Cancers 2019, 11, 1014). Thus, degradation of CK1α stabilizes p53 and induces growth arrest (see, e.g., Huart et al., PLoS One 2012, 7(8), e43391). Elevation of p53 activity has been shown to have an antiproliferative and proapoptotic effect in MCL (see, e.g., Tabe et al., Clin. Cancer Res. 2009, 15(3), 933-942; Liang et al., Mod. Pathol. 2010, 23(3), 389-91).

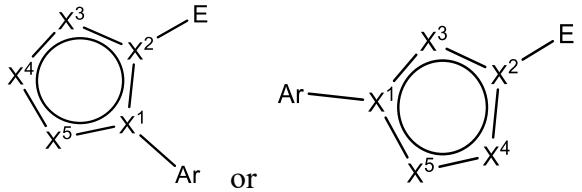
[0007] GSPT1 is a translation termination factor that is currently being explored as a therapeutic target for the treatment of acute myeloid leukemia (AML). Recent studies have identified molecular glues that degrade GSPT1 without degrading CK1α (see, e.g., Powell et al., ACS Chem. Biol. 2020, 15, 2722−2730) or that degrade GSPT1 without degrading IKZF1 (Ikaros) (see, e.g., Nishiguchi et al., J. Med. Chem. 2021, 64, 7296-7311).

[0008] Thus, there is a need for molecular glues that degrade CK1α or CK1α/GSPT1. Such molecular glues provide therapeutic options for treatment of a variety of proliferative diseases, including cancer and autoimmune diseases

SUMMARY

[0009] Provided herein are compounds and compositions that degrade CK1α or CK1α/GSPT1. In one example, the compounds are molecular glues that bind an E3 ubiquitin ligase and CK1α. In another example, the compounds are molecular glues that bind cereblon and CK1α.

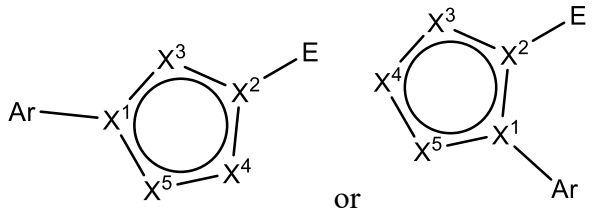
[0010] The compounds for use in the compositions and methods provided herein have Formula I or II:



I II

[0011] wherein the variables Ar, E and X^1-X^5 are as defined elsewhere herein.

[0011a] In one aspect, provided is a compound of Formula II or I:



II I

or a pharmaceutically acceptable derivative thereof, wherein:

Ar is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_{5-7}cycloalkyl, optionally substituted C_{5-7}cycloalkenyl, an optionally substituted 5-7 membered heterocyclyl, or an optionally substituted 5-7 membered heterocycloalkenyl;
E is a moiety that binds to an E3 ubiquitin ligase;
X^1-X^2 are each independently N or C; and
X^3-X^5 are each independently CR, N, NR, S or O;
where each R is independently H, alkyl, alkenyl, alkynyl, cycloalkyl or heterocyclyl wherein alkyl is optionally substituted with 1, 2 or 3 groups independently selected from halo and deuterium; or two R groups that are on adjacent positions on the ring together form alkylene; or R and Ar that are on adjacent positions on the 5 membered ring together form a fused ring;
with the provisos:
i) in Formula II, when X^1 is C, X^2, X^4 and X^5 are N and X^3 is CH, or when X^1 and X^2 are C, X^3 is NMe, X^4 is N and X^5 is CH, then E is not an isoindolindione moiety;
ii) in Formula II, when X^1 and X^2 are C, X^3 is CH, X^4 is N and X^5 is NMe, then Ar is not 5-fluoro-2-pyridyl;
iii) in Formula II, when X^1 is N, X^2 is C, X^3 and X^4 are CH and X^5 is N, or when X^1 and X^3 are N, X^2 is C, and X^4 and X^5 are CH, or when then Ar is not phenyl;
iv) in Formula II, the ring containing X^1-X^5 is not 1,2,3-triazol-1,4-diyl;
v) Ar is not tetrahydropyran-2-yl; and
vi) the compound is not 3-[1,3-dihydro-1-oxo-5-(5-phenyl-4-oxazolyl)-2*H*-isoindol-2-yl]-2,6-piperidinedione, 3-[1,3-dihydro-1-oxo-5-(2-phenyl-4-oxazolyl)-2*H*-isoindol-2-yl]-2,6-piperidinedione, or 3-[1,3-dihydro-1-oxo-5-(3-phenyl-1*H*-1,2,4-triazol-5-yl)-2*H*-isoindol-2-yl]-2,6-piperidinedione.

[0012] In another aspect, provided are pharmaceutical compositions containing a compound provided herein and a pharmaceutically acceptable carrier.

[0013] In another example, provided are methods of degrading CK1α or CK1α/GSPT1 using a compound or composition provided herein. The methods provided herein include methods of treatment of CK1α or CK1α/GSPT1 mediated diseases. In one example, the CK1α disease is a B-cell lymphoma or a BTK inhibitor resistant cancer. In another example, the CK1α/GSPT1 disease is AML or breast cancer. In another example, the CK1α degraders provided herein are used in combination with a checkpoint inhibitor,

including a CTLA-4, PD-1 or PD-L1 inhibitor, such as anti-CTLA-4, anti-PD-1 or anti-PD-L1 antibodies, in the treatment of cancer.

[0013a] In another aspect, provided is a compound as provided herein or the composition as provided herein for use in degrading CK1α in a cell or subject.

[0013b] In another aspect, provided is a compound as provided herein or the composition as provided herein for use in inhibiting Card11/BCL10/MALT1 (CBM) complex activation in a subject.

[0013c] In another aspect, provided is a compound as provided herein or the composition as provided herein for use in regulating cellular proliferation in a subject or treating a subject having a proliferative disease.

[0013d] In another aspect, provided is a compound as provided herein or the composition as provided herein for use in treating a subject having cancer.

[0013e] In another aspect, provided is a compound as provided herein or the composition as provided herein for use in treating AML, glioma, thyroid cancer, lung cancer, colorectal cancer, head and neck cancer, stomach cancer, liver cancer, pancreatic cancer, renal cancer, urothelial cancer, prostate cancer, testis cancer, breast cancer, cervical cancer, endometrial cancer, ovarian cancer, melanoma, multiple myeloma, hepatocellular carcinoma or gastric cancer in a subject.

[0013f] In another aspect, provided is a compound as provided herein or the composition as provided herein for use in treating a subject having an autoimmune disorder, optionally wherein the autoimmune disorder is Addison disease, Celiac disease - sprue (gluten-sensitive enteropathy), dermatomyositis, Graves' disease, Hashimoto thyroiditis, multiple sclerosis, myasthenia gravis, pernicious anemia, reactive arthritis, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus or type I diabetes.

[0013g] In another aspect, provided is a compound as provided herein or the composition as provided herein for use in treating a RAS-driven cancer in a subject, optionally wherein the RAS-driven cancer is a RAS-mutant cancer or $KRAS^{G12D}$-driven cancer or optionally wherein the RAS-driven cancer is lung cancer, head and neck cancer, pancreatic cancer, breast cancer, colorectal cancer, gastrointestinal cancer, melanoma, myeloid cancer, bladder cancer, cervical cancer, ovarian cancer or uterine cancer.

[0013h] In another aspect, provided is a compound as provided herein or the composition as provided herein for use in preventing acquired resistance to erlotinib in EGFR-mutant non-small cell lung cancer in a subject.

DETAILED DESCRIPTION

I. DEFINITIONS

[0014] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

[0015] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0016] The singular forms "a," "an," and "the" include plural references, unless the context clearly dictates otherwise.

