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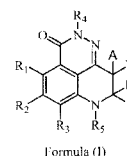
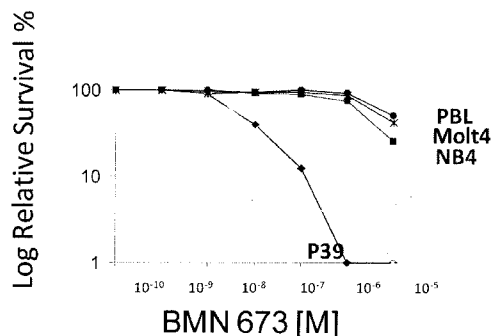
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(54) Title: USE OF DIHYDROPYRIDOPHTHALAZINONE INHIBITORS OF POLY (ADP-RIBOSE) POLYMERASE (PARP) IN THE TREATMENT OF MYELODYSPLASTIC SYNDROME (MDS) AND ACUTE MYELOID LEUKAEMIA (AML)



(57) Abstract: Disclosed herein are compounds of Formula (I) where R₁, R₂, R₃, R₄, R₅, A, B, Y, and Z are as defined herein for use in the treatment of MDS or AML. Also disclosed are the methods of identifying a patient with MDS or AML who is sensitive to treatment with a PARP inhibitor, in particular a compound of Formula (I).

**USE OF DIHYDROPYRIDOPHTHALAZINONE INHIBITORS OF POLY (ADP-RIBOSE)
POLYMERASE
(PARP) IN THE TREATMENT OF MYELOYDYSPLASTIC SYNDROME (MDS) AND ACUTE
MYELOID**

FIELD OF THE INVENTION

[0001] Described herein are methods of using dihydropyridophthalazinone inhibitors of Poly(ADP-Ribose)Polymerase (PARP) to treat or prevent Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukaemia (AML). Also described herein are methods of determining a subject's sensitivity to such PARP inhibitors, based on their Microsatellite Instability (MSI) status.

BACKGROUND OF THE INVENTION

[0002] The family of poly(ADP-ribose)polymerases (PARP) includes approximately 18 proteins, which all display a certain level of homology in their catalytic domain but differ in their cellular functions (Ame *et al.*, *BioEssays*, 26(8), 882-893 (2004)). PARP-1 and PARP-2 are unique members of the family, in that their catalytic activities are stimulated by the occurrence of DNA strand breaks.

[0003] PARP has been implicated in the signaling of DNA damage through its ability to recognize and rapidly bind to DNA single or double strand breaks (D'Amours, *et al.*, *Biochem. J.*, 342, 249-268 (1999)). It participates in a variety of DNA-related functions including gene amplification, cell division, differentiation, apoptosis, DNA base excision repair as well as effects on telomere length and chromosome stability (d'Adda di Fagagna, *et al.*, *Nature Gen.*, 23(1), 76-80 (1999)).

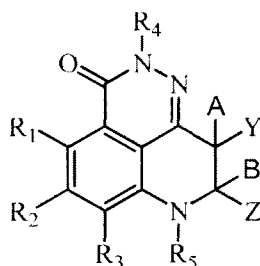
[0004] Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukaemia (AML) are characterized by chromosomal instability, and leukemic cells have inherent defects in double strand DNA repair (Gaymes, *et al.*, *Cancer Res.*, 62, 2791-2797 (2002)). Furthermore, a study of PARP inhibitors on AML cell lines showed that a proportion (15%) of cells derived from the AML patients demonstrated significant cytotoxic responses to PARP inhibitors (Gaymes, *et al.*, *Haematologica*, 94(5), 638-646 (2009)).

[0005] Microsatellite Instability (MSI) can be defined as an elevated rate of uncorrected replication errors in microsatellite sequences (Han, *et al.*, *Science*, 97, 226-234 (2006)). Disruption of the mismatch repair machinery results in MSI and loss of mismatch repair and subsequent MSI is observed in 12% of colorectal cancers. MSI in other cancers are less well characterized, but reports show the presence of mismatch repair defects and MSI in haematological malignancies (Han, *et al.*, *Science*, 97, 226-234 (2006); Gu, *et al.*, *Oncogene*, 21, 5758-5764 (2002)). As microsatellite sequences appear in the exons of prominent DSB DNA repair genes, MSI has the potential to inflict frameshift mutations in genes that confer PARP inhibitor sensitivity.

[0006] PARP inhibitors and use of PARP inhibitors for treatment of certain cancers are known in the art, as described previously in International Patent Publication No. WO 2010/017055 A2, incorporated herein by reference in its entirety. Methods of DNA repair pathway profiling and analyzing MSI are also known in the art, as described previously in Gaymes *et al.*, *Clin. Cancer Res.*, 12, 5104-5111 (2006), incorporated herein by reference in its entirety. Additional PARP inhibitor therapies are sought for certain cancers, *e.g.*, MDS and AML, which are associated with MSI. A method for screening of candidates for PARP inhibitor therapy through DNA repair pathway profiling and analysis of MSI is also sought.

SUMMARY OF THE INVENTION

[0007] In one aspect, described herein is a method of treating Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) in a patient with MDS or AML, comprising administering to a patient with MDS or AML a therapeutically effective amount of a compound of Formula (I):



Formula (I),

wherein:

Y and Z are each independently selected from the group consisting of:

- an aryl group optionally substituted with 1, 2, or 3 R_6 ;
- a heteroaryl group optionally substituted with 1, 2, or 3 R_6 ; and
- a substituent independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkylene, oxo, heterocycloalkyl, heterocycloalkylalkyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, $(NR_A R_B)$ alkylene, $(NR_A R_B)$ carbonyl, $(NR_A R_B)$ carbonylalkylene, $(NR_A R_B)$ sulfonyl, and $(NR_A R_B)$ sulfonylalkylene;

R_1 , R_2 , and R_3 are each independently selected from the group consisting of hydrogen, halogen, alkenyl, alkoxy, alkoxycarbonyl, alkyl, cycloalkyl, alkynyl, cyano, haloalkoxy, haloalkyl, hydroxyl, hydroxyalkylene, nitro, $NR_A R_B$, $NR_A R_B$ alkylene, and $(NR_A R_B)$ carbonyl;

A and B are each independently selected from the group consisting of hydrogen, Br, Cl, F, I, OH, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, alkoxy, and alkoxyalkyl, wherein C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, alkoxy, and

alkoxyalkyl are optionally substituted with at least one substituent selected from the group consisting of OH, NO₂, CN, Br, Cl, F, I, C₁-C₆alkyl, and C₃-C₈cycloalkyl, wherein B is not OH;

R_A and R_B are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, and alkylcarbonyl; or R_A and R_B taken together with the atom to which they are attached form a 3-10 membered heterocycle ring optionally having one to three heteroatoms or hetero functionalities selected from the group consisting of -O-, -NH-, -N(C₁-C₆-alkyl)-, -NCO(C₁-C₆-alkyl)-, -N(aryl)-, -N(aryl-C₁-C₆-alkyl)-, -N(substituted-aryl-C₁-C₆-alkyl)-, -N(heteroaryl)-, -N(heteroaryl-C₁-C₆-alkyl)-, -N(substituted-heteroaryl-C₁-C₆-alkyl)-, and -S- or S(O)_q-, wherein q is 1 or 2 and the 3-10 membered heterocycle ring is optionally substituted with one or more substituents;

R₄ and R₅ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxyalkyl, haloalkyl, hydroxyalkylene, and (NR_AR_B)alkylene; and

each R₆ is selected from the group consisting of OH, NO₂, CN, Br, Cl, F, I, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₈heterocycloalkyl, C₂-C₆alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C₂-C₆alkynyl, aryl, arylalkyl, C₃-C₈cycloalkylalkyl, haloalkoxy, haloalkyl, hydroxyalkylene, oxo, heteroaryl, heteroarylalkoxy, heteroaryloxy, heteroarylthio, heteroarylalkylthio, heterocycloalkoxy, C₂-C₈heterocycloalkylthio, heterocyclooxy, heterocyclothio, NR_AR_B, (NR_AR_B)C₁-C₆alkylene, (NR_AR_B)carbonyl, (NR_AR_B)carbonylalkylene, (NR_AR_B)sulfonyl, and (NR_AR_B)sulfonylalkylene.

[0008] In certain embodiments, the compound is administered as a single isomer, stereoisomer, or enantiomer, or mixture thereof.

[0009] In certain embodiments, the compound is administered as a salt, solvate, chemically protected form or prodrug thereof.

[0010] In certain embodiments, the compound is administered with at least one of a pharmaceutically acceptable diluent, excipient, and carrier.

[0011] In certain embodiments, the malignant cells of the patient exhibit Microsatellite Instability (MSI) in a microsatellite. In certain embodiments, the malignant cells contain an insertion or deletion in at least one microsatellite. In some embodiments, the malignant cells of the patient exhibit MSI in two, three, four, five, six, seven or more microsatellites. In certain embodiments, the MSI in the at least one microsatellite comprises a plurality of insertions and/or deletions. In certain embodiments, the MSI in the at least one microsatellite may be detected using primers designed to detect insertion or deletion in the microsatellite. In some embodiments, the at least one microsatellite is *NR21*, *NR22*, *NR24*, *Bat25*, *Bat26*, *Mono27* and/or a microsatellite as described herein in the DNA repair genes *CTiP*, *Mre11*, *ATM*, *Rad50*, *Chk1*, *BLM*, *PTEN*, *ATM* and *ATR*. In certain embodiments, the at least one microsatellite is selected from the group consisting of *NR21*, *NR22*, *Bat25*, *Bat26*, *Mono27* and a microsatellite as described herein in the DNA repair genes *CTiP*, *Mre11* and *ATM*. In

certain embodiments, the at least one microsatellite is selected from the group consisting of *NR21*, *NR24* and *Bat25*. In certain embodiments, the MSI comprises deletion or insertion of 3 or more base pairs in the microsatellite(s). In certain embodiments, MSI comprises insertion(s) or deletion(s) of base pairs in microsatellite(s) that lead to inactivation of DNA repair function and/or results in a frameshift mutation in a double stranded DNA repair gene expression product. In certain embodiments, the DNA repair function is governed by a double stranded DNA repair gene selected from the group consisting of *Mre11*, *ATM* and *CTIP*. In certain embodiments, the method further comprises analyzing for MSI in at least one microsatellite of a patient's malignant cell DNA.

[0012] In certain embodiments, the compound is 5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-8,9-dihydro-2H-pyrido[4,3,2-de]phthalazin-3(7H)-one, or a pharmaceutically acceptable salt thereof.

[0013] In certain embodiments, described is a method of treating AML in a patient with AML, comprising administering to a patient with AML a therapeutically effective amount of a compound of Formula (I) or stereoisomer or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is 5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-8,9-dihydro-2H-pyrido[4,3,2-de]phthalazin-3(7H)-one, or a stereoisomer or a pharmaceutically acceptable salt thereof.

[0014] In another aspect, described herein is a compound of Formula (I), or a salt, solvate, single isomer, stereoisomer, or enantiomer, or mixture thereof, or chemically protected form or prodrug thereof, for use in the treatment of MDS or AML in a patient with MDS or AML. In certain embodiments, the malignant cells in the patient exhibit MSI in a microsatellite. In certain embodiments, the malignant cells in the patient exhibit MSI in at least two, three, four, five, six or more microsatellites.

[0015] In another aspect, described herein is a use of a compound of Formula (I), or a salt, solvate, single isomer, stereoisomer, or enantiomer, or mixture thereof, or chemically protected form or prodrug thereof, in the formulation of a medicament for the treatment of MDS or AML in a patient with MDS or AML. In certain embodiments, the malignant cells in the patient exhibit MSI in a microsatellite. In certain embodiments, the malignant cells in the patient exhibit MSI in at least two, three, four, five, six or more microsatellites.

[0016] In another aspect, described herein is a method for identifying MSI in an MDS or AML patient. In certain embodiments, the method comprises analyzing for MSI in at least one microsatellite in a patient's malignant cell DNA. In certain embodiments, the MSI comprises three or more inserted or deleted base pairs in the at least one microsatellite. In certain embodiments, the presence of MSI in the at least one microsatellite in the patient's malignant cell DNA identifies the patient's malignancy as likely to be sensitive to therapy Compound of Formula I. In certain embodiments, the MSI in the at least one microsatellite may be detected using a primer designed to

detect insertion or deletion in the microsatellite. In certain embodiments, the at least one microsatellite is *NR21*, *NR22*, *NR24*, *Bat25*, *Bat26*, *Mono27* and/or a microsatellite as described herein in the DNA repair genes *CTiP*, *Mre11*, *ATM*, *Rad50*, *Chk1*, *BLM*, *PTEN*, *ATM* and *ATR*. In certain embodiments, the at least one microsatellite is *NR21*, *NR22*, *Bat25*, *Bat26*, *Mono27*, or a microsatellite as described herein in the DNA repair genes *CTiP*, *Mre11* and *ATM*. In some embodiments, the at least one microsatellite is selected from the group consisting of *NR21*, *NR24* and *Bat25*. In certain embodiments, the microsatellite(s) that contain insertion(s) or deletion(s) of base pairs lead to inactivation of DNA repair function. In certain embodiments, the DNA repair function is governed by a double stranded DNA repair gene selected from the group consisting of *Mre11*, *ATM* and *CTiP*.

[0017] In another aspect, described herein is a method for identifying an MDS or AML patient likely to respond to treatment with a compound of Formula (I). In certain embodiments, the compound of Formula (I) is 5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one. In certain embodiments, the method comprises analyzing for MSI in at least one microsatellite(s) in a patient's malignant cell DNA. In certain embodiments, the MSI comprises three or more inserted or deleted base pairs in at least one microsatellite in the patient's malignant cell DNA. In certain embodiments, the presence of MSI in at least one microsatellite of the patient's malignant cell DNA indicates that the patient's malignancy is likely to be sensitive to treatment with a compound of Formula (I). In certain embodiments, the MSI in the at least one microsatellite may be detected using a primer designed to detect insertion or deletion in the microsatellite. In certain embodiments, the at least one microsatellite is *NR21*, *NR22*, *NR24*, *Bat25*, *Bat26*, *Mono27* and/or a microsatellite as described herein in the DNA repair genes *CTiP*, *Mre11*, *ATM*, *Rad50*, *Chk1*, *BLM*, *PTEN*, *ATM* and *ATR*. In certain embodiments, the at least one microsatellite is *NR21*, *NR22*, *Bat25*, *Bat26*, *Mono27*, or a microsatellite as described herein in the DNA repair genes *CTiP*, *Mre11* and *ATM*. In certain embodiments, the at least one microsatellite is selected from the group consisting of *NR21*, *NR24* and *Bat25*. In certain embodiments, the at least one microsatellite contains insertion(s) or deletion(s) of base pairs leads to inactivation of DNA repair function. In certain embodiments, the DNA repair function is governed by a double stranded DNA repair gene selected from the group consisting of *Mre11*, *ATM* and *CTiP*. In certain embodiments, the method further comprises cytogenetic analysis of chromosomal abnormalities in the patient's malignant cell DNA.

DESCRIPTION OF THE FIGURES

[0018] **FIG. 1.** Response to PARP inhibition in MDS/AML cell lines. Varying concentrations of Compound 1 were added to MDS/AML cell lines and peripheral blood lymphocytes (PBL) continuously for 12-14 days. Soft agar clonogenic assays were used to determine cell survival.

[0019] **FIG. 2.** Composite microsatellite analysis of mononucleotide repeat *NR21* (21 consecutive thymines in 5'UTR of the solute carrier gene, *SLC7A8*, shown underlined in legend) in cell lines NB4, KG-1 and P39; comparison to normal PBL cell line.

[0020] **FIG. 3.** Composite microsatellite analysis of mononucleotide repeat *Mono27* (27 consecutive intronic adenines in *MAP4K3*, shown underlined in legend) in cell lines KG-1, Molm-13, Molt 4, NB4 and P39; comparison to normal PBL cell line.

[0021] **FIG. 4.** Composite microsatellite analysis of mononucleotide repeat *CTiP* (9 consecutive thymines in exon 11, shown underlined in legend) in MSI-high cell lines Molm-13, KG-1 and P39; comparison to normal PBL cell line. Fluorescent PCR image shown on left, Sanger sequence on right.

[0022] **FIG. 5.** Composite microsatellite analysis of mononucleotide repeat *Mre11* (11 consecutive intronic thymines, shown underlined in legend) in MSI-high cell lines KG-1, NB4, P39 and Molm-13; comparison to normal PBL cell line. Fluorescent PCR image shown on left, Sanger sequence on right.

[0023] **FIG. 6.** Composite microsatellite analysis of mononucleotide repeat *Mre11* (11 consecutive intronic thymines, shown underlined in legend) in MSI-stable cell lines HL60, Jurkat, DNA ligase IV^{-/-} (DNL), OCI-AML3 and U937. Fluorescent PCR image shown on left, Sanger sequence on right.

[0024] **FIG. 7.** Composite microsatellite analysis of mononucleotide repeat *ATM* (15 consecutive intronic thymines, shown underlined in legend) in cell lines Jurkat, KG-1, DNA ligase IV^{-/-} (DNL), NB4, P39, Molm-13 and OCI-AML3. Fluorescent PCR image shown on left, Sanger sequence on right.

[0025] **FIG. 8.** PCR for exon 8 of *ATM* was performed on the cDNA of cell lines DNL, Jurkat, K562, KG-1, Molm-13, Molt 4, NB4 and P39. The ratio of intensity (RI) of aberrant to wild-type bands was measured using Adobe PhotoshopTM.

[0026] **FIG. 9.** PCR for exon 5 of *Mre11* was performed on the cDNA of cell lines DNL, Jurkat, K562, KG-1, Molm-13, Molt 4, NB4 and P39. The ratio of intensity (RI) of aberrant to wild-type bands was measured using Adobe PhotoshopTM.

[0027] **FIG. 10.** Composite microsatellite analysis of *CTiP* (9 consecutive thymines in exon 11, shown underlined in legend) in 5 patients with high risk MDS. Fluorescent PCR image shown on left, Sanger sequence on right.

DETAILED DESCRIPTION OF THE INVENTION

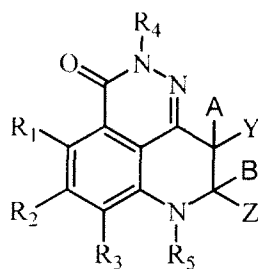
Compounds of Formula (I) or Formula (II)

[0028] In certain embodiments, disclosed herein are methods of treating Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) in a patient with MDS or AML, comprising administering to a patient with MDS or AML a therapeutically effective amount of a compound having the structure of Formula (I) or Formula (II).

[0029] In certain embodiments, the methods comprise administering to the patient pharmaceutically acceptable salts, solvates, esters, acids and chemically protected forms or prodrugs thereof of the compounds having the structure of Formula (I) and Formula (II).

[0030] In certain embodiments, the methods comprise administering to the patient isomers including single isomers, stereoisomers, enantiomers, diastereoisomers, or mixtures thereof, of compounds having the structure of Formula (I) and Formula (II).

[0031] Formula (I) is as follows:



Formula (I)

wherein:

Y and Z are each independently selected from the group consisting of:

- an aryl group optionally substituted with 1, 2, or 3 R₆;
- a heteroaryl group optionally substituted with 1, 2, or 3 R₆;
- a substituent independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkylene, oxo, heterocycloalkyl, heterocycloalkylalkyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, (NR_AR_B)alkylene, (NR_AR_B)carbonyl, (NR_AR_B)carbonylalkylene, (NR_AR_B)sulfonyl, and (NR_AR_B)sulfonylalkylene;

R₁, R₂, and R₃ are each independently selected from the group consisting of hydrogen, halogen, alkenyl, alkoxy, alkoxycarbonyl, alkyl, cycloalkyl, alkynyl, cyano, haloalkoxy, haloalkyl, hydroxyl, hydroxyalkylene, nitro, NR_AR_B, NR_AR_Balkylene, and (NR_AR_B)carbonyl;

A and B are each independently selected from hydrogen, Br, Cl, F, I, OH, C₁-C₆alkyl, C₃-C₈cycloalkyl, alkoxy, alkoxyalkyl wherein C₁-C₆alkyl, C₃-C₈cycloalkyl, alkoxy, alkoxyalkyl are optionally

substituted with at least one substituent selected from OH, NO₂, CN, Br, Cl, F, I, C₁-C₆alkyl, and C₃-C₈cycloalkyl, wherein B is not OH;

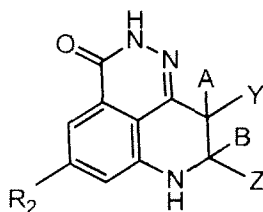
R_A and R_B are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, and alkylcarbonyl; or R_A and R_B taken together with the atom to which they are attached form a 3-10 membered heterocycle ring optionally having one to three heteroatoms or hetero functionalities selected from the group consisting of -O-, -NH-, -N(C₁-C₆-alkyl)-, -NCO(C₁-C₆-alkyl)-, -N(aryl)-, -N(aryl-C₁-C₆-alkyl)-, -N(substituted-aryl-C₁-C₆-alkyl)-, -N(heteroaryl)-, -N(heteroaryl-C₁-C₆-alkyl)-, -N(substituted-heteroaryl-C₁-C₆-alkyl)-, and -S- or S(O)_q-, wherein q is 1 or 2 and the 3-10 membered heterocycle ring is optionally substituted with one or more substituents;

R₄ and R₅ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxyalkyl, haloalkyl, hydroxyalkylene, and (NR_AR_B)alkylene; and

each R₆ is selected from the group consisting of OH, NO₂, CN, Br, Cl, F, I, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₈heterocycloalkyl, C₂-C₆alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C₂-C₆alkynyl, aryl, arylalkyl, C₃-C₈cycloalkylalkyl, haloalkoxy, haloalkyl, hydroxyalkylene, oxo, heteroaryl, heteroarylalkoxy, heteroaryloxy, heteroarylthio, heteroarylalkylthio, heterocycloalkoxy, C₂-C₈heterocycloalkylthio, heterocyclooxy, heterocyclothio, NR_AR_B, (NR_AR_B)C₁-C₆alkylene, (NR_AR_B)carbonyl, (NR_AR_B)carbonylalkylene, (NR_AR_B)sulfonyl, and (NR_AR_B)sulfonylalkylene; or

and isomers, salts, solvates, chemically protected forms, and prodrugs thereof.

[0032] Formula (II) is as follows:



Formula (II);

wherein:

Y is an aryl or heteroaryl group optionally substituted with at least one R₆;

Z is an aryl group optionally substituted with at least one R₆;

A and B are each independently selected from hydrogen, Br, Cl, F, I, OH, C₁-C₆alkyl, C₃-C₈cycloalkyl, alkoxy, alkoxyalkyl wherein C₁-C₆alkyl, C₃-C₈cycloalkyl, alkoxy, alkoxyalkyl are optionally substituted with at least one substituent selected from OH, NO₂, CN, Br, Cl, F, I, C₁-C₆alkyl, and C₃-C₈cycloalkyl, wherein B is not OH;

R₆ is selected from OH, NO₂, CN, Br, Cl, F, I, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₈heterocycloalkyl; C₂-C₆alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C₂-C₆alkynyl, aryl, arylalkyl, C₃-C₈cycloalkylalkyl, haloalkoxy, haloalkyl, hydroxyalkylene, oxo, heteroaryl,

heteroarylalkoxy, heteroaryloxy, heteroarylthio, heteroarylalkylthio, heterocycloalkoxy, C₂-C₈heterocycloalkylthio, heterocyclooxy, heterocyclothio, NR_AR_B, (NR_AR_B)C₁-C₆alkylene, (NR_AR_B)carbonyl, (NR_AR_B)carbonylalkylene, (NR_AR_B)sulfonyl, and (NR_AR_B)sulfonylalkylene; R₂ is selected from hydrogen, Br, Cl, I, or F;

R_A and R_B are independently selected from the group consisting of hydrogen, C₁-C₆alkyl, C₃-C₈cycloalkyl, and alkylcarbonyl; or R_A and R_B taken together with the atom to which they are attached form a 3-10 membered heterocycle ring optionally having one to three heteroatoms or hetero functionalities selected from the group consisting of -O-, -NH-, -N(C₁-C₆alkyl)-, -NCO(C₁-C₆alkyl)-, -NCO(C₃-C₈cycloalkyl)-, -N(aryl)-, -N(aryl-C₁-C₆alkyl)-, -N(substituted-aryl-C₁-C₆alkyl)-, -N(heteroaryl)-, -N(heteroaryl-C₁-C₆alkyl)-, -N(substituted-heteroaryl-C₁-C₆alkyl)-, and -S- or S(O)_q-, wherein q is 1 or 2 and the 3-10 membered heterocycle ring is optionally substituted with one or more substituents; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0033] In certain embodiments the compounds administered in the methods provided herein are compounds of Formula (I) or a therapeutically acceptable salt thereof, wherein R₁, R₂, R₃ are independently selected from a group consisting of hydrogen, alkyl, and halogen; R₄ is hydrogen and R₅ is selected from the group consisting hydrogen, alkyl, cycloalkyl, alkoxyalkyl, haloalkyl, hydroxyalkylene, and (NR_AR_B)alkylene; R_A and R_B are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, and alkylcarbonyl; or R_A and R_B taken together with the atom to which they are attached form a 3-10 membered heterocycle ring optionally having one to three heteroatoms or hetero functionalities selected from the group consisting of -O-, -NH-, -N(C₁-C₆-alkyl)-, -NCO(C₁-C₆-alkyl)-, -N(aryl)-, -N(aryl-C₁-C₆-alkyl)-, -N(substituted-aryl-C₁-C₆-alkyl)-, -N(heteroaryl)-, -N(heteroaryl-C₁-C₆-alkyl)-, -N(substituted-heteroaryl-C₁-C₆-alkyl)-, and -S- or S(O)_q-, wherein q is 1 or 2 and the 3-10 membered heterocycle ring is optionally substituted with one or more substituents.

