COMBINATION OF PolQ INHIBITOR AND ANTI-CANCER THERAPEUTIC AGENT

TECHNICAL FIELD

The present disclosure relates to combination therapies, and methods of treating diseases and/or conditions with combination therapies descried herein.

BACKGROUND

DNA damage repair processes are critical for genome maintenance and cell viability. Double strand breaks (DSBs) can be repaired by one of three main pathways: homologous recombination (HR), non-homologous end-joining (NHEJ) and alternative NHEJ (alt-NHEJ). An alternative end joining (alt-NHEJ), also known as microhomology-mediated end-joining (MMEJ) pathway, is commonly considered as a "backup" DSB repair pathway when NHEJ or HR are compromised (Truong *et al.* PNAS 2013, 110 (19), 7720-7725).

An aberrant DNA damage response (DDR) often can sensitize cancer cells to specific types of DNA damage. Thus, defective DDR can be developed into targeted cancer therapies. Targeting DNA repair deficiencies has become a proven and effective strategy in cancer treatment. For example, the success of poly (ADP-ribose) polymerase (PARP) inhibitors in treating BRCA-deficient breast, ovarian, prostate and pancreatic cancers (Audeh M. W., et al., Lancet (2010); 376 (9737): 245-51).

Numerous genetic, cell biological and biochemical studies have demonstrated that DNA polymerase theta (PolQ, UniProtKB-075417 (DPOLQ_HUMAN) is a key protein involved in MMEJ (Kent *et al.* Nature Structural & Molecular Biology (2015), 22(3), 230-237, Mateos-Gomez *et al.* Nature (2015), 518(7538), 254-257).

PolQ is distinct among human DNA polymerases, comprising an N-terminal helicase domain (SF2 HEL308-type) and a C-terminal low-fidelity DNA polymerase domain (A-type) (Wood & Doublie DNA Repair (2016), 44, 22-32). In homologous recombination deficient (HRD) cells, PolQ can carry out error-prone DNA synthesis at DNA damage sites through alt-NHEJ pathway. It has been shown that the helicase domain of PolQ mediates the removal of RPA protein from ssDNA ends and stimulates annealing. This anti-recombinase activity of PolQ promotes the alt-NHEJ pathway. In addition, the helicase domain of PolQ contributes to microhomology-mediated strand annealing (Chan SH et al., PLoS Genet. (2010); 6: el001005; and Kawamura K et al., Int. J. Cancer (2004); 109: 9-16). PolQ can promote end joining in alt-NHEJ pathway by employing this annealing activity when ssDNA overhangs contain >2 bp of microhomology (Kent T., et al., Elife (2016); 5: el3740), and Kent T., et al., Nat. Struct. Mol. Biol. (2015); 22: 230-237). This reannealing activity is obtained through coupled actions of Rad51 interaction followed by ATPase-mediated displacement of Rad51 from DSB damage sites. Once annealed, the polymerase domain extends the ssDNA ends and fills the remaining gaps.

The expression of PolQ is low in normal cells but significantly over-expressed in subsets of HRD ovarian, uterine and breast cancers with associated poor prognosis (Higgins *et al.* Oncotarget (2010), 1, 175-184, Lemee *et al.* PNAS (2010), 107(30), 13390-13395, Ceccaldi *et al.* (2015), *supra).* Secondly, recent studies suggest that cancer cells with deficiency in HR, NHEJ or ATM are

highly dependent on PolQ expression (Ceccaldi R., et al., Nature (2015); 518: 258-62, Mateos-Gomez PA et al., Nature (2015); 518: 254-57, and Wyatt D.W., et al., Mol. Cell (2016); 63: 662-73). Finally, PolQ inhibition could conceivably prevent the MMEJ-dependent functional reversion of BRCA1- or BRCA2- mutations that underlies the emergence of cisplatin and PARPi resistance in tumors (Zatreanu D., et al., Nature Communications (2021)12: 3636). Therefore, PolQ is an attractive target for novel synthetic lethal therapy in cancers containing DNA repair defects.

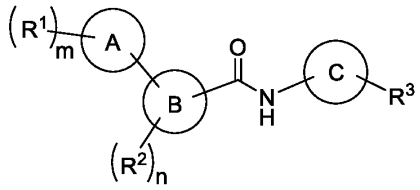
PolQ inhibitors are disclosed in International Application No. PCT/CN2022/124933 (WO2023061415A), PCT/CN2022/131231, PCT/CN2023/130324 (WO2024099336A), PCT/CN2023/082601, PCT/CN2023/130329 (WO2024099337A), PCT/CN2023/087991, PCT/CN2024/087388 (WO2024213082A), PCT/CN2023/092300, PCT/CN2024/090758 (WO2024230578A).

Thus, there exists a need for alternative treatments for solid tumor cancers, such as novel combination therapies.

SUMMARY

Some embodiments disclosed herein relate to the use of a combination for treating a disease or condition, wherein the combination can include PolQ inhibitor and a second anti-cancer therapeutic agent;

wherein, the PolQ inhibitor is a small molecule compound selected from anyone of the compounds of Formula (I):



(I);

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof; wherein the variables are as defined below;

optionally in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

The details of one or more embodiments are set forth in the description below. Other features, objects, and advantages will be apparent from the description and from the claims.

Detailed description

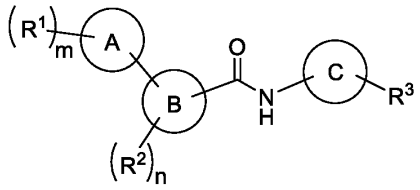
The present disclosure may be more fully appreciated by reference to the following description, including the following definitions and examples. Certain features of the disclosed compositions and methods which are described herein in the context of separate aspects, may also be provided in combination in a single aspect. Alternatively, various features of the disclosed compositions and methods that are, for brevity, described in the context of a single aspect, may also be provided separately or in any sub-combination.

Before the present invention is further described, it is to be understood that the invention is not

limited to the particular embodiments set forth herein, and it is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

The present disclosure relates to, inter alia, a combination for treating a disease or condition, wherein the combination include PolQ inhibitor and a second anti-cancer therapeutic agent;

wherein, the PolQ inhibitor is represented by the compounds of Formula (I):



(I);

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof, wherein:

ring A is selected from C_6-C_{14} aryl or 5-14 membered heteroaryl;

ring B is selected from partially unsaturated 5-14 membered heterocycloalkyl, C_6-C_{14} aryl or 5-14 membered heteroaryl;

ring C is selected from partially unsaturated 5-10 membered heterocycloalkyl or 5-10 membered heteroaryl; each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^6;

m is 1, 2, 3, 4 or 5;

n is 1, 2, 3, 4 or 5;

each R^1 is independently selected from H, D, halogen, -CN, -NO_2, N_3, -SF_5, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl, -NR^CR^D, -OR^A, -SR^A, -NR^COR^A, -$C(O)R^B$, -$C(O)NR^CR^D$, -$C(O)OR^A$, -$OC(O)R^B$, -$NR^CC(O)R^B$, -$S(O)R^B$, -$S(O)_2R^B$, -$S(O)NR^CR^D$, -$NR^CS(O)_2R^D$, -$S(O)_2NR^CR^D$, -$NR^CS(O)_2NR^CR^D$, -$NR^CS(O)(=NR^B)R^B$, $SiR^GR^HR^I$, $B(OR^C)(OR^D)$, -$P(O)R^ER^F$, -$P(O)OR^EOR^F$, -$OP(O)OR^EOR^F$; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}; or

two R^1 together with the atoms to which they are attached form oxo, C_3-C_7 cycloalkyl or 4-7 membered heterocycloalkyl; wherein, the C_3-C_7 cycloalkyl or 4-7 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A};

each R^{1A} is independently selected from D, halogen, CN, -NO_2, N_3, oxo, OR^a, NR^cR^d, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or 4-6 membered heterocycloalkyl is optionally substituted with D, halogen, CN, OH, NH_2, oxo, NR^cR^d, OR^a, SR^a, C_1-C_6 alkyl, C_1-C_6 haloalkyl;

each R^2 is independently selected from H, D, CN, NO_2, N_3, oxo, SF_5, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, -NR^CR^D, -OR^A, -SR^A, -NR^COR^A, -$C(O)R^B$, -$C(O)NR^CR^D$, -$C(O)OR^A$, -

$OC(O)R^B$, $-NR^CC(O)R^B$, $-S(O)R^B$, $-S(O)_2R^B$, $-S(O)NR^CR^D$, $-NR^CS(O)_2R^D$, $-S(O)_2NR^CR^D$, $-NR^CS(O)_2NR^CR^D$, $-NR^CS(O)(=NR^B)R^B$, $SiR^GR^HR^I$, $B(OR^C)(OR^D)$, $-P(O)R^ER^F$, $-P(O)OR^EOR^F$, $-OP(O)OR^EOR^F$; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}; or

two R^2 together with the atoms to which they are attached form oxo, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl; wherein, the C_3-C_7 cycloalkyl, or 4-7 membered heterocycloalkyl is optionally substituted by 1, 2, 3 or 4 substituents independently selected from R^{2A};

each R^{2A} is independently selected from D, halogen, CN, OH, NH_2, NO_2, SF_5, oxo, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, NR^cR^d, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)(=NR^b)R^b$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^d$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$; wherein, the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl is optionally substituted with D, halogen, CN, OH, NH_2, oxo, $NR^{c1}R^{d1}$, OR^{a1}, SR^{a1}, C_1-C_6 alkyl, C_1-C_6 haloalkyl;

R^3 is selected from H, D, halo, CN, oxo, NO_2, SF_5, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{14} cycloalkyl, 4-14 membered heterocycloalkyl, C_6-C_{14} aryl, 5-14 membered heteroaryl, OR^A, SR^A, NR^COR^A, NR^CR^D, $C(O)R^B$, $C(O)NR^CR^D$, $NR^CC(O)R^B$, $NR^CC(O)OR^A$, $NR^CS(O)_2R^D$, $NR^CS(O)_2NR^CR^D$, $S(O)R^B$, $S(O)_2R^B$; wherein, the C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{14} cycloalkyl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl, 5-14 membered heteroaryl is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4;

each R^4 is independently selected from D, halo, CN, NO_2, N_3, oxo, NR^CR^D, OR^A, SR^A, NR^COR^A, $C(O)R^B$, $C(O)NR^CR^D$, $C(O)OR^A$, $OC(O)R^B$, $OC(O)NR^CR^D$, $NR^CC(O)R^B$, $NR^CC(O)NR^CR^D$, $NR^CC(O)OR^A$, $S(O)R^B$, $S(O)_2R^B$, $S(O)NR^CR^D$, $NR^CS(O)_2R^D$, $S(O)_2NR^CR^D$, $NR^CS(O)_2NR^CR^D$, $C(O)NR^CS(O)_2R^B$, $NR^CS(O)(=NR^B)R^B$, $SiR^GR^HR^I$, $B(OR^C)(OR^D)$, $-P(O)R^ER^F$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^5;

each R^5 is independently selected from D, CN, halo, NO_2, SF_5, oxo, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted 4-6 membered heterocycloalkyl, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)(=NR^b)R^b$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^d$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$;

each R^6 is independently selected from D, halo, CN, NO_2, $-N_3$, oxo, SF_5, NR^CR^D, OR^A, SR^A, $SiR^GR^HR^I$, $B(OR^C)(OR^D)$, $-P(O)R^ER^F$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered

heterocycloalkyl is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^{6A};

two R^6 on the same ring carbon atom form oxo, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl; wherein, the C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl is optionally substituted by 1, 2, 3 or 4 substituents independently selected from R^{6A};

two adjacent R^6 together with the atoms to which they are attached form C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl; wherein, the C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl is optionally substituted by 1, 2, 3 or 4 substituents independently selected from R^{6A};

each R^{6A} is independently selected from D, halogen, CN, OH, NH_2, NO_2, SF_5, oxo, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, NR^cR^d, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)(=NR^b)R^b$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^d$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$; wherein, the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl is optionally substituted with D, halogen, CN, OH, NH_2, oxo, $NR^{c1}R^{d1}$, OR^{a1}, SR^{a1}, C_1-C_6 alkyl, C_1-C_6 haloalkyl;

each R^A is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, $NR^cS(O)(=NR^b)R^b$ or $SiR^gR^hR^i$;

each R^B is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, OR^a, $C(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$;

R^C and R^D are each independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, OR^a, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$ or $B(OR^c)(OR^d)$;

or R^C and R^D together with the N atom to which they are attached form 4-7 membered heterocycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, OH, oxo, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, or OC_1-C_4 haloalkyl;

R^a and R^{a1} are each independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, halo, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, C_1-C_4 alkyl, OC_1-C_4 alkyl, C_1-C_4 haloalkyl, or OC_1-C_4 haloalkyl;

R^b and R^{b1} are each independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl;

R^c, R^d, R^{c1}, R^{d1} are each independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, 4-10 membered heterocycloalkyl-C_1-C_6 alkyl, C_6-C_{10} aryl-C_3-C_{10} cycloalkyl, C_6-C_{10} aryl-4-10 membered heterocycloalkyl, C_6-C_{10} aryl-heteroaryl, bi(C_6-C_{10} aryl), 5-10 membered heteroaryl-C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl-4-10 membered heterocycloalkyl, 5-10 membered

heteroaryl-C_6-C_{10} aryl, or bi(5-10 membered heteroaryl); wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, 4-10 membered heterocycloalkyl-C_1-C_6 alkyl, C_6-C_{10} aryl-C_3-C_{10} cycloalkyl, C_6-C_{10} aryl-4-10 membered heterocycloalkyl, C_6-C_{10} aryl-heteroaryl, bi(C_6-C_{10} aryl), 5-10 membered heteroaryl-C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl-4-10 membered heterocycloalkyl, 5-10 membered heteroaryl-C_6-C_{10} aryl, or bi(5-10 membered heteroaryl) is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 cyanoalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C(O)OR^{a1}, C(O)R^{b1}, S(O)$_2R^{b1}$, C_1-C_4 alkyl-O-C_1-C_4 alkyl or C_1-C_4 alkyl-O-C_1-C_4 alkyl-O-;

or R^c and R^d together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 cyanoalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_1-C_4 alkoxy-C_1-C_4 alkyl or C_1-C_4 alkoxy-C_1-C_4 alkoxy;

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, OH, CN, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 cyanoalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_1-C_4 alkoxy-C_1-C_4 alkyl or C_1-C_4 alkoxy-C_1-C_4 alkoxy;

R^E and R^e are each independently selected from H, D, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, (C_1-C_4 alkoxy)-C_1-C_4 alkyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkyl, C_3-C_{10} cycloalkyl-C_1-C_4 alkyl, 5-10 membered heteroaryl-C_1-C_4 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_4 alkyl;

R^F and R^f are each independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, or 4-10 membered heterocycloalkyl;

R^G, R^H and R^I, R^g, R^h and R^i are each independently selected from optional substituted C_1-C_4 alkyl or optional substituted phenyl;

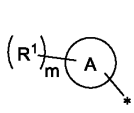
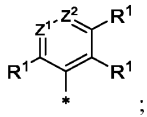
the second anti-cancer therapeutic agent is PARP inhibitor, PolQ inhibitor, chemotherapy, ionizing radiation or immune oncology medicine.

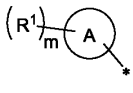
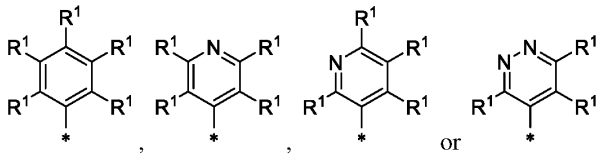
In some embodiments, ring A is selected from C_6-C_{14} aryl or 5-14 membered heteroaryl.

In some embodiments, ring A is C_6-C_{14} aryl. In some embodiments, ring A is C_6-C_{10} aryl.

In some embodiments, ring A is phenyl, naphthalenyl, anthracenyl, phenanthrenyl. In some embodiments, ring A is phenyl.

In some embodiments, ring A is 5-14 membered heteroaryl. In some embodiments, ring A is 5-10 membered heteroaryl. In some embodiments, ring A is 5 membered heteroaryl. In some embodiments, ring A is 6 membered heteroaryl.

In some embodiments,  is  ; wherein, Z^1 and Z^2 are each independently selected from N or CR^1.

In some embodiments,  is  .

In some embodiments, ring B is selected from partially unsaturated 5-14 membered heterocycloalkyl, C_6-C_{14} aryl or 5-14 membered heteroaryl.

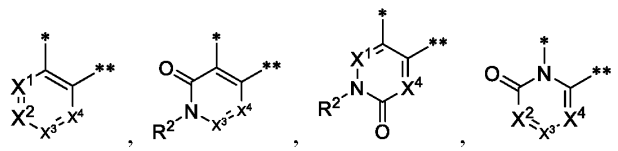
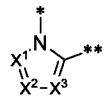
In some embodiments, ring B is partially unsaturated 5-14 membered heterocycloalkyl. In some embodiments, ring B is partially unsaturated 5-6 membered heterocycloalkyl.

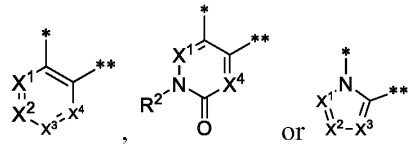
In some embodiments, ring B is C_6-C_{14} aryl. In some embodiments, ring B is C_6-C_{10} aryl.

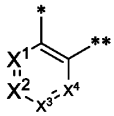
In some embodiments, ring B is phenyl, naphthalenyl, anthracenyl, phenanthrenyl. In some embodiments, ring B is phenyl.

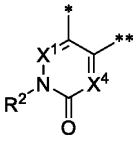
In some embodiments, ring B is 5-14 membered heteroaryl.

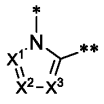
In some embodiments, ring B is 5-10 membered heteroaryl. In some embodiments, ring B is 5-6 membered heteroaryl.

In some embodiments, ring B is  ,  ; wherein, X^1, X^2, X^3 and X^4 are each independently selected from N or CR^2; and the position * is attached to C=O, the position ** is attached to ring A.

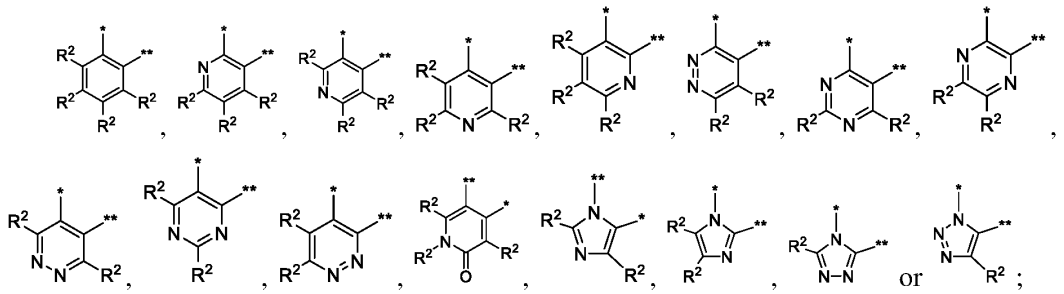
In some embodiments, ring B is  .

In some embodiments, ring B is  . In some embodiments, one of X^1, X^2, X^3, X^4 is selected from N. In some embodiments, two of X^1, X^2, X^3, X^4 are selected from N. In some embodiments, all of X^1, X^2, X^3, X^4 are selected from CR^2.

In some embodiments, ring B is  .

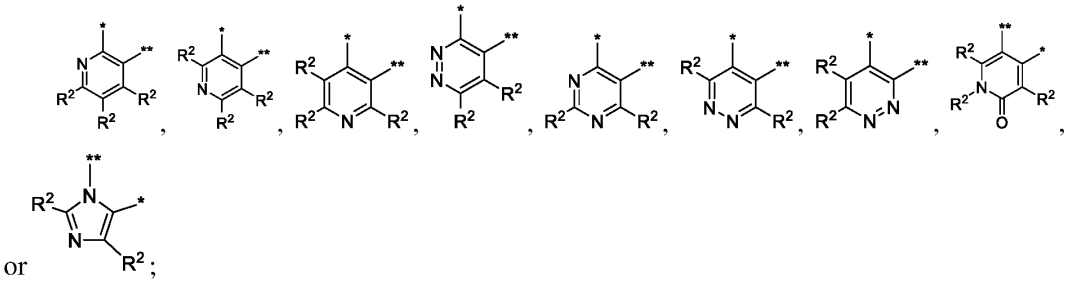
In some embodiments, ring B is  . In some embodiments, one of X^1, X^2, X^3 is selected from N. In some embodiments, two of X^1, X^2, X^3 are selected from N.

In some embodiments, ring B is:



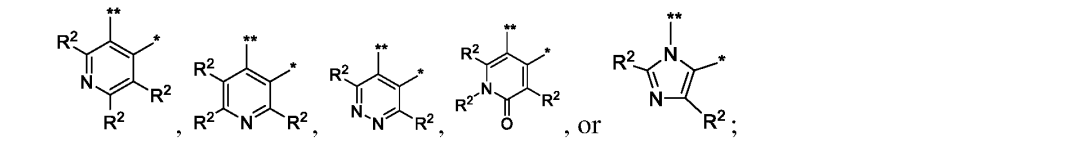
wherein, the position * is attached to ring A, the position ** is attached to C=O.

In some embodiments, ring B is:



wherein, the position * is attached to ring A, the position ** is attached to C=O.

In some embodiments, ring B is:



wherein, the position * is attached to C=O, the position ** is attached to ring A.

In some embodiments, each R^1 is independently selected from H, D, halogen, -CN, $-NO_2$, N_3, $-SF_5$, oxo.

In some embodiments, each R^1 is independently selected from H. In some embodiments, each R^1 is independently selected from D.

In some embodiments, each R^1 is independently selected from halogen. In some embodiments, each R^1 is independently selected from F, Cl, Br, I. In some embodiments, each R^1 is F. In some embodiments, each R^1 is Cl. In some embodiments, each R^1 is Br. In some embodiments, each R^1 is I.

In some embodiments, each R^1 is independently selected from CN. In some embodiments, each R^1 is independently selected from NO_2. In some embodiments, each R^1 is independently selected from N_3. In some embodiments, each R^1 is independently selected from SF_5. In some embodiments, each R^1 is independently selected from oxo.

In some embodiments, each R^1 is independently selected from NR^CR^D. In some embodiments,

for example, each R^1 is independently selected from NH_2, $NHCH_3$, $NHCH(CH_3)_2$, $NHCH_3$, $N(CH_3)_2$, $N(CH_2CH_3)_2$.

In some embodiments, each R^1 is independently selected from OR^A. In some embodiments, for example, each R^1 is independently selected from OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_2F, OCH_2CHF_2, OCH_2CF_3, -CH(OH)CH_3, OCH_2CN, OCH_2CONH_2. In some embodiments, each R^1 is independently selected from OCH_3. In some embodiments, each R^1 is independently selected from OCH_2CH_3. In some embodiments, each R^1 is independently selected from $OCH(CH_3)_2$. In some embodiments, each R^1 is independently selected from OCF_3. In some embodiments, each R^1 is independently selected from $OCHF_2$. In some embodiments, each R^1 is independently selected from OCH_2F. In some embodiments, each R^1 is independently selected from OCF_3. In some embodiments, each R^1 is independently selected from OCH_2CH_2F. In some embodiments, each R^1 is independently selected from OCH_2CHF_2. In some embodiments, each R^1 is independently selected from OCH_2CF_3. In some embodiments, each R^1 is independently selected from OCH_2CN. In some embodiments, each R^1 is independently selected from OCH_2CONH_2.

In some embodiments, each R^1 is independently selected from SR^A. In some embodiments, each R^1 is independently selected from SCH_3. In some embodiments, each R^1 is independently selected from SCH_2CH_3.

In some embodiments, each R^1 is independently selected from -$C(O)R^B$, -$C(O)NR^CR^D$, -$C(O)OR^A$, -$OC(O)R^B$, -NR^CR^D, -$NR^CC(O)R^B$, -$S(O)R^B$, -$S(O)_2R^B$, -$S(O)NR^CR^D$, -$NR^CS(O)_2R^D$, -$S(O)_2NR^CR^D$, -$NR^CS(O)_2NR^CR^D$, -$NR^CS(O)(=NR^B)R^B$, $SiR^GR^HR^I$, $B(OR^C)(OR^D)$, -$P(O)R^ER^F$, -$P(O)OR^EOR^F$, -$OP(O)OR^EOR^F$.

In some embodiments, each R^1 is independently selected from $C(O)R^B$. In some embodiments, each R^1 is independently selected from CHO, $C(O)CH_3$, $C(O)CH_2CH_3$,  , . In some embodiments, each R^1 is independently selected from $C(O)NR^CR^D$. In some embodiments, each R^1 is independently selected from -$CONH_2$, -$CONHCH_3$, -$CON(CH_3)_2$,  . In some embodiments, each R^1 is independently selected from -$C(O)OR^A$. In some embodiments, each R^1 is independently selected from -COOH. In some embodiments, each R^1 is independently selected from -$OC(O)R^B$. In some embodiments, each R^1 is independently selected from $NR^CC(O)R^B$.

In some embodiments, each R^1 is independently selected from $S(O)R^B$. In some embodiments, for example, each R^1 is independently selected from $S(O)CH_3$, $S(O)CH_2CH_3$,  , . In some embodiments, each R^1 is independently selected from $S(O)_2R^B$. In some embodiments, for example, each R^1 is independently selected from $S(O)_2CH_3$, $S(O)_2CH_2CH_3$,  , . In some embodiments, each R^1 is independently selected from $S(O)NR^CR^D$. In some embodiments, for example, each R^1 is independently selected from $S(O)_2NH_2$, $S(O)_2NHCH_3$, $S(O)_2N(CH_3)_2$. In some embodiments, each R^1 is independently selected from -$NR^CS(O)_2R^D$. In some embodiments, each

R^1 is independently selected from $NHS(O)_2CH_3$. In some embodiments, each R^1 is independently selected from $-S(O)_2NR^CR^D$. In some embodiments, each R^1 is independently selected from $-NR^CS(O)_2NR^CR^D$. In some embodiments, each R^1 is independently selected from $-NR^CS(O)(=NR^B)R^B$.

In some embodiments, each R^1 is independently selected from $SiR^GR^HR^I$. In some embodiments, each R^1 is independently selected from $B(OR^C)(OR^D)$. In some embodiments, each R^1 is independently selected from $-P(O)R^ER^F$. In some embodiments, each R^1 is independently selected from $-P(O)(CH_3)_2$. In some embodiments, each R^1 is independently selected from $-P(O)OR^EOR^F$. In some embodiments, each R^1 is independently selected from $-OP(O)OR^EOR^F$.

In some embodiments, each R^1 is independently selected from C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}.

In some embodiments, each R^1 is independently selected from C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}.

In some embodiments, each R^1 is independently selected from CD_3, CH_3, CH_2CH_3, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CH_2OH, $-CH(OH)CH_3$, CH_2CH_2OH, $-CH_2OCH_3$, $-CH_2OCHF_2$, $-CH_2OCH_2F$, $-CH_2OCF_3$, $-CH(OCH_3)CH_3$, $CH_2CH_2NH_2$, $-CH(NH_2)CH_3$, $CH_2N(CH_3)_2$, $CH_2CH_2N(CH_3)_2$, CH_2CN.

In some embodiments, each R^1 is independently selected from C_2-C_6 alkenyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}. In some embodiments, each R^1 is independently selected from $-CH=CH_2$, $-CH=CHCH_3$.

In some embodiments, each R^1 is independently selected from C_2-C_6 alkynyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}. In some embodiments, each R^1 is independently selected from $-C\equiv CH$, $-C\equiv CCH_3$.

In some embodiments, each R^1 is independently selected from C_3-C_6 cycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}. In some embodiments, each R^1 is independently selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, each ring is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}.

In some embodiments, each R^1 is independently selected from 4-6 membered heterocycloalkyl having 1 or 2 heteroatoms selected from N, O, S and B, and wherein the heteroatoms can be optionally substituted by one or more oxo (e.g., S(O), or $S(O)_2$) optionally substituted with 1, 2, 3, 4 or 5 substituents independently R^{1A}.

In some embodiments, each R^1 is independently selected from azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, or thiomorpholine dioxide, each ring is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}.