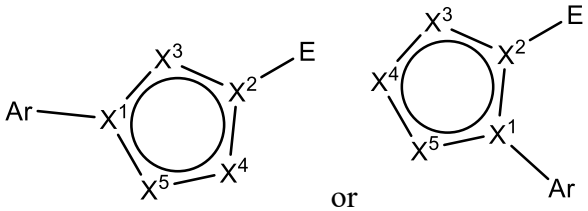
[0017] As used herein "subject" is an animal, such as a mammal, including human, such as a patient.

[0018] As used herein, biological activity refers to the in vivo activities of a compound or physiological responses that result upon in vivo administration of a compound, composition or other mixture. Biological activity, thus, encompasses therapeutic effects and pharmacokinetic behavior of such compounds, compositions and mixtures. Biological activities can be observed in in vitro systems designed to test for such activities.

[0019] As used herein, pharmaceutically acceptable derivatives of a compound include, but are not limited to, salts, esters, enol ethers, enol esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, clathrates, solvates or hydrates thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but

WHAT IS CLAIMED IS:

1. A compound of Formula II or I:



II I

or a pharmaceutically acceptable derivative thereof, wherein:

Ar is optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_{5-7}cycloalkyl, optionally substituted C_{5-7}cycloalkenyl, an optionally substituted 5-7 membered heterocyclyl, or an optionally substituted 5-7 membered heterocycloalkenyl;

E is a moiety that binds to an E3 ubiquitin ligase;

X^1-X^2 are each independently N or C; and

X^3-X^5 are each independently CR, N, NR, S or O;

where each R is independently H, alkyl, alkenyl, alkynyl, cycloalkyl or heterocyclyl wherein alkyl is optionally substituted with 1, 2 or 3 groups independently selected from halo and deuterium; or two R groups that are on adjacent positions on the ring together form alkylene; or R and Ar that are on adjacent positions on the 5 membered ring together form a fused ring;

with the provisos:

i) in Formula II, when X^1 is C, X^2, X^4 and X^5 are N and X^3 is CH, or when X^1 and X^2 are C, X^3 is NMe, X^4 is N and X^5 is CH, then E is not an isoindolindione moiety;

ii) in Formula II, when X^1 and X^2 are C, X^3 is CH, X^4 is N and X^5 is NMe, then Ar is not 5-fluoro-2-pyridyl;

iii) in Formula II, when X^1 is N, X^2 is C, X^3 and X^4 are CH and X^5 is N, or when X^1 and X^3 are N, X^2 is C, and X^4 and X^5 are CH, or when then Ar is not phenyl;

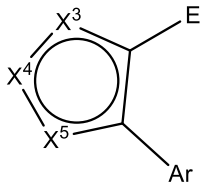
iv) in Formula II, the ring containing X^1-X^5 is not 1,2,3-triazol-1,4-diyl;

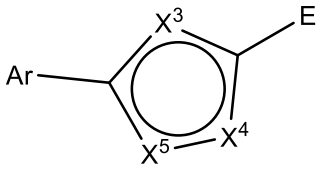
v) Ar is not tetrahydropyran-2-yl; and

vi) the compound is not 3-[1,3-dihydro-1-oxo-5-(5-phenyl-4-oxazolyl)-2*H*-isoindol-2-yl]-2,6-piperidinedione, 3-[1,3-dihydro-1-oxo-5-(2-phenyl-4-oxazolyl)-2*H*-isoindol-2-yl]-2,6-piperidinedione, or 3-[1,3-dihydro-1-oxo-5-(3-phenyl-1*H*-1,2,4-triazol-5-yl)-2*H*-isoindol-2-yl]-2,6-piperidinedione.

2. The compound of claim 1, wherein X^1 is C and X^2 is N or X^1 is N and X^2 is C.

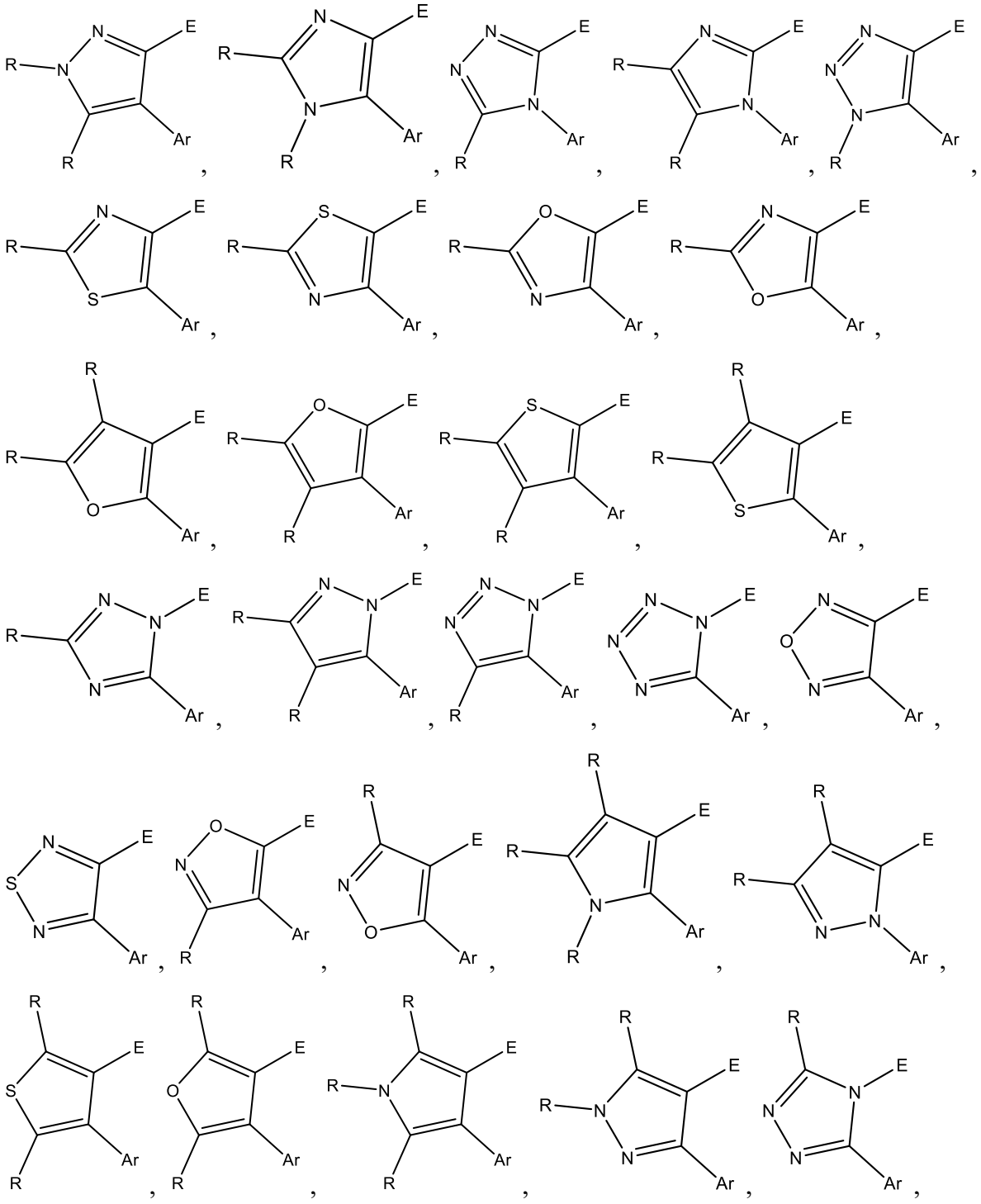
3. The compound of claim 1, wherein the compound has the structure:

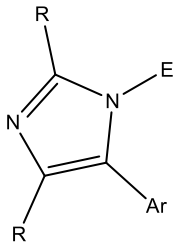
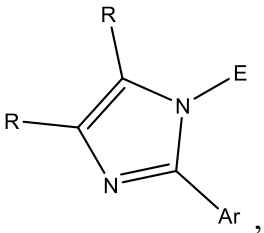


