division, the cellular response to stress and to extracellular modulators, morphogenesis of neuronal networks, modulation of cell surface receptors, ion channels, the secretory pathway, DNA repair and biogenesis of organelles.

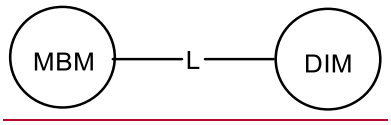
[0006] Aberrations in the process have recently been implicated in the pathogenesis of several diseases, both inherited and acquired. These diseases fall into two major groups: (a) those that result from loss of function with the resultant stabilization of certain proteins, and (b) those that result from gain of function, i.e. abnormal or accelerated degradation of the protein target.

[0007] The UPP is used to induce selective protein degradation, including use of fusion proteins to artificially ubiquitinate target proteins and synthetic small-molecule probes to induce proteasome-dependent degradation. Bifunctional compounds composed of a target protein-binding ligand and an E3 ubiquitin ligase ligand, induced proteasome-mediated degradation of selected proteins via their recruitment to E3 ubiquitin ligase and subsequent ubiquitination. These drug-like molecules offer the possibility of temporal control over protein expression. Such compounds are capable of inducing the inactivation of a protein of interest upon addition to cells or administration to an animal or human, and could be useful as biochemical reagents and lead to a new paradigm for the treatment of diseases by removing pathogenic or oncogenic proteins (Crews C, Chemistry & Biology, 2010, 17(6):551-555; Schnnekloth JS Jr., Chembiochem, 2005, 6(l):40-46).

[0008] An ongoing need exists in the art for effective treatments for disease, especially hyperplasia and cancer, such as breast cancer. However, non-specific effects, and the inability to target and modulate certain classes of proteins altogether, such as transcription factors, remain as obstacles to the development of effective anti-cancer agents. As such, small molecule therapeutic agents that leverage E3 ligase mediated protein degradation to target cancer-associated proteins such as mouse double minute 2 homolog ("MDM2") hold promise as therapeutic agents. Accordingly, there remains a need to find compounds that are MDM2 degraders useful as therapeutic agents.

SUMMARY ~~OF THE INVENTION~~

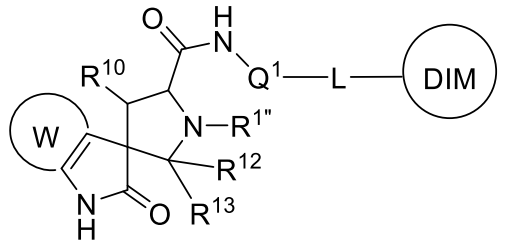
[0008a] In an aspect of the present disclosure, there is provided a compound of formula **I**:



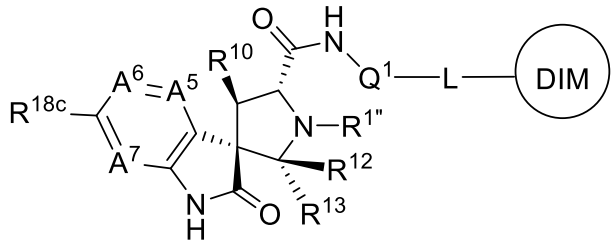
I

or a pharmaceutically acceptable salt thereof, wherein:

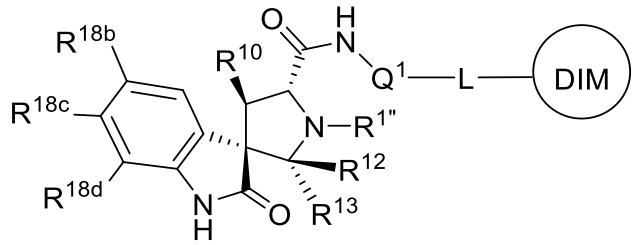
MBM is a MDM2 binding moiety capable of binding to MDM2 protein, said compound of formula **I** is a compound selected from formula:



I-bbb-1



I-bbb-2



I-bbb-3

or a pharmaceutically acceptable salt thereof, wherein:

