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(71) Applicant: **IDEAYA BIOSCIENCES, INC.** [US/US]; 7000 Shoreline Court, Suite 350, South San Francisco, CA 94080 (US).

(72) Inventors: **BECK, Hilary, Plake**; 7000 Shoreline Court, Suite 350, South San Francisco, CA 94080 (US). **JONES, Brian, Thomas**; 7000 Shoreline Court, Suite 350, South San Francisco, CA 94080 (US). **MARTINEZ, Luisruben, P.**; 7000 Shoreline Court, Suite 350, South San Francisco, CA 94080 (US).

(74) Agent: **YIN, Hao** et al.; GlaxoSmithKline, Global Patents, UP4110, 1250 South Collegeville Road, Collegeville, PA 19426 (US).

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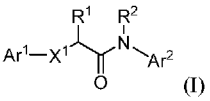
(54) Title: ACETAMIDO-AMINO AND ACETAMIDO-SULFUR DERIVATIVES AS DNA POLYMERASE THETA INHIBITORS



(I)

(57) Abstract: Disclosed herein are certain acetamido derivatives that are DNA Polymerase Theta (Polθ) inhibitors of Formula (I). Also, disclosed are pharmaceutical compositions comprising such compounds and methods of treating diseases treatable by inhibition of Polθ such as cancer, including homologous recombination (HR) deficient cancers.

ACETAMIDO-AMINO AND ACETAMIDO-SULFUR DERIVATIVES AS DNA POLYMERASE THETA INHIBITORS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. 119(e) of U.S. Provisional Application No. 63/058,344, filed on July 29, 2020, which is hereby incorporated herein by reference in its entirety for all purposes.

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0002] This application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on July 23, 2021, is named LU67028 WO PCT 052326-534P01US_SL_ST25.txt and is 1,388 bytes in size.

BACKGROUND

[0003] Targeting DNA repair deficiencies has become a proven and effective strategy in cancer treatment. However, DNA repair deficient cancers often become dependent on backup DNA repair pathways, which present an "Achilles heel" that can be targeted to eliminate cancer cells, and is the basis of synthetic lethality. Synthetic lethality is exemplified by the success of poly (ADP-ribose) polymerase (PARP) inhibitors in treating BRCA-deficient breast and ovarian cancers (Audeh M. W., et al., Lancet (2010); 376 (9737): 245-51).

[0004] DNA damage repair processes are critical for genome maintenance and stability, among which, double strand breaks (DSBs) are predominantly repaired by the nonhomologous end joining (NHEJ) pathway in G1 phase of the cell cycle and by homologous recombination (HR) in S-G2 phases. A less addressed alternative end-joining (alt-EJ), also known as microhomology-mediated end-joining (MMEJ) pathway, is commonly considered as a "backup" DSB repair pathway when NHEJ or HR are compromised. Numerous genetic studies have highlighted a role for polymerase theta (Polθ, encoded by *POLQ*) in stimulating MMEJ in higher organisms (*see* Chan S. H., et al., PLoS Genet. (2010); 6: e1001005; Roerink S. F., et al., Genome research. (2014); 24: 954–962;

Ceccaldi R., et. al., Nature (2015); 518: 258-62; and Mateos-Gomez P. A., et al., Nature (2015); 518: 254-57).

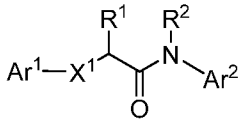
[0005] The identification of mammalian *POLQ* initially arose from interest in the *POLQ* ortholog *Mus308* gene product of *Drosophila melanogaster*. *Mus308* mutants are hypersensitive to agents that cause DNA inter-strand cross-links (ICL) (Aguirrezabalaga I., et al., Genetics. (1995); 139:649–658), which implied that Mus308 may play a specific role in repair of ICLs in DNA. Characterization of the *POLQ* gene showed that it encodes an unusual domain configuration, with a large central portion flanking by a N-terminal DNA helicase domain and a C-terminal DNA polymerase domain (see Harris P. V., et al., Mol Cell Biol. (1996); 16: 5764–5771). The mechanisms by which Polθ polymerase functions in alt-EJ were also found to efficiently promote end-joining when overhangs contained >2 bp of microhomology were present (*see* Kent T., et al., Elife (2016); 5: e13740), and Kent T., et al., Nat. Struct. Mol. Biol. (2015); 22: 230–237. On the other hand, the helicase domain of Polθ contributes to microhomology annealing (*see* Chan S H et al., PLoS Genet. (2010); 6: e1001005; and Kawamura K et al., Int. J. Cancer (2004); 109: 9-16).

[0006] The expression of Polθ is largely absent in normal cells but upregulated in breast, lung, and ovarian cancers (*see* Ceccaldi R., et al., Nature (2015); 518, 258-62). Additionally, the increase of Polθ expression correlates with poor prognosis in breast cancer (*see* Lemee F et al., Proc Natl Acad Sci USA. (2010) ;107: 13390-5). It has been shown that cancer cells with deficiency in HR, NHEJ or ATM are highly dependent on Polθ expression (*see* 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). Therefore, Polθ is an attractive target for novel synthetic lethal therapy in cancers containing DNA repair defects.

SUMMARY

[0007] Disclosed herein are certain acetamido derivatives that are DNA Polymerase Theta (Polθ) inhibitors, in particular compounds that inhibit polynerase domain of Polθ. Also, disclosed are pharmaceutical compositions comprising such compounds and methods of treating and/or preventing diseases treatable by inhibition of Polθ such as cancer, including homologous recombination (HR) deficient cancers.

[0008] In a first aspect, provided is a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

X^1 is selected from the group consisting of $–NR^3–$ and –S–;

Ar^1 is selected from the group consisting of phenyl and six- to ten-membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein phenyl and heteroaryl are substituted with 0 to 4 moieties selected from R^a R^b, R^c, and R^j, wherein

R^a, R^b, R^c, and R^j are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, cyanomethyl, and aminocarbonylmethyl; or R^c and R^j, when on adjacent ring vertices, combine to form a 3-6 membered cycloalkyl ring;

R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{1-6} aminocarbonylalkyl, and C_{1-6} phenalkyl, wherein phenyl in C_{1-6} phenalkyl is substituted with R^d, R^e, and R^f, wherein

R^d, R^e, and R^f are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, and cyano;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} deuteroalkyl, C_{3-6} cycloalkyl, and C_{1-6} haloalkyl;

Ar^2 is selected from the group consisting of phenyl and six- to ten-membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein said phenyl and heteroaryl are substituted with 0 to 3 moieties selected from R^g, R^h, and R^i, wherein

R^g, R^h, and R^i are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, and $-CONH_2$; or

R^2 and Ar^2 combine with the nitrogen to which they are attached to form a 4- to 6- membered heterocycloalkyl having 0 to 2 additional heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein the said heterocycloalkyl is substituted with R^k, R^l, and R^m, wherein

R^k, R^l, and R^m are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, and -

$CONH_2$; or R^1 and R^m, when on adjacent ring vertices, combine to form a phenyl ring;

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{1-6} aminocarbonylalkyl, and C_{3-6} cycloalkyl.

[0009] In a second aspect, provided is a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient.

[0010] In a third aspect, provided are methods for treating and/or preventing a disease characterized by overexpression of Polθ in a patient comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof; or a phamaceutical composition comprising a compound of Formula (I) (or a subembodiment described herein) and at least one pharmaceutically acceptable excipient.

[0011] In a fourth aspect, provided are methods of treating and/or preventing a homologous recombinant (HR) deficient cancer in a patient comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof.

[0012] In a fifth aspect, provided are methods for inhibiting DNA repair by Polθ in a cancer cell comprising contacting the cell with an effective amount of a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof. In a first embodiment, the cancer is HR deficient cancer.

[0013] In a sixth aspect, provided are methods for treating and/or preventing a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, or reduced function of BRCA protein, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof optionally in a pharmaceutical composition.

[0014] In a seventh aspect, provided are compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof for inhibiting DNA repair by Polθ in a cell. In a first embodiment, the cell is HR deficient cell.

[0015] In an eighth aspect, provided are compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of a disease in a patient, wherein the disease is characterized by overexpression of Polθ.

[0016] In a ninth aspect, provided are compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, or reduced function of BRCA protein.

[0017] In a tenth aspect, provided are compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of a HR deficient cancer in a patient.

[0018] In an eleventh aspect, provided are compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of a cancer that is resistant to poly(ADP-ribose)polymerase (PARP) inhibitor therapy in a patient.

[0019] In a twelfth aspect, provided herein are methods of identifying Polθ polymerase domain inhibitory activity in a test compound, said method comprising

(i) contacting the test compound and Polθ polymerase domain (residues 1819-2590) in an assay buffer to form a reaction pre-mixture;

(ii) contacting the reaction pre-mixture of (i) with (a) a dNTP substrate mixture, and (b) a primed molecular beacon DNA to form a test solution,
wherein the primed molecular beacon DNA comprises a labeled template annealed to a primer, wherein the labeled template is SEQ ID NO: 1 (5′-CCTTCCTCCCGTGTCTTGTACCTTCCCGTCAGGAGGAAGG-3’) having one or more fluorescent labels, and the primer is SEQ ID NO: 3 (5′-GACGGGAAGG-3’); and

(iii) measuring fluorescence intensity of the test reaction mixture, wherein said method further comprises performing steps (i)-(iii) with a positive control sample represented by Formula (I) (or any embodiments thereof).

[0020] Other aspects, features, and advantages of the present disclosure will be apparent to a person of skill in the art upon review of the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] NOT APPLICABLE

DETAILED DESCRIPTION

[0022] 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.

[0023] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0024] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Further, the dates of publication provided may be different from the actual publication dates, which may need to be independently confirmed.

Definitions:

[0025] Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning:

[0026] The singular forms “a,” “an,” and “the” as used herein and in the appended claims 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.

[0027] "Alkyl" means a linear saturated monovalent hydrocarbon radical of one to eight carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl, pentyl, and the like. It will be recognized by a person skilled in the art that the term "alkyl" may include "alkylene" groups.

[0028] "Alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms unless otherwise stated e.g., methylene, ethylene, propylene, 1-methylpropylene, 2-methylpropylene, butylene, pentylene, and the like.

[0029] "Alkoxy" means a -OR radical where R is alkyl as defined above, e.g., methoxy, ethoxy, propoxy, or 2-propoxy, *n*-, *iso*-, or *tert*-butoxy, and the like.

[0030] "Aminoalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with –NR'R" where R' and R" are independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, or alkylcarbonyl, each as defined herein, e.g., aminomethyl, aminoethyl, methylaminomethyl, and the like.

[0031] "Aminocarbonylalkyl" means a –(alkylene)-$CONH_2$ radical wherein alkylene as defined herein, e.g., aminocarbonylmethyl, aminocarbonylethyl, aminocarbonylethyl, and the like. When the group is –CH_2CONH_2, it may be referred to herein as aminocarbonylmethyl.

[0032] "Aryl" means a monovalent monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 10 ring atoms e.g., phenyl or naphthyl.

[0033] "Phenalkyl" means a –(alkylene)-R radical where R is phenyl e.g., benzyl, phenethyl, and the like.

[0034] "Cycloalkyl" means a monocyclic monovalent hydrocarbon radical of three to six carbon atoms which may be saturated or contain one double bond. Cycloalkyl may be unsubstituted or substituted with one or two substituents independently selected from alkyl, halo, alkoxy, hydroxy, or cyano. Examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyanocycloprop-1-yl, 1-cyanomethylcycloprop-1-yl,

3-fluorocyclohexyl, and the like. When cycloalkyl contains a double bond, it may be referred to herein as cycloalkenyl.

[0035] "Cycloalkyloxy" means -O-R radical where R is cycloalkyl as defined above. Examples include, but are not limited to, cyclopropyloxy, cyclobutyloxy, and the like.

[0036] "Deuteroalkyl" means an alkyl radical as defined above wherein one to six hydrogen atoms in the alkyl radical are replaced by deuterium, e.g., $-CD_3$, $-CH_2CD_3$, and the like.

[0037] "Halo" means fluoro, chloro, bromo, or iodo, preferably fluoro or chloro.

[0038] "Haloalkyl" means alkyl radical as defined above, which is substituted with one to five halogen atoms, such as fluorine or chlorine, including those substituted with different halogens, e.g., $-CH_2Cl$, $-CF_3$, $-CHF_2$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF(CH_3)_2$, and the like. When the alkyl is substituted with only fluoro, it can be referred to in this Application as fluoroalkyl.

[0039] "Haloalkoxy" means a –OR radical where R is haloalkyl as defined above e.g., $-OCF_3$, $-OCHF_2$, and the like. When R is haloalkyl where the alkyl is substituted with only fluoro, it is referred to in this Application as fluoroalkoxy.

[0040] "Heterocycloalkyl" means a monocylic or bicyclic ring system having from 3 ring members to 10 ring members and from 1 to about 5 heteroatom ring vertices selected fom N, O and S. The heteroatoms can also be oxidized, such as, but not limited to, -S(O)- and $-S(O)_2-$. Heterocycloalkyl moieties can be saturated or include one double bond. For example, heterocycloalkyl groups include, but are not limited to, tetrahydrofuranyl, tetrahydrothiophenyl, morpholino, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, and piperidinyl.

[0041] "Hydroxyalkyl" means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbons substituted with one or two hydroxy groups, provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxy-ethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, and 1-(hydroxymethyl)-2-hydroxyethyl.

[0042] "Heteroaryl" means a monovalent monocyclic or bicyclic aromatic radical of 5 to 10 ring atoms, unless otherwise stated, where one or more, (in one embodiment, one, two, or three), ring atoms are heteroatom selected from N, O, or S, the remaining ring atoms being carbon, unless stated otherwise. Non-limiting examples of heteroaryl groups include pyridyl, pyridazinyl, pyrazinyl, pyrimindinyl, triazinyl, quinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, benzotriazinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiaxolyl, benzofuranyl, benzothienyl, indolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl, thienyl, and the like. As defined herein, the terms "heteroaryl" and "aryl" are mutually exclusive. When the heteroaryl ring contains 5- or 6 ring atoms it is also referred to herein as 5-or 6-membered heteroaryl.

[0043] "Heterocyclyl" means a saturated or unsaturated monovalent monocyclic group of 4 to 8 ring atoms in which one or two ring atoms are heteroatom selected from N, O, or $S(O)_n$, where n is an integer from 0 to 2, the remaining ring atoms being C. Additionally, one or two ring carbon atoms in the heterocyclyl ring can optionally be replaced by a –CO- group. More specifically the term heterocyclyl includes, but is not limited to, azetidinyl, oxetanyl, pyrrolidino, piperidino, homopiperidino, 2-oxopyrrolidinyl, 2-oxopiperidinyl, morpholino, piperazino, tetrahydro-pyranyl, thiomorpholino, and the like. When the heterocyclyl ring is unsaturated it can contain one or two ring double bonds provided that the ring is not aromatic.

[0044] "Oxo," as used herein, alone or in combination, refers to =(O).

[0045] When needed, any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkoxyalkyl means that an alkoxy group is attached to the parent molecule through an alkyl group.

[0046] "Pharmaceutically acceptable salts" as used herein is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds disclosed herein contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired

base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occuring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogen carbonic, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, sulfuric, monohydrogen sulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0047] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0048] The present disclosure also includes protected derivatives of compounds of the present disclosure. For example, when compounds of the present disclosure contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can

be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, 5th Ed., John Wiley & Sons, Inc. (2014) , the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of the present disclosure can be prepared by methods well known in the art.

[0049] The present disclosure also includes prodrugs of the compound of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) or a pharmaceutically acceptable salt thereof. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0050] Certain compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of Formula (I) may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

[0051] Certain compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention. When a stereochemical depiction is shown, it is meant to refer the compound in which one of the isomers is present and substantially free of the other isomer. 'Substantially free of' another isomer indicates at least an 80/20 ratio of the two isomers, more preferably 90/10, or 95/5 or more. In some embodiments, one of the isomers will be present in an amount of at least 99%.