In some embodiments, each R^1 is independently selected from phenyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}.

In some embodiments, each R^1 is independently selected from 5-6 membered heteroaryl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}.

In some embodiments, two R^1 together with the atoms to which they are attached form oxo, C_3-C_7 cycloalkyl or 4-7 membered heterocycloalkyl; wherein, the C_3-C_7 cycloalkyl or 4-7 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}.

In some embodiments, two R^1 together with the atoms to which they are attached form oxo.

In some embodiments, two R^1 together with the atoms to which they are attached form C_3-C_7 cycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}.

In some embodiments, two R^1 together with the atoms to which they are attached form 4-7 membered heterocycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}.

In some embodiments, each R^{1A} is independently selected from D, halogen, CN, -NO_2, N_3, oxo, OR^a, NR^cR^d, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or 4-6 membered heterocycloalkyl is optionally substituted with D, halogen, CN, OH, NH_2, oxo, NR^cR^d, OR^a, SR^a, C_1-C_6 alkyl, C_1-C_6 haloalkyl.

In some embodiments, each R^{1A} is independently selected from D, halogen, CN, -NO_2, N_3, oxo, OR^a, NR^cR^d. In some embodiments, each R^{1A} is independently selected from D. In some embodiments, each R^{1A} is independently selected from halogen (such as F, Cl, Br, I). In some embodiments, each R^{1A} is independently selected from CN. In some embodiments, each R^{1A} is independently selected from -NO_2. In some embodiments, each R^{1A} is independently selected from N_3. In some embodiments, each R^{1A} is independently selected from oxo. In some embodiments, each R^{1A} is independently selected from OR^a (such as OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, OCH_2F, $OCHF_2$, OCF_3). In some embodiments, each R^{1A} is independently selected from NR^cR^d (NH_2, $NHCH_3$, $N(CH_3)_2$, $NHCH_2CH_2OH$, $N(CH_3)CH_2CH_2OH$).

In some embodiments, each R^{1A} is independently selected from C_1-C_6 alkyl optionally substituted with D, halogen, CN, OH, NH_2, oxo, NR^cR^d, OR^a, SR^a.

In some embodiments, each R^{1A} is independently selected from C_2-C_6 alkenyl optionally substituted with D, halogen, CN, OH, NH_2, oxo, NR^cR^d, OR^a, SR^a.

In some embodiments, each R^{1A} is independently selected from C_2-C_6 alkynyl optionally substituted with D, halogen, CN, OH, NH_2, oxo, NR^cR^d, OR^a, SR^a.

In some embodiments, each R^{1A} is independently selected from C_3-C_6 cycloalkyl (such as C_3 cycloalkyl, C_4 cycloalkyl, C_5 cycloalkyl, C_6 cycloalkyl) optionally substituted with D, halogen, CN, OH, NH_2, oxo, NR^cR^d, OR^a, SR^a, C_1-C_6 alkyl, C_1-C_6 haloalkyl.

In some embodiments, each R^{1A} is independently selected from 4-6 membered heterocycloalkyl (such as 4-membered heterocycloalkyl, 5-membered heterocycloalkyl, 6-membered heterocycloalkyl) optionally substituted with D, halogen, CN, OH, NH_2, oxo, NR^cR^d, OR^a, SR^a, C_1-C_6 alkyl, C_1-C_6 haloalkyl.

In some embodiments, each R^2 is independently selected from H, D, CN, NO_2, N_3, oxo, SF_5,

halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, $-NR^CR^D$, $-OR^A$, $-SR^A$, $-NR^COR^A$, $-C(O)R^B$, $-C(O)NR^CR^D$, $-C(O)OR^A$, $-OC(O)R^B$, $-NR^CC(O)R^B$, $-S(O)R^B$, $-S(O)_2R^B$, $-S(O)NR^CR^D$, $-NR^CS(O)_2R^D$, $-S(O)_2NR^CR^D$, $-NR^CS(O)_2NR^CR^D$, $-NR^CS(O)(=NR^B)R^B$, $SiR^GR^HR^I$, $B(OR^C)(OR^D)$, $-P(O)R^ER^F$, $-P(O)OR^EOR^F$, $-OP(O)OR^EOR^F$; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}.

In some embodiments, each R^2 is independently selected from H, D, CN, NO_2, N_3, oxo, SF_5, halogen. In some embodiments, each R^2 is independently selected from H. In some embodiments, each R^2 is independently selected from is D. In some embodiments, each R^2 is independently selected from is CN. In some embodiments, each R^2 is independently selected from is NO_2. In some embodiments, each R^2 is independently selected from is N_3. In some embodiments, each R^2 is independently selected from is SF_5.

In some embodiments, each R^2 is independently selected from is halogen. In some embodiments, each R^2 is independently selected from is F, Cl, Br or I. In some embodiments, each R^2 is independently selected from F. In some embodiments, each R^2 is independently selected from Cl. In some embodiments, each R^2 is independently selected from Br. In some embodiments, each R^2 is independently selected from I.

In some embodiments, each R^2 is independently selected from is $-NR^CR^D$. In some embodiments, each R^2 is independently selected from is NH_2, $NHCH_3$, $N(CH_3)_2$, $NHCH_2CH_3$, $N(CH_2CH_3)_2$, $NHCH_2CH_2CH_3$, $N(CH_2CH_2CH_3)_2$, $NHCH(CH_3)_2$, $NHCH_2CH_2OH$.

In some embodiments, each R^2 is independently selected from is OR^A. In some embodiments, each R^2 is independently selected from OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, OCH_2F, $OCHF_2$, OCF_3,  or  .

In some embodiments, each R^2 is independently selected from SR^A. In some embodiments, each R^2 is independently selected from SMe.

In some embodiments, each R^2 is independently selected from $-NR^COR^A$. In some embodiments, each R^2 is independently selected from $-C(O)R^B$. In some embodiments, each R^2 is independently selected from $-C(O)NR^CR^D$. In some embodiments, each R^2 is independently selected from $-C(O)OR^A$. In some embodiments, each R^2 is independently selected from $-OC(O)R^B$. In some embodiments, each R^2 is independently selected from $-NR^CC(O)R^B$. In some embodiments, each R^2 is independently selected from $-S(O)R^B$. In some embodiments, each R^2 is independently selected from $-S(O)_2R^B$. In some embodiments, each R^2 is independently selected from $-S(O)NR^CR^D$. In some embodiments, each R^2 is independently selected from $-NR^CS(O)_2R^D$. In some embodiments, each R^2 is independently selected from $-S(O)_2NR^CR^D$. In some embodiments, each R^2 is independently selected from $-NR^CS(O)_2NR^CR^D$. In some embodiments, each R^2 is independently selected from $-NR^CS(O)(=NR^B)R^B$. In some embodiments, each R^2 is independently selected from $SiR^GR^HR^I$. In some embodiments, each R^2 is independently selected from $B(OR^C)(OR^D)$. In some embodiments, each R^2 is independently selected from $-P(O)R^ER^F$. In some embodiments, each R^2 is

independently selected from -P(O)$OR^E OR^F$. In some embodiments, each R^2 is independently selected from -OP(O)$OR^E OR^F$.

In some embodiments, each R^2 is independently selected from C_1-C_6 alkyl (such as C_1-C_5 alkyl, C_1-C_4 alkyl, C_1-C_3 alkyl, C_1-C_2 alkyl) optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}. In some embodiments, each R^2 is independently selected from CH_3, CD_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2F, CHF_2, CF_3, CH_2OH, CH_2CH_2OH, CH_2CN.

In some embodiments, each R^2 is independently selected from C_2-C_6 alkenyl (such as C_2-C_5 alkenyl, C_2-C_4 alkenyl, C_2-C_3 alkenyl) optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}.

In some embodiments, each R^2 is independently selected from C_2-C_6 alkynyl (such as C_2-C_5 alkynyl, C_2-C_4 alkynyl, C_2-C_3 alkynyl) optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}.

In some embodiments, each R^2 is independently selected from C_3-C_{10} cycloalkyloptionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}.

In some embodiments, each R^2 is independently selected from saturated C_3-C_{10} cycloalkyl or partially unsaturated C_3-C_{10} cycloalkyl; each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}.

In some embodiments, each R^2 is independently selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl; each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}.

In some embodiments, each R^2 is independently selected from 4-10 membered heterocycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}.

In some embodiments, each R^2 is independently selected from saturated 4-10 membered heterocycloalkyl or partially unsaturated 4-10 membered heterocycloalkyl; each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}.

In some embodiments, each R^2 is independently selected from azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl; each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}.

In some embodiments, each R^2 is independently selected from C_6-C_{10} aryl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}.

In some embodiments, each R^2 is independently selected from C_6-C_{10} aryl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}. In some embodiments, each R^2 is independently selected from phenyl, naphthalenyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}.

In some embodiments, each R^2 is independently selected from 5-10 membered heteroaryl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}.

In some embodiments, each R^2 is independently selected from pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, tetrazolyl, pyrazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, isoindolyl, indolizinyl, benzofuranyl, isobenzofuranyl,

benzo[b]thiophenyl, benzo[c]thiophenyl, indazolyl, benzo[d]imidazolyl, pyrrolo[3,2-b]pyridinyl, pyrrolo[3,2-c]pyridinyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,4-b]pyridinyl, pyrrolo[3,4-c]pyridinyl, benzo[d]isoxazolyl, benzo[d]oxazolyl, furo[3,2-b]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, furo[2,3-b]pyridinyl, benzo[c]isoxazolyl, furo[3,4-b]pyridinyl, furo[3,4-c]pyridinyl, benzo[d]isothiazolyl, benzo[d]thiazolyl, thieno[3,2-b]pyridinyl, thieno[3,4-c]pyridinyl, benzo[d][1,2,3]triazolyl, pyrazolo[4,3-b]pyridinyl, pyrazolo[4,3-c]pyridinyl, pyrazolo[3,4-c]pyridinyl, pyrazolo[3,4-b]pyridinyl, imidazo[4,5-b]pyridinyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-b]pyridinyl, pyrrolo[3,2-c]pyridazinyl, pyrrolo[3,2-d]pyrimidinyl, pyrrolo[2,3-b]pyrazinyl, pyrrolo[2,3-d]pyridazinyl, pyrrolo[2,3-d]pyrimidinyl, pyrrolo[2,3-c]pyridazinyl, pyrrolo[3,4-c]pyridazinyl, pyrrolo[3,4-d]pyrimidinyl, pyrrolo[3,4-b]pyrazinyl, pyrrolo[3,4-d]pyridazinyl, pyrrolo[3,4-d]pyrimidinyl, 6H-pyrrolo[3,4-c]pyridazinyl; each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}.

In some embodiments, two R^2 together with the atoms to which they are attached form oxo, C_3-C_7 cycloalkyl or 4-7 membered heterocycloalkyl; wherein, the C_3-C_7 cycloalkyl or 4-7 membered heterocycloalkyl is optionally substituted by 1, 2, 3 or 4 substituents independently selected from R^{2A}.

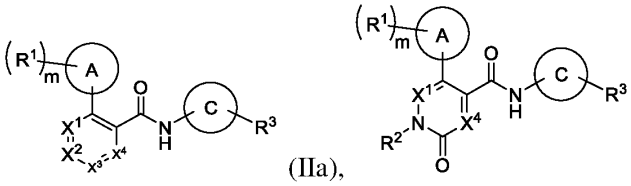
In some embodiments, two R^2 together with the atoms to which they are attached form oxo.

In some embodiments, two R^2 together with the atoms to which they are attached form C_3-C_7 cycloalkyl (such as C_3 cycloalkyl, C_4 cycloalkyl, C_5 cycloalkyl, C_6 cycloalkyl, C_7 cycloalkyl) optionally substituted by 1, 2, 3 or 4 substituents independently selected from R^{2A}.

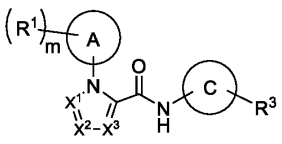
In some embodiments, two R^2 together with the atoms to which they are attached form 4-7 membered heterocycloalkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from R^{2A}.

In some embodiments, R^3 is selected from H, D, halo, CN, oxo, NO_2, SF_5, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{14} cycloalkyl, 4-14 membered heterocycloalkyl, C_6-C_{14} aryl, 5-14 membered heteroaryl, OR^A, SR^A, NR^COR^A, NR^CR^D, $C(O)R^B$, $C(O)NR^CR^D$, $NR^CC(O)R^B$, $NR^CC(O)OR^A$, $NR^CS(O)_2R^D$, $NR^CS(O)_2NR^CR^D$, $S(O)R^B$, $S(O)_2R^B$; wherein, the C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{14} cycloalkyl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl, 5-14 membered heteroaryl is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, the compounds of Formula (I) are represented by compounds of Formula (IIa), (IIb) or (IIc):


(IIa),

(IIb),

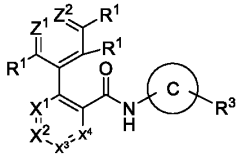
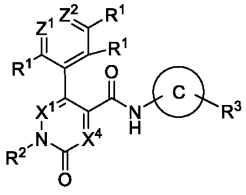
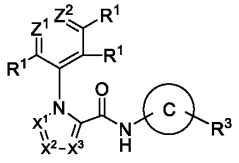

(IIc);

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof;

X^1, X^2, X^3, X^4 are each independently selected from N or CR^2;

wherein, ring A, ring C, R^1, R^2, R^3 and m are defined with respect to Formula (I).

In some embodiments, the compounds of Formula (I) are represented by compounds of Formula (IIIa), (IIIb) or (IIIc):

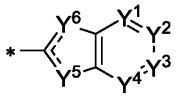
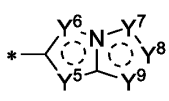
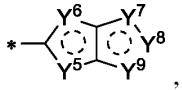
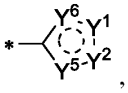
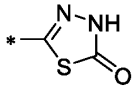
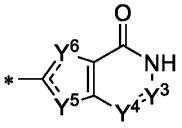
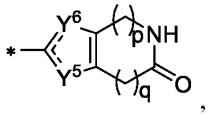
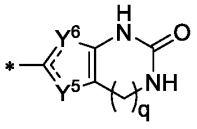
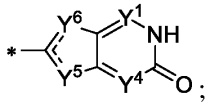

(IIIa),

(IIIb),

(IIIc);

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof;

Z^1, Z^2 are each independently selected from N or CR^1;

wherein, ring C, X^1, X^2, X^3, X^4, R^1, R^3 and m are defined as above.

In some embodiments, ring C is partially unsaturated 5-10 membered heterocycloalkyl or 5-10 membered heteroaryl; each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^6.

In some embodiments, ring C is selected from  ,  ,  ,  ,  ,  ,  ,  ,  ;

wherein, === is a single bond or double bond;

Y^1, Y^2, Y^3, Y^4 is same or different, and independently N or CH;

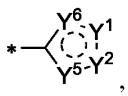
Y^5 is N, or S;

Y^6 is N, or S;

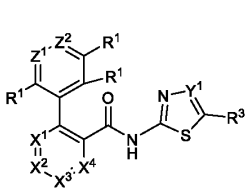
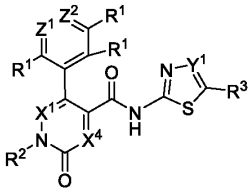
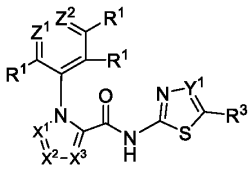
Y^7, Y^8, Y^9 are each independently selected from CH, NH, N, S;

p and q are each independently selected from 0, 1 or 2;

the position * is attached to -NHC(=O)-, R^3 is attached to any possible position on the ring C and one hydrogen atom of ring C replaced with R^3; and one or more hydrogen atoms of ring C are optionally preplaced with 1, 2, 3, 4 or 5 substituents independently selected from R^6.

In some embodiments, ring C is selected from  , and R^3 is attached to any possible position on the ring C and one hydrogen atom of ring C replaced with R^3; and one or more hydrogen atoms of ring C are optionally preplaced with 1, 2 or 3 substituents independently selected from R^6.

In some embodiments, the compounds of Formula (I) are represented by compounds of Formula (IVa), (IVb) or (IVc):


(IVa),

(IVb),

(IVc);

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof;

Y^1 is N or CR^6;

wherein, X^1, X^2, X^3, X^4, Z^1, Z^2, R^1, R^3 and m are defined as above.

In some embodiments, Y^1 is N.

In some embodiments, Y^1 is CR^6; and R^6 is H.

In some embodiments, R^3 is selected from C_1-C_{10} alkyl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$; each is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CF_2CH_3, CF_2CF_3, $CF_2CH_2CH_3$, CH_2OH, CH_2CH_2OH, $CH(OH)CH_3$, $CH_2CH_2CH_2OH$, $CH(OH)CH_2CH_2OH$, CH_2OCH_3, $CH_2CH_2OCH_3$, $CH_2CH_2CH_2OCH_3$, $CH(OH)CH_2CH_2OCH_3$, CH_2CN, CH_2CH_2CN, $CH_2CH_2CH_2CN$.

In some embodiments, R^3 is selected from C_1-C_2 alkyl optionally substituted by 1, 2, 3, or 4 substituents independently selected from R^4; and one of R^4 is OR^A, $C(O)R^B$, $C(O)NR^CR^D$, $S(O)_2R^B$, $S(O)_2NR^CR^D$ or $C(O)NR^CS(O)_2R^B$.

In some embodiments, R^3 is selected from CH_2R^4, $CH(R^4)_2$ or $C(R^4)_3$; and one of R^4 is OR^A, $C(O)R^B$, $C(O)NR^CR^D$, $S(O)_2R^B$, $S(O)_2NR^CR^D$ or $C(O)NR^CS(O)_2R^B$.

In some embodiments, R^3 is CH_2OR^A, $CH_2C(O)R^B$, $CH_2C(O)NR^CR^D$, $CH_2S(O)_2R^B$, $CH_2S(O)_2NR^CR^D$ or $C(O)NR^CS(O)_2R^B$; and CH_2 is optionally substituted by 1 or 2 R^4, and each R^4 is independently selected from D, halo, C_1-C_6 alkyl.

In some embodiments, R^A is H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CF_2CF_3, CH_2CH_2OH, $CH_2CH_2OCH_3$.

In some embodiments, R^A is phenyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, dioxanyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, azepanyl, 2-oxa-6-azaspiro[3.3]heptanyl, octahydropyrrolo[3,2-b]pyridinyl, 2-azabicyclo[2.2.2]octanyl, 2,3,4,6-tetrahydropyrrolo[3,4-b]pyrazinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, bicyclo[3.2.0]heptanyl; and each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$,

$NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, $NR^cS(O)(=NR^b)R^b$ or $SiR^gR^hR^i$.

In some embodiments, R^B is 4-10 membered heterocycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, OR^a, $C(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In some embodiments, R^B is azetidinyl, pyrrolidinyl, piperidinyl, dioxanyl, piperazinyl, morpholinyl, azepanyl; each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, OR^a, $C(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

In some embodiments, R^C is selected from H, D, C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, OR^a, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$ or $B(OR^c)(OR^d)$, and R^D is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, OR^a, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$ or $B(OR^c)(OR^d)$.

In some embodiments, R^C is H, D, CH_3, CH_2CH_3; and R^D is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2(CH_3)_2$, $CH(CH_3)_3$, CH_2CF_3, CH_2CH_2OH, $CH_2CH_2OCH_3$, CH_2CH_2CN, $CH_2CH_2N(CH_3)C(O)CH_3$, $CH_2CH_2N(CH_3)S(O)_2CH_3$, $CH_2CH_2N(CH_3)S(O)_2N(CH_3)_2$.

In some embodiments, R^3 is selected from C_2-C_{10} alkenyl (such as C_2-C_{10} alkenyl, C_2-C_9 alkenyl, C_2-C_8 alkenyl, C_2-C_7 alkenyl, C_2-C_6 alkenyl, C_2-C_5 alkenyl, C_2-C_4 alkenyl, C_2-C_3 alkenyl) optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from C_2-C_{10} alkynyl (such as C_2-C_{10} alkynyl, C_2-C_9 alkynyl, C_2-C_8 alkynyl, C_2-C_7 alkynyl, C_2-C_6 alkynyl, C_2-C_5 alkynyl, C_2-C_4 alkynyl, C_2-C_3 alkynyl) optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from C_2 alkynyl optionally substituted by R^4; and R^4 is C_1-C_6 alkyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered

heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^5.

In some embodiments, R^3 is selected from C_3-C_{14} cycloalkyl (such as C_3 cycloalkyl, C_4 cycloalkyl, C_5 cycloalkyl, C_6 cycloalkyl, C_7 cycloalkyl, C_8 cycloalkyl, C_9 cycloalkyl, C_{10} cycloalkyl, C_{11} cycloalkyl, C_{12} cycloalkyl, C_{13} cycloalkyl, C_{14} cycloalkyl) optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, spiro[3.4]octanyl, bicyclo[3.1.1]heptyl, octahydropentalenyl, cyclopentenyl, cyclopentadienyl; each is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from 4-14 membered heterocycloalkyl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from azetidinyl, oxetanyl, pyrrolidinyl, piperidinyl, dioxanyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, azepanyl, 2,7-diazaspiro[4.4]nonanyl, 3,9-diazaspiro[5.5]undecanyl, octahydropyrano[3,2-b]pyrrolyl, octahydropyrrolo[3,2-b]pyridinyl, 3-azabicyclo[3.2.1]octanyl, 3-azabicyclo[3.3.1]nonanyl, 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidinyl, 2,3,4,6-tetrahydropyrrolo[3,4-b]pyrazinyl; each is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from C_6-C_{14} aryl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4. In some embodiments, R^3 is selected from phenyl, naphthalenyl, anthracenyl, phenanthrenyl; each is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from phenyl, naphthalenyl; each is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from 5-14 membered heteroaryl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, tetrazolyl, pyrazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-b]pyridinyl, pyrrolo[3,2-c]pyridazinyl, pyrrolo[3,2-d]pyrimidinyl, pyrrolo[2,3-b]pyrazinyl, pyrrolo[2,3-d]pyridazinyl, pyrrolo[2,3-d]pyrimidinyl, pyrrolo[2,3-c]pyridazinyl, pyrrolo[3,4-c]pyridazinyl; each is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is OR^A, and R^A is selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH,

C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, $NR^cS(O)(=NR^b)R^b$ or $SiR^gR^hR^i$.

In some embodiments, R^3 is OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_2F, OCH_2CHF_2, OCH_2CF_3, OCF_2CF_3, OCH_2CH_2OH, $OCH_2CH(OH)_2$, $OCH_2CH_2OCH_3$, $OCH(CH_3)CH_2OH$, $OCH(CH_3)CH_2OCH_3$, $OCH_2CH(CH_3)OH$, $OCH_2CH(CH_3)OCH_3$, $OCH_2Si(CH_3)_3$, $OCH_2CH_2Si(CH_3)_3$, $OCH_2CH_2B(OH)_2$.

In some embodiments, R^3 is OR^A, and R^A is C_2-C_6 alkenyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is C_2-C_6 alkynyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is C_3-C_{10} cycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is 4-10 membered heterocycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$,

$S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

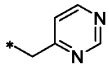
In some embodiments, R^3 is OR^A, and R^A is C_6-C_{10} aryl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is 5-10 membered heteroaryl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is C_6-C_{10} aryl-C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^A is  ; wherein, R^A is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is 5-10 membered heteroaryl-C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^A is  ,  ,  ; wherein, R^A is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4

haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is C_3-C_{10} cycloalkyl-C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^A is -CH_2-cyclopropyl, -CH_2-cyclobutyl, -CH_2-cyclopentyl, -CH_2-cyclohexyl, -CH_2-cycloheptyl; wherein R^A is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is 4-10 membered heterocycloalkyl-C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^A is -CH_2-azetidinyl, -CH_2-pyrrolidinyl, -CH_2-piperidinyl, -CH_2-dioxanyl, -CH_2-piperazinyl, -CH_2-morpholinyl, -CH_2-azepanyl, -CH_2-diazocanyl, -CH_2-2,6-diazaspiro[3.3]heptanyl, -CH_2-octahydropyrrolo[3,4-c]pyrrolyl, -CH_2-2-azabicyclo[2.2.2]octanyl, -CH_2-4,5,6,7-tetrahydropyrrolo[2,3-b]pyridinyl; wherein R^A is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is SR^A, and R^A is C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$,

$NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, $NR^cS(O)(=NR^b)R^b$ or $SiR^gR^hR^i$.

In some embodiments, R^3 is SCH_3, SCH_2CH_3, $SCH_2CH_2CH_3$, $SCH(CH_3)_2$, SCH_2CF_3, SCH_2CH_2CN, $SCH_2CH_2CH_2CN$, SCH_2CH_2OH, $SCH_2CH_2OCH_3$, $SCH_2CH_2OCH_2CH_3$, $SCH(CH_3)CH_2OCH_3$, $SCH_2CH(CH_3)OCH_3$, $SCH_2C(CH_3)_2OCH_3$, $SCH(CH_3)CH_2OH$, $SCH_2CH(CH_3)OH$, $SCH_2C(CH_3)_2OH$.

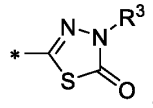
In some embodiments, R^3 is NR^COR^A.

In some embodiments, R^3 is NR^CR^D; wherein, R^C is selected from H, D, C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, OR^a, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$ or $B(OR^c)(OR^d)$, and R^D is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, OR^a, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$ or $B(OR^c)(OR^d)$.

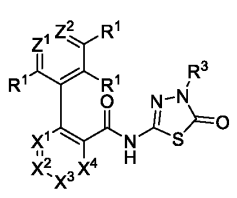
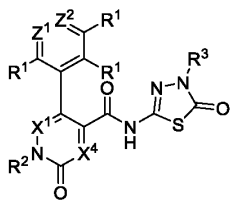
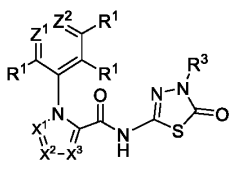
In some embodiments, R^3 is NR^CR^D; R^C is H, D, CH_3, CH_2CH_3; and R^D is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2(CH_3)_2$, $CH(CH_3)_3$, CH_2CF_3, CH_2CH_2OH, $CH_2CH_2OCH_3$, CH_2CH_2CN, $CH_2CH_2N(CH_3)C(O)CH_3$, $CH_2CH_2N(CH_3)S(O)_2CH_3$, $CH_2CH_2N(CH_3)S(O)_2N(CH_3)_2$.

In some embodiments, R^3 is $C(O)R^B$. In some embodiments, R^3 is $C(O)NR^CR^D$. In some embodiments, R^3 is $NR^CC(O)R^B$. In some embodiments, R^3 is $NR^CC(O)OR^A$.

In some embodiments, R^3 is $NR^CS(O)_2R^D$. In some embodiments, R^3 is $NR^CS(O)_2NR^CR^D$. In some embodiments, R^3 is $S(O)R^B$. In some embodiments, R^3 is $S(O)_2R^B$.

In some embodiments, ring C is  .

In some embodiments, the compounds of Formula (I) are represented by compounds of Formula (Va), (Vb) or (Vc):

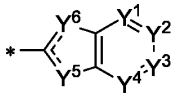
 (Va),  (Vb),  (Vc);

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof;

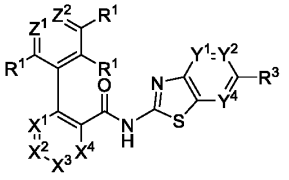
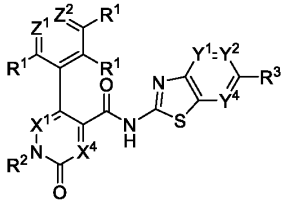
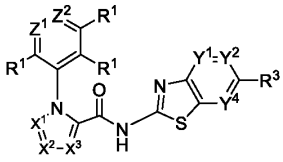
wherein, X^1, X^2, X^3, X^4, Z^1, Z^2, R^1, R^3 and m are defined as above.