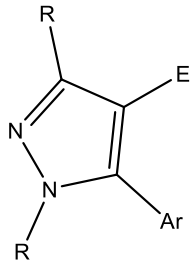
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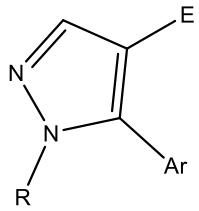
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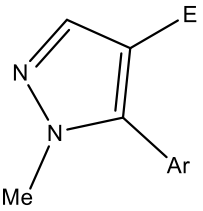
4. The compound of claim 1 having one of the following formulae:

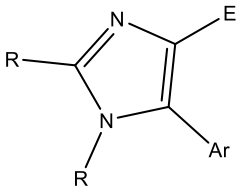


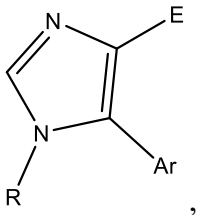



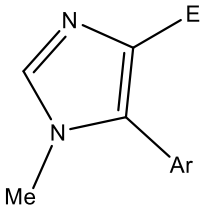


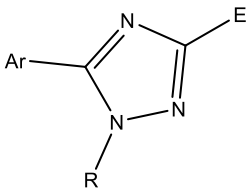
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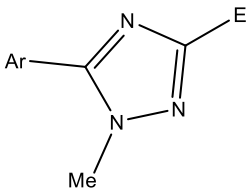
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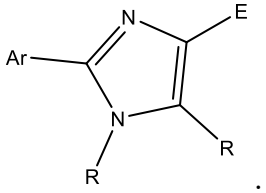
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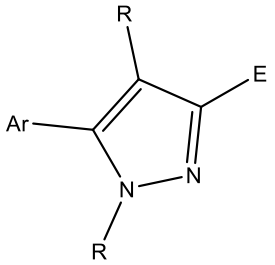
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6. The compound of claim 1 having the structure:



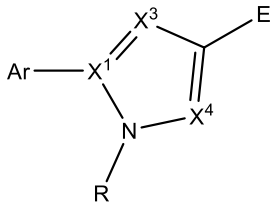
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7. The compound of claim 1 having the structure:



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8. The compound of claim 1 having the structure:



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9. The compound of any one of claims 1-8, wherein each R is independently H, alkyl, cycloalkyl, heterocyclyl or aryl; or two R groups that are on adjacent positions on the ring together form lower alkylene.

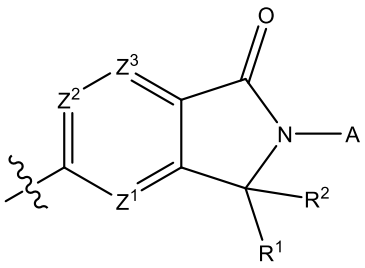
10. The compound of any one of claims 1-8, wherein each R is independently H or alkyl; or two R groups that are on adjacent positions on the ring together form lower alkylene.

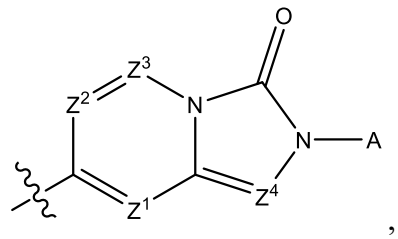
11. The compound of any one of claims 1-8, wherein each R is independently, H, methyl, ethyl, isopropyl, difluoromethyl, fluoromethyl, trifluoromethyl, 2,2-difluoro-1-ethyl, 2,2,2-trifluoro-1-ethyl, difluoropropyl, cyclopropyl, trideuteromethyl, ethyl, 2-hydroxy-2-methylpropyl, cyclohexyl, 1,3-dioxanyl, 4-pyranyl or phenyl; or two R groups that are on adjacent positions on the ring together form propylene.

12. The compound of any one of claims 1-8, wherein each R is independently H or methyl.

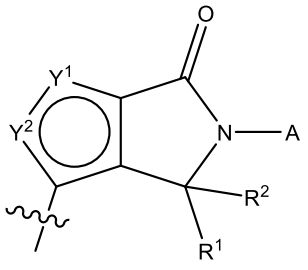
13. The compound of any one of claims 1-12, wherein E is a moiety that binds to cereblon; contains an imide, amide, thioamide or thioimide derived moiety; contains a phthalimido group or an analog or derivative thereof; contains a phthalimido-glutarimide group or an analog or derivative thereof; and/or contains a thalidomide, lenalidomide or pomalidomide moiety, or an analog or derivative thereof.

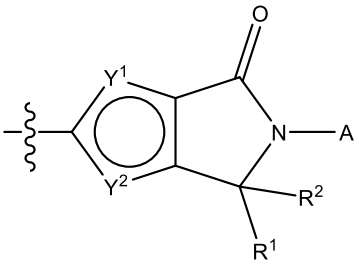
14. The compound of any one of claims 1-13, wherein E has one of the following formulae:



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or


wherein:

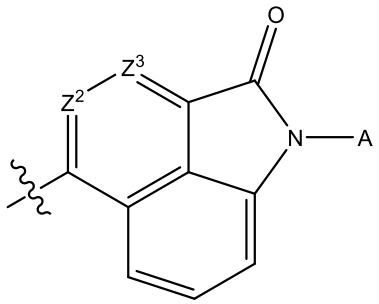
A is a cyclic amide or cyclic imide or a derivative thereof;

R^1 and R^2 are each independently H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl;

one of Y^1 and Y^2 is S and the other is CR^3, where R^3 is H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl; and

Z^1-Z^4 are each independently N or CR^4, where each R^4 is independently H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl; or

wherein E has the formula:

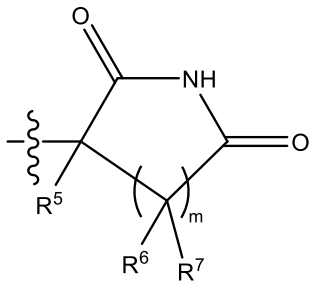


wherein:

A is a cyclic amide or cyclic imide or a derivative thereof; and

Z^2 and Z^3 are each independently N or CR^4, where each R^4 is independently H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl.

15. The compound of claim 14, wherein A is a cyclic imide having the structure:



wherein: R^5 is H or alkyl; R^6 and R^7 are each independently H, alkyl, alkenyl, alkynyl, cycloalkyl or heterocyclyl; and m is an integer from 1-4.

16. The compound of claim 15, wherein R^5 is H or lower alkyl, optionally wherein R^5 is H or methyl.

17. The compound of any one of claims -15-16, wherein R^5 is H.

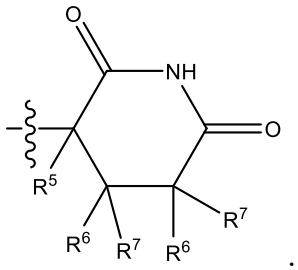
18. The compound of any one of claims 15-17, wherein R^6 and R^7 are each independently H or alkyl, optionally wherein R^6 and R^7 are each independently H or methyl.

19. The compound of any one of claims 15-18, wherein R^6 and R^7 both H.

20. The compound of any one of claims 15-19, wherein m is 1, 2 or 3.

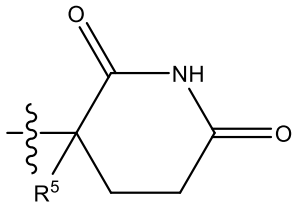
21. The compound of any one of claims 15-20, wherein m is 2.