[0034] In certain embodiments the compounds administered in the methods provided herein are compounds of Formula (I) wherein Y is an aryl group. In another embodiment the aryl group is a phenyl group. In yet another embodiment the phenyl group is substituted with at least one R₆ selected from Br, Cl, F, or I. In one embodiment R₆ is F. In one embodiment the phenyl group is substituted with at least one R₆ selected from (NR_AR_B)C₁-C₆alkylene, (NR_AR_B)carbonyl, (NR_AR_B)carbonylalkylene, (NR_AR_B)sulfonyl, and (NR_AR_B)sulfonylalkylene. In one embodiment R₆ is (NR_AR_B)C₁-C₆alkylene. In another embodiment C₁-C₆alkyl is selected from methylene, ethylene, n-propylene, iso-propylene, n-butylene, iso-butylene, and tert-butylene. In yet another embodiment C₁-C₆alkyl is methylene. In yet a further embodiment R_A and R_B are each independently hydrogen, C₁-C₆alkyl, or C₃-C₈cycloalkyl. In one embodiment C₁-C₆alkyl is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In one embodiment C₁-C₆alkyl is methyl. In another embodiment C₁-C₆alkyl is ethyl. In yet another embodiment C₃-C₈cycloalkyl is cyclopropyl,

cyclobutyl, cyclopentyl, and cyclohexyl. In a further embodiment C_3 - C_8 cycloalkyl is cyclopropyl. In yet a further embodiment R_6 is hydroxyalkylene. In one embodiment hydroxyalkylene is selected from CH_2OH , CH_2CH_2OH , $CH_2CH_2CH_2OH$, $CH(OH)CH_3$, $CH(OH)CH_2CH_3$, $CH_2CH(OH)CH_3$, and $CH_2CH_2CH_2CH_2OH$. In another embodiment R_A and R_B taken together with the nitrogen to which they are attached form a 6 membered heterocycle ring having 1 heteroatom or hetero functionality selected from the group consisting of -O-, -NH, or -N(C_1 - C_6 alkyl). In yet another embodiment the hetero functionality is -N(C_1 - C_6 alkyl). In a further embodiment C_1 - C_6 alkyl is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In yet a further embodiment C_1 - C_6 alkyl is methyl. In one embodiment Y is a heteroaryl group optionally substituted with at least one R_6 . In another embodiment the heteroaryl group is selected from furan, pyridine, pyrimidine, pyrazine, imidazole, thiazole, isothiazole, pyrazole, triazole, pyrrole, thiophene, oxazole, isoxazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-triazine, indole, benzothiophene, benzoimidazole, benzofuran, pyridazine, 1,3,5-triazine, thienothiophene, quinoxaline, quinoline, and isoquinoline. In yet another embodiment the heteroaryl group is imidazole. In a further embodiment imidazole is substituted with C_1 - C_6 alkyl selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In yet a further embodiment C_1 - C_6 alkyl is methyl. In one embodiment the heteroaryl group is furan. In another embodiment the heteroaryl group is thiazole. In yet another embodiment the heteroaryl group is 1,3,4-oxadiazole. In a further embodiment heteroaryl group is substituted with C_1 - C_6 alkyl selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In yet a further embodiment C_1 - C_6 alkyl is methyl. In one embodiment Z is an aryl group. In another embodiment the aryl group is a phenyl group. In yet another embodiment the phenyl group is substituted with at least one R_6 selected from Br, Cl, F, or I. In a further embodiment R_6 is F. In yet a further embodiment R_6 is Cl. In one embodiment the phenyl group is substituted with at least one R_6 selected from $(NR_AR_B)C_1$ - C_6 alkylene, (NR_AR_B) carbonyl, (NR_AR_B) carbonylalkylene, (NR_AR_B) sulfonyl, and (NR_AR_B) sulfonylalkylene. In another embodiment R_6 is $(NR_AR_B)C_1$ - C_6 alkylene. In yet another embodiment C_1 - C_6 alkyl is selected from methylene, ethylene, n-propylene, iso-propylene, n-butylene, iso-butylene, and tert-butylene. In yet a further embodiment C_1 - C_6 alkyl is methylene. In a further embodiment R_A and R_B are each independently hydrogen, C_1 - C_6 alkyl, or C_3 - C_8 cycloalkyl. In one embodiment C_1 - C_6 alkyl is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In another embodiment C_1 - C_6 alkyl is methyl. In yet another embodiment R_A and R_B taken together with the nitrogen to which they are attached form a 6 membered heterocycle ring having 1 heteroatom or hetero functionality selected from the group consisting of -O-, -NH, or -N(C_1 - C_6 alkyl). In a further embodiment the hetero functionality is -N(C_1 - C_6 alkyl). In one embodiment C_1 - C_6 alkyl is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In yet a further embodiment C_1 - C_6 alkyl is methyl. In one embodiment Z is a heteroaryl group optionally substituted with at least one R_6 . In another embodiment the heteroaryl group is selected from furan, pyridine, pyrimidine, pyrazine, imidazole, thiazole, isothiazole, pyrazole, triazole, pyrrole, thiophene,

oxazole, isoxazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-triazine, indole, benzothiophene, benzoimidazole, benzofuran, pyridazine, 1,3,5-triazine, thienothiophene, quinoxaline, quinoline, and isoquinoline. In yet another embodiment the heteroaryl group is imidazole. In a further embodiment imidazole is substituted with C₁-C₆alkyl selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In yet a further embodiment C₁-C₆alkyl is methyl. In one embodiment the heteroaryl group is furan. In another embodiment the heteroaryl group is thiazole. In yet another embodiment the heteroaryl group is 1,3,4-oxadiazole. In a further embodiment heteroaryl group is substituted with C₁-C₆alkyl selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In yet a further embodiment C₁-C₆alkyl is methyl. In another embodiment R₂ is hydrogen. In yet another embodiment R₂ is selected from F, Cl, Br, and I. In a further embodiment R₂ is F.

[0035] In certain embodiments the compounds administered in the methods provided herein are compounds of Formula (I) wherein A is hydrogen. In another embodiment A is C₁-C₆alkyl. In a further embodiment, A is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, and n-hexyl. In yet another embodiment, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, and n-hexyl are optionally substituted with OH, NO₂, CN, Br, Cl, F, and I. In a further embodiment A is methyl. In yet another embodiment, A is selected from F, Cl, Br, and I. In another embodiment, A is C₃-C₈cycloalkyl. In another embodiment, A is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In one embodiment, A is substituted with OH, NO₂, or CN. In a further embodiment, B is C₁-C₆alkyl. In a further embodiment, B is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, and n-hexyl. In yet another embodiment, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, and n-hexyl are optionally substituted with OH, NO₂, CN, Br, Cl, F, and I. In one embodiment the administered compound is a compound of Formula (I) wherein B is hydrogen. In a further embodiment B is methyl. In yet another embodiment, B is selected from F, Cl, Br, and I. In another embodiment, B is C₃-C₈cycloalkyl. In another embodiment, B is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In one embodiment, A is substituted with OH, NO₂, or CN. In a further embodiment, the administered compound is a compound of Formula (I) wherein A is hydrogen and B is selected from Br, Cl, F, I, C₁-C₆alkyl, C₃-C₈cycloalkyl, alkoxy, alkoxyalkyl wherein C₁-C₆alkyl, C₃-C₈cycloalkyl, alkoxy, alkoxyalkyl are optionally substituted with at least one substituent selected from OH, NO₂, CN, Br, Cl, F, I, C₁-C₆alkyl, and C₃-C₈cycloalkyl. In another embodiment, the administered compound is a compound of Formula (I) wherein B is hydrogen and A is selected from Br, Cl, F, I, C₁-C₆alkyl, C₃-C₈cycloalkyl, alkoxy, alkoxyalkyl wherein C₁-C₆alkyl, C₃-C₈cycloalkyl, alkoxy, alkoxyalkyl are optionally substituted with at least one substituent selected from OH, NO₂, CN, Br, Cl, F, I, C₁-C₆alkyl, and C₃-C₈cycloalkyl. In yet another embodiment, both A and B are hydrogen. In a further embodiment, both A and B are selected from Br, Cl, F, I, C₁-C₆alkyl, C₃-C₈cycloalkyl, alkoxy,

alkoxyalkyl wherein C₁-C₆alkyl, C₃-C₈cycloalkyl, alkoxy, alkoxyalkyl are optionally substituted with at least one substituent selected from OH, NO₂, CN, Br, Cl, F, I, C₁-C₆alkyl, and C₃-C₈cycloalkyl.

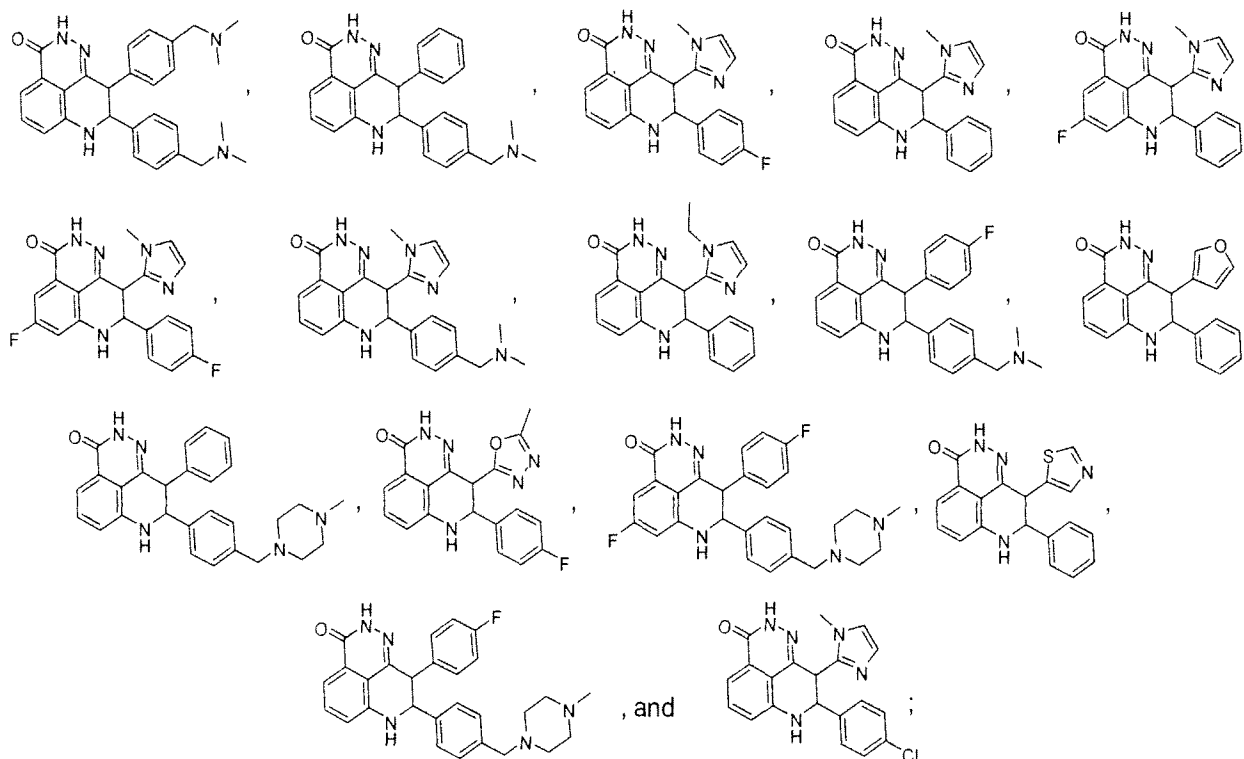
[0036] In certain embodiments the compounds administered in the methods provided herein are compounds of Formula (II) wherein Y is an aryl group. In another embodiment the aryl group is a phenyl group. In yet another embodiment the phenyl group is substituted with at least one R₆ selected from Br, Cl, F, or I. In one embodiment R₆ is F. In one embodiment the phenyl group is substituted with at least one R₆ selected from (NR_AR_B)C₁-C₆alkylene, (NR_AR_B)carbonyl, (NR_AR_B)carbonylalkylene, (NR_AR_B)sulfonyl, and (NR_AR_B)sulfonylalkylene. In one embodiment R₆ is (NR_AR_B)C₁-C₆alkylene. In another embodiment C₁-C₆alkyl is selected from methylene, ethylene, n-propylene, iso-propylene, n-butylene, iso-butylene, and tert-butylene. In yet another embodiment C₁-C₆alkylene is methylene. In yet a further embodiment R_A and R_B are each independently hydrogen, C₁-C₆alkyl, or C₃-C₈cycloalkyl. In one embodiment C₁-C₆alkyl is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In one embodiment C₁-C₆alkyl is methyl. In another embodiment C₁-C₆alkyl is ethyl. In yet another embodiment C₃-C₈cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In a further embodiment C₃-C₈cycloalkyl is cyclopropyl. In yet a further embodiment R₆ is hydroxyalkylene. In one embodiment hydroxyalkylene is selected from CH₂OH, CH₂CH₂OH, CH₂CH₂CH₂OH, CH(OH)CH₃, CH(OH)CH₂CH₃, CH₂CH(OH)CH₃, and CH₂CH₂CH₂CH₂OH. In another embodiment R_A and R_B taken together with the nitrogen to which they are attached form a 6 membered heterocycle ring having 1 heteroatom or hetero functionality selected from the group consisting of -O-, -NH-, or -N(C₁-C₆alkyl). In yet another embodiment the hetero functionality is -N(C₁-C₆alkyl). In a further embodiment C₁-C₆alkyl is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In yet a further embodiment C₁-C₆alkyl is methyl. In one embodiment Y is a heteroaryl group optionally substituted with at least one R₆. In another embodiment the heteroaryl group is selected from furan, pyridine, pyrimidine, pyrazine, imidazole, thiazole, isothiazole, pyrazole, triazole, pyrrole, thiophene, oxazole, isoxazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-triazine, indole, benzothiophene, benzoimidazole, benzofuran, pyridazine, 1,3,5-triazine, thienothiophene, quinoxaline, quinoline, and isoquinoline. In yet another embodiment the heteroaryl group is imidazole. In a further embodiment imidazole is substituted with C₁-C₆alkyl selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In yet a further embodiment C₁-C₆alkyl is methyl. In one embodiment the heteroaryl group is furan. In another embodiment the heteroaryl group is thiazole. In yet another embodiment the heteroaryl group is 1,3,4-oxadiazole. In a further embodiment heteroaryl group is substituted with C₁-C₆alkyl selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In yet a further embodiment C₁-C₆alkyl is methyl. In one embodiment Z is an aryl group. In another embodiment the aryl group is a phenyl group. In yet another embodiment the phenyl group is substituted with at least one R₆ selected from Br, Cl, F, or I. In a further embodiment R₆ is F. In yet a further embodiment R₆

is Cl. In one embodiment the phenyl group is substituted with at least one R_6 selected from $(NR_AR_B)C_1-C_6$ alkylene, (NR_AR_B) carbonyl, (NR_AR_B) carbonylalkylene, (NR_AR_B) sulfonyl, and (NR_AR_B) sulfonylalkylene. In another embodiment R_6 is $(NR_AR_B)C_1-C_6$ alkylene. In yet another embodiment C_1-C_6 alkylene is selected from methylene, ethylene, n-propylene, iso-propylene, n-butylene, iso-butylene, and tert-butylene. In yet a further embodiment C_1-C_6 alkyl is methylene. In a further embodiment R_A and R_B are each independently hydrogen, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl. In one embodiment C_1-C_6 alkyl is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In another embodiment C_1-C_6 alkyl is methyl. In yet another embodiment R_A and R_B taken together with the nitrogen to which they are attached form a 6 membered heterocycle ring having 1 heteroatom or hetero functionality selected from the group consisting of -O-, -NH, or -N(C_1-C_6 alkyl). In a further embodiment the hetero functionality is -N(C_1-C_6 alkyl). In one embodiment C_1-C_6 alkyl is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl. In yet a further embodiment C_1-C_6 alkyl is methyl. In another embodiment R_2 is hydrogen. In yet another embodiment R_2 is selected from F, Cl, Br, and I. In a further embodiment R_2 is F.

[0037] In certain embodiments the compounds administered in the methods provided herein are compounds of Formula (II) wherein A is hydrogen. In another embodiment A is C_1-C_6 alkyl. In a further embodiment, A is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, and n-hexyl. In yet another embodiment, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, and n-hexyl are optionally substituted with OH, NO_2 , CN, Br, Cl, F, and I. In a further embodiment A is methyl. In yet another embodiment, A is selected from F, Cl, Br, and I. In another embodiment, A is C_3-C_8 cycloalkyl. In another embodiment, A is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In one embodiment, A is substituted with OH, NO_2 , or CN. In one embodiment, the administered compound is of Formula (II) wherein B is hydrogen. In a further embodiment, B is C_1-C_6 alkyl. In a further embodiment, B is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, and n-hexyl. In yet another embodiment, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, and n-hexyl are optionally substituted with OH, NO_2 , CN, Br, Cl, F, and I. In a further embodiment B is methyl. In yet another embodiment, B is selected from F, Cl, Br, and I. In another embodiment, B is C_3-C_8 cycloalkyl. In another embodiment, B is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In one embodiment, A is substituted with OH, NO_2 , or CN. In a further embodiment, the administered compound is a compound of Formula (II) wherein A is hydrogen and B is selected from Br, Cl, F, I, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, alkoxy, alkoxyalkyl wherein C_1-C_6 alkyl, C_3-C_8 cycloalkyl, alkoxy, alkoxyalkyl are optionally substituted with at least one substituent selected from OH, NO_2 , CN, Br, Cl, F, I, C_1-C_6 alkyl, and C_3-C_8 cycloalkyl. In another embodiment, the administered compound is a compound of Formula (II) wherein B is hydrogen and A is selected from Br, Cl, F, I, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, alkoxy, alkoxyalkyl wherein C_1-C_6 alkyl, C_3-C_8 cycloalkyl, alkoxy, alkoxyalkyl are optionally

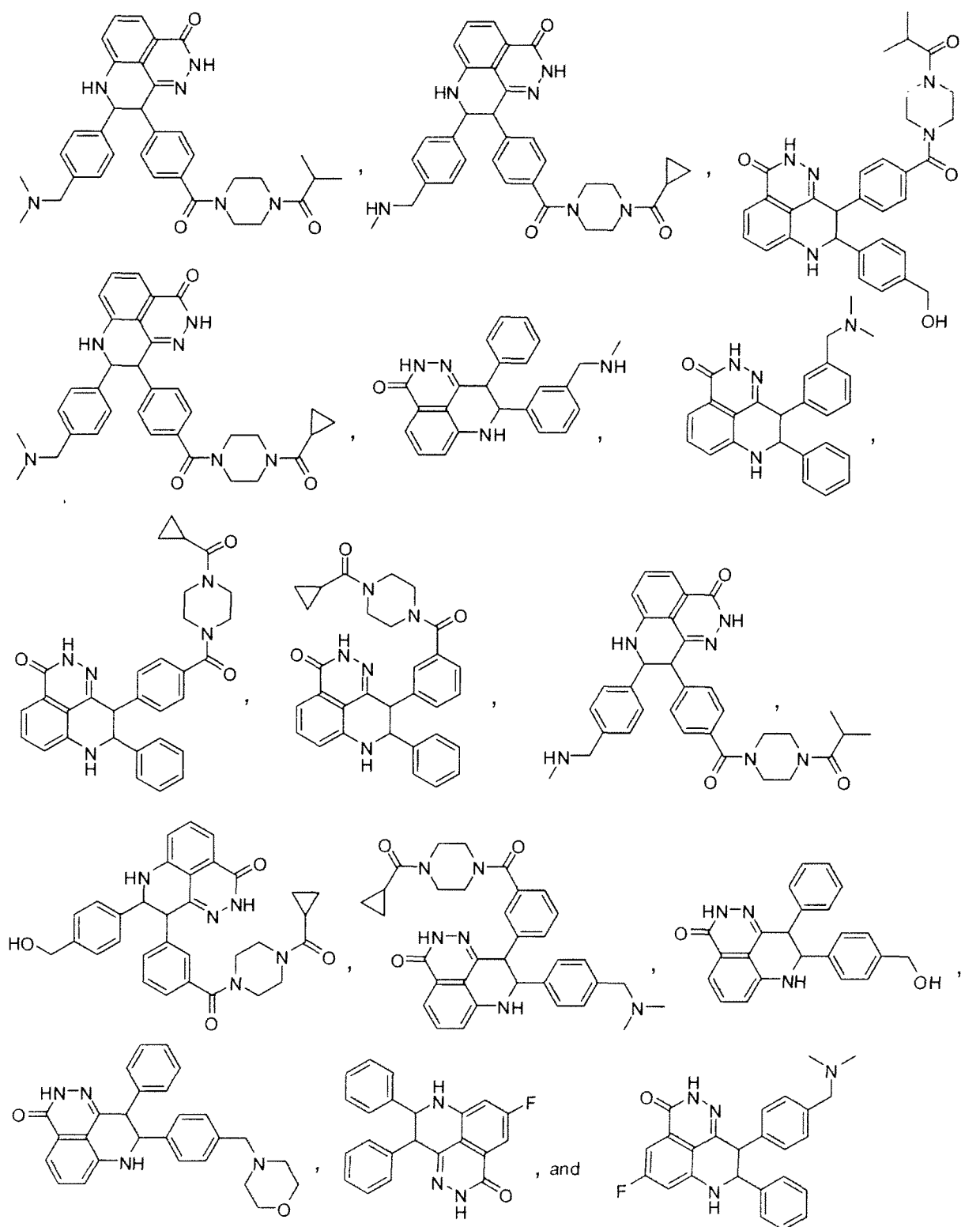
substituted with at least one substituent selected from OH, NO₂, CN, Br, Cl, F, I, C₁-C₆alkyl, and C₃-C₈cycloalkyl. In yet another embodiment, both A and B are hydrogen. In a further embodiment, both A and B are selected from Br, Cl, F, I, C₁-C₆alkyl, C₃-C₈cycloalkyl, alkoxy, alkoxyalkyl wherein C₁-C₆alkyl, C₃-C₈cycloalkyl, alkoxy, alkoxyalkyl are optionally substituted with at least one substituent selected from OH, NO₂, CN, Br, Cl, F, I, C₁-C₆alkyl, and C₃-C₈cycloalkyl.