[0052] The compounds of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) may also contain unnatural amounts of isotopes at one or more of the atoms that constitute such compounds. Unnatural amounts of an isotope may be defined as ranging from the amount found in nature to an amount 100% of the atom in question. Exemplary isotopes that can be incorporated into compounds of the present invention, such as a compound of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and $^{125}1$, respectively. Isotopically labeled compounds (e.g., those labeled with ^{3}H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes can be useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, in compounds disclosed herein, including in Table 1 below one or more hydrogen atoms are replaced by ^{2}H or ^{3}H, or one or more carbon atoms are replaced by ^{13}C- or ^{14}C-enriched carbon. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{15}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed in the Schemes or in the Examples herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0053] "Pharmaceutically acceptable carrier or excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier/excipient" as used in the specification and claims includes both one and more than one such excipient.

[0054] "About," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass ± 10%, preferably ± 5%, the recited value and the range is included.

[0055] "Disease" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disorder," "syndrome," and "condition" (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

[0056] "Patient" is generally synonymous with the term "subject" and as used herein includes all mammals including humans. Examples of patients include humans, livestock such as cows, goats, sheep, pigs, and rabbits, and companion animals such as dogs, cats, rabbits, and horses. Preferably, the patient is a human.

[0057] "In need of treatment" as used herein means the patient is being treated by a physician or other caregiver after diagnoses of the disease. For example, the patient has been diagonosed as having a disease linked to overexpression of Polθ or a homologous recombination (HR)-deficient cancer.

[0058] "Administration", "administer" and the like, as they apply to, for example, a patient, cell, tissue, organ, or biological fluid, refer to contact of, for example, a compound of Formula (I), a pharmaceutical composition comprising same, or a diagnostic agent to the subject, cell, tissue, organ, or biological fluid. In the context of a cell, administration includes contact (e.g., in vitro or ex vivo) of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell.

[0059] "Therapeutically effective amount" as used herein means the amount of a compound of Formula (I) (and any embodiment thereof disclosed herein including specific compounds) or a pharmaceutically acceptable salt thereof that, when administered to a patient for treating a disease either alone or as part of a pharmaceutical composition and either in a single dose or as part of a series of doses, is sufficient to affect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated. The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject's condition, and the like. By way of example, measurement of the serum level of a compound of Formula (I) (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been used.

[0060] "Treating" or "treatment" of a disease includes:

(1) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or

(2) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

[0061] "Inhibiting", "reducing," or any variation of these terms in relation of Polθ, includes any measurable decrease or complete inhibition to achieve a desired result. For example, there may be a decrease of about, at most about, or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more, or any range derivable therein, reduction of Polθ activity compared to its normal activity.

[0062] The term "preventing" refers to causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease.

[0063] The term "homologous recombination" refers to the cellular process of genetic recombination in which nucleotide sequences are exchanged between two similar or identical DNA.

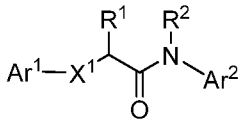
[0064] The term "homologous recombination (HR) deficient cancer" refers to a cancer that is characterized by a reduction or absence of a functional HR repair pathway. HR deficiency may arise from absence of one or more HR-assocated genes or presence of one or more mutations in one or more HR-assocated genes. Examples of HR-assocated genes include BRCA1 BRCA2, RAD54, RAD51B, Ct1P (Choline Transporter-Like Protein), PALB2 (Partner and Localizer of BRCA2), XRCC2 (X-ray repair complementing defective repair in Chinese hamster cells 2), RECQL4 (RecQ Protein-like 4), BLM (Bloom syndrome, RecQ helicase-like), WRN (Werner syndrome, one or more HR-associated genes), Nbs 1 (Nibrin), and genes coding Fanconi anemia (FA) proteins or FA like genes e.g., FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANJ (BRIP1), FANCL, FANCM, FANCN (RALB2), FANCP (SLX4), FANCS (BRCA1), RAD51C and XPF.

[0065] The term "Polθ overexpression" refers to the increased expression or activity of Polθ enzyme in a diseased cell e.g., cancer cell, relative to expression or activity of Polθ enzyme in a control cell *(e.g.,* non-diseased cell of the same type). The amount of The

amount of Polθ overexpression can be at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, Polθ 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 Polθ expression in a control cell. Examples of Polθ overexpressing cancers include, but are not limited to, certain ovarian, breast, cervical, lung, colorectal, gastric, bladder, and prostate cancers.

Compounds of Formula (I)

[0066] In some aspects provided herein is a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

X^1 is selected from the group consisting of $-NR^3-$ and $-S-$;

Ar^1 is selected from the group consisting of phenyl and six- to ten-membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein phenyl and heteroaryl are substituted with 0 to 4 moieties selected from R^a R^b, R^c, and R^j, wherein

R^a, R^b, R^c, and R^j are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, cyanomethyl, and aminocarbonylmethyl; or R^c and R^j, when on adjacent ring vertices, combine to form a 3-6 membered cycloalkyl ring;

R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{1-6} aminocarbonylalkyl, and C_{1-6} phenalkyl, wherein phenyl in C_{1-6} phenalkyl is substituted with R^d, R^e, and R^f, wherein

R^d, R^e, and R^f are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, and cyano;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} deuteroalkyl, C_{3-6} cycloalkyl, and C_{1-6} haloalkyl;

Ar^2 is selected from the group consisting of phenyl and six- to ten-membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein said phenyl and heteroaryl are substituted with 0 to 3 moieties selected from R^g, R^h, and R^i, wherein

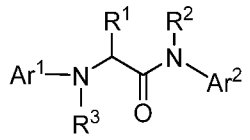
R^g, R^h, and R^i are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, and $-CONH_2$; or

R^2 and Ar^2 combine with the nitrogen to which they are attached to form a 4- to 6- membered heterocycloalkyl having 0 to 2 additional heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein the said heterocycloalkyl is substituted with R^k, R^l, and R^m, wherein

R^k, R^l, and R^m are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, and $-CONH_2$; or R^l and R^m, when on adjacent ring vertices, combine to form a phenyl ring;

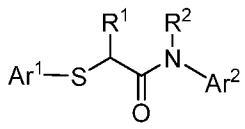
R^3 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{1-6} aminocarbonylalkyl, and C_{3-6} cycloalkyl.

[0067] In some embodiments of Formula (I) and relevant subembodmients thereof, X^1 is $-NR^3-$. Such compouds are sometimes referred to as Formula (Ia)



(Ia)

[0068] In some embodiments of Formula (I) and relevant subembodmients thereof, X^1 is $-S-$. Such compouds are sometimes referred to as Formula (Ib)



(Ib).

[0069] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^1 is a six-membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S substituted with R^a, R^b, R^c, and R^j. In some embodiments, at least one of R^a, R^b, R^c, and R^j is other than H.

[0070] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^1 is pyridinyl substituted with R^a, R^b, R^c, and R^j. In some embodiments, at least one of R^a, R^b, R^c, and R^j is other than H.

[0071] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^1 is pyridinyl substituted with R^a, where R^a is methyl, difluoromethyl or trifluoromethyl, and further substituted with R^b, R^c, and R^j. In some embodiments, at least one of R^a, R^b, R^c, and R^j is other than H.

[0072] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^1 is pyridinyl substituted with R^a, where R^a is methyl, difluoromethyl or trifluoromethyl, and further substituted with R^b, R^c, and R^j, where R^b and R^j are each independently C_{1-6} haloalkyl, C_{1-6} alkoxy, halo, C_{1-6} haloalkoxy, hydroxy, or cyano, and R^c is hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, cyanomethyl, and aminocarbonylmethyl.

[0073] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^1 is pyridinyl substituted with R^a R^b, R^c, and R^j, wherein R^a and R^b are each independently cyano, methyl, difluoromethyl, or trifluoromethyl.

[0074] In some embodiments of Formula (I) and relevant subembodmients thereof, R^c and R^j combine to form a 3-6 membered cycloalkyl ring.

[0075] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^1 is phenyl substituted with R^a R^b, R^c, and R^j. In some embodiments, at least one of R^a, R^b, R^c, and R^j is other than H.

[0076] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^1 is phenyl substituted with R^a, where R^a is methyl, difluoromethyl or trifluoromethyl, and further substituted with R^b, R^c, and R^j.

[0077] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^1 is phenyl substituted with R^a R^b, R^c, and R^j, where R^a is methyl, difluoromethyl or trifluoromethyl, R^b and R^j are each independently C_{1-6} haloalkyl, C_{1-6} alkoxy, halo, C_{1-6} haloalkoxy, hydroxy, or cyano, and R^c is hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, cyanomethyl, and aminocarbonylmethyl.

[0078] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^1 is phenyl substituted with R^a R^b, R^c, and R^j, wherein R^a and R^b are each independently cyano, methyl, difluoromethyl, or trifluoromethyl.

[0079] In some embodiments of Formula (I) and relevant subembodmients thereof, R^c and R^j combine to form a 3-6 membered cycloalkyl ring.

[0080] In some embodiments of Formula (I) and relevant subembodmients thereof, R^1 is C_{1-6} hydroxyalkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} aminoalkyl, or C_{1-6} aminocarbonylalkyl.

[0081] In some embodiments of Formula (I) and relevant subembodmients thereof, R^1 is hydrogen, methyl, hydroxymethyl, 2-hydroxyethyl, 4-hydroxybenzyl, or aminocarbonylethyl.

[0082] In some embodiments of Formula (I) and relevant subembodmients thereof, R^2 is alkyl, cycloalkyl, or haloalkyl.

[0083] In some embodiments of Formula (I) and relevant subembodmients thereof, R^1 is hydrogen and R^2 is methyl, ethyl, isopropyl, cyclopropyl, or 2,2,2-trifluoroethyl.

[0084] In some embodiments of Formula (I) and relevant subembodmients thereof, R^1 is hydrogen and R^2 is methyl.

[0085] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^2 is phenyl, wherein said phenyl is substituted with R^g, R^h, and R^i independently selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, cycloalkyloxy, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, and -$CONH_2$. In some embodiments, at least one of R^g, R^h, and R^i is other than H.

[0086] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^2 is phenyl substituted with R^g, R^h, and R^i, wherein R^g, R^h, and R^i are independently selected from the group consisting of hydrogen, -$CONH_2$, fluoro, chloro, bromo, cyano, methoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, trifluoromethyl, or trifluoromethoxy. In some embodiments, at least one of R^g, R^h, and R^i is other than H.

[0087] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^2 is phenyl substituted with R^g, R^h, and R^i, wherein R^g, R^h, and R^i are independently selected from the group consisting of hydrogen, fluoro, chloro, and bromo. In some embodiments, at least one of R^g, R^h, and R^i is other than H.

[0088] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^2 is six- to ten-membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S wherein said heteroaryl is substituted with R^g, R^h, and R^i independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6}

cycloalkyl, C_{3-6} cycloalkyloxy, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, and -$CONH_2$. In some embodiments, at least one of R^g, R^h, and R^i is other than H.

[0089] In some embodiments of Formula (I) and relevant subembodmients thereof, Ar^2 is a six- membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S wherein said heteroaryl is substituted with R^g, R^h, and R^i independently selected from the group consisting of hydrogen, fluoro, chloro, and bromo. In some embodiments, at least one of R^g, R^h, and R^i is other than H.

[0090] In some embodiments of Formula (I) and relevant subembodmients thereof, R^2 and Ar^2 combine with the nitrogen to which they are attached to form a 4- to 6- membered heterocycloalkyl having 0 to 2 additional heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein the said heterocycloalkyl is substituted with R^k, R^l, and R^m.

[0091] In some embodiments of Formula (I) and relevant subembodmients thereof, R^2 and Ar^2 combine with the nitrogen to which they are attached to form a 4- to 6- membered heterocycloalkyl having 0 additional heteroatom ring vertices.

[0092] In some embodiments of Formula (I) and relevant subembodmients thereof, R^3 is C_{1-6} alkyl or C_{1-6} haloalkyl.

[0093] In some embodiments of Formula (I) and relevant subembodmients thereof, R^3 is C_{3-6} cycloalkyl.

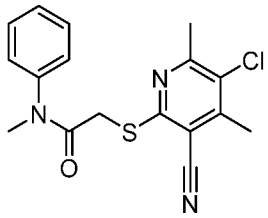
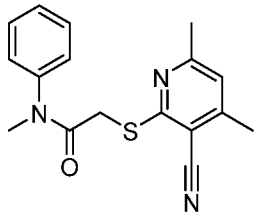
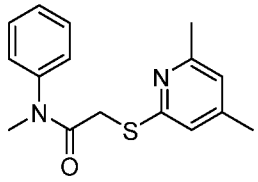
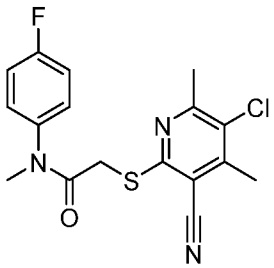
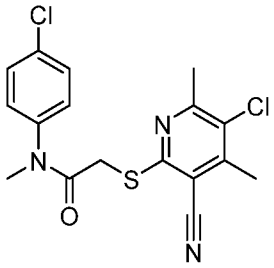
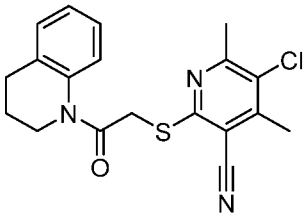
[0094] In some embodiments of Formula (I) and relevant subembodmients thereof, R^3 is methyl or ethyl.

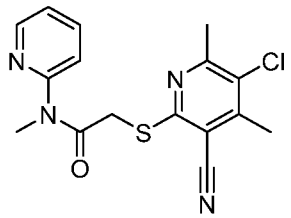
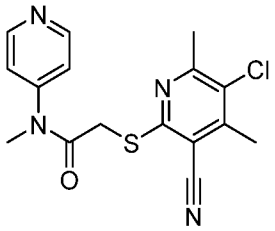
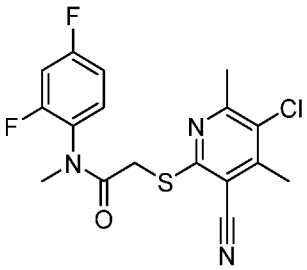
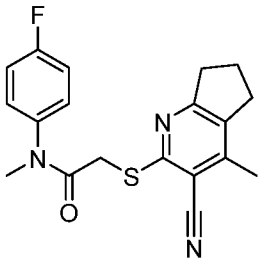
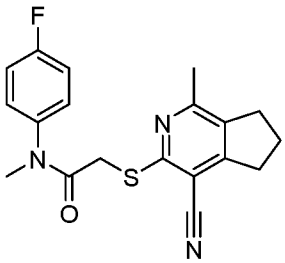
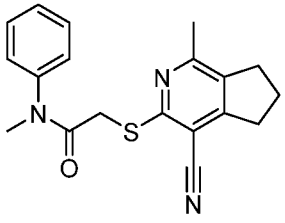
[0095] In some embodiments of Formula (I) and relevant subembodmients thereof, R^3 is selected from the group consisting of C_{1-6} hydroxyalkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} aminoalkyl, and C_{1-6} aminocarbonylalkyl.

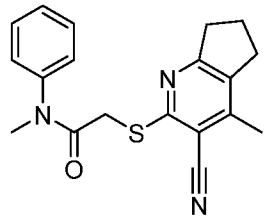
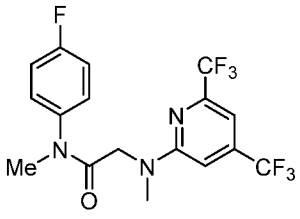
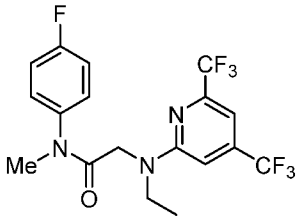
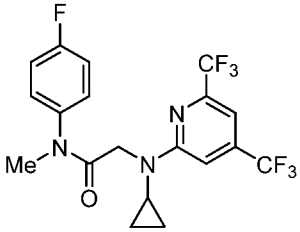
[0096] Representative compound of Formula (I) are listed in Table 1 below:

Table 1

Cpd. No.	Structure	Name

1.001		2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-phenylacetamide
1.002		2-((3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-phenylacetamide
1.003		2-((4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-phenylacetamide
1.004		2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-(4-fluorophenyl)-N-methylacetamide
1.005		2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-(4-chlorophenyl)-N-methylacetamide
1.006		5-chloro-2-((2-(3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)thio)-4,6-dimethylnicotinonitrile

1.007		2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-(pyridin-2-yl)acetamide
1.008		2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-(pyridin-4-yl)acetamide
1.009		2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-(2,4-difluorophenyl)-N-methylacetamide
1.010		2-((3-cyano-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)thio)-N-(4-fluorophenyl)-N-methylacetamide
1.011		2-((4-cyano-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)thio)-N-(4-fluorophenyl)-N-methylacetamide
1.012		2-((4-cyano-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)thio)-N-methyl-N-phenylacetamide

1.013		2-((3-cyano-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)thio)-N-methyl-N-phenylacetamide
1.014		2-((4,6-bis(trifluoromethyl)pyridin-2-yl)(methyl)amino)-N-(4-fluorophenyl)-N-methylacetamide
1.015		2-((4,6-bis(trifluoromethyl)pyridin-2-yl)(ethyl)amino)-N-(4-fluorophenyl)-N-methylacetamide
1.016		2-((4,6-bis(trifluoromethyl)pyridin-2-yl)(cyclopropyl)amino)-N-(4-fluorophenyl)-N-methylacetamide

General Synthetic Schemes

[0097] Compounds of this disclosure can be made by the methods depicted in the reaction schemes shown below.