22. The compound of any one of claims 14-21, wherein A has the structure:

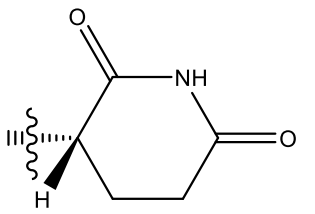


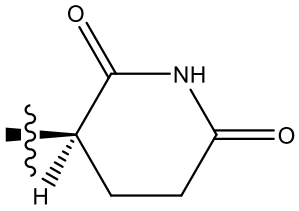
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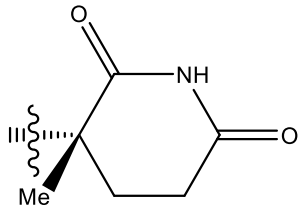
23. The compound of any one of claims 14-22, wherein A has the structure:

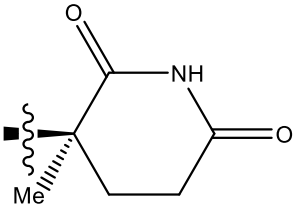


, optionally wherein A has one of the following structures:







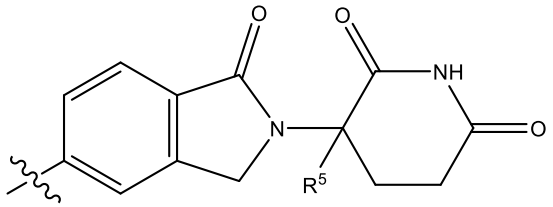


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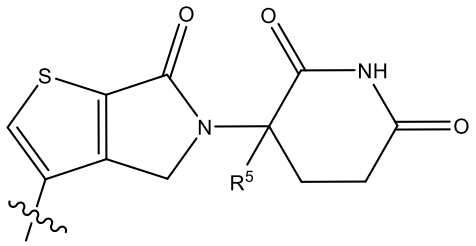
24. The compound of any one of claims 14-23, wherein R^1 and R^2 are each independently H or alkyl, optionally wherein R^1 and R^2 are each independently H or methyl.

25. The compound of any one of claims 14-24, wherein R^1 and R^2 are each H.

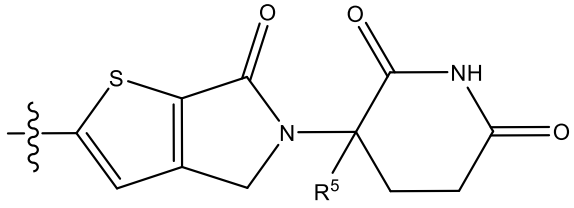
26. The compound of any one of claims 1-25, wherein E is selected from:



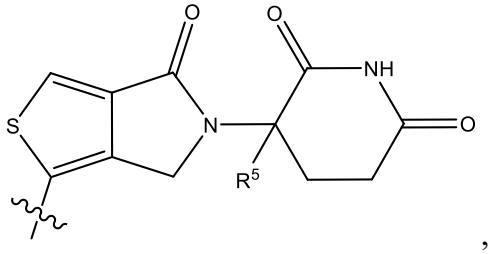
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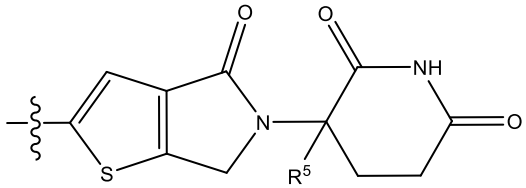
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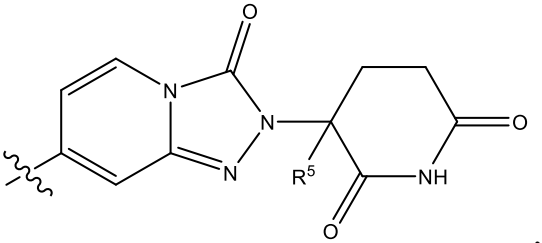
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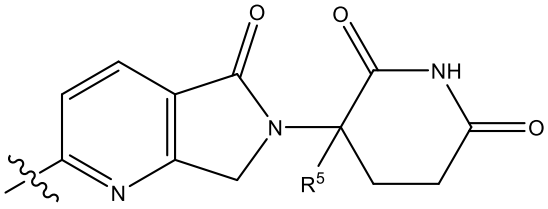
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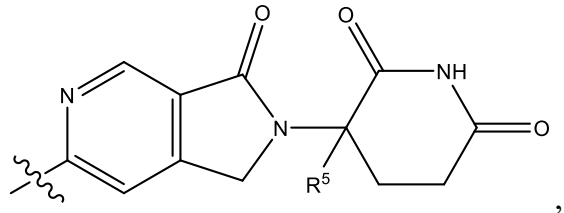


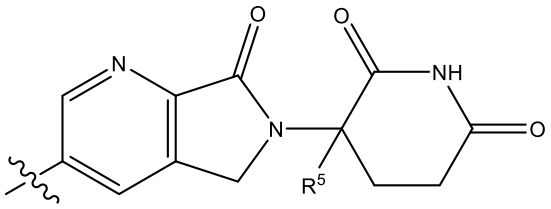
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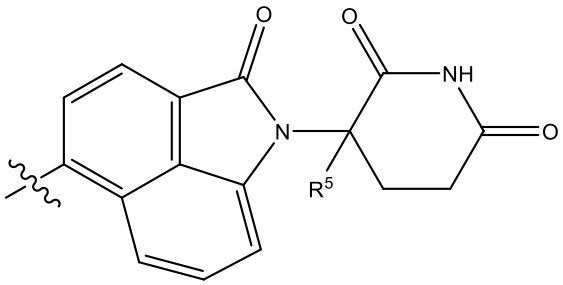


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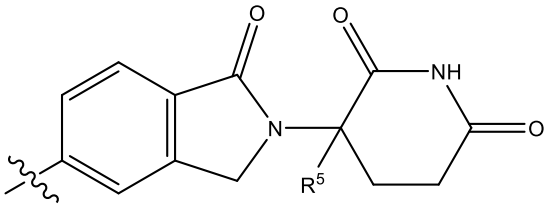
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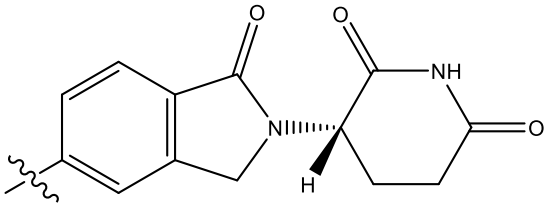


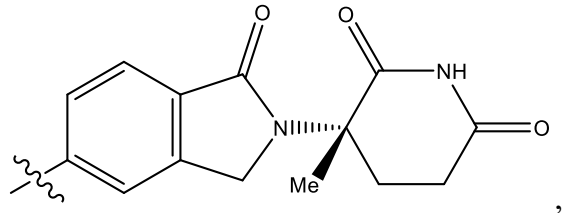
and .

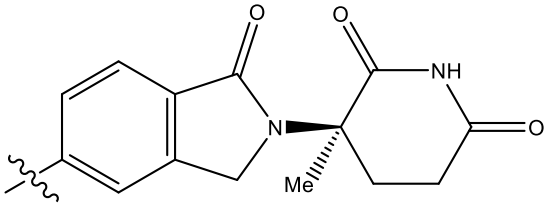
27. The compound of any one of claims 1-26, wherein E has the structure:

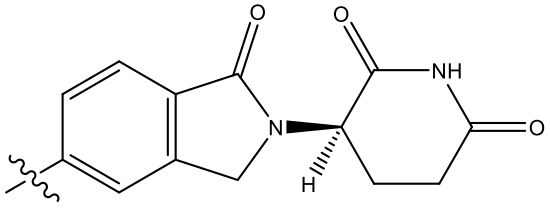


, optionally wherein E is selected from:



,


,




and .