In some embodiments, R^3 is C_1-C_{10} alkyl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4. In some embodiments, R^3 is C_1-C_8 alkyl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4. In some embodiments, R^3 is C_1-C_6 alkyl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CF_2CH_3, CF_2CF_3, $CF_2CH_2CH_3$, CH_2OH, CH_2CH_2OH, $CH(OH)CH_3$, $CH_2CH_2CH_2OH$, $CH(OH)CH_2CH_2OH$, CH_2OCH_3, $CH_2CH_2OCH_3$, $CH_2CH_2CH_2OCH_3$, $CH(OH)CH_2CH_2OCH_3$, CH_2CN, CH_2CH_2CN, $CH_2CH_2CH_2CN$.

In some embodiments, ring C is selected from  ; and R^3 is attached to any possible position on the ring C and one hydrogen atom of ring C replaced with R^3; and one or more hydrogen atoms of ring C are optionally preplaced with 1, 2, 3, 4 or 5 substituents independently selected from R^6.

In some embodiments, the compounds of Formula (I) are represented by compounds of Formula (VIa), (VIb) or (VIc):

 (VIa),  (VIb),  (VIc);

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof;

Y^1, Y^2, Y^4 are each independently selected from N or CR^6;

wherein, X^1, X^2, X^3, X^4, Z^1, Z^2, R^1, R^3 and m are defined with respect to Formula (I).

In some embodiments, Y^1 is CR^6, Y^2 is CR^6, and Y^4 is CR^6.

In some embodiments, Y^1 is CR^6, Y^2 is CR^6, and Y^4 is N.

In some embodiments, Y^1 is CR^6, Y^2 is N, and Y^4 is CR^6.

In some embodiments, Y^1 is CR^6, Y^2 is N, and Y^4 is N.

In some embodiments, Y^1 is N, Y^2 is CR^6, and Y^4 is CR^6.

In some embodiments, Y^1 is N, Y^2 is CR^6, and Y^4 is N.

In some embodiments, R^3 is OR^A, and R^A is selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclalkyl, C_6-C_{10} aryl, 5-10 membered

heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, $NR^cS(O)(=NR^b)R^b$ or $SiR^gR^hR^i$.

In some embodiments, R^3 is OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_2F, OCH_2CHF_2, OCH_2CF_3, OCF_2CF_3, OCH_2CH_2OH, $OCH_2CH_2OCH_3$, $OCH(CH_3)CH_2OH$, $OCH(CH_3)CH_2OCH_3$, $OCH_2CH(CH_3)OH$, $OCH_2CH(CH_3)OCH_3$, $OCH_2Si(CH_3)_3$, $OCH_2CH_2Si(CH_3)_3$.

In some embodiments, R^3 is OR^A, and R^A is C_2-C_6 alkenyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is C_2-C_6 alkynyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is C_3-C_{10} cycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is 4-10 membered heterocycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4

haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is C_6-C_{10} aryl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is 5-10 membered heteroaryl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is C_6-C_{10} aryl-C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is 5-10 membered heteroaryl-C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is C_3-C_{10} cycloalkyl-C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is OR^A, and R^A is 4-10 membered heterocycloalkyl-C_1-C_6 alkyl

optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$.

In some embodiments, R^3 is selected from C_1-C_{10} alkyl (such as C_1-C_{10} alkyl, C_1-C_9 alkyl, C_1-C_8 alkyl, C_1-C_7 alkyl, C_1-C_6 alkyl, C_1-C_5 alkyl, C_1-C_4 alkyl, C_1-C_3 alkyl, C_1-C_2 alkyl) optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CF_2CH_3, CF_2CF_3, $CF_2CH_2CH_3$, CH_2OH, CH_2CH_2OH, $CH(OH)CH_3$, $CH_2CH_2CH_2OH$, $CH(OH)CH_2CH_2OH$, CH_2OCH_3, $CH_2CH_2OCH_3$, $CH_2CH_2CH_2OCH_3$, $CH(OH)CH_2CH_2OCH_3$, CH_2CN, CH_2CH_2CN, $CH_2CH_2CH_2CN$.

In some embodiments, R^3 is selected from C_3-C_{14} cycloalkyl (such as C_3 cycloalkyl, C_4 cycloalkyl, C_5 cycloalkyl, C_6 cycloalkyl, C_7 cycloalkyl, C_8 cycloalkyl, C_9 cycloalkyl, C_{10} cycloalkyl, C_{11} cycloalkyl, C_{12} cycloalkyl, C_{13} cycloalkyl, C_{14} cycloalkyl) optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, spiro[3.4]octanyl, bicyclo[3.1.1]heptyl, octahydropentalenyl, cyclopentenyl, cyclopentadienyl; each is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

In some embodiments, R^3 is selected from 4-14 membered heterocycloalkyl (such as 4-membered heterocycloalkyl, 5-membered heterocycloalkyl, 6-membered heterocycloalkyl, 7-membered heterocycloalkyl, 8-membered heterocycloalkyl, 9-membered heterocycloalkyl, 10-membered heterocycloalkyl, 11-membered heterocycloalkyl, 12-membered heterocycloalkyl, 13-membered heterocycloalkyl, 14-membered heterocycloalkyl) optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

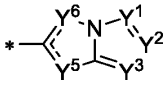
In some embodiments, R^3 is selected from azetidinyl, oxetanyl, pyrrolidinyl, piperidinyl, dioxanyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, azepanyl, 2,7-diazaspiro[4.4]nonanyl, 3,9-diazaspiro[5.5]undecanyl, octahydropyrano[3,2-b]pyrrolyl, octahydropyrrolo[3,2-b]pyridinyl, 3-azabicyclo[3.2.1]octanyl, 3-azabicyclo[3.3.1]nonanyl, 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidinyl, 2,3,4,6-tetrahydropyrrolo[3,4-b]pyrazinyl; each is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

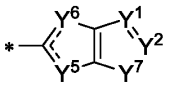
In some embodiments, R^3 is selected from C_6-C_{14} aryl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4. In some embodiments, R^3 is selected from phenyl, naphthalenyl, anthracenyl, phenanthrenyl; each is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

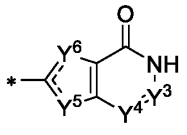
In some embodiments, R^3 is selected from 5-14 membered heteroaryl (such as 5-membered heteroaryl, 6-membered heteroaryl, 7-membered heteroaryl, 8-membered heteroaryl, 9-membered heteroaryl, 10-membered heteroaryl, 11-membered heteroaryl, 12-membered heteroaryl, 13-

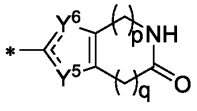
membered heteroaryl, 14-membered heteroaryl) optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

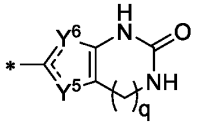
In some embodiments, R^3 is selected from pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, tetrazolyl, pyrazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-b]pyridinyl, pyrrolo[3,2-c]pyridazinyl, pyrrolo[3,2-d]pyrimidinyl, pyrrolo[2,3-b]pyrazinyl, pyrrolo[2,3-d]pyridazinyl, pyrrolo[2,3-d]pyrimidinyl, pyrrolo[2,3-c]pyridazinyl, pyrrolo[3,4-c]pyridazinyl; each is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

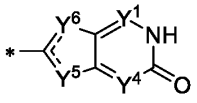
In some embodiments, ring C is  ; R^3 is attached to any possible position on the ring C and one hydrogen atom of ring C replaced with R^3; and one or more hydrogen atoms of ring C are optionally preplaced with 1, 2, 3, 4 or 5 substituents independently selected from R^6.

In some embodiments, ring C is  ; and R^3 is attached to any possible position on the ring C; and ring C is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^6.

In some embodiments, ring C is  ; and R^3 is attached to any possible position on the ring C and one hydrogen atom of ring C replaced with R^3; and one or more hydrogen atoms of ring C are optionally preplaced with 1, 2, 3, 4 or 5 substituents independently selected from R^6.

In some embodiments, ring C is  ; and R^3 is attached to any possible position on the ring C and one hydrogen atom of ring C replaced with R^3; and one or more hydrogen atoms of ring C are optionally preplaced with 1, 2, 3, 4 or 5 substituents independently selected from R^6.

In some embodiments, ring C is  ; and R^3 is attached to any possible position on the ring C and one hydrogen atom of ring C replaced with R^3; and one or more hydrogen atoms of ring C are optionally preplaced with 1, 2, 3, 4 or 5 substituents independently selected from R^6.

In some embodiments, ring C is  ; and R^3 is attached to any possible position on the ring C and one hydrogen atom of ring C replaced with R^3; and one or more hydrogen atoms of ring C are optionally preplaced with 1, 2, 3, 4 or 5 substituents independently selected from R^6.

In some embodiments, the compound of Formula (I) is:

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-

yl)-6-methylnicotinamide;

N-(5-((4-cyanophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxy-3-(trifluoromethyl)phenyl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoroethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-((2-methoxyethyl)thio)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-(dimethylamino)-1,1-difluoro-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(6-(2-methoxyethoxy)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-methoxyethoxy)thiazolo[5,4-d]pyrimidin-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoro-2-(methylamino)-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methyl-N-(5-((trimethylsilyl)methoxy)-1,3,4-thiadiazol-2-yl)nicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1-fluorocyclopropyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoro-2-hydroxyethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoro-2-hydroxyethyl-2,2-d2)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(4-(3-hydroxypropyl)-5-oxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoro-2-(4-methylpiperazin-1-yl)-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-(4-cyanopiperidin-1-yl)-1,1-difluoro-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-(4-ethylpiperazin-1-yl)-1,1-difluoro-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-hydroxyethoxy)thiazolo[5,4-d]pyrimidin-2-yl)-6-methylnicotinamide;

4-(2-fluoro-6-methoxyphenyl)-N-(5-(2-methoxypropoxy)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinamide;

2'-chloro-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-7-fluorothiazolo[4,5-c]pyridin-2-yl)-3'-fluoro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide;

2'-chloro-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-7-fluorothiazolo[4,5-c]pyridin-2-yl)-5'-

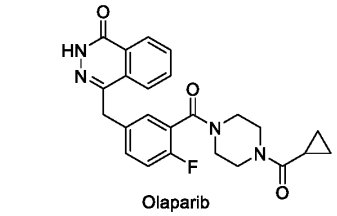
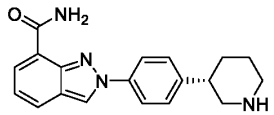
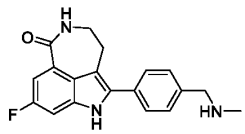
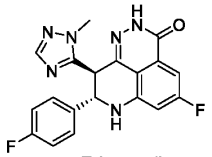
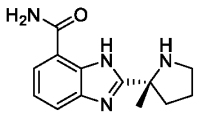
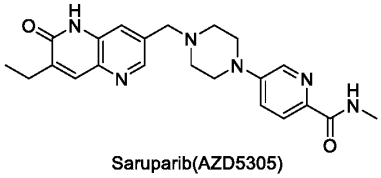
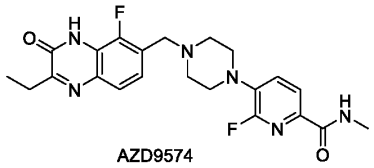
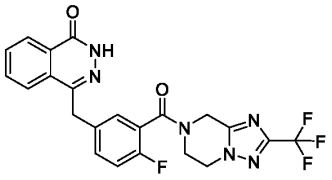
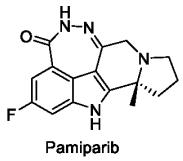
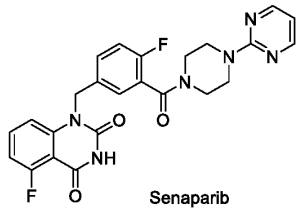
methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide;

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof.

In some embodiments, the compound of Formula (I) is optionally in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

In some embodiments, the second anti-cancer therapeutic agent is PARP inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof; preferably, the PARP inhibitor is selected from Olaparib, Rucaparib, Niraparib, Talazoparib, Fluzoparib, Pamiparib, Veliparib, Senaparib, Saruparib, AZD9574, TQB3823, HTMC0435, SC10914, TSL-1502, WXFL10040340, RP12146, IMP1734, HRS-1167, NMS-293, NMS-P515, HS-10502, SNV-001, or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof.

In some embodiments, the PARP inhibitor is:


Olaparib ,

Niraparib ,

Rucaparib ,

Talazoparib ,

Veliparib ,

Saruparib(AZD5305) ,

AZD9574 ,

Fluzoparib ,

Pamiparib ,

Senaparib , or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof.

In some embodiments, the PARP inhibitor is Olaparib.

In some embodiments, the PARP inhibitor is Niraparib or Niraparib tosylate monohydrate.

In some embodiments, the PARP inhibitor is Saruparib.

In some embodiments, the PARP inhibitor is AZD9574.

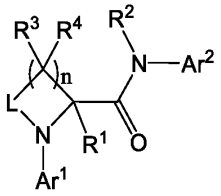
In some embodiments, the second anti-cancer therapeutic agent is chemotherapies; preferably, chemotherapy is Bleomycin or Irinotecan.

In some embodiments, the chemotherapy is Bleomycin.

In some embodiments, the chemotherapy is Irinotecan.

In some embodiments, the second anti-cancer therapeutic agent is another PolQ inhibitor.

In some embodiments, another PolQ inhibitor is represented by the compound of formula (Ia):



(Ia),

or pharmaceutically acceptable salt, stereoisomer, solvate, hydrate, tautomeric, isotopic variants, prodrugs, N-oxide or deuterated compound thereof;

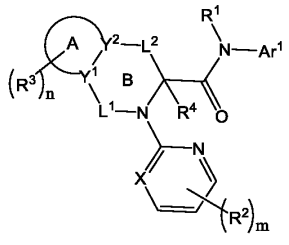
wherein each of the variables Ar^1, Ar^2, L, R^1, R^2, R^3, R^4 and n is as defined and described in PCT/CN2023/095706 (WO2023226964A1), filing date: May 23, 2023.

In some embodiments, the compound of Formula (Ia) is:

(S)-N-(4-chloro-3-methylphenyl)-N,5-dimethyl-2-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-1,2,5-thiadiazolidine-3-carboxamide 1,1-dioxide;

or pharmaceutically acceptable salt, stereoisomer, solvate, hydrate, tautomeric, isotopic variants, prodrugs, N-oxide or deuterated compound thereof.

In some embodiments, another PolQ inhibitor is represented by the compound of formula compound of formula (Ib):



(Ib)

or pharmaceutically acceptable salt, stereoisomer, solvate, hydrate, tautomeric, isotopic variants, prodrugs, N-oxide or deuterated compound thereof, wherein:

wherein each of the variables Ar^1, L^1, L^2, Y^1, Y^2, R^1, R^2, R^3, R^4, m and n is as defined and described in PCT/CN2023/095881 (WO2023241322A1), filing date: May 23, 2023.

In some embodiments, the second anti-cancer therapeutic agent is optionally in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

The present disclosure also provides a method of treating and/or preventing of a cancer in a subject, wherein the cancer is characterized by increased dependence upon MMEJ DSB repair; the cancer is characterized by HR-deficiency, a reduction or absence of expression of HR-associated genes; the cancer is lack of 53BP1/Shieldin complex in a patient;; or the cancer is characterized by NHEJ deficiency, a reduction or absence of expression of NHEJ-associated genes; or the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, absence of BRCA protein, or reduced function of BRCA protein, comprising administering to the patient a therapeutically effective amount of a combination of the present disclosure.

In some embodiments, the cancer is endometrial cancer, pancreatic cancer, breast cancer,

ovarian cancer (ovary cancer), prostate cancer, lymphoma, rhabdoid tumor, multiple myloma, uterine cancer, gastric cancer, peripheral nervous system cancer, rhabdomyosarcoma, bone cancer, colorectal cancer, mesothelioma, lung cancer, fibroblast cancer, central nervous system cancer, urinary tract cancer, upper aerodigestive cancer, leukemia, kidney cancer, skin cancer, esophageal cancer.

The present disclosure also provides a combination of the present disclosure for use in the treatment of a cancer in a subject, wherein the cancer is characterized by increased dependence upon MMEJ DSB repair; the cancer is characterized by HR-deficiency, a reduction or absence of expression of HR-associated genes; the cancer is lack of 53BP1/Shieldin complex in a patient; the cancer is characterized by NHEJ deficiency, a reduction or absence of expression of NHEJ-associated genes; or the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, absence of BRCA protein, or reduced function of BRCA protein.

In some embodiments, the cancer is endometrial cancer, pancreatic cancer, breast cancer, ovarian cancer (ovary cancer), prostate cancer, lymphoma, rhabdoid tumor, multiple myloma, uterine cancer, gastric cancer, peripheral nervous system cancer, rhabdomyosarcoma, bone cancer, colorectal cancer, mesothelioma, lung cancer, fibroblast cancer, central nervous system cancer, urinary tract cancer, upper aerodigestive cancer, leukemia, kidney cancer, skin cancer, esophageal cancer.

The present disclosure also provides use of a combination of the present disclosure in the treatment of a cancer in a subject, wherein the cancer is characterized by increased dependence upon MMEJ DSB repair; the cancer is characterized by HR-deficiency, a reduction or absence of expression of HR-associated genes; the cancer is lack of 53BP1/Shieldin complex in a patient; the cancer is characterized by NHEJ deficiency, a reduction or absence of expression of NHEJ-associated genes; or the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, absence of BRCA protein, or reduced function of BRCA protein.

In some embodiments, the cancer is endometrial cancer, pancreatic cancer, breast cancer, ovarian cancer (ovary cancer), prostate cancer, lymphoma, rhabdoid tumor, multiple myloma, uterine cancer, gastric cancer, peripheral nervous system cancer, rhabdomyosarcoma, bone cancer, colorectal cancer, mesothelioma, lung cancer, fibroblast cancer, central nervous system cancer, urinary tract cancer, upper aerodigestive cancer, leukemia, kidney cancer, skin cancer, esophageal cancer.

The present disclosure also provides use of a combination of the present disclosure in the preparation of a medicament for the treatment of a cancer in a subject, wherein the cancer is characterized by increased dependence upon MMEJ DSB repair; the cancer is characterized by HR-deficiency, a reduction or absence of expression of HR-associated genes; the cancer is lack of 53BP1/Shieldin complex in a patient; the cancer is characterized by NHEJ deficiency, a reduction or absence of expression of NHEJ-associated genes; or the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, absence of BRCA protein, or reduced function of BRCA protein.

In some embodiments, the cancer is endometrial cancer, pancreatic cancer, breast cancer,

ovarian cancer (ovary cancer), prostate cancer, lymphoma, rhabdoid tumor, multiple myloma, uterine cancer, gastric cancer, peripheral nervous system cancer, rhabdomyosarcoma, bone cancer, colorectal cancer, mesothelioma, lung cancer, fibroblast cancer, central nervous system cancer, urinary tract cancer, upper aerodigestive cancer, leukemia, kidney cancer, skin cancer, esophageal cancer.

The present disclosure also provides use of a combination of the present disclosure in the manufacture of a medicament for treating a disease characterized by overexpression of PolQ in a patient.

The present disclosure also provides a kit comprising a combination of the present disclosure, in which optionally both or either of the PolQ inhibitor and the second anti-cancer therapeutic agent in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the assessment of viability of Compound 1 in combination with Bleomycin against Ishikawa cells.

Figure 2 depicts the assessment of viability of Compound 1 in combination with Olaparib against Ishikawa cells.

Figure 3 depicts the assessment of viability of Compound 1 in combination with Olaparib against DLD1-BRCA2-KO cells.

Figure 4 depicts the assessment of viability of Compound 3 in combination with Olaparib against Canpan-1 cells.

Figure 5 depicts the assessment of viability of Compound 4 in combination with Olaparib against Canpan-1 cells.

Figure 6 depicts the assessment of viability of Compound 5 in combination with Olaparib against Canpan-1 cells.

Figure 7 depicts the assessment of viability of Compound 1 in combination with Olaparib against HCC1569 cells.

Figure 8 depicts the assessment of viability of Compound 3 in combination with Olaparib against MDA-MB-436 cells.

Figure 9 depicts the assessment of viability of Compound 4 in combination with Olaparib against MDA-MB-436 cells.

Figure 10 depicts the assessment of viability of Compound 7 in combination with Olaparib against MDA-MB-436 cells.

Figure 11 depicts the assessment of viability of Compound 3 in combination with Niraparib against HCC1937 cells.

Figure 12 depicts the assessment of viability of Compound 4 in combination with Olaparib against HCC1937 cells.

Figure 13 depicts the assessment of viability of Compound 5 in combination with Olaparib against HCC1937 cells.

Figure 14 depicts the assessment of viability of Compound 6 in combination with Olaparib

against HCC1937 cells.

Figure 15 depicts the assessment of viability of Compound 7 in combination with Olaparib against HCC1937 cells.

Figure 16 depicts the assessment of viability of Compound 2 in combination with Compound A against HCC1937 cells.

Figure 17 depicts the assessment of viability of Compound 1 in combination with Olaparib against TOV21G cells.

Figure 18 shows the anti-tumor effects of female nude mice orally treated once daily with 100 mg/kg Compound 9 as a single agent or in combination with 25 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 19 shows the anti-tumor effects of female nude mice orally treated once daily with 50 mg/kg Compound 5 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 20 shows the anti-tumor effect of female nude mice orally treated once daily with 100 mg/kg Compound 4 as a single agent or in combination with 25 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 21 shows the anti-tumor effect of female nude mice orally treated once daily with 100 mg/kg compound 10 as a single agent or in combination with 25 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 22 shows the anti-tumor effect of female nude mice orally treated once daily with 100 mg/kg Compound 11 as a single agent or in combination with 25 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 23 shows the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg, 50 mg/kg, Compound 3 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 24 shows the anti-tumor effect of female nude mice orally treated once daily with 50 mg/kg Compound 12 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 25 shows the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 13 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 26 shows the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 7 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 27 shows the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 14 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 28 shows the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 15 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 29 shows the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 16 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 30 shows the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 8 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 31 shows the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 17 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

Figure 32 shows the anti-tumor effects in female nude mice treated once daily with Compound 5, either alone or in combination with 30 mg/kg Niraparib, in the DLD1-BRCA2-KO CDX model.

Figure 33 shows the anti-tumor effects in female nude mice treated once daily with Compound 5, either alone or in combination with 30 mg/kg Niraparib, in the DLD1-BRCA2-KO CDX model.

Figure 34 shows the anti-tumor effects in female nude mice treated once daily with Compound 13, either alone or in combination with 30 mg/kg Niraparib, in the DLD1-BRCA2-KO CDX model.

Figure 35 shows the anti-tumor effects in female nude mice treated once daily with Compound 2, Compound 19, Compound 20, either alone or in combination with 100 mg/kg Olaparib, in the DLD1-BRCA2-KO CDX model.

Figure 36 shows the anti-tumor effects in female NCG mice treated twice daily with Compound 5, either in combination with 20 mg/kg Niraparib (once daily), in the MDA-MB-436 CDX model.

Figure 37 shows the anti-tumor effects in female NCG mice treated twice daily with Compound 13, either in combination with 20 mg/kg Niraparib (once daily), in the MDA-MB-436 CDX model.

Figure 38 shows the anti-tumor effects in female nude mice treated once daily with Compound 13, either in combination with 50 mg/kg Olaparib, in the MDA-MB-436 CDX model.

Figure 39 shows the anti-tumor effects in female nude mice treated once daily with Compound 13, either in combination with 5 mg/kg Irinotecan (i.p., once weekly), in the MDA-MB-436 CDX model.

Definitions

Unless other indicated, the following terms are intended to have the meaning set forth below. Other terms are defined elsewhere throughout the specification.

As used herein, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology such as “solely”, “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation.

At various places in the present specification, variables defining divalent linking groups are described. It is specifically intended that each linking substituent include both the forward and backward forms of the linking substituent. For example, -NR(CR'R”)- includes both -NR(CR'R”)-

and -(CR'R")NR- and is intended to disclose each of the forms individually. Where the structure requires a linking group, the Markush variables listed for that group are understood to be linking groups. For example, if the structure requires a linking group and the Markush group definition for that variable list "alkyl" or "aryl" then it is understood that the "alkyl" or "aryl" represents a linking alkylene group or arylene group, respectively.

The term "substituted" means that an atom or group of atoms formally replaces hydrogen as a "substituent" attached to another group. The term "substituted", unless otherwise indicated, refers to any level of substitution, *e.g.,* mono-, di-, tri-, tetra- or penta-substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position. It is to be understood that substitution at a given atom is limited by valency. The phrase "optionally substituted" means unsubstituted or substituted. The term "substituted" means that a hydrogen atom is removed and replaced by a substituent. A single divalent substituent, *e.g.,* oxo, can replace two hydrogen atoms.

The term "Cn-Cm" indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. For example, the term "C_1-C_6 alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl. "C_0 alkyl" refers to a covalent bond.

It is further intended that the compounds of the invention are stable. As used herein "stable" refers to a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and preferably capable of formulation into an efficacious therapeutic agent.

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable sub-combination.

As used herein, unless otherwise indicated, the term "alkyl", by itself or as part of another substituent, is meant to refer to a saturated hydrocarbon group which is straight-chained or branched. An alkyl group can contain from 1 to about 20, from 2 to about 20, from 1 to about 10, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3 carbon atoms. Examples, alkyl can include any number of carbons, such as C_{1-2} alkyl, C_{1-3} alkyl, C_{1-4} alkyl, C_{1-5} alkyl, C_{1-6} alkyl, C_{1-7} alkyl, C_{1-8} alkyl, C_{1-9} alkyl, C_{1-10} alkyl, C_{2-3} alkyl, C_{2-4} alkyl, C_{2-5} alkyl, C_{2-6} alkyl, C_{3-4} alkyl, C_{3-5} alkyl, C_{3-6} alkyl, C_{4-5} alkyl, C_{4-6} alkyl and C_{5-6} alkyl. Similarly, C_{1-8}, as in C_{1-8} alkyl is defined to identify the group as having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms in a linear or branched arrangement. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, t-butyl), pentyl (e.g., n-pentyl, isopentyl, neopentyl), hexyl, heptyl, octyl, and the like.

As used herein, unless otherwise indicated, "alkenyl" refers to an alkyl group having one or more double carbon-carbon bonds. Alkenyl can include any number of carbons, such as C_{2-3} alkenyl, C_{2-4} alkenyl, C_{2-5} alkenyl, C_{2-6} alkenyl, C_{2-7} alkenyl, C_{2-8} alkenyl, C_{2-9} alkenyl, C_{2-10} alkenyl, C_{3-4} alkenyl, C_{3-5} alkenyl, C_{3-6} alkenyl, C_{4-5} alkenyl, C_{4-6} alkenyl and C_{5-6} alkenyl. Example alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, pentenyl, hexenyl, and the like.

The one or more carbon-carbon double bonds can be internal (such as in 2-butene) or terminal (such as in 1-butene).

As used herein, unless otherwise indicated, "alkynyl" refers to an alkyl group having one or more triple carbon-carbon bonds. Alkynyl can include any number of carbons, such as C_{2-3} alkynyl, C_{2-4} alkynyl, C_{2-5} alkynyl, C_{2-6} alkynyl, C_{2-7} alkynyl, C_{2-8} alkynyl, C_{2-9} alkynyl, C_{2-10} alkynyl, C_{3-4} alkynyl, C_{3-5} alkynyl, C_{3-6} alkynyl, C_{4-5} alkynyl, C_{4-6} alkynyl and C_{5-6} alkynyl. Example alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, and the like. The one or more carbon-carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne).

As used herein, unless otherwise indicated, "haloalkyl" refers to an alkyl group having one or more halogen substituents. Example haloalkyl groups include, but are not limited to, CF_3, C_2F_5, CHF_2, CH_2F, CCl_3, $CHCl_2$, C_2Cl_5, and the like.

As used herein, unless otherwise indicated, "aryl" refers to an unsubstituted or substituted monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic hydrocarbons. In some embodiments, aryl groups have from 6 to about 20 carbon atoms. In some embodiments, aryl groups have from 6 to about 14 carbon atoms. In some embodiments, aryl groups have from 6 to about 10 carbon atoms. Example aryl groups include, but are not limited to, phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like.

