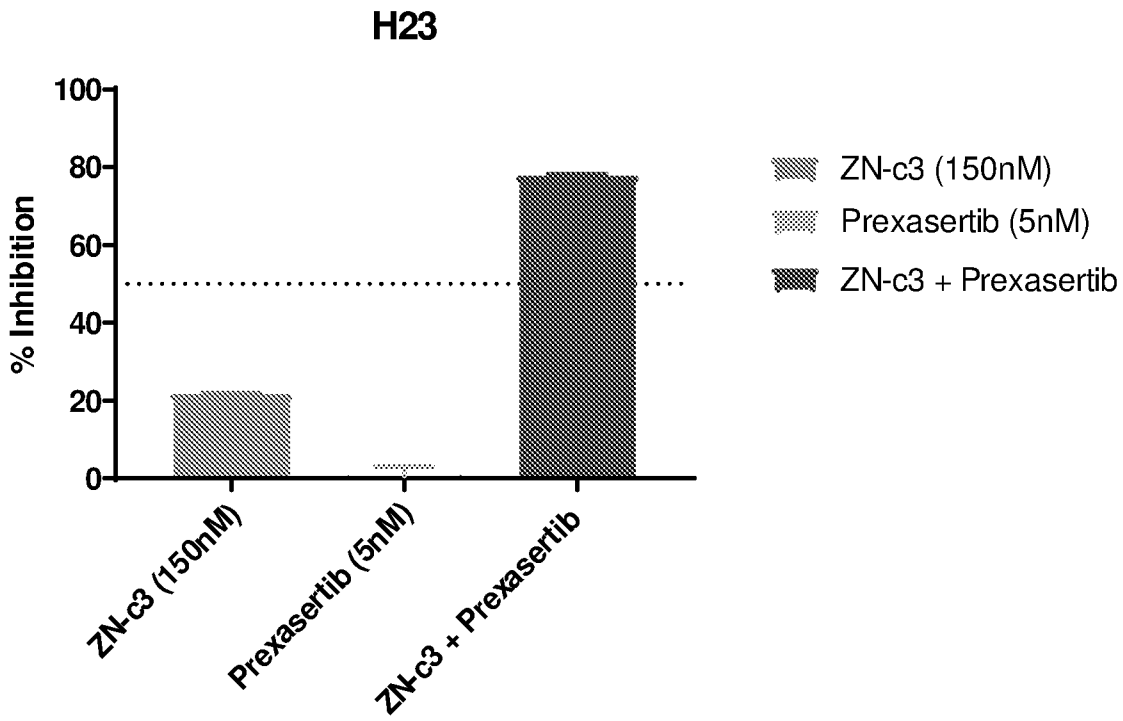
Cell line	MDA-MB-231
	% inhibition
ZN-c3	35
Prexasertib	26
Prexasertib + ZN-c3	81

FIG. 1



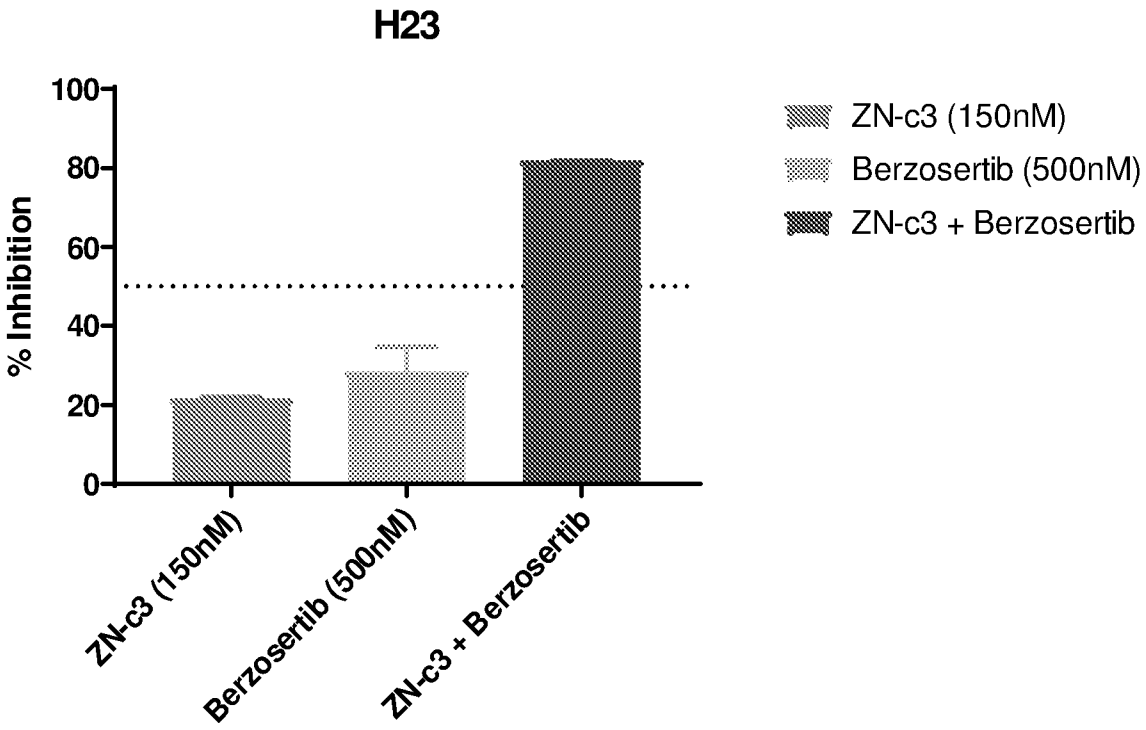
Cell line	MDA-MB-231
	% inhibition
ZN-c3	35
Berzosertib	33
Berzosertib + ZN-c3	80

FIG. 2



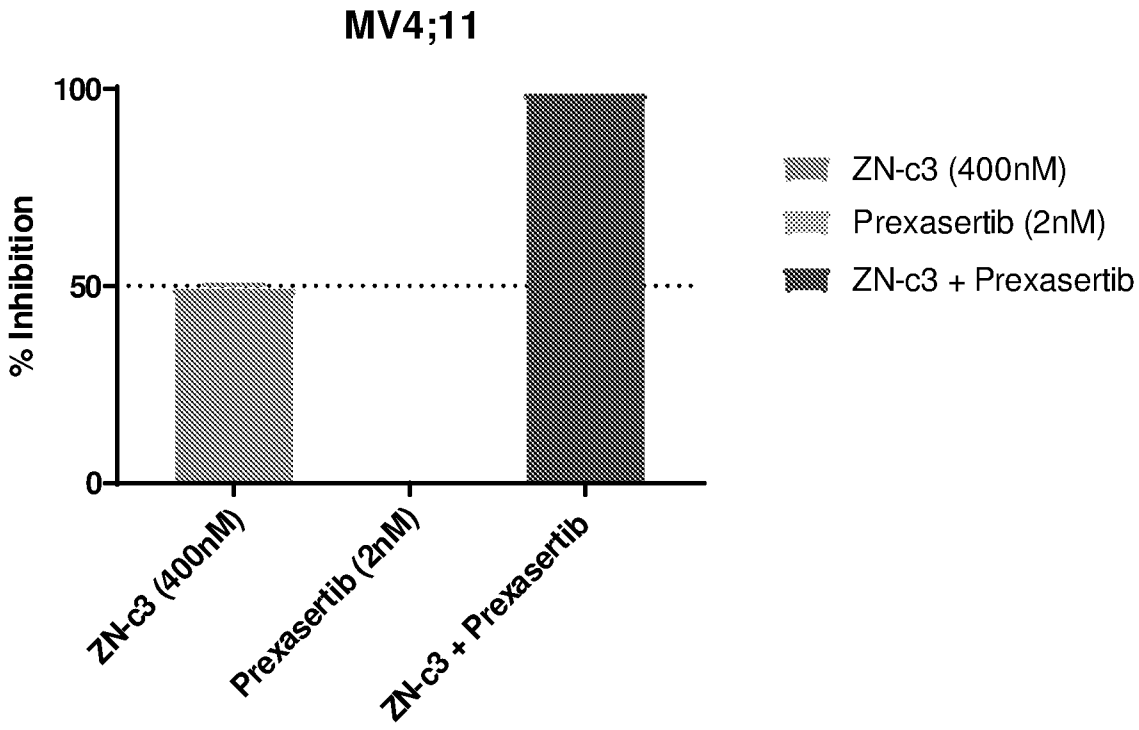
Cell line	H23
	% inhibition
ZN-c3	22
Prexasertib	1
Prexasertib + ZN-c3	78