28. The compound of any one of claims 1-27, wherein Ar is optionally substituted phenyl, optionally substituted biphenyl, optionally substituted naphthyl, optionally substituted pyridyl, optionally substituted pyrimidinyl, optionally substituted pyridazinyl, optionally substituted pyrazolyl, optionally substituted pyridopyrazolyl, optionally substituted isoxazolyl, optionally substituted indolyl, optionally substituted isoindolyl, optionally substituted thienyl, optionally substituted benzofuryl, optionally substituted imidazopyridyl, optionally substituted benzopyrazolyl, optionally substituted pyrrolopyridyl, optionally substituted benzimidazolyl, optionally substituted benzothiazolyl, optionally substituted thienopyridyl, optionally substituted dihydrobenzofuryl, optionally substituted benzopyridazinyl, optionally substituted benzopyranyl, optionally substituted benzothienyl,

optionally substituted triazolopyrimidinyl, optionally substituted piperidinyl, optionally substituted cyclohexenyl, optionally substituted tetrahydropyridyl, optionally substituted tetrahydrofuranyl, optionally substituted dihydrofuranyl, optionally substituted morpholinyl, optionally substituted tetrahydroisoquinolinyl, optionally substituted azepinyl, optionally substituted isoquinolinyl, optionally substitutedcycloheptenyl, optionally substituted indenyl, optionally substituted dihydronaphthyl, optionally substituted 8-azabicyclooctanyl, optionally substituted adamantanyl, optionally substituted dihydroindenyl, optionally substituted cyclopropyl or optionally substituted cyclohexyl.

29. The compound of any one of claims 1-28, wherein Ar is phenyl, biphenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazolyl, pyridopyrazolyl, isoxazolyl, indolyl, isoindolyl, thienyl, dihydrobenzofuryl, dihydroindenyl, cyclopropyl or cyclohexyl, each optionally substituted with one or more substituents each independently selected from halo, cyano, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, COR^8, OR^9, $NR^{10}R^{11}$ and $S(O)_nR^{12}$, wherein:

R^8 is alkyl, OR^{13} or $NR^{14}R^{15}$;

R^9 is H, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or COR^{16};

R^{10} and R^{11} are each independently H, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl or COR^{17};

R^{12} is alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, OR^{18} or $NR^{14}R^{15}$;

R^{13}, R^{14} and R^{15} are each independently H, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl;

R^{16} is alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, OR^{13} or $NR^{14}R^{15}$;

R^{17} is alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, OR^{13} or $NR^{14}R^{15}$;

R^{18} is alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl; and

n is 0, 1 or 2.

30. The compound of any one of claims 1-29, wherein Ar is substituted with 1 to 5, 1 to 3, or 1 or 2 substituents.

31. The compound of any one of claims 1-29, wherein Ar is unsubstituted.

32. The compound of any one of claims 1-29, wherein Ar is phenyl, optionally substituted with one or more substituents each independently selected from halo; cyano; alkyl; alkenyl; alkynyl; haloalkyl; cycloalkyl; heterocyclyl; aryl; heteroaryl; cycloalkylalkyl; heterocyclylalkyl; COR^8, optionally $CONR^{14}R^{15}$; OR^9; $NR^{10}R^{11}$; and $S(O)_nR^{12}$, optionally $S(O)_2R^{12}$.

33. The compound of any one of claims 1-28, wherein Ar is phenyl, optionally substituted with one or more substituents each independently selected from chloro, fluoro,

cyano, methyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, difluoromethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclopropyl, 1-cyano-1-cyclopropyl, 1-piperidinyl, 1-pyrrolidinylmethyl, morpholin-4-yl, 4-methylpiperazin-1-yl, 4-methylpiperazin-1-ylmethyl, 4-tert-butyloxycarbonyl-1-piperazinyl, morpholin-4-ylmethyl, 1-pyrrolidinyl, phenyl, 4-cyanophenyl, 4-hydroxyphenyl, 1-pyrazolyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, benzyloxy, (3-methoxybenzyl)oxy, 3-pyridinyloxy, 3-(4-morpholinyl)propoxy, $CONH_2$, CONHMe, $CONMe_2$, CONH-cyclopentyl, CONH-cyclohexyl, CONH-benzyl, CO-(4-morpholinyl), CO-(4-methylpiperazin-1-yl), NH_2, NMe_2, NHCOPh, SO_2Me, SO_2NH-cyclohexyl and SO_2-(1-pyrrolidinyl).

34. The compound of any one of claims 1-29, wherein Ar is unsubstituted phenyl.

35. The compound of any one of claims 1-29, wherein Ar is thienyl, optionally substituted with one or more substituents each independently selected from halo; cyano; alkyl; alkenyl; alkynyl; haloalkyl; cycloalkyl; heterocyclyl; aryl; heteroaryl; cycloalkylalkyl; heterocyclylalkyl; COR^8, optionally $CONR^{14}R^{15}$; OR^9; $NR^{10}R^{11}$; and $S(O)_nR^{12}$, optionally $S(O)_2R^{12}$.

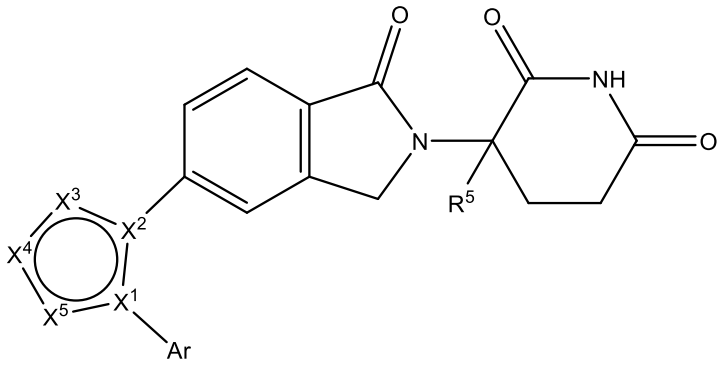
36. The compound of any one of claims 1-29, wherein Ar is thienyl, optionally substituted with one or more substituents each independently selected from chloro, fluoro, cyano, methyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, difluoromethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclopropyl, 1-cyano-1-cyclopropyl, 1-piperidinyl, 1-pyrrolidinylmethyl, morpholin-4-yl, 4-methylpiperazin-1-yl, 4-methylpiperazin-1-ylmethyl, 4-tert-butyloxycarbonyl-1-piperazinyl, morpholin-4-ylmethyl, 1-pyrrolidinyl, phenyl, 4-cyanophenyl, 4-hydroxyphenyl, 1-pyrazolyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, hydroxy, methoxy, benzyloxy, 3-methoxybenzyloxy, 3-pyridinyloxy, 3-(4-morpholinyl)propoxy, $CONH_2$, CONHMe, $CONMe_2$, CONH-cyclopentyl, CONH-cyclohexyl, CONH-benzyl, CO-(4-morpholinyl), CO-(4-methylpiperazin-1-yl), NH_2, NMe_2, NHCOPh, SO_2Me, SO_2NH-cyclohexyl and SO_2-(1-pyrrolidinyl).

37. The compound of any one of claims 1-29, wherein Ar is pyrazolyl, optionally substituted with one or more substituents each independently selected from halo, cyano, alkyl, haloalkyl, cycloalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, $CONR^{14}R^{15}$, OR^9, $NR^{10}R^{11}$ and $S(O)_2R^{12}$.