[0038] In certain embodiments the compound administered in the methods provided herein is a compound selected from:



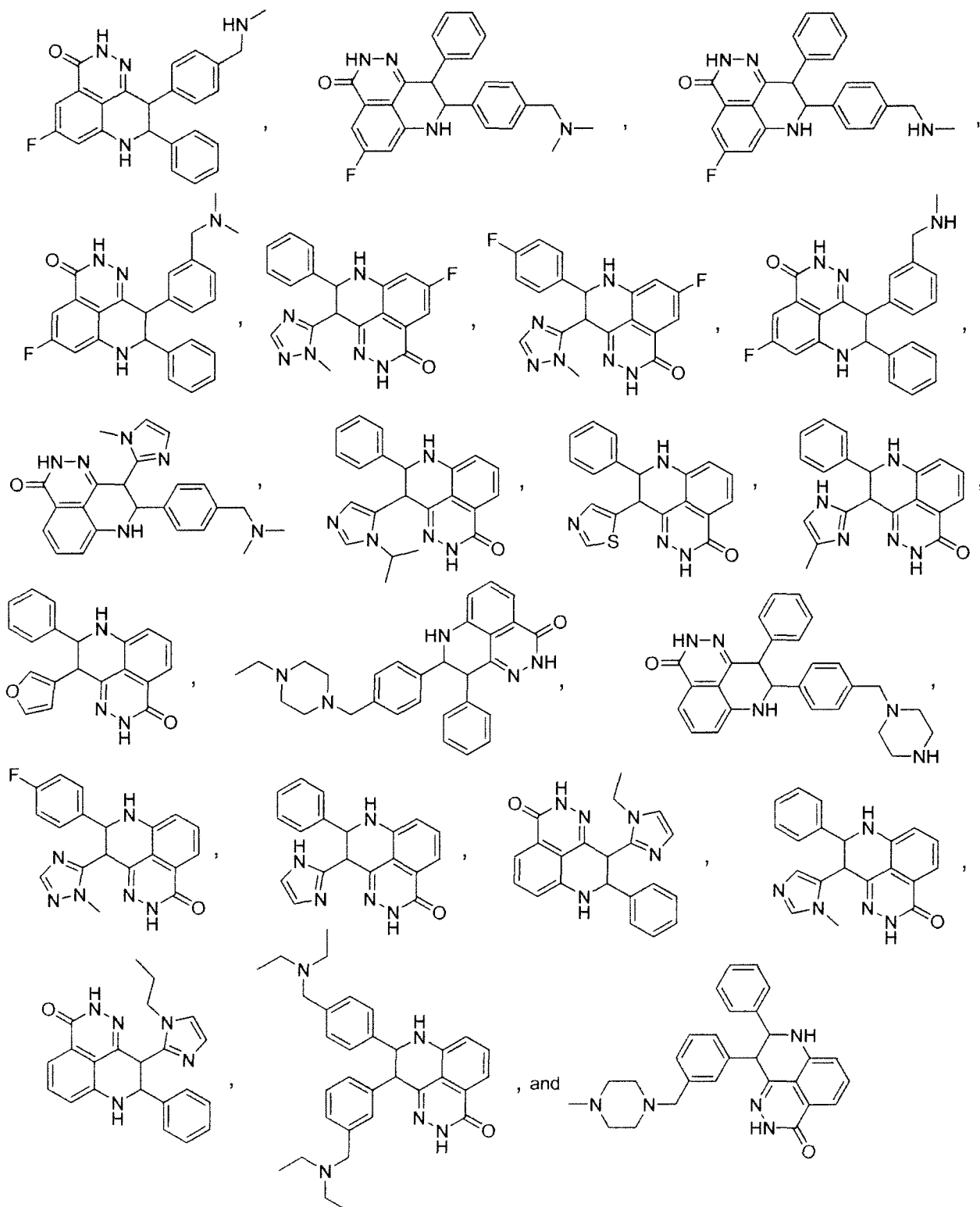
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0039] In certain embodiments the compound administered in the methods provided herein is a compound selected from:

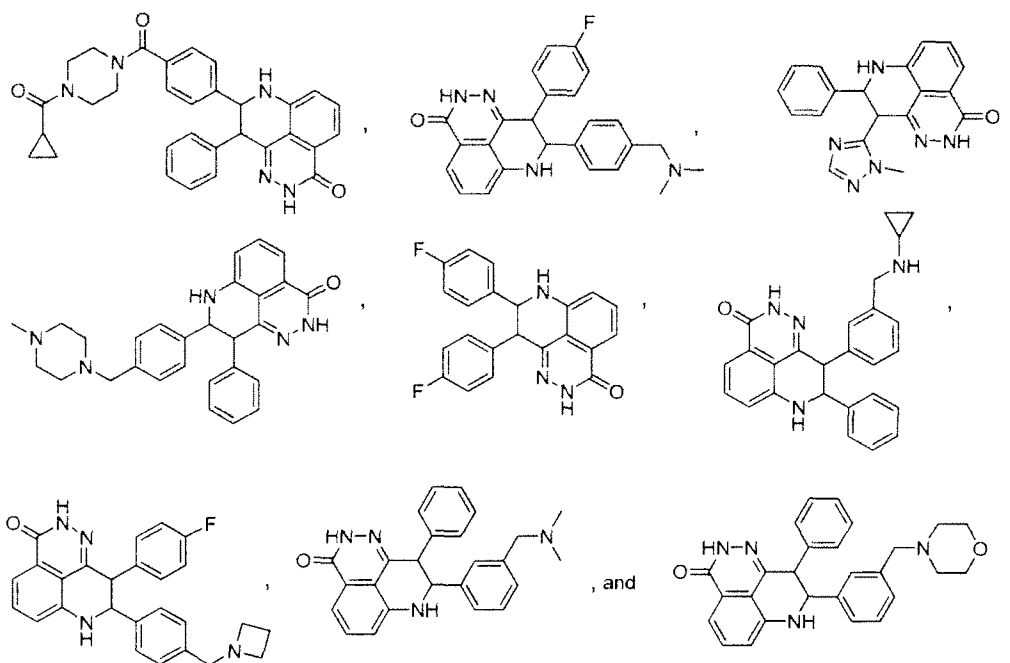


or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0040] In certain embodiments the compound administered in the methods provided herein is a compound selected from:



[0041] In certain embodiments the compound administered in the methods provided herein is a compound selected from:



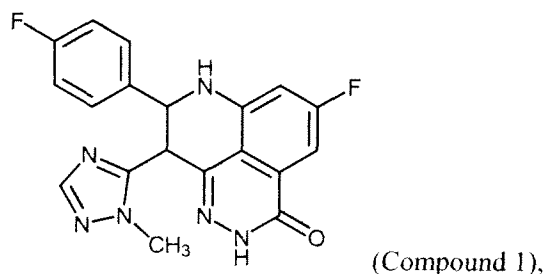
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0042] In certain embodiments the compound administered in the methods provided herein is a compound selected from:

(8*S*,9*R*)-5-fluoro-9-(1-methyl-1*H*-imidazol-2-yl)-8-phenyl-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*R*,9*S*)-5-fluoro-9-(1-methyl-1*H*-imidazol-2-yl)-8-phenyl-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-imidazol-2-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*R*,9*S*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-imidazol-2-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*S*,9*R*)-8-(4-fluorophenyl)-9-(1-methyl-1*H*-imidazol-2-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*R*,9*S*)-8-(4-fluorophenyl)-9-(1-methyl-1*H*-imidazol-2-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*S*,9*R*)-5-fluoro-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8-phenyl-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*R*,9*S*)-5-fluoro-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8-phenyl-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,

(8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*R*,9*S*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*S*,9*R*)-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*R*,9*S*)-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*R*,9*S*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*S*,9*R*)-8-(4-((dimethylamino)methyl)phenyl)-5-fluoro-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one, and
 (8*R*,9*S*)-8-(4-((dimethylamino)methyl)phenyl)-5-fluoro-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0043] In certain embodiments the compound administered in the methods provided herein is of the following formula:



or a pharmaceutically acceptable salt thereof.

[0044] In certain embodiments, the compound administered in the methods provided herein is 5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one (Compound 1), or a pharmaceutically acceptable salt thereof.

[0045] In certain embodiments, the compound administered in the methods provided herein is selected from the group consisting of:

(8*S*,9*R*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,
 (8*R*,9*S*)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one,

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0046] In certain embodiments, the compound administered in the methods provided herein is (8S,9R)-5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one, or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0047] In certain embodiments, the compounds envisioned to be administered in the methods provided herein are disclosed in International Patent Publication No. WO 2010/017055 A2, which is incorporated by reference in its entirety in the instant application. Additional compounds are disclosed in International Patent Publication No. WO 2010/017055 A2.

Methods of Treatment

[0048] Provided herein are methods of treating cancer comprising administering to a subject in need of treatment a therapeutically effective amount of a compound that is a modulator of PARP activity. In certain embodiments, the methods comprise administering to a subject in need of treatment a therapeutically effective amount of a PARP inhibitor, such as, for example, a compound of Formula (I) or (II). In certain embodiments, the cancer is leukemia. In certain embodiments, the cancer is Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML). In certain embodiments, the subject is a patient with MDS or AML. In certain embodiments, the cancer is AML.

[0049] Accordingly, in one aspect, described herein is a method of treating Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) in a patient with MDS or AML, comprising administering to a patient with MDS or AML a therapeutically effective amount of a compound of Formula (I). In certain embodiments, described herein is a method of treating Acute Myeloid Leukemia (AML) in a patient with AML, comprising administering to a patient with AML a therapeutically effective amount of a compound of Formula (I).

[0050] In one embodiment, a compound of Formula (I) or (II) is used for the treatment of MDS or AML in a patient with MDS or AML, or for the preparation of a medicament for the treatment of MDS or AML in a patient with MDS or AML. In one embodiment, a compound of Formula (I) or (II) is used for the treatment of AML in a patient with AML, or for the preparation of a medicament for the treatment of AML in a patient with AML.

[0051] Accordingly, in yet another aspect is a method of treating a cancer deficient in Homologous Recombination (HR) dependent DNA double strand break (DSB) repair pathway, comprising administering to a subject in need of treatment a therapeutically effective amount of a PARP inhibitor, such as, for example, a compound of Formula (I) or (II).

[0052] In one embodiment, a compound of Formula (I) or (II) is used for the treatment of cancer, or for the preparation of a medicament for the treatment of cancer, which is deficient in HR dependent DNA DSB repair activity.

[0053] In one embodiment the cancer comprises one or more cancer cells having a reduced or abrogated ability to repair DNA DSB by HR relative to normal cells. In another embodiment the subject is heterozygous for a mutation in a gene encoding a component of the HR dependent DNA DSB repair pathway. In one embodiment the cancer is leukemia. In one embodiment the cancer is Acute Myeloid Leukemia (AML). In another embodiment the cancer is Myelodysplastic Syndrome (MDS). In another embodiment the treatment further comprises administration of ionizing radiation or a chemotherapeutic agent.

[0054] The HR dependent DNA DSB repair pathway repairs double-strand breaks (DSBs) in DNA via homologous mechanisms to reform a continuous DNA helix. The components of the HR dependent DNA DSB repair pathway include, but are not limited to, ATM (NM_000051), ATR (NM_001184), CTIP (NM_002894), BLM (NM_000057), RAD51 (NM_002875), RAD51L1 (NM_002877), RAD51C (NM_002876), RAD51L3 (NM_002878), DMC1 (NM_007068), XRCC2 (NM_005431), XRCC3 (NM_005432), RAD52 (NM_002879), RAD54L (NM_003579), RAD54B (NM_012415), BRCA1 (NM_007295), BRCA2 (NM_000059), RAD50 (NM_005732), MRE11A (NM_005590) and NBS1 (NM_002485). Other proteins involved in the HR dependent DNA DSB repair pathway include regulatory factors such as EMSY. HR components are also described in Wood, *et al.*, *Science*, 291, 1284-1289 (2001), which is hereby incorporated by reference for such disclosure. K. K. Khanna and S. P. Jackson, *Nat. Genet.* 27(3): 247-254 (2001); and Hughes-Davies, *et al.*, *Cell*, 115, pp 523-535 are also incorporated herein by reference for such disclosure.

[0055] In some embodiments, a cancer which is deficient in HR dependent DNA DSB repair includes one or more cancer cells which have a reduced or abrogated ability to repair DNA DSBs through that pathway, relative to normal cells, *i.e.* the activity of the HR dependent DNA DSB repair pathway are reduced or abolished in the one or more cancer cells.

[0056] In certain embodiments, the activity of one or more components of the HR dependent DNA DSB repair pathway is abolished in the one or more cancer cells of an individual having a cancer which is deficient in HR dependent DNA DSB repair. Components of the HR dependent DNA DSB repair pathway include the components listed above.

[0057] In yet another aspect is a method of treating a cancer deficient in DNA mismatch repair (MMR), comprising administering to a subject in need of treatment a therapeutically effective amount of a PARP inhibitor, such as, for example, a compound of Formula (I) or (II).

[0058] In one embodiment, a compound of Formula (I) or (II) is used for the treatment of a cancer deficient in MMR, or for the preparation of a medicament for the treatment of a cancer deficient in MMR, which is deficient in HR dependent DNA DSB repair activity.

[0059] The primary function of the DNA mismatch repair (MMR) system is to eliminate single-base mismatches and insertion-deletion loops that may arise during DNA replication. Insertion-deletion loops result from gains or losses of short repeat units within microsatellite sequences, also known as Microsatellite Instability (MSI). At least six different MMR proteins are required. For mismatch recognition, the MSH2 protein forms a heterodimer with either MSH6 or MSH3 depending on the type of lesion to be repaired (MSH6 is required for the correction of single-base mispairs, whereas both MSH3 and MSH6 may contribute to the correction of insertion-deletion loops). A heterodimer of MLH1 and PMS2 coordinates the interplay between the mismatch recognition complex and other proteins necessary for MMR. These additional proteins may include at least exonuclease 1 (EXO1), possibly helicase(s), proliferating cell nuclear antigen (PCNA), single-stranded DNA-binding protein (RPA), and DNA polymerases δ and ϵ . In addition to PMS2, MLH1 may heterodimerize with two additional proteins, MLH3 and PMS1. Recent observations indicate that PMS2 is required for the correction of single-base mismatches, and PMS2 and MLH3 both contribute to the correction of insertion-deletion loops. Additional homologs of the human MMR proteins are known that are required for functions other than MMR. These proteins include MSH4 and MSH5 that are necessary for meiotic (and possibly mitotic) recombination but are not presumed to participate in MMR.

[0060] Germline mutations of human MMR genes cause susceptibility to hereditary nonpolyposis colon cancer (HNPCC), one of the most common cancer syndromes in humans. An excess of colon cancer and a defined spectrum of extracolonic cancers, diagnosed at an early age and transmitted as an autosomal dominant trait, constitute the clinical definition of the syndrome. MSI, the hallmark of HNPCC, occurs in approximately 15% to 25% of sporadic tumors of the colorectum and other organs as well. According to international criteria, a high degree of MSI (MSI-high) is defined as instability at two or more of five loci or $\geq 30\%$ to 40% of all microsatellite loci studied, whereas instability at fewer loci is referred to as MSI-low (MSI-low). MSI occurs in a substantial proportion (2% to 50% of tumors) among non-HNPCC cancers (*e.g.*, cancers of the breast, prostate, and lung). On the basis of the proportion of unstable markers, categories MSS, MSI-L, and MSI-H can be distinguished in these cancers in analogy to HNPCC cancers. In one embodiment is a method for treating a cancer deficient in mismatch DNA repair pathway. In another embodiment is a method for treating a cancer demonstrating microsatellite instability due to reduced or impaired DNA repair pathways. In another embodiment is a method for treating a cancer demonstrating genomic instability due to reduced or impaired DNA repair pathways.

[0061] The role of nuclear PTEN in the maintenance of chromosomal stability has also been demonstrated in both mouse and human systems (Shen *et al.*, *Cell* 128:157-170 (2007)). First, PTEN interacts with centromeres and maintains their stability. It is believed that PTEN does so through its C2 domain, as mutant PTEN without this C2 domain loses the capability to interact with centromeres. Second, PTEN may be necessary for DNA repair because loss of PTEN results in a high frequency of double-strand breaks. PTEN affects double-strand breaks through regulation of Rad51, a key component for homologous recombination repair of DNA double-strand breaks. It has also been demonstrated that PTEN physically associates with an integral component of centromeres in the nucleus, disruption of which causes centromere breakage and massive chromosomal aberrations (Shen *et al.*, *Cell* 128:157-170 (2007)).

[0062] A list of human DNA repair genes associated with the HR dependent DNA DSB repair and MMR repair pathways described above, and additional DNA repair pathways, such as Base Excision Repair (BER) and Nucleotide Excision Repair (NER) pathways, is disclosed in, *e.g.*, Wood *et al.*, *Science*, 291, 1294 (2001), updated in Wood *et al.*, *Mutation Res.*, 577, 275 (2005), each of which is hereby incorporated herein by reference in its entirety. The protein sequences for the protein products of these DNA repair genes will be known by one of skill in the art, and are disclosed at publicly-available databases as, *e.g.*, GenPept, RefSeq, Swiss-Prot, PIR, PRF, and PDB, such as those found at the website for the National Center for Biotechnology Information (NCBI) (*see* www.ncbi.nlm.nih.gov).

[0063] In certain embodiments, the patient's malignant cell DNA exhibits Microsatellite Instability (MSI) in a microsatellite, wherein MSI is explained in the Definition section of the instant application. In certain embodiments, the patient's malignant cell DNA exhibits MSI in at least two microsatellites.

[0064] Microsatellites in which MSI is exhibited can include, for example, any microsatellite known to those of skill in the art. Such microsatellites can include, for example, those identified in U.S. Patent No. 6,150,100, and U.S. Patent Publication No. 2009/0317815, each of which is incorporated herein by reference in its entirety for all purposes. In certain embodiments, a microsatellite in which MSI is exhibited is *NR21*, *NR22*, *NR24*, *Bat25*, *Bat26*, *Mono27* and/or a microsatellite as described herein in the DNA repair genes *CTiP*, *Mre11*, *ATM*, *Rad50*, *Chk1*, *BLM*, *PTEN*, *ATM* and *ATR*. In certain embodiments, the microsatellite is *NR21*, *NR22*, *Bat25*, *Bat26*, *Mono27*, or a microsatellite as described herein in the DNA repair genes *CTiP*, *Mre11* and *ATM*.

[0065] In certain instances, mutations and polymorphisms associated with cancer are detected at the nucleic acid level by detecting the presence of a variant nucleic acid sequence or at the protein level by detecting the presence of a variant (*i.e.*, a mutant or allelic variant) polypeptide.

[0066] In certain embodiments, the methods comprise administering to a subject in need of treatment a therapeutically effective amount of a compound of Formula (I) and Formula (II) in combination with ionizing radiation, one or more chemotherapeutic agents, or a combination thereof.

[0067] Certain embodiments provide a method of potentiation of cytotoxic cancer therapy of MDS or AML in a subject in recognized need of such treatment comprising administering to the subject a therapeutically acceptable amount of a compound of Formula (I) or (II) or a therapeutically acceptable salt thereof.

[0068] In some embodiments, provided herein is a method for the treatment of MDS or AML, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound of Formula (I) or (II) in combination with ionizing radiation or one or more chemotherapeutic agents. In some embodiments, the subject is a patient with MDS or AML. In some embodiments, the compound described herein is administered simultaneously with ionizing radiation or one or more chemotherapeutic agents. In other embodiments, the compound described herein is administered sequentially with ionizing radiation or one or more chemotherapeutic agents.

[0069] In certain embodiments, the one or more chemotherapeutic agents are selected from among alemtuzumab, arsenic trioxide, asparaginase (pegylated or non-), bevacizumab, cetuximab, platinum-based compounds such as cisplatin, cladribine, daunorubicin/doxorubicin/idarubicin, irinotecan, fludarabine, 5-fluorouracil, gemtuzumab, methotrexate, paclitaxel, Taxol®, temozolomide, thioguanine, and classes of drugs including hormones (an antiestrogen, an antiandrogen, or gonadotropin releasing hormone analogues, interferons such as, for example, alpha interferon, nitrogen mustards such as, for example, busulfan, melphalan or mechlorethamine, retinoids such as, for example, tretinoin, topoisomerase inhibitors such as, for example, irinotecan or topotecan, tyrosine kinase inhibitors such as, for example, gefinitinib or imatinib, and agents to treat signs or symptoms induced by such therapy including allopurinol, filgrastim, granisetron/ondansetron/palonosetron, and dronabinol.

[0070] In certain embodiments, the one or more chemotherapeutic agents are selected from: alkylating agents, such as methyl methanesulfonate (MMS), temozolomide and dacarbazine (DTIC); topoisomerase-I inhibitors, such as Topotecan, Irinotecan, Rubitecan, Exatecan, Lurtotecan, Gimetecan, Diflomotecan (homocamptothecins), the 7-substituted non-silatecans, the 7-silyl camptothecins and BNP 1350; non-camptothecin topoisomerase-I inhibitors, such as indolocarbazoles; and dual topoisomerase-I and II inhibitors, such as the benzophenazines, XR 11576/MLN 576 and benzopyrindolindoles.

Methods of Identifying an MDS or AML Patient Likely to Respond to Treatment

[0071] In one aspect, provided herein are methods of identifying malignant cells having MSI in an MDS or AML patient which comprise analyzing for MSI in one or more microsatellites of a

patient's malignant cell DNA, wherein the presence of MSI in at least one microsatellite of the patient's malignant cell DNA identifies the patient as likely to be sensitive to therapy with a compound of Formula I or II.

[0072] In certain embodiments, the compound of Formula I or II is 5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-8,9-dihydro-2H-pyrido[4,3,2-de]phthalazin-3(7H)-one, or a stereoisomer thereof.

[0073] In certain embodiments, the methods comprise analyzing for MSI in at least one microsatellite of the patient's malignant cell DNA. In certain embodiments, the methods comprise analyzing for MSI in at least two microsatellites of the patient's malignant cell DNA. In certain embodiments, the methods comprise analyzing for MSI in at least three microsatellites of the patient's malignant cell DNA.

[0074] As explained in the Definition section of the instant application, MSI comprises an insertion or deletion of one or more base pairs in a microsatellite of a patient's malignant cell DNA. Accordingly, in certain embodiments, the MSI comprises one or more deleted base pairs; two or more deleted base pairs; or three or more deleted base pairs in the microsatellite(s) of the patient's malignant cell DNA.

[0075] As further explained in the Definition section of the instant application, low-level MSI (MSI-low) is defined as a 1 base pair (bp) deletion or insertion in a microsatellite; mid-level MSI (MSI-mid) is defined as ≥ 2 bp deletion or insertion in a microsatellite; high-level MSI (MSI-high) is defined as a ≥ 3 bp deletion or insertion in a microsatellite; and MSI stable (MSI-stable) is defined as no deletion or insertion in a microsatellite. Accordingly, in certain embodiments, the MSI may be MSI-low. In other embodiments, the MSI may be MSI-mid. In still further embodiments, the MSI may be MSI-high.

[0076] The methods disclosed herein envision that the presence of low-, mid- or high-level MSI in just one microsatellite of the patient's genomic DNA will identify a patient as likely to respond to therapy with a compound of Formula I or II. However, the presence of MSI (low-, mid- or high-) in additional microsatellites of the patient's DNA may also be helpful in such patient identification. Accordingly, in certain embodiments, the presence of MSI in at least one microsatellite of the patient's malignant cell DNA identifies the patient as likely to respond to therapy with a compound of Formula I or II. In certain embodiments, the presence of MSI in at least two microsatellites of the patient's malignant cell DNA identifies the patient as likely to respond to therapy with a compound of Formula I or II. In certain embodiments, the presence of MSI in at least three microsatellites of the patient's malignant cell DNA identifies the patient as likely to respond to therapy with a compound of Formula I or II.

[0077] The presence or absence of MSI within microsatellites in malignant cell DNA may be assessed using methods well known of those of skill in the art. For instance, a fluorescent multiplex assay that uses a panel of markers to analyze five nearly monomorphic mononucleotide microsatellite loci (*NR21*, *NR24*, *Bat25*, *Bat26* and *Mono27*) is commercially available from Promega Corp (Madison, WI). See also e.g., Nardon *et al.*, *Diagn. Mol. Pathol.*, 19(4), 236-242 (2010); Bacher *et al.*, *Dis. Markers*, 20 (4-5), 237-250 (2004); and U.S. Patent Publication No. 2009/0317815.

DEFINITIONS

[0078] Unless defined otherwise, all technical and scientific terms used herein have the standard meaning pertaining to the claimed subject matter belongs. In the event that there are a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

[0079] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not limiting.

[0080] Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed. Unless specific definitions are provided, the standard nomenclature employed in connection with, and the standard laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry are employed. In certain instances, standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. In certain embodiments, standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). In some embodiments, reactions and purification techniques are performed e.g., using kits of manufacturer's specifications or as commonly accomplished or as described herein.