FIG. 3



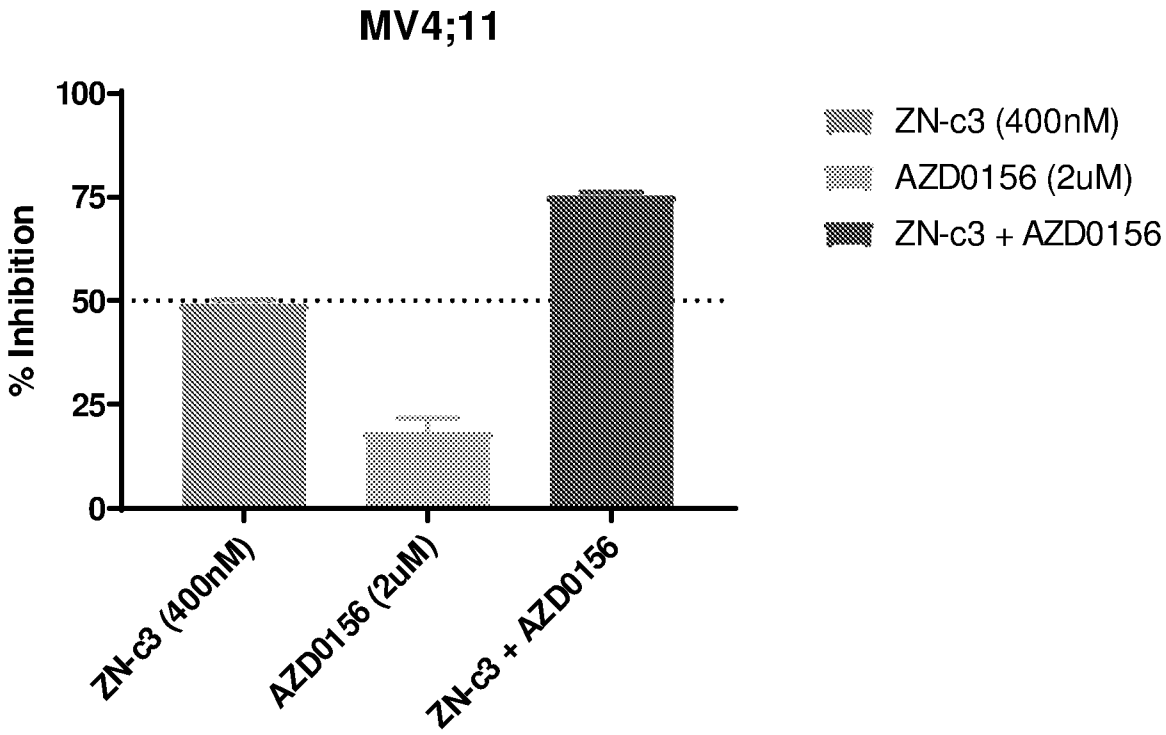
Cell line	H23
	% inhibition
ZN-c3	22
Berzosertib	35
Berzosertib + ZN-c3	82

FIG. 4



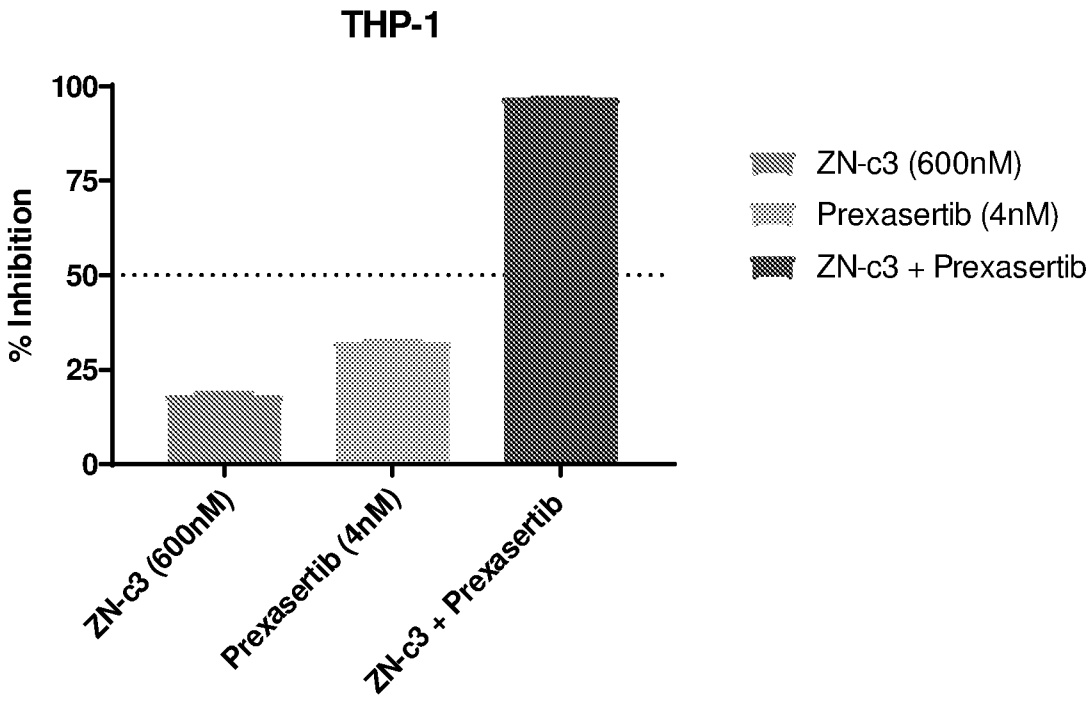
Cell line	MV4-11
	% inhibition
ZN-c3	49
Prexasertib	0
Prexasertib + ZN-c3	99

FIG. 5



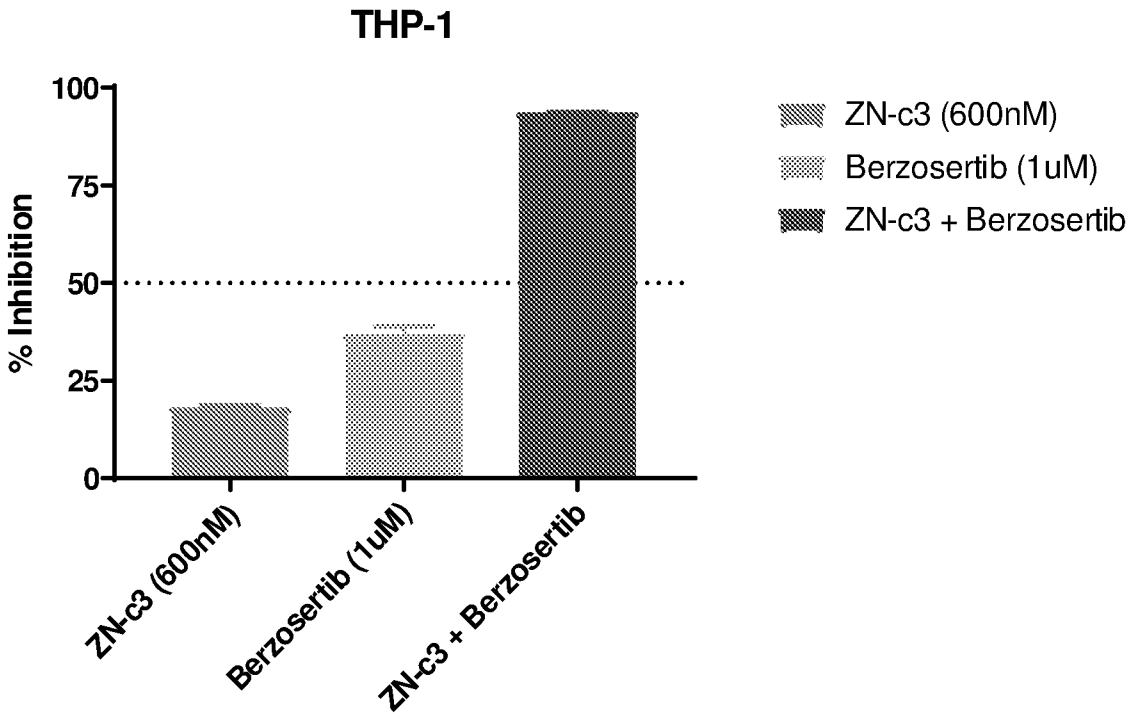
Cell line	MV4-11
	% inhibition
ZN-c3	49
AZD0156	18
AZD0156 + ZN-c3	76