38. The compound of any one of claims 1-29, wherein Ar is pyrazolyl, optionally substituted with one or more substituents each independently selected from chloro, fluoro, cyano, methyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, difluoromethyl,

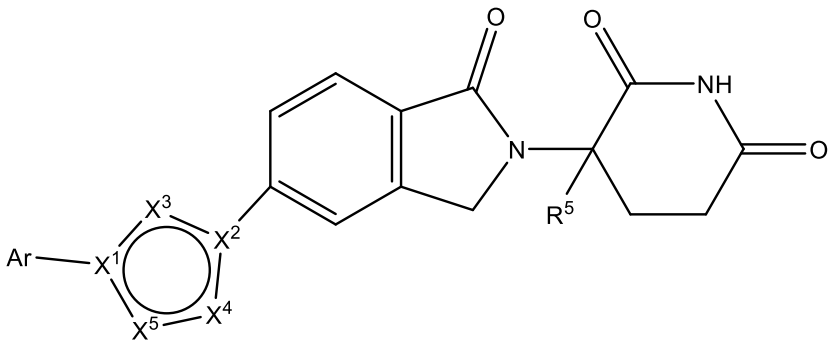
hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclopropyl, 1-cyano-1-cyclopropyl, 1-piperidinyl, 1-pyrrolidinylmethyl, morpholin-4-yl, 4-methylpiperazin-1-yl, 4-methylpiperazin-1-ylmethyl, 4-tert-butyloxycarbonyl-1-piperazinyl, morpholin-4-ylmethyl, 1-pyrrolidinyl, phenyl, 4-cyanophenyl, 4-hydroxyphenyl, 1-pyrazolyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, hydroxy, methoxy, benzyloxy, 3-methoxybenzyloxy, 3-pyridinyloxy, 3-(4-morpholinyl)propoxy, $CONH_2$, CONHMe, $CONMe_2$, CONH-cyclopentyl, CONH-cyclohexyl, CONH-benzyl, CO-(4-morpholinyl), CO-(4-methylpiperazin-1-yl), NH_2, NMe_2, NHCOPh, SO_2Me, SO_2NH-cyclohexyl and SO_2-(1-pyrrolidinyl).

39. The compound of claim 1 having the structure:



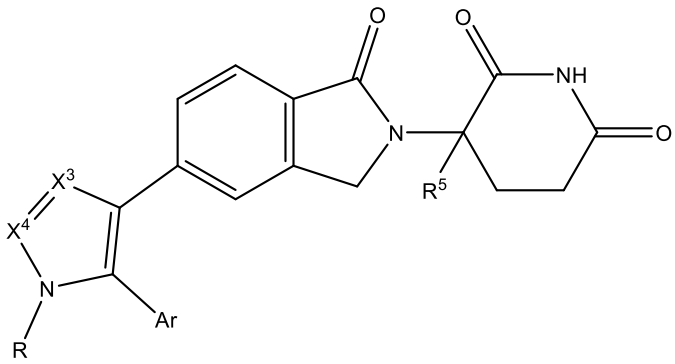
wherein R^5 is H or alkyl.

40. The compound of claim 1 having the structure:

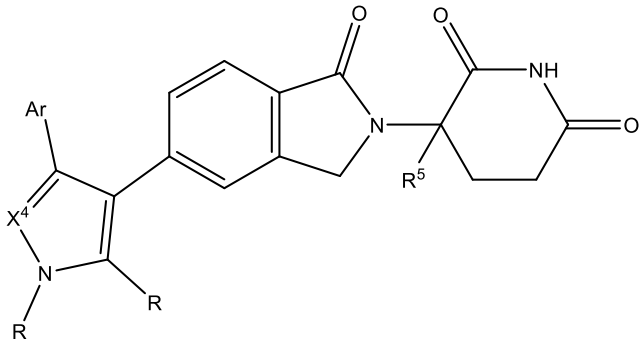


wherein R^5 is H or alkyl.

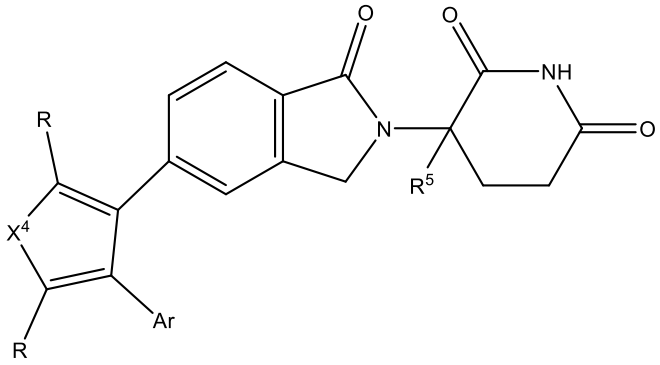
41. The compound of claim 1 having the structure:



,



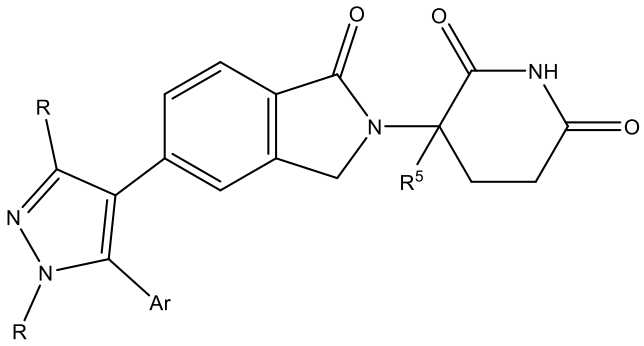
, or



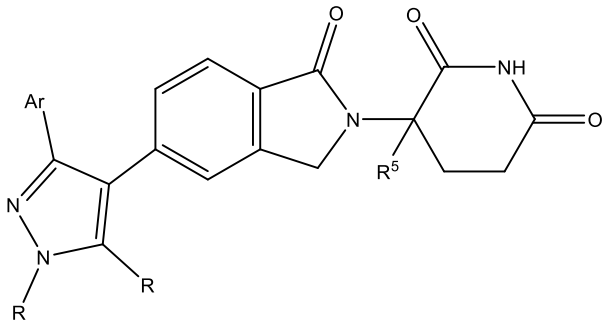
;

wherein R^5 is H or alkyl.

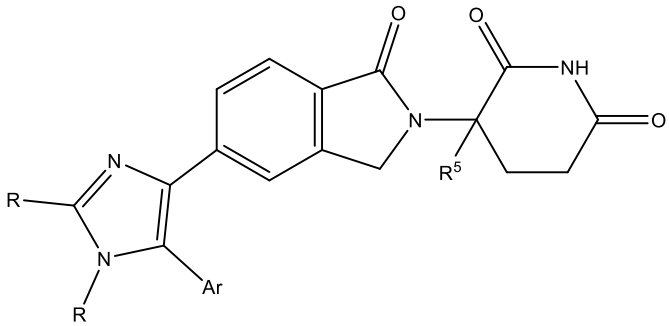
42. The compound of claim 1 having the structure:



,



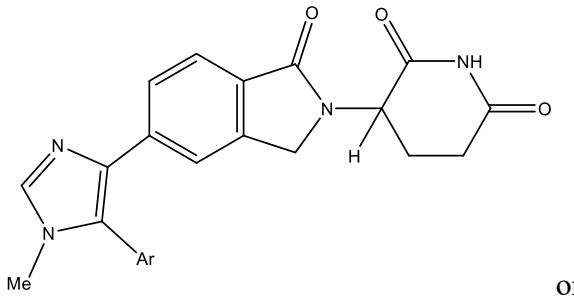
, or



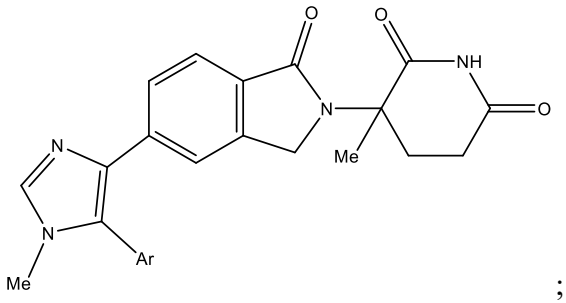
;

wherein R^5 is H or alkyl.