As used herein, unless otherwise indicated, "cycloalkyl" refers to an unsubstituted or substituted non-aromatic carbocycles including cyclized alkyl, alkenyl, and alkynyl groups. Cycloalkyl groups can include mono- or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) ring systems, including fused rings, spirocyclic rings, and bridged rings (*e.g.*, a bridged bicycloalkyl group). In some embodiments, cycloalkyl groups can have from 3 to about 20 carbon atoms, 3 to about 14 carbon atoms, 3 to about 10 carbon atoms, or 3 to 7 carbon atoms. Cycloalkyl groups can further have 0, 1, 2, or 3 double bonds and/or 0, 1, or 2 triple bonds. Cycloalkyl groups can be optionally substituted by oxo or sulfido (e.g., -C(O)- or -C(S)-). Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo derivatives of pentane, pentene, hexane, and the like. A cycloalkyl group having one or more fused aromatic rings can be attached though either the aromatic or non-aromatic portion. One or more ring-forming carbon atoms of a cycloalkyl group can be oxidized, for example, having an oxo or sulfido substituent. In some embodiments, the cycloalkyl is a C_3-C_7 monocyclic cycloalkyl. In some embodiments, the cycloalkyl is a C_4-C_{10} spirocycle or bridged cycloalkyl. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, cubane, adamantane, bicyclo[l.l.l]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, bicyclo[2.2.2]octanyl, spiro[3.3]heptanyl, and the like. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, cycloalkyl are cyclic-containing, non-aromatic hydrocarbon groups having from 3 to 12 carbon atoms ("C_3-C_{12}"), preferably from 3 to 6 carbon atoms ("C_3-C_6"). Examples of cycloalkyl groups include, for example,

cyclopropyl (C_3; 3-membered), cyclobutyl (C_4; 4-membered), cyclopropylmethyl (C_4), cyclopentyl (C_5), cyclohexyl (C_6), 1-methylcyclopropyl (C_4), 2-methylcyclopentyl (C_4), adamantanyl (C_{10}), and the like.

The term "spirocycloalkyl" when used alone or as part of a substituent group refers to a non-aromatic hydrocarbon group containing two cycloalkyl rings, and wherein the two cycloalyl rings share a single carbon atom in common.

As used herein, unless otherwise indicated, a "heteroaryl" group refers to an unsubstituted or substituted aromatic heterocycle having at least one heteroatom ring member such as boron, silicon, sulfur, oxygen, nitrogen or phosphine. Heteroaryl groups include monocyclic and polycyclic (e.g., having 2, 3 or 4 fused rings) systems. Any ring-forming N atom in a heteroaryl group can also be oxidized to form an N-oxo moiety. Examples of heteroaryl groups include without limitation, pyridyl, N-oxopyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrryl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, and the like. A heteroaryl group containing a fused non-aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused non-aromatic ring. In some embodiments, the heteroaryl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heteroaryl group contains 3 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heteroaryl group has 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms.

As used herein, unless otherwise indicated, "heterocycloalkyl" refers to an unsubstituted or substituted monocyclic (saturated or partially unsaturated ring) or polycyclic heterocycles having at least one non-aromatic ring (saturated or partially unsaturated ring), wherein one or more of the ring-forming carbon atoms of the heterocycloalkyl is replaced by a heteroatom selected from N, O, P, S, Si and B, and wherein the ring-forming carbon atoms and heteroatoms of the heterocycloalkyl group can be optionally substituted by one or more oxo or sulfido (e.g., C(O), P(O), S(O), C(S), or $S(O)_2$, etc.). Heterocycloalkyl groups include monocyclic and polycyclic (e.g., having 2, 3 or 4 fused rings) systems. Included in heterocycloalkyl are monocyclic and polycyclic 3-10, 4-10, 3-7, 4-7, and 5-6 membered heterocycloalkyl groups. Heterocycloalkyl groups can also include spirocycles and bridged rings (e.g., a 5-10 membered bridged biheterocycloalkyl ring having one or more of the ring-forming carbon atoms replaced by a heteroatom independently selected from N, O, P, S, Si and B). The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds.

Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the non-aromatic heterocyclic ring, for example, benzo or thienyl derivatives of piperidine, morpholine, azepine, etc. A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring- forming atom including a ring-forming atom of the fused aromatic ring. In some embodiments, the heterocycloalkyl group contains

3 to 10 ring-forming atoms, 4 to 10 ring- forming atoms, 3 to 7 ring-forming atoms, or 5 to 6 ring-forming atoms. In some embodiments, the heterocycloalkyl group has 1 to 4 heteroatoms, 1 to 3 heteroatoms, 1 to 2 heteroatoms or 1 heteroatom. In some embodiments, the heterocycloalkyl is a monocyclic 4-6 membered heterocycloalkyl having 1 or 2 heteroatoms independently selected from N, O, S and B and having one or more oxidized ring members.

Example heterocycloalkyl groups include, but are not limited to, pyrrolidin-2-one, l,3-isoxazolidin-2-one, pyranyl, tetrahydropyran, oxetanyl, azetidinyl, morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, azepanyl, benzazapene, 1,2,3,4-tetrahydroisoquinoline, azabicyclo[3.1.0]hexanyl, diazabicyclo[3.l.0]hexanyl, oxabicyclo[2.1.l]hexanyl, azabicyclo[2.2.l]heptanyl, diazabicyclo[2.2.1]heptanyl, azabicyclo[3.1.l] heptanyl, diazabicyclo[3.1.l]heptanyl, azabicyclo[3.2.l]octanyl, diazabicyclo[3.2.1]octanyl, oxabicyclo[2.2.2]octanyl, azabicyclo[2.2.2]octanyl, diazabicyclo[2.2.2]octanyl, azaadamantanyl, diazaadamantanyl, oxa-adamantanyl, azaspiro[3.3]heptanyl, diazaspiro[3.3]heptanyl, oxa-azaspiro[3.3]heptanyl, azaspiro[3.4]octanyl, diazaspiro[3.4]octanyl, oxa-azaspiro[3.4]octanyl, oxa-azaspiro[3.5]nonanyl, azaspiro[2.5]octanyl, diazaspiro[2.5]octanyl, azaspiro[4.4]nonanyl, diazaspiro[4.4]nonanyl, oxa-azaspiro[4.4]nonanyl, azaspiro[4.5]decanyl, diazaspiro[4.5]decanyl, diazaspiro[4.4]nonanyl, oxa-diazaspiro[4.4]nonanyl, octahydropyrrolo[3,4-c]pyrrolyl and the like.

In some embodiments, heterocycloalkyl refers to any three to ten membered monocyclic or bicyclic, saturated ring structure containing at least one heteroatom selected from the group consisting of O, N and S. The heterocycloalkyl group may be attached at any heteroatom or carbon atom of the ring such that the result is a stable structure. Examples of suitable heterocycloalkyl groups include, but are not limited to, azepanyl, aziridinyl, azetidinyl, pyrrolidinyl, dioxolanyl, imidazolidinyl, pyrazolidinyl, piperazinyl, piperidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, oxazepanyl, oxiranyl, oxetanyl, quinuclidinyl, tetrahydrofuranyl, tetrahydropyranyl, piperazinyl, and the like.

In some embodiments, the term “spiroheterocycloalkyl” when used alone or as part of a substituent group refers to a non-aromatic group containing two rings, at least one of which is a heterocycloalkyl ring, and wherein the two rings share a single carbon atom in common.

As used herein, “halo” or “halogen” includes fluoro, chloro, bromo, and iodo.

As used herein, unless otherwise indicated, “alkoxy” refers to an –O-alkyl group. Example alkoxy groups include methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), t-butoxy, and the like.

As used herein, unless otherwise indicated, “hydroxylalkyl” refers to an alkyl group substituted by OH.

As used herein, unless otherwise indicated, “cyanoalkyl” refers to an alkyl group substituted by CN.

As used herein, unless otherwise indicated, “alkoxyalkyl” refers to an alkyl group substituted by an alkoxy group.

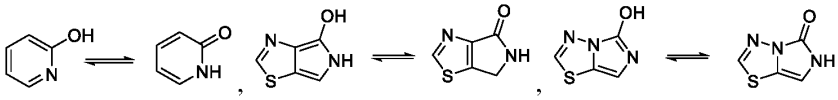
As used herein, unless otherwise indicated, “haloalkoxy” refers to an –O-(haloalkyl) group.

As used herein, unless otherwise indicated, "arylalkyl" refers to alkyl substituted by aryl and "cycloalkylalkyl" refers to alkyl substituted by cycloalkyl. An example arylalkyl group is benzyl.

As used herein, unless otherwise indicated, "heteroarylalkyl" refers to alkyl substituted by heteroaryl and "heterocycloalkylalkyl" refers to alkyl substituted by heterocycloalkyl.

As used herein, unless otherwise indicated, "oxo" refers to an oxygen substituent that is connected by a double bond (i.e., =O).

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms. Furthermore, atropisomers and mixtures thereof such as those resulting from restricted rotation about two aromatic or heteroaromatic rings bonded to one another are intended to be encompassed within the scope of the invention. For example, when Cy is a phenyl group and is substituted with two groups bonded to the C atoms adjacent to the point of attachment to the C atom of the pyridine, then rotation of the phenyl may be restricted. In some instances, the barrier of rotation is high enough that the different atropisomers may be separated and isolated.

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone–enol pairs, amide-imidic acid pairs, lactam-lactim pairs, amide-imidic acid pairs, enamine- imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole; certain hydroxy substituted compounds may exist as tautomers as shown below:  , etc.. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

In some cases, the compounds of the present disclosure may exist as rotational isomers. Descriptions of a compound of the invention that do not indicate a particular rotational isomer are intended to encompass any individual rotational isomers, as well as mixtures of rotational isomers in any proportion. Depiction of a particular rotational isomer is meant to refer to the depicted rotational isomer, substantially free of other rotational isomers.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

As used herein, unless otherwise indicated, the phrase "optionally substituted" means unsubstituted or substituted.

As used herein, unless otherwise indicated, the term "substituted" refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s). Typical substituents include, but are not limited to, D, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl-NR^cR^d, -$(CH_2CH_2O)_oC_1$-C_6alkyl wherein o is 1-10; C_{2-6} alkenyl-NR^cR^d, C_{2-6} alkynyl-NR^cR^d, OC_{2-6} alkyl-NR^cR^d, CN, NO_2, N_3, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, -$CH_2C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, -NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^c)NR^cR^d$, $NR^cC(=NR^c)NR^cR^d$, $P(R^f)_2$, $P(OR^e)_2$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $S(O)R^b$, -$SO(=NR^b)$; $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$; aryl, heteroaryl, spirocycloalkyl, spiroheterocycloalkyl, cycloalkyl, or heterocycloalkyl, wherein the aryl, heteroaryl, spirocycloalkyl, spiroheterocycloalkyl, cycloalkyl, or heterocycloalkyl are optionally substituted with D, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl-NR^cR^d, C_{2-6} alkenyl-NR^cR^d, C_{2-6} alkynyl-NR^cR^d, OC_{2-6} alkyl-NR^cR^d, CN, NO_2, N_3, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, -$CH_2C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, -NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $C(=NR^c)NR^cR^d$, $NR^cC(=NR^c)NR^cR^d$, $P(R^f)_2$, $P(OR^e)_2$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$.

In some embodiments, the compounds of the invention, and salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which was formed or detected. Partial separation can include, for example, a composition enriched in the compound of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the invention, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

The present disclosure also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated

herein by reference in its entirety.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

A "pharmaceutically acceptable excipient" refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of an agent and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

A "solvate" refers to a physical association of a compound of Formula I with one or more solvent molecules.

"Subject" includes humans. The terms "human," "patient," and "subject" are used interchangeably herein.

"Treating" or "treatment" of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, "treating" or "treatment" refers to delaying the onset of the disease or disorder.

"Compounds of the present disclosure" and equivalent expressions, are meant to embrace compounds of Formula I as described herein, as well as its subgenera, which expression includes the stereoisomers (e.g., entaniomers, diastereomers) and constitutional isomers (e.g., tautomers) of compounds of Formula I as well as the pharmaceutically acceptable salts, where the context so permits.

As used herein, the term "isotopic variant" refers to a compound that contains proportions of isotopes at one or more of the atoms that constitute such compound that is greater than natural abundance. For example, an "isotopic variant" of a compound can be radiolabeled, that is, contain one or more radioactive isotopes, or can be labeled with non-radioactive isotopes such as for example, deuterium (^{2}H or D), carbon-13 (^{13}C), nitrogen-15 (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be ^{2}H/D, any carbon may be ^{13}C, or any nitrogen may be ^{15}N, and that the presence and placement of such atoms may be determined within the skill of the art.

It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are

termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers," for example, diastereomers, enantiomers, and atropisomers. The compounds of this disclosure may possess one or more asymmetric centers; such compounds can therefore be produced as individual (*R*)-or (*S*)-stereoisomers at each asymmetric center, or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include all stereoisomers and mixtures, racemic or otherwise, thereof. Where one chiral center exists in a structure, but no specific stereochemistry is shown for that center, both enantiomers, individually or as a mixture of enantiomers, are encompassed by that structure. Where more than one chiral center exists in a structure, but no specific stereochemistry is shown for the centers, all enantiomers and diastereomers, individually or as a mixture, are encompassed by that structure. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise a compound represented by Formula (I) (or a pharmaceutically acceptable salt thereof) as an active ingredient, and pharmaceutically acceptable excipients.

The compositions may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for injection use (for example as aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

The pharmaceutically acceptable excipient(s) can be selected from, for example, carriers (e.g. a solid, liquid or semi-solid carrier), adjuvants, diluents, fillers or bulking agents, granulating agents, coating agents, release-controlling agents, binding agents, disintegrants, lubricating agents, preservatives, antioxidants, buffering agents, suspending agents, thickening agents, flavouring agents, sweeteners, taste masking agents, stabilisers or any other excipients conventionally used in pharmaceutical compositions.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include such as lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers include such as sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include such as carbon dioxide and nitrogen. In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents,

granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

Pharmaceutical dosage forms suitable for oral administration include tablets (coated or uncoated), capsules (hard or soft shell), caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches such as buccal patches.

Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, e.g., lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as microcrystalline cellulose (MCC), methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g., swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g., stearates), preservatives (e.g., parabens), antioxidants (e.g., BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here. The table compositions may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient. For example, a formulation intended for the oral administration to humans may contain from about 0.5 mg to about 5 g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about l mg to about 2 g of the active ingredient, typically 25 mg, 50 mg, l00 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or l000 mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropyl cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage;

thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention, or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

The compositions may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

An effective amount of a compound of Formula (I) or a pharmaceutically salt thereof for use in therapy is an amount sufficient to treat or prevent a proliferative condition referred to herein, slow its progression and/or reduce the symptoms associated with the condition.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the individual treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.1 mg to 1000 mg of Formula (I) or a pharmaceutically salt thereof with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula (I) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound, or a pharmaceutically acceptable salt, of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including antioxidants) and the like. Furthermore, other adjuvants can be included to

render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of from about 0.01 mg/kg to about 150 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, colon cancer, rectal cancer, mantle cell lymphoma, multiple myeloma, breast cancer, prostate cancer, glioblastoma, squamous cell esophageal cancer, liposarcoma, T-cell lymphoma melanoma, pancreatic cancer, or lung cancer, may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

It is understood, however, that lower or higher doses than those recited above may be required. Specific dose level and treatment regimens for any particular subject will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, the severity and course of the particular disease undergoing therapy, the subject disposition to the disease, and the judgment of the treating physician.

These and other aspects will become apparent from the following written description of the invention.

Described below are non-limiting exemplary pharmaceutical compositions and methods for preparing the same.

Methods of Administration

The compounds of Formula (I) or a pharmaceutically salt thereof or pharmaceutical compositions comprising these compounds may be administered to a subject by any convenient route of administration, whether systemically/peripherally or topically (i.e., at the site of desired action).

Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eye drops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intra-arterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrastemal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

Methods of Use

The method typically comprises administering to a subject a therapeutically effective amount of a compound of the invention. The therapeutically effective amount of the subject combination of compounds may vary depending upon the intended application (in vitro or in vivo), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the

disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, e.g., reduction of proliferation or downregulation of activity of a target protein. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

The term "PolQ overexpression" refers to the increased expression or activity of PolQ enzyme in a diseased cell e.g., cancer cell, relative to expression or activity of PolQ enzyme in a control cell (e.g., non-diseased cell of the same type). The amount of the amount of PolQ overexpression can be at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, PolQ overexpression can be at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 10-fold, at least 20-fold, at least 50-fold, relative to PolQ expression in a control cell.

Synthesis

Compounds of the invention, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes, such as those in the Schemes below.

The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates or products at the temperatures at which the reactions are carried out, *e.g.,* temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups is described, *e.g.,* in Kocienski, *Protecting Groups,* (Thieme, 2007); Robertson, *Protecting Group Chemistry,* (Oxford University Press, 2000); Smith *el ah, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,* 6th Ed. (Wiley, 2007); Peturssion *et al,* Protecting Groups in Carbohydrate Chemistry, *J Chem. Educ.,* 1997, *74(*11), 1297; and Wuts *et al., Protective Groups in Organic Synthesis,* 4th Ed., (Wiley, 2006).

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

The expressions, "ambient temperature", "room temperature" and "r.t." as used herein, are understood in the art, and refer generally to a temperature, e.g. a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

Compounds of the invention can be prepared according to numerous preparatory routes known in the literature. The Schemes below provide general guidance in connection with preparing the compounds of the invention. One skilled in the art would understand that the preparations shown in the Schemes can be modified or optimized using general knowledge of organic chemistry to prepare various compounds of the invention. Example synthetic methods for preparing compounds of the invention are provided in the Schemes below.

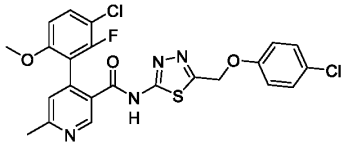
The following Examples are provided to illustrate some of the concepts described within this disclosure. While the Examples are considered to provide an embodiment, it should not be considered to limit the more general embodiments described herein.

Abbreviations

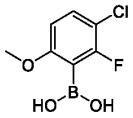
BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
PyBOP	(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
HATU	2-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU	O-(Benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate
EDCI	N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
T_3P	1-Propanephosphonic anhydride
DMAP	4-Dimethylaminopyridine
DAST	Diethylaminosulfur trifluoride
TCFH	Chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate
CuTC	Copper(I) thiophene-2-carboxylate
BrettPhos Pd G3	[(2-Di-cyclohexylphosphino-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate methanesulfonate
t-BuXphos Pd G3	[(2-Di-tert-butylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate
RuPhos Pd G3	(2-Dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate
XantPhos Pd G3	[(4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate
$Pd(OAc)_2$	Palladium (II) Acetate
$Pd(dppf)Cl_2$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd_2(dba)_3$	Bis(dibenzylideneacetone)palladium(0)
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
$Pd(DTBPF)Cl_2$	1,1'-Bis (di-*t*-butylphosphino)ferrocene palladium dichloride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
TEA	Triethylamine
LDA	Lithium diisopropylamide
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl Azodicarboxylate
TFA	Trifluoroacetic acid

NaHMDS	Sodium bis(trimethylsilyl)amide
PPA	Polyphosphoric acid
EtOAc	Ethyl acetate
DMF	N,N-dimethylformamide
PE	Petroleum ether
CS_2	Carbon disulfide
THF	Tetrahydrofuran
DMSO	Dimethylsulfoxide
DCM	Dichloromethane
MeCN/ACN	Acetonitrile
LCMS	liquid chromatography-mass spectrometry
^{1}HNMR	Hydrogen-1 nuclear magnetic resonance spectroscopy
ATP	Adenosine triphosphate
ADP	Adenosine diphosphate
DTT	DL-Dithiothreitol
BSA	Bovine albumin
brine	saturated solution of sodium chloride
r.t.	Room temperature
aq.	Aqueous
1 M or 1 N = 1 mol/L, 2 M or 2 N = 2 mol/L etc.	

Example 1: 4-(3-Chloro-2-fluoro-6-methoxyphenyl)-N-(5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (Compound 1)

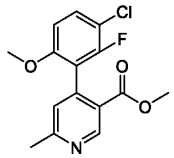


Step 1: (3-chloro-2-fluoro-6-methoxyphenyl)boronic acid



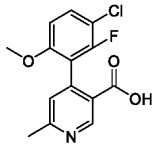
To a solution of 1-chloro-2-fluoro-4-methoxybenzene (2.0 g, 12.5 mmol) in dry THF (20 mL) was added LDA (2.0 M in THF, 12.5 mL) at -70 °C under N_2 atmosphere. The mixture was stirred at -70 °C for 1 h., and then triisopropyl borate (4.7 g, 25 mmol) was added at -70 °C. The resulting mixture was stirred at -70 °C for 2 h. The reaction mixture was quenched by sat. NH_4Cl aq. solution (50 mL) at 0 °C. The aqueous layer was adjusted to pH ~ 2 - 3 with HCl (1.0 M) and extracted with EtOAc (40 mL x 5). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (0 - 10%) to afford (3-chloro-2-fluoro-6-methoxyphenyl)boronic acid (1.6 g) as an off-white solid.

Step 2: methyl 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinate



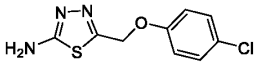
A mixture of methyl 4-chloro-6-methylnicotinate (3.0 g, 16 mmol), (3-chloro-2-fluoro-6-methoxyphenyl)boronic acid (3.2 g, 16 mmol), K_2CO_3 (4.4 g, 32 mmol) and $Pd(dppf)Cl_2$ (1.1 g, 1.6 mmol) in 1,4-dioxane (24 mL) and H_2O (3 mL) was degassed and recharged with nitrogen for 3 cycles. The mixture was stirred at 80 °C for 16 h. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (0 - 20%) to give the title compound (2.8 g) as a yellow solid. LCMS calc. for $C_{15}H_{14}FClNO_3$ $[M+H]^+$: m/z = 310.1; Found: 310.0.

Step 3: 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid



To a solution of methyl 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinate (70 mg, 0.23 mmol) in MeOH (2 mL) and H_2O (2 mL) was added $LiOH·H_2O$ (28 mg, 1.0 mmol). After it was stirred at r.t. overnight, the reaction mixture was diluted with water and adjusted to pH~3 - 4 with HCl aq. (2 M), extracted with DCM (20 mL x 5). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product (50 mg) as a yellow oil. LCMS calc. for $C_{14}H_{12}FClNO_3$ $[M+H]^+$: m/z = 296.0; Found: 296.0.

Step 4: 5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-amine



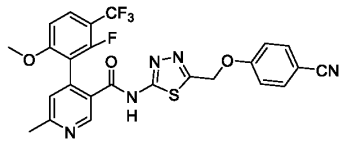
To a mixture of 2-(4-chlorophenoxy)acetic acid (2.0 g, 10.7 mmol) and thiosemicarbazide (0.98 mg, 10.7 mmol) was slowly added $POCl_3$ (8 mL) at 0 °C. The mixture was stirred at 75 °C for 1 h. The reaction mixture was poured into the ice water (30 mL) and stirred at 0 °C for 2 h. The mixture was adjusted to pH~8-10 with NaOH solid. The precipitate was filtered and dried for 2 h. at 80 - 100 °C to afford the title compound (2.1 g) as a white solid. LCMS calc. for $C_9H_9ClN_3OS$ $[M+H]^+$: m/z = 242.0; Found: 242.1.

Step 5: 4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol -2-yl)-6-methylnicotinamide

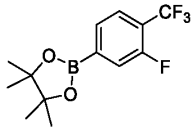
To a mixture of 5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-amine (48 mg, 0.2 mmol), 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid (60 mg, 0.2 mmol) and NMI (82 mg, 1 mmol) in DMF (1 mL) was added TCFH (84 mg, 0.3 mmol). The reaction mixture was stirred at r.t. for 1 h. and concentrated under reduced pressure. The residue was purified by prep-HPLC on a C18 column eluting with ACN/H_2O (45 - 75% with 0.5% TFA) to afford the title compound (14 mg) as a

white solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 13.2 (s, 1H), 8.89 (s, 1H), 7.59 (t, J = 8.8 Hz, 1H), 7.43 (s, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 1H), 5.50 (s, 2H), 3.53 (s, 3H), 2.59 (s, 3H). LCMS calc. for $C_{23}H_{18}Cl_2FN_4O_3S$ $[M+H]^+$: m/z = 519.0; Found: 519.1.

Example 2: N-(5-((4-Cyanophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxy-3-(trifluoromethyl)phenyl)-6-methylnicotinamide (Compound 2)

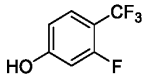


Step 1: 2-(3-fluoro-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



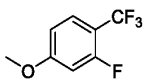
A mixture of 4-bromo-2-fluoro-1-(trifluoromethyl)benzene (9.7 g, 40 mmol), bis(pinacolato)diboron (12.7 g, 50 mmol), KOAc (9.8 g, 100 mmol) and Pd(dppf)Cl_2 (0.87 g, 1.2 mmol) in 1,4-dioxane (120 mL) was degassed and recharged with nitrogen for 3 cycles. The reaction mixture was stirred at 100 °C for 16 h.. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was disolved in PE (100 mL), fitered under a short pad of a silica gel and concentrated under reduced pressure to afford the title compound (11.5 g, 99% yield) as a yellow oil. TLC Rf = 0.4 (EtOAc/PE = 1/50, UV 254 nm).

Step 2: 3-fluoro-4-(trifluoromethyl)phenol



To a cooled (ice-water bath) mixture of 2-(3-fluoro-4-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11.5 g, 40 mmol), NaOH (6.4 g, 160 mmol) in THF (400 mL) and water (20 mL) was added H_2O_2 (16 mL, 33%). The reaction mixture was stirred at 0 °C for 4 h., and concentrated under reduced pressure. The residue was diluted with PE (300 mL) and filtered. The filtrate was washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to affored the title compound (7.0 g, 97% yield) as a yellow oil. LCMS calc. for $C_7H_3F_4O$ $[M-H]^-$: m/z = 179.0; Found: 179.0. TLC Rf = 0.45 (EtOAc/PE = 1/25, UV 254 nm).

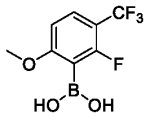
Step 3: 2-fluoro-4-methoxy-1-(trifluoromethyl)benzene



To a mixture of 3-fluoro-4-(trifluoromethyl)phenol (7.0 g, 38.9 mmol), K_2CO_3 (13.8 g, 100 mmol) in MeCN (40 mL) was added MeI (8.5 g, 60 mmol) The reaction mixture was stirred at 40 °C for 4 h., and concentrated under reduced pressure. The residue was diluted with PE (200 mL) and filtered. The filtrate was washed with water and brine, dried over anhydrous Na_2SO_4, filtered

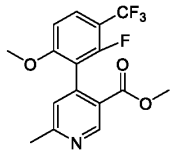
and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (0 - 5%) to afforded the title compound (4.2 g, 56% yield) as a colorless oil. TLC Rf = 0.55 (EtOAc/PE = 1/25, UV 254 nm).

Step 4: (2-fluoro-6-methoxy-3-(trifluoromethyl)phenyl)boronic acid



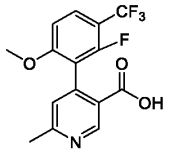
To a solution of 2-fluoro-4-methoxy-1-(trifluoromethyl)benzene (3.9 g, 20 mmol) in THF (40 mL) was added *n*-BuLi (10 mL, 2.5 M in hexane) at -60 °C. After being stirred for 1 h., 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.6 g, 25 mmol) was added at -60 °C. The reaction mixture was stirred at r.t. for 1 h. The reaction mixture was quenched by aq HCl (2.0 M) solution (20 mL) at 0 °C, stirred for 30 min., and extracted with EtOAc (40 mL x 5). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compoud (2.0 g, 42%) as a yellow oil without further purification.

Step 5: methyl 4-(2-fluoro-6-methoxy-3-(trifluoromethyl)phenyl)-6-methylnicotinate



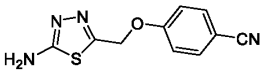
This compound was prepared as a yellow solid by procedures analogous to those described for Example 1 Step 2 using (2-fluoro-6-methoxy-3-(trifluoromethyl)phenyl)boronic acid to replace (3-chloro-2-fluoro-6-methoxyphenyl)boronic acid. LCMS calc. for $C_{16}H_{14}F_4NO_3$ $[M+H]^+$: m/z = 344.1; Found: 344.1.