FIG. 6



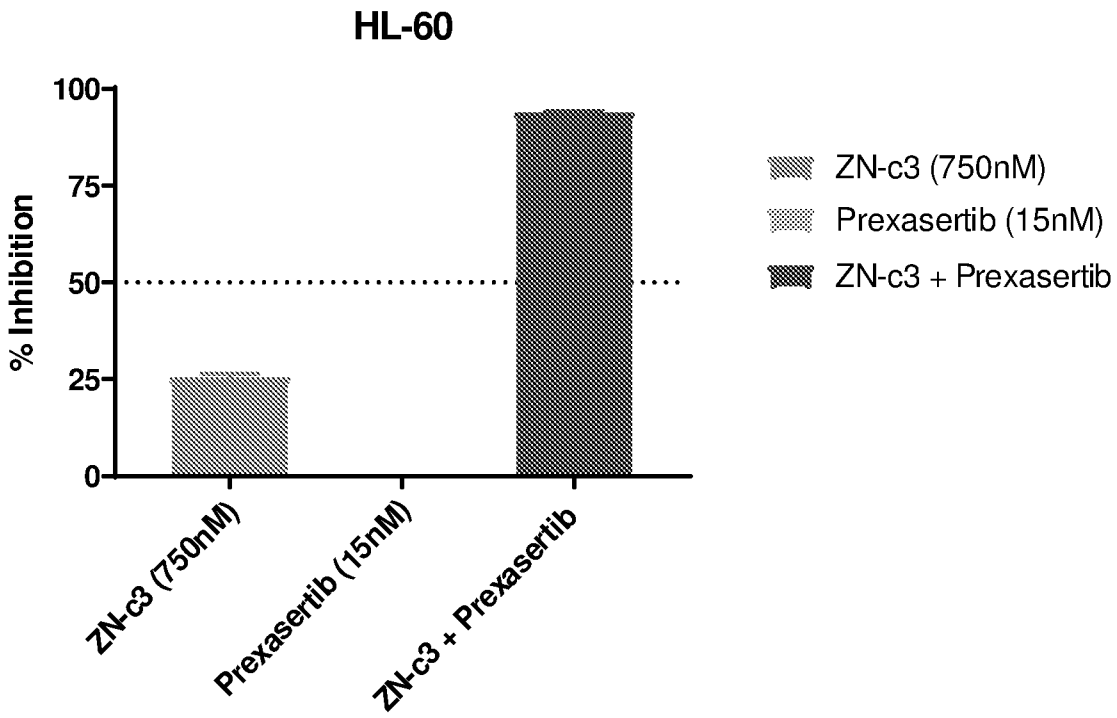
Cell line	THP-1
	% inhibition
ZN-c3	18
Prexasertib	32
Prexasertib + ZN-c3	97

FIG. 7



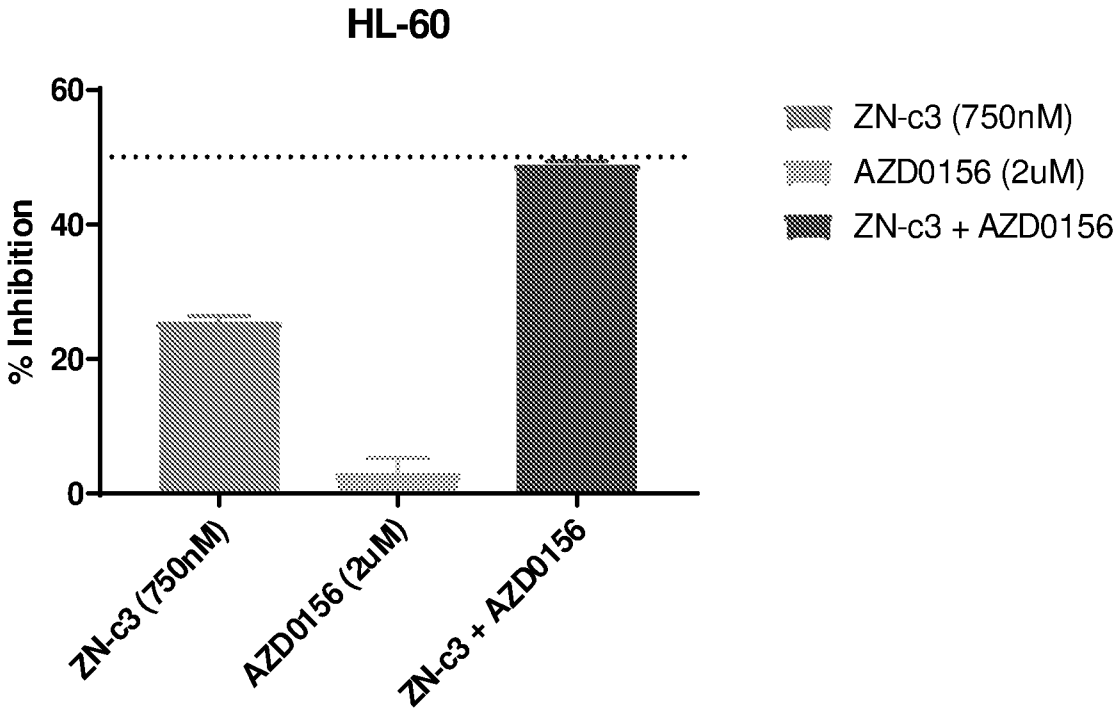
Cell line	THP-1
	% inhibition
ZN-c3	18
Berzosertib	37
Berzosertib + ZN-c3	94

FIG. 8



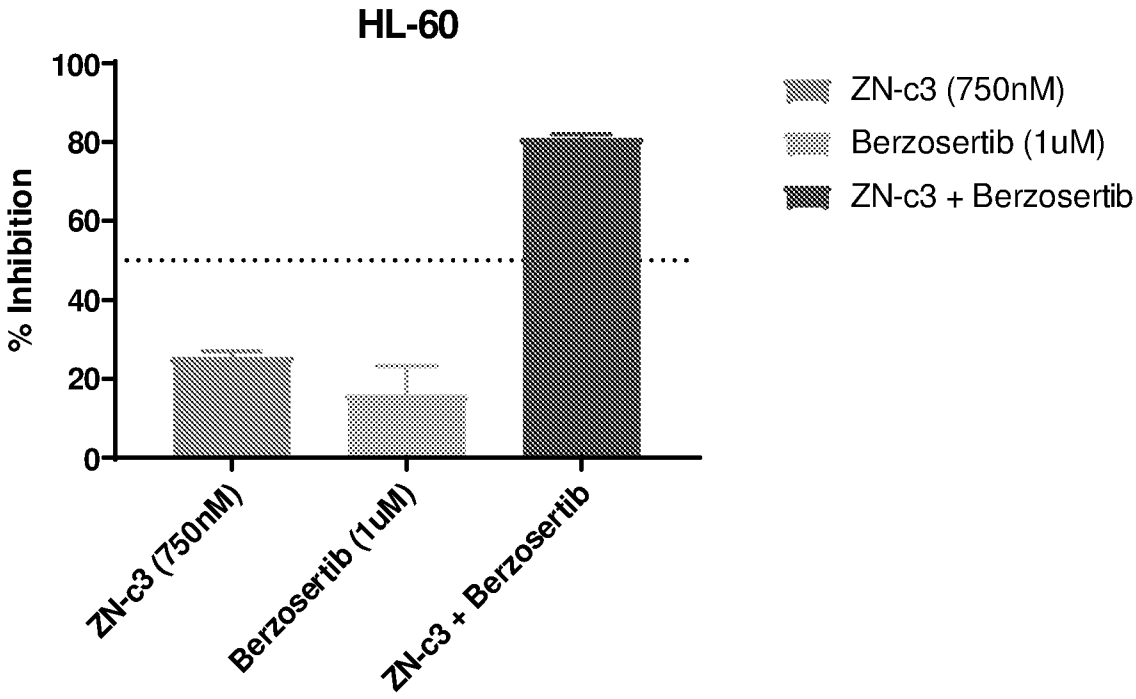
Cell line	HL-60
	% inhibition
ZN-c3	25
Prexasertib	0
Prexasertib + ZN-c3	94

FIG. 9



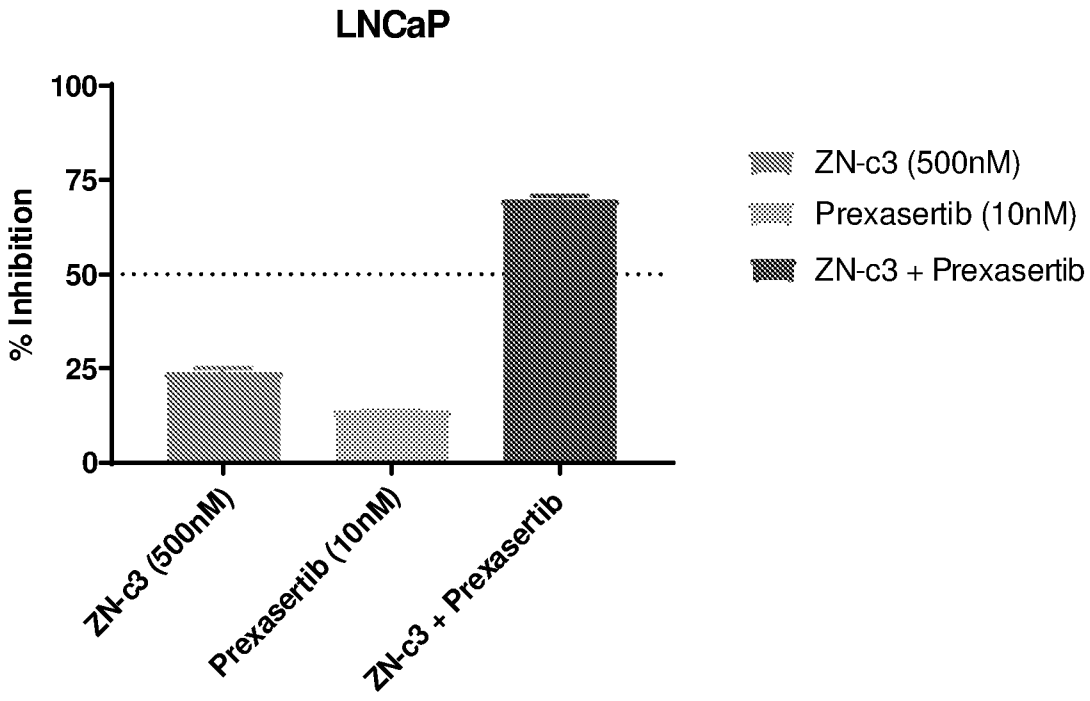
Cell line	HL-60
	% inhibition
ZN-c3	25
AZD0156	3
AZD0156 + ZN-c3	45