43. The compound of claim 1 or 42 having the structure:



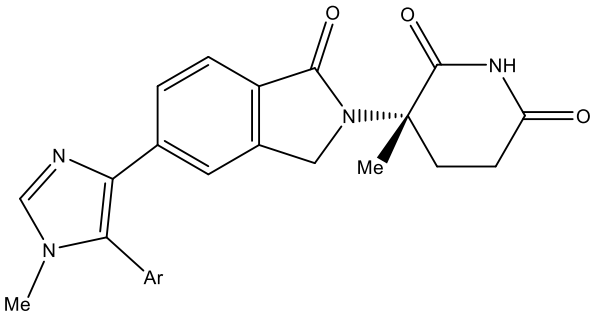
or

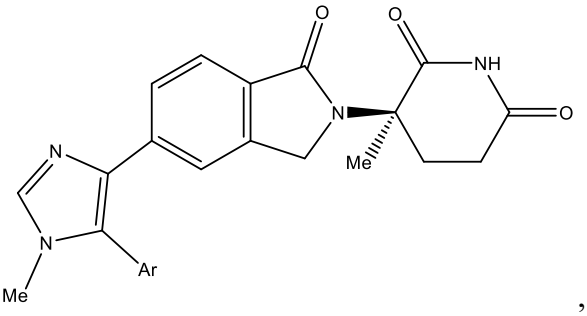


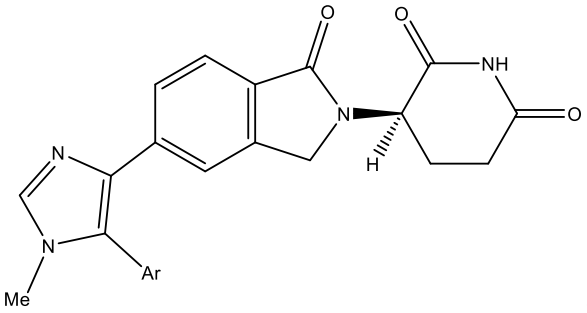
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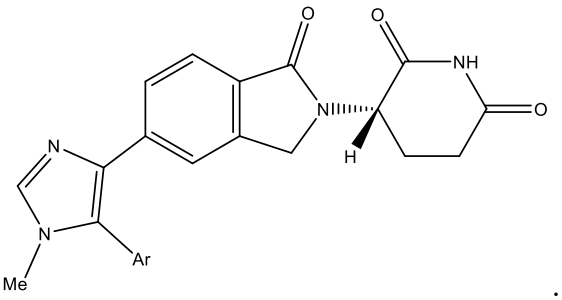
optionally

having the structure:



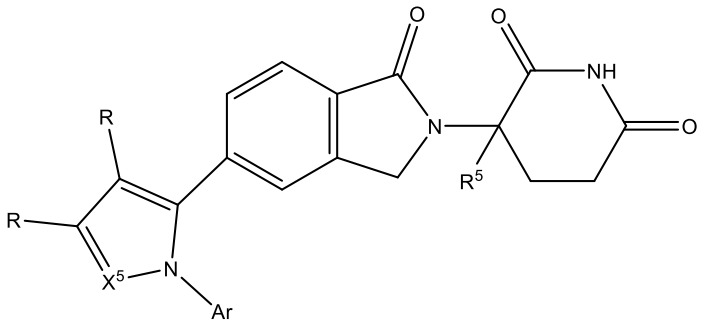
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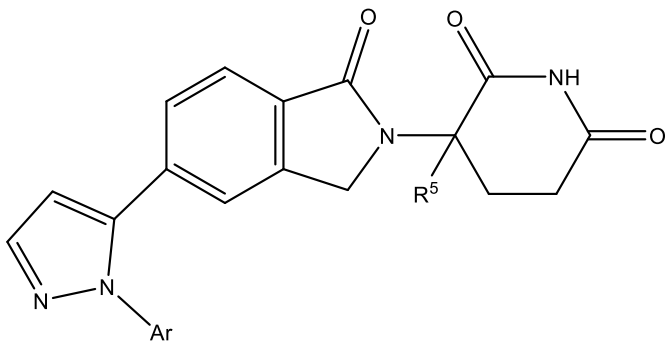
or


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44. The compound of claim 1 having the structure:

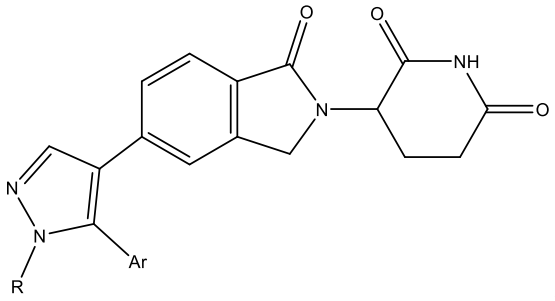
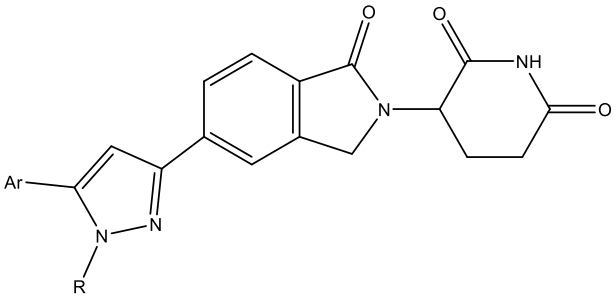
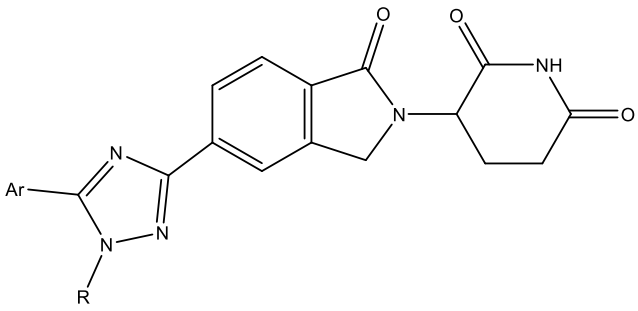


; optionally having the structure:



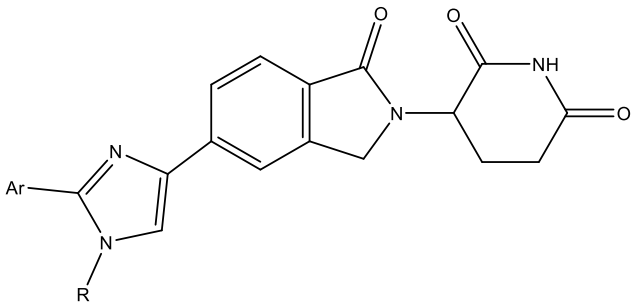
.

45. The compound of claim 1 having the structure:

or .

46. The compound of claim 1 having the structure:



.

47. The compound of any one of claims 39-46, wherein Ar is phenyl, optionally substituted with one or more substituents each independently selected from halo; cyano; alkyl;, haloalkyl; cycloalkyl; heterocyclyl; heteroaryl; heterocyclylalkyl; COR^8, optionally $CONR^{14}R^{15}$; OR^9; $NR^{10}R^{11}$; and $S(O)_nR^{12}$, optionally $S(O)_2R^{12}$.

48. The compound of any one of claims 39-46, wherein Ar is phenyl, optionally substituted with one or more substituents each independently selected from chloro, fluoro, cyano, methyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, difluoromethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclopropyl, 1-cyano-1-cyclopropyl, 1-piperidinyl, 1-pyrrolidinylmethyl, morpholin-4-yl, 4-methylpiperazin-1-yl, 4-methylpiperazin-1-ylmethyl, 4-tert-butyloxycarbonyl-1-piperazinyl, morpholin-4-ylmethyl, 1-pyrrolidinyl, phenyl, 4-cyanophenyl, 4-hydroxyphenyl, 1-pyrazolyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, benzyloxy, (3-methoxybenzyl)oxy, 3-pyridinyloxy, 3-(4-morpholinyl)propoxy, $CONH_2$, CONHMe, $CONMe_2$, CONH-cyclopentyl, CONH-cyclohexyl, CONH-benzyl, CO-(4-

morpholinyl), CO-(4-methylpiperazin-1-yl), NH_2, NMe_2, NHCOPh, SO_2Me, SO_2NH-cyclohexyl and SO_2-(1-pyrrolidinyl).