$R^{1''}$ is selected from hydrogen and R^A;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{10} is selected from an optionally substituted monocyclic or bicyclic ring selected from phenyl, a 5-10 membered aryl, and a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{12} and R^{13} are each independently selected from hydrogen and R^A, or:

R^{12} and R^{13} are optionally taken together with their intervening atoms to form an optionally substituted 4-8 membered saturated, partially unsaturated, carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

A^5 is selected from -C(R^{18a})= and -N=;

A^6 is selected from -C(R^{18b})= and -N=;

A^7 is selected from -C(R^{18d})= and -N=;

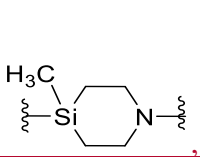
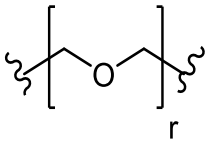
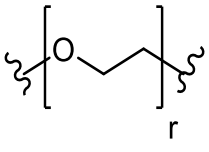
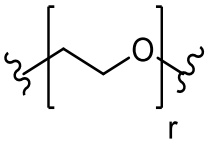
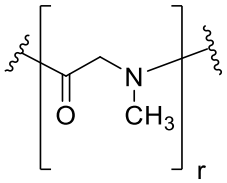
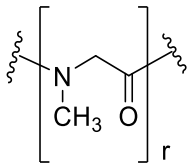
R^{18a}, R^{18b}, R^{18c}, and R^{18d} are each independently selected from hydrogen, halogen, R^A, and –OR;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered

heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring W is an optionally substituted fused ring selected from benzo and a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Q^1 is and optionally substituted bivalent group selected from alkylenyl, phenylenyl, heteroarylenyl, cycloalkylenyl, and heterocyclenyl;

L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy-, -O-, -N(R)-, $–Si(R)_2–$, $–Si(OH)(R)–$, $–Si(OH)_2–$, –P(O)(OR)–, –P(O)(R)–, $–P(O)(NR_2)–$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, –N(R)C(O)O-,  ,  ,  ,  ,  , or  ;

each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

DIM is a degradation moiety selected from an E3 ubiquitin ligase binding moiety (LBM), a lysine mimetic, and hydrogen.

[0008b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0008c] In a further aspect of the present disclosure, there is provided a compound disclosed herein or a pharmaceutical composition thereof, for use in degrading MDM2 protein in a patient or biological sample.

[0008d] In another aspect of the present disclosure, there is provided a compound disclosed herein or a pharmaceutical composition thereof, for use in therapy.

[0008e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an MDM2-mediated disorder, disease, or condition in a patient.

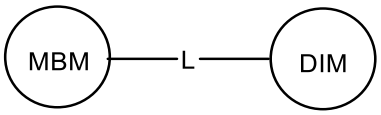
[0008f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein or a pharmaceutical composition thereof, in the manufacture of a medicament for treating a patient in need thereof, wherein the patient has cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

[0009] The present application relates novel bifunctional compounds, which function to recruit MDM2 protein to E3 ubiquitin ligase for degradation, and methods of preparation and uses thereof. In particular, the present disclosure provides bifunctional compounds, which find utility as modulators of targeted ubiquitination of MDM2, which is then degraded and/or otherwise inhibited by the bifunctional compounds as described herein. Also provided are monovalent compounds, which find utility as inducers of targeted ubiquitination of MDM2, which are then degraded and/or otherwise inhibited by the monovalent compounds as described herein. An advantage of the compounds provided herein is that a broad range of pharmacological activities is possible, consistent with the degradation/inhibition of MDM2. In addition,

the description provides methods of using an effective amount of the compounds as described herein for the treatment or amelioration of a disease condition, such as cancer, e.g., breast cancer.

[0010] The present application further relates to targeted degradation of MDM2 protein through the use of bifunctional molecules, including bifunctional molecules that link a cereblon-binding moiety to a ligand that binds MDM2 protein.