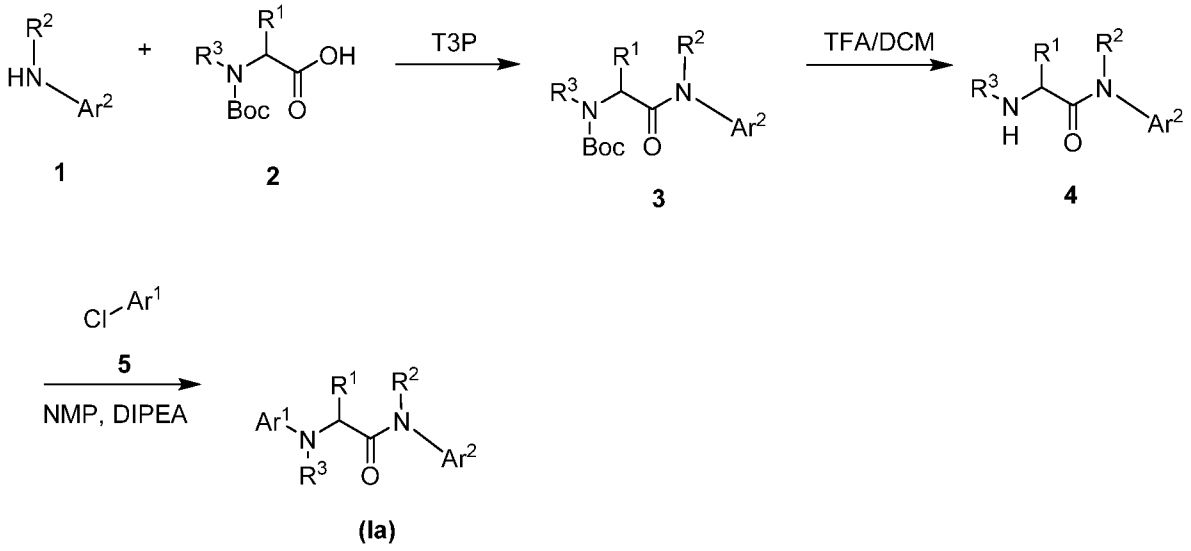
[0098] The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's

Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this disclosure can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art reading this disclosure. The starting materials and the intermediates, and the final products of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[0099] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about –78 °C to about 150 °C, such as from about 0 °C to about 125 °C and further such as at about room (or ambient) temperature, e.g., about 20 °C.

[0100] Compounds of Formula (I) where X^1 is NR^3 and other groups are as defined in the Summary can be prepared by the methods illustrated and described in Scheme 1 below.

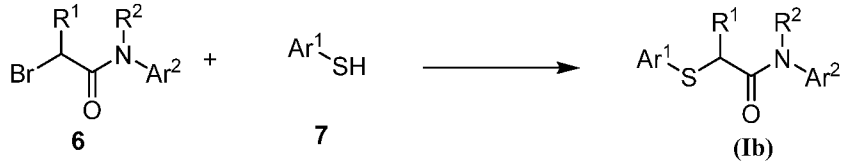
Scheme 1



[0101] With reference to the scheme above, reaction of a Formula **1** where Ar^2 and R^2 are as defined in the Summary with Formula **2** where R^1 and R^3 are as defined in the Summary in the presence of T3P (2,4,6-Tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide) or a similar coupling reagent forms Formula **3**. Compounds of Formula **1** and Formula **2** are commercially available or can be prepared by methods well known in the art. Deprotection

of Formula **3** in conditions such as TFA/DCM provides Formula **4**. Reacting Formula **4** with Formula **5** where Ar^1 is as defined in the summary in the presence of NMP and a suitable base such as DIPEA provides Formula (Ia).

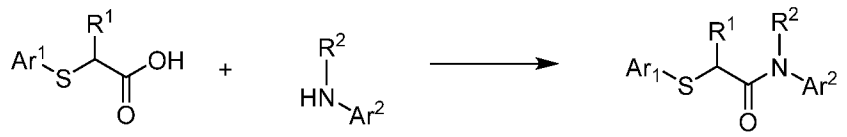
Scheme 2



6 **7** **(Ib)**

[0102] With reference to the scheme above, reaction of a Formula **6** where Ar^2, R^1 and R^2 are as defined in the Summary with Formula **7** where Ar^1 is as defined in the Summary in the presence of a base such as triethylamine, diisopropylamine, pyridine, N-methylpyridine, and the like, forms Formula **(Ib)**. Compounds of Formula **6** and Formula **7** are commercially available or can be prepared by methods well known in the art.

Scheme 3



8 **9** **(Ib)**

[0103] With reference to the scheme above, reaction of a Formula **8** where Ar^1 and R^1 are as defined in the Summary with Formula **9** where R^2 and Ar^2 are as defined in the Summary in the presence of T3P (2,4,6-Tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide) or a similar coupling reagent forms Formula **(Ib)**. Compounds of Formula **8** and Formula **9** are commercially available or can be prepared by methods well known in the art.

Utility

[0104] In a third aspect, provided are methods for treating and/or preventing a disease characterized by overexpression of Polθ in a patient comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof; or a phamaceutical composition comprising a compound of Formula (I) and at least one pharmaceutically acceptable excipient.

[0105] In first embodiment of the third aspect, the patient is in recognized need of such treatment. In second embodiment of the third aspect and first embodiment contained therein,

the compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof is administered in a pharmaceutical composition. In third embodiment of the third aspect and first and second embodiments contained therein, the disease is a cancer.

[0106] In a fourth aspect, provided are methods of treating and/or preventing a homologous recombinant (HR) deficient cancer in a patient comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof. In first embodiment of the fourth aspect, the patient is in recognized need of such treatment. In second embodiment of the fourth aspect and first embodiment contained therein, the compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof is administered in a pharmaceutical composition.

[0107] In a fifth aspect, provided are methods for inhibiting DNA repair by Polθ in a cancer cell comprising contacting the cell with an effective amount of a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof. In a first embodiment, the cancer is HR deficient cancer.

[0108] In a sixth aspect, provided are methods for treating and/or preventing a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, or reduced function of BRCA protein, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof optionally in a pharmaceutical composition.

[0109] In a seventh aspect, provided are compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof for inhibiting DNA repair by Polθ in a cell. In a first embodiment, the cell is HR deficient cell.

[0110] In an eighth aspect, provided are compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of a disease in a patient, wherein the disease is characterized by overexpression of Polθ.

[0111] In a ninth aspect, provided are compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof for use in the treatment and/or

prevention of a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, or reduced function of BRCA protein.

[0112] In a tenth aspect, provided are compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of a HR deficient cancer in a patient.

[0113] In an eleventh aspect, provided are compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof for use in the treatment or prevention of a cancer that is resistant to poly(ADP-ribose)polymerase (PARP) inhibitor therapy in a patient. Examples of cancers that are resistant to PARP-inhibitors include, but are not limited to, breast cancer, ovarian cancer, lung cancer, bladder cancer, liver cancer, head and neck cancer, pancreatic cancer, gastrointestinal cancer and colorectal cancer.

[0114] In any of the third to eleventh aspect, the cancer is lymphoma, soft tissue, rhabdoid, multiple myeloma, uterus, gastric, peripheral nervous system, rhabdomyosarcoma, bone, colorectal, mesothelioma, breast, ovarian, lung, fibroblast, central nervous system, urinary tract, upper aerodigestive, leukemia, kidney, skin, esophagus, or pancreas (data from large scale drop out screens in cancer cell lines indicate that some cell lines from the above cancers are dependent on polymerase theta for proliferation see https://depmap.org/portal/).

[0115] In first embodiment, a HR-deficient cancer is breast cancer. Breast cancer includes, but is not limited to, lobular carcinoma *in situ*, a ductal carcinoma *in situ*, an invasive ductal carcinoma, triple negative, HER positive, estrogen receptor positive, progesterone receptor positive, HER and estrogen receptor positive, HER and estrogen and progesterone receptor, positive inflammatory breast cancer, Paget disease of nipple, Phyllodes tumor, angiosarcoma, adenoid cystic carcinoma, low-grade adenosquamous carcinoma, medullary carcinoma, mucinous carcinoma, papillary carcinoma, tubular carcinoma, metaplastic carcinoma, micropapillary carcinoma, and mixed carcinoma. In second embodiment, HR-deficient cancer is ovarian cancer. Ovarian can includes, but is not limited to, epithelial ovarian carcinomas, maturing teratomas, dysgerminomas, endodermal sinus tumors, granulosa-theca tumors, Sertoli-Leydig cell tumors, and primary peritoneal carcinoma.

[0116] In some aspects, provided are use of the compounds of Formula (I), (II), a subembodiment described herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prevention of the methods and uses

described herein. This includes, for example, the treatment or prevention of a disease characterized by overexpression of Polθ; a homologous recombinant (HR) deficient cancer; a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, or reduced function of BRCA protein; a cancer that is resistant to poly(ADP-ribose)polymerase (PARP) inhibitor therapy in a patient.

Assays

[0117] The ability of compounds of the disclosure to inhibit Polθ can be measured as described in Biological Example 1 below.

[0118] In some aspects, provided herein are methods of identifying Polθ polymerase domain inhibitory activity in a test compound, said methods comprising

(i) contacting the test compound and Polθ polymerase domain (residues 1819-2590) in an assay buffer to form a reaction pre-mixture;

(ii) contacting the reaction pre-mixture of (i) with (a) a dNTP substrate mixture, and (b) a primed molecular beacon DNA to form a test solution,
wherein the primed molecular beacon DNA comprises a labeled template annealed to a primer, wherein the labeled template is SEQ ID NO: 1 (5′-CCTTCCTCCCGTGTCTTGTACCTTCCCGTCAGGAGGAAGG-3’) having one or more fluorescent labels, and the primer is SEQ ID NO: 3 (5′-GACGGGAAGG-3’); and

(iii) measuring fluorescence intensity of the test reaction mixture, wherein said method further comprises performing steps (i)-(iii) with a positive control sample represented by Formula (I) (or any embodiments thereof).

[0119] In some embodiments, the final concentration of Polθ polymerase domain in the test reaction mixture is 4 nM.

[0120] In some embodiments, the assay buffer is 20m M TRIS, pH 7.80, 50 mM KCl, 10 mM $MgCl_2$, 1mM DTT, 0.01% BSA, 0.01% Tween20.

[0121] In some embodiments, the dNTP substrate mixture is an equal mixture of each natural dNTP (dTTP, dATP, dCTP, and dGTP). In some embodiments the dNTP in the substrate mixture is 48 μM.

[0122] In some embodiments the labeled template is fluorescently labeled with one or more fluorescent labels. A number of fluorescent labels (and quenchers) are known in the art. In some embodiments the one or more fluorescent labels comprise 5′-TAMRA and 3′-BHQ. In some embodiments the sequence of the labeled template is SEQ ID NO 2: 5′-CCTTCCTCCCGTGTCTTGTACCTTCCCGTCAGGAGGAAGG-3' with 5′-TAMRA and 3′-BHQ.

[0123] In some embodiments the primed molecular beacon DNA further comprises a priming buffer. In some embodiments, the buffer is 10 mM Tris-HCl pH 8.0, 100 mM NaCl buffer, and the concentration of the primed molecular beacon DNA is 96 nM.

[0124] A person of skill in the art will recognize that the fluorescence measured will depent on the labels being used in the assay. In some embodiments, absorbance (λ_{ex} = 485 nm, λ_{em}=535 nm) of the Pol theta reaction mixture.

Pharmaceutical Composition

[0125] The compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof, provided herein may be in the form of compositions suitable for administration to a subject. In general, such compositions are pharmaceutical compositions comprising a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable or physiologically acceptable excipients. In certain embodiments, the compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof is present in a therapeutically effective amount. The pharmaceutical compositions may be used in the methods disclosed herein; thus, for example, the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice the therapeutic methods and uses described herein.

[0126] The pharmaceutical compositions can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein. Furthermore, the pharmaceutical compositions may be used in combination with other therapeutically active agents or compounds as described herein in order to treat the diseases, disorders and conditions contemplated by the present disclosure.

[0127] The pharmaceutical compositions containing the active ingredient (e.g., a compound of Formula (I), a subembodiment described herein, a pharmaceutically acceptable salt

thereof) may be in a form suitable for oral use, for example, as tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets, capsules and the like contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets, capsules, and the like. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

[0128] The tablets, capsules and the like suitable for oral administration may be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action. For example, a time-delay material such as glyceryl monostearate or glyceryl di-stearate may be employed. The tablets may also be coated by techniques known in the art to form osmotic therapeutic tablets for controlled release. Additional agents include biodegradable or biocompatible particles or a polymeric substance such as polyesters, polyamine acids, hydrogel, polyvinyl pyrrolidone, polyanhydrides, polyglycolic acid, ethylene-vinyl acetate, methylcellulose, carboxymethylcellulose, protamine sulfate, or lactide and glycolide copolymers, polylactide and glycolide copolymers, or ethylene vinyl acetate copolymers in order to control delivery of an administered composition. For example, the oral agent can be entrapped in microcapsules prepared by coacervation techniques or by interfacial polymerization, by the use of hydroxymethyl cellulose or gelatin-microcapsules or poly (methyl methacrylate) microcapsules, respectively, or in a colloid drug delivery system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, microbeads, and lipid-based systems, including oil-in-water emulsions, micelles, mixed micelles, and liposomes. Methods for the preparation of the above-mentioned formulations are known in the art.

[0129] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, kaolin or microcrystalline cellulose, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0130] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture thereof. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, (hydroxypropyl)methyl cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, for example a naturally-occurring phosphatide (e.g., lecithin), or condensation products of an alkylene oxide with fatty acids (e.g., poly-oxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols (e.g., for heptdecaethyleneoxycetanol), or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol (e.g., polyoxyethylene sorbitol monooleate), or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides (e.g., polyethylene sorbitan monooleate). The aqueous suspensions may also contain one or more preservatives.

[0131] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

[0132] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified herein.

[0133] The pharmaceutical compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example, gum acacia or gum tragacanth; naturally occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty

acids; hexitol anhydrides, for example, sorbitan monooleate; and condensation products of partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate.

[0134] The pharmaceutical compositions typically comprise a therapeutically effective amount of a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipient. Suitable pharmaceutically acceptable excipients include, but are not limited to, antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids, lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer, N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES), 2-(N-Morpholino)ethanesulfonic acid (MES), 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES), 3-(N-Morpholino)propanesulfonic acid (MOPS), and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

[0135] After a pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form, a lyophilized form requiring reconstitution prior to use, a liquid form requiring dilution prior to use, or other acceptable form. In some embodiments, the pharmaceutical composition is provided in a single-use container (e.g., a single-use vial, ampoule, syringe, or autoinjector (similar to, e.g., an EpiPen®)), whereas a multi-use container (e.g., a multi-use vial) is provided in other embodiments.