FIG. 10



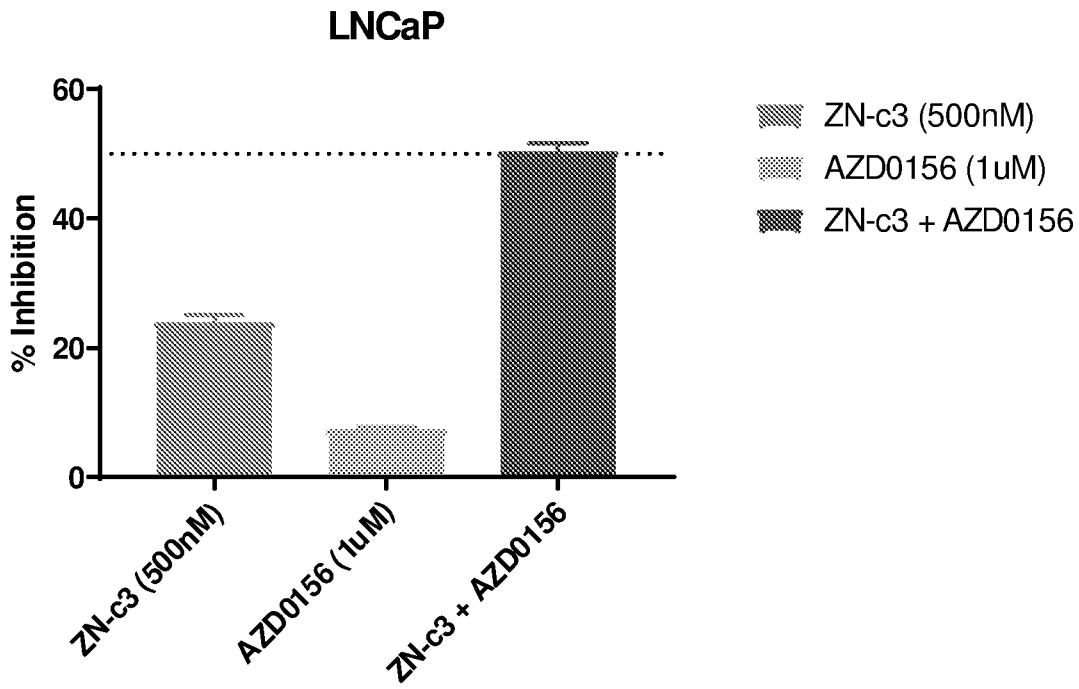
Cell line	HL-60
	% Inhibition
ZN-c3	25
Berzosertib	15
Berzosertib + ZN-c3	81

FIG. 11



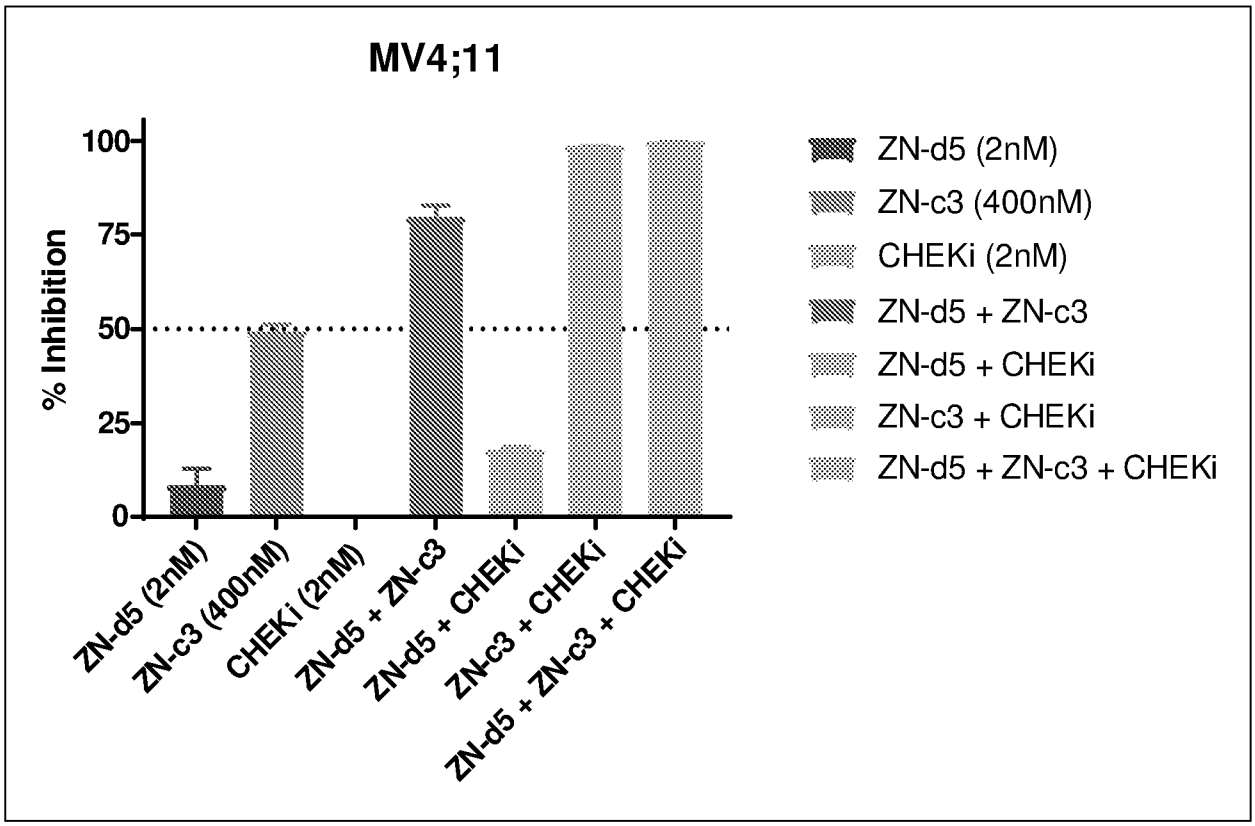
Cell line	LNCaP
	% Inhibition
ZN-c3	24
Prexasertib	14
Prexasertib + ZN-c3	70

FIG. 12



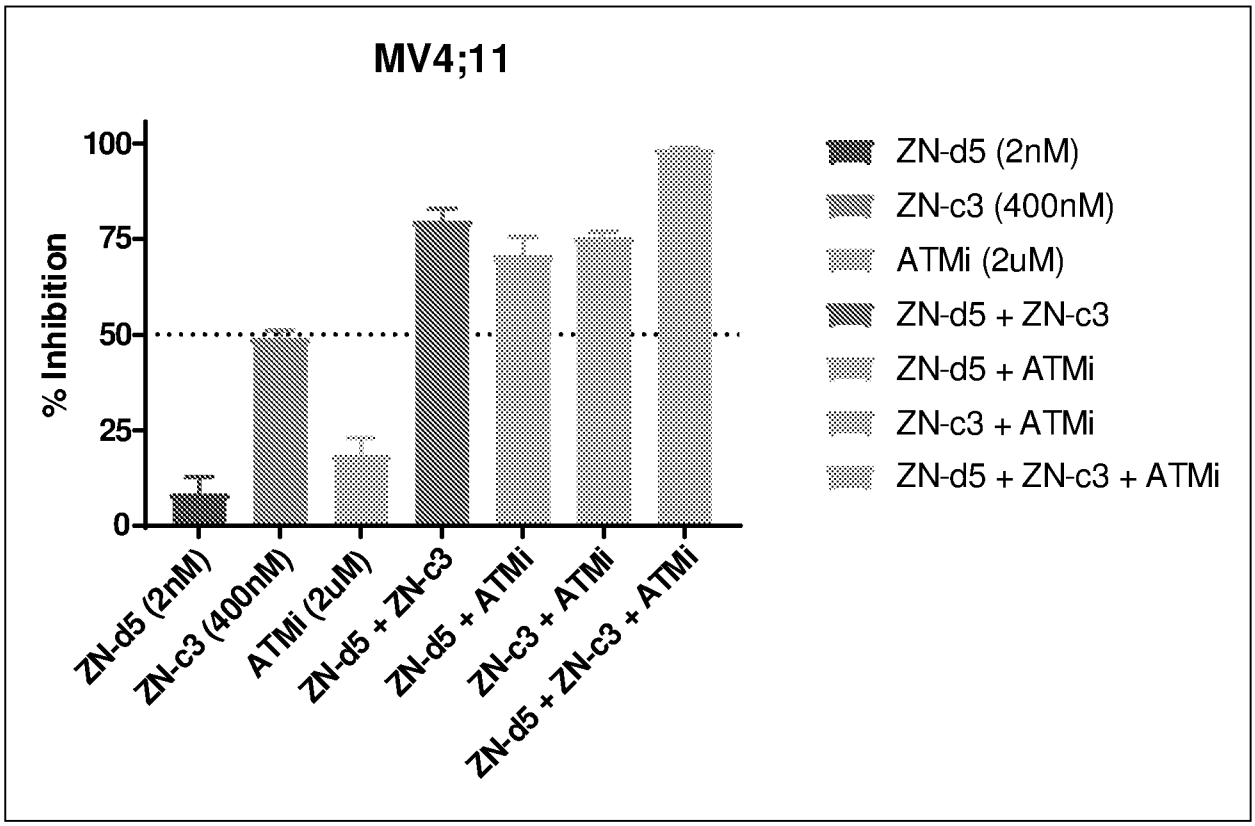
Cell line	LNCaP
	% inhibition
ZN-c3	24
AZD0156	14
AZD0156 + ZN-c3	50