Step 6: 4-(2-fluoro-6-methoxy-3-(trifluoromethyl)phenyl)-6-methylnicotinic acid



This compound was prepared as an white solid by procedures analogous to those described for Example 1 Step 3 using methyl 4-(2-fluoro-6-methoxy-3-(trifluoromethyl)phenyl)-6-methylnicotinate. LCMS calc. for $C_{15}H_{12}F_4NO_3$ $[M+H]^+$: m/z = 330.1; Found: 330.1.

Step 7: 4-((5-amino-1,3,4-thiadiazol-2-yl)methoxy)benzonitrile

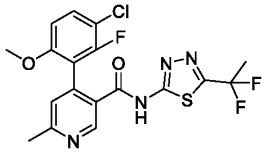


To a cooled mixture of thiosemicarbazide (1.2 g, 6.3 mmol) and 2-(4-cyanophenoxy)acetic acid (0.9 g, 5.0 mmol) was added $POCl_3$ (8 mL) dropwise at 0 °C. The mixture was stirred at 75 °C for 1 h. The reaction mixture was cooled and poured into the ice water (30 mL) at 0 °C and stirred for 2 h. The precipitate was filtered and purified by prep-HPLC on a C18 column eluting with MeCN/H_2O (0%-40%, 0.5% TFA) to afford the title compound (0.19 g) as a brown solid. LCMS calc. for $C_{10}H_9N_4OS$ $[M+H]^+$: m/z = 233.0; Found: 233.1.

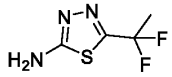
Step 8: N-(5-((4-cyanophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxy-3-(trifluoromethyl)phenyl)-6-methylnicotinamide

This compound was prepared using procedures analogous to those described for Example 1 Step 5 using 4-(2-fluoro-6-methoxy-3-(trifluoromethyl)phenyl)-6-methylnicotinic acid and 4-((5-amino-1,3,4-thiadiazol-2-yl)methoxy)benzonitrile as the starting material. ^{1}HNMR: (400 MHz, DMSO-d_6) δ 13.3 (s, 1H), 8.92 (s, 1H), 7.80-7.82 (d, J = 8.0 Hz, 3H), 7.43 (s, 1H), 7.23-7.25 (d, J = 8.0 Hz, 2H), 7.05-7.07 (d, J = 8.0 Hz, 1H), 5.61 (s, 2H), 3.64 (s, 3H), 2.59 (s, 3H). LCMS calc. for $C_{25}H_{18}F_4N_5O_3S$ $[M+H]^+$: m/z = 544.10; Found: 544.1.

Example 3: 4-(3-Chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoroethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (Compound 3)



Step 1: 5-(1,1-difluoroethyl)-1,3,4-thiadiazol-2-amine

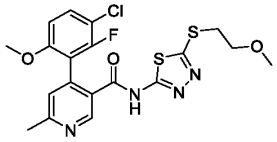


To a mixture of 2,2-difluoropropionic acid (1.1 g, 10 mmol) and thiosemicarbazide (910 mg, 10 mmol) was slowly added $POCl_3$ (8 mL) at 0 °C. The mixture was stirred at 75 °C for 3 h., poured into the ice water (30 mL) and stirred at 0 °C for 2 h.. The resulting mixture was adjusted to pH~8 - 10 with NaOH solid. The aqueous phase was extracted with EtOAc (30 mL x 4). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with MeCN/H_2O (10 - 30%) to afford the title compound (170 mg) as a yellow solid. LCMS calculated for $C_4H_6F_2N_3S$ $[M+H]^+$: m/z = 166.0; Found: 166.1.

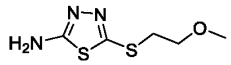
Step 2: 4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoroethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

This compound was prepared using procedures analogous to those described for Example 1 Step 5 using intermediate 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid (Example 1 Step 3) and 5-(1,1-difluoroethyl)-1,3,4-thiadiazol-2-amine as the starting material. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.59 (s, 1H), 8.92 (s, 1H), 7.60 (t, J = 8.4 Hz, 1H), 7.43 (s, 1H), 6.94 (d, J = 8.4 Hz, 1H), 3.55 (s, 3H), 2.60 (s, 3H), 2.19 (t, J_{F-H} = 19.2 Hz, 3H). LCMS calc. for $C_{18}H_{15}ClF_3N_4O_2S$ $[M+H]^+$: m/z = 443.1; Found: 443.1.

Example 4: 4-(3-Chloro-2-fluoro-6-methoxyphenyl)-N-(5-((2-methoxyethyl)thio)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (Compound 4)



Step 1: 5-((2-methoxyethyl)thio)-1,3,4-thiadiazol-2-amine

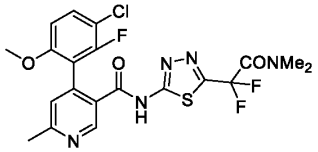


To a mixture of 5-amino-1,3,4-thiadiazole-2-thiol (265 mg, 2.0 mmol) and KOH (1.12 g, 20.0 mmol) in water (10 mL) was slowly added 1-iodo-2-methoxyethane (370 mg, 2.0 mmol) under ice-water bath. The mixture was stirred at 0 °C for 1 h., and diluted with water (30 mL). The aqueous was extracted with DCM (30 mL x 3). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (300 mg) as a white solid. LCMS calculated for $C_5H_{10}N_3OS_2$ $[M+H]^+$: m/z = 192.0; Found: 192.0.

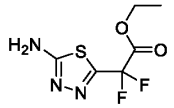
Step 2: 4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-((2-methoxyethyl)thio)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

This compound was prepared by procedures analogous to those described for Example 1 Step 5 using 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid (Example 1 Step 3) and 5-((2-methoxyethyl)thio)-1,3,4-thiadiazol-2-amine as the starting material. LCMS calc. for $C_{19}H_{19}ClFN_4O_3S_2$ $[M+H]^+$: m/z = 469.1; Found: 469.1.

Example 5: 4-(3-Chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-(dimethylamino)-1,1-difluoro-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (Compound 5)

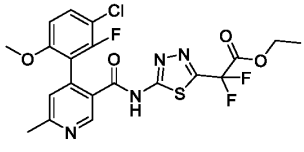


Step 1: ethyl 2-(5-amino-1,3,4-thiadiazol-2-yl)-2,2-difluoroacetate



To a mixture of 1,3,4-thiadiazol-2-amine (5 g, 49.5 mmol), Cp_2Fe (931 mg, 4.95 mmol) and ethyl 2-bromo-2,2-difluoroacetate (20 g, 99 mmol) in DMSO (25 mL) was added hydrogen peroxide (11.22 g, 99 mmol, 30% in water) slowly at 0 °C. The reaction mixture was stirred at r.t. overnight, and quenched with 10% $Na_2S_2O_3$ aq. at 0 °C. The aqueous layer was extracted with EA (100 mL x 2). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (10 - 47%) to afford the product (1.89 g) as a brown oil. LCMS calc. for $C_6H_8F_2N_3O_2S$ $[M+H]^+$: m/z = 224.0; Found: 224.0.

Step 2: ethyl 2-(5-(4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinamido)-1,3,4-thiadiazol-2-yl)-2,2-difluoroacetate



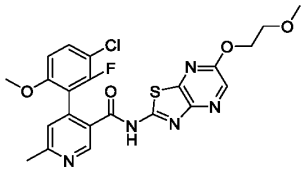
To a mixture of ethyl 2-(5-amino-1,3,4-thiadiazol-2-yl)-2,2-difluoroacetate (223 mg, 1.0 mmol), 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid (295 mg, 1.0 mmol, Int-1)

and NMI (410 mg, 5 mmol) in DMF (2 mL) was added TCFH (336 mg, 1.2 mmol). The reaction mixture was stirred at r.t. for 1 h., and then concentrated under reduced pressure. The residue was purified by prep-HPLC on a C18 column eluting with ACN/H_2O (50 - 70%) to afford the title compound (260 mg) as a white solid. LCMS calc. for $C_{20}H_{17}ClF_3N_4O_4S$ $[M+H]^+$: m/z = 501.1; Found: 501.1.

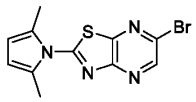
Step 3: 4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-(dimethylamino)-1,1-difluoro-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

A solution of ethyl 2-(5-(4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinamido)-1,3,4-thiadiazol-2-yl)-2,2-difluoroacetate (50 mg, 0.1 mmol) in $HNMe_2$ solution (1.0 mL, 2.0 M in THF, 2 mmol) was heated at 70 °C for 4 h.. After it was cooled to r.t., the mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC on a C18 column eluting with ACN/H_2O (40 - 60% with 0.1% NH_4HCO_3) to afford the title compound (34 mg) as a white solid. ^1H NMR (600 MHz, DMSO-d_6) δ 13.74 (s, 1H), 8.93 (s, 1H), 7.61 (t, J = 8.4 Hz, 1H), 7.44 (s, 1H), 6.94 (t, J = 8.4 Hz, 1H), 3.56 (s, 3H), 3.01 (s, 6H), 2.60 (s, 3H). LCMS calc. for $C_{20}H_{18}ClF_3N_5O_3S$ $[M+H]^+$: m/z = 500.1; Found: 500.1.

Example 6: 4-(3-Chloro-2-fluoro-6-methoxyphenyl)-N-(6-(2-methoxyethoxy)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide (Compound 6)

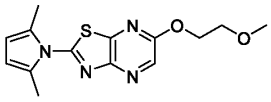


Step 1: 6-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)thiazolo[4,5-b]pyrazine



To a mixture of 6-bromothiazolo[4,5-b]pyrazin-2-amine (230 mg, 1.0 mmol) and 2,3-butanedione (170 mg, 2.0 mmol) in toluene (10 mL) was added *p*-TsOH (1 mg) and 4 A molecular sieve (200 mg). The reaction mixture was stirred at 100 °C overnight. The reaction mixture was concentrated under vacuum, diluted with H_2O and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (300 mg) as yellow oil. LCMS calc for $C_{11}H_{10}BrN_4S$ $[M+H]^+$: m/z = 309.0; Found: 309.1.

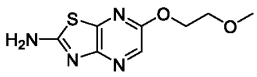
Step 2: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-(2-methoxyethoxy)thiazolo[4,5-b]pyrazine



To a solution of 6-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-methoxythiazolo[4,5-b]pyridine (150 mg, 0.49 mmol) in 2-methoxyethan-1-ol (5 mL) was added NaH (80 mg, 2 mmol, 60% in mineral oil). The reaction mixture was stirred at 70 °C overnight, and concentrated under reduced pressure. The resulting mixture was diluted with EtOAc, and washed with water. The organic layer

was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC on a C18 column eluting with ACN/water (30 - 50%) to afford the title compound (100 mg) as a yellow solid. LCMS calc. for $C_{14}H_{17}N_4O_2S$ $[M+H]^+$: m/z = 305.1; Found: 305.1.

Step 3: 6-(2-methoxyethoxy)thiazolo[4,5-b]pyrazin-2-amine

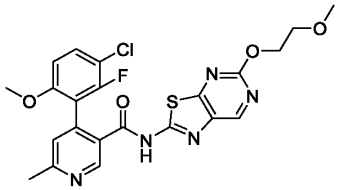


A solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-(2-methoxyethoxy)thiazolo[4,5-b]pyrazine (100 mg, 0.3 mmol) in TFA (1 mL) and H_2O (1 mL) was stirred at 60 °C for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC on a C18 column eluting with ACN/water (10 - 40%) to afford the title compound (30 mg) as a yellow solid. LCMS calc. for $C_8H_{10}N_4O_2S$ $[M+H]^+$: m/z = 226.1; Found: 226.0.

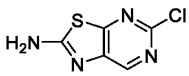
Step 5: 4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(6-(2-methoxyethoxy)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide

This compound was prepared by procedures analogous to those described for Example 1 Step 5 using 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid (Example 1 Step 3) and 6-(2-methoxyethoxy)thiazolo[4,5-b]pyrazin-2-amine as the starting material. LCMS calc. for $C_{22}H_{20}ClFN_5O_4S$ $[M+H]^+$: m/z = 504.1; Found: 504.1.

Example 7: 4-(3-Chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-methoxyethoxy)thiazolo[5,4-d]pyrimidin-2-yl)-6-methylnicotinamide (Compound 7)

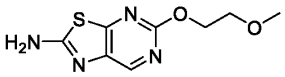


Step 1: 5-chlorothiazolo[5,4-d]pyrimidin-2-amine



To a solution of 2,4-dichloropyrimidin-5-amine (1 g, 10 mmol) in AcOH (16 mL) was added potassium thiocyanate (5.93 g, 60 mmol). The reaction mixture was stirred at 80 °C for 4 h., and adjusted to pH ~ 7 - 8 with saturated aq. $NaHCO_3$. The precipitates formed were filtered to afford the product (500 mg) as a brown solid. ^1H NMR: (400 MHz, DMSO-d^6) δ 8.53 (s, 1H), 8.30 (s, 2H). LCMS calc for $C_5H_4ClN_4S$ $[M+H]^+$: m/z = 187.0; Found: 187.1.

Step 2: 5-(2-methoxyethoxy)thiazolo[5,4-d]pyrimidin-2-amine



To a solution of 2-methoxyethanol (122 mg, 1.61 mmol) in THF (5 mL) was added NaH (129 mg, 3.2 mmol, 60% in mineral oil). The mixture was stirred at 25 °C for 1 h. 5-chlorothiazolo[5,4-d]pyrimidin-2-amine (200 mg, 1.1 mmol) was added to the mixture, and stirred at 60 °C overnight.

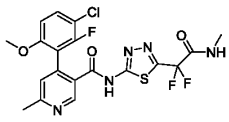
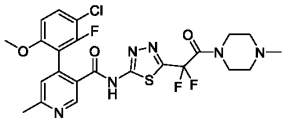
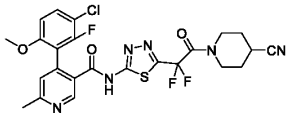
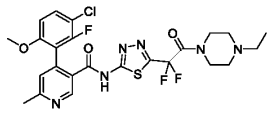
The reaction mixture was quenched with saturated aq. NH_4Cl and extracted with EtOAc (25 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC eluting with MeOH/DCM (5%) to afford the title compound (50 mg) as a yellow solid. ^1H NMR: (400 MHz, DMSO-d^6) δ 8.40 (s, 1H), 7.83 (s, 2H), 4.44-4.30 (m, 2H), 3.70-3.58 (m, 2H), 3.29 (s, 3H). LCMS calc for $C_8H_{11}N_4O_2S$ $[M+H]^+$: m/z = 227.1; Found: 227.1.

Step 3: 4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-methoxyethoxy)thiazolo[5,4-d]pyrimidin-2-yl)-6-methylnicotinamide

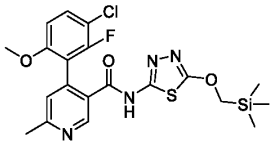
This compound was prepared by procedures analogous to those described for Example 1 Step 5 using 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid (Example 1 Step 3) and 5-(2-methoxyethoxy)thiazolo[5,4-d]pyrimidin-2-amine as the starting material. ^1H NMR: (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 8.99 (s, 1H), 8.89 (s, 1H), 7.61 (t, J = 9.2 Hz, 1H), 7.43 (s, 1H), 6.94 (d, J = 9.2 Hz, 1H), 4.48-4.46 (m, 2H), 3.70-3.68 (m, 2H), 3.58 (s, 3H), 3.31 (s, 3H), 2.59 (s, 3H). LCMS calc. for $C_{22}H_{20}ClFN_5O_4S$ $[M+H]^+$: m/z = 504.1; Found: 504.0.

Example 8, 14-16 listed in Table 1 below were prepared by using an intermediate ethyl 2-(5-(4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinamido)-1,3,4-thiadiazol-2-yl)-2,2-difluoroacetate (Example 5 Step 2) and an appropriate amine derivative as the methods analogous to those described for preparing Example 5.

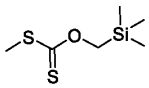
Table 1 Preparations of Examples (Ex)

Ex#	Amine	Structure	Name	LCMS Cacl./ Found
8 (Compound 8)	$MeNH_2$ (30% in EtOH)		4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoro-2-(methylamino)-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	$[M+H]^+$ 486.1/ 486.1
14 (Compound 14)			4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoro-2-(4-methylpiperazin-1-yl)-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	$[M+H]^+$ 555.1/ 555.1
15 (Compound 15)			4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-(4-cyanopiperidin-1-yl)-1,1-difluoro-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	$[M+H]^+$ 565.1/ 565.1
16 (Compound 16)			4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-(4-ethylpiperazin-1-yl)-1,1-difluoro-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide	$[M+H]^+$ 569.1/ 569.1

Example 9: 4-(3-Chloro-2-fluoro-6-methoxyphenyl)-6-methyl-N-(5-((trimethylsilyl)methoxy)-1,3,4-thiadiazol-2-yl)nicotinamide (Compound 9)

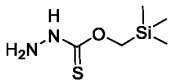


Step 1: S-methyl O-((trimethylsilyl)methyl) carbonodithioate



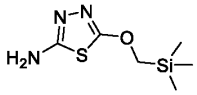
To a solution of (trimethylsilyl)methanol (3.12 g, 30 mmol) in THF (50 mL) was added NaH (2.4 g, 60 mmol, 60% in mineral oil) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. CS_2 (3.43 g, 45.0 mmol) was added to the above minxture at 0 °C. After stirring for 10 min., MeI (5.54 g, 39.0 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at r.t. for 16 h., and then quenched by NH_4Cl (aq., 50 mL). The aqueous phase was extracted with EtOAc (50 mL x 4). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford S-methyl O-((trimethylsilyl)methyl) carbonodithioate as a crude product without further purification.

Step 2: O-((trimethylsilyl)methyl) hydrazinecarbothioate



To a solution of S-methyl O-((trimethylsilyl)methyl) carbonodithioate (5.83 g, 30 mmol) in MeOH (50 mL) was added hydrazine hydrate (2.81 g, 45 mmol, 80% purity) at r.t.. The reaction mixture was stirred at r.t. for 30 min., and then concentrated under reduced pressure to afford O-((trimethylsilyl)methyl) hydrazinecarbothioate as a crude product without further purification. LCMS calc. for $C_5H_{15}N_2OSSi$ $[M+H]^+$: m/z = 179.1; Found: 179.1.

Step 3: 5-((trimethylsilyl)methoxy)-1,3,4-thiadiazol-2-amine



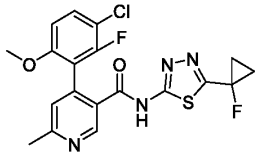
To a mixture of O-((trimethylsilyl)methyl) hydrazinecarbothioate (5.34 g, 30 mmol) and BrCN (3.82 g, 36 mmol) in MeOH (30 mL) was added TEA (6.1 g, 60.0 mmol) at 0 °C. The mixture was stirred at r.t. for 1 h., and then concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EtOAc/PE (0 - 20%) to afford the title compound (3.8 g, 62% yield) as a colorless oil. LCMS calc. for $C_6H_{14}N_3OSSi$ $[M+H]^+$: m/z = 204.1; Found: 204.1.

Step 4: 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methyl-N-(5-((trimethylsilyl)methoxy)-1,3,4-thiadiazol-2-yl)nicotinamide

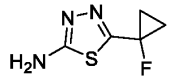
This compound was prepared using procedures analogous to those described for Example 1 Step 5 using intermediate 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid (Example 1 Step 3) and 5-((trimethylsilyl)methoxy)-1,3,4-thiadiazol-2-amine as the starting material. ^1H NMR: (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 8.84 (s, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.38 (s, 1H), 6.93 (d, J = 8.0 Hz, 6H), 4.20 (s, 2H), 3.58 (s, 3H), 2.57 (s, 3H), 0.10 (s, 9H). LCMS calc. for

$C_{20}H_{23}ClFN_4O_3SSi$ $[M+H]^+$: m/z = 481.1; Found: 481.1.

Example 10: 4-(3-Chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1-fluorocyclopropyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (Compound 10)



Step 1: 5-(1-fluorocyclopropyl)-1,3,4-thiadiazol-2-amine

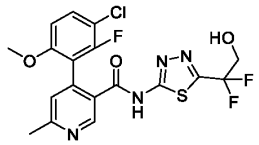


To a cooled mixture (ice water) of thiosemicarbazide (1.09 g, 12 mmol) and 1-fluorocyclopropane-1-carboxylic acid (1.04 g, 10 mmol) was added $POCl_3$ (10 mL) dropwise. The mixture was then stirred at 75 °C for 3 h., cooled and poured into the ice water (50 mL). The aqueous phase was adjusted to pH 12 with KOH solid and then concentrated under reduced pressure. The residue was purified by prep-HPLC on a C18 column eluting with MeCN/H_2O (0 - 10%) to afford the title compound (0.6 g) as yellow oil. LCMS calc. for $C_5H_7FN_3S$ $[M+H]^+$: m/z = 160.0; Found: 160.0.

Step 2: 4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1-fluorocyclopropyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

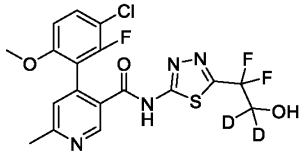
This compound was prepared using procedures analogous to those described for Example 1 Step 5 using intermediate 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid (Example 1 Step 3) and 5-(1-fluorocyclopropyl)-1,3,4-thiadiazol-2-amine as the starting material. LCMS calc. for $C_{19}H_{16}ClF_2N_4O_2S$ $[M+H]^+$: m/z = 437.1; Found: 437.1.

Example 11: 4-(3-Chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoro-2-hydroxyethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (Compound 11)



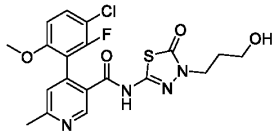
To a solution of ethyl 2-(5-(4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinamido)-1,3,4-thiadiazol-2-yl)-2,2-difluoroacetate (10 mg, 0.02 mmol, Example 5 Step 2) in EtOH (0.2 mL) was added $NaBH_4$ (3.78 mg, 0.1 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 30 min., concentrated under reduced pressure. The residue was purified by prep-HPLC on a C18 column eluting with ACN/H_2O (30 - 58% with 10 mM NH_4HCO_3) to afford the title compound (7.2 mg) as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.13 (s, 1H), 7.52 (t, J = 8.4 Hz, 1H), 7.16 (s, 1H), 6.91 (d, J = 8.4 Hz, 1H), 5.73 (s, 1H), 4.00-4.10 (m, 2H), 3.57 (s, 3H), 2.52 (s, 3H). LCMS calc. for $C_{18}H_{15}ClFN_4O_3S$ $[M+H]^+$: m/z = 459.0; found: 459.0.

Example 12: 4-(3-Chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoro-2-hydroxyethyl-2,2-d2)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (Compound 12)

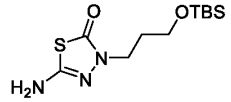


To a solution of ethyl 2-(5-(4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinamido)-1,3,4-thiadiazol-2-yl)-2,2-difluoroacetate (200 mg, 0.4 mmol, Example 5 Step 2) in MeOH-d_4 (2.0 mL) was added $NaBD_4$ (167 mg, 4.0 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 30 min., and concentrated under reduced pressure. The residue was purified by prep-HPLC on a C18 column eluting with ACN/H_2O (30 - 60% with 0.5% TFA) to afford the title compound (109.3 mg) as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.56 (s, 1H), 9.09 (s, 1H), 7.53 (t, J = 8.4 Hz, 1H), 7.21 (s, 1H), 6.91 (d, J = 8.4 Hz, 1H), 5.73 (s, 1H), 3.57 (s, 3H), 2.51 (s, 3H). LCMS calc. for $C_{18}H_{13}D_2ClF_3N_4O_3S$ $[M+H]^+$: m/z = 461.1; Found: 461.0.

Example 13: 4-(3-Chloro-2-fluoro-6-methoxyphenyl)-N-(4-(3-hydroxypropyl)-5-oxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (Compound 13)

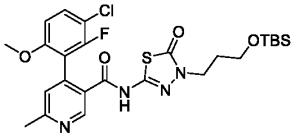


Step 1: 5-amino-3-(3-((tert-butyldimethylsilyl)oxy)propyl)-1,3,4-thiadiazol-2(3H)-one



To a solution of 5-amino-1,3,4-thiadiazol-2(3H)-one (120 mg, 1.0 mmol) in DMF (1 mL) was added NaH (60 mg, 1.5 mmol, 60% in mineral oil) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h., and then (3-bromopropoxy)(tert-butyl)dimethylsilane (252 mg, 1.0 mmol) was added. The mixture was stirred at 90 °C overnight. The reaction mixture was quenched with water at 0 °C, and concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with ACN/water (30- 55%) to afford the title compound (100 mg) as an off-white solid. LCMS calc. for $C_{11}H_{24}N_3O_2SSi$ $[M+H]^+$: m/z = 290.1; Found: 290.1.

Step 2: N-(4-(3-((tert-butyldimethylsilyl)oxy)propyl)-5-oxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinamide

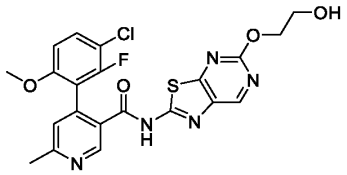


To a mixture of 5-amino-3-(3-((tert-butyldimethylsilyl)oxy)propyl)-1,3,4-thiadiazol-2(3H)-one (58 mg, 0.2 mmol) and 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid (61 mg, 0.2 mmol, Example 1 Step 3) in MeCN (0.5 mL) was added NMI (87 mg, 1.1 mmol) and TCFH (75 mg, 0.26 mmol). The reaction mixture was stirred at 40 °C overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC on a C18 column eluting with ACN/water (40 - 59%) to afford the title compound (56 mg) as an off-white solid. LCMS calc. for $C_{24}H_{31}ClFN_4O_4SSi$ $[M+H]^+$: m/z = 567.2; Found: 567.2.

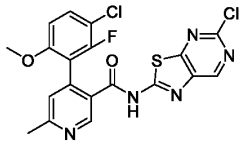
Step 3: 4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(4-(3-hydroxypropyl)-5-oxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

To a solution of N-(4-(3-((tert-butyldimethylsilyl)oxy)propyl)-5-oxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinamide (56 mg, 0.1 mmol) in THF (0.5 mL) was added TBAF (0.3 mL, 0.3 mmol, 1.0 M in THF). The reaction mixture was stirred at r.t. overnight and concentrated under reduced pressure. The residue was purified by prep-HPLC on a C18 column eluting with ACN/water (10 - 40%) to afford the title compound (9.4 mg) as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.57 (s, 1H), 8.81 (s, 1H), 7.60 (t, J = 9.0 Hz, 1H), 7.38 (s, 1H), 6.96 (d, J = 9.0 Hz, 1H), 4.56 (s, 1H), 3.90-3.78 (m, 2H), 3.64 (s, 3H), 3.48-3.40 (m, 2H), 2.51 (s, 3H), 1.84-1.75 (m, 2H). LCMS calc. for $C_{19}H_{19}ClFN_4O_4S$ $[M+H]^+$: m/z = 453.1; Found: 453.1.

Example 17: 4-(3-Chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-hydroxyethoxy)thiazolo[5,4-d]pyrimidin-2-yl)-6-methylnicotinamide (Compound 17)



Step 1 : 4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-chlorothiazolo[5,4-d]pyrimidin-2-yl)-6-methylnicotinamide



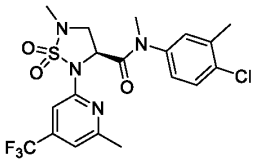
To a mixture of 5-chlorothiazolo[5,4-d]pyrimidin-2-amine (187 mg, 1.0 mmol), 4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid (300 mg, 1.0 mmol, Example 1 Step 3) and NMI (250 mg, 3.0 mmol) in DMF (3 mL) was added TCFH (420 mg, 1.5 mmol). The reaction mixture was stirred at 40 °C overnight and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EA/PE (50 - 100%) to afford the title compound (170 mg) as a yellow solid. LCMS calc. for $C_{19}H_{13}Cl_2FN_5O_2S$ $[M+H]^+$: m/z = 464.0; Found: 464.0.