[0136] Formulations can also include carriers to protect the composition against rapid degradation or elimination from the body, such as a controlled release formulation, including liposomes, hydrogels, prodrugs and microencapsulated delivery systems. For example, a time delay material such as glyceryl monostearate or glyceryl stearate alone, or in combination with a wax, may be employed. Any drug delivery apparatus may be used to deliver a compound of Formula (I), a subembodiment described herein, or a salt thereof, including implants (e.g., implantable pumps) and catheter systems, slow injection pumps and devices, all of which are well known to the skilled artisan.

[0137] Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to release the compound of Formula (I), a subembodiment described herein, or a salt thereof disclosed herein over a defined period of time. Depot injections are usually either solid- or oil-based and generally comprise at least one of the formulation components set forth herein. One of ordinary skill in the art is familiar with possible formulations and uses of depot injections.

[0138] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. The suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Acceptable diluents, solvents and dispersion media that may be employed include water, Ringer's solution, isotonic sodium chloride solution, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS), ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. Moreover, fatty acids such as oleic acid, find use in the preparation of injectables. Prolonged absorption of particular injectable formulations can be achieved by including an agent that delays absorption (e.g., aluminum monostearate or gelatin).

[0139] A compound of Formula (I), a subembodiment described herein, or a salt thereof may also be administered in the form of suppositories for rectal administration or sprays for nasal or inhalation use. The suppositories can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal

temperature and will therefore melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter and polyethylene glycols.

Routes of Administration

[0140] Compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof and compositions containing the same may be administered in any appropriate manner. Suitable routes of administration include oral, parenteral (e.g., intramuscular, intravenous, subcutaneous (e.g., injection or implant), intraperitoneal, intracisternal, intraarticular, intraperitoneal, intracerebral (intraparenchymal) and intracerebroventricular), nasal, vaginal, sublingual, intraocular, rectal, topical (e.g., transdermal), buccal and inhalation. Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to administer the compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof over a defined period of time. Particular embodiments of the present invention contemplate oral administration.

Combination Therapy

[0141] The present invention contemplates the use of compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof in combination with one or more active therapeutic agents (e.g., chemotherapeutic agents) or other prophylactic or therapeutic modalities (e.g., radiation). In such combination therapy, the various active agents frequently have different, complementary mechanisms of action. Such combination therapy may be especially advantageous by allowing a dose reduction of one or more of the agents, thereby reducing or eliminating the adverse effects associated with one or more of the agents. Furthermore, such combination therapy may have a synergistic therapeutic or prophylactic effect on the underlying disease, disorder, or condition.

[0142] As used herein, "combination" is meant to include therapies that can be administered separately, for example, formulated separately for separate administration (e.g., as may be provided in a kit), and therapies that can be administered together in a single formulation (i.e., a "co-formulation").

[0143] In certain embodiments, the compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof are administered or applied sequentially, e.g., where one agent is administered prior to one or more other agents. In other

embodiments, the compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof are administered simultaneously, e.g., where two or more agents are administered at or about the same time; the two or more agents may be present in two or more separate formulations or combined into a single formulation (i.e., a co-formulation). Regardless of whether the two or more agents are administered sequentially or simultaneously, they are considered to be administered in combination for purposes of the present disclosure.

[0144] The compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof may be used in combination with at least one other (active) agent in any manner appropriate under the circumstances. In one embodiment, treatment with the at least one active agent and at least one compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof is maintained over a period of time. In another embodiment, treatment with the at least one active agent is reduced or discontinued (e.g., when the subject is stable), while treatment with the compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof is maintained at a constant dosing regimen. In a further embodiment, treatment with the at least one active agent is reduced or discontinued (e.g., when the subject is stable), while treatment with a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof is reduced (e.g., lower dose, less frequent dosing or shorter treatment regimen). In yet another embodiment, treatment with the at least one active agent is reduced or discontinued (e.g., when the subject is stable), and treatment with the compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof is increased (e.g., higher dose, more frequent dosing or longer treatment regimen). In yet another embodiment, treatment with the at least one active agent is maintained and treatment with the compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof is reduced or discontinued (e.g., lower dose, less frequent dosing or shorter treatment regimen). In yet another embodiment, treatment with the at least one active agent and treatment with the compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof are reduced or discontinued (e.g., lower dose, less frequent dosing or shorter treatment regimen).

[0145] The present disclosure provides methods for treating cancer with a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof and at least one additional therapeutic or diagnostic agent.

[0146] In some embodiments, the compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof is administered in combination with at least one additional therapeutic agent, selected from Temozolomide, Pemetrexed, Pegylated liposomal doxorubicin (Doxil), Eribulin (Halaven), Ixabepilone (Ixempra), Protein-bound paclitaxel (Abraxane), Oxaliplatin, Irinotecan, Venatoclax (bcl2 inhibitor), 5-azacytadine, Anti-CD20 therapeutics, such as Rituxan and obinutuzumab, Hormonal agents (anastrozole, exemestand, letrozole, zoladex, lupon eligard), CDK4/6 inhibitors, Palbociclib, Abemaciclib, CPI (Avelumab, Cemiplimab-rwlc, and Bevacizumab.

[0147] In certain embodiments, the present disclosure provides methods for treating cancer comprising administration of a compound of Formula (I), a subembodiment described herein, or a salt thereof described herein in combination with a signal transduction inhibitor (STI) to achieve additive or synergistic suppression of tumor growth. As used herein, the term "signal transduction inhibitor" refers to an agent that selectively inhibits one or more steps in a signaling pathway. Examples of signal transduction inhibitors (STIs) useful in methods described herein include, but are not limited to: (i) bcr/abl kinase inhibitors (e.g., GLEEVEC); (ii) epidermal growth factor (EGF) receptor inhibitors, including kinase inhibitors and antibodies; (iii) her-2/neu receptor inhibitors (e.g., HERCEPTIN); (iv) inhibitors of Akt family kinases or the Akt pathway (e.g., rapamycin); (v) cell cycle kinase inhibitors (e.g., flavopiridol); and (vi) phosphatidyl inositol kinase inhibitors. Agents involved in immunomodulation can also be used in combination with one or more compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof described herein for the suppression of tumor growth in cancer patients.

[0148] In certain embodiments, the present disclosure provides methods for treating cancer comprising administration of a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof described herein in combination with a chemotherapeutic agents. Examples of chemotherapeutic agents include, but are not limited to, alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamime; nitrogen mustards such as chiorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide

hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside (Ara-C); cyclophosphamide; thiotepa; taxoids, e.g., paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum and platinum coordination complexes such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT11; topoisomerase inhibitors; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine; PARP inhibitors such as olaparib, rucaparib, niraparib, talazoparib, veliparib, and pamiparib, DNA damage repair inhibitors such as inhibitors of ATM [such as AZ: (AZD1390) Astrazeneca's AZD0156, AZ31, AZ32; Kudos' KU-55933, KU-60019, and KU-59403; and Pfizer's CP-466722]; ATR [such as Astrazeneca's Ceralasertib (AZD6738); Repare's RP-3500; Vertex/EMD Serono's Berzosertib (VX-970/M6620); and EMD Serono's M4344; and DNA-PK (such as Astrazeneca's AZD7648; NU7441; NU7026; Kudos' KU-0060648; Vertex's VX-984; and EMD Serono's Nedisertib (M3814)] and Cyteir

Therapeutics RAD51 inhibitor CYT-0851and pharmaceutically acceptable salts, acids or derivatives of any of the above. In a particular embodiment, compounds of the present disclosure are coadministered with a cytostatic compound selected from the group consisting of cisplatin, doxorubicin, taxol, taxotere and mitomycin C. In a particular embodiment, the cytostatic compound is doxorubicin.

[0149] Chemotherapeutic agents also include anti-hormonal agents that act to regulate or inhibit hormonal action on tumors such as anti-estrogens, including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, onapristone, and toremifene; and antiandrogens such as flutamide, nilutamide, bicalutamide, enzalutamide, apalutamide, abiraterone acetate, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above. In certain embodiments, combination therapy comprises administration of a hormone or related hormonal agent.

[0150] The present disclosure also contemplates the use of the compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof described herein in combination with immune checkpoint inhibitors. The tremendous number of genetic and epigenetic alterations that are characteristic of all cancers provides a diverse set of antigens that the immune system can use to distinguish tumor cells from their normal counterparts. In the case of T cells, the ultimate amplitude (e.g., levels of cytokine production or proliferation) and quality (e.g., the type of immune response generated, such as the pattern of cytokine production) of the response, which is initiated through antigen recognition by the T-cell receptor (TCR), is regulated by a balance between co-stimulatory and inhibitory signals (immune checkpoints). Under normal physiological conditions, immune checkpoints are crucial for the prevention of autoimmunity (i.e., the maintenance of self-tolerance) and also for the protection of tissues from damage when the immune system is responding to pathogenic infection. The expression of immune checkpoint proteins can be dysregulated by tumors as an important immune resistance mechanism. Examples of immune checkpoint inhibitors include but are not limited to CTLA-4, PD-1, PD-L1, BTLA, TIM3, LAG3, OX40, 41BB, VISTA, CD96, TGFβ, CD73, CD39, A2AR, A2BR, IDO1, TDO2, Arginase, B7-H3, B7-H4. Cell-based modulators of anti-cancer immunity are also contemplated. Examples of such modulators include but are not limited to chimeric antigen receptor T-cells, tumor infiltrating T-cells and dendritic-cells.

[0151] The present disclosure contemplates the use of compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof described herein in combination with inhibitors of the aforementioned immune-checkpoint receptors and ligands, for example ipilimumab, abatacept, nivolumab, pembrolizumab, atezolizumab, nivolumab, and durvalumab.

[0152] Additional treatment modalities that may be used in combination with a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof disclosed herein include radiotherapy, a monoclonal antibody against a tumor antigen, a complex of a monoclonal antibody and toxin, a T-cell adjuvant, bone marrow transplant, or antigen presenting cells (e.g., dendritic cell therapy).

[0153] The present disclosure contemplates the use of compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof described herein for the treatment of glioblastoma either alone or in combination with radiation and/or temozolomide (TMZ), avastin or lomustine.

[0154] The present disclosure encompasses pharmaceutically acceptable salts, acids or derivatives of any of the above.

Dosing

[0155] The compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof provided herein may be administered to a subject in an amount that is dependent upon, for example, the goal of administration (e.g., the degree of resolution desired); the age, weight, sex, and health and physical condition of the subject to which the formulation is being administered; the route of administration; and the nature of the disease, disorder, condition or symptom thereof. The dosing regimen may also take into consideration the existence, nature, and extent of any adverse effects associated with the agent(s) being administered. Effective dosage amounts and dosage regimens can readily be determined from, for example, safety and dose-escalation trials, in vivo studies (e.g., animal models), and other methods known to the skilled artisan.

[0156] In general, dosing parameters dictate that the dosage amount be less than an amount that could be irreversibly toxic to the subject (the maximum tolerated dose (MTD)) and not less than an amount required to produce a measurable effect on the subject. Such amounts are determined by, for example, the pharmacokinetic and pharmacodynamic parameters

associated with ADME, taking into consideration the route of administration and other factors.

[0157] An effective dose (ED) is the dose or amount of an agent that produces a therapeutic response or desired effect in some fraction of the subjects taking it. The "median effective dose" or ED_{50} of an agent is the dose or amount of an agent that produces a therapeutic response or desired effect in 50% of the population to which it is administered. Although the ED_{50} is commonly used as a measure of reasonable expectance of an agent's effect, it is not necessarily the dose that a clinician might deem appropriate taking into consideration all relevant factors. Thus, in some situations the effective amount is more than the calculated ED_{50}, in other situations the effective amount is less than the calculated ED_{50}, and in still other situations the effective amount is the same as the calculated ED_{50}.

[0158] In addition, an effective dose of a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof, as provided herein, may be an amount that, when administered in one or more doses to a subject, produces a desired result relative to a healthy subject. For example, for a subject experiencing a particular disorder, an effective dose may be one that improves a diagnostic parameter, measure, marker and the like of that disorder by at least about 5%, at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or more than 90%, where 100% is defined as the diagnostic parameter, measure, marker and the like exhibited by a normal subject.

[0159] In certain embodiments, the compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof disclosed herein may be administered (e.g., orally) at dosage levels of about 0.01 mg/kg to about 50 mg/kg, or about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0160] For administration of an oral agent, the compositions can be provided in the form of tablets, capsules and the like containing from 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 3.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient.

[0161] In certain embodiments, the dosage of the compound of Formula (I), a subembodiment described herein, or a pharmaceutically salt thereof is contained in a "unit dosage form". The phrase "unit dosage form" refers to physically discrete units, each unit

containing a predetermined amount of the compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof, either alone or in combination with one or more additional agents, sufficient to produce the desired effect. It will be appreciated that the parameters of a unit dosage form will depend on the particular agent and the effect to be achieved.

Kits

[0162] The present invention also contemplates kits comprising a compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof, and pharmaceutical compositions thereof. The kits are generally in the form of a physical structure housing various components, as described below, and may be utilized, for example, in practicing the methods described above.

[0163] A kit can include one or more of the compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof disclosed herein (provided in, e.g., a sterile container), which may be in the form of a pharmaceutical composition suitable for administration to a subject. The compound of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof can be provided in a form that is ready for use (e.g., a tablet or capsule) or in a form requiring, for example, reconstitution or dilution (e.g., a powder) prior to administration. When the compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof are in a form that needs to be reconstituted or diluted by a user, the kit may also include diluents (e.g., sterile water), buffers, pharmaceutically acceptable excipients, and the like, packaged with or separately from the compounds of Formula (I), a subembodiment described herein, or a pharmaceutically acceptable salt thereof. When combination therapy is contemplated, the kit may contain the several agents separately or they may already be combined in the kit. Each component of the kit may be enclosed within an individual container, and all of the various containers may be within a single package. A kit of the present invention may be designed for conditions necessary to properly maintain the components housed therein (e.g., refrigeration or freezing).

[0164] A kit may contain a label or packaging insert including identifying information for the components therein and instructions for their use (e.g., dosing parameters, clinical pharmacology of the active ingredient(s), including mechanism of action, pharmacokinetics and pharmacodynamics, adverse effects, contraindications, etc.). Labels or inserts can

include manufacturer information such as lot numbers and expiration dates. The label or packaging insert may be, e.g., integrated into the physical structure housing the components, contained separately within the physical structure, or affixed to a component of the kit (e.g., an ampule, tube or vial).

[0165] Labels or inserts can additionally include, or be incorporated into, a computer readable medium, such as a disk (e.g., hard disk, card, memory disk), optical disk such as CD- or DVD-ROM/RAM, DVD, MP3, magnetic tape, or an electrical storage media such as RAM and ROM or hybrids of these such as magnetic/optical storage media, FLASH media or memory-type cards. In some embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, e.g., via the internet, are provided.

EXAMPLES

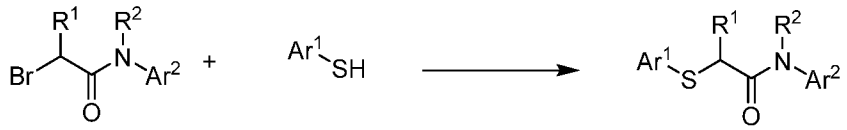
[0166] The following examples and references (intermediates) are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention, nor are they intended to represent that the experiments below were performed or that they are all of the experiments that may be performed. It is to be understood that exemplary descriptions written in the present tense were not necessarily performed, but rather that the descriptions can be performed to generate data and the like of a nature described therein. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.), but some experimental errors and deviations should be accounted for.