FIG. 13



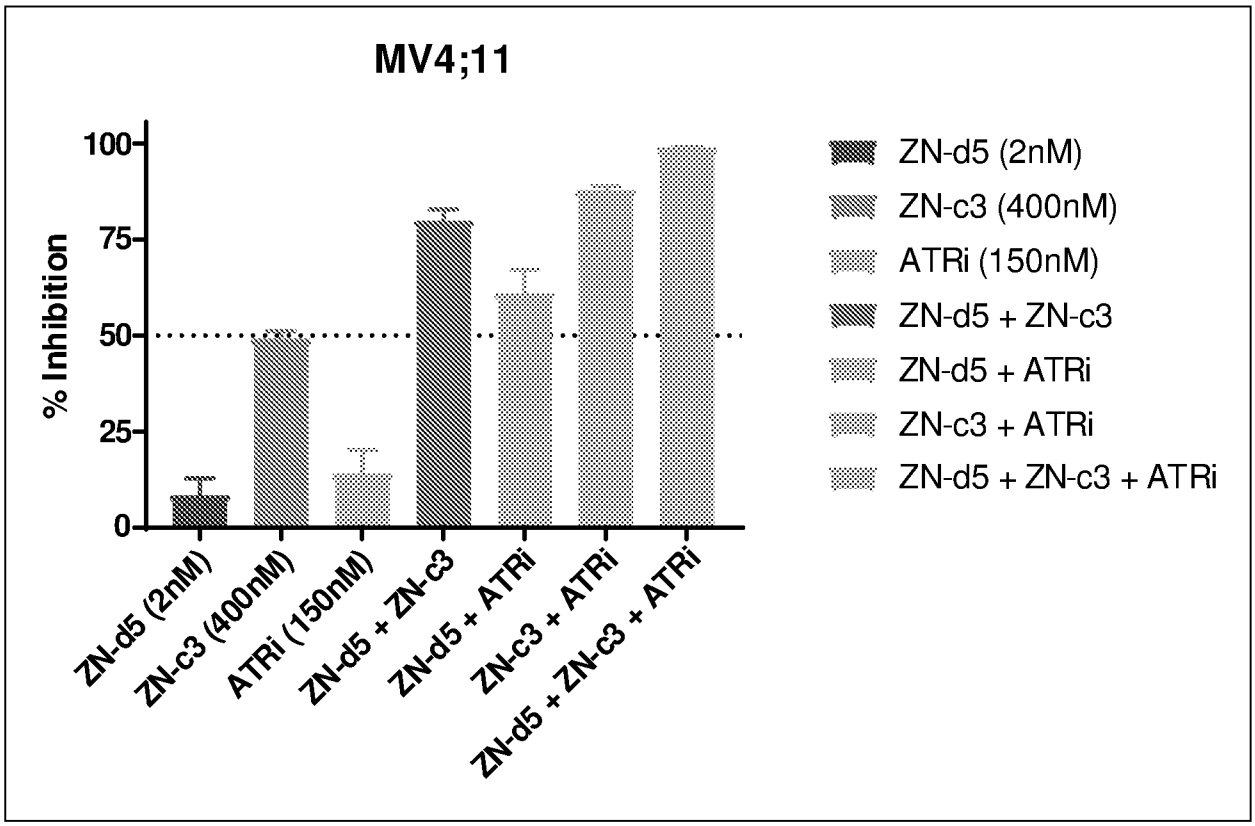
	% Inhibition (Avg.)
ZN-d5	8.44
ZN-c3	49.18
CHEKi	0
ZN-d5 + ZN-c3	79.84
ZN-d5 + CHEKi	17.79
ZN-c3 + CHEKi	98.73
ZN-d5 + ZN-c3+ CHEKi	99.84

FIG. 14



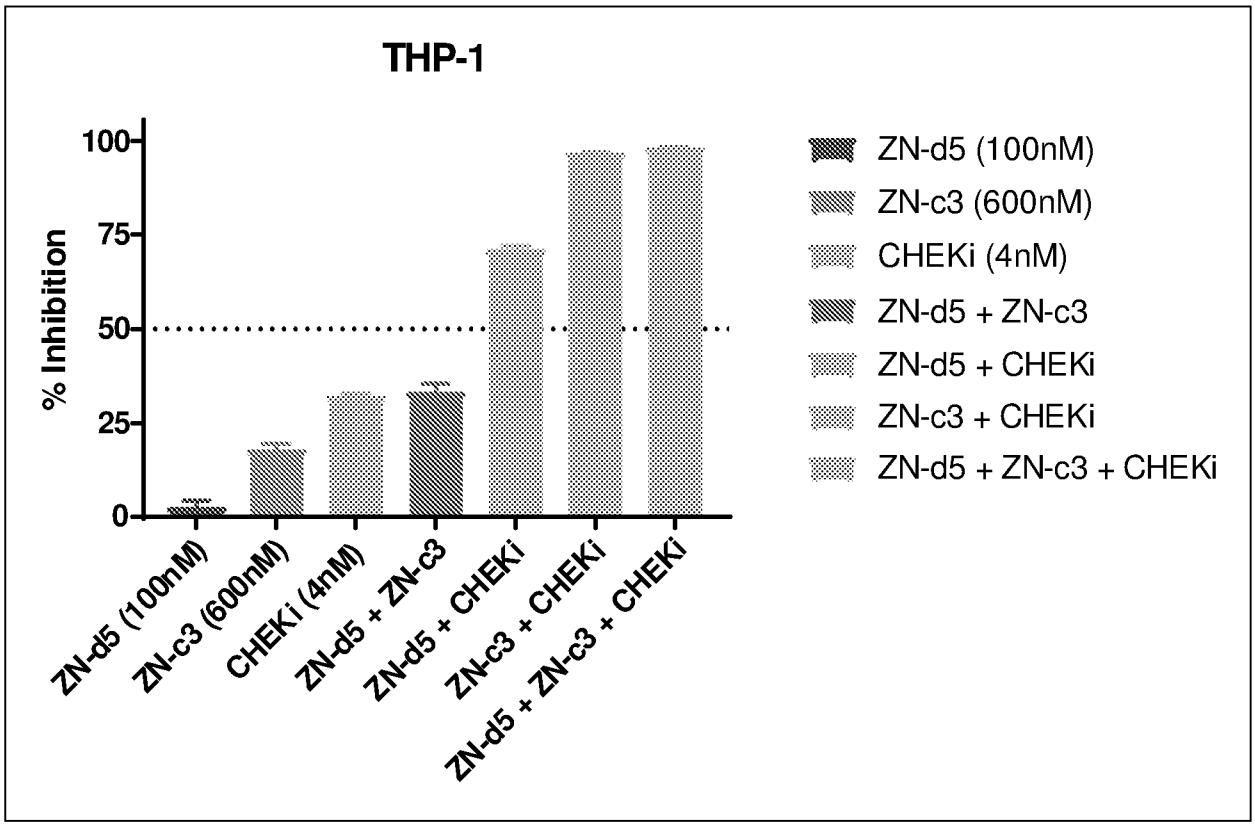
	% Inhibition (Avg.)
ZN-d5	8.44
ZN-c3	49.18
ATMi	18.48
ZN-d5 + ZN-c3	79.84
ZN-d5 + ATMi	70.71
ZN-c3 + ATMi	75.50
ZN-d5 + ZN-c3+ ATMi	98.46