[0081] As used throughout this application and the appended claims, the following terms have the following meanings:

[0082] The term “microsatellite” as used herein means repeating sequences of 1-6 base pairs of DNA, and includes those DNA sequences known in the art as simple sequence repeats (SSR), short

tandem repeats (STR), or variable number tandem repeats (VNTR). The repeated sequence may consist, *e.g.*, of a sequence of one, two, three, four, five or six nucleotides (mono-, di-, tri-, tetra-, penta-, and hexa-nucleotide repeats, respectively), and can, for instance, be repeated 3 to 100 times. *See, e.g.*, Eckert *et al.*, *Mol Carcinog*, 48(4), 379-388 (2009). In certain embodiments, the microsatellite is a mononucleotide repeat sequence, *e.g.*, TTTTTTTTTT (SEQ ID NO. 1), referred to as (T)₉; TTTTTTTTTTTT (SEQ ID NO. 2), referred to as (T)₁₁; TTTTTTTTTTTTTTTT (SEQ ID NO. 3), referred to as (T)₁₅; TTTTTTTTTTTTTTTTTTTT (SEQ ID NO. 4), referred to as (T)₂₁; and AAAAAAAAAAAAAAAAAAAAAAAAAA (SEQ ID NO. 5), referred to as (A)₂₇. In certain embodiments, the microsatellite is a dinucleotide repeat sequence, *e.g.*, GTGTGTGTGTGT (SEQ ID NO. 6), referred to as (GT)₆. In certain embodiments, the microsatellite is a trinucleotide repeat sequence, *e.g.*, CTGCTGCTGCTG (SEQ ID NO. 7), referred to as (CTG)₄. In certain embodiments, the microsatellite is a tetranucleotide repeat sequence, *e.g.*, ACTCACTCACTCACTC (SEQ ID NO. 8), referred to as (ACTC)₄. In certain embodiments, the microsatellite is a monomorphic, or nearly monomorphic, mononucleotide repeat (*e.g.*, *NR21*, *NR24*, *Bat25*, *Bat26* and *Mono27*). For example, a microsatellite may contain one or up to six or seven, or more, nucleotides that interrupt the repeat sequence within the microsatellite.

[0083] Those of skill in the art recognize microsatellites are typically present in human genomic DNA. In certain embodiments, the microsatellite is located within a gene, *e.g.*, a DNA repair gene. In certain embodiments, the microsatellite can, *e.g.*, be located within the following genes: ATM (NM_000051), ATR (NM_001184), CTIP (NM_002894), BLM (NM_000057), RAD51 (NM_002875), RAD51L1 (NM_002877), RAD51C (NM_002876), RAD51L3 (NM_002878), DMC1 (NM_007068), XRCC2 (NM_005431), XRCC3 (NM_005432), RAD52 (NM_002879), RAD54L (NM_003579), RAD54B (NM_012415), BRCA1 (NM_007295), BRCA2 (NM_000059), RAD50 (NM_005732), MRE11A (NM_005590) or NBS1 (NM_002485), among others.

[0084] In certain embodiments, the microsatellite is located within the intron/exon splice junction of a gene. In certain embodiments, the microsatellite is located within the intron of a gene. In certain embodiments, the microsatellite is located within the exon of a gene. In certain embodiments, the microsatellite is located within one of the control elements of a gene, *e.g.*, the promoter of the gene. In certain embodiments, the gene is a DNA repair gene. In certain embodiments, the gene is other than a DNA repair gene. In certain embodiments, the microsatellite is located outside of a gene.

[0085] The term “Microsatellite Instability” (MSI) as used herein, means an alteration in a microsatellite found in human genomic DNA, *e.g.*, an insertion or deletion of one or more base pairs, as compared to a reference microsatellite. For instance, an MSI may be characterized such that the microsatellite length or repeat sequence is different than that, for instance, which was in the genomic DNA when it was inherited, or, for instance, as compared to the microsatellite length or repeat

sequence in the general human population. In certain embodiments, a reference microsatellite is found in the genome of a cell from a human not having MDS or AML, or cells from a population of humans characterized as being cancer free. As used herein, low-level MSI (MSI-low) is defined as 1 base pair (bp) deletion or insertion in a microsatellite; mid-level MSI (MSI-mid) is defined as ≥ 2 bp deletion or insertion in a microsatellite; high-level MSI (MSI-high) is defined as a ≥ 3 bp deletion or insertion in a microsatellite; and MSI stable (MSI-stable) is defined as no deletion or insertion in a microsatellite.

[0086] The term “alkenyl” as used herein, means a straight, branched chain, or cyclic (in which case, it would also be known as a “cycloalkenyl”) hydrocarbon containing from 2-10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. In some embodiments, depending on the structure, an alkenyl group is a monoradical or a diradical (*i.e.*, an alkenylene group). In some embodiments, alkenyl groups are optionally substituted. Illustrative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-ecenyl.

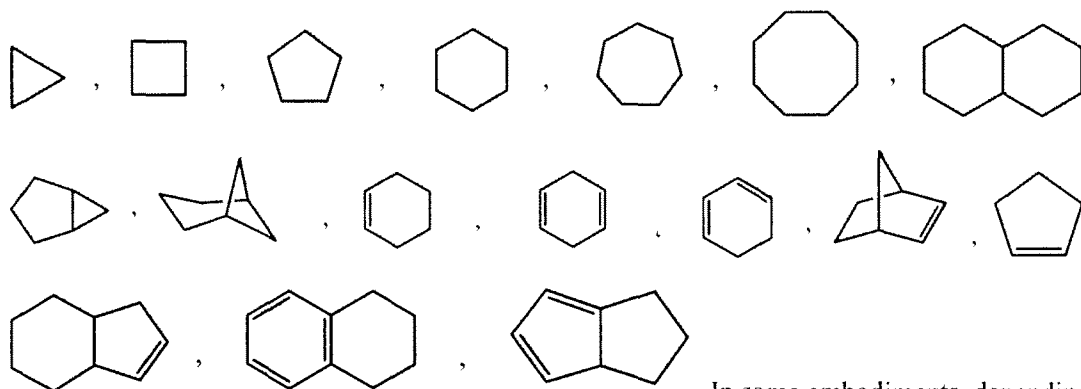
[0087] The term “alkoxy” as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Illustrative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy.

[0088] The term “alkyl” as used herein, means a straight, branched chain, or cyclic (in this case, it would also be known as “cycloalkyl”) hydrocarbon containing from 1-10 carbon atoms. Illustrative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylhexyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

[0089] The term “C₁-C₆-alkyl” as used herein, means a straight, branched chain, or cyclic (in this case, it would also be known as “cycloalkyl”) hydrocarbon containing from 1-6 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, cyclopentyl, n-butyl, sec-butyl, tert-butyl, cyclobutyl, n-pentyl, isopentyl, neopentyl, cyclopentyl, and n-hexyl.

[0090] The term “cycloalkyl” as used herein, means a monocyclic or polycyclic radical that contains only carbon and hydrogen, and includes those that are saturated, partially unsaturated, or fully unsaturated. Cycloalkyl groups include groups having from 3 to 10 ring atoms. Representative examples of cyclic include but are not limited to, the following moieties:





. In some embodiments, depending on the structure, a cycloalkyl group is a monoradical or a diradical (e.g., a cycloalkylene group).

[0091] The term “cycloalkyl groups” as used herein refers to groups which are optionally substituted with 1, 2, 3, or 4 substituents selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylthio, alkylthioalkyl, alkynyl, carboxy, cyano, formyl, haloalkoxy, haloalkyl, halogen, hydroxyl, hydroxyalkylene, mercapto, oxo, -NR_AR_A, and (NR_AR_B)carbonyl.

[0092] The term “cycloalkylalkyl” as used herein, means a cycloalkyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of cycloalkylalkyl include, but are not limited to, cyclopropylmethyl, 2-cyclobutylethyl, cyclopentylmethyl, cyclohexylmethyl, and 4-cycloheptylbutyl.

[0093] The term “carbocyclic” as used herein, refers to a compound which contains one or more covalently closed ring structures, and that the atoms forming the backbone of the ring are all carbon atoms.

[0094] The term “carbocycle” as used herein, refers to a ring, wherein each of the atoms forming the ring is a carbon atom. Carbocyclic rings include those formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Carbocycles are optionally substituted.

[0095] The term “alkoxyalkyl” as used herein, means at least one alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Illustrative examples of alkoxyalkyl include, but are not limited to, 2-methoxyethyl, 2-ethoxyethyl, tert-butoxyethyl and methoxymethyl.

[0096] The term “alkoxycarbonyl” as used herein, means an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Illustrative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, and tert-butoxycarbonyl.

[0097] The term “alkoxycarbonylalkyl” as used herein, means an alkoxycarbonyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

[0098] The term “alkylcarbonyl” as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Illustrative examples of alkylcarbonyl include, but are not limited to, acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, and 1-oxopentyl.

[0099] The term “alkylcarbonyloxy” as used herein, means an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Illustrative examples of alkylcarbonyloxy include, but are not limited to, acetyloxy, ethylcarbonyloxy, and tert-butylcarbonyloxy.

[0100] The term “alkylthio” or “thioalkoxy” as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfur atom. Illustrative examples of alkylthio include, but are not limited to, methylthio, ethylthio, butylthio, tert-butylthio, and hexylthio.

[0101] The term “alkylthioalkyl” as used herein, means an alkylthio group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Illustrative examples of alkylthioalkyl include, but are not limited to, methylthiomethyl, 2-(ethylthio)ethyl, butylthiomethyl, and hexylthioethyl.

[0102] The term “alkynyl” as used herein, means a straight, branched chain hydrocarbon containing from 2-10 carbons and containing at least one carbon-carbon triple bond. In some embodiments, alkynyl groups are optionally substituted. Illustrative examples of alkynyl include, but are not limited to, acetylenyl, 1-propynyl, 2-propynyl, 3-butyne, 2-pentyne, and 1-butyne.

[0103] The term “aromatic” as used herein, refers to a planar ring having a delocalized π -electron system containing $4n+2$ π electrons, where n is an integer. In some embodiments, aromatic rings are formed by five, six, seven, eight, nine, or more than nine atoms. In other embodiments, aromatics are optionally substituted. The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

[0104] The term “aryl” as used herein, refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. In some embodiments, aryl rings are formed by five, six, seven, eight, nine, or more than nine carbon atoms. Examples of aryl groups include, but are not limited to phenyl, naphthalenyl, phenanthrenyl, anthracenyl, fluorenyl, and indenyl.

[0105] In some embodiments, the term “aryl” as used herein means an aryl group that is optionally substituted with one, two, three, four or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylthio, alkylthioalkyl, alkynyl, carbonyl, cyano, formyl, haloalkoxy, haloalkyl, halogen, hydroxyl, hydroxyalkylene, mercapto, nitro, $-NR_A R_A$, and $(NR_A R_B)$ carbonyl.

[00106] The term “arylalkyl” as used herein, means an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Illustrative examples of arylalkyl include, but are not limited to benzyl, 2-phenylethyl, -phenylpropyl, 1-methyl-3-phenylpropyl, and 2-naphth-2-ylethyl.

[00107] The term “carbonyl” as used herein, means a -C(O)- group.

[00108] The term “carboxy” as used herein, means a -COOH group.

[00109] The term “cyano” as used herein, means a -CN group.

[00110] The term “formyl” as used herein, means a -C(O)H group.

[00111] The term “halo” or “halogen” as used herein, means a -Cl, -Br, -I or -F.

[00112] The term “mercapto” as used herein, means a -SH group.

[00113] The term “nitro” as used herein, means a -NO₂ group.

[00114] The term “hydroxy” as used herein, means a -OH group.

[00115] The term “oxo” as used herein, means a =O group.

[00116] The term “bond” or “single bond” as used herein, refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure.

[00117] The terms “haloalkyl,” “haloalkenyl,” “haloalkynyl” and “haloalkoxy” as used herein, include alkyl, alkenyl, alkynyl and alkoxy structures in which at least one hydrogen is replaced with a halogen atom. In certain embodiments in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are all the same as one another. In other embodiments in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are not all the same as one another. The terms “fluoroalkyl” and “fluoroalkoxy” include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine. In certain embodiments, haloalkyls are optionally substituted.

[00118] The term “ester” refers to a chemical moiety with formula -COOR, where R is selected from among alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heterocycloalkyl (bonded through a ring carbon). In some embodiments, any hydroxy, or carboxyl side chain on the compounds described herein is esterified.

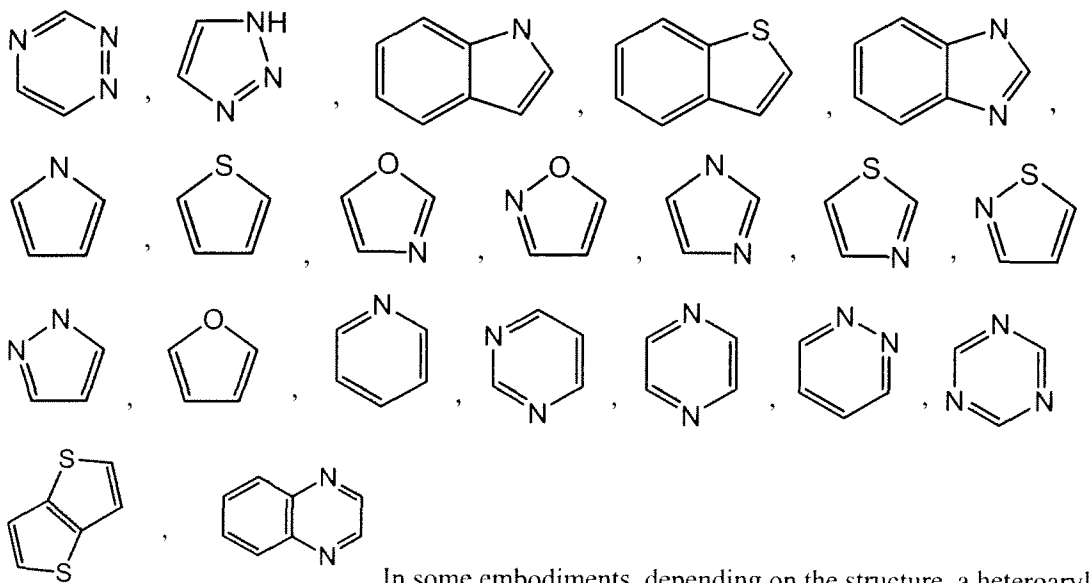
[00119] The terms “heteroalkyl” “heteroalkenyl” and “heteroalkynyl” as used herein, include optionally substituted alkyl, alkenyl and alkynyl radicals in which one or more skeletal chain atoms are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, silicon, phosphorus or combinations thereof.

[00120] The term “heteroatom” as used herein refers to an atom other than carbon or hydrogen. Heteroatoms are typically independently selected from among oxygen, sulfur, nitrogen, silicon and phosphorus, but are not limited to these atoms. In embodiments in which two or more heteroatoms are present, the two or more heteroatoms are all the same as one another, or some or all of the two or more heteroatoms are each different from the others.

[00121] The term “ring” as used herein, refers to any covalently closed structure. Rings include, for example, carbocycles (*e.g.*, aryls and cycloalkyls), heterocycles (*e.g.*, heteroaryl and heterocycloalkyls), aromatics (*e.g.* aryls and heteroaryl), and non-aromatics (*e.g.*, cycloalkyls and heterocycloalkyls). In some embodiments, rings are optionally substituted. In some embodiments, rings form part of a ring system.

[00122] As used herein, the term “ring system” refers to two or more rings, wherein two or more of the rings are fused. The term “fused” refers to structures in which two or more rings share one or more bonds.

[00123] The terms “heteroaryl” or, alternatively, “heteroaromatic” refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. An *N*-containing “heteroaromatic” or “heteroaryl” moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. In some embodiments, the polycyclic heteroaryl group is fused or non-fused. Illustrative of heteroaryl groups include, but are not limited to, the following moieties:



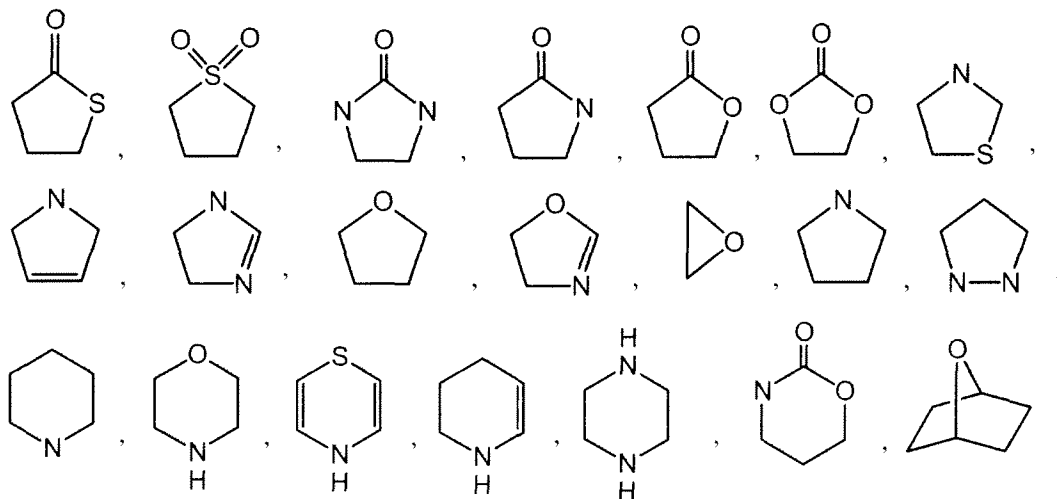
. In some embodiments, depending on the structure, a heteroaryl group is a monoradical or a diradical (*i.e.*, a heteroarylene group).

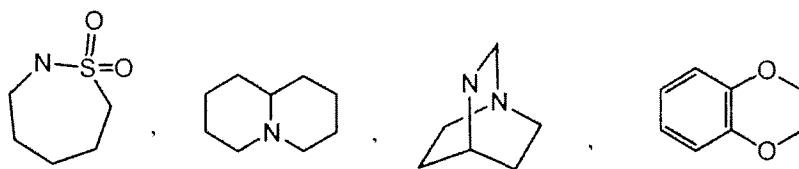
[00124] The term “heteroaryl” means heteroaryl groups that are substituted with 0, 1, 2, 3, or 4 substituents independently selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylthio, alkylthioalkyl, alynyl, carboxy, cyano, formyl,

haloalkoxy, haloalkyl, halogen, hydroxyl, hydroxyalkylene, mercapto, nitro, $-NR_A R_B$, and $-(NR_A R_B)\text{carbonyl}$.

[00125] The term “heteroarylalkyl” as used herein, means a heteroaryl, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Illustrative examples of heteroarylalkyl include, but are not limited to, pyridinylmethyl.

[00126] The term “heterocycloalkyl” or “non-aromatic heterocycle” as used herein, refers to a non-aromatic ring wherein one or more atoms forming the ring is a heteroatom. A “heterocycloalkyl” or “non-aromatic heterocycle” group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, the radicals are fused with an aryl or heteroaryl. In some embodiments, heterocycloalkyl rings are formed by three, four, five, six, seven, eight, nine, or more than nine atoms. In some embodiments, heterocycloalkyl rings are optionally substituted. In certain embodiments, heterocycloalkyls contain one or more carbonyl or thiocarbonyl groups such as, for example, oxo- and thio-containing groups. Examples of heterocycloalkyls include, but are not limited to, lactams, lactones, cyclic imides, cyclic thioimides, cyclic carbamates, tetrahydrothiopyran, 4H-pyran, tetrahydropyran, piperidine, 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,3-oxathiane, 1,4-oxathiin, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouacil, morpholine, trioxane, hexahydro-1,3,5-triazine, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, pyrrolidone, pyrrolidione, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,3-dioxole, 1,3-dioxolane, 1,3-dithiole, 1,3-dithiolane, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, and 1,3-oxathiolane. Illustrative examples of heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include, but are not limited to





. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides.

[00127] The term “heterocycle” refers to heteroaryl and heterocycloalkyl used herein, refers to groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocycle group has from 4 to 10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Herein, whenever the number of carbon atoms in a heterocycle is indicated (*e.g.*, C₁-C₆ heterocycle), at least one other atom (the heteroatom) must be present in the ring. Designations such as “C₁-C₆ heterocycle” refer only to the number of carbon atoms in the ring and do not refer to the total number of atoms in the ring. In some embodiments, it is understood that the heterocycle ring has additional heteroatoms in the ring. Designations such as “4-6 membered heterocycle” refer to the total number of atoms that are contained in the ring (*i.e.*, a four, five, or six membered ring, in which at least one atom is a carbon atom, at least one atom is a heteroatom and the remaining two to four atoms are either carbon atoms or heteroatoms). In some embodiments, in heterocycles that have two or more heteroatoms, those two or more heteroatoms are the same or different from one another. In some embodiments, heterocycles are optionally substituted. In some embodiments, binding to a heterocycle is at a heteroatom or via a carbon atom. Heterocycloalkyl groups include groups having only 4 atoms in their ring system, but heteroaryl groups must have at least 5 atoms in their ring system. The heterocycle groups include benzo-fused ring systems. An example of a 4-membered heterocycle group is azetidiny (derived from azetidine). An example of a 5-membered heterocycle group is thiazolyl. An example of a 6-membered heterocycle group is pyridyl, and an example of a 10-membered heterocycle group is quinoliny. Examples of heterocycloalkyl groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperaziny, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepiny, diazepiny, thiazepiny, 1,2,3,6-tetrahydropyridiny, 2-pyrroliny, 3-pyrroliny, indoliny, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazoliny, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidiny, imidazoliny, imidazolidiny, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indoly and quinoliziny. Examples of heteroaryl groups are pyridiny, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyraziny, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinoliny, isoquinoliny, indoly, benzimidazolyl, benzofuranyl, cinnoliny, indazolyl, indoliziny, phthalaziny, pyridaziny, triaziny, isoindoly, pteridiny, puriny, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl,

benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalyl, naphthyridinyl, and furopyridinyl. In some embodiments, the foregoing groups, as derived from the groups listed above, are C-attached or *N*-attached where such is possible. For instance, in some embodiments, a group derived from pyrrole is pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, in some embodiments, a group derived from imidazole is imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocycle groups include benzo-fused ring systems and ring systems substituted with one or two oxo (=O) moieties such as pyrrolidin-2-one. In some embodiments, depending on the structure, a heterocycle group is a monoradical or a diradical (*i.e.*, a heterocyclene group).

[00128] The heterocycles described herein are substituted with 0, 1, 2, 3, or 4 substituents independently selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylthio, alkylthioalkyl, alynyl, carboxy, cyano, formyl, haloalkoxy, haloalkyl, halogen, hydroxyl, hydroxyalkylene, mercapto, nitro, -NR_AR_B, and -(NR_AR_B)carbonyl.

[00129] The term “heterocycloalkoxy” refers to a heterocycloalkyl group, as defined herein, appended to the parent molecular moiety through an alkoxy group.

[00130] The term “heterocycloalkylthio” refers to a heterocycloalkyl group, as defined herein, appended to the parent molecular moiety through an alkylthio group.

[00131] The term “heterocyclooxy” refers to a heterocycloalkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

[00132] The term “heterocyclothio” refers to a heterocycloalkyl group, as defined herein, appended to the parent molecular moiety through a sulfur atom.

[00133] The term “heteroarylalkoxy” refers to a heteroaryl group, as defined herein, appended to the parent molecular moiety through an alkoxy group.

[00134] The term “heteroarylalkylthio” refers to a heteroaryl group, as defined herein, appended to the parent molecular moiety through an alkylthio group.

[00135] The term “heteroaryloxy” refers to a heteroaryl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

[00136] The term “heteroarylthio” refers to a heteroaryl group, as defined herein, appended to the parent molecular moiety through a sulfur atom.

[00137] In some embodiments, the term “membered ring” embraces any cyclic structure. The term “membered” is meant to denote the number of skeletal atoms that constitute the ring. Thus, for example, cyclohexyl, pyridine, pyran and thiopyran are 6-membered rings and cyclopentyl, pyrrole, furan, and thiophene are 5-membered rings.