[0167] Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius (°C), and pressure is at or near atmospheric. Standard abbreviations are used, including the following: μg = microgram; μl or μL = microliter; mM = millimolar; μM = micromolar; THF= tetrahydrofuran; DIEA = diisopropylethylamine; EtOAc = ethyl acetate; NMP = N-methylpyridine, TFA = trifluoroacetic acid; DCM = dichloromethane; DHP = dihydropyran; TsOH = p-Toluenesulfonic acid; FA = formic acid; TCFH = N,N,N,N'-tetramethylchloroformamidinium hexafluorophosphate; T3P = 2,4,6-Tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide; TEA = Triethylamine; AcOH = Acetic acid; NMI = N-methylimidazole; Cs_2CO_3= cesium carbonate; XPhos Pd G3 = 2-dicyclohexylphosphino-

2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium-(II) methanesulfonate; LiCl = lithium chloride; $POCl_3$ = phosphoryl chloride; PE = petroleum ether; DMSO = dimethylsulfoxide; HCl = hydrochloric acid; Na_2SO_4 = sodium sulfate; DMF = dimethylformamide; NaOH = sodium hydroxide; K_2CO_3 = potassium carbonate; MeCN= acetonitrile; BOC= tert-butoxycarbonyl; MTBE = methyl tert-butyl ether; MeOH = methanol; $NaHCO_3$ = sodium bicarbonate; $NaBH_3CN$ = sodium cyanoborohydride; EtOH = ethanol; PCl_5 = phosphorus pentachloride; NH_4OAc = ammonium acetate; Et_2O = ether; HOAc = acetic acid; Ac_2O = acetic anhydride; *i*-PrOH = isopropanol; NCS = N-chlorosuccinimide; K_3PO_4 = potassium phosphate; $Pd(dtbpf)Cl_2$ =1,1′-bis(di-*tert*-butylphosphino)ferrocene]-dichloropalladium(II); $Pd(dppf)Cl_2$ = [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II); $Pd(dppf)Cl_2$-DCM = [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane; $Zn(CN)_2$ = Zinc cyanide; $Pd(PPh_3)_4$ = tetrakis(triphenylphosphine)-palladium(0); Et_3N = triethylamine; CuCN = copper cyanide; *t*-BuONO = tert-butyl nitrite; HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate; DBU= 1,8-diazabicyclo(5.4.0)undec-7-ene; $LiAlH_4$ = lithium aluminium hydride; NH_3 = ammonia; H_2SO_4 = sulfuric acid; H_2O_2 = hydrogen peroxide; NMP = *N*-methyl-2-pyrrolidone; $MgSO_4$ = magnesium sulphate.

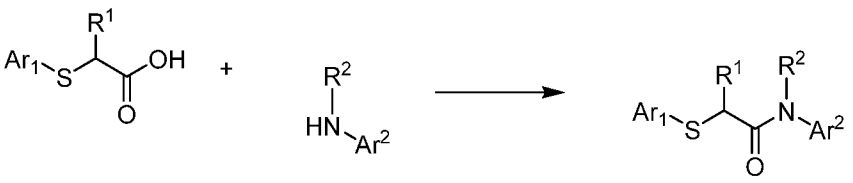
Synthetic Examples

General Procedure A: Preparation of Arylthioether



[0168] To a solution of bromide (1.05 eq.) and aryl thiol (1.0 eq.) in MeOH (0.1 M) at RT was added triethylamine (1 eq.). The reaction mixture was stirred for 15 min and concentrated under reduced pressure. The residue was purified by combiflash (silica gel).

General Procedure B: Preparation of Alkyl or Aryl amide

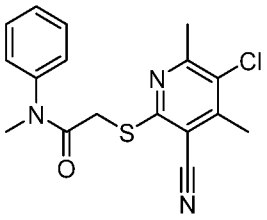


[0169] To a solution of sulfanyl acetic acid (1 eq.) and T3P (1.5 eq.) in DMF (0.1 M) at room temperature was added pyridine (3.0 eq.). After stirring the reaction mixture for 15 min

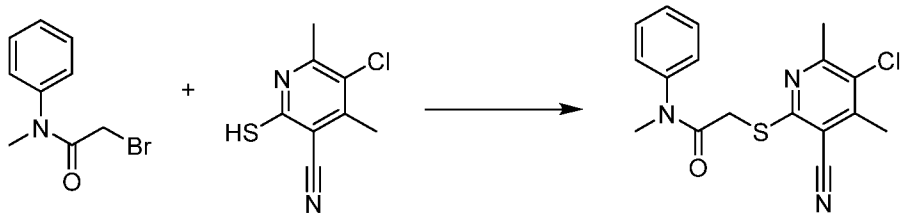
at room temperature was added aniline (1.0 eq.) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction mixture was quenched by adding water (4x). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were concentrated under reduced pressure.

Example 1

Synthesis of 2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-phenylacetamide



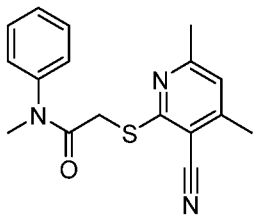
Step 1: Preparation of 2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-phenylacetamide



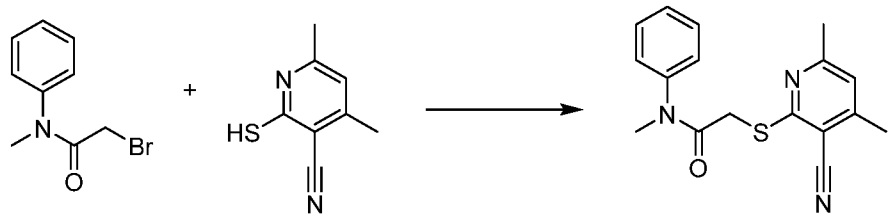
[0170] The title compound was synthesized by using general procedure A, employing 2-bromo-N-methyl-N-phenylacetamide and 5-chloro-2-mercapto-4,6-dimethylnicotinonitrile. The residue was recrystallized from iso-propyl alcohol to to afford the title compound (616 mg, 71%) as light yellow crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44 (t, J = 7.5 Hz, 2H), 7.37 (d, J = 7.2 Hz, 1H), 7.30 (d, J = 7.8 Hz, 2H), 3.89 (s, 2H), 3.32 (s, 3H), 2.55 (s, 3H), 2.52 (s, 3H). *m/z* 346 ($M+H^+$).

Example 2

Synthesis of 2-((3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-phenylacetamide



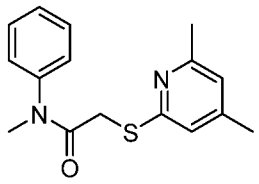
Step 1: Preparation of 2-((3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-phenylacetamide



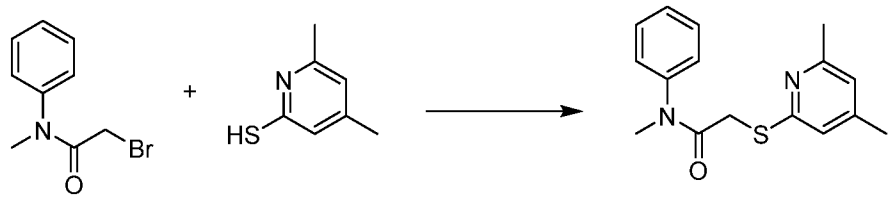
[0171] The title compound was synthesized by using general procedure A, employing 2-bromo-N-methyl-N-phenylacetamide and 2-mercapto-4,6-dimethylnicotinonitrile. The residue was purified by combiflash (12 g, 0-10% EtOAC in DCM) to afford the title compound (32 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43 (t, J = 7.6 Hz, 2H), 7.38 – 7.29 (m, 3H), 6.77 (s, 1H), 3.95 (s, 2H), 3.31 (s, 3H), 2.47 (s, 3H), 2.42 (s, 3H). *m/z* 312 ($M+H^+$).

Example 3

Synthesis of 2-((4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-phenylacetamide



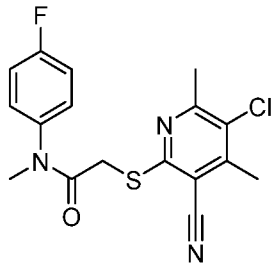
Step 1: Preparation of 2-((4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-phenylacetamide



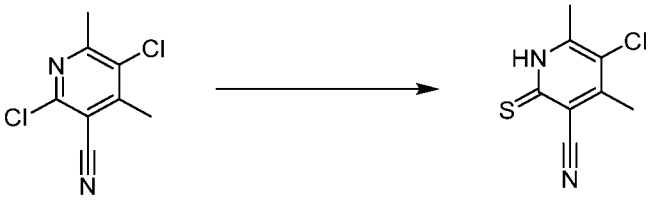
[0172] The title compound was synthesized by using general procedure A, employing 2-bromo-N-methyl-N-phenylacetamide and 4,6-dimethylpyridine-2-thiol. The residue was purified by combiflash (12 g, 0-20% EtOAC in DCM) to afford the title compound (55 mg, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.51 – 7.31 (m, 5H), 6.86 (s, 1H), 6.76 (s, 1H), 3.82 (s, 2H), 3.20 (s, 3H), 2.29 (s, 3H), 2.18 (s, 3H). *m/z* 287 ($M+H^+$).

Example 4

Synthesis of 2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-(4-fluorophenyl)-N-methylacetamide

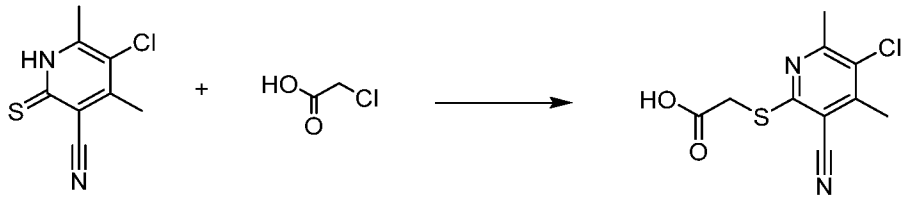


Step 1: Preparation of 5-chloro-4,6-dimethyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile



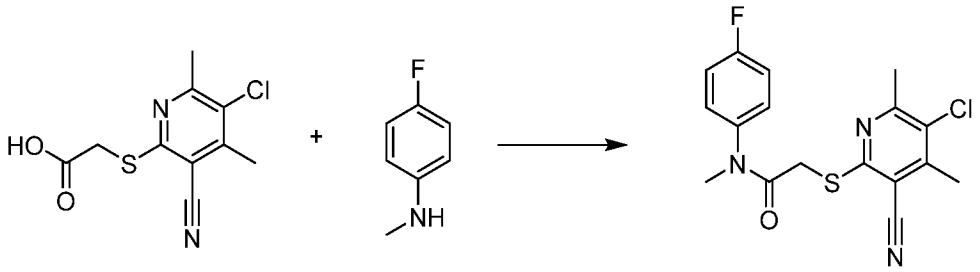
[0173] To a solution of 2,5-dichloro-4,6-dimethylpyridine-3-carbonitrile (25 g, 124.35 mmol, 1 equiv) in DMF (125 mL) at rt was added (19.4 g, 248.72 mmol, 2.00 equiv) and stirred overnight. The reaction mixture was diluted with water (200 mL) and neutralized to pH~7 with aq. HCl (1M). The solids were collected by filtration and the filter cake was washed with water (3x200 mL). The crude product was re-crystallized from EtOH (500 mL) to afford the title compound (13 g, 53%) as a yellow solid.

Step 2: Preparation of 2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)acetic acid



[0174] To a solution of 5-chloro-4,6-dimethyl-2-sulfanylidene-1,2-dihydropyridine-3-carbonitrile (3 g, 15.10 mmol, 1 equiv) in MeOH (30 mL) at rt were added 2-chloroacetic acid (1.6 g, 16.61 mmol, 1.1 equiv) and TEA (3.1 g, 30.20 mmol, 2 equiv). The resulting mixture was stirred for 24 h at room temperature. The mixture was acidified to pH~5 with AcOH. The resulting mixture was concentrated under reduced pressure and diluted with water (40 mL). The solids were collected by filtration and the filter cake was washed with water (3x10 mL). The solids were dried under high vacuum to afford 2-[(5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)sulfanyl]acetic acid (3.01 g, 75%) as a yellow solid.

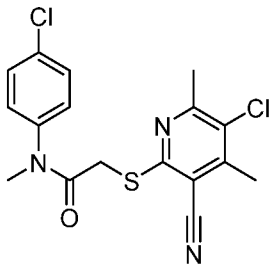
Step 3: Preparation of 2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-(4-fluorophenyl)-N-methylacetamide



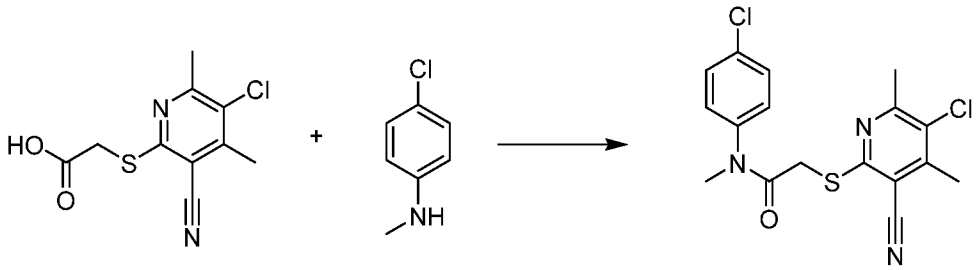
[0175] The title compound was synthesized by using general procedure B, employing 2-[(5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)sulfanyl]acetic acid and 4-fluoro-N-methylaniline. The residue was purified by Prep-TLC (CH_2Cl_2/MeOH=80:1) to afford the title compound (73.6 mg, 35%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.48 (s, 6H), 3.19 (s, 3H), 3.96 (s, 2H), 7.29-7.34 (m, 2H), 7.50 (s, 2H). *m/z* 364 ($M+H^+$).

Example 5

Synthesis of 2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-(4-chlorophenyl)-N-methylacetamide



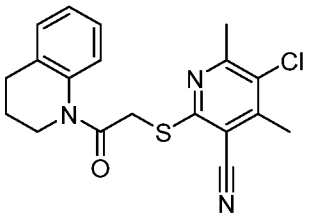
Step 1: Preparation of 2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-(4-chlorophenyl)-N-methylacetamide



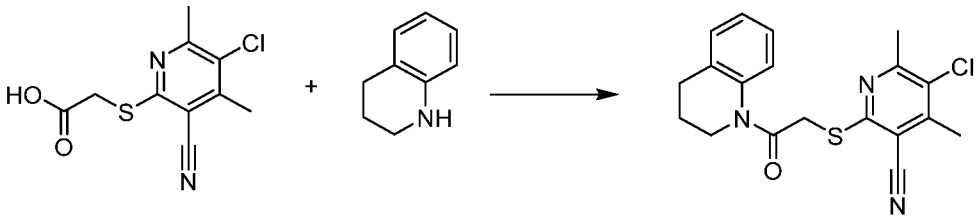
[0176] The title compound was synthesized by using general procedure B, employing 2-[(5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)sulfanyl]acetic acid and 4-chloro-N-methylaniline. The residue was purified by Prep-TLC (DCM/MeOH 80:1) to afford the title compound (59.7 mg, 27%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 7.50 (t, 2H), 7.30-7.36 (m, 2H), 4.00 (s, 2H), 3.32 (m, 3H), 2.51 – 2.46 (m, 6H). *m/z* 380 $[M+H]^+$.

Example 6

Synthesis of 5-chloro-2-((2-(3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)thio)-4,6-dimethylnicotinonitrile



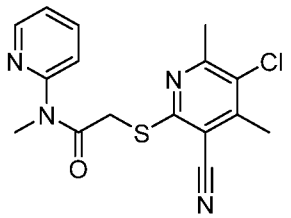
Step 1: Preparation of 5-chloro-2-((2-(3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)thio)-4,6-dimethylnicotinonitrile



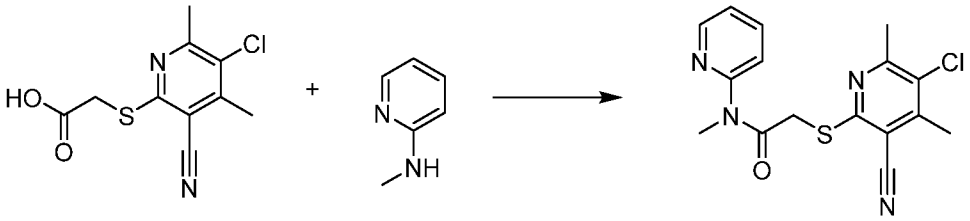
[0177] The title compound was synthesized by using general procedure B, employing 2-[(5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)sulfanyl]acetic acid and 1,2,3,4-tetrahydroquinoline. The crude product was re-crystallized from EtOAc/MeOH (1:1, 10 mL) to afford the title compound (57.3 mg, 26%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.51 (d, 1H), 7.28 - 7.04 (m, 3H), 4.44 (s, 2H), 3.75 (m, 2H), 2.74 (t, 6H), 1.96 - 1.80 (m, 4H). *m/z* 372 ($M+H^+$).