FIG. 15



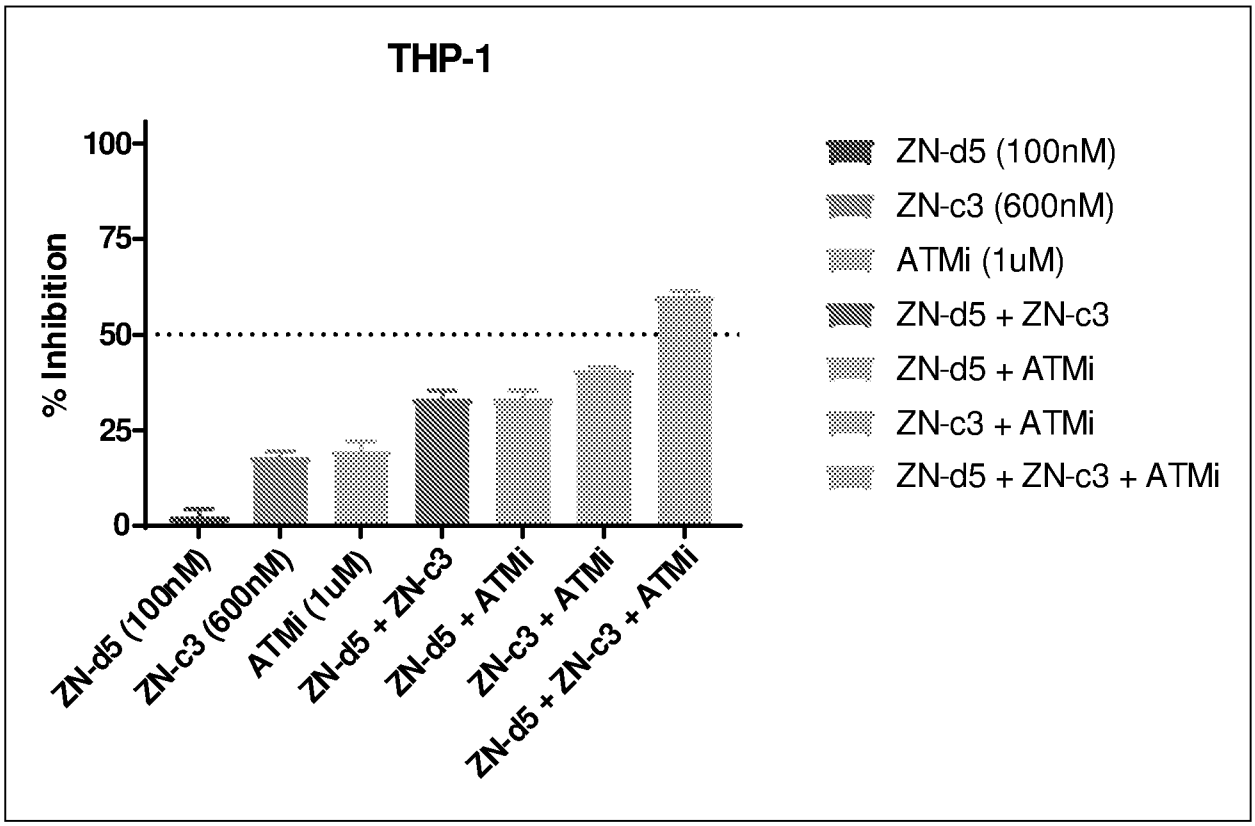
	% Inhibition (Avg.)
ZN-d5	8.44
ZN-c3	49.18
ATRi	13.99
ZN-d5 + ZN-c3	79.84
ZN-d5 + ATRi	61.00
ZN-c3 + ATRi	87.94
ZN-d5 + ZN-c3+ ATRi	98.91

FIG. 16



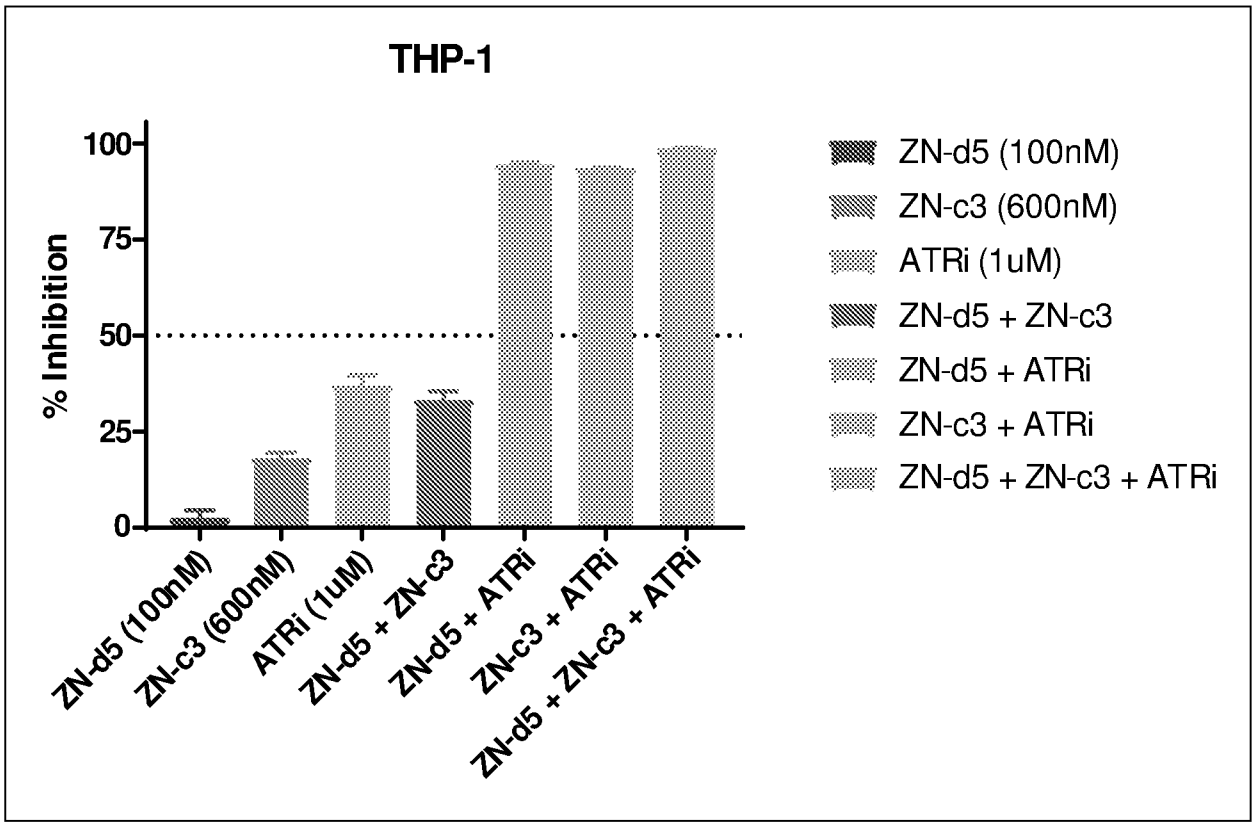
	% Inhibition (Avg.)
ZN-d5	2.6
ZN-c3	18.08
CHEKi	32.29
ZN-d5 + ZN-c3	33.32
ZN-d5 + CHEKi	71.28
ZN-c3 + CHEKi	96.88
ZN-d5 + ZN-c3+ CHEKi	98.40

FIG. 17



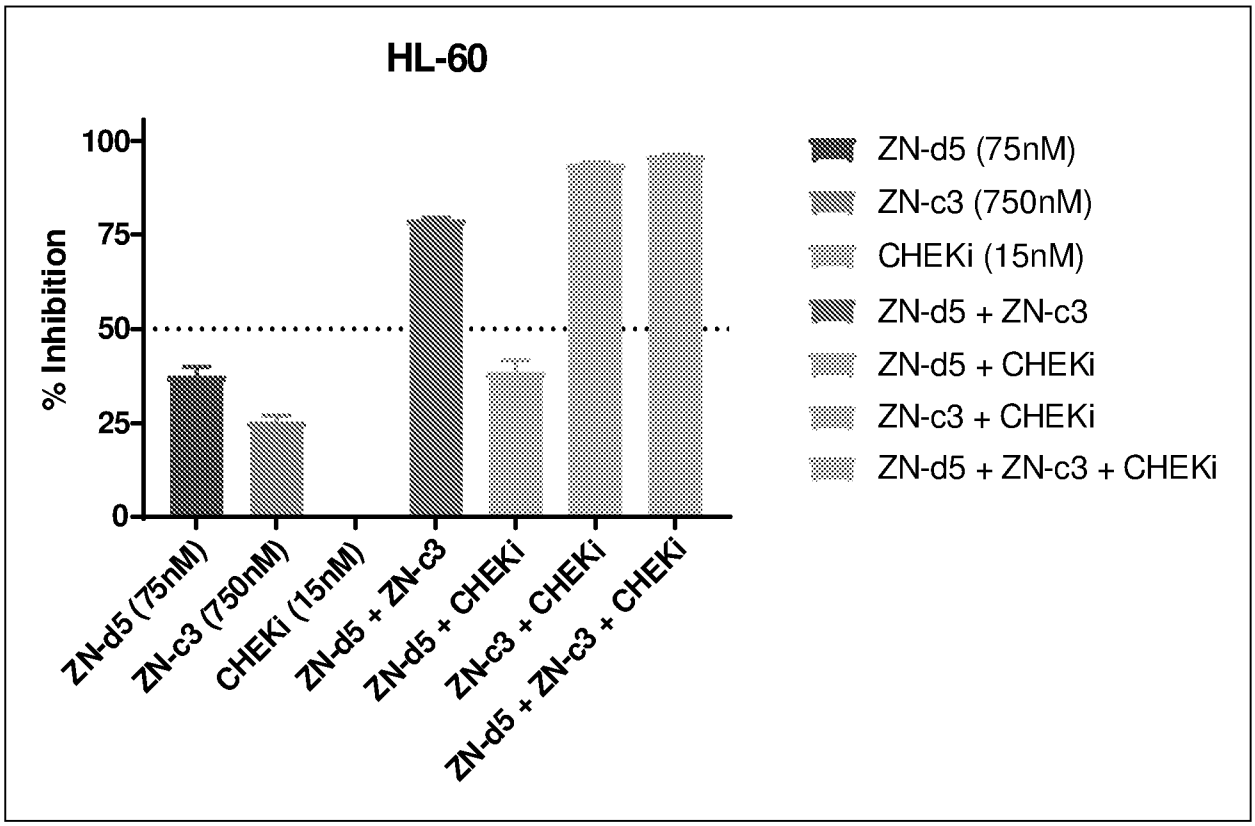
	% Inhibition (Avg.)
ZN-d5	2.60
ZN-c3	18.08
ATMi	19.52
ZN-d5 + ZN-c3	33.32
ZN-d5 + ATMi	35.78
ZN-c3 + ATMi	40.82
ZN-d5 + ZN-c3+ ATMi	60.09