[00138] The term “non-aromatic 5, 6, 7, 8, 9, 10, 11 or 12- bicyclic heterocycle” as used herein, means a heterocycloalkyl, as defined herein, consisting of two carbocyclic rings, fused together at the same carbon atom (forming a spiro structure) or different carbon atoms (in which two rings share one or more bonds), having 5 to 12 atoms in its overall ring system, wherein one or more atoms forming the ring is a heteroatom. Illustrative examples of non-aromatic 5, 6, 7, 8, 9, 10, 11, or 12- bicyclic heterocycle ring include, but are not limited to, 2-azabicyclo[2.2.1]heptanyl, 7-azabicyclo[2.2.1]heptanyl, 2-azabicyclo[3.2.0]heptanyl, 3-azabicyclo[3.2.0]heptanyl, 4-azaspiro[2.4]heptanyl, 5-azaspiro[2.4]heptanyl, 2-oxa-5- azabicyclo[2.2.1]heptanyl, 4-azaspiro[2.5]octanyl, 5-azaspiro[2.5]octanyl, 5-azaspiro[3.4]octanyl, 6-azaspiro[3.4]octanyl, 4-oxa-7-azaspiro[2.5]octanyl, 2-azabicyclo[2.2.2]octanyl, 1,3-diazabicyclo[2.2.2]octanyl, 5-azaspiro[3.5]nonanyl, 6-azaspiro[3.5]nonanyl, 5-oxo-8-azaspiro[3.5]nonanyl, octahydrocyclopenta[c]pyrrolyl, octahydro-1*H*-quinolizinyll, 2,3,4,6,7,9a-hexahydro-1*H*-quinolizinyll, decahydropyrido[1,2-*a*]azepinyll, decahydro-1*H*-pyrido[1,2-*a*]azocinyll, 1-azabicyclo[2.2.1]heptanyl, 1-azabicyclo[3.3.1]nonanyl, quinuclidinyll, and 1-azabicyclo[4.4.0]decanyl.

[00139] The term “hydroxyalkylene” as used herein, means at least one hydroxyl group, as defined herein, is appended to the parent molecular moiety through an alkylene group, as defined herein. Illustrative examples of hydroxyalkylene include, but not limited to hydroxymethylene, 2-hydroxy-ethylene, 3-hydroxypropylene and 4-hydroxyheptylene.

[00140] As used herein, the term “moiety” refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00141] As used herein, the term “sulfonyl” refers to a -S(=O)₂-R, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heterocycloalkyl (bonded through a ring carbon).

[00142] As used herein, the term “acetyl” refers to a group of formula -C(=O)CH₃.

[00143] As used herein, the term “isocyanato” refers to a group of formula -NCO.

[00144] As used herein, the term “thiocyanato” refers to a group of formula -CNS.

[00145] As used herein, the term “isothiocyanato” refers to a group of formula -NCS.

[00146] As used herein, the substituent “R” appearing by itself and without a number designation refers to a substituent selected from among from alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and non-aromatic heterocycle (bonded through a ring carbon).

[00147] The term “substituted” means that the referenced group is optionally substituted (substituted or unsubstituted) with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto,

alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, cyano, halo, carbonyl, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, perhaloalkyl, perfluoroalkyl, silyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. By way of example an optional substituents is L_sR_s , wherein each L_s is independently selected from a bond, -O-, -C(=O)-, -S-, -S(=O)-, -S(=O)₂-, -NH-, -NHC(O)-, -C(O)NH-, S(=O)₂NH-, -NHS(=O)₂-, -OC(O)NH-, -NHC(O)O-, -(substituted or unsubstituted C₁-C₆ alkyl), or -(substituted or unsubstituted C₂-C₆ alkenyl); and each R_s is independently selected from H, (substituted or unsubstituted lower alkyl), (substituted or unsubstituted lower cycloalkyl), heteroaryl, or heteroalkyl.

[00148] The term “protecting group” refers to a removable group which modifies the reactivity of a functional group, for example, a hydroxyl, ketone or amine, against undesirable reaction during synthetic procedures and to be later removed. Examples of hydroxy-protecting groups include, but not limited to, methylthiomethyl, tert-dimethylsilyl, tert-butyldiphenylsilyl, ethers such as methoxymethyl, and esters including acetyl, benzoyl, and the like. Examples of ketone protecting groups include, but not limited to, ketals, oximes, O-substituted oximes for example O-benzyl oxime, O-phenylthiomethyl oxime, 1-isopropoxycyclohexyl oxime, and the like. Examples of amine protecting groups include, but are not limited to, tert-butoxycarbonyl (Boc) and carbobenzyloxy (Cbz).

[00149] The term “optionally substituted” as defined herein, means the referenced group is substituted with zero, one or more substituents as defined herein.

[00150] In some embodiments, compounds of the described herein exist as stereoisomers, wherein asymmetric or chiral centers are present. Stereoisomers are designated (R) or (S) depending on the configuration of substituents around the chiral carbon atom. The term (R) and (S) used herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, *Pure Appl. Chem.*, (1976), 45:13-30, hereby incorporated by reference. The embodiments described herein specifically includes the various stereoisomers and mixtures thereof. Stereoisomers include enantiomers, diastereomers, and mixtures of enantiomers or diastereomers. In some embodiments, individual stereoisomers of compounds are prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic column.

[00151] The methods and formulations described herein include the use of *N*-oxides, crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds described

herein, as well as active metabolites of these compounds having the same type of activity. In some situations, compounds exist as tautomers. All tautomers are included within the scope of the compounds presented herein. In some embodiments, the compounds described herein exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00152] Throughout the specification, groups and substituents thereof are chosen, in certain embodiments, to provide stable moieties and compounds.

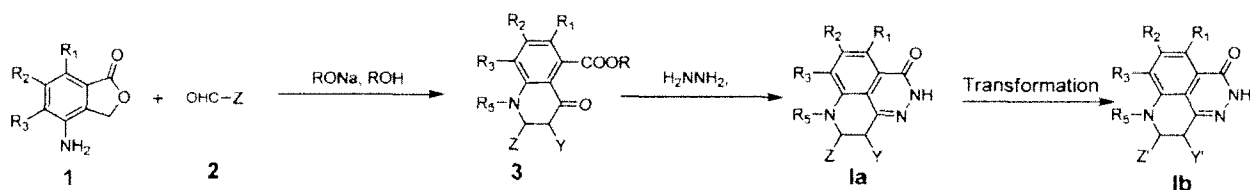
Preparation of Compounds Described Herein

[00153] In certain embodiments, the compounds described herein are synthesized using any synthetic techniques including standard synthetic techniques and the synthetic processes described herein. In specific embodiments, the following synthetic processes are utilized.

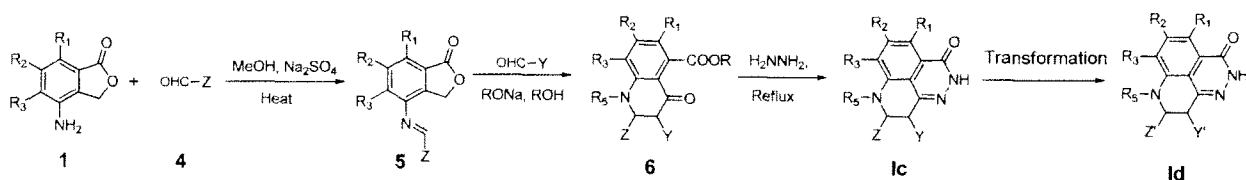
Synthetic Schemes

[00154] In certain embodiments, compounds of Formula (I), composing of **Ia** to **If**, are prepared in various ways, as outlined in Synthetic Schemes 1 and 2. In each scheme, the variables (*e.g.*, R₁, R₂, R₃, R₄, R₅, Y, and Z) correspond to the same definitions as those recited above while R is alkyl and Y' is the same or different group defined by Y and Z' is the same or different group defined by Z. In some embodiments, compounds are synthesized using methodologies analogous to those described below by the use of appropriate alternative starting materials.

[00155] In certain embodiments, compounds of Formula (**Ia**, and **Ib**) wherein Y is identical to Z are synthesized according to Synthetic Scheme 1. Thus, the preparation of the intermediate **3** wherein R₅ is hydrogen is achieved by condensation of 4-aminoisobenzofuran-1(3H)-one **1** with an aldehyde **2** in the presence of a base preferably alkaline alkoxides in appropriate solvents such as ethyl acetate or ethyl propionate at either ambient or elevated temperature. Compounds of Formula **Ia** wherein R₅ is hydrogen is prepared by treating the intermediate **3** with hydrazine hydrate at ambient or elevated temperature. Compounds of Formula **Ia** wherein R₅ is alkyl or substituted alkyl is prepared from compound of Formula **Ia** wherein R₅ is hydrogen by reductive amination reaction with R₇-CHO wherein R₇ is alkyl, substituted alkyl. In some embodiments, the preparation of the compounds in Formula **Ib** is accomplished by further modification of **Ia**. Through appropriate functional group transformations on the moiety of Y and Z, one affords the compounds of Formula **Ib** with different entities of Y' and Z' at 2- or 3-positions.

Synthetic Scheme 1

[00156] In certain embodiments, compounds of Formula (1c, and 1d) are synthesized according to Synthetic Scheme 2. For example, the intermediate 5 is prepared by condensation of the reagent 1 with an aldehyde 4 in the presence of water absorbent such sodium sulfate or magnesium sulfate at elevated temperature. A subsequent condensation reaction of this intermediate with another aldehyde in the presence of a base preferably alkaline alkoxides in appropriate solvents such as ethyl acetate or ethyl propionate at either ambient or elevated temperature gives the intermediate 6 wherein R_5 is hydrogen. Compounds of Formula 1c wherein R_5 is hydrogen is prepared by treating the intermediate 6 with hydrazine hydrate at ambient or elevated temperature. Compounds of Formula 1c wherein R_5 is alkyl, substituted alkyl are prepared from compounds of Formula 1c wherein R_5 is hydrogen by reductive amination reaction with $R_7\text{-CHO}$ wherein R_7 is alkyl, or substituted alkyl. In some embodiments, the preparation of compounds of Formula 1d are accomplished by further modification of 1c. Through appropriate functional group transformations on the moiety of Y and Z, one could afford the compounds of Formula 1c with different entities of Y' and Z' at 2- or 3-positions.

Synthetic Scheme 2

[00157] Examples 2 – 159 of International Patent Publication No. WO 2010/017055 A2, which is incorporated by reference in its entirety in the instant application, disclose exemplary syntheses of compounds of Formula (I).

Certain Pharmaceutical Terminology

[00158] The term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00159] As used herein, the term “selective binding compound” refers to a compound that selectively binds to any portion of one or more target proteins.

[00160] As used herein, the term “selectively binds” refers to the ability of a selective binding compound to bind to a target protein, such as, for example, PARP, with greater affinity than it binds to a non-target protein. In certain embodiments, specific binding refers to binding to a target with an affinity that is at least about 10, about 50, about 100, about 250, about 500, about 1000 or more times greater than the affinity for a non-target.

[00161] As used herein, the term “target protein” refers to a molecule or a portion of a protein capable of being bound by a selective binding compound. In certain embodiments, a target protein is the enzyme poly(ADP-ribose)polymerase (PARP).

[00162] As used herein, the terms “treating” or “treatment” encompass either or both responsive and prophylaxis measures, *e.g.*, designed to inhibit, slow or delay the onset of a symptom of a disease or disorder, achieve a full or partial reduction of a symptom or disease state, and/or to alleviate, ameliorate, lessen, or cure a disease or disorder and/or its symptoms.

[00163] As used herein, amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening of severity, delay in onset, slowing of progression, or shortening of duration, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the compound or composition.

[00164] As used herein, the term “modulator” refers to a compound that alters an activity of a molecule. For example, a modulator includes a compound that causes an increase or a decrease in the magnitude of a certain activity of a molecule compared to the magnitude of the activity in the absence of the modulator. In certain embodiments, a modulator is an inhibitor, which decreases the magnitude of one or more activities of a molecule. In certain embodiments, an inhibitor completely prevents one or more activities of a molecule. In certain embodiments, a modulator is an activator, which increases the magnitude of at least one activity of a molecule. In certain embodiments the presence of a modulator results in an activity that does not occur in the absence of the modulator.

[00165] As used herein, the term “selective modulator” refers to a compound that selectively modulates a target activity.

[00166] As used herein, the term “PARP” refers to the family of the enzyme poly(ADP-ribose)polymerase which includes approximately 18 proteins, particularly poly(ADP-ribose)polymerase-1 (PARP-1) and poly(ADP-ribose)polymerase-2 (PARP-2).

[00167] As used herein, the term “selective PARP modulator” refers to a compound that selectively modulates at least one activity associated with the enzyme poly(ADP-ribose)polymerase (PARP). In various embodiments, the selective modulator selectively modulates the activity of PARP-1, PARP-2, both PARP-1 and PARP-2 or several members of the family of the enzyme poly(ADP-ribose)polymerase (PARP).

[00168] As used herein, the term “method of inhibiting PARP” refers to a method of inhibiting the activity of either one or more of the family of enzyme poly(ADP-ribose)polymerase (PARP). As used herein, the term “inhibition of PARP” refers to inhibition of the activity of either one or more of the family of enzyme poly(ADP-ribose)polymerase (PARP).

[00169] As used herein, the term “modulating the activity of the enzyme poly(ADP-ribose)polymerase” refers to a modulating the activity of either one or more of the family of enzyme poly(ADP-ribose)polymerase (PARP).

[00170] As used herein, the term “selectively modulates” refers to the ability of a selective modulator to modulate a target activity to a greater extent than it modulates a non-target activity. In certain embodiments the target activity is selectively modulated by, for example about 2 fold up to more than about 500 fold, in some embodiments, about 2, 5, 10, 50, 100, 150, 200, 250, 300, 350, 400, 450 or more than 500 fold.

[00171] The term “cancer”, as used herein refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread). The types of cancer include, but are not limited to, solid tumors (such as those of the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, lymphatic tissue (lymphoma), ovary, pancreas or other endocrine organ (thyroid), prostate, skin (melanoma) or hematological tumors (such as the leukemias MDS and AML).

[00172] The term “carrier,” as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of a compound into cells or tissues.

[00173] The terms “co-administration” or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[00174] The term “diluent” refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents include chemicals used to stabilize compounds because they provide a more stable environment. Salts dissolved in buffered solutions (which also can provide pH control or maintenance) are utilized as diluents in certain embodiments, including, but not limited to a phosphate buffered saline solution.

[00175] The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the

amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is determined using any suitable technique, such as a dose escalation study.

[00176] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00177] The term "enzymatically cleavable linker," as used herein refers to unstable or degradable linkages which are degraded by one or more enzymes.

[00178] The term "PARP-mediated", as used herein, refers to conditions or disorders that are ameliorated by the one or more of the family of enzyme poly(ADP-ribose)polymerase (PARP).

[00179] A "metabolite" of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. Thus, in certain instances, enzymes produce specific structural alterations to a compound. In some embodiments, metabolites of the compounds disclosed herein are identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells *in vitro* and analysis of the resulting compounds.

[00180] The term "modulate," as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00181] By "pharmaceutically acceptable" or "therapeutically acceptable", as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic. In certain instances, nontoxic and non-abrogative materials includes materials that when administered to an individual do not cause substantial, undesirable biological effects and/or do not interact in a deleterious manner with any of the components of the composition in which it is contained.

[00182] The term "pharmaceutically acceptable salt" or "therapeutically acceptable salt", refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain

instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined.

[00183] The term “pharmaceutical combination” as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, *e.g.* a compound described herein and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, *e.g.* a compound described herein and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, *e.g.* the administration of three or more active ingredients.

[00184] The term “pharmaceutical composition” refers to a mixture of a compound described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary and topical administration.

[00185] A “prodrug” refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they are easier to administer than the parent drug. In certain instances, a prodrug is bioavailable by oral administration whereas the parent is not. In some instances, a prodrug has improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug is a compound described herein, which is administered as an ester (the “prodrug”) to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid or amino group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically more active

form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, a pharmaceutically active compound is modified such that the active compound will be regenerated upon *in vivo* administration. In some embodiments, the prodrug is designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug.

[00186] The term “subject” or “patient” encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

[00187] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, *e.g.*, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

Pharmaceutical Composition/Formulation

[00188] Provided herein are pharmaceutical compositions that include a compound described herein and a pharmaceutically acceptable diluent(s), excipient(s), and/or carrier(s). In addition, in some embodiments, the compounds described herein are administered as pharmaceutical compositions in which compounds described herein are mixed with other active ingredients, as in combination therapy.

[00189] A pharmaceutical composition, as used herein, refers to a mixture of a compound described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, a pharmaceutical composition facilitates administration of the compound to an organism. In some embodiments, practicing the methods of treatment or use provided herein, includes administering or using a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein. In specific embodiments, the methods of treatment provided for herein include administering such a pharmaceutical composition to a mammal having a disease or condition to be treated. In one embodiment, the mammal is a human. In some embodiments, the therapeutically

effective amount varies widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In various embodiments, the compounds described herein are used singly or in combination with one or more therapeutic agents as components of mixtures.

[00190] In certain embodiments, the pharmaceutical compositions provided herein are formulated for intravenous injections. In certain aspects, the intravenous injection formulations provided herein are formulated as aqueous solutions, and, in some embodiments, in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, the pharmaceutical compositions provided herein are formulated for transmucosal administration. In some aspects, transmucosal formulations include penetrants appropriate to the barrier to be permeated. In certain embodiments, the pharmaceutical compositions provided herein are formulated for other parenteral injections, appropriate formulations include aqueous or nonaqueous solutions, and in one embodiment, with physiologically compatible buffers or excipients.

[00191] In certain embodiments, the pharmaceutical compositions provided herein are formulated for oral administration. In certain aspects, the oral formulations provided herein comprise compounds described herein that are formulated with pharmaceutically acceptable carriers or excipients. Such carriers enable the compounds described herein to be formulated as tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

[00192] In some embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents are optionally added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[00193] In certain embodiments, provided herein is a pharmaceutical composition formulated as dragee cores with suitable coatings. In certain embodiments, concentrated sugar solutions are used in forming the suitable coating, and optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. In some embodiments, dyestuffs and/or pigments are added to tablets, dragees

and/or the coatings thereof for, *e.g.*, identification or to characterize different combinations of active compound doses.

[00194] In certain embodiments, pharmaceutical preparations which are used include orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In some embodiments, the push-fit capsules contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In certain embodiments, in soft capsules, the active compounds are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers are optionally added. In certain embodiments, the formulations for oral administration are in dosages suitable for such administration.

[00195] In certain embodiments, the pharmaceutical compositions provided herein are formulated for buccal or sublingual administration. In certain embodiments, buccal or sublingual compositions take the form of tablets, lozenges, or gels formulated in a conventional manner. In certain embodiments, parenteral injections involve bolus injection or continuous infusion. In some embodiments, formulations for injection are presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. In some embodiments, the pharmaceutical composition described herein is in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and optionally contains formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. In some embodiments, suspensions of the active compounds are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In certain embodiments, aqueous injection suspensions contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspensions also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. In alternative embodiments, the active ingredient is in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[00196] In some embodiments, the compounds described herein are administered topically. In specific embodiments, the compounds described herein are formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compounds optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and/or preservatives.

[00197] In certain embodiments, the pharmaceutical compositions provided herein are formulated for transdermal administration of compounds described herein. In some embodiments, administration

of such compositions employs transdermal delivery devices and transdermal delivery patches. In certain embodiments, the compositions are lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. Such patches include those constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. In some embodiments, transdermal delivery of the compounds described herein is accomplished by use of iontophoretic patches and the like. In certain embodiments, transdermal patches provide controlled delivery of the compounds provided herein, such as, for example, compounds of Formula (I) or (II). In certain embodiments, the rate of absorption is slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. Conversely, absorption enhancers are optionally used to increase absorption. Absorption enhancer and carrier include absorbable pharmaceutically acceptable solvents that assist in passage of the compound through the skin. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[00198] In certain embodiments, the pharmaceutical compositions provided herein are formulated for administration by inhalation. In certain embodiments, in such pharmaceutical compositions formulated for inhalation, the compounds described herein are in a form as an aerosol, a mist or a powder. In some embodiments, pharmaceutical compositions described herein are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In certain aspects of a pressurized aerosol, the dosage unit is determined by providing a valve to deliver a metered amount. In certain embodiments, capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator is formulated containing a powder mix of the compound described herein and a suitable powder base such as lactose or starch.

[00199] In some embodiments, the compounds described herein are formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas. In certain embodiments, rectal compositions optionally contain conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In certain suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

[00200] In various embodiments provided herein, the pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into pharmaceutically acceptable

preparations. In certain embodiments, proper formulation is dependent upon the route of administration chosen. In various embodiments, any of the techniques, carriers, and excipients is used as suitable. In some embodiments, pharmaceutical compositions comprising a compound described herein are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00201] In certain embodiments, the pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent or excipient and a compound described herein described herein as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of *N*-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. In some situations, compounds described herein exist as tautomers. All tautomers are included within the scope of the compounds presented herein. Additionally, included herein are the solvated and unsolvated forms of the compounds described herein. Solvated compounds include those that are solvated with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In some embodiments, the pharmaceutical compositions described herein include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, and/or buffers. In additional embodiments, the pharmaceutical compositions described herein also contain other therapeutically valuable substances.

[00202] Methods for the preparation of compositions containing the compounds described herein include formulating the compounds with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels, suspensions and creams. In various embodiments, the compositions are in liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

[00203] In some embodiments, a composition comprising a compound described herein takes the form of a liquid where the agents are present in solution, in suspension or both. In some embodiments, when the composition is administered as a solution or suspension a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid

matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

[00204] Useful aqueous suspension optionally contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers, *e.g.*, hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Useful compositions optionally comprise an mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[00205] Useful compositions optionally include solubilizing agents to aid in the solubility of a compound described herein. The term "solubilizing agent" generally includes agents that result in formation of a micellar solution or a true solution of the agent. Solubilizing agents include certain acceptable nonionic surfactants, for example polysorbate 80, and ophthalmically acceptable glycols, polyglycols, *e.g.*, polyethylene glycol 400, and glycol ethers.

[00206] Useful compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[00207] Useful compositions optionally include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[00208] Certain useful compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

[00209] Some useful compositions optionally include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, *e.g.*, polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, *e.g.*, octoxynol 10, octoxynol 40.

[00210] Certain useful compositions optionally one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

[00211] In some embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. In alternative embodiments, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

[00212] In various embodiments, any delivery system for hydrophobic pharmaceutical compounds is employed. Liposomes and emulsions are examples of delivery vehicles or carriers for hydrophobic drugs. In certain embodiments, certain organic solvents such as *N*-methylpyrrolidone are employed. In some embodiments, the compounds are delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials are utilized in the embodiments herein. In certain embodiments, sustained-release capsules release the compounds for a few weeks up to over 100 days. In some embodiments, depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization are employed.

[00213] In certain embodiments, the formulations or compositions described herein benefit from and/or optionally comprise antioxidants, metal chelating agents, thiol containing compounds and other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

Methods of Dosing and Treatment Regimens

[00214] In any of the aforementioned embodiments are further embodiments in which administration is enteral, parenteral, or both, and wherein:

- (a) the effective amount of the compound is systemically administered to the subject;
- (b) the effective amount of the compound is administered orally to the subject;
- (c) the effective amount of the compound is intravenously administered to the subject;
- (d) the effective amount of the compound administered by inhalation;
- (e) the effective amount of the compound is administered by nasal administration;
- (f) the effective amount of the compound is administered by injection to the subject;
- (g) the effective amount of the compound is administered topically (dermal) to the subject;
- (h) the effective amount of the compound is administered by ophthalmic administration; and/or
- (i) the effective amount of the compound is administered rectally to the subject.

[00215] In any of the aforementioned embodiments are further embodiments that include single administrations of the effective amount of the compound, including further embodiments in which the compound is administered to the subject (i) once; (ii) multiple times over the span of one day; (iii) continually; or (iv) continuously.

[00216] In any of the aforementioned embodiments are further embodiments that include multiple administrations of the effective amount of the compound, including further embodiments wherein:

- (i) the compound is administered in a single dose;
- (ii) the time between multiple administrations is every 6 hours;
- (iii) the compound is administered to the subject every 8 hours.

[00217] In further or alternative embodiments, the method includes a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In some embodiments, the length of the drug holiday varies from 2 days to 1 year.

[00218] In certain embodiments, the compounds described herein are used in the preparation or manufacture of medicaments for the treatment of diseases or conditions that are mediated by the enzyme poly(ADP-ribose)polymerase (PARP) or in which inhibition of the enzyme poly(ADP-ribose)polymerase (PARP) ameliorates the disease or condition. In some embodiments, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions containing at least one compound described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said subject.

[00219] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. In some embodiments, amounts effective for this use will depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. In certain instances, it is considered appropriate for the caregiver to determine such therapeutically effective amounts by routine experimentation (including, but not limited to, a dose escalation clinical trial).

[00220] In certain prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. In some embodiments, the amount administered is defined to be a "prophylactically effective amount or dose." In certain embodiments of this use, the precise amounts of compound

administered depend on the patient's state of health, weight, and the like. In some embodiments, it is considered appropriate for the caregiver to determine such prophylactically effective amounts by routine experimentation (*e.g.*, a dose escalation clinical trial). In certain embodiments, when used in a patient, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician.