49. The compound of any one of claims 39-46, wherein Ar is thienyl, optionally substituted with one or more substituents each independently selected from halo, cyano, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, COR^8, OR^9, $NR^{10}R^{11}$ and $S(O)_nR^{12}$.

50. The compound of any one of claims 39-46, wherein Ar is thienyl, optionally substituted with one or more substituents each independently selected from chloro, fluoro, cyano, methyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, difluoromethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclopropyl, 1-cyano-1-cyclopropyl, 1-piperidinyl, 1-pyrrolidinylmethyl, morpholin-4-yl, 4-methylpiperazin-1-yl, 4-methylpiperazin-1-ylmethyl, 4-tert-butyloxycarbonyl-1-piperazinyl, morpholin-4-ylmethyl, 1-pyrrolidinyl, phenyl, 4-cyanophenyl, 4-hydroxyphenyl, 1-pyrazolyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, hydroxy, methoxy, benzyloxy, 3-methoxybenzyloxy, 3-pyridinyloxy, 3-(4-morpholinyl)propoxy, $CONH_2$, CONHMe, $CONMe_2$, CONH-cyclopentyl, CONH-cyclohexyl, CONH-benzyl, CO-(4-morpholinyl), CO-(4-methylpiperazin-1-yl), NH_2, NMe_2, NHCOPh, SO_2Me, SO_2NH-cyclohexyl and SO_2-(1-pyrrolidinyl).

51. The compound of any one of claims 39-46, wherein Ar is pyrazolyl, optionally substituted with one or more substituents each independently selected from halo, cyano, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, COR^8, OR^9, $NR^{10}R^{11}$ and $S(O)_nR^{12}$.

52. The compound of any one of claims 39-46, wherein Ar is pyrazolyl, optionally substituted with one or more substituents each independently selected from chloro, fluoro, cyano, methyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, difluoromethyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, cyclopropyl, 1-cyano-1-cyclopropyl, 1-piperidinyl, 1-pyrrolidinylmethyl, morpholin-4-yl, 4-methylpiperazin-1-yl, 4-methylpiperazin-1-ylmethyl, 4-tert-butyloxycarbonyl-1-piperazinyl, morpholin-4-ylmethyl, 1-pyrrolidinyl, phenyl, 4-cyanophenyl, 4-hydroxyphenyl, 1-pyrazolyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, hydroxy, methoxy, benzyloxy, 3-methoxybenzyloxy, 3-pyridinyloxy, 3-(4-morpholinyl)propoxy, $CONH_2$, CONHMe, $CONMe_2$, CONH-cyclopentyl, CONH-cyclohexyl, CONH-benzyl, CO-(4-morpholinyl), CO-(4-methylpiperazin-1-yl), NH_2, NMe_2, NHCOPh, SO_2Me, SO_2NH-cyclohexyl and SO_2-(1-pyrrolidinyl).

53. The compound of claim 1, wherein the compound is any one of Examples 1-735.

54. A pharmaceutical composition, comprising the compound of any one of claims 1-53 and a pharmaceutically acceptable carrier.

55. A compound of any one of claims 1-53 or the composition of claim 54 for use in degrading CK1α in a cell or subject.

56. A compound of any one of claims 1-53 or the composition of claim 54 for use in inhibiting Card11/BCL10/MALT1 (CBM) complex activation in a subject.

57. A compound of any one of claims 1-53 or the composition of claim 54 for use in regulating cellular proliferation in a subject or treating a subject having a proliferative disease.

58. A compound of any one of claims 1-53 or the composition of claim 54 for use in treating a subject having cancer.

59. The compound or composition for use of claim 58, wherein the cancer is acute myeloid leukemia (AML), myelodysplastic syndrome, (MDS) (including 5q-MDS), colon cancer, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), B-cell lymphoma or mantle cell lymphoma (MCL).

60. The compound or composition for use of claim 59, wherein the B-cell lymphoma is diffuse large B-cell lymphoma (DLBCL).

61. The compound or composition for use of claim 58, wherein the cancer is a BTK inhibitor resistant cancer optionally where the BTK inhibitor resistant cancer is ibrutinib resistant cancer

62. The compound or composition for use of claim 61, wherein the BTK inhibitor resistant cancer is resistant to one or more of acalabrutinib, zanubrutinib, pirtobrutinib, spebrutinib, evobrutinib, olmutinib, tirabrutinib, elsubrutinib (ABBV-105), tolebrutinib (SAR 442168), fenebrutinib, vacabrutinib, rilzabrutinib, M7583, BMS-986142, CT-1530, TG-1701, AC0058, SHR1459, RN-486, BIIB068 or DTRMWXHA-12 or wherein the BTK inhibitor resistant cancer is chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), Waldenstrom macroglobulinemia or chronic graft-versus-host disease.

63. A compound of any one of claims 1-53 or the composition of claim 54 for use in treating AML, glioma, thyroid cancer, lung cancer, colorectal cancer, head and neck cancer, stomach cancer, liver cancer, pancreatic cancer, renal cancer, urothelial cancer, prostate cancer, testis cancer, breast cancer, cervical cancer, endometrial cancer, ovarian cancer, melanoma, multiple myeloma, hepatocellular carcinoma or gastric cancer in a subject.

64. A compound of any one of claims 1-53 or the composition of claim 54 for use in treating a subject having an autoimmune disorder, optionally wherein the autoimmune disorder is Addison disease, Celiac disease - sprue (gluten-sensitive enteropathy), dermatomyositis, Graves' disease, Hashimoto thyroiditis, multiple sclerosis, myasthenia gravis, pernicious anemia, reactive arthritis, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus or type I diabetes.

65. The compound or composition for use of claim 64, wherein a second active agent is to be further administered to the subject, optionally wherein the second active agent is a checkpoint inhibitor, such as an anti-CTLA-4, an anti-PD-1 or anti-PD-L1 antibody or wherein the second active agent is nivolumab, pembrolizumab, pidilizumab, atezolizumab, ipilimumab, tramelimumab, or a combination thereof.

66. The compound or composition for use of claim 65, wherein the proliferative disease to be treated is melanoma; unresectable or metastatic melanoma; BRAF 600 mutation positive and melanoma with lymph node involvement; non-small cell lung cancer; metastatic non-small cell lung cancer; renal cell carcinoma; Hodgkin lymphoma; relapsed/refractory Hodgkin lymphoma; squamous cell carcinoma of the head and neck; metastatic squamous cell carcinoma of the head and neck; urothelial carcinoma; metastatic urothelial carcinoma; colorectal cancer; metastatic colorectal cancer; or hepatocellular carcinoma.

67. A compound of any one of claims 1-53 or the composition of claim 54 for use in treating a RAS-driven cancer in a subject, optionally wherein the RAS-driven cancer is a RAS-mutant cancer or $KRAS^{G12D}$-driven cancer or optionally wherein the RAS-driven cancer is lung cancer, head and neck cancer, pancreatic cancer, breast cancer, colorectal cancer, gastrointestinal cancer, melanoma, myeloid cancer, bladder cancer, cervical cancer, ovarian cancer or uterine cancer.

68. A compound of any one of claims 1-53 or the composition of claim 54 for use in preventing acquired resistance to erlotinib in EGFR-mutant non-small cell lung cancer in a subject.