FIG. 18



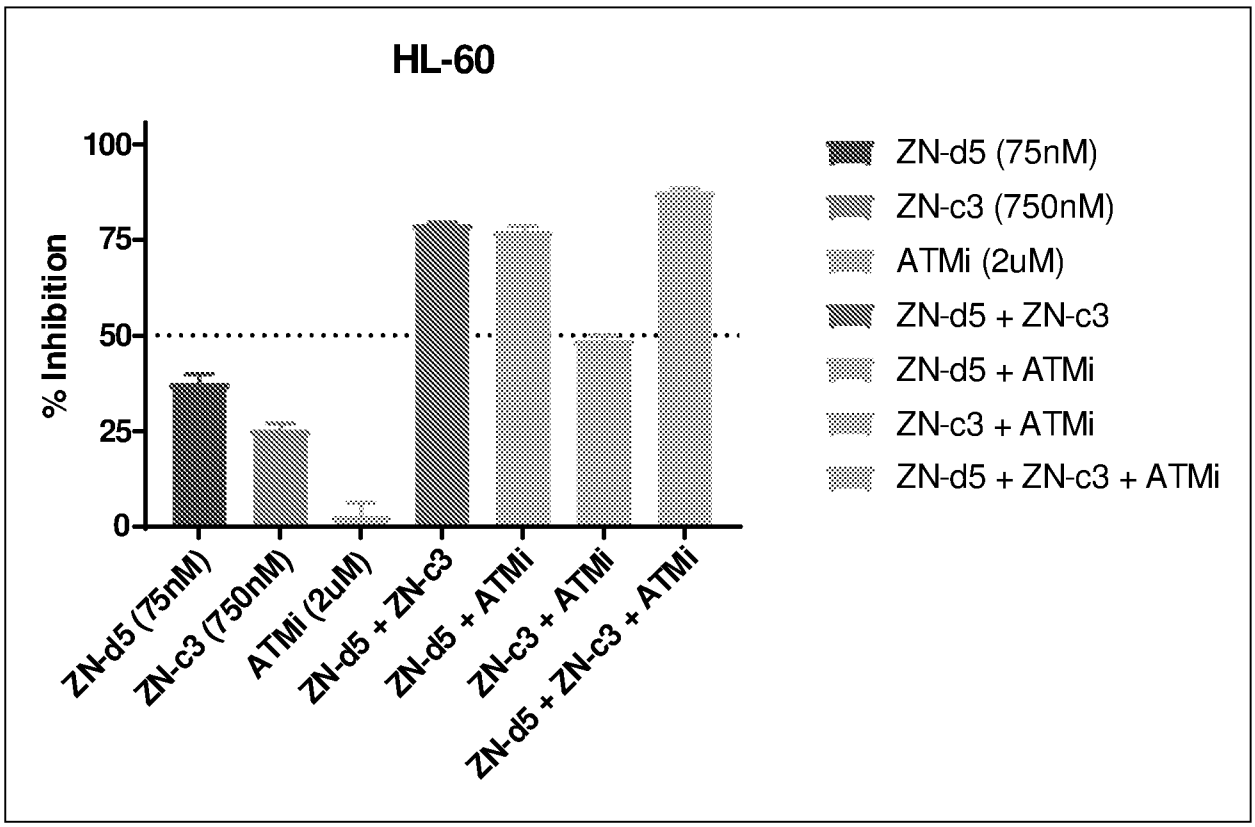
	% Inhibition (Avg.)
ZN-d5	2.60
ZN-c3	18.08
ATRi	36.93
ZN-d5 + ZN-c3	33.32
ZN-d5 + ATRi	94.63
ZN-c3 + ATRi	93.72
ZN-d5 + ZN-c3+ ATRi	98.76

FIG. 19



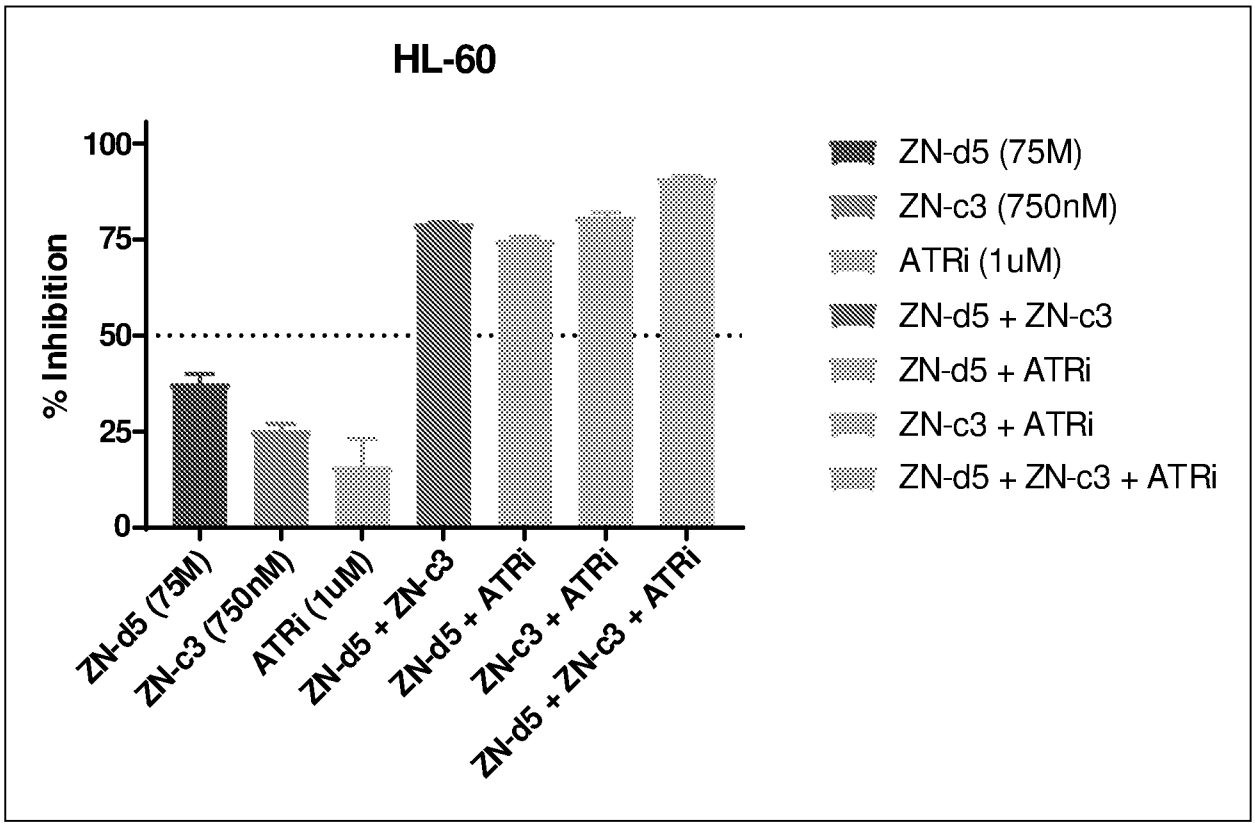
	% Inhibition (Avg.)
ZN-d5	37.56
ZN-c3	25.46
CHEKi	0
ZN-d5 + ZN-c3	79.17
ZN-d5 + CHEKi	38.55
ZN-c3 + CHEKi	93.97
ZN-d5 + ZN-c3+ CHEKi	96.16

FIG. 20



	% Inhibition (Avg.)
ZN-d5	37.56
ZN-c3	25.46
ATMi	2.95
ZN-d5 + ZN-c3	79.17
ZN-d5 + ATMi	77.29
ZN-c3 + ATMi	48.83
ZN-d5 + ZN-c3+ ATMi	87.56