[00221] In certain instances, a patient's condition does not improve or does not significantly improve following administration of a compound or composition described herein and, upon the doctor's discretion the administration of the compounds is optionally administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00222] In certain cases wherein the patient's status does improve or does not substantially improve, upon the doctor's discretion the administration of the compounds are optionally given continuously; alternatively, the dose of drug being administered is optionally temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In certain embodiments, the length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday includes a reduction from about 10% to about 100%, including, by way of example only, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%.

[00223] In certain embodiments, once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. In some embodiments, the dosage, *e.g.*, of the maintenance dose, or the frequency of administration, or both, are reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, patients are optionally given intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00224] In certain embodiments, the amount of a given agent that corresponds to an effective amount varies depending upon factors such as the particular compound, disease or condition and its severity, the identity (*e.g.*, weight) of the subject or host in need of treatment. In some embodiments, the effective amount is, nevertheless, determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent that is administered, the route of administration, the condition being treated, and the subject or host being treated. In certain embodiments, however, doses employed for adult human treatment is in the range of about 0.02 to

about 5000 mg per day, in a specific embodiment about 1 to about 1500 mg per day. In various embodiments, the desired dose is conveniently presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00225] In some embodiments, the pharmaceutical compositions described herein are in a unit dosage form suitable for single administration of precise dosages. In some instances, in unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compound. In certain embodiments, the unit dosage is in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. In some embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. In alternative embodiments, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection are, in some embodiments, presented in unit dosage form, which include, but are not limited to ampoules, or in multi-dose containers, with an added preservative.

[00226] In certain embodiments, the daily dosages appropriate for the compounds described herein described herein are from about 0.01 to about 2.5 mg/kg per body weight. In some embodiments, an indicated daily dosage in the larger subject, including, but not limited to, humans, is in the range from about 0.5 mg to about 100 mg, conveniently administered in divided doses, including, but not limited to, up to four times a day or in extended release form. In certain embodiments, suitable unit dosage forms for oral administration comprise from about 1 to about 50 mg active ingredient. The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon. In certain embodiments, the dosages are altered depending on a number of variables, not limited to the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00227] In certain embodiments, toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. In certain embodiments, compounds exhibiting high therapeutic indices are preferred. In some embodiments, the data obtained from cell culture assays and animal studies is used in formulating a range of dosage for use in human. In specific embodiments, the dosage of such compounds lies within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. In certain

embodiments, the dosage varies within this range depending upon the dosage form employed and the route of administration utilized.

Combination Treatments

[00228] In certain instances, it is appropriate to administer at least one compound described herein in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is inflammation, then, in some embodiments, it is appropriate to administer an anti-inflammatory agent in combination with the initial therapeutic agent. In some embodiments, the therapeutic effectiveness of one of the compounds described herein is enhanced by administration of an adjuvant (*i.e.*, in some embodiments, by itself the adjuvant has minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). In certain embodiments, the benefit experienced by a patient is increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. In some embodiments, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient as a result of a combination treatment is additive or synergistic.

[00229] In certain embodiments, therapeutically-effective dosages vary when the drugs are used in treatment combinations. In some embodiments, therapeutically-effective dosages of drugs and other agents for use in combination treatment regimens is determined in any suitable manner, *e.g.*, through the use of metronomic dosing, *i.e.*, providing more frequent, lower doses in order to minimize toxic side effects. In some embodiments, combination treatment regimen described herein encompass treatment regimens in which administration of a PARP inhibitor described herein is initiated prior to, during, or after treatment with a second agent described above, and continues until any time during treatment with the second agent or after termination of treatment with the second agent. It also includes treatments in which a PARP inhibitor described herein and the second agent being used in combination are administered simultaneously or at different times and/or at decreasing or increasing intervals during the treatment period. Combination treatment further includes periodic treatments that start and stop at various times to assist with the clinical management of the patient. For example, in some embodiments, a PARP inhibitor described herein in the combination treatment is administered weekly at the onset of treatment, decreasing to biweekly, and decreasing further as appropriate.

[00230] In certain embodiments, compositions and methods for combination therapy are provided herein. In accordance with one aspect, the pharmaceutical compositions disclosed herein are used to in a method of treating a PARP mediated disease or condition or a disease or condition that is ameliorated by inhibition of PARP. In accordance with certain aspects, the pharmaceutical compositions disclosed herein are used to treat vascular disease; septic shock; ischaemic injury; reperfusion injury; neurotoxicity; hemorrhagic shock; inflammatory diseases; multiple sclerosis;

secondary effects of diabetes; and acute treatment of cytotoxicity following cardiovascular surgery. In a certain aspect, the pharmaceutical compositions disclosed herein are used in combination, either simultaneously or sequentially, with ionizing radiation or one or more chemotherapeutic agents.

[00231] In certain embodiments, combination therapies described herein are used as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of a PARP inhibitor described herein and a concurrent treatment. It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, is optionally modified in accordance with a variety of factors.

[00232] In certain combination therapies described herein, dosages of the co-administered compounds vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In some embodiments, when co-administered with one or more biologically active agents, the compound provided herein is administered either simultaneously with the biologically active agent(s), or sequentially. In certain aspects wherein the agents are administered sequentially, the attending physician will decide on the appropriate sequence of administering protein in combination with the biologically active agent(s).

[00233] In various embodiments, the multiple therapeutic agents (one of which is one of the compounds described herein) are administered in any order or even simultaneously. In certain instances, administration is simultaneous and the multiple therapeutic agents are, optionally, provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). In some embodiments, one of the therapeutic agents is given in multiple doses, or both are given as multiple doses. In some instances, administration is not simultaneous and the timing between the multiple doses varies, by way of non-limiting example, from more than zero weeks to less than four weeks. In addition, the combination methods, compositions and formulations are not to be limited to the use of only two agents; the use of multiple therapeutic combinations are also envisioned.

[00234] In additional embodiments, the compounds described herein are used in combination with procedures that provide additional or synergistic benefit to the patient. By way of example only, patients are expected to find therapeutic and/or prophylactic benefit in the methods described herein, wherein pharmaceutical composition of a compound disclosed herein and/or combinations with other therapeutics are combined with genetic testing to determine whether that individual is a carrier of a mutant gene that is known to be correlated with certain diseases or conditions.

[00235] In certain embodiments, the compounds described herein and combination therapies are administered before, during or after the occurrence of a disease or condition. In certain embodiments, the timing of administering the composition containing a compound varies. Thus, for example, in some embodiments, the compounds are used as a prophylactic and are administered continuously to

subjects with a propensity to develop conditions or diseases in order to prevent the occurrence of the disease or condition. In some embodiments, the compounds and compositions are administered to a subject during or as soon as possible after the onset of the symptoms. In certain embodiments, the administration of the compounds is initiated within the first 48 hours of the onset of the symptoms, within the first 6 hours of the onset of the symptoms, or within 3 hours of the onset of the symptoms. The initial administration is achieved via any route practical, such as, for example, an intravenous injection, a bolus injection, infusion over 5 minutes to about 5 hours, a pill, a capsule, transdermal patch, buccal delivery, and the like, or combination thereof. In some embodiments, a compound is administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease, such as, from about 1 month to about 3 months. In certain embodiments, the length of treatment varies for each subject, and the length is determined using any criteria. In exemplary embodiments, a compound or a formulation containing the compound is administered for at least 2 weeks, for about 1 month to about 5 years, or for about 1 month to about 3 years.

Other Combination Therapies

[00236] In certain embodiments described herein, methods for treatment of PARP mediated conditions or diseases, such as proliferative disorders, including cancer, include administration to a patient compounds, pharmaceutical compositions, or medicaments described herein in combination with at least one additional agent selected from the group consisting of alemtuzumab, arsenic trioxide, asparaginase (pegylated or non-), bevacizumab, cetuximab, platinum-based compounds such as cisplatin, cladribine, daunorubicin/doxorubicin/idarubicin, irinotecan, fludarabine, 5-fluorouracil, gemtuzumab, methotrexate, PaclitaxelTM, taxol, temozolomide, thioguanine, or classes of drugs including hormones (an antiestrogen, an antiandrogen, or gonadotropin releasing hormone analogues, interferons such as alpha interferon, nitrogen mustards such as busulfan or melphalan or mechlorethamine, retinoids such as tretinoin, topoisomerase inhibitors such as irinotecan or topotecan, tyrosine kinase inhibitors such as gefinitinib or imatinib, or agents to treat signs or symptoms induced by such therapy including allopurinol, filgrastim, granisetron/ondansetron/palonosetron, and dronabinol.

[00237] In certain embodiments, the compounds, pharmaceutical compositions, or medicaments described herein are administered in combination with ionizing radiation, one or more chemotherapeutic agents, or a combination thereof.

[00238] In certain embodiments, the chemotherapeutic agent is independently selected from the group consisting of alemtuzumab, arsenic trioxide, pegylated asparaginase, non-pegylated asparaginase, bevacizumab, cetuximab, cisplatin, cladribine, daunorubicin/doxorubicin/idarubicin, irinotecan, fludarabine, 5-fluorouracil, gemtuzumab, methotrexate, PaclitaxelTM, taxol, temozolomide,

thioguanine, an antiestrogen hormone analogue, an antiandrogen hormone analogue, a gonadotropin releasing hormone analogue, alpha interferon, busulfan, melphalan, mechlorethamine, tretinoin, irinotecan, topotecan, gefinitinib, imatinib, allopurinol, filgrastim, granisetron/ondansetron/palonosetron, and dronabinol.

[00239] In certain embodiments, the compounds, pharmaceutical compositions, or medicaments described herein are administered in combination with one or more of chemotherapeutic agents where each chemotherapeutic agent is independently an alkylating agent or a topoisomerase-1 inhibitor.

[00240] In certain embodiments, the compounds, pharmaceutical compositions, or medicaments described herein are administered in combination with one or more chemotherapeutic agents where each chemotherapeutic agent is independently selected from the group consisting of methyl methanesulfonate, temozolomide, dacarbazine (DTIC), Topotecan, Irinotecan, Rubitecan, Exatecan, Lurtotecan, Gimetecan, Diflomotecan (homocamptothecins), 7-substituted non-silatecans, 7-silyl camptothecins, BNP 1350, and XR 11576/MLN 576.

[00241] In certain embodiments, the compounds, pharmaceutical compositions, or medicaments described herein are administered in combination with one chemotherapeutic agent where the chemotherapeutic agent is irinotecan, cisplatin, or temozolomide.

EXAMPLES

[00242] The following Examples are intended as an illustration of the various embodiments as defined in the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

[00243] Examples 1-4 were disclosed in a poster which was presented December 4, 2010, at the 52nd American Society of Hematology Annual Meeting and Exposition in Orlando, Florida.

Example 1: PARP Inhibitor Sensitivity in MDS/AML Cell Lines Correlates with the Presence of High Grade Microsatellite Instability (MSI)

[00244] This example demonstrates that MDS/AML cell lines that are sensitive to PARP inhibitor, Compound 1, exhibit high grade MSI.

[00245] **FIG. 1** shows that MDS/AML cell lines exhibited a varied response to PARP inhibitor, Compound 1. Cell lines, P39, KG-1 and Molm-13 exhibited significant cytotoxicity to Compound 1, whereas MDS/AML cell lines Molt 4, NB4 and normal peripheral blood lymphocytes exhibited relative insensitivity to Compound 1. MDS/AML cell lines were obtained from American Type Culture Collection (ATCC).

[00246] A panel of six mononucleotide repeat sequence markers (*NR21*, *NR22*, *NR24*, *Bat25*, *Mono27* and *Bat26*) were used to estimate MSI in each cell line. Cell lines sensitive to Compound 1 (P39, KG-1 and Molm-13) exhibited high grade MSI (≥ 2 loci with ≥ 3 nucleotide errors) (see **FIG. 2** and **FIG. 3**). For example, P39 showed 5/6 monoallelic variation in MSI loci, while KG-1 and Molm-13 showed 5/6 mono and bi-allelic variation in MSI loci.

[00247] **TABLE 1** presents mononucleotide repeat sequence (*NR21*, *NR22*, *NR24*, *Bat25*, *Mono27*, and *Bat26*) versus MDS/AML cell line (PBL, HL60, Jurkat, KG-1, Molm-13, Molt 4, NB4, OCI-AML3, P39, Raji, REH, DS-1, U937 and DLD1). Values refer to the size of fluorescent PCR product run in an ABI Genetic Analyzer 3130XL (bp, base pair). Underlined and bolded values were PCR products with ≥ 3 bp deletions or additions. Cell lines were classified as one of four groups: (1) MSI-stable with no aberrant MSI; (2) MSI-low with one aberrant microsatellite; (3) MSI-mid with ≥ 2 aberrant microsatellite loci; and (4) MSI-high (high grade MSI) with ≥ 3 aberrant microsatellite loci (e.g., P39, KG-1, NB4 and Molm-13).

TABLE 1: Mononucleotide repeat sequence versus MDS/AML cell line

Cell Line	<i>NR21</i> (bp) SLC7A8, 5'UTR	<i>NR22</i> (bp) TPPB5, 3'UTR	<i>NR24</i> (bp) ZNF-2, 3'UTR	<i>Bat25</i> (bp) C-kit, Intron 16	<i>Mono27</i> (bp) (map4K) Intronic	<i>Bat26</i> (bp) MSH2, Intron 5	Compound 1 sensitivity
PBL	98	136	126	126	139	116	-
HL60	98	135	126	125	140	<u>104</u> , 116	-
Jurkat	98	135	126	125	138	115	
KG-1	<u>90</u> , <u>92</u>	<u>128</u> , 132	125	<u>119</u>	<u>130</u>	<u>104</u>	+
Molm-13	<u>90</u> , 94	<u>128</u> , 132	125	<u>120</u>	<u>130</u>	<u>105</u>	+
Molt 4	96	136	126	124	<u>132</u>	114	-
NB4	<u>90</u>	<u>129</u>	125	<u>119</u> , 125	<u>130</u> , <u>136</u>	<u>104</u> , 116	-
OCI-AML3	98	135	125	120	139	116	-
P39	<u>90</u> , 98	<u>129</u> , 136	126	<u>119</u> , 123	<u>131</u> , <u>139</u>	<u>104</u> , 116	++
Raji	97	134	126	121	136	117	-
REH	98	133	125	125	137	<u>112</u>	-
SD-1	98	136	125	124	137	116	-
U937	97	135	126	<u>115</u>	139	116	-
DLD1	98	135	<u>123</u>	122	<u>132</u>	<u>113</u>	Not tested

**Example 2: MSI-high MDS/AML Cell Lines Possess MSI in the Coding Region
Microsatellites of Double Stranded DNA Repair Genes**

[00248] This example demonstrates that MSI-high MDS/AML cell lines possess MSI in the coding region of microsatellites of double stranded repair genes *Mre11*, *ATM* and *CTiP*.

[00249] Double stranded DNA repair genes *Mre11*, *ATM*, *CTiP*, *CHK1*, *PTEN*, *BLM* and *ATR* possess specific microsatellites that when mutated produce frameshift mutations. Using fluorescent PCR and Sanger sequencing, MSI at these loci in a panel of MDS/AML cell lines were tested.

[00250] Monoallelic 1 bp deletions were observed in the microsatellites of double stranded DNA repair genes *CTiP* and *Mre11* (see FIG. 4 and FIG. 5, respectively; TABLE 2) and a 2 bp deletion was observed in the microsatellite of double stranded DNA repair gene *ATM* (see FIG. 7) of the MSI-high cell lines P39, KG-1, NB4 and Molm-13. These specific microsatellite deletions were not observed in cell lines that were MSI-stable (see FIG. 6; TABLE 2). No microsatellite deletions were observed for any of the cell lines for *CHK1*, *Rad50*, *PTEN*, *BLM* and *ATR*.

[00251] TABLE 2 presents the MSI data for double stranded DNA repair genes (*Rad50*, *Mre11*, *CTiP*, *CHK1*, *BLM*, *PTEN*, *ATM* and *ATR*) versus MDS/AML cell line (PBL, KG-1, Molm-13, Molt 4, NB4, P39 and DLD1). Values refer to the size of fluorescent PCR product run in an ABI Genetic Analyzer 3130XL (bp, base pair). Underlined and bolded values were PCR products with ≥ 3 bp deletions or additions.

TABLE 2: Microsatellite deletions in double stranded DNA repair genes in various MDS/AML cell line

Cell Line	<i>Rad50</i>	<i>Mre11</i>	<i>CTiP</i>	<i>CHK1</i>	<i>BLM</i>	<i>PTEN</i>	<i>ATM</i>	<i>ATR</i>
PBL	124	110/111	133	135	147	110,138	140	145
KG-1	124	<u>109</u> /111	<u>132</u> /133	135	147	110	<u>138</u>	144/145
Molm-13	124	<u>109</u> /111	<u>132</u> /133	135	147	110	<u>138</u>	144/145
Molt 4	124	110/111	133	135	147	110	140	145
NB4	124	<u>109</u> /111	<u>132</u> /133	135	147	110	<u>138</u>	144/145
P39	124	<u>109</u> /111	<u>132</u> /133	135	147	110	<u>139</u>	144/145
DLD1	124	<u>109</u>	133	136	147	110	<u>138</u>	145

Example 3: Intronic Mononucleotide Microsatellite Mutations Generate Aberrant Transcript Splice Products in *ATM* (497del22) and *Mre11* (315d3el88)

[00252] This example demonstrates that intronic mononucleotide microsatellite mutations generate aberrant transcript splice products in double stranded DNA repair genes *ATM* (497del22) and *Mre11* (315d3el88) in MSI-high MDS/AML cell lines only.

[00253] PCR for exon 8 of *ATM* and exon 5 of *Mre11* was performed on the cDNA of cell lines DNL, Jurkat, K562, KG-1, Molm-13, Molt 4, NB4 and P39. The PCR of cDNA from exon 8 of *ATM* (FIG. 8) and exon 5 of *Mre11* (FIG. 9) showed aberrant splice transcripts in MSI-high cell lines P39, Molm-13 and KG-1.

Example 4: High Risk MDS Patients' Cells Exhibit MSI Correlating with Chromosomal Instability

[00254] This example demonstrates that high risk MDS patients exhibit MSI correlating with chromosomal instability.

[00255] High risk MDS is associated with chromosomal instability, an increased likelihood of AML transformation and poor prognosis. High risk MDS patients were tested using a panel of six mononucleotide repeat sequence markers (*NR21*, *NR22*, *NR24*, *Bat25*, *Mono27* and *Bat26*) by Sanger sequencing and fluorescent PCT MSI analysis, and were further tested for chromosomal instability and mutations in their *CTiP* DNA repair genes. Cytogenetics were determined using Giemsa staining at metaphase spreads. Single Nucleotide Polymorphisms Analysis (SNPA) was used to determine cryptic chromosomal abnormalities, e.g., uniparental disomy (UPD), not seen using conventional cytogenetic analysis.

[00256] The results are presented in FIG. 10 and TABLE 3. Of the 63 high risk MDS patients, 13 (21%) exhibited MSI (9 MSI-low and 4 MSI-high). Of these 13 MSI-positive patients, 7 (4 MSI-high, 3 MSI-low) exhibited monosomy 7 and other complex chromosomal abnormalities (Group 1); 2 (MSI-low) patients exhibited isolated monosomy 7 (Group 2); and 4 (MSI-low) exhibited normal cytogenetics (Group 3). Significantly, Group 3 with MSI and normal cytogenetics all exhibited widespread uniparental disomy (UPD) and cryptic chromosome changes, as determined by single nucleotide polymorphism analysis (SNPA). By contrast, 12 of the 63 high risk MDS patients (19%) found to be cytogenetically normal and lacking UPD and genomic aberrations by SNPA did not exhibit MSI. Further, 3 patients with MSI-high (Group 1) and 1 patient with MSI-low (Group 3) exhibited a monoallelic 1 bp deletion in the *CTiP* exon coding microsatellite (see FIG. 10), which would result in an abbreviated *CTiP* gene transcript.

TABLE 3: Incidence of chromosomal instability in high risk MDS patients

Patient	Loci (No.; Mononucleotide Repeat Sequence)	Cytogenetics abnormal?	SNPA/UPD?	CTiP Mutation?
1	1; <i>NR21</i>	No	Yes	No
2	2; <i>NR21</i> + <i>Bat25</i>	Yes	Yes	Yes
3	1; <i>Bat25</i>	No	Yes	No
4	1; <i>NR21</i>	No	Yes	No

5	1; <i>NR24</i>	Yes	Yes	Yes
6	2; <i>NR21 + Bat25</i>	Yes	Yes	Yes
7	1; <i>NR21 + Bat25</i>	Yes	Yes	Yes
8	1; <i>Bat25</i>	Yes	Yes	No
9	1; <i>Bat25</i>	Yes	Yes	No
10	1; <i>NR24</i>	Yes	Yes	No
11	2; <i>NR21 + Bat25</i>	Yes	Yes	No
12	1; <i>NR21</i>	No	Yes	No
13	1; <i>Bat25</i>	Yes	Yes	No

[00257] Identification of a cohort of MDS/AML patients with MSI would be helpful for screening of candidates for PARP inhibitor therapy.

Example 5: Screening of MDS/AML Patients for PARP Inhibitor Therapy

[00258] This example provides an exemplary screening of MDS/AML patients for PARP inhibitor therapy.

[00259] Microsatellite markers in genomic DNA of a sample from a MDS/AML patient, *e.g.*, a tumor biopsy sample, may be isolated and compared to microsatellite markers in genomic DNA isolated from normal tissue or cells in the patient, or in a healthy reference individual, in order to detect MSI. Specifically, microsatellite loci may be amplified and genotyped. Specific procedures used in this example are provided below.

[00260] Samples and DNA isolation. The sample may be a histological sample, a biopsy, or a cytological sample such as, *e.g.*, a smear, a swab, a wash, a body fluid containing. The sample may comprise a fixed or preserved specimen, such as a cytological or a histological specimen. The sample may be a tumor biopsy tissue obtained by surgical resection.

[00261] PCR and Microsatellite Analysis. A panel of five nearly monomorphic mononucleotide markers (*NR21*, *NR22*, *NR24*, *Bat25*, *Bat26* and *Mono27*) may be used for MSI determination of the patient's genomic DNA. The analysis may involve fluorescent polymerase chain reaction (PCR) and/or Sanger sequencing.

[00262] Immunohistochemistry: Conventional cytogenetic may be used to analyze for chromosomal abnormalities in the patient's sample. Single Nucleotide Polymorphisms Analysis (SNPA) may be used to analyze for cryptic chromosomal abnormalities in the patient's sample.

[00263] Result: MSI comprising a ≥ 3 bp deletion or insertion in one or more microsatellite(s) of the patient's malignant DNA, correlating with chromosomal instability, indicates that the patient is likely to respond to treatment with a compound of Formula I or II.

Example 6: Phase II Clinical Trial of the Safety and Efficacy of Compounds of Formula (I) or (II)

[00264] This example provides an exemplary phase II trial which purpose is to study the side effects and best dose of a compound of Formula (I) or (II) and to determine how well it works in treating MDS/AML patients with MSI in malignant cells.