Step 2: 4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-hydroxyethoxy)thiazolo[5,4-d]pyrimidin-2-yl)-6-methylnicotinamide

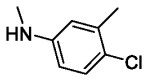
A mixture of 4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-chlorothiazolo[5,4-d]pyrimidin-2-yl)-6-methylnicotinamide (93 mg, 0.2 mmol) and Cs_2CO_3 (330 mg, 1.0 mmol) in ethylene glycol (5 mL) was stirred at 80 °C overnight. The reaction mixture was diluted with DCM (50 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC on a C18 column eluting with ACN/water (10 - 40%) to afford the title compound (36 mg) as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.17 (s, 1H), 8.99 (s, 1H), 8.90 (s, 1H), 7.61 (t, J = 8.4 Hz, 1H), 7.44 (s, 1H), 6.94 (d, J = 8.4 Hz, 1H), 4.91 (t, J = 5.4 Hz, 1H), 4.38 (t, J = 5.4 Hz, 2H), 3.75 (t, J = 5.4 Hz, 2H), 3.59 (s,

3H), 2.60 (s, 3H). LCMS calc. for $C_{21}H_{18}ClFN_5O_4S$ $[M+H]^+$: m/z = 490.1; Found: 490.0.

Example 18: (S)-N-(4-Chloro-3-methylphenyl)-N,5-dimethyl-2-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-1,2,5-thiadiazolidine-3-carboxamide 1,1-dioxide (Compound A)

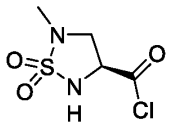


Step 1: 4-chloro-N,3-dimethylaniline



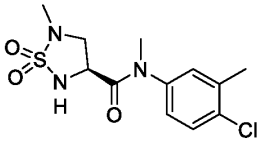
A mixture of 3-methyl-4-chloroaniline (500 mg, 3.53 mmol), paraformaldehyde (424 mg, 14.1 mmol), MeONa (572 mg, 10.5 mmol) and MeOH (20 mL) was refluxed for 4 h under nitrogen atmosphere. The mixture was cooled to 0°C and $NaBH_4$ (400 mg, 10.5 mmol) was added to the mixture above at 0°C. The resulting mixture was refluxed for 4 h and then quenched with water (50 mL). The water layer was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 4-chloro-N,3-dimethylaniline (280 mg, 50% yield) as a yellow liquid. LCMS calculated for $C_8H_{11}ClN$ $[M+H]^+$: m/z = 156.1; found: 156.1.

Step 2: (S)-5-methyl-1,2,5-thiadiazolidine-3-carbonyl chloride 1,1-dioxide



A mixture of (S)-5-methyl-1,2,5-thiadiazolidine-3-carboxylic acid 1,1-dioxide (80.0 mg, 0.444 mmol), oxalyl chloride (112 mg, 0.888 mmol), DMF (a drop) in DCM (2 mL) was stirred at r.t. for 2 h. Then the reaction mixture was concentrated under reduced pressure to afford (S)-5-methyl-1,2,5-thiadiazolidine-3-carbonyl chloride 1,1-dioxide (85 mg, crude) as a yellow semi-solid. The crude product was used in the next step directly without further purification.

Step3: (S)-N-(4-chloro-3-methylphenyl)-N,5-dimethyl-1,2,5-thiadiazolidine-3-carboxamide 1,1-dioxide

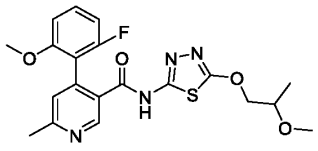


A mixture of (S)-5-methyl-1,2,5-thiadiazolidine-3-carbonyl chloride 1,1-dioxide, 4-chloro-N,3-dimethylaniline (73.2 mg, 0.471 mmol), pyridine (67.7 mg, 0.856 mmol) and THF (3 mL) was stirred at 60 °C for overnight. Then the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column eluting with EA/PE (0–30%) to afford the title product (40.0 mg, 19% yield) as a white solid. LCMS calculated for $C_{12}H_{17}ClN_3O_3S$ $[M+H]^+$: m/z = 318.1; found: 318.1.

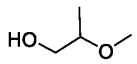
Step 4: (S)-N-(4-chloro-3-methylphenyl)-N,5-dimethyl-2-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-1,2,5-thiadiazolidine-3-carboxamide 1,1-dioxide

A mixture of (S)-N-(4-chloro-3-methylphenyl)-N,5-dimethyl-1,2,5-thiadiazolidine-3-carboxamide 1,1-dioxide (40.0 mg, 0.126 mmol), 2-bromo-6-methyl-4-(trifluoromethyl)pyridine (33.2 mg, 0.139 mmol), N^1,N^2-dimethylethane-1,2-diamine (4.44 mg, 0.050 mmol), CuI (4.79 mg, 0.025 mmol), Cs_2CO_3 (123 mg, 0.378 mmol) and 1,4-dioxane (3 mL) was stirred at 100 °C for overnight under nitrogen atmosphere. Then the reaction mixture was concentrated under reduced pressure and the residue was purified by prep HPLC eluting with ACN/H_2O (51% to 81% with 10 mmol/L NH_4HCO_3) to afford the title product (26.0 mg, 43% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50-7.46 (m, 2H), 7.35 (s, 1H), 7.22-7.19 (d, J = 4.5 Hz, 1H), 7.07 (s, 1H), 5.13-5.09 (m, 1H), 3.45-3.35 (m, 2H), 3.31 (s, 3H), 2.87 (s, 3H), 2.60 (s, 3H), 2.45 (s, 3H). LCMS calculated for $C_{19}H_{21}ClF_3N_4O_3S$ $[M+H]^+$: m/z =477.1; found: 477.0.

Example 19: 4-(2-Fluoro-6-methoxyphenyl)-N-(5-(2-methoxypropoxy)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide (Compound 19)

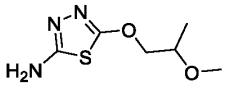


Step 1: 2-methoxypropan-1-ol



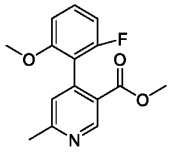
To a solution of 2-methoxypropanoic acid (1.04 g, 10 mmol) in THF (10 mL) was added BH_3-THF complex (15 mL, 1.0 M in THF), then the mixture was stirred at 70 °C overnight. The reaction mixture was cooled with ice-water bath, and then quenched by MeOH (20 mL) for 2 h.. The resulting mixture was evaporated under reduced pressure to afford 2-methoxypropan-1-ol without further purification.

Step 2: 5-(2-methoxypropoxy)-1,3,4-thiadiazol-2-amine



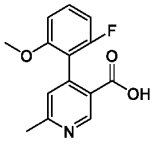
To a mixture of 2-methoxypropan-1-ol (1.0 g, 10.0 mmol) and 5-bromo-1,3,4-thiadiazol-2-amine (0.9 g, 5.0 mmol) in DMF (10 mL) was added NaH (0.6 g, 15.0 mmol 60% suspension in mineral oil) at 0 °C. The mixture was stirred at r.t. overnight, quenced with water (30 mL), and then extracted with EtOAc (20 mL x 4). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a C18 column eluting with MeCN/H_2O (2 - 15%) to afford the the title compound (230 mg, 14% yield) as yellow oil. LCMS calc. for $C_6H_{12}N_3O_2S$ $[M+H]^+$: m/z = 190.1; Found: 190.1.

Step 3: methyl 4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinate



This compound was prepared as yellow solid by procedures analogous to those described for Example 1 Step 2 using 2-fluoro-6-methoxyphenylboronic acid to replace (3-chloro-2-fluoro-6-methoxyphenyl)boronic acid. LCMS calc. for $C_{15}H_{15}FNO_3$ $[M+H]^+$: m/z = 276.1; Found: 276.0.

Step 4: 4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid

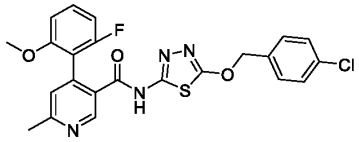


This compound was prepared as off-white solid by procedures analogous to those described for Example 1 Step 3 using methyl 4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinate . LCMS calc. for $C_{14}H_{13}FNO_3$ $[M+H]^+$: m/z = 261.1; Found: 261.0.

Step 5: 4-(2-fluoro-6-methoxyphenyl)-N-(5-(2-methoxypropoxy)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide

To a mixture of 4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinic acid (106 mg, 0.4 mmol), TCFH (168 mg, 0.6 mmol) and NMI (66 mg, 0.8 mmol) in DMF (3 mL) was added 5-(2-methoxypropoxy)-1,3,4-thiadiazol-2-amine (80 mg, 0.4 mmol). The reaction mixture was stirred at r.t. for 5 h., and then concentrated under reduced pressure. The residue was purified by prep-HPLC eluting on a C18 column with MeCN/H_2O (15 - 45%) to afford the title compound (82.9 mg, 48% yield) as white solid. LCMS calc. for $C_{20}H_{22}FN_4O_4S$ [M+H]+: m/z = 433.1; Found: 433.2.

Example 20: N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinamide (Compound 20)



This compound above was synthesized by referring to the method desdcribed in WO2020243459A1 Example 183.

Example A1: Assessment of viability of Compound 1 in combination with Bleomycin and Olaparib in Ishikawa cells

The combination experiments were performed in Ishikawa cells. Cells were maintained in RPMI1640 (Hyclone, Catalog #: SH30024.01) supplemented with 10% v/v FBS (AusGeneX, Catalog #: FBS500-S), 1% v/v Penicillin Streptomycin (Gibco, Catalog#: 15140122). Cells were seeded in 96-well plates (PerkinElmer, Catalog #: 6005680) at a density of 600 cells/well. Compounds dissolved in DMSO were plated in duplicate using a multichannel pipette, and tested on serial dilution either POLQ inhibitor (compound 1), Bleomycin and Olaparib alone or in combination. Cells were incubated for 7 days in a 37 °C active humidified incubator at 5% CO_2. Cell viability was measured using the Cell Titer-Glo reagent (Promega, Catalog#: G7573) as

manufacturer's instructions. Luminescence signal was measured with a multimode plate reader (BMG, ClarioStar Plus). Average values of DMSO treated wells in a plate was calculated and as high control (HC).

%control=(Signal_cmpd)/(SignalAve_HC) ×100%.

A representative dose combination was then plotted for POLQ inhibitor and PARP inhibitor alone and their certain combinations.

Figure 1. As single agents, the doses of 308 nM Bleomycin had obvious inhibition in cell viability, 2 μM Compound 1 had slightly inhibition in cell viability. Surprisingly, the combination of 308 nM Bleomycin and 2 μM Compound 1 led to significant inhibition in cell viability (i. e. ~70% inhibition).

Figure 2. As single agents, the doses of 123 nM Olaparib had no obvious inhibition in cell viability, 2 μM Compound 1 have obvious inhibition in cell viability. Surprisingly, the combination of 123 nM Olaparib and 2 μM Compound 1 led to significant inhibition in cell viability (i. e. ~70% inhibition).

Example A2: Assessment of viability of Compound 1 in combination with Olaparib in DLD1-BRCA2-KO cells

The combination experiments were performed in DLD1-BRCA2-KO cells. Cells were maintained in RPMI1640 (Hyclone, Catalog #: SH30024.01) supplemented with 10% v/v FBS (AusGeneX, Catalog #: FBS500-S), 1% v/v Penicillin Streptomycin (Gibco, Catalog#: 15140122), 1% v/v Hygromycin B Gold (InvivoGen, Catalog#: ant-hg-1). Cells were seeded in 96-well plates (PerkinElmer, Catalog #: 6005680) at a density of 100 cells/well. Compounds dissolved in DMSO were plated in duplicate using a multichannel pipette, and tested on serial dilution either POLQ inhibitor (compound 1), Olaparib alone or in combination. Cells were incubated for 13 days in a 37 °C active humidified incubator at 5% CO_2. Cell viability was measured using the Cell Titer-Glo reagent (Promega, Catalog#: G7573) as manufacturer's instructions. Luminescence signal was measured with a multimode plate reader (BMG, ClarioStar Plus). Average values of DMSO treated wells in a plate was calculated and as high control (HC).

%control= (Signalcmpd)/(SignalAve_HC) ×100%.

A representative dose combination was then plotted for POLQ inhibitor and PARP inhibitor alone and their certain combinations.

Figure 3. As single agents, the doses of 9.77 nM Olaparib had no obvious inhibition in cell viability, 0.15 μM Compound 1 have obvious inhibition in cell viability. Surprisingly, the combination of 9.77 nM Olaparib and 0.15 μM Compound 1 led to significant inhibition in cell viability (i. e. ~75% inhibition).

Example A3: Assessment of viability of Compound 3, 4, 5 in combination with Olaparib in Canpan-1 cells

The combination experiments were performed in Capan-1 cells. Cells were maintained in RPMI1640 (Hyclone, Catalog #: SH30024.01) supplemented with 10% v/v FBS (AusGeneX, Catalog #: FBS500-S), 1% v/v Penicillin Streptomycin (Gibco, Catalog#: 15140122). Cells were seeded in 96-well plates (PerkinElmer, Catalog #: 6005680) at a density of 100 cells/well.

Compounds dissolved in DMSO were plated in duplicate using a multichannel pipette, and tested on serial dilution either POLQ inhibitor (compound 3, 4, 5), Olaparib alone or in combination. Cells were incubated for 13 days in a 37 °C active humidified incubator at 5% CO_2. Cell viability was measured using the Cell Titer-Glo reagent (Promega, Catalog#: G7573) as manufacturer's instructions. Luminescence signal was measured with a multimode plate reader (BMG, ClarioStar Plus). Average values of DMSO treated wells in a plate was calculated and as high control (HC).

%control=(Signalcmpd)/(SignalAve_HC) ×100%.

A representative dose combination was then plotted for POLQ inhibitor and PARP inhibitor alone and their certain combinations.

Figure 4. As single agents, the doses of 13 nM Olaparib and 0.33 μM Compound 3 had no obvious inhibition in cell viability. Surprisingly, the combination of 13 nM Olaparib and 0.33 μM Compound 3 led to slightly inhibition in cell viability (i. e. ~40% inhibition).

Figure 5. As single agents, the doses of 41 nM Olaparib and 0.15μM Compound 4 had no obvious inhibition in cell viability. Surprisingly, the combination of 41 nM Olaparib and 0.15μM Compound 4 led to obvious inhibition in cell viability (i. e. ~50% inhibition).

Figure 6. As single agents, the doses of 4.3 nM Olaparib and 0.33 μM Compound 5 had no obvious inhibition in cell viability, the combination of 4.3 nM Olaparib and 0.33 μM Compound 5 also had no obvious inhibition in cell viability (i. e. ~30% inhibition).

Example A4: Assessment of viability of Compound 1 in combination with Olaparib in HCC1569 cells

The combination experiments were performed in HCC1569 cells. Cells were maintained in RPMI1640 (Hyclone, Catalog #: SH30024.01) supplemented with 10% v/v FBS (AusGeneX, Catalog #: FBS500-S), 1% v/v Penicillin Streptomycin (Gibco, Catalog#: 15140122). Cells were seeded in 96-well plates (PerkinElmer, Catalog #: 6005680) at a density of 400 cells/well. Compounds dissolved in DMSO were plated in duplicate using a multichannel pipette, and tested on serial dilution either POLQ inhibitor (compound 1), Olaparib alone or in combination. Cells were incubated for **13** days in a 37 °C active humidified incubator at 5% CO_2. Cell viability was measured using the Cell Titer-Glo reagent (Promega, Catalog#: G7573) as manufacturer's instructions. Luminescence signal was measured with a multimode plate reader (BMG, ClarioStar Plus). Average values of DMSO treated wells in a plate was calculated and as high control (HC).

%control=(Signalcmpd)/(SignalAve_HC) ×100%.

A representative dose combination was then plotted for POLQ inhibitor and PARP inhibitor alone and their certain combinations.

Figure 7. As single agents, the doses of 123 nM Olaparib had no obvious inhibition in cell viability, the doses of 5 μM Compound 1 had slightly inhibition in cell viability, the combination of 123 nM Olaparib and 5 μM Compound 1 led to obvious inhibition in cell viability (i. e. ~60% inhibition).

Example A5: Assessment of viability of Compound 3, 4, 7 in combination with Olaparib in MDA-MB-436 cells

The combination experiments were performed in MDA-MB-436 cells. Cells were maintained

in RPMI1640 (Hyclone, Catalog #: SH30024.01) supplemented with 10% v/v FBS (AusGeneX, Catalog #: FBS500-S), 1% v/v Penicillin Streptomycin (Gibco, Catalog#: 15140122). Cells were seeded in 96-well plates (PerkinElmer, Catalog #: 6005680) at a density of 150 cells/well. Compounds dissolved in DMSO were plated in duplicate using a multichannel pipette, and tested on serial dilution either POLQ inhibitor (compound 3, 4, 7), Niraparib and Olaparib alone or in combination. Cells were incubated for 13 days in a 37 °C active humidified incubator at 5% CO_2. Cell viability was measured using the Cell Titer-Glo reagent (Promega, Catalog#: G7573) as manufacturer's instructions. Luminescence signal was measured with a multimode plate reader (BMG, ClarioStar Plus). Average values of DMSO treated wells in a plate was calculated and as high control (HC). %control=(Signalcmpd)/(SignalAve_HC) ×100%. A representative dose combination was then plotted for POLQ inhibitor and PARP inhibitor alone and their certain combinations.

Figure 8. As single agents, the doses of 0.41 nM Olaparib and 0.15μM Compound 3 had no obvious inhibition in cell viability. Surprisingly, the combination of the 0.41 nM Olaparib and 0.15μM Compound 3 led to obvious inhibition in cell viability (i. e. ~60% inhibition).

Figure 9. As single agents, the doses of 1.23 nM Olaparib and 0.33μM Compound 4 had no obvious inhibition in cell viability. Surprisingly, the combination of the 1.23 nM Olaparib and 0.33μM Compound 4 led to significant inhibition in cell viability (i. e. ~70% inhibition).

Figure 10. As single agents, the doses of 1.23 nM Olaparib had no obvious inhibition in cell viability, 0.67 μM Compound 7 had obvious inhibition in cell viability. Surprisingly, the combination of the 1.23nM Olaparib and 0.67 μM Compound 7 led to significant inhibition in cell viability (i. e. ~90% inhibition).

Example A6: Assessment of viability of Compound 2, 3, 4, 5, 6, 7, in combination with A, Olaparib or Niraparib in HCC1937 cells

The combination experiments were performed in **HCC1937** cells. Cells were maintained in RPMI1640 (Hyclone, Catalog #: SH30024.01) supplemented with 10% v/v FBS (AusGeneX, Catalog #: FBS500-S), 1% v/v Penicillin Streptomycin (Gibco, Catalog#: 15140122). Cells were seeded in 96-well plates (PerkinElmer, Catalog #: 6005680) at a density of 400 cells/well. Compounds dissolved in DMSO were plated in duplicate using a multichannel pipette, and tested on serial dilution either POLQ inhibitor (compound 2, 3, 4, 5, 6, 7, A), Niraparib and Olaparib alone or in combination. Cells were incubated for 13 days in a 37 °C active humidified incubator at 5% CO_2. Cell viability was measured using the Cell Titer-Glo reagent (Promega, Catalog#: G7573) as manufacturer's instructions. Luminescence signal was measured with a multimode plate reader (BMG, ClarioStar Plus). Average values of DMSO treated wells in a plate was calculated and as high control (HC).

%control= (Signalcmpd)/(SignalAve_HC) ×100%.

A representative dose combination was then plotted for POLQ inhibitor and PARP inhibitor alone and their certain combinations.

Figure 11. As single agents, the doses of 123 nM Compound 3 and 250nM Niraparib had no obvious inhibition in cell viability. Surprisingly, the combination of 123 nM Compound 3 and

250nM Niraparib led to obvious inhibition in cell viability (i. e. ~50% inhibition).

Figure 12. As single agents, the doses of 13 nM Olaparib and 0.33μM Compound 4 had no obvious inhibition in cell viability. Surprisingly, the combination of the 13 nM Olaparib and 0.33μM Compound 4 led to slightly inhibition in cell viability (i. e. ~40% inhibition).

Figure 13. As single agents, the doses of 370nM Olaparib and 2.68μM Compound 5 had no obvious inhibition in cell viability. Surprisingly, the combination of the 370nM Olaparib and 2.68μM Compound 5 led to obvious inhibition in cell viability (i. e. ~50% inhibition).

Figure 14. As single agents, the doses of 41 nM Olaparib and 0.33μM Compound 6 had no obvious inhibition in cell viability. Surprisingly, the combination of the 41 nM Olaparib and 0.33μM Compound 6 led to slightly inhibition in cell viability (i. e. ~30% inhibition).

Figure 15. As single agents, the doses of 123 nM Olaparib and 0.11μM Compound 7 had no obvious inhibition in cell viability. Surprisingly, the combination of the 123 nM Olaparib and 0.11μM Compound 7 led to slightly inhibition in cell viability (i. e. ~70% inhibition).

Figure 16. As single agents, the doses of 205 nM Compound A and 150 nM Compound 2 had no obvious inhibition in cell viability. Surprisingly, the combination of the 205 nM Compound A and 150 nM Compound 2 led to slightly inhibition in cell viability (i. e. ~40% inhibition).

Example A7: Assessment of viability of Compound 1 in combination with Olaparib in TOV21G cells

The combination experiments were performed in TOV21G cells. Cells were maintained in RPMI1640 (Hyclone, Catalog #: SH30024.01) supplemented with 10% v/v FBS (AusGeneX, Catalog #: FBS500-S), 1% v/v Penicillin Streptomycin (Gibco, Catalog#: 15140122). Cells were seeded in 96-well plates (PerkinElmer, Catalog #: 6005680) at a density of 100 cells/well. Compounds dissolved in DMSO were plated in duplicate using a multichannel pipette, and tested on serial dilution either POLQ inhibitor (compound 1), Niraparib and Olaparib alone or in combination. Cells were incubated for 9 days in a 37 °C active humidified incubator at 5% CO_2. Cell viability was measured using the Cell Titer-Glo reagent (Promega, Catalog#: G7573) as manufacturer's instructions. Luminescence signal was measured with a multimode plate reader (BMG, ClarioStar Plus). Average values of DMSO treated wells in a plate was calculated and as high control (HC).

%control=(Signalcmpd)/(SignalAve_HC) × 100%.

A representative dose combination was then plotted for POLQ inhibitor and PARP inhibitor alone and their certain combinations.

Figure 17. As single agents, the doses of 41 nM Olaparib and 0.67 μM Compound 1 had no obvious inhibition in cell viability. Surprisingly, the combination of 41 nM Olaparib and 0.67 μM Compound 1 led to obvious inhibition in cell viability (i. e. ~60% inhibition).

Example B: Determination of Compound Synergy in vivo

Efficacy of POLQ inhibitor as monotherapy or in combination with PARP inhibitors (Niraparib or Olaparib) was assessed in the DLD-1 BRCA2 KO xenograft model.

Each Nude mouse was inoculated subcutaneously in the right flank region with DLD-1 BRCA2 KO cells ($3x10^6$) in 0.1 mL of PBS and Matrigel (1:1) for tumor development. The treatments were started when the mean tumor volume reached approximately 100-150 mm^3.

POLQ inhibitor was orally (PO) administered once daily as a solution, in 10% DMSO, 20% Solutol, 70% PBS as vehicle control; Niraparib was administered daily by oral gavage in 10% DMSO, 10% castor oil (EL), 80% PBS vehicle. The PO administration volume (0.1 mL/ 10 g body weight) was calculated from the body weight (BW) prior to compound administration. Body weights and tumor volume measurements were recorded twice per week. The tumor volume (TV) in mm^3 was calculated according to the following formula.

TV = a x b x b x 0.5

a: largest diameter of tumor (mm)

b: diameter perpendicular to length (mm)

The Tumor Growth Inhibition (TGI, %) was calculated according to the following formula:

TGI % = (Average Control TV Day X-Treatment TV Day X)/ Average Control TV Day X x 100%.

When Day X is any day of measurement.

Mice with > 20% body weight loss compared with Day 0 body weight, or bearing tumor with a mass >10% animal body weight were euthanized to prevent any pain and suffering to the animal. All studies were performed according to guidelines approved by the Institutional Animal Care and Use Committee (IACUC).

Statistical Analysis

Data are expressed as mean SEM for TV and BW. Tumor volume (TV) was measured using a digital caliper and calculated using the formula a x b x b x 0.5. Results are expressed as mean SEM, N=6/group. Statistical significance relative to vehicle control was established by One-Way ANOVA followed by Bonferroni post hoc test (GraphPadPrism v8).

Example B1: Antitumor Effect of Oral Compound 9 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 18 show the anti-tumor effects of female nude mice orally treated once daily with 100 mg/kg Compound 9 as a single agent or in combination with 25 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

The treatment with Compound 9 at 100 mg/kg induced tumor growth inhibition, with 37% tumor growth inhibition (TGI) on day 19, respectively. Niraparib, as single agent at 25 mg/kg did not significantly inhibit tumor growth with 36% TGI, whereas the combination of 100 mg/kg Compound 9 and 25 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 98% TGI.

Example B2: Antitumor Effect of Oral Compound 5 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 19 show the anti-tumor effects of female nude mice orally treated once daily with 50 mg/kg Compound 5 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

The treatment with Compound 5 at 50 mg/kg induced tumor growth inhibition, with 0% tumor growth inhibition (TGI) on day 28, respectively. Niraparib, as single agent at 30 mg/kg did not significantly inhibit tumor growth with 50% TGI, whereas the combination of 50 mg/kg Compound

5 and 30 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 112% TGI.

Example B3: Antitumor Effect of Oral Compound 4 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 20. show the anti-tumor effect of female nude mice orally treated once daily with 100 mg/kg Compound 4 as a single agent or in combination with 25 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

The treatment with Compound 4 at 100 mg/kg induced tumor growth inhibition, with 30% tumor growth inhibition (TGI) on day 16, respectively. Niraparib, as single agent at 25 mg/kg did not significantly inhibit tumor growth with 45% TGI, whereas the combination of 100 mg/kg Compound 4 and 25 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 110% TGI.

Example B4: Antitumor Effect of Oral Compound 10 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 21 show the anti-tumor effect of female nude mice orally treated once daily with 100 mg/kg compound 10 as a single agent or in combination with 25 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

The treatment with compound 10 at 100 mg/kg induced tumor growth inhibition, with 44% tumor growth inhibition (TGI) on day 16, respectively. Niraparib, as single agent at 25 mg/kg did not significantly inhibit tumor growth with 45% TGI, whereas the combination of 100 mg/kg Compound 10 and 25 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 109% TGI.

Example 5: Antitumor Effect of Oral Compound 11 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 22 show the anti-tumor effect of female nude mice orally treated once daily with 100 mg/kg Compound 11 as a single agent or in combination with 25 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

The treatment with Compound 11 at 100 mg/kg induced tumor growth inhibition, with 33% tumor growth inhibition (TGI) on day 16, respectively. Niraparib, as single agent at 25 mg/kg did not significantly inhibit tumor growth with 45% TGI, whereas the combination of 100 mg/kg Compound 11 and 25 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 106% TGI.

Example B6: Antitumor Effect of Oral Compound 3 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 23 show the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg, 50 mg/kg, Compound 3 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

The treatment with Compound 3 at 25 mg/kg induced tumor growth inhibition, with 25% tumor growth inhibition (TGI) on day 35, respectively. The treatment with Compound 3 at 50 mg/kg induced tumor growth inhibition, with 15% tumor growth inhibition (TGI) on day 35,

respectively. Niraparib, as single agent at 30 mg/kg did not significantly inhibit tumor growth with 62% TGI, whereas the combination of 25 mg/kg Compound 3 and 30 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 110% TGI and the combination of 50 mg/kg Compound 3 and 30 mg/kg Niraparib also resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 110% TGI.

Example B7: Antitumor Effect of Oral Compound 12 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 24 show the anti-tumor effect of female nude mice orally treated once daily with 50 mg/kg Compound 12 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

The treatment with Compound 12 at 50 mg/kg induced tumor growth inhibition, with 59% tumor growth inhibition (TGI) on day 24, respectively. Niraparib, as single agent at 30 mg/kg did not significantly inhibit tumor growth with 73% TGI, whereas the combination of 50 mg/kg Compound 12 and 30 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 110% TGI.