FIG. 21



	% Inhibition (Avg.)
ZN-d5	37.56
ZN-c3	25.46
ATRi	15.91
ZN-d5 + ZN-c3	79.17
ZN-d5 + ATRi	74.91
ZN-c3 + ATRi	81.05
ZN-d5 + ZN-c3+ ATRi	91.14

FIG. 22

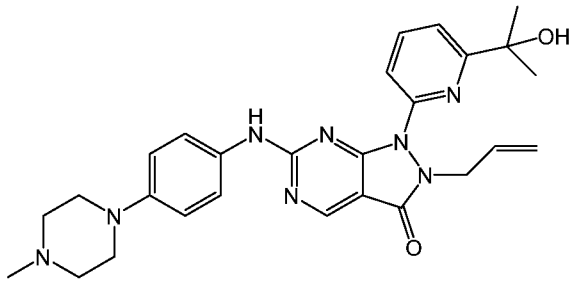
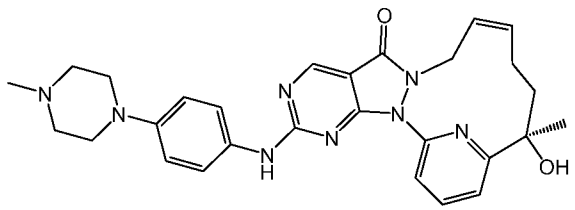
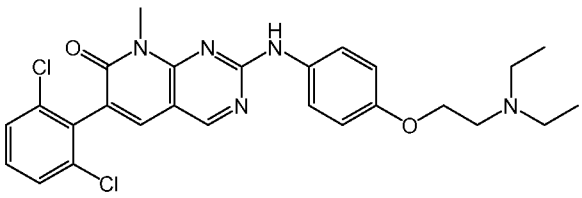
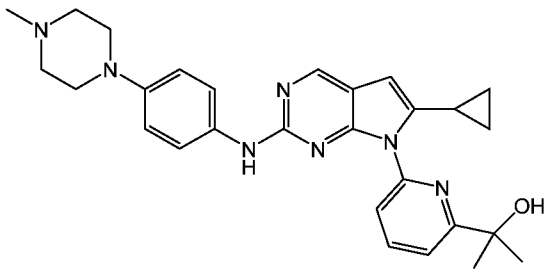
Structure
 (AZD1775)
 (SC0191)
 (PD0166285)


FIG. 23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/048037

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/437 (2006.01) A61K 31/497 (2006.01) A61K 31/519 (2006.01) A61P 35/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases Searched: EPOQUE, REGISTRY, HCAPLUS, BIOSIS, EMBASE, MEDLINE and Clinicaltrials.gov. **Search terms:** AZD1775, Adavosertib, MK1775, ZN-c3, WEE1 inhibitor, Gartisertib, Berzosertib, AZD6738, Dactolisib, ATR inhibitor, AZD7468, AZD1056, AZD1390, AZ31, AZ32, ATM inhibitor, Prexasertib, AZD7762, Rabusertib, MK8776, PF00477736, CHK1 inhibitor, Combination, Combotherapy and like terms. **CPC/IPC symbols searched:** A61K2300 and A61P35/00.

Applicant and Inventor names searches conducted in Espacenet, Pubmed, Australian Preliminary Search Tool (APST - uses DOCDB and DWPI databases), AusPat and non-OPI IP Australia internal databases.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2023	11 January 2023
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Nicolas Alcaraz AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 2 6283 2316

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2022/048037**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012074754 A1 (ARRAY BIOPHARMA INC.) 07 June 2012 Title, Abstract, [0011], [0040]-[0046], Examples 1-6 and Claims 2 and 33-40	1, 3-9 and 12-19
X	WO 2013039854 A1 (MERCK SHARP & DOHME CORP.) 21 March 2013 Title, Abstract, Pages 6-8, Examples 1-5, Figures 1-4 and Claim 1	1, 3-9 and 12-19
X	CARRASSA L., et al., "Combined inhibition of Chk1 and Wee1: In vitro synergistic effect translates to tumor growth inhibition in vivo", Cell Cycle (2012), 11:13, 2507-2517, DOI: 10.4161/cc.20899 Title, Abstract, Results and Discussion	1, 3-9 and 12-19
X	QI W., et al., "CHK1 plays a critical role in the anti-leukemic activity of the wee1 inhibitor MK-1775 in acute myeloid leukemia cells", Journal of Hematology & Oncology (2014), 7:53, 1-12, DOI: 10.1186/s13045-014-0053-9 Title, Abstract, Results and Discussion	1, 3-9 and 12-19
X	RESTELLI V., et al., "DNA Damage Response Inhibitor Combinations Exert Synergistic Antitumor Activity in Aggressive B-Cell Lymphomas", Molecular Cancer Therapeutics (2019), 18, 1255-1264, DOI: 10.1158/1535-7163.MCT-18-0919 Title, Abstract, Results and Discussion	1, 3-10 and 13-19
X	JIN J., et al., "Combined Inhibition of ATR and WEE1 as a Novel Therapeutic Strategy in Triple-Negative Breast Cancer", Neoplasia (2018), 20:5, 478-488, DOI: 10.1016/j.neo.2018.03.003 Title, Abstract, Result and Discussion	1, 3-10 and 13-19
X	BUKHARI A. B., et al., "Inhibiting Wee1 and ATR kinases produces tumor-selective synthetic lethality and suppresses metastasis", The Journal of Clinical Investigation (2019), 129:3, 1329-1344, DOI: 10.1172/JCI122622 Title, Abstract, Results and Discussion	1, 3-10 and 13-19
X	NAM A., et al., "Inhibition of ATR Increases the Sensitivity to WEE1 Inhibitor in Biliary Tract Cancer", Cancer Research Treatment (2020), 52:3, 945-956, DOI: 10.4143/crt.2020.080 Title, Abstract, Results and Discussion	1, 3-10 and 13-19
X	JIN M. H., et al., "Therapeutic Co-targeting of WEE1 and ATM Downregulates PD-L1 Expression in Pancreatic Cancer", Cancer Research Treatment (2020), 52:1, 149-166, DOI: 10.4143/crt.2019.183 Title, Abstract, Introduction, Results and Discussion	1, 3-9, 11 and 13-19
A	YAP T. A., et al., "The DNA Damaging Revolution: PARP Inhibitors and Beyond", American Society of Clinical Oncology Educational Book 39 (2019), 185-195, DOI: 10.1200/EDBK_238473 Whole Document	1 and 3-19
A	RONCO C., et al., "ATM, ATR, CHK1, CHK2 and WEE1 inhibitors in cancer and cancer stem cells", MedChemComm (2017), 8, 295-319, DOI: 10.1039/C6MD00439C Whole Document	1 and 3-19
A	HUANG P. Q., et al., "Discovery of ZN-c3, a Highly Potent and Selective Wee1 Inhibitor Undergoing Evaluation in Clinical Trials for the Treatment of Cancer", Journal of Medicinal Chemistry (2021), 64, 13004-13024, DOI: 10.1021/acs.jmedchem.1c01121 Whole Document	4-9

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2022/048037**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WILLEMIJN DE JONG M. R., et al., "WEE1 Inhibition Enhances Anti-Apoptotic Dependency as a Result of Premature Mitotic Entry and DNA Damage", Cancers (2019), 11:1743, 1-14, DOI: 10.3390/cancers11111743 Whole Document	13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/048037

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☒ Claims Nos.: **2**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See Supplemental Box

3. ☐ Claims Nos:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Supplemental Box

Continuation of **Box II**

Appended claim 2 does not comply with Rule 6.2(a) because it relies on references to the description, regarding patent publications to define WEE1 inhibitors.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2022/048037**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2012074754 A1	07 June 2012	WO 2012074754 A1	07 Jun 2012
		BR 112013011918 A2	25 Aug 2020
		CA 2817968 A1	07 Jun 2012
		CN 103442710 A	11 Dec 2013
		CN 103442710 B	29 May 2018
		CN 108721284 A	02 Nov 2018
		EP 2640386 A1	25 Sep 2013
		EP 2640386 B1	18 Jan 2017
		JP 2013542997 A	28 Nov 2013
		JP 6091422 B2	08 Mar 2017
		JP 2017014291 A	19 Jan 2017
		KR 20130114181 A	16 Oct 2013
		KR 101884960 B1	30 Aug 2018
		MX 2013005471 A	02 Sep 2013
		MX 343669 B	16 Nov 2016
		RU 2013127323 A	27 Dec 2014
		RU 2017127088 A	04 Feb 2019
		TW 201304778 A	01 Feb 2013
		US 2013231301 A1	05 Sep 2013
		US 9370567 B2	21 Jun 2016
		US 2016375002 A1	29 Dec 2016
		US 10434094 B2	08 Oct 2019
WO 2013039854 A1	21 March 2013	WO 2013039854 A1	21 Mar 2013
		EP 2755482 A1	23 Jul 2014
		EP 2755482 B1	01 Jun 2016
		US 2014343071 A1	20 Nov 2014
		US 9345705 B2	24 May 2016

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2022/048037**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.