Example 7

Synthesis of 2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-(pyridin-2-yl)acetamide



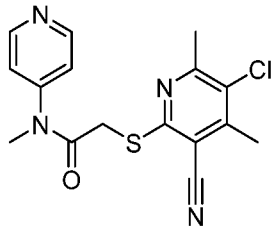
Step 1: Preparation of 2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-(pyridin-2-yl)acetamide



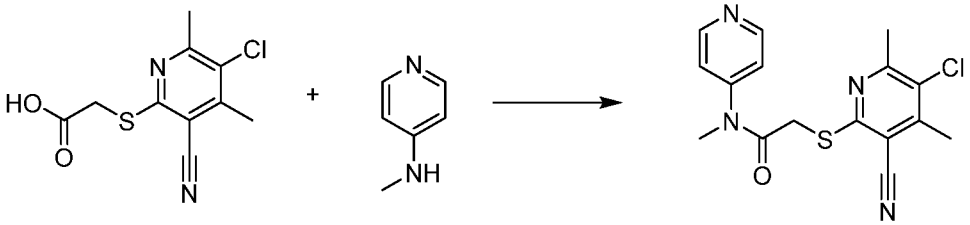
[0178] The title compound was synthesized by using general procedure B, employing 2-[(5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)sulfanyl]acetic acid and N-methylpyridin-2-amine. The residue was purified by Prep-TLC (hexane:EtOAc=2:1) to afford the title compound (95.8 mg, 47%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.52-2.56 (m, 6H), 3.48 (s, 3H), 4.19 (s, 2H), 7.23-7.24 (m, 1H), 7.36-7.38 (d, 1H), 7.79-7.83 (m, 1H), 8.51-8.52 (m, 1H). *m/z* 347 ($M+H^+$).

Example 8

Synthesis of 2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-(pyridin-4-yl)acetamide



Step 1: Preparation of 2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-methyl-N-(pyridin-4-yl)acetamide

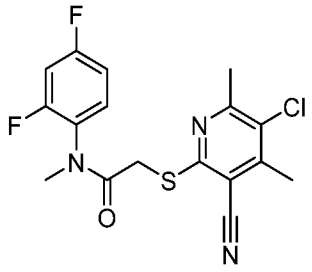


[0179] The title compound was synthesized by using general procedure B, employing 2-[(5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)sulfanyl]acetic acid and N-methylpyridin-4-amine. The residue was purified by Prep-TLC (CH_2Cl_2:MeOH=30:1) to afford the title

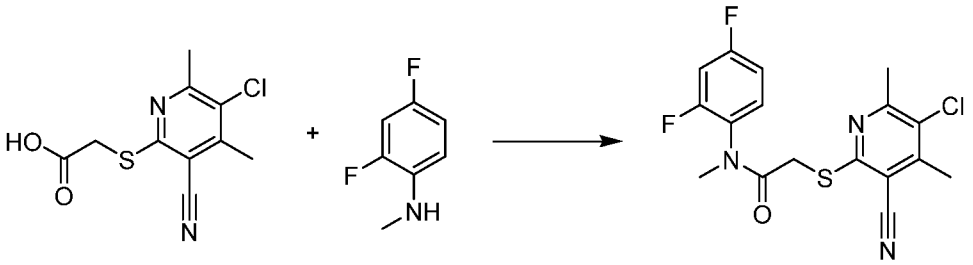
compound (103 mg, 51%) as a green solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.53-2.55 (d, 6H), 3.41 (s, 3H), 4.05 (s, 2H), 7.30-7.32 (d, 2H), 8.68-8.69 (d, 2H). *m/z* 347 ($M+H^+$).

Example 9

Synthesis of 2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-(2,4-difluorophenyl)-N-methylacetamide



Step 1: Preparation of 2-((5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)thio)-N-(2,4-difluorophenyl)-N-methylacetamide

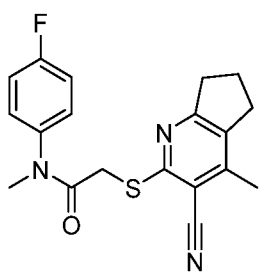


[0180] The title compound was synthesized by using general procedure B, employing 2-[(5-chloro-3-cyano-4,6-dimethylpyridin-2-yl)sulfanyl]acetic acid and 2,4-difluoro-N-methylaniline. The residue was purified by silica gel column chromatography (eluent: 0-1% MeOH in CH_2Cl_2). The crude product was recrystallized from MeOH (2 mL) to afford the title compound (47.1 mg, 32%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.52-2.56 (d, 6H), 3.26 (s, 3H), 3.86-3.87 (d, 2H), 6.92-7.00 (m, 2H), 7.31-7.37 (m, 1H). *m/z* 382 ($M+H^+$).

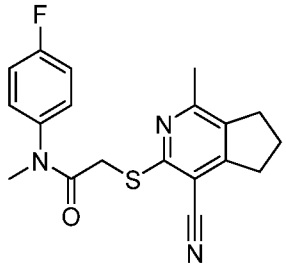
Example 10 and 11

Synthesis of 2-((3-cyano-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)thio)-N-(4-fluorophenyl)-N-methylacetamide and 2-((4-cyano-1-methyl-6,7-dihydro-5H-

cyclopenta[c]pyridin-3-yl)thio)-N-(4-fluorophenyl)-N-methylacetamide

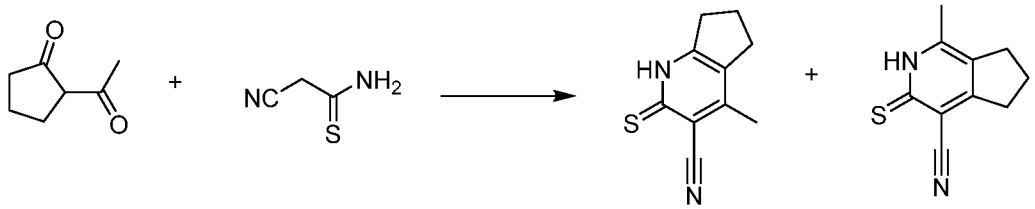


Example 10



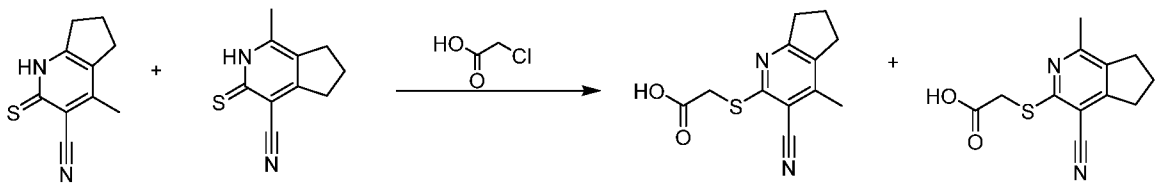
Example 11

Step 1: Preparation of 4-methyl-2-thioxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carbonitrile and 1-methyl-3-thioxo-3,5,6,7-tetrahydro-2H-cyclopenta[c]pyridine-4-carbonitrile



[0181] To a solution of acetylcyclopentanone (4.00 g, 31.707 mmol, 1.00 equiv) and 2-cyanoethanethioamide (3175.14 mg, 31.707 mmol, 1.00 equiv) in EtOH (50.00 mL) was added Et_3N (6416.87 mg, 63.414 mmol, 2.00 equiv). The reaction mixture was heated to 50 °C and stirred for 8 h. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 0-20% EtOAc in PE) to afford the mixture of 4-methyl-2-sulfanylidene-1H,5H,6H,7H-cyclopenta[b]pyridine-3-carbonitrile and 1-methyl-3-sulfanylidene-2H,5H,6H,7H-cyclopenta[c]pyridine-4-carbonitrile (580 mg, 9.61%) as a yellow solid.

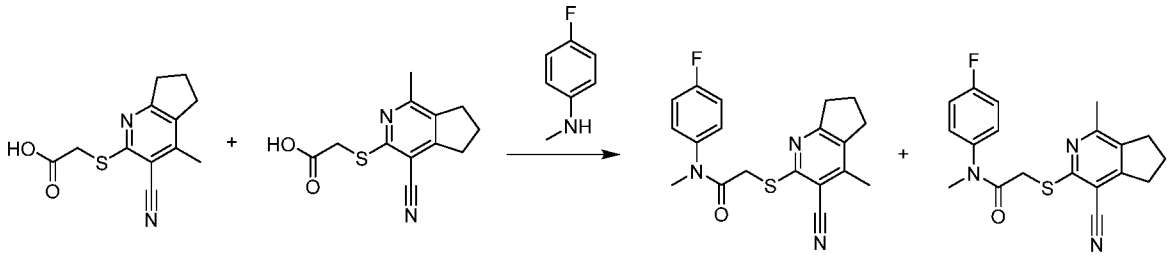
Step 2: Preparation of 2-((3-cyano-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)thio)acetic acid and 2-((4-cyano-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)thio)acetic acid



[0182] To a solution of 4-methyl-2-sulfanylidene-1H,5H,6H,7H-cyclopenta[b]pyridine-3-carbonitrile and 1-methyl-3-sulfanylidene-2H,5H,6H,7H-cyclopenta[c]pyridine-4-carbonitrile (488.00 mg, 2.565 mmol, 1.00 equiv) in DMF (5.00 mL) at RT were added

chloroacetic acid (290.83 mg, 3.078 mmol, 1.20 equiv) and TEA (519.09 mg, 5.130 mmol, 2.00 equiv) respectively. The resulting mixture was stirred overnight at room temperature. The reaction mixture was diluted with water (30 mL) and the aqueous layer was extracted with EtOAc (2x10 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by Prep-TLC (CH_2Cl_2 / MeOH 20:1) to afford a mixture of ([3-cyano-4-methyl-5H,6H,7H-cyclopenta[b]pyridin-2-yl]sulfanyl)acetic acid and ([4-cyano-1-methyl-5H,6H,7H-cyclopenta[c]pyridin-3-yl]sulfanyl)acetic acid (380 mg, 60%) as a yellow solid.

Step 3: Preparation of 2-((3-cyano-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)thio)-N-(4-fluorophenyl)-N-methylacetamide (10) and 2-((4-cyano-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)thio)-N-(4-fluorophenyl)-N-methylacetamide (11)



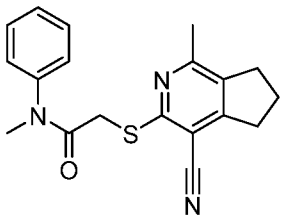
[0183] The title compounds were synthesized by using general procedure B, employing ([4-cyano-1-methyl-5H,6H,7H-cyclopenta[c]pyridin-3-yl]sulfanyl)acetic acid, [3-cyano-4-methyl-5H,6H,7H-cyclopenta[b]pyridin-2-yl]sulfanyl)acetic acid and 4-fluoro-N-methylaniline respectively. The crude product was purified by Chiral-Prep-HPLC with the following conditions (Agela High-pressure Flash): Column, CHIRALPAK IC, 2*25cm,5um; mobile phase, Hex:DCM=1:1(10mM NH_3-MEOH)- and MeOH (hold 35% MeOH in 22 min) retention time 19 min to afford title compound **10** (37 mg, 15%) and title compound **11** (52 mg, 21%) as white solids.

[0184] Example 10: ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 7.50-7.45 (m, 2H), 7.32-7.27 (m, 2H), 3.89 (s, 2H), 3.17 (s, 3H), 2.95-2.86 (m, 2H), 2.84-2.73 (m, 2H), 2.35 (s, 3H), 2.12-2.01 (m, 2H). *m/z* 356 $[M+H]^+$

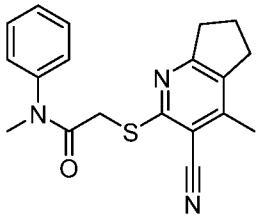
[0185] Example 11: ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 7.50-7.48 (m, 2H), 7.32-7.27 (m, 2H), 3.94 (s, 2H), 3.18 (s, 3H), 3.02-2.97 (m, 2H), 2.85-2.81 (m, 2H), 2.35 (s, 3H), 2.13-2.03 (m, 2H). *m/z* 356 $[M+H]^+$

Example 12 and 13

Synthesis of 2-((4-cyano-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)thio)-N-methyl-N-phenylacetamide and 2-((3-cyano-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)thio)-N-methyl-N-phenylacetamide

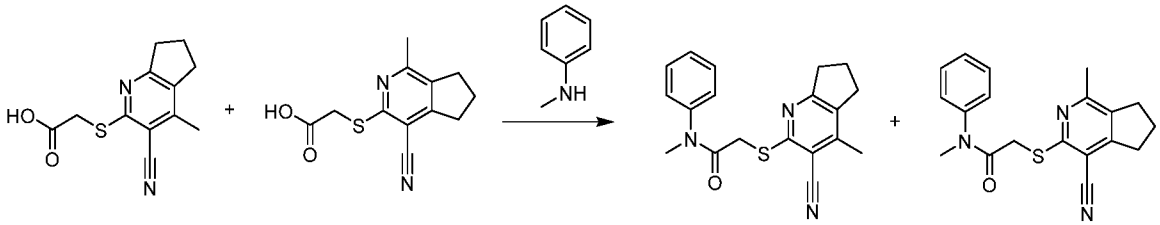


Example 12



Example 13

Step 1: Preparation of 2-((4-cyano-1-methyl-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)thio)-N-methyl-N-phenylacetamide (12) and 2-((3-cyano-4-methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-2-yl)thio)-N-methyl-N-phenylacetamide (13)



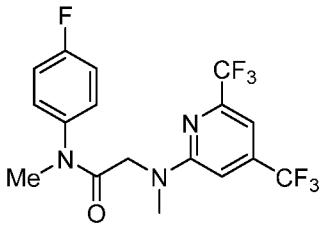
[0186] The title compounds were synthesized by using general procedure B, employing ([4-cyano-1-methyl-5H,6H,7H-cyclopenta[c]pyridin-3-yl]sulfanyl)acetic acid, [3-cyano-4-methyl-5H,6H,7H-cyclopenta[b]pyridin-2-yl]sulfanyl)acetic acid and N-methylaniline respectively. The crude product was purified by Chiral-Prep-HPLC with the following conditions (Agela High-pressure Flash): Column, CHIRALPAK IC, 2*25cm,5um; mobile phase, Hex:DCM=1:1(10mM NH_3-MEOH) and MeOH (hold 35% MeOH- in 25 min) retention time 18 min to afford title compound **12** (36 mg, 16%) and title compound **13** (26 mg, 11%) as white solids.

[0187] Example 12: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.48-7.38 (m, 5H), 4.12-3.95 (m, 2H), 3.38 (s, 3H), 3.02-2.94 (m, 2H), 2.88-2.79 (m, 2H), 2.54-2.45 (m, 3H), 2.17-2.02 (m, 2H). *m/z* 338 $[M+H]^+$.

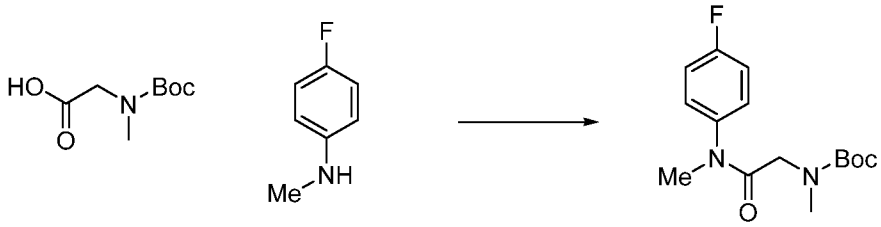
[0188] Example 13: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.50-7.37 (m, 5H), 3.90 (s, 2H), 3.16 (s, 3H), 2.94-2.89 (m, 2H), 2.85-2.80 (m, 2H), 2.34 (s, 3H), 2.12-2.01 (m, 2H). *m/z* 338 $[M+H]^+$.