Objectives:

Primary:

- A. To determine the response rate to a compound of Formula (I) or (II) in MDS/AML patients with or without MSI
- B. To evaluate the toxicity of a compound of Formula (I) or (II) in these patients

Secondary:

- A. To evaluate the time to progression and overall survival in patients treated with a compound of Formula (I) or (II)
- B. To study pharmacokinetics of a compound of Formula (I) or (II) in these patients
- C. To evaluate the Poly(ADP-ribose) polymerase (PARP) activity in peripheral blood lymphocytes from these patients

Tertiary:

- A. To evaluate PARP expression using quantitative western blotting immuno-assays
- B. To investigate pharmacogenomics, including CYP2D6 and CYP3A5, drug transport proteins, as well as polymorphisms in the genes coding for the PARP enzymes themselves
- C. To analyze for mutations in their DNA repair genes from original diagnostic biopsies (when possible)
- D. To analyze paraffin sections for DNA repair enzyme status using immunohistochemical techniques (from biopsies, when possible)
- E. To analyze cells obtained from ascitic or pleural fluid (where possible) for primary cell culture for DNA double strand break repair pathway function
- F. To perform composite microsatellite analysis of mononucleotide repeat sequences to determine MSI (from biopsies, when possible)
- G. To perform conventional cytogenetic analysis to determine chromosomal abnormalities (from biopsies, when possible)
- H. To perform Single Nucleotide Polymorphisms Analysis (SNPA) to determine cryptic chromosomal abnormalities (from biopsies, when possible)
- F. To analyze for PARP activity and PARP expression (from biopsies, when possible)

Patients: Eligible subjects will be men and women 18 years and older

Criteria:

- Disease Characteristics:

- Patients with one of the following types of bone marrow disorders as determined by the Laboratory of Pathology or Hematology at the Clinical Center, National Institutes of Health: MDS, AML or chronic myelomonocytic leukemia
- No more than 3 prior chemotherapy regimens for patients with leukemia
- Measurable disease, as defined by RECIST criteria and measured by X-ray, CT scan, or MRI
 - Patients with bone disease must have other measurable disease for evaluation
 - Previously irradiated lesions cannot be used for measurable disease
- No known brain metastases
- Patient Characteristics:
 - WHO performance status 0-1
 - Life expectancy ≥ 12 weeks
 - Hemoglobin ≥ 9.0 g/dL
 - Absolute neutrophils $\geq 1,500/\text{mm}^3$
 - Platelets $\geq 100,000/\text{mm}^3$
 - Serum bilirubin ≤ 1.5 times upper limit of normal (ULN)
 - ALT or AST ≤ 2.5 times ULN (≤ 5 times ULN if due to tumor)
 - Glomerular filtration rate (GFR) ≥ 50 mL/min
 - Not pregnant or nursing
 - Negative pregnancy test
 - Fertile patients must use two highly effective forms of contraception (*i.e.*, oral, injected, or implanted hormonal contraception, intrauterine device, barrier method of condom plus spermicide, or are surgically sterile) 4 weeks prior to (females), during, and for 6 months after (males and females) completion of study therapy
 - Able to cooperate with treatment and follow-up
 - No non-malignant systemic disease, including active uncontrolled infection
 - No other concurrent malignancy, except adequately treated cone-biopsied carcinoma in situ of the uterine cervix, basal cell or squamous cell carcinoma of the skin, or breast and ovarian carcinoma
 - Cancer survivors who have undergone potentially curative therapy for a prior malignancy, have no evidence of that disease for 5 years, and are deemed at low risk for recurrence are eligible
 - No active or unstable cardiac disease or history of myocardial infarction within the past 6 months
 - Patients with cardiovascular signs or symptoms should have a MUGA scan or echocardiogram, and those with a left ventricular ejection fraction (LVEF) below the institutional limit of normal should be excluded

- No other condition which, in the investigator's opinion, would not make the patient a good candidate for this study

Prior Concurrent Therapy:

- At least 4 weeks since prior radiotherapy (except for palliative reasons), endocrine therapy, immunotherapy or chemotherapy (6 weeks for nitrosoureas and mitomycin C)
- At least 4 weeks since prior major thoracic and/or abdominal surgery and recovered
- Concurrent radiotherapy for the control of bone pain or skin lesions allowed, but not within 5 days of the last dose of study drug
- Concurrent bisphosphonates allowed provided the dose is stable and treatment was started at least 2 weeks prior to recruitment
- No unresolved toxicities (CTCAE $\geq$ grade 1) from prior treatments (except for alopecia)
- No concurrent anticancer therapy or investigational drugs
- No concurrent tetracycline antibiotic therapy for prolonged periods (short courses [5-7 days] for treatment of infection are allowed)
- Study Design: This is a dose-escalation study followed by an open label multicenter study. Patients will be stratified according to disease state (MDS vs AML vs chronic myelomonocytic leukemia) and MSI status. Patients will receive a compound of Formula (I) or (II) (at one of several possible dosages) over 30 minutes once daily on days 1-5. Treatment repeats every 21 days for 12 courses in the absence of disease progression or unacceptable toxicity. Patients who achieve stable or responding disease may receive additional courses of treatment at the discretion of the chief investigator or Drug Development Office (DDO). Patients will undergo blood sample collection periodically for pharmacokinetic and pharmacodynamic studies. Samples will be analyzed for tumor marker measurements, plasma levels of a compound of Formula (I) or (II) via liquid chromatography/mass spectrometry/mass spectrometry, PARP activity, and PARP protein expression via western blotting immunoassays. Paraffin embedded sections from original diagnostic biopsy are also collected and analyzed for PARP protein expression via immunohistochemical technique. Pleural and ascitic fluid may be collected and analyzed for DNA DS break repair proficiency via immunohistochemical technique. Some patients will also undergo biopsy of tumors and samples will be analyzed for DNA repair enzyme mutation status, PARP activity via validated PARP immunoblotting assay, and chromosomal status using conventional cytogenetic analysis and SNPA analysis. After completion of the study treatment, patients will be followed for 28 days.

Primary Outcome Measures:

- Assessment of antitumor activity according to RECIST using tumor size measured clinically or radiologically with CT scan, MRI, plain x-ray, or other imaging techniques

- Safety profile

Secondary Outcome Measures:

- Time to progression and overall survival
- Plasma levels by Liquid Chromatography/Mass Spectrometry/Mass Spectrometry
- Poly(ADP-ribose) polymerase (PARP) activity measured *ex vivo* using validated assays
- PARP expression using quantitative Western blotting immuno-assays
- Pharmacogenomics including CYP2D6 and CYP3A5, drug transport proteins, as well as polymorphisms in the genes coding for the PARP enzymes themselves
- DNA repair enzyme mutation status, MSI status, PARP activity, and PARP expression in tumor biopsy samples (when possible)
- DNA repair enzyme status using immunohistochemical techniques in paraffin sections from original diagnostic biopsies/operative procedures (when possible)
- Chromosomal status using conventional cytogenetic analysis and SNPA analysis (when possible)
- DNA double strand break repair pathway function in cells obtained from ascitic or pleural fluid (when possible) for primary cell culture

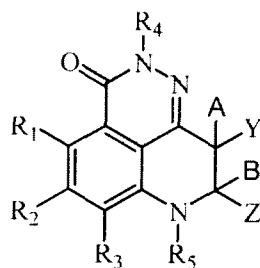
[00265] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following description. It should be understood, however, that the description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the present description will become apparent from this detailed description.

[00266] All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) in a patient with MDS or AML, comprising administering to a patient with MDS or AML a therapeutically effective amount of a compound of Formula (I):



Formula (I),

wherein:

Y and Z are each independently selected from the group consisting of:

- a) an aryl group optionally substituted with 1, 2, or 3 R_6 ;
- b) a heteroaryl group optionally substituted with 1, 2, or 3 R_6 ; and
- c) a substituent independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkylene, oxo, heterocycloalkyl, heterocycloalkylalkyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl alkylsulfonyle, arylsulfonyle, heteroarylsulfonyle, $(NR_A R_B)$ alkylene, $(NR_A R_B)$ carbonyl, $(NR_A R_B)$ carbonylalkylene, $(NR_A R_B)$ sulfonyle, and $(NR_A R_B)$ sulfonylealkylene;

R_1 , R_2 , and R_3 are each independently selected from the group consisting of hydrogen, halogen, alkenyl, alkoxy, alkoxy carbonyl, alkyl, cycloalkyl, alkynyl, cyano, haloalkoxy, haloalkyl, hydroxyl, hydroxyalkylene, nitro, $NR_A R_B$, $NR_A R_B$ alkylene, and $(NR_A R_B)$ carbonyl;

A and B are each independently selected from the group consisting of hydrogen, Br, Cl, F, I, OH, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, alkoxy, and alkoxyalkyl, wherein C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, alkoxy, and alkoxyalkyl are optionally substituted with at least one substituent selected from the group consisting of OH, NO_2 , CN, Br, Cl, F, I, C_1 - C_6 alkyl, and C_3 - C_8 cycloalkyl, wherein B is not OH;

R_A and R_B are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, and alkylcarbonyl; or R_A and R_B taken together with the atom to which they are attached form a 3-10 membered heterocycle ring optionally having one to three heteroatoms or hetero functionalities selected from the group consisting of -O-, -NH-, -N(C_1 - C_6 alkyl)-, -NCO(C_1 - C_6 alkyl)-, -N(aryl)-, -N(aryl- C_1 - C_6 alkyl)-, -N(substituted-aryl- C_1 - C_6 alkyl)-, -N(heteroaryl)-, -N(heteroaryl- C_1 - C_6 alkyl)-, -N(substituted-heteroaryl- C_1 - C_6 alkyl)-, and -S- or $S(O)_q$ -, wherein q is 1 or 2 and the 3-10 membered heterocycle ring is optionally substituted with one or more substituents;

R₄ and R₅ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxyalkyl, haloalkyl, hydroxyalkylene, and (NR_AR_B)alkylene; and each R₆ is selected from the group consisting of OH, NO₂, CN, Br, Cl, F, I, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₈heterocycloalkyl, C₂-C₆alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C₂-C₆alkynyl, aryl, arylalkyl, C₃-C₈cycloalkylalkyl, haloalkoxy, haloalkyl, hydroxyalkylene, oxo, heteroaryl, heteroarylalkoxy, heteroaryloxy, heteroarylthio, heteroarylalkylthio, heterocycloalkoxy, C₂-C₈heterocycloalkylthio, heterocyclooxy, heterocyclothio, NR_AR_B, (NR_AR_B)C₁-C₆alkylene, (NR_AR_B)carbonyl, (NR_AR_B)carbonylalkylene, (NR_AR_B)sulfonyl, and (NR_AR_B)sulfonylalkylene; or a single isomer, stereoisomer, or enantiomer, or mixture thereof; optionally as a salt, solvate, chemically protected form or prodrug thereof; and additionally optionally with at least one of a pharmaceutically acceptable diluent, excipient, and carrier.

2. The method of claim 1, wherein a malignant cell's DNA from the patient exhibits Microsatellite Instability (MSI) in at least one microsatellite.

3. The method of claim 2, wherein the MSI comprises an insertion or deletion in the at least one microsatellite.

4. The method of claim 1, further comprising analyzing for MSI in at least one microsatellite in a malignant cell from the patient, wherein said analyzing comprises using primers to amplify the at least one microsatellite nucleotide sequence.

5. The method of claim 4, wherein the at least one microsatellite is *NR21*, *NR22*, *NR24*, *Bat25*, *Bat26*, *Mono27*, or a microsatellite in a gene selected from the group consisting of *Mre11*, *ATM* and *CTIP*.

6. The method of claim 5, wherein the at least one microsatellite is selected from the group consisting of *NR21*, *NR24* and *Bat25*.

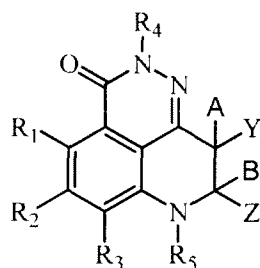
7. The method of claim 3, wherein the MSI comprises an insertion or deletion of 3 or more base pairs in the at least one microsatellite.

8. The method of claim 3, where the at least one microsatellite is in a gene coding a double stranded DNA repair protein, and/or wherein the MSI leads to an inactivation of a DNA repair function, and/or wherein the MSI results in a frameshift mutation in expression of a double stranded DNA repair gene.

9. The method of claim 8, wherein the MSI leads to an inactivation of a DNA repair function, wherein the DNA repair function is governed by a double stranded DNA repair gene selected from the group consisting of *Mre11*, *ATM* and *CTiP*.

10. The method of claim 1, wherein the compound is 5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-8,9-dihydro-2*H*-pyrido[4,3,2-*de*]phthalazin-3(7*H*)-one, or a single isomer, stereoisomer, or enantiomer, or mixture thereof, or a pharmaceutically acceptable salt thereof.

11. A compound of Formula (I):



Formula (I),

wherein:

Y and Z are each independently selected from the group consisting of:

- an aryl group optionally substituted with 1, 2, or 3 R_6 ;
- a heteroaryl group optionally substituted with 1, 2, or 3 R_6 ; and
- a substituent independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkynyl, arylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkylene, oxo, heterocycloalkyl, heterocycloalkylalkyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, $(NR_A R_B)$ alkylene, $(NR_A R_B)$ carbonyl, $(NR_A R_B)$ carbonylalkylene, $(NR_A R_B)$ sulfonyl, and $(NR_A R_B)$ sulfonylalkylene;

R_1 , R_2 , and R_3 are each independently selected from the group consisting of hydrogen, halogen, alkenyl, alkoxy, alkoxycarbonyl, alkyl, cycloalkyl, alkynyl, cyano, haloalkoxy, haloalkyl, hydroxyl, hydroxyalkylene, nitro, $NR_A R_B$, $NR_A R_B$ alkylene, and $(NR_A R_B)$ carbonyl;

A and B are each independently selected from the group consisting of hydrogen, Br, Cl, F, I, OH, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, alkoxy, and alkoxyalkyl, wherein C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, alkoxy, and alkoxyalkyl are optionally substituted with at least one substituent selected from the group consisting of OH, NO_2 , CN, Br, Cl, F, I, C_1 - C_6 alkyl, and C_3 - C_8 cycloalkyl, wherein B is not OH;

R_A and R_B are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, and alkylcarbonyl; or R_A and R_B taken together with the atom to which they are attached form a 3-10

membered heterocycle ring optionally having one to three heteroatoms or hetero functionalities selected from the group consisting of -O-, -NH-, -N(C₁-C₆-alkyl)-, -NCO(C₁-C₆-alkyl)-, -N(aryl)-, -N(aryl-C₁-C₆-alkyl)-, -N(substituted-aryl-C₁-C₆-alkyl)-, -N(heteroaryl)-, -N(heteroaryl-C₁-C₆-alkyl)-, -N(substituted-heteroaryl-C₁-C₆-alkyl)-, and -S- or S(O)_q-, wherein q is 1 or 2 and the 3-10 membered heterocycle ring is optionally substituted with one or more substituents;

R₄ and R₅ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxyalkyl, haloalkyl, hydroxyalkylene, and (NR_AR_B)alkylene; and

each R₆ is selected from the group consisting of OH, NO₂, CN, Br, Cl, F, I, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₈heterocycloalkyl, C₂-C₆alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, C₂-C₆alkynyl, aryl, arylalkyl, C₃-C₈cycloalkylalkyl, haloalkoxy, haloalkyl, hydroxyalkylene, oxo, heteroaryl, heteroarylalkoxy, heteroaryloxy, heteroarylthio, heteroarylalkylthio, heterocycloalkoxy, C₂-C₈heterocycloalkylthio, heterocyclooxy, heterocyclothio, NR_AR_B, (NR_AR_B)C₁-C₆alkylene, (NR_AR_B)carbonyl, (NR_AR_B)carbonylalkylene, (NR_AR_B)sulfonyl, and (NR_AR_B)sulfonylalkylene; or

a single isomer, stereoisomer, or enantiomer, or mixture thereof;

optionally as a salt, solvate, chemically protected form or prodrug thereof; and additionally optionally with at least one of a pharmaceutically acceptable diluent, excipient, and carrier,

for use in the treatment of MDS or AML in a patient with MDS or AML.

12. The compound of claim 11, wherein a malignant cell from the patient exhibits MSI in a microsatellite.

13. The compound of claim 12, wherein the malignant cell exhibits MSI in at least two microsatellites.

14. A method for identifying an MDS or AML patient likely to respond to PARP inhibitor therapy for treatment of MDS or AML comprising:

analyzing for MSI in at least one microsatellite in a malignant cell from the MDS or AML patient;

wherein the MSI comprises a deletion or insertion of three or more base pairs in the at least one microsatellite; and

wherein the presence of MSI in the at least one microsatellite identifies the patient as likely to respond to PARP inhibitor therapy.

15. The method of claim 14, wherein the PARP inhibitor is 5-fluoro-8-(4-fluorophenyl)-9-(1-methyl-1H-1,2,4-triazol-5-yl)-8,9-dihydro-2H-pyrido[4,3,2-de]phthalazin-3(7H)-one, or a single isomer, stereoisomer, or enantiomer, or mixture thereof, or a pharmaceutically acceptable salt thereof.

16. The method of claim 14, wherein said analyzing comprises using primers to amplify the at least one microsatellite nucleotide sequence.

17. The method of claim 14, wherein the at least one microsatellite is *NR21*, *NR22*, *NR24*, *Bat25*, *Bat26*, *Mono27* or a microsatellite in a gene selected from the group consisting of *Mre11*, *ATM* and *CTiP*.

18. The method of claim 17, wherein the at least one microsatellite selected from the group consisting of *NR21*, *NR24* and *Bat25*.

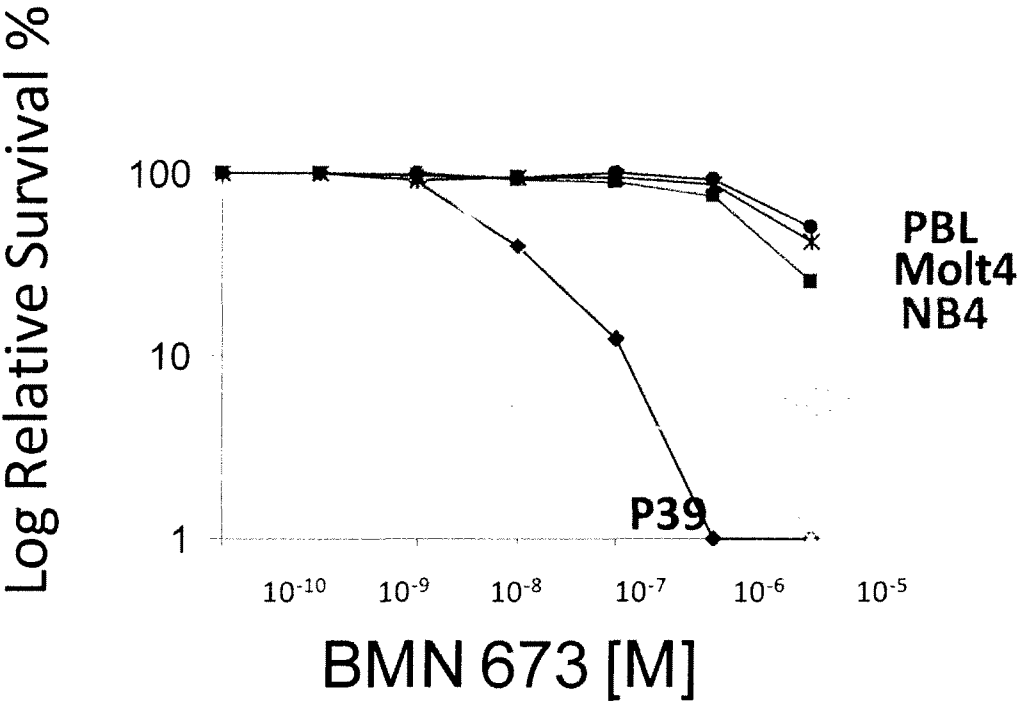
19. The method of claim 14, wherein the MSI leads to inactivation of a DNA repair function.

20. The method of claim 19, wherein the DNA repair function is that of a double stranded DNA repair gene expression product selected from the group of double stranded DNA repair genes consisting of *Mre11*, *ATM* and *CTiP*.

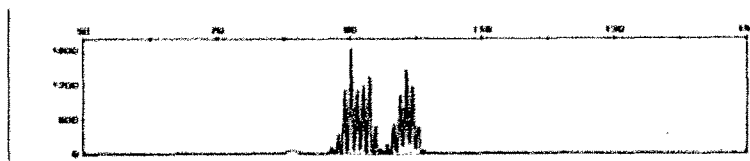
21. The method of claim 14, further comprising performing a cytogenetic analysis for chromosomal abnormalities in the malignant cell.

22. The method of claim 14, wherein at least three microsatellites are analyzed for MSI.

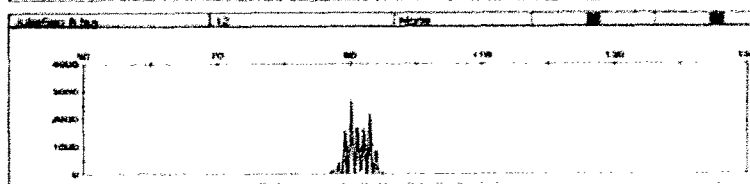
23. The method of claim 14, wherein the at least one microsatellite is in a double stranded DNA repair gene.



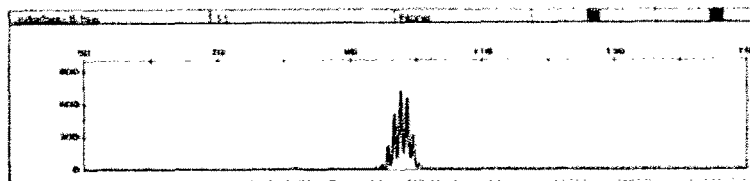
2 / 10

NR21(SLC7A8, 5'UTR), T₂₁

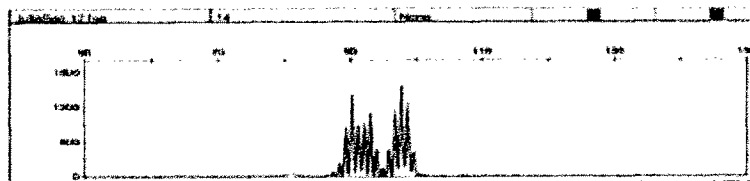
NB4



KG-1



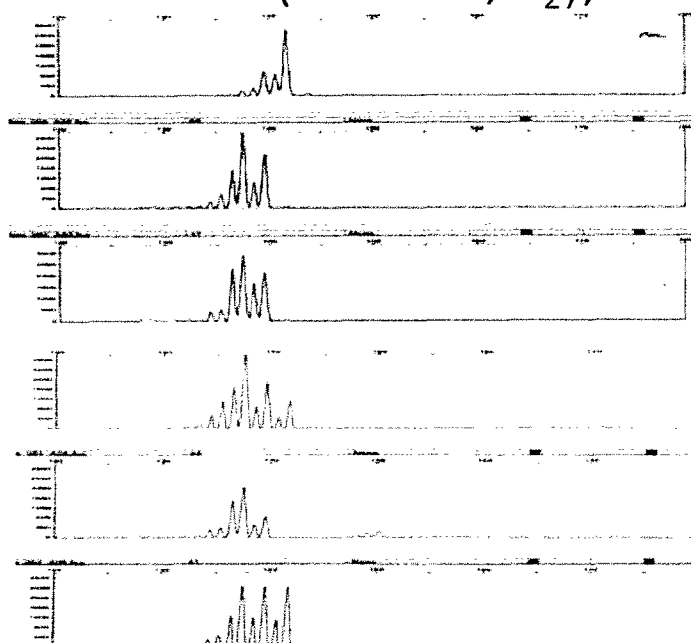
Normal PBL



P39

ATTCCAGCCGGAGTCGCTGGCACAGTTCTATTTTATAT
TTAAATGTATGTCTCCCTGGCCTTTTTTTTTTTTTTTT
TTTTAGCAACACTTTTCTTGTTTGTAACGCGAGTGAC
CAG (SEQ ID NO. 9)

3 / 10

Mono27 (MAP4K3, A₂₇)