Example B8: Antitumor Effect of Oral Compound 13 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 25 show the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 13 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

The treatment with Compound 13 at 25 mg/kg induced tumor growth inhibition, with -25% tumor growth inhibition (TGI) on day 21, respectively. Niraparib, as single agent at 30 mg/kg did not significantly inhibit tumor growth with 11% TGI, whereas the combination of 25 mg/kg Compound 13 and 30 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 116% TGI.

Example B9: Antitumor and Body Weight Effects of Oral Compound 7 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 26 show the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 7 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

The treatment with Compound 7 at 25 mg/kg induced tumor growth inhibition, with 0% tumor growth inhibition (TGI) on day 21, respectively. Niraparib, as single agent at 30 mg/kg did not significantly inhibit tumor growth with 11% TGI, whereas the combination of 25 mg/kg Compound 7 and 30 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 120% TGI.

Example B10: Antitumor Effect of Oral Compound 14 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 27 show the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 14 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-

BRCA2-KO CDX model.

The treatment with Compound 14 at 25 mg/kg induced tumor growth inhibition, with 13% tumor growth inhibition (TGI) on day 21, respectively. Niraparib, as single agent at 30 mg/kg did not significantly inhibit tumor growth with 11% TGI, whereas the combination of 25 mg/kg Compound 14 and 30 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 90% TGI.

Example B11: Antitumor Effect of Oral Compound 15 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 28 show the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 15 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

The treatment with Compound 15 at 25 mg/kg induced tumor growth inhibition, with -9% tumor growth inhibition (TGI) on day 20, respectively. Niraparib, as single agent at 30 mg/kg did not significantly inhibit tumor growth with 44% TGI, whereas the combination of 25 mg/kg Compound 15 and 30 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 75% TGI.

Example B12: Antitumor Effect of Oral Compound 16 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 29 show the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 16 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

The treatment with Compound 16 at 25 mg/kg induced tumor growth inhibition, with 0% tumor growth inhibition (TGI) on day 20, respectively. Niraparib, as single agent at 30 mg/kg did not significantly inhibit tumor growth with 44% TGI, whereas the combination of 25 mg/kg Compound 16 and 30 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 99% TGI.

Example B13: Antitumor Effects of Oral Compound 8 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 30 show the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 8 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-BRCA2-KO CDX model.

The treatment with Compound 8 at 25 mg/kg induced tumor growth inhibition, with 11% tumor growth inhibition (TGI) on day 30, respectively. Niraparib, as single agent at 30 mg/kg did not significantly inhibit tumor growth with 57% TGI, whereas the combination of 25 mg/kg Compound 8 and 30 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 112% TGI.

Example B14: Antitumor Effects of Oral Compound 17 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 31 show the anti-tumor effect of female nude mice orally treated once daily with 25 mg/kg Compound 17 as a single agent or in combination with 30 mg/kg Niraparib in the DLD1-

BRCA2-KO CDX model.

The treatment with Compound 17 at 25 mg/kg induced tumor growth inhibition, with 16% tumor growth inhibition (TGI) on day 30, respectively. Niraparib, as single agent at 30 mg/kg did not significantly inhibit tumor growth with 57% TGI, whereas the combination of 25 mg/kg Compound 17 and 30 mg/kg Niraparib resulted in significant enhancement of tumor growth inhibition relative to vehicle controls, tumor growth with 112% TGI.

Example B15: Antitumor Effects of Oral Compound 5 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 32 illustrates the anti-tumor effects in female nude mice treated once daily with Compound 5, either alone or in combination with 30 mg/kg Niraparib, in the DLD1-BRCA2-KO CDX model.

Monotherapy with Compound 5 showed limited efficacy, and both the vehicle and Compound 5 groups were terminated on day 28. Niraparib, administered at 30 mg/kg once daily, delayed tumor growth by approximately 24 days compared to the vehicle (tumor volume reaching 1000 mm^3 at 28 days for the vehicle vs. 52 days for Niraparib), achieving 50% tumor growth inhibition (TGI) by day 28. The study continued with the combination treatment groups, where complete tumor regressions were observed. The combination of Niraparib (30 mg/kg) with Compound 5 at doses of 5, 10, and 25 mg/kg resulted in tumor growth inhibition of 107%, 110%, and 112% on day 28, respectively, with tumor regression occurring in 83.3%, 100%, and 100% of mice during the later stages of treatment.

Example B16: Antitumor Effects of Oral Compound 5 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 33 illustrates the anti-tumor effects in female nude mice treated once daily with Compound 5, either alone or in combination with 30 mg/kg Niraparib, in the DLD1-BRCA2-KO CDX model.

Monotherapy with Compound 5 showed limited efficacy, and both the vehicle and Compound 5 groups were terminated on day 27. Niraparib, administered at 30 mg/kg once daily, delayed tumor growth compared to the vehicle (tumor volume reaching 1000 mm^3 at 27 days for the vehicle vs. 850 mm^3 at 38 days for Niraparib), achieving 41% tumor growth inhibition (TGI) by day 27. The study continued with the combination treatment groups, where complete tumor regressions were observed. The combination of Niraparib (30 mg/kg) with Compound 5 at doses of 1, 2.5 and 5 mg/kg resulted in tumor growth inhibition of 94%, 100%, and 108% on day 27, respectively, with tumor regression occurring in 16.7%, 83.3%, and 100% of mice during the later stages of treatment. The frequency of tumor regressions was enhanced by escalating doses of compound 5.

Example B17: Antitumor and Body Weight Effects of Oral Compound 13 and PARP inhibitor (Niraparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 34 illustrates the anti-tumor effects in female nude mice treated once daily with Compound 13, either alone or in combination with 30 mg/kg Niraparib, in the DLD1-BRCA2-KO CDX model.

Monotherapy with Compound 13 showed limited efficacy, and both the vehicle and Compound

13 groups were terminated on day 32. Niraparib, administered at 30 mg/kg once daily, delayed tumor growth compared to the vehicle (tumor volume reaching 1600 mm^3 at 32 days for the vehicle vs. 1200 mm^3 at 53 days for Niraparib), achieving 56% tumor growth inhibition (TGI) by day 32. The study continued with the combination treatment groups, where complete tumor regressions were observed. The combination of Niraparib (30 mg/kg) with Compound 13 at doses of 5 and 10 mg/kg resulted in tumor growth inhibition of 104%, and 107% on day 32, respectively, with tumor regression occurring in 66.7%, and 100% of mice during the later stages of treatment. All treatments were discontinued on day 67, and the combination groups did not progress off treatment. The combination of Compound 13 with Niraparib enriched for tumor regressions and the response was maintained during the observation period until day 102.

Example B18: Antitumor and Body Weight Effects of Oral Compound 2, Compound 19, Compound 20 and PARP inhibitor (Olaparib) in Female Nude Mice Bearing DLD1-BRCA2-KO Tumor Xenografts

Figure 35 illustrates the anti-tumor effects in female nude mice treated once daily with Compound 2, Compound 19, Compound 20, either alone or in combination with 100 mg/kg Olaparib, in the DLD1-BRCA2-KO CDX model.

All groups were terminated on day 14. Compound 2, Compound 19, Compound 20, Olaparib and the combination of Olaparib (100 mg/kg) with Compounds achieving 11.25%, 20.3%, -2.5%, 38.6%, 71.0%, 83.7%, 60.2% tumor growth inhibition (TGI) by day 14, respectively.

Example C: Determination of Compound Synergy in vivo

Efficacy of POLQ inhibitor as monotherapy or in combination with PARP inhibitors (Niraparib or Olaparib) or Irinotecan was assessed in the MDA-MB-436 xenograft model.

Each immunodeficient mouse was inoculated subcutaneously in the right flank region with MDA-MB-436 cells ($8x10^6$) in 0.15 mL of PBS and Matrigel (1:1) for tumor development. The treatments were started when the mean tumor volume reached approximately 100-150 mm^3.

POLQ inhibitor, Niraparib, Olaparib were orally (PO) administered once daily or twice daily as a solution, in 10% DMSO, 90% (20% sulfobutyl cyclodextrin physiological saline solution) as vehicle control. Irinotecan was intraperitoneal (i.p.) administered once weekly as a solution. The PO administration volume (0.1 mL/ 10 g body weight) was calculated from the body weight (BW) prior to compound administration. The i.p. administration volume (0.1 mL/ 10 g body weight) was calculated from the body weight (BW) prior to compound administration. Body weights and tumor volume measurements were recorded twice per week. The tumor volume (TV) in mm^3 was calculated according to the following formula.

TV = a x b x b x 0.5

a: largest diameter of tumor (mm)

b: diameter perpendicular to length (mm)

The Tumor Growth Inhibition (TGI, %) was calculated according to the following formula:

TGI % = (Average Control TV Day X-Treatment TV Day X)/ Average Control TV Day X x 100%.

When Day X is any day of measurement.

Mice with > 20% body weight loss compared with Day 0 body weight, or bearing tumor with a mass >10% animal body weight were euthanized to prevent any pain and suffering to the animal. All studies were performed according to guidelines approved by the Institutional Animal Care and Use Committee (IACUC).

Example C1: Antitumor Effects of Oral Compound 5 and PARP inhibitor (Niraparib) in Female NCG Mice Bearing MDA-MB-436 Tumor Xenografts

Figure 36 illustrates the anti-tumor effects in female NCG mice treated twice daily with Compound 5, either in combination with 20 mg/kg Niraparib (once daily), in the MDA-MB-436 CDX model.

The vehicle was terminated on day 33. Niraparib, administered at 20 mg/kg once daily, delayed tumor growth compared to the vehicle (tumor volume reaching 1970 mm^3 at 33 days for the vehicle vs. 2283 mm^3 at 54 days for Niraparib), achieving 63% tumor growth inhibition (TGI) by day 33. The combination of Niraparib (20 mg/kg) with Compound 5 at doses of 25 and 50 mg/kg twice daily resulted in tumor growth inhibition of 85%, and 90% on day 33, respectively. All treatments were discontinued on day 54, and tumor size was assessed for both the Niraparib monotherapy and combination groups. Tumor volumes in the Niraparib monotherapy group reached 2283 mm^3. In contrast, the combination therapy groups, receiving 25 mg/kg and 50 mg/kg BID of Compound 5, exhibited tumor volumes of 563 mm^3 and 324 mm^3, respectively, highlighting a significant enhancement in tumor growth inhibition with the combination therapy compared to PARP inhibitor monotherapy.

Example C2: Antitumor Effects of Oral Compound 13 and PARP inhibitor (Niraparib) in Female NCG Mice Bearing MDA-MB-436 Tumor Xenografts

Figure 37 illustrates the anti-tumor effects in female NCG mice treated twice daily with Compound 13, either in combination with 20 mg/kg Niraparib (once daily), in the MDA-MB-436 CDX model.

Monotherapy with Compound 13 showed limited efficacy, and both the vehicle and Compound 13 groups were terminated on day 33. Niraparib, administered at 20 mg/kg once daily, delayed tumor growth compared to the vehicle (tumor volume reaching 1970 mm^3 at 33 days for the vehicle vs. 2283 mm^3 at 54 days for Niraparib), achieving 63% tumor growth inhibition (TGI) by day 33. The combination of Niraparib (20 mg/kg) with Compound 13 at doses of 25 and 50 mg/kg twice daily resulted in tumor growth inhibition of 88%, and 95% on day 33, respectively. All treatments were discontinued on day 54, and tumor size was assessed for both the Niraparib monotherapy and combination groups. Tumor volumes in the Niraparib monotherapy group reached 2283 mm^3. In contrast, the combination therapy groups, receiving 25 mg/kg and 50 mg/kg BID of Compound 13, exhibited tumor volumes of 585 mm^3 and 394 mm^3, respectively, highlighting a significant enhancement in tumor growth inhibition with the combination therapy compared to PARP inhibitor monotherapy.

Example C3: Antitumor Effects of Oral Compound 13 and PARP inhibitor (Olaparib) in Female nude Mice Bearing MDA-MB-436 Tumor Xenografts

Figure 38 illustrates the anti-tumor effects in female nude mice treated once daily with

Compound 13, either in combination with 50 mg/kg Olaparib, in the MDA-MB-436 CDX model.

All groups were terminated on day 25. Compound 13, Olaparib and the combination of Olaparib (50 mg/kg) with Compounds 13 (25 mg/kg) achieving 41%, 94%, 117% tumor growth inhibition (TGI) by day 25, respectively. The combination treatment group, where complete tumor regressions were observed, with tumor regression occurring in 100% of mice during the treatment.

Example C4: Antitumor Effects of Oral Compound 13 and Irinotecan in Female nude Mice Bearing MDA-MB-436 Tumor Xenografts

Figure 39 illustrates the anti-tumor effects in female nude mice treated once daily with Compound 13, either in combination with 5 mg/kg Irinotecan (i.p., once weekly), in the MDA-MB-436 CDX model.

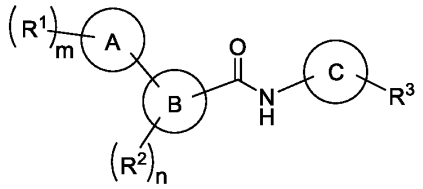
All groups were terminated on day 25. Compound 13 (25 mg/kg) and Irinotecan (5 mg/kg) monotherapy group achieving 41%, 68% tumor growth inhibition (TGI) by day 25, respectively. The combination of Irinotecan (5 mg/kg) with Compounds 13 (25 mg/kg and 50 mg/kg) achieving 82%, 93% tumor growth inhibition (TGI) by day 25, respectively. Tumor volumes in the Compound 13 and Irinotecan monotherapy group reached 432 mm^3 and 293 mm^3, respectively. In contrast, the combination therapy groups, receiving 25 mg/kg and 50 mg/kg of Compound 13, exhibited tumor volumes of 215 mm^3 and 158 mm^3, respectively.

Although the present invention has been comprehensively described through its embodiments, it is worth noting that various changes and modifications are obvious to those skilled in the art. Such changes and modifications should be included in the scope of the appended claims of the present invention.

What is Claimed:

1. A combination comprising a PolQ inhibitor and a second anti-cancer therapeutic agent, wherein:

the PolQ inhibitor is represented by compounds of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof, wherein:



(I);

ring A is selected from C_6-C_{14} aryl or 5-14 membered heteroaryl;

ring B is selected from partially unsaturated 5-14 membered heterocycloalkyl, C_6-C_{14} aryl or 5-14 membered heteroaryl;

ring C is selected from partially unsaturated 5-10 membered heterocycloalkyl or 5-10 membered heteroaryl; each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^6;

m is 1, 2, 3, 4 or 5;

n is 1, 2, 3, 4 or 5;

each R^1 is independently selected from H, D, halogen, -CN, -NO_2, N_3, -SF_5, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl, -NR^CR^D, -OR^A, -SR^A, -NR^COR^A, -$C(O)R^B$, -$C(O)NR^CR^D$, -$C(O)OR^A$, -$OC(O)R^B$, -$NR^CC(O)R^B$, -$S(O)R^B$, -$S(O)_2R^B$, -$S(O)NR^CR^D$, -$NR^CS(O)_2R^D$, -$S(O)_2NR^CR^D$, -$NR^CS(O)_2NR^CR^D$, -$NR^CS(O)(=NR^B)R^B$, $SiR^GR^HR^I$, $B(OR^C)(OR^D)$, -$P(O)R^ER^F$, -$P(O)OR^EOR^F$, -$OP(O)OR^EOR^F$; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}; or

two R^1 together with the atoms to which they are attached form oxo, C_3-C_7 cycloalkyl or 4-7 membered heterocycloalkyl; wherein, the C_3-C_7 cycloalkyl or 4-7 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A};

each R^{1A} is independently selected from D, halogen, CN, -NO_2, N_3, oxo, OR^a, NR^cR^d, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or 4-6 membered heterocycloalkyl is optionally substituted with D, halogen, CN, OH, NH_2, oxo, NR^cR^d, OR^a, SR^a, C_1-C_6 alkyl, C_1-C_6 haloalkyl;

each R^2 is independently selected from H, D, CN, NO_2, N_3, oxo, SF_5, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, -NR^CR^D, -OR^A, -SR^A, -NR^COR^A, -$C(O)R^B$, -$C(O)NR^CR^D$, -$C(O)OR^A$, -$OC(O)R^B$, -$NR^CC(O)R^B$, -$S(O)R^B$, -$S(O)_2R^B$, -$S(O)NR^CR^D$, -$NR^CS(O)_2R^D$, -$S(O)_2NR^CR^D$, -$NR^CS(O)_2NR^CR^D$, -$NR^CS(O)(=NR^B)R^B$, $SiR^GR^HR^I$, $B(OR^C)(OR^D)$, -$P(O)R^ER^F$, -$P(O)OR^EOR^F$, -$OP(O)OR^EOR^F$; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10}

cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}; or

two R^2 together with the atoms to which they are attached form oxo, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl; wherein, the C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl is optionally substituted by 1, 2, 3 or 4 substituents independently selected from R^{2A};

each R^{2A} is independently selected from D, halogen, CN, OH, NH_2, NO_2, SF_5, oxo, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, NR^cR^d, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)(=NR^b)R^b$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^d$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$; wherein, the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl is optionally substituted with D, halogen, CN, OH, NH_2, oxo, $NR^{c1}R^{d1}$, OR^{a1}, SR^{a1}, C_1-C_6 alkyl, C_1-C_6 haloalkyl;

R^3 is selected from H, D, halo, CN, oxo, NO_2, SF_5, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{14} cycloalkyl, 4-14 membered heterocycloalkyl, C_6-C_{14} aryl, 5-14 membered heteroaryl, OR^A, SR^A, NR^COR^A, NR^CR^D, $C(O)R^B$, $C(O)NR^CR^D$, $NR^CC(O)R^B$, $NR^CC(O)OR^A$, $NR^CS(O)_2R^D$, $NR^CS(O)_2NR^CR^D$, $S(O)R^B$, $S(O)_2R^B$; wherein, the C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{14} cycloalkyl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl, 5-14 membered heteroaryl is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4;

each R^4 is independently selected from D, halo, CN, NO_2, N_3, oxo, NR^CR^D, OR^A, SR^A, NR^COR^A, $C(O)R^B$, $C(O)NR^CR^D$, $C(O)OR^A$, $OC(O)R^B$, $OC(O)NR^CR^D$, $NR^CC(O)R^B$, $NR^CC(O)NR^CR^D$, $NR^CC(O)OR^A$, $S(O)R^B$, $S(O)_2R^B$, $S(O)NR^CR^D$, $NR^CS(O)_2R^D$, $S(O)_2NR^CR^D$, $NR^CS(O)_2NR^CR^D$, $NR^CS(O)(=NR^B)R^B$, $SiR^GR^HR^I$, $B(OR^C)(OR^D)$, $-P(O)R^ER^F$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^5;

each R^5 is independently selected from D, CN, halo, NO_2, SF_5, oxo, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_3-C_6 cycloalkyl, optionally substituted 4-6 membered heterocycloalkyl, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)(=NR^b)R^b$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^d$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$;

each R^6 is independently selected from D, halo, CN, NO_2, $-N_3$, oxo, SF_5, NR^CR^D, OR^A, SR^A, $SiR^GR^HR^I$, $B(OR^C)(OR^D)$, $-P(O)R^ER^F$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, C_3-C_7 cycloalkyl, 5-6 membered heteroaryl, or 4-7 membered heterocycloalkyl is optionally substituted by 1, 2, 3, 4 or 5 substituents

independently selected from R^{6A};

two R^6 on the same ring carbon atom form oxo, C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl; wherein, the C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl is optionally substituted by 1, 2, 3 or 4 substituents independently selected from R^{6A};

two adjacent R^6 together with the atoms to which they are attached form C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl; wherein, the C_3-C_7 cycloalkyl, 4-7 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl is optionally substituted by 1, 2, 3 or 4 substituents independently selected from R^{6A};

each R^{6A} is independently selected from D, halogen, CN, OH, NH_2, NO_2, SF_5, oxo, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, 5-6 membered heteroaryl, NR^cR^d, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)(=NR^b)R^b$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^d$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$; wherein, the C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl is optionally substituted with D, halogen, CN, OH, NH_2, oxo, $NR^{c1}R^{d1}$, OR^{a1}, SR^{a1}, C_1-C_6 alkyl, C_1-C_6 haloalkyl;

each R^A is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocyclalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, $NR^cS(O)(=NR^b)R^b$ or $SiR^gR^hR^i$;

each R^B is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, OR^a, $C(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$,

$S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$;

R^C and R^D are each independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, OR^a, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$ or $B(OR^c)(OR^d)$;

or R^C and R^D together with the N atom to which they are attached form 4-7 membered heterocycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, OH, oxo, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, OC_1-C_4 alkyl, or OC_1-C_4 haloalkyl;

R^a and R^{a1} are each independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, halo, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, C_1-C_4 alkyl, OC_1-C_4 alkyl, C_1-C_4 haloalkyl, or OC_1-C_4 haloalkyl;

R^b and R^{b1} are each independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl;

R^c, R^d, R^{c1}, R^{d1} are each independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, 4-10 membered heterocycloalkyl-C_1-C_6 alkyl, C_6-C_{10} aryl-C_3-C_{10} cycloalkyl, C_6-C_{10} aryl-4-10 membered heterocycloalkyl, C_6-C_{10} aryl-heteroaryl, bi(C_6-C_{10} aryl), 5-10 membered

heteroaryl-C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl-4-10 membered heterocycloalkyl, 5-10 membered heteroaryl-C_6-C_{10} aryl, or bi(5-10 membered heteroaryl); wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, 4-10 membered heterocycloalkyl-C_1-C_6 alkyl, C_6-C_{10} aryl-C_3-C_{10} cycloalkyl, C_6-C_{10} aryl-4-10 membered heterocycloalkyl, C_6-C_{10} aryl-heteroaryl, bi(C_6-C_{10} aryl), 5-10 membered heteroaryl-C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl-4-10 membered heterocycloalkyl, 5-10 membered heteroaryl-C_6-C_{10} aryl, or bi(5-10 membered heteroaryl) is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 cyanoalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, $C(O)OR^{a1}$, $C(O)R^{b1}$, $S(O)_2R^{b1}$, C_1-C_4 alkyl-O-C_1-C_4 alkyl or C_1-C_4 alkyl-O-C_1-C_4 alkyl-O-;

or R^c and R^d together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 cyanoalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_1-C_4 alkoxy-C_1-C_4 alkyl or C_1-C_4 alkoxy-C_1-C_4 alkoxy;

or R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, OH, CN, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$_2$, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 hydroxyalkyl, C_1-C_4 cyanoalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_1-C_4 alkoxy-C_1-C_4 alkyl or C_1-C_4 alkoxy-C_1-C_4 alkoxy;

R^E and R^e are each independently selected from H, D, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_4 alkenyl, (C_1-C_4 alkoxy)-C_1-C_4 alkyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl-C_1-C_4 alkyl, C_3-C_{10} cycloalkyl-C_1-C_4 alkyl, 5-10 membered heteroaryl-C_1-C_4 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_4 alkyl;

R^F and R^f are each independently selected from H, D, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_{10} cycloalkyl, or 4-10 membered heterocycloalkyl;

R^G, R^H and R^I, R^g, R^h and R^i are each independently selected from optional substituted C_1-C_4 alkyl or optional substituted phenyl;

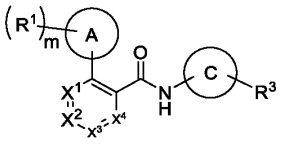
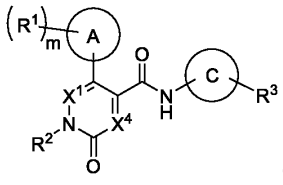
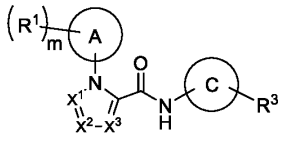
the second anti-cancer therapeutic agent is PARP inhibitor, PolQ inhibitor, chemotherapy, ionizing radiation or immune oncology medicine.

2. The compound of claim 1, wherein, each R^1 is independently selected from H, D, halogen, -CN, $-NO_2$, N_3, $-SF_5$, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl, $-NR^CR^D$, $-OR^A$, $-SR^A$, $-NR^COR^A$, $-C(O)R^B$, $-C(O)NR^CR^D$, $-C(O)OR^A$, $-OC(O)R^B$, $-NR^CC(O)R^B$, $-S(O)R^B$, $-S(O)_2R^B$, $-S(O)NR^CR^D$, $-NR^CS(O)_2R^D$, $-S(O)_2NR^CR^D$, $-NR^CS(O)_2NR^CR^D$, $-NR^CS(O)(=NR^B)R^B$, $SiR^GR^HR^I$,

$B(OR^C)(OR^D)$, $-P(O)R^ER^F$, $-P(O)OR^EOR^F$, $-OP(O)OR^EOR^F$; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl or 5-6 membered heteroaryl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{1A}; preferably, each R^1 is independently selected from H, D, F, Cl, Br, -CN, $-NO_2$, N_3, $-SF_5$, CD_3, CH_3, CH_2CH_3, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CH_2OH, $-CH(OH)CH_3$, CH_2CH_2OH, $-CH_2OCH_3$, $-CH_2OCHF_2$, $-CH_2OCH_2F$, $-CH_2OCF_3$, $-CH(OCH_3)CH_3$, $CH_2CH_2NH_2$, $-CH(NH_2)CH_3$, $CH_2N(CH_3)_2$, $CH_2CH_2N(CH_3)_2$, CH_2CN, NH_2, $NHCH_3$, $NHCH(CH_3)_2$, $NHCH_3$, $N(CH_3)_2$, $N(CH_2CH_3)_2$, OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_2F, OCH_2CHF_2, OCH_2CF_3, $-CH(OH)CH_3$, OCH_2CN or OCH_2CONH_2.

3. The compound of claim 1 or 2, wherein, each R^2 is independently selected from H, D, CN, NO_2, N_3, oxo, SF_5, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, $-NR^CR^D$, $-OR^A$, $-SR^A$, $-NR^COR^A$, $-C(O)R^B$, $-C(O)NR^CR^D$, $-C(O)OR^A$, $-OC(O)R^B$, $-NR^CC(O)R^B$, $-S(O)R^B$, $-S(O)_2R^B$, $-S(O)NR^CR^D$, $-NR^CS(O)_2R^D$, $-S(O)_2NR^CR^D$, $-NR^CS(O)_2NR^CR^D$, $-NR^CS(O)(=NR^B)R^B$, $SiR^GR^HR^I$, $B(OR^C)(OR^D)$, $-P(O)R^ER^F$, $-P(O)OR^EOR^F$, $-OP(O)OR^EOR^F$; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from R^{2A}; preferably, each R^2 is independently selected from H, D, CN, NO_2, N_3, oxo, SF_5, halogen, CH_3, CD_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2F, CHF_2, CF_3, CH_2OH, CH_2CH_2OH, CH_2CN, NH_2, $NHCH_3$, $N(CH_3)_2$, $NHCH_2CH_3$, $N(CH_2CH_3)_2$, $NHCH_2CH_2CH_3$, $N(CH_2CH_2CH_3)_2$, $NHCH(CH_3)_2$, $NHCH_2CH_2OH$, OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, OCH_2F, $OCHF_2$, OCF_3,  ,  , optionally substituted pyrrolyl or optionally substituted imidazolyl.

4. The combination of anyone of claim 1-3, wherein, the compounds of Formula (I) are represented by compounds of Formula (IIa), (IIb) or (IIc):

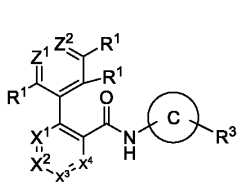
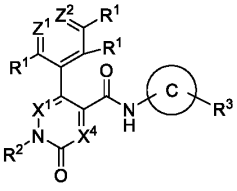
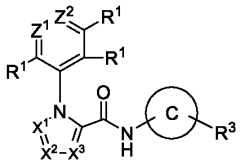
 (IIa),  (IIb),  (IIc);

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof;

X^1, X^2, X^3, X^4 are each independently selected from N or CR^2;

wherein, ring A, ring C, R^1, R^2, R^3 and m are defined with respect to Formula (I).