Example 14

Synthesis of 2-((4,6-bis(trifluoromethyl)pyridin-2-yl)(methyl)amino)-N-(4-fluorophenyl)-N-methylacetamide



Step-1: Synthesis of tert-butyl N-(((4-fluorophenyl)(methyl)carbamoyl)methyl)-N-methylcarbamate

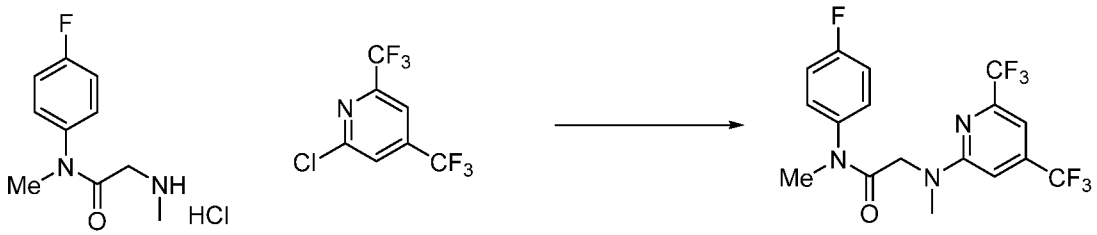


To a stirred solution of 4-fluoro-N-methylaniline (300 mg, 2.40 mmol) and ((tert-butoxycarbonyl)(methyl)amino)acetic acid (454 mg, 2.40 mmol) in DMF (3 mL) were added HATU (1.37 g, 3.60 mmol) and DIEA (929 mg, 7.12 mmol) at room temperature. The resulting mixture was stirred at room temperature for overnight under nitrogen atmosphere. The residue was purified by reverse phase with acetonitrile in water 5~60% to afford tert-butyl N-(((4-fluorophenyl)(methyl)carbamoyl)methyl)-N-methylcarbamate (570 mg, 76%) as a brown oil. MS (ESI) calculated for ($C_{15}H_{21}FN_2O_3$) $(M+1)^+$, 297.2; found, 297.0.

Step-2: Synthesis of afford N-(4-fluorophenyl)-N-methyl-2-(methylamino)acetamide HCl salt

A mixture of tert-butyl N-(((4-fluorophenyl)(methyl)carbamoyl)methyl)-N-methylcarbamate (545 mg, 1.84 mmol) in HCl (10 mL, 4 M in dioxane) was stirred at room temperature for 30 min. The resulting mixture was concentrated under vacuum to afford N-(4-fluorophenyl)-N-methyl-2-(methylamino)acetamide HCl salt (400 mg, crude) as a yellow solid. MS (ESI) calculated for ($C_{10}H_{13}FN_2O$) $(M+1)^+$, 197.1; found, 197.0.

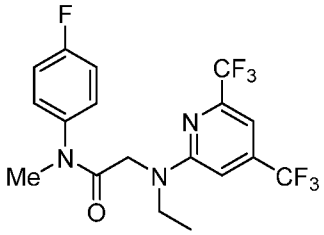
Step-3: Synthesis of 2-((4,6-bis(trifluoromethyl)pyridin-2-yl)(methyl)amino)-N-(4-fluorophenyl)-N-methylacetamide



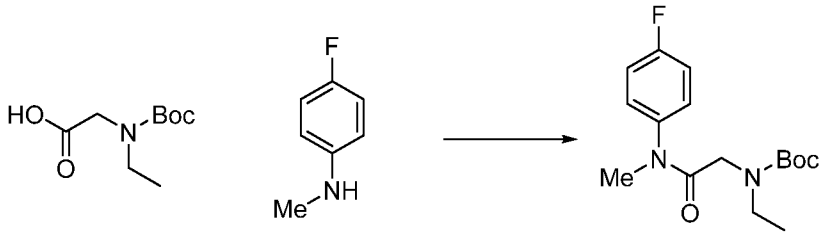
To a stirred solution of N-(4-fluorophenyl)-N-methyl-2-(methylamino)acetamide (50 mg, 0.25 mmol) and 2-chloro-4,6-bis(trifluoromethyl)pyridine (63 mg, 0.25 mmol) in acetonitrile (1 mL) was added DIEA (99 mg, 0.76 mmol) dropwise at room temperature. The resulting mixture was stirred at 60 °C for overnight under nitrogen atmosphere before concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 19*250 mm,10 um; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate:60 mL/min; Gradient:53 B to 66 B in 8 min, 66 B to B in min, B to B in min, B to B in min, B to B in min; 220/254 nm; RT1:6.3) to afford 2-((4,6-bis(trifluoromethyl)pyridin-2-yl)(methyl)amino)-N-(4-fluorophenyl)-N-methylacetamide (38 mg, 36%) as a white solid. MS (ESI) calculated for ($C_{17}H_{14}F_7N_3O$) $(M+1)^+$, 410.1; found, 410.1. ^1H NMR (400 MHz, DMSO-d_6) δ 7.47 (s, 2H), 7.37 – 7.29 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 4.13 (s, 2H), 3.13 (s, 3H), 3.12 (s, 3H).

[0189] Example 15

2-((4,6-bis(trifluoromethyl)pyridin-2-yl)(ethyl)amino)-N-(4-fluorophenyl)-N-methylacetamide



Step-1:Synthesis of tert-butyl N-ethyl-N-(((4-fluorophenyl)(methyl)carbamoyl)methyl)carbamate

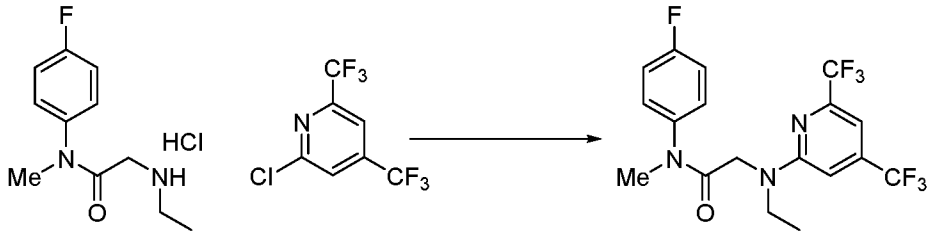


To a stirred solution of 4-fluoro-N-methylaniline (300 mg, 2.39 mmol) and DIEA (929 mg, 7.19 mmol) in DMF (3 mL) were added ((tert-butoxycarbonyl)(ethyl)amino)acetic acid (487 mg, 2.39 mmol) and HATU (1.37 g, 3.60 mmol) at room temperature. The resulting mixture was stirred at room temperature for overnight under nitrogen atmosphere. The residue was purified by reverse phase flash column chromatography with 5~64% acetonitrile in water to afford tert-butyl N-ethyl-N-(((4-fluorophenyl)(methyl)carbamoyl)methyl)carbamate (630 mg, 75%) as a brown oil. MS (ESI) calculated for ($C_{16}H_{23}FN_2O_3$) $(M+1)^+$, 311.2; found, 311.2.

Step-2: Synthesis of 2-(ethylamino)-N-(4-fluorophenyl)-N-methylacetamide HCl salt

A solution of tert-butyl N-ethyl-N-(((4-fluorophenyl)(methyl)carbamoyl)methyl)carbamate (630 mg, 2.03 mmol) in HCl (10 mL, 4 M in dioxane) was stirred at room temperature for 30 min. The resulting mixture was concentrated under vacuum to afford 2-(ethylamino)-N-(4-fluorophenyl)-N-methylacetamide HCl salt (500 mg, crude) as a brown solid. MS (ESI) calculated for ($C_{11}H_{15}FN_2O$) $(M+1)^+$, 211.1; found, 211.2.

Step-3: Synthesis of 2-((4,6-bis(trifluoromethyl)pyridin-2-yl)(ethyl)amino)-N-(4-fluorophenyl)-N-methylacetamide

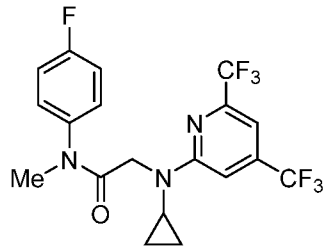


To a stirred solution of 2-(ethylamino)-N-(4-fluorophenyl)-N-methylacetamide (50 mg, 0.24 mmol) and 2-chloro-4,6-bis(trifluoromethyl)pyridine (59 mg, 0.24 mmol) in acetonitrile

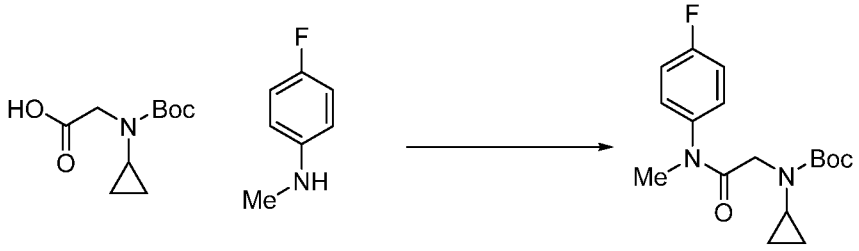
(1 mL) was added DIEA (92 mg, 0.71 mmol) at room temperature. The resulting mixture was stirred at 60 °C for overnight under nitrogen atmosphere before concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30×150 mm 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 50 B to 80 B in 8 min; 220 nm; RT1:7.23) to afford 2-((4,6-bis(trifluoromethyl)pyridin-2-yl)(ethyl)amino)-N-(4-fluorophenyl)-N-methylacetamide (14 mg, 13%) as a brown oil. MS (ESI) calculated for ($C_{18}H_{16}F_7N_3O$) $(M+1)^+$, 424.1; found, 424.1. ^1H NMR (400 MHz, DMSO-d_6) δ 7.48 – 7.47 (m, 2H), 7.33 – 7.32 (m, 2H), 7.20 – 7.18 (m, 2H), 4.06 (s, 2H), 3.57 (d, J = 6.8 Hz, 2H), 3.14 (s, 3H), 1.08 – 1.06 (m, 3H).

[0190] Example 16

2-((4,6-bis(trifluoromethyl)pyridin-2-yl)(cyclopropyl)amino)-N-(4-fluorophenyl)-N-methylacetamide



Step-1: Synthesis of tert-butyl cyclopropyl(2-((4-fluorophenyl)(methyl)amino)-2-oxoethyl)carbamate



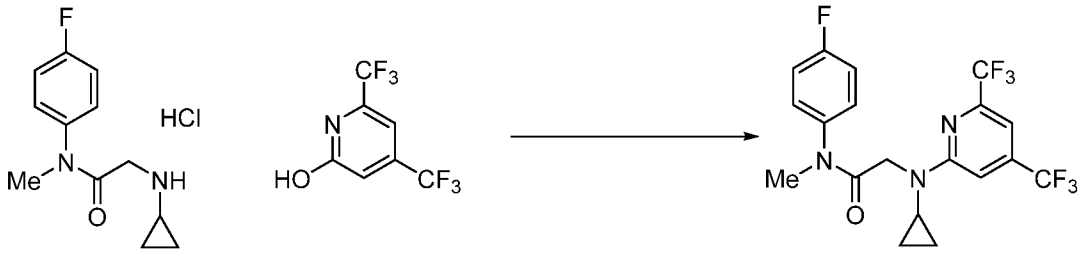
To a stirred solution of ((tert-butoxycarbonyl)(cyclopropyl)amino)acetic acid (200 mg, 0.93 mmol) and 4-fluoro-N-methylaniline (116 mg, 0.93 mmol) in DMF (2.00 mL) were added HATU (530 mg, 1.39 mmol) and DIEA (360 mg, 2.79 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for overnight under nitrogen atmosphere. The residue was purified by reverse phase flash column chromatography

with 5~70% acetonitrile in water to afford tert-butyl cyclopropyl(2-((4-fluorophenyl)(methyl)amino)-2-oxoethyl)carbamate (250 mg, 76%) as a brown oil. MS (ESI) calculated for ($C_{17}H_{23}FN_2O_3$) $(M+1)^+$, 323.2; found, 323.3.

Step-2: Synthesis of 2-(cyclopropylamino)-N-(4-fluorophenyl)-N-methylacetamide HCl salt

A mixture of tert-butyl cyclopropyl(2-((4-fluorophenyl)(methyl)amino)-2-oxoethyl)carbamate (250 mg, 0.77 mmol) in HCl (5 mL, 4 M in dioxane) was stirred at room temperature for 30 min. The resulting mixture was concentrated under vacuum to afford 2-(cyclopropylamino)-N-(4-fluorophenyl)-N-methylacetamide HCl salt (190 mg, crude) as a brown solid. MS (ESI) calculated for ($C_{12}H_{15}FN_2O$) $(M+1)^+$, 223.1; found, 223.1.

Step-3: Synthesis of 2-((4,6-bis(trifluoromethyl)pyridin-2-yl)(cyclopropyl)amino)-N-(4-fluorophenyl)-N-methylacetamide



To a stirred solution of 2-(cyclopropylamino)-N-(4-fluorophenyl)-N-methylacetamide (210 mg, 0.94 mmol) and 4,6-bis(trifluoromethyl)pyridin-2-ol (218 mg, 0.94 mmol) in ACN (2.00 mL) were added BOP (543 mg, 1.23 mmol) and DBU (287 mg, 1.89 mmol) at room temperature. The resulting mixture was stirred at 80 °C for overnight before concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: (Column: XSelect CSH Prep C18 OBD Column,, 19*250 mm, 5 um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 60 B to 90 B in 10 min; 254 nm; RT1: 7) to afford 2-((4,6-bis(trifluoromethyl)pyridin-2-yl)(cyclopropyl)amino)-N-(4-fluorophenyl)-N-methylacetamide (32 mg, 7%) as a brown oil. MS (ESI) calculated for ($C_{19}H_{16}F_7N_3O$) $(M+1)^+$, 436.1; found, 436.1. ^1H NMR (400 MHz, DMSO-d_6) δ 7.49 – 7.46 (m,

3H), 7.39 – 7.24 (m, 3H), 4.08 (s, 2H), 3.11 (s, 3H), 2.94 – 2.84 (m, 1H), 0.98 – 0.85 (m, 2H), 0.70 – 0.68 (m, 2H).

Biological Examples

Biologic Example 1: Primer Extension Assay

[0191] The ability of the compounds of Formula (I) to inhibit polymerase activity of Pol theta was determined using the primer extension assay described below.

[0192] A mixture of 20 uL of Pol theta polymerase domain (residues 1819-2590) at a final concentration of 4 nM in assay buffer (20m M TRIS, pH 7.80, 50 mM KCl, 10 mM $MgCl_2$, 1mM DTT, 0.01% BSA, 0.01% Tween20) was added to test compounds (11-point dilution series of test compounds) except the low control wells without test compounds. The above enzyme and test compound inhibitor mixture was then incubated at room temperature for 15 min. An equal volume (20 µl) of dNTP substrate mixture (48 µM) and primed molecular beacon DNA (obtained by annealing template SEQ ID NO 2: (5′-CCTTCCTCCCGTGTCTTG-TACCTTCCCGTCA-GGAGGAAGG-3') with 5′-TAMRA and 3′-BHQ and primer DNA (SEQ ID NO: 3; 5′-GACGGGAAGG-3') in 10 mM Tris-HCl pH 8.0, 100 mM NaCl buffer) (96 nM) in assay buffer was added to all the test wells. The inhibition activity was measured by monitoring the fluorescence change over 30 min at 535 nm upon excitation at 485 nm. The high control (DMSO with enzyme) with high fluorescence intensity represents no inhibition of polymerase reaction while the low control (DMSO with buffer) with low fluorescence intensity represents full inhibition of polymerase activity. Slope of the reaction progress curves were used to calculate the rate of polymerization. The rates were used to determine the percent inhibition using a four-parameter inhibition model to generate IC_{50}, Hill slope and max inhibition.

[0193] The IC_{50} of the compounds in Table 1 above are disclosed in Table 2 below:

20 µM ≥ (+) > 1 µM; 1 µM ≥ (++) > 500 nM; 500 nM ≥ (+++) > 200 nM; 200 nM ≥ (++++)

Table 2: Primer Extension Assay

Cpd. No.	Primer extension Assay IC_{50}	Cpd. No.	Primer extension Assay IC_{50}
1.001	+++	1.008	+
1.002	+++	1.009	+++

1.003	+	1.010	+++
1.004	+++	1.011	++++
1.005	+++	1.012	++++
1.006	++	1.013	+++
1.007	+	1.014	++++
1.015	++++	1.016	++++

Biologic Example 2: PPi Assay

[0194] The ability of the compounds of Formula (I) or Formula (II) to inhibit polymerase activity of Pol theta was determined using the PPi assay described below.