Normal PBL

KG-1

Molm-13

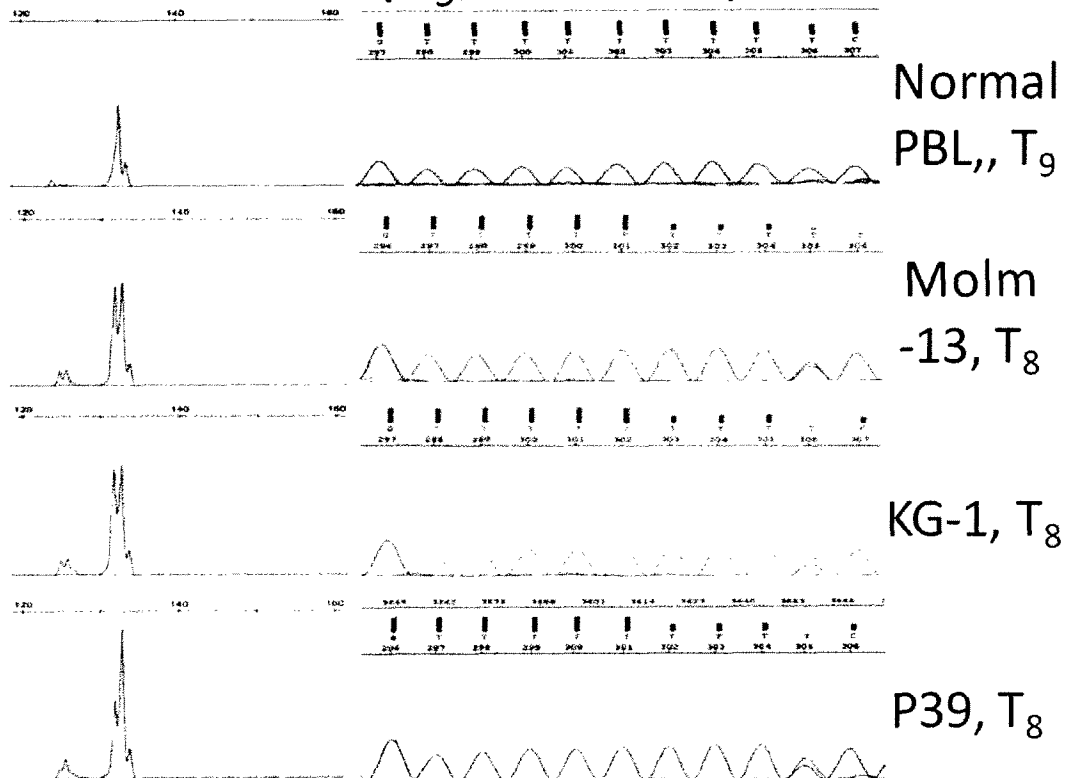
Molt 4

NB4

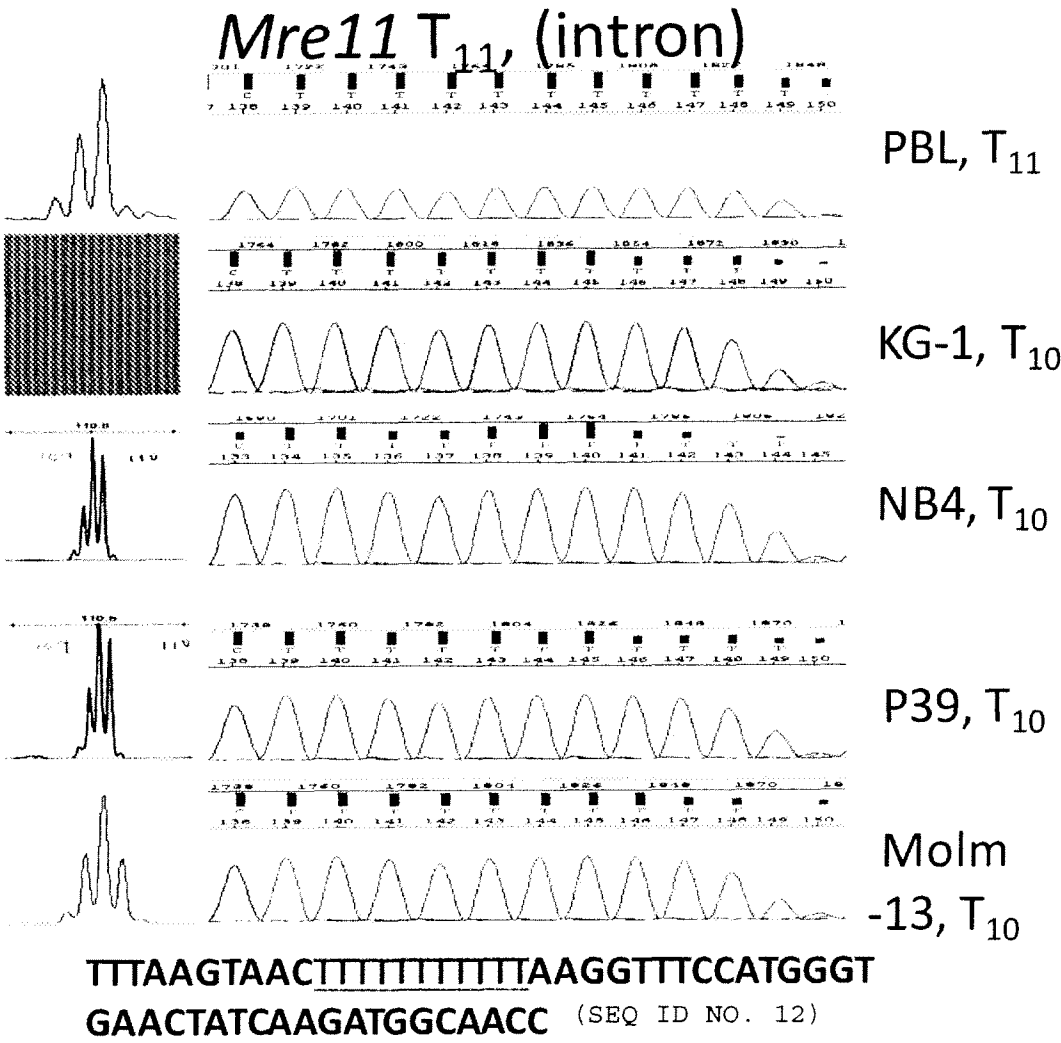
P39

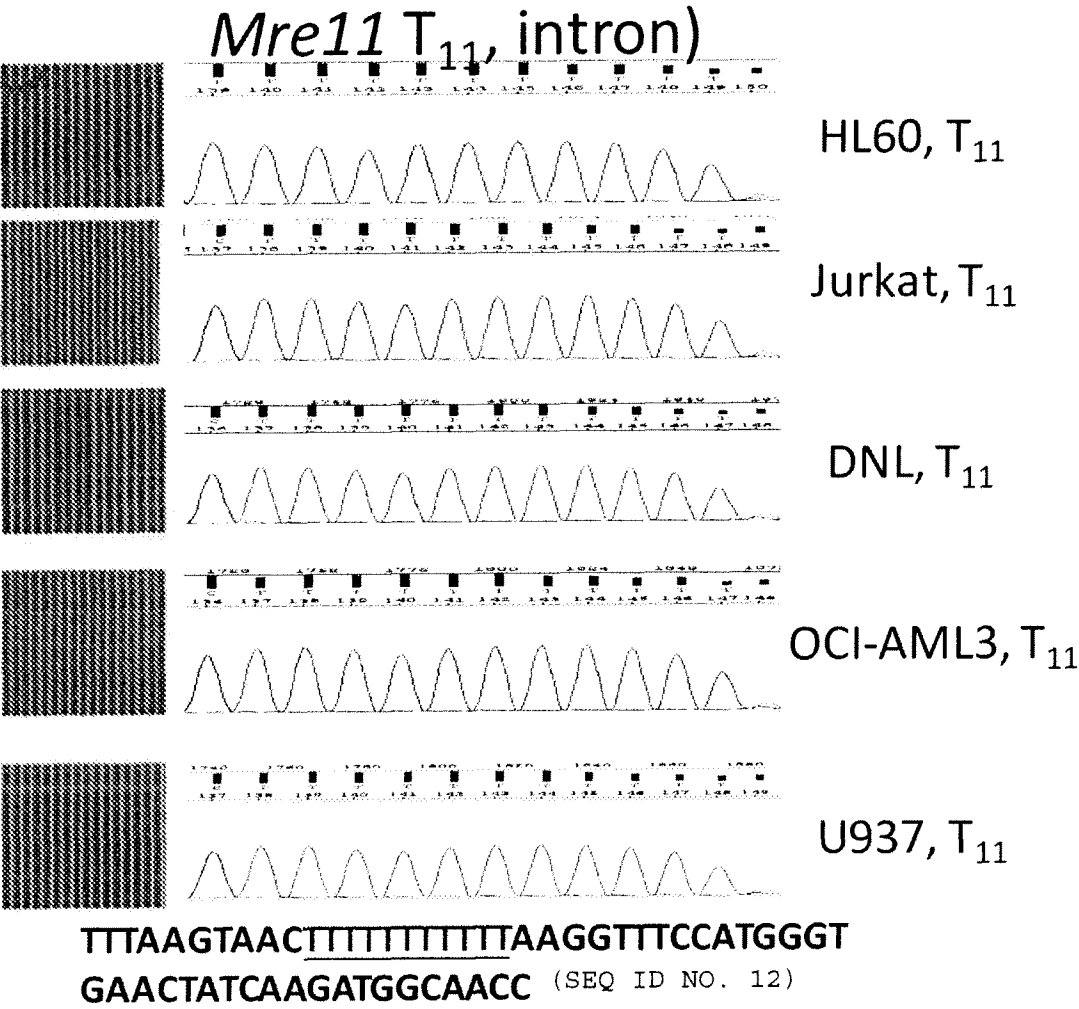
TGCAGTGAGCTGAGATTGCGCCACTGCACTCCAGCGTG
GGAGACAGAGCAAGACTCTGCCTCAAAAAAAAAAAAAA
AAAAAAAAAAAAATCCTGGTTTACTTTTTTTCTTTT (SEQ ID NO. 10)

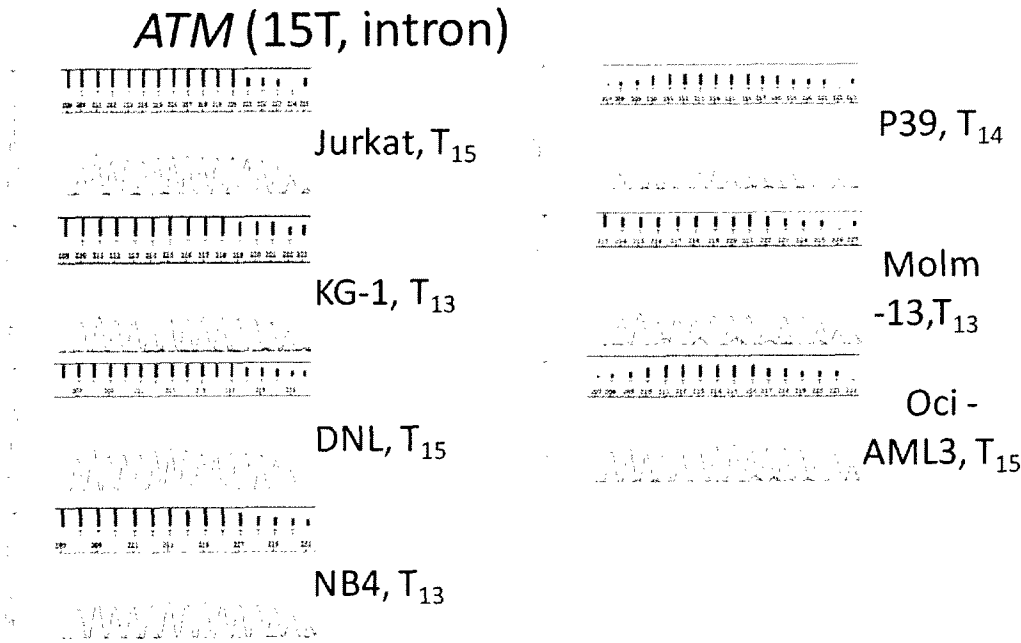
4 / 10

CTiP (T₉, exon 11)

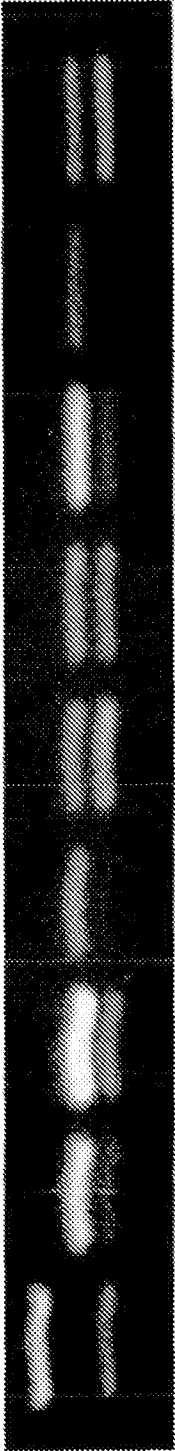
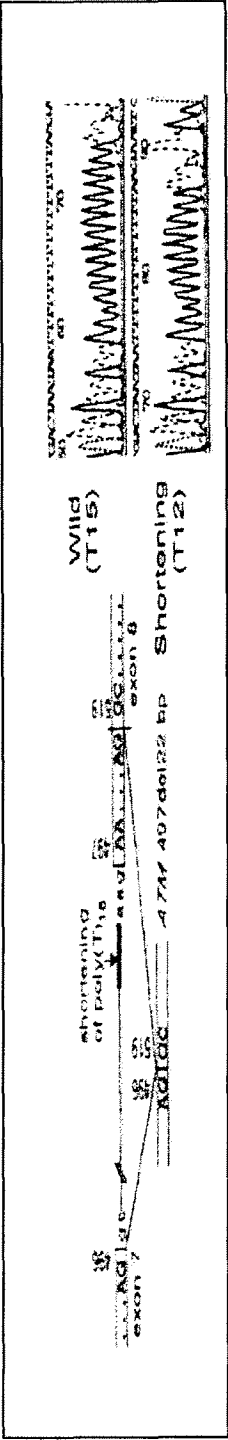
CAGATTTTGATCTAGTTTTTTCTAATCTAGATATACA
 AGTGTTGCTAAAAGGGAGTGTTCAGATGTTTTT
 TTTTCCAGGCTGTAAAAAAGAAGGGGA (SEQ ID NO. 11)



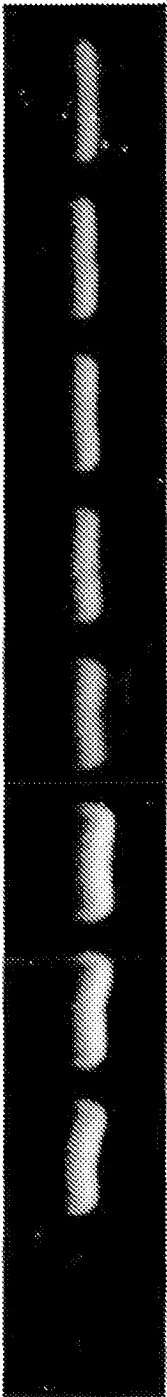
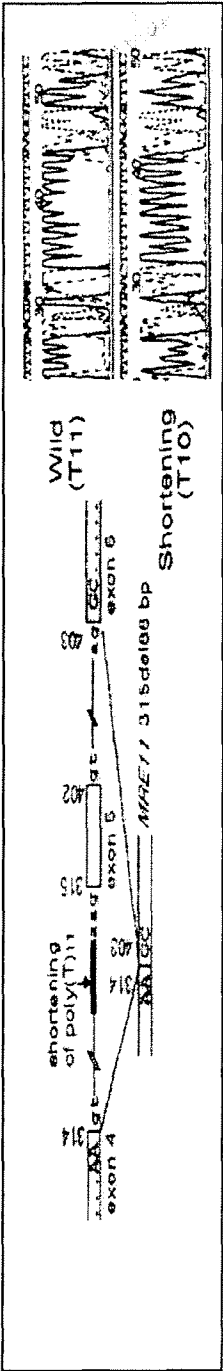




TACATTTTGATTTTTAAAAAATCATGACTAATAATTTTTTTTTTTTTTTTAAG
AATTGTTCTCTGTGTACT (SEQ ID NO. 13)

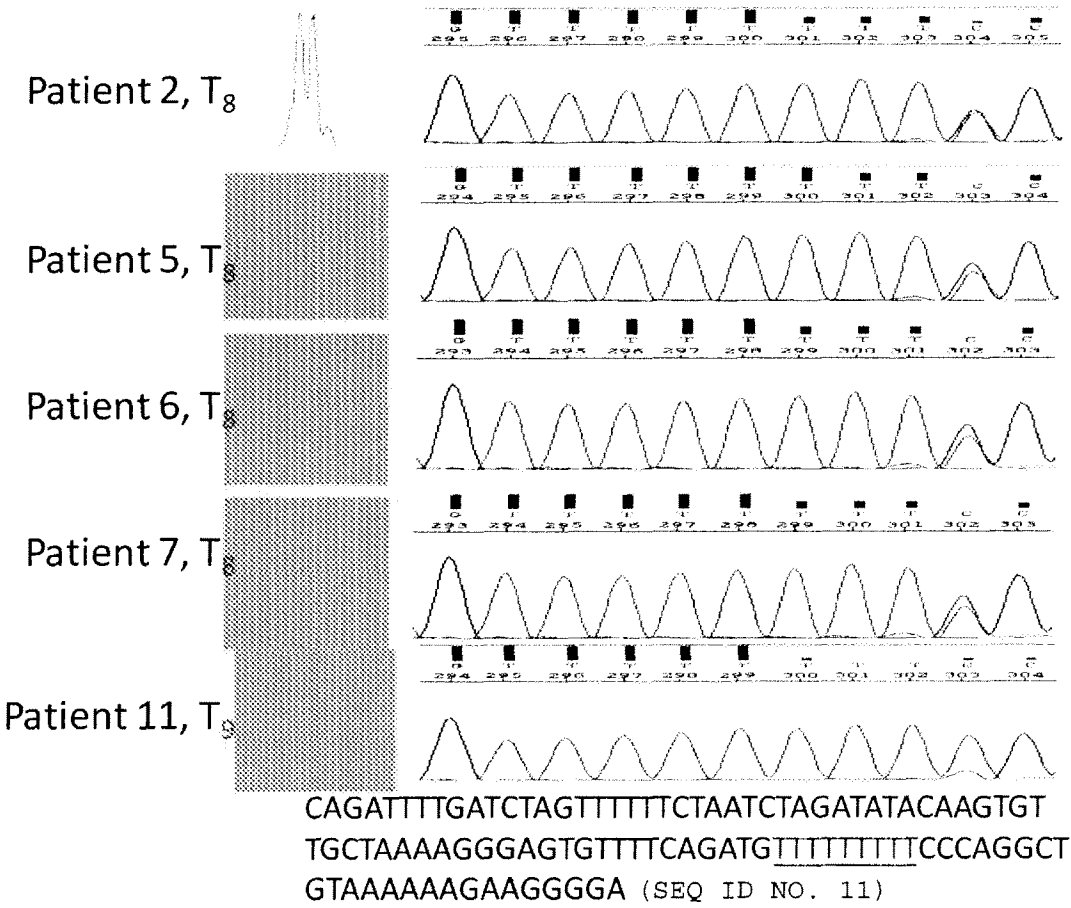


	DNL	Jurkat	K562	KG-1Molm-13	Molt4	NB4	P39
RI	0.3	0.45	0.2	1.15	1.05	0.20	1.0
Poly(T) ₁₅ mutation	0	0	0	-2	-2	-2	-1



	DNL	Jurkat	K562	KG-1	Molm-13	Molt4	NB4	P39
RI	0.1	0.1	0.15	0.55	0.35	0.25	0.20	0.5
Poly(T) ₁₁ mutation	0	0	0	-1	-1	0	-1	-1

CTiP (T₉, exon 11)



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/039045

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/5025 C12Q1/68 A61P35/02
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)

A61K C12Q

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 practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GAYMES TERRY J ET AL: "Microsatellite Instability (MSI) In High Risk Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukaemia (AML) Cells Promotes Frameshift Mutations In DNA Repair Genes: Indications for PARP Inhibitor Therapy", BLOOD; 52ND ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY (ASH), AMERICAN SOCIETY OF HEMATOLOGY, US; ORLANDO, FL, USA, vol. 116, no. 21, 1 November 2010 (2010-11-01), page 513, XP008147850, ISSN: 0006-4971 the whole document ----- -/--	1-13

☒ Further documents are listed in the continuation of Box C.

☒ 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 document 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

23 April 2012

Date of mailing of the international search report

27/04/2012

Name and mailing address of the ISA/

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Fax: (+31-70) 340-3016

Authorized officer

Cielen, Elsie

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/039045

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GAYMES TERRY J ET AL: "Inhibitors of poly ADP-ribose polymerase (PARP) induce apoptosis of myeloid leukemic cells: potential for therapy of myeloid leukemia and myelodysplastic syndromes", HAEMATOLOGICA, FONDAZIONE FERRATA STORTI, ROME, IT, vol. 94, no. 5, 1 May 2009 (2009-05-01), pages 638-646, XP008147848, ISSN: 0390-6078, DOI: 10.3324/HAEMATOL.2008.001933 cited in the application abstract page 639, column 1, paragraph 3 page 644, column 1, paragraph 2 - column 2, paragraph 1 page 645, column 1, paragraph 2 page 646, column 1, paragraph 2 - column 2, paragraph 1	1-13
Y	----- HAM MARIA FRANCISCA ET AL: "Impairment of double-strand breaks repair and aberrant splicing of ATM and MRE11 in leukemia-lymphoma cell lines with microsatellite instability", CANCER SCIENCE, vol. 97, no. 3, March 2006 (2006-03), pages 226-234, XP002668278, ISSN: 1347-9032 cited in the application abstract page 227, column 1, paragraph 1 page 227, column 1, paragraph 3 - column 2, paragraph 1 page 228, column 2, paragraph 3 - page 229, column 1, paragraph 1 table 1	1-13
Y	----- WO 2010/017055 A2 (LEAD THERAPEUTICS INC [US]; WANG BING [US]; CHU DANIEL [US]) 11 February 2010 (2010-02-11) cited in the application page 1, paragraph [0005] - page 4, paragraph [0010] page 8, paragraph [0015] - page 12, paragraph [0018] page 12, line 20 - page 13, line 4 page 13, paragraphs [0022], [0024] page 14, paragraph [0027] page 42, paragraph [0078] page 42, paragraph [0082] - page 43 page 43, paragraph [0085] - page 44 page 45, paragraph [0099] claims 1, 2, 52, 55, 72 ----- -/--	1-13

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/039045

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 340 819 A1 (INST NAT SANTE RECH MED [FR]) 3 September 2003 (2003-09-03) page 2, paragraph [0001] page 3, paragraph [0018] - [0029] page 4, paragraph [0037] - [0038] page 5, paragraph [0043] -----	4-6
A	WO 2004/105700 A2 (GUILDFORD PHARMACEUTICALS INC [US]; KALISH VINCENT J [US]; ZHANG JIE []) 9 December 2004 (2004-12-09) page 9, paragraph 3 - page 10, paragraph 3 page 10, last paragraph - page 11, paragraph 1 page 14, last paragraph - page 15, paragraph 1 page 19, paragraph 3 table I -----	1-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/039045

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

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

1-13

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-13

A method of treating Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) in a patient with MDS or AML, comprising administering to a patient with MDS or AML a therapeutically effective amount of a compound of Formula (I), as defined in claim 1, or a single isomer, stereoisomer, or enantiomer, or mixture thereof; optionally as a salt, solvate, chemically protected form or prodrug thereof; and additionally optionally with at least one of a pharmaceutically acceptable diluent, excipient, and carrier. A compound of formula (I) as defined in claim 11, or a single isomer, stereoisomer, or enantiomer, or mixture thereof; optionally as a salt, solvate, chemically protected form or prodrug thereof; and additionally optionally with at least one of a pharmaceutically acceptable diluent, excipient, and carrier, for use in the treatment of MDS or AML in a patient with MDS or AML.

2. claims: 14-23

A method for identifying an MDS or AML patient likely to respond to PARP inhibitor therapy for treatment of MDS or AML comprising:
analyzing for MSI in at least one microsatellite in a malignant cell from the MDS or AML patient; wherein the MSI comprises a deletion or insertion of three or more base pairs in the at least one microsatellite; and wherein the presence of MSI in the at least one microsatellite identifies the patient as likely to respond to PARP inhibitor therapy.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/039045

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010017055 A2	11-02-2010	AR 072970 A1 AU 2009279944 A1 CA 2732797 A1 CN 102171214 A EP 2326650 A2 GB 2462361 A JP 2011530513 A KR 20110040973 A TW 201018688 A US 2010035883 A1 US 2011237581 A1 WO 2010017055 A2	06-10-2010 11-02-2010 11-02-2010 31-08-2011 01-06-2011 10-02-2010 22-12-2011 20-04-2011 16-05-2010 11-02-2010 29-09-2011 11-02-2010
EP 1340819 A1	03-09-2003	AT 464396 T AU 2003227532 A1 CA 2476892 A1 EP 1340819 A1 EP 1478781 A2 ES 2344636 T3 JP 4436685 B2 JP 2005518798 A US 2006068385 A1 US 2009317815 A1 WO 03072822 A2	15-04-2010 09-09-2003 04-09-2003 03-09-2003 24-11-2004 02-09-2010 24-03-2010 30-06-2005 30-03-2006 24-12-2009 04-09-2003
WO 2004105700 A2	09-12-2004	AU 2004242947 A1 AU 2010206033 A1 CA 2527420 A1 EP 1633362 A2 JP 4824566 B2 JP 2007505161 A JP 2011026347 A JP 2011032285 A MX PA05012812 A US 2005020595 A1 US 2008058325 A1 US 2009088407 A1 US 2009298837 A1 US 2010256095 A1 WO 2004105700 A2	09-12-2004 19-08-2010 09-12-2004 15-03-2006 30-11-2011 08-03-2007 10-02-2011 17-02-2011 28-02-2006 27-01-2005 06-03-2008 02-04-2009 03-12-2009 07-10-2010 09-12-2004