5. The combination of claim 4, wherein, the compounds of Formula (I) are represented by compounds of Formula (IIIa), (IIIb) or (IIIc):

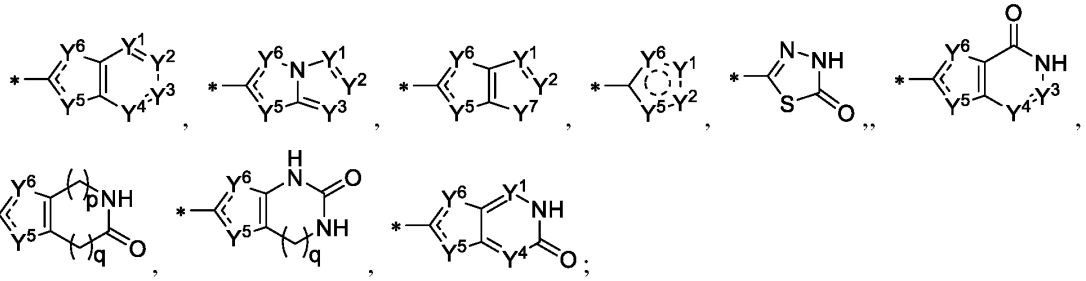

(IIIa),

(IIIb),

(IIIc);

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof;

Z^1 and Z^2 are each independently selected from N or CR^1;

wherein, ring C, X^1, X^2, X^3, X^4, R^1, R^3 and m are defined with respect to Formula (I).

6. The combination of anyone of claim 1-5, wherein, ring C is selected from:



wherein, ═══ is a single bond or double bond;

Y^1, Y^2, Y^3, Y^4 is same or different, and independently N or CH;

Y^5 is N, or S;

Y^6 is N, or S;

Y^7 is NH, O, or S;

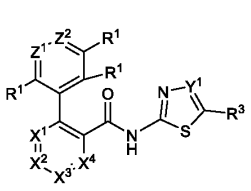
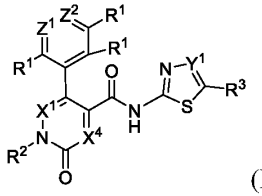
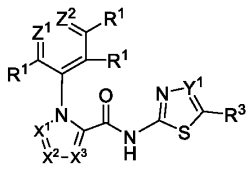
p and q are each independently selected from 0, 1 or 2;

the position * is attached to -NHC(=O)-;

R^3 is attached to any possible position on the ring C and one hydrogen atom of ring C replaced with R^3;

and one or more hydrogen atoms of ring C are optionally preplaced with 1, 2, 3, 4 or 5 substituents independently selected from R^6.

7. The combination of anyone of claim 1-6, wherein, the compounds of Formula (I) are represented by compounds of Formula (IVa), (IVb) or (IVc):


(IVa),

(IVb),

(IVc);

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof;

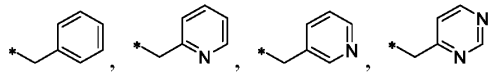
Y^1 is N or CR^6;

wherein, X^1, X^2, X^3, X^4, Z^1, Z^2, R^1, R^3 and m are defined with respect to Formula (I).

8. The combination of claim 7, wherein, Y^1 is N.

9. The combination of claim 7, wherein, Y^1 is CR^6 and R^6 is H.

10. The combination of anyone of claim 7-9, wherein, R^3 is OR^A and R^A is C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, $NR^cS(O)(=NR^b)R^b$ or $SiR^gR^hR^i$; preferably, R^3 is OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_2F, OCH_2CHF_2, OCH_2CF_3, OCF_2CF_3, OCH_2CH_2OH, $OCH_2CH(OH)_2$, $OCH_2CH_2OCH_3$, $OCH(CH_3)CH_2OH$, $OCH(CH_3)CH_2OCH_3$, $OCH_2CH(CH_3)OH$, $OCH_2CH(CH_3)OCH_3$, $OCH_2Si(CH_3)_3$, $OCH_2CH_2Si(CH_3)_3$, $OCH_2CH_2B(OH)_2$.

11. The combination of anyone of claim 7-9, wherein, R^3 is OR^A and R^A is C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; preferably, R^A is  , -CH_2-cyclopropyl, -CH_2-cyclobutyl, -CH_2-cyclopentyl, -CH_2-cyclohexyl, -CH_2-cycloheptyl, -CH_2-azetidinyl, -CH_2-pyrrolidinyl, -CH_2-piperidinyl, -CH_2-dioxanyl, -CH_2-piperazinyl, -CH_2-morpholinyl, -CH_2-azepanyl, -CH_2-diazocanyl, -CH_2-2,6-diazaspiro[3.3]heptanyl, -CH_2-octahydropyrrolo[3,4-c]pyrrolyl, -CH_2-2-azabicyclo[2.2.2]octanyl, -CH_2-4,5,6,7-tetrahydropyrrolo[2,3-b]pyridinyl; each R^A is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$, $NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $NR^cS(O)(=NR^b)R^b$;

12. The combination of anyone of claim 7-9, wherein, R^3 is SR^A, and R^A is C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, $NR^cS(O)(=NR^b)R^b$ or $SiR^gR^hR^i$; preferably, R^3 is SCH_3, SCH_2CH_3, $SCH_2CH_2CH_3$, $SCH(CH_3)_2$, SCH_2CF_3, SCH_2CH_2CN, $SCH_2CH_2CH_2CN$, SCH_2CH_2OH, $SCH_2CH_2OCH_3$, $SCH_2CH_2OCH_2CH_3$, $SCH(CH_3)CH_2OCH_3$, $SCH_2CH(CH_3)OCH_3$, $SCH_2C(CH_3)_2OCH_3$, $SCH(CH_3)CH_2OH$, $SCH_2CH(CH_3)OH$, $SCH_2C(CH_3)_2OH$.

13. The combination of anyone of claim 7-9, wherein, R^3 is NR^CR^D; wherein, R^C is selected from H, D, C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, OR^a, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$,

$S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$ or $B(OR^c)(OR^d)$, and R^D is independently selected from H, D, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl; wherein, the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, 4-10 membered heterocycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_6-C_{10} aryl-C_1-C_6 alkyl, 5-10 membered heteroaryl-C_1-C_6 alkyl, C_3-C_{10} cycloalkyl-C_1-C_6 alkyl, or 4-10 membered heterocycloalkyl-C_1-C_6 alkyl is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, OR^a, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$ or $B(OR^c)(OR^d)$; preferably, R^3 is NR^CR^D; R^C is H, D, CH_3, CH_2CH_3; and R^D is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2(CH_3)_2$, $CH(CH_3)_3$, CH_2CF_3, CH_2CH_2OH, $CH_2CH_2OCH_3$, CH_2CH_2CN, $CH_2CH_2N(CH_3)C(O)CH_3$, $CH_2CH_2N(CH_3)S(O)_2CH_3$, $CH_2CH_2N(CH_3)S(O)_2N(CH_3)_2$.

14. The combination of anyone of claim 7-9, wherein, R^3 is $S(O)_2R^B$.
15. The combination of anyone of claim 7-9, wherein, R^3 is C_1-C_{10} alkyl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4; and each R^4 is independently selected from D, halo, CN, NO_2, N_3, oxo, NR^CR^D, OR^A, SR^A, $C(O)R^B$, $C(O)NR^CR^D$, $C(O)OR^A$, $S(O)_2R^B$, $S(O)_2NR^CR^D$, $C(O)NR^CS(O)_2R^B$; preferably, R^3 is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CF_2CH_3, CF_2CF_3, $CF_2CH_2CH_3$, CH_2OH, CH_2CH_2OH, $CH(OH)CH_3$, $CH_2CH_2CH_2OH$, $CH(OH)CH_2CH_2OH$, CH_2OCH_3, $CH_2CH_2OCH_3$, $CH_2CH_2CH_2OCH_3$, $CH(OH)CH_2CH_2OCH_3$, CH_2CN, CH_2CH_2CN, $CH_2CH_2CH_2CN$.
16. The combination of claim 15, wherein, R^3 is C_1-C_2 alkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from R^4; and one of R^4 is OR^A, $C(O)R^B$, $C(O)NR^CR^D$, $C(O)OR^A$, $S(O)_2R^B$, $S(O)_2NR^CR^D$ or $C(O)NR^CS(O)_2R^B$.
17. The combination of claim 15, wherein, R^3 is C_1-C_2 alkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from R^4; and one of R^4 is OR^A; preferably, R^A is H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CF_2CF_3, CH_2CH_2OH, $CH_2CH_2OCH_3$, phenyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, dioxanyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, azepanyl, 2-oxa-6-azaspiro[3.3]heptanyl, octahydropyrrolo[3,2-b]pyridinyl, 2-azabicyclo[2.2.2]octanyl, 2,3,4,6-tetrahydropyrrolo[3,4-b]pyrazinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, bicyclo[3.2.0]heptanyl; and each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, SF_5, $NHOR^a$, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $C(=NR^c)NR^cR^d$, $NR^dC(=NR^c)NR^cR^d$,

$NR^dC(=NR^c)R^b$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, $NR^cS(O)(=NR^b)R^b$ or $SiR^gR^hR^i$.

18. The combination of claim 15, wherein, R^3 is C_1-C_2 alkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from R^4; and one of R^4 is $C(O)R^B$; preferably, R^B is azetidinyl, pyrrolidinyl, piperidinyl, dioxanyl, piperazinyl, morpholinyl, azepanyl; each is optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, oxo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 cyanoalkyl, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, SF_5, OR^a, $C(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, or $B(OR^c)(OR^d)$.

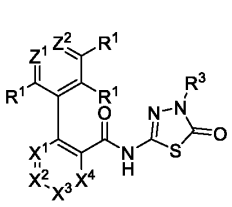
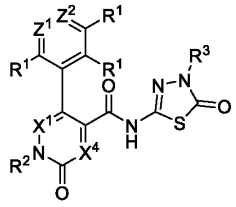
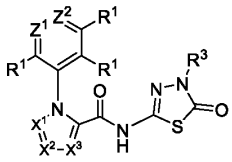
19. The combination of claim 15, wherein, R^3 is C_1-C_2 alkyl optionally substituted by 1, 2, 3 or 4 substituents independently selected from R^4; and one of R^4 is $C(O)NR^CR^D$; preferably, R^C is H, D, CH_3, CH_2CH_3; and R^D is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2(CH_3)_2$, $CH(CH_3)_3$, CH_2CF_3, CH_2CH_2OH, $CH_2CH_2OCH_3$, CH_2CH_2CN, $CH_2CH_2N(CH_3)C(O)CH_3$, $CH_2CH_2N(CH_3)S(O)_2CH_3$, $CH_2CH_2N(CH_3)S(O)_2N(CH_3)_2$.

20. The combination of anyone of claim 7-9, wherein, R^3 is C_2-C_{10} alkenyl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

21. The combination of anyone of claim 7-9, wherein, R^3 is C_2 alkynyl optionally substituted by R^4; and R^4 is C_1-C_6 alkyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl; wherein, the C_1-C_6 alkyl, C_6-C_{10} aryl, C_3-C_{10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^5.

22. The combination of anyone of claim 7-9, wherein, R^3 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, spiro[3.4]octanyl, bicyclo[3.1.1]heptyl, octahydropentalenyl, cyclopentenyl, cyclopentadienyl, azetidinyl, oxetanyl, pyrrolidinyl, piperidinyl, dioxanyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, azepanyl, 2,7-diazaspiro[4.4]nonanyl, 3,9-diazaspiro[5.5]undecanyl, octahydropyrano[3,2-b]pyrrolyl, octahydropyrrolo[3,2-b]pyridinyl, 3-azabicyclo[3.2.1]octanyl, 3-azabicyclo[3.3.1]nonanyl, 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidinyl, 2,3,4,6-tetrahydropyrrolo[3,4-b]pyrazinyl, phenyl, naphthalenyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, tetrazolyl, pyrazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-b]pyridinyl, pyrrolo[3,2-c]pyridazinyl, pyrrolo[3,2-d]pyrimidinyl, pyrrolo[2,3-b]pyrazinyl, pyrrolo[2,3-d]pyridazinyl, pyrrolo[2,3-d]pyrimidinyl, pyrrolo[2,3-c]pyridazinyl, pyrrolo[3,4-c]pyridazinyl; each is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

23. The combination of anyone of claim 1-5, wherein, the compounds of Formula (I) are represented by compounds of Formula (Va), (Vb) or (Vc):

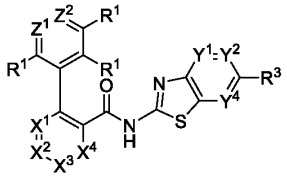
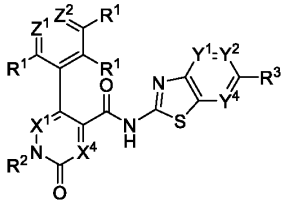
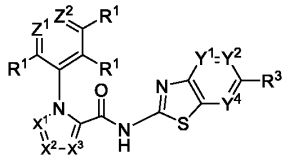

(Va),

(Vb),

(Vc);

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof;

wherein, X^1, X^2, X^3, X^4, Z^1, Z^2, R^1, R^3 and m are defined with respect to Formula (I).

24. The combination of claim 23, wherein, R^3 is C_1-C_{10} alkyl optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4; preferably, R^3 is selected from CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CF_2CH_3, CF_2CF_3, $CF_2CH_2CH_3$, CH_2OH, CH_2CH_2OH, $CH(OH)CH_3$, $CH_2CH_2CH_2OH$, $CH(OH)CH_2CH_2OH$, CH_2OCH_3, $CH_2CH_2OCH_3$, $CH_2CH_2CH_2OCH_3$, $CH(OH)CH_2CH_2OCH_3$, CH_2CN, CH_2CH_2CN, $CH_2CH_2CH_2CN$.

25. The combination of anyone of claim 1-5, wherein, the compounds of Formula (I) are represented by compounds of Formula (VIa), (VIb) or (VIc):


(VIa),

(VIb),

(VIc);

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof;

Y^1, Y^2, Y^4 are each independently selected from N or CR^6;

wherein, X^1, X^2, X^3, X^4, Z^1, Z^2, R^1, R^3 and m are defined with respect to Formula (I).

26. The combination of claim 25, wherein, Y^1 is CR^6, Y^2 is CR^6, and Y^4 is CR^6.
27. The combination of claim 25, wherein, Y^1 is CR^6, Y^2 is CR^6, and Y^4 is N.
28. The combination of claim 25, wherein, Y^1 is CR^6, Y^2 is N, and Y^4 is N.
29. The combination of claim 25, wherein, Y^1 is N, Y^2 is CR^6, and Y^4 is N.
30. The combination of anyone of claim 25-29, wherein, R^3 is OR^A, and R^A is C_1-C_6 alkyl optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from D, CN, halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkyl-OH, C_1-C_4 alkyl-CN, C_1-C_4 alkyl-O-C_1-C_4 alkyl, C_1-C_4 alkyl-O-C_1-C_4 haloalkyl, NO_2, oxo, OR^a, SR^a, $C(O)R^b$, $C(O)NR^cR^d$, $C(O)OR^a$, $OC(O)R^b$, $OC(O)NR^cR^d$, NR^cR^d, $NR^cC(O)R^b$, $NR^cC(O)NR^cR^d$, $NR^cC(O)OR^a$, $B(OR^c)(OR^d)$, $P(O)R^eR^f$, $P(O)OR^eOR^f$, $OP(O)OR^eOR^f$, $S(O)R^b$, $S(O)NR^cR^d$, $S(O)_2R^b$, $NR^cS(O)_2R^b$, $S(O)_2NR^cR^d$, $NR^cS(O)_2NR^cR^d$, $NR^cS(O)(=NR^b)R^b$ or $SiR^gR^hR^i$; preferably, R^3 is OH, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, OCH_2F, $OCHF_2$, OCF_3, OCH_2CH_2F, OCH_2CHF_2, OCH_2CF_3, OCF_2CF_3, OCH_2CH_2OH, $OCH_2CH_2OCH_3$, $OCH(CH_3)CH_2OH$, $OCH(CH_3)CH_2OCH_3$, $OCH_2CH(CH_3)OH$, $OCH_2CH(CH_3)OCH_3$, $OCH_2Si(CH_3)_3$, $OCH_2CH_2Si(CH_3)_3$.
31. The combination of anyone of claim 25-29, wherein, R^3 is C_1-C_{10} alkyl optionally substituted

by 1, 2, 3, 4 or 5 substituents independently selected from R^4; preferably, R^3 is selected from CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $C(CH_3)_3$, CH_2F, CHF_2, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, CF_2CH_3, CF_2CF_3, $CF_2CH_2CH_3$, CH_2OH, CH_2CH_2OH, $CH(OH)CH_3$, $CH_2CH_2CH_2OH$, $CH(OH)CH_2CH_2OH$, CH_2OCH_3, $CH_2CH_2OCH_3$, $CH_2CH_2CH_2OCH_3$, $CH(OH)CH_2CH_2OCH_3$, CH_2CN, CH_2CH_2CN, $CH_2CH_2CH_2CN$.

32. The combination of anyone of claim 25-29, wherein, R^3 is C_3-C_{14} cycloalkyl, 4-14 membered heterocycloalkyl, C_6-C_{14} aryl, 5-14 membered heteroaryl; wherein, the C_3-C_{14} cycloalkyl, 4-14 membered heterocycloalkyl, C_6-C_{10} aryl, 5-14 membered heteroaryl is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4; preferably, R^3 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, spiro[3.4]octanyl, bicyclo[3.1.1]heptyl, octahydropentalenyl, cyclopentenyl, cyclopentadienyl, azetidinyl, oxetanyl, pyrrolidinyl, piperidinyl, dioxanyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, azepanyl, 2,7-diazaspiro[4.4]nonanyl, 3,9-diazaspiro[5.5]undecanyl, octahydropyrano[3,2-b]pyrrolyl, octahydropyrrolo[3,2-b]pyridinyl, 3-azabicyclo[3.2.1]octanyl, 3-azabicyclo[3.3.1]nonanyl, 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrimidinyl, 2,3,4,6-tetrahydropyrrolo[3,4-b]pyrazinyl, phenyl, naphthalenyl, anthracenyl, phenanthrenyl, pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, tetrazolyl, pyrazolyl, triazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-c]pyridinyl, imidazo[4,5-b]pyridinyl, pyrrolo[3,2-c]pyridazinyl, pyrrolo[3,2-d]pyrimidinyl, pyrrolo[2,3-b]pyrazinyl, pyrrolo[2,3-d]pyridazinyl, pyrrolo[2,3-d]pyrimidinyl, pyrrolo[2,3-c]pyridazinyl, pyrrolo[3,4-c]pyridazinyl; each is optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from R^4.

33. The combination of anyone of claim 1-32, wherein, the compounds of Formula (I) is:

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-((4-chlorophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

N-(5-((4-cyanophenoxy)methyl)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxy-3-(trifluoromethyl)phenyl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoroethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-((2-methoxyethyl)thio)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-(dimethylamino)-1,1-difluoro-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(6-(2-methoxyethoxy)thiazolo[4,5-b]pyrazin-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-methoxyethoxy)thiazolo[5,4-d]pyrimidin-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoro-2-(methylamino)-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-6-methyl-N-(5-((trimethylsilyl)methoxy)-1,3,4-

thiadiazol-2-yl)nicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1-fluorocyclopropyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoro-2-hydroxyethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoro-2-hydroxyethyl-2,2-d2)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(4-(3-hydroxypropyl)-5-oxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(1,1-difluoro-2-(4-methylpiperazin-1-yl)-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-(4-cyanopiperidin-1-yl)-1,1-difluoro-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-(4-ethylpiperazin-1-yl)-1,1-difluoro-2-oxoethyl)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

4-(3-chloro-2-fluoro-6-methoxyphenyl)-N-(5-(2-hydroxyethoxy)thiazolo[5,4-d]pyrimidin-2-yl)-6-methylnicotinamide;

4-(2-fluoro-6-methoxyphenyl)-N-(5-(2-methoxypropoxy)-1,3,4-thiadiazol-2-yl)-6-methylnicotinamide;

N-(5-((4-chlorobenzyl)oxy)-1,3,4-thiadiazol-2-yl)-4-(2-fluoro-6-methoxyphenyl)-6-methylnicotinamide;

2'-chloro-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-7-fluorothiazolo[4,5-c]pyridin-2-yl)-3'-fluoro-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide;

2'-chloro-N-(6-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-7-fluorothiazolo[4,5-c]pyridin-2-yl)-5'-methoxy-6-methyl-[4,4'-bipyridine]-3-carboxamide;

or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof.

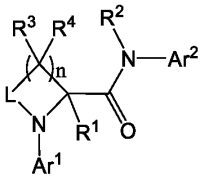
34. The combination of anyone of claim 1-33, wherein, the second anti-cancer therapeutic agent is PARP inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof; preferably, the PARP inhibitor is selected from Olaparib, Rucaparib, Niraparib, Talazoparib, Fluzoparib, Pamiparib, Veliparib, Senaparib, Saruparib, AZD9574, TQB3823, HTMC0435, SC10914, TSL-1502, WXFL10040340, RP12146, IMP1734, HRS-1167, NMS-293, NMS-P515, HS-10502, SNV-001 or a pharmaceutically acceptable salt, solvate, hydrate, tautomeric, stereoisomer, atropisomer, isotopic variants, prodrugs, N-oxide or deuterated compound thereof; preferably, the PARP inhibitor is selected from Olaparib, Rucaparib, Niraparib, Talazoparib, Fluzoparib, Pamiparib, Veliparib, Senaparib, Saruparib, or AZD9574; preferably, the PARP inhibitor is Olaparib; preferably, PARP inhibitor is Niraparib or Niraparib tosylate monohrdrate; preferably, PARP inhibitor is Saruparib; preferably, PARP inhibitor is AZD9574.

35. The combination of anyone of claim 1-33, wherein, the second anti-cancer therapeutic agent is

chemotherapies; preferably, chemotherapy is Bleomycin or Irinotecan; preferably, the chemotherapy is Bleomycin; preferably, the chemotherapy is Irinotecan.

36. The combination of anyone of claim 1-33, wherein, the second anti-cancer therapeutic agent is another PolQ inhibitor.

37. The combination of anyone of claim 1-33, wherein, another PolQ inhibitor is represented by the compound of formula (Ia):

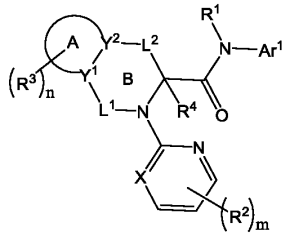


(Ia);

or pharmaceutically acceptable salt, stereoisomer, solvate, hydrate, tautomeric, isotopic variants, prodrugs, N-oxide or deuterated compound thereof;

wherein each of the variables Ar^1, Ar^2, L, R^1, R^2, R^3, R^4 and n is as defined and described in PCT/CN2023/095706, filing date: May 23, 2023.

38. The combination of anyone of claim 1-33, wherein, another PolQ inhibitor is represented by the compound of formula compound of formula (Ib):



(Ib);

or pharmaceutically acceptable salt, stereoisomer, solvate, hydrate, tautomeric, isotopic variants, prodrugs, N-oxide or deuterated compound thereof, wherein:

wherein each of the variables Ar^1, L^1, L^2, Y^1, Y^2, R^1, R^2, R^3, R^4, m and n is as defined and described in PCT/CN2023/095881, filing date: May 23, 2023.

39. The combination of claim 37, wherein, the compound of Formula (Ia) is:

(S)-N-(4-chloro-3-methylphenyl)-N,5-dimethyl-2-(6-methyl-4-(trifluoromethyl)pyridin-2-yl)-1,2,5-thiadiazolidine-3-carboxamide 1,1-dioxide;

or pharmaceutically acceptable salt, stereoisomer, solvate, hydrate, tautomeric, isotopic variants, prodrugs, N-oxide or deuterated compound thereof.

40. A method of treating and/or preventing a cancer in a subject, wherein the cancer is characterized by increased dependence upon MMEJ DSB repair; the cancer is characterized by HR-deficiency, a reduction or absence of expression of HR-associated genes; the cancer is lack of 53BP1/Shieldin complex in a patient; the cancer is characterized by NHEJ deficiency, a reduction or absence of expression of NHEJ-associated genes; or the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, absence of BRCA protein, or reduced function of BRCA protein, comprising administering to a subject a therapeutically effective amount of a combination of anyone of claim 1-39.

41. The method of claim 40, wherein, the cancer is endometrial cancer, pancreatic cancer, breast

cancer, ovarian cancer (ovary cancer), prostate cancer, lymphoma, rhabdoid tumor, multiple myloma, uterine cancer, gastric cancer, peripheral nervous system cancer, rhabdomyosarcoma, bone cancer, colorectal cancer, mesothelioma, lung cancer, fibroblast cancer, central nervous system cancer, urinary tract cancer, upper aerodigestive cancer, leukemia, kidney cancer, skin cancer, esophageal cancer.

42. A combination of anyone of claim 1-39 for use in the treatment of a cancer in a subject, wherein the cancer is characterized by increased dependence upon MMEJ DSB repair; the cancer is characterized by HR-deficiency, a reduction or absence of expression of HR-associated genes; the cancer is lack of 53BP1/Shieldin complex in a patient; the cancer is characterized by NHEJ deficiency, a reduction or absence of expression of NHEJ-associated genes; or the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, absence of BRCA protein, or reduced function of BRCA protein.
43. The method of claim 42, wherein, the cancer is endometrial cancer, pancreatic cancer, breast cancer, ovarian cancer (ovary cancer), prostate cancer, lymphoma, rhabdoid tumor, multiple myloma, uterine cancer, gastric cancer, peripheral nervous system cancer, rhabdomyosarcoma, bone cancer, colorectal cancer, mesothelioma, lung cancer, fibroblast cancer, central nervous system cancer, urinary tract cancer, upper aerodigestive cancer, leukemia, kidney cancer, skin cancer, esophageal cancer.
44. Use of a combination of anyone of claim 1-39 in the treatment of a cancer in a subject, wherein the cancer is characterized by increased dependence upon MMEJ DSB repair; the cancer is characterized by HR-deficiency, a reduction or absence of expression of HR-associated genes; the cancer is lack of 53BP1/Shieldin complex in a patient; the cancer is characterized by NHEJ deficiency, a reduction or absence of expression of NHEJ-associated genes; or the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, absence of BRCA protein, or reduced function of BRCA protein.
45. The method of claim 44, wherein, the cancer is endometrial cancer, pancreatic cancer, breast cancer, ovarian cancer (ovary cancer), prostate cancer, lymphoma, rhabdoid tumor, multiple myloma, uterine cancer, gastric cancer, peripheral nervous system cancer, rhabdomyosarcoma, bone cancer, colorectal cancer, mesothelioma, lung cancer, fibroblast cancer, central nervous system cancer, urinary tract cancer, upper aerodigestive cancer, leukemia, kidney cancer, skin cancer, esophageal cancer.
46. Use of a combination of anyone of claim 1-39 in the preparation of a medicament for the treatment of a cancer in a subject, wherein the cancer is characterized by increased dependence upon MMEJ DSB repair; the cancer is characterized by HR-deficiency, a reduction or absence of expression of HR-associated genes; the cancer is lack of 53BP1/Shieldin complex in a patient; the cancer is characterized by NHEJ deficiency, a reduction or absence of expression of NHEJ-associated genes; or the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, absence of BRCA protein, or reduced function of BRCA protein.
47. The method of claim 46, wherein, the cancer is endometrial cancer, pancreatic cancer, breast

cancer, ovarian cancer (ovary cancer), prostate cancer, lymphoma, rhabdoid tumor, multiple myloma, uterine cancer, gastric cancer, peripheral nervous system cancer, rhabdomyosarcoma, bone cancer, colorectal cancer, mesothelioma, lung cancer, fibroblast cancer, central nervous system cancer, urinary tract cancer, upper aerodigestive cancer, leukemia, kidney cancer, skin cancer, esophageal cancer.

48. Use of a combination of anyone of claim 1-39 in the manufacture of a medicament for treating a disease characterized by overexpression of PolQ in a patient.

49. A kit comprising a combination of anyone of claim 1-39, in which optionally both or either of the PolQ inhibitor and the second anti-cancer therapeutic agent in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.