[0195] A mixture of template DNA strand (SEQ ID NO 4: 5' ATT ACT GAC CTC ATA CTT CTG CCC TTC CAT GTT CTG TGC CCT CCT TCC 3') and primer DNA strand (SEQ ID NO 5: 5' GGA AGG AGG GCA CAG AAC 3') was annealed in 10 mM Tris-HCl pH 8.0, 50 NaCl buffer to form the primed DNA substrate. A 10-point dilution series of compounds were used in a 384 well format for the inhibition assay. Pol theta (residues 1819-2590) (2.8 nM) in assay buffer (20 mM Tris-HCl pH 7.8, 50 mM KCl, 10 mM $MgCl_2$, 1 mM DTT, 0.01% BSA, 0.01% Tween-20) was transferred to the test wells (10 uL), except for the low control wells. The plate was then incubated at room temperature for 15 mins. An equal volume (10 µL) of dNTP substrate (40 µM) and primed DNA substrate (800 nM) in assay buffer was added to all the test wells. 20 µL of PPi detection reagent (PPiLite inorganic pyrophosphate assay, Lonzo) was then added to all test wells. The plate was then centrifuged at 1000 rpm for 1 min. The reaction was monitored in a Tecan M1000 Pro plate reader in luminescence kinetic mode for 90 min. The high control (DMSO with enzyme) with high luminescence represents no inhibition of the polymerase reaction while the low control (DMSO with buffer) with low luminescence represents full inhibition of the polymerase activity. Slope of the reaction progress curves were used to calculate the rate of polymerization. The rates were used to determine the percent inhibition using a four-parameter inhibition model to generate IC_{50}, Hill slope, maximum inhibition, and minimum inhibition.

[0196] The IC_{50} of the compounds in Table 1 above are provided in Table 3 below:

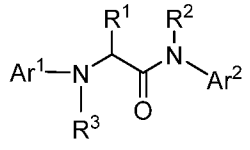
10 µM ≥ (+) > 1 µM; 1 µM ≥ (++) > 500 nM; 500 nM ≥ (+++) > 200 nM; 200 nM ≥ (++++)

Table 3: PPi Assay

Cpd. No.	PPi Assay IC_{50}
1.001	+++

What is Claimed:

1. A compound of Formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof, wherein

Ar^1 is selected from the group consisting of phenyl and six- to ten-membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein phenyl and heteroaryl are substituted with 0 to 4 moieties selected from R^a, R^b, R^c, and R^j, wherein

R^a, R^b, R^c, and R^j are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, cyanomethyl, and aminocarbonylmethyl; or R^c and R^j, when on adjacent ring vertices, combine to form a 3-6 membered cycloalkyl ring;

R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{1-6} aminocarbonylalkyl, and C_{1-6} phenalkyl, wherein phenyl in C_{1-6} phenalkyl is substituted with R^d, R^e, and R^f, wherein

R^d, R^e, and R^f are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, and cyano;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} deuteroalkyl, C_{3-6} cycloalkyl, and C_{1-6} haloalkyl;

Ar^2 is selected from the group consisting of phenyl and six- to ten-membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein said phenyl and heteroaryl are substituted with 0 to 3 moieties selected from R^g, R^h, and R^i, wherein

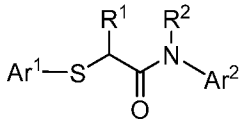
R^g, R^h, and R^i are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, and $-CONH_2$; or

R^2 and Ar^2 combine with the nitrogen to which they are attached to form a 4- to 6- membered heterocycloalkyl having 0 to 2 additional heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein the said heterocycloalkyl is substituted with R^k, R^l, and R^m, wherein

R^k, R^l, and R^m are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, and -$CONH_2$; or R^l and R^m, when on adjacent ring vertices, combine to form a phenyl ring;

R^3 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{1-6} aminocarbonylalkyl, and C_{3-6} cycloalkyl.

2. A compound of Formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof, wherein

Ar^1 is selected from the group consisting of phenyl and six- to ten-membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein phenyl and heteroaryl are substituted with 0 to 4 moieties selected from R^a, R^b, R^c, and R^j, wherein

R^a, R^b, R^c, and R^j are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, cyanomethyl, and aminocarbonylmethyl; or R^c and R^j, when on adjacent ring vertices, combine to form a 3-6 membered cycloalkyl ring;

R^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} aminoalkyl, C_{1-6} aminocarbonylalkyl, and C_{1-6} phenalkyl, wherein phenyl in C_{1-6} phenalkyl is substituted with R^d, R^e, and R^f, wherein

R^d, R^e, and R^f are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, and cyano;

R^2 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} deuteroalkyl, C_{3-6} cycloalkyl, and C_{1-6} haloalkyl;

Ar^2 is selected from the group consisting of phenyl and six- to ten-membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein said phenyl and heteroaryl are substituted with 0 to 3 moieties selected from R^g, R^h, and R^i, wherein

R^g, R^h, and R^i are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, and -$CONH_2$; or

R^2 and Ar^2 combine with the nitrogen to which they are attached to form a 4- to 6- membered heterocycloalkyl having 0 to 2 additional heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein the said heterocycloalkyl is substituted with R^k, R^l, and R^m, wherein

R^k, R^l, and R^m are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, and -$CONH_2$; or R^l and R^m, when on adjacent ring vertices, combine to form a phenyl ring.

3. The compound of any one of claims 1 to 2, wherein Ar^1 is a six-membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S substituted with 0 to 4 moieties selected from R^a, R^b, R^c, and R^j.

4. The compound of claim 3, wherein Ar^1 is pyridinyl substituted with 0 to 4 moieties selected from R^a, R^b, R^c, and R^j.

5. The compound of claim 3, wherein Ar^1 is pyridinyl substituted with R^a, where R^a is selected from the group consisting of methyl, difluoromethyl and trifluoromethyl, and further substituted with R^b, R^c, and R^j.

6. The compound of claim 3, wherein Ar^1 is pyridinyl substituted with R^a, where R^a is selected from the group consisting of methyl, difluoromethyl and trifluoromethyl, and further substituted with R^b, R^c, and R^j, where R^b and R^j are each independently selected from the group consisting of C_{1-6} haloalkyl, C_{1-6} alkoxy, halo, C_{1-6} haloalkoxy, hydroxy, and cyano, and R^c is selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, cyanomethyl, and aminocarbonylmethyl.

7. The compound of claim 3, wherein Ar^1 is pyridinyl substituted with R^a, R^b, R^c, and R^j, wherein R^a and R^b are each independently selected from the group consisting of cyano, methyl, difluoromethyl, and trifluoromethyl.

8. The compound of claim 7, wherein R^c and R^j combine to form a 3-6 membered cycloalkyl ring.

9. The compound of claim 1, wherein Ar^1 is phenyl substituted with R^a, R^b, R^c, and R^j.

10. The compound of claim 9, wherein Ar^1 is phenyl substituted with R^a, where R^a is selected from the group consisting of methyl, difluoromethyl and trifluoromethyl, and further substituted with R^b, R^c, and R^j.

11. The compound of claim 9, wherein Ar^1 is phenyl substituted with R^a, R^b, R^c, and R^j, where R^a is selected from the group consisting of methyl, difluoromethyl and trifluoromethyl, R^b and R^j are each independently selected from the group consisting of C_{1-6} haloalkyl, C_{1-6} alkoxy, halo, C_{1-6} haloalkoxy, hydroxy, and cyano, and R^c is selected from the group consisting of hydrogen, C_{1-6} alkyl, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, cyanomethyl, and aminocarbonylmethyl.

12. The compound of claim 9, wherein Ar^1 is phenyl substituted with R^a, R^b, R^c, and R^j, wherein R^a and R^b are each independently selected from the group consisting of cyano, methyl, difluoromethyl, and trifluoromethyl.

13. The compound of claim 12, wherein R^c and R^j combine to form a 3-6 membered cycloalkyl ring.

14. The compound of any one of claims 1 to 13, wherein R^1 is selected from the group consisting of C_{1-6} hydroxyalkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} aminoalkyl, and C_{1-6} aminocarbonylalkyl.

15. The compound of any one of claims 1 to 13, wherein R^1 is selected from the group consisting of hydrogen, methyl, hydroxymethyl, 2-hydroxyethyl, 4-hydroxybenzyl, and aminocarbonylethyl.

16. The compound of any one of claims 1 to 15, wherein R^2 is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{1-6} haloalkyl.

17. The compound of any of of claims 1 to 13, wherein R^1 is hydrogen and R^2 is selected from the group consisting of methyl, ethyl, isopropyl, cyclopropyl, and 2,2,2-trifluoroethyl.

18. The compound of any of of claims 1 to 13, wherein R^1 is hydrogen and R^2 is methyl.

19. The compound of any of of claims 1 to 18, wherein Ar^2 is phenyl, wherein said phenyl is substituted with R^g, R^h, and R^i independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, and -$CONH_2$.

20. The compound of any one of claims 1 to 18, wherein Ar^2 is phenyl substituted with R^g, R^h, and R^i, wherein R^g, R^h, and R^i are independently selected from the group consisting of hydrogen, -$CONH_2$, fluoro, chloro, bromo, cyano, methoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, trifluoromethyl, and trifluoromethoxy.

21. The compound of any one of claims 1 to 18, wherein Ar^2 is phenyl substituted with R^g, R^h, and R^i, wherein R^g, R^h, and R^i are independently selected from the group consisting of hydrogen, fluoro, chloro, and bromo.

22. The compound of any one of claims 1 to 18, wherein Ar^2 is six- to ten-membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S wherein said heteroaryl is substituted with 0 to 3 moieties selected from R^g, R^h, and R^i independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyloxy, halo, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, hydroxy, cyano, and -$CONH_2$.

23. The compound of any one of claims 1 to 18, wherein Ar^2 is a six-membered heteroaryl having 1 to 4 heteroatom ring vertices independently selected from the group consisting of N, O, and S wherein said heteroaryl is substituted with 0 to 3 moieties selected from R^g, R^h, and R^i independently selected from the group consisting of hydrogen, fluoro, chloro, and bromo.

24. The compound of any one of claims 1 to 15, wherein R^2 and Ar^2 combine with the nitrogen to which they are attached to form a 4- to 6- membered heterocycloalkyl having 0 to 2 additional heteroatom ring vertices independently selected from the group consisting of N, O, and S, wherein the said heterocycloalkyl is substituted with R^k, R^l, and R^m.

25. The compound of any one of claims 1 to 15, wherein R^2 and Ar^2 combine with the nitrogen to which they are attached to form a 4- to 6- membered heterocycloalkyl having 0 additional heteroatom ring vertices.

26. The compound of any one of claims 1 or 3 to 25, wherein R^3 is selected from the group consisting of C_{1-6} alkyl and C_{1-6} haloalkyl.

27. The compound of any one of claims 1 or 3 to 25, wherein R^3 is C_{3-6} cycloalkyl.

28. The compound of any one of claims 1 or 3 to 25, wherein R^3 is selected from the group consisting of methyl and ethyl.

29. The compound of any one of claims 1 or 3 to 25, wherein R^3 is selected from the group consisting of C_{1-6} hydroxyalkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} aminoalkyl, and C_{1-6} aminocarbonylalkyl.

30. A pharmaceutical composition comprising a compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient.

31. A method for treating a disease characterized by overexpression of Polθ in a patient comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 29, or a pharmaceutical composition of claim 30.

32. The method of claim 31, wherein the patient is in recognized need of such treatment and the disease is a cancer.

33. A method of treating a homologous recombinant (HR) deficient cancer in a patient comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 29, or a pharmaceutical composition of claim 30.

34. The method of claim 33, wherein the patient is in recognized need of such treatment.

35. A method for treating a cancer in a patient, wherein the cancer is characterized by a reduction or absence of BRCA gene expression, the absence of the BRCA gene, or reduced function of BRCA protein, comprising administering to the subject a

therapeutically effective amount of a compound of any one of claims 1 to 29, or a pharmaceutical composition of claim 30.

36. The method of any one of claims 32 to 35, wherein the cancer is lymphoma, soft tissue, rhabdoid, multiple myeloma, uterus, gastric, peripheral nervous system, rhabdomyosarcoma, bone, colorectal, mesothelioma, breast, ovarian, lung, fibroblast, central nervous system, urinary tract, upper aerodigestive, leukemia, kidney, skin, esophagus, or pancreas.

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/70 C07D213/74 C07D213/85 C07D221/04 C07D401/12
A61P35/00 A61K31/44 A61K31/444 A61K31/4709 A61K31/435
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JI HONGHE ET AL: "Active sp 3 C-H Bond Oxidation Initiated sp 3 -sp 2 Consecutive C-H Functionalization of N -Arylglycine Amides: Construction of Isatins", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 82, no. 18, 15 September 2017 (2017-09-15), pages 9859-9865, XP055848962, ISSN: 0022-3263, DOI: 10.1021/acs.joc.7b01480 compounds 1aa, 1ba, 1ca, 1da, 1ea, 1fa, 1ga, 1la, 1ab, 1ac, 1bb, 1bc, 1bd, and 1be	1,9,10, 15-21, 26,28

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2021	19/10/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Moriggi, J

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FERRUTI PAOLO ET AL: "Substituted 3-anilinoindoles and anilinoacetanilides from the reaction of glyoxal with N-alkylanilines: crystal structure of 5-chloro-3-(4-chloro-N-methylanilino)-1-me thylindole", JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, no. 0, 1 January 1972 (1972-01-01), pages 2001-2003, XP055848965, Cambridge, UK ISSN: 0300-922X, DOI: 10.1039/P19720002001 compounds VIII-XIII -----	1,9,10, 15-21, 26,28
X	CN 109 020 887 A (SHAOXING CONGLING PHARMACEUTICAL TECH CO LTD ET AL.) 18 December 2018 (2018-12-18) sixth, ninth, eleventh and fifteenth compounds on page 9 -----	1,9,15, 24-26, 28,29
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X	WO 03/103651 A1 (CV THERAPEUTICS INC [US]; IBRAHIM PRABHA N [US] ET AL.) 18 December 2003 (2003-12-18) page 41; page 42, line 4 - line 8; example 6 -----	2,9,15, 16,19-21
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International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JIANG YI ET AL: "Direct access to [alpha]-sulfenylated amides/esters via sequential oxidative sulfenylation and C-C bond cleavage of 3-oxobutyric amides/esters", CHEMICAL COMMUNICATIONS, vol. 54, no. 7, 1 January 2018 (2018-01-01), pages 802-805, XP055848584, UK ISSN: 1359-7345, DOI: 10.1039/C7CC09026A compounds 3ac, 3ad, 3af	2,9,15, 19-21, 24,25
X	WO 2006/122156 A2 (HYDRA BIOSCIENCES INC [US]; CHONG JAYHONG A [US] ET AL.) 16 November 2006 (2006-11-16) compounds 16-18, 22, 23, 25, 26, 29, 30, 32, 36, 40, 41, 44, 47, 64, 69, 73, 76, 79	2,15,24, 25
X	ESKER JOHN L. ET AL: "Chemistry of amidyl radicals produced from N-hydroxypyridine-2-thione imidate esters", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 58, no. 18, 1 August 1993 (1993-08-01), pages 4933-4940, XP055848926, ISSN: 0022-3263, DOI: 10.1021/jo00070a033 page 4936; compound 15a	2-4,24, 25
X	RU 2 557 550 C1 (FEDERAL NOE G BJUDZHETNOE OBRAZOVATEL NOE UCHREZHDENIE VYSSHEGO PROFES) 27 July 2015 (2015-07-27) precursor of compound 3; page 4	2-7, 15-21
X	FU DONG-JUN ET AL: "Discovery of novel tertiary amide derivatives as NEDDylation pathway activators to inhibit the tumor progression in vitro and in vivo", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL, vol. 192, 28 February 2020 (2020-02-28), XP086102495, ISSN: 0223-5234, DOI: 10.1016/J.EJMECH.2020.112153 [retrieved on 2020-02-28] table 3; compound VII48	1-36
X,P	WO 2020/160134 A1 (IDEAYA BIOSCIENCES INC [US]) 6 August 2020 (2020-08-06) paragraph [0008]; claim 1	1-36

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☒ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2021/043456

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		WO 2020160134 A1	06-08-2020