[0011] It has now been found that compounds of this ~~invention~~disclosure, and pharmaceutically acceptable compositions thereof, are effective as degraders of MDM2 protein. Such compounds have the general formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0012] Compounds of the present ~~invention~~disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of signaling pathways implicating MDM2 protein. Such diseases, disorders, or conditions include those described herein.

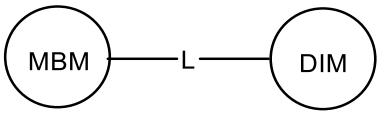
[0013] Compounds provided by this ~~invention~~disclosure are also useful for the study of MDM2 protein in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new MDM2 inhibitors or MDM2 degraders or other regulators of cell cycling, metastasis, angiogenesis, and immune cell evasion, *in vitro* or *in vivo*.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Certain Embodiments of the Invention:

[0014] Compounds of the present invention, and compositions thereof, are useful as degraders and/or inhibitors of MDM2 protein. In some embodiments, a provided compound degrades and/or inhibits MDM2 protein.

[0015] In certain embodiments, the present invention provides a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

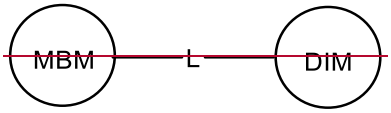
MBM is a MDM2 binding moiety capable of binding MDM2 protein;

L is a bivalent moiety that connects MBM to DIM; and

CLAIMS

We claim:

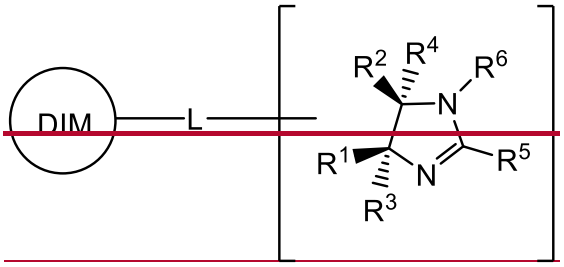
~~1. A compound of formula I:~~



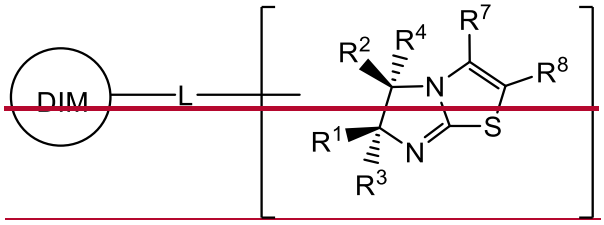
~~I~~

~~or a pharmaceutically acceptable salt thereof, wherein:~~

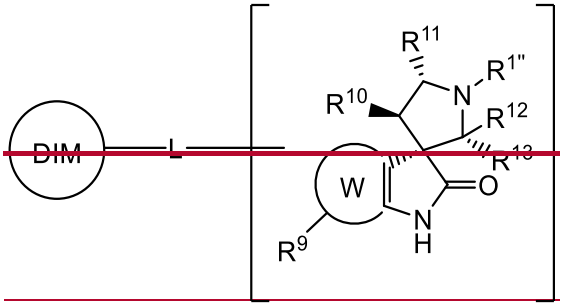
~~MBM is a MDM2 binding moiety capable of binding to MDM2 protein, said compound of formula I is a compound selected from formula:~~



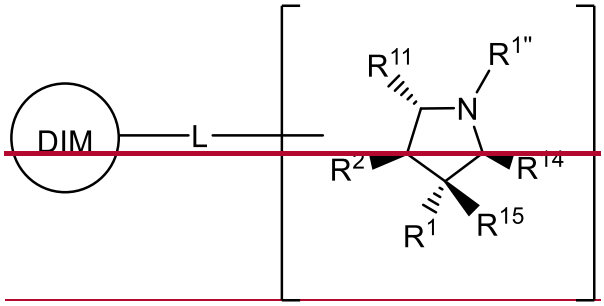
~~I-aaa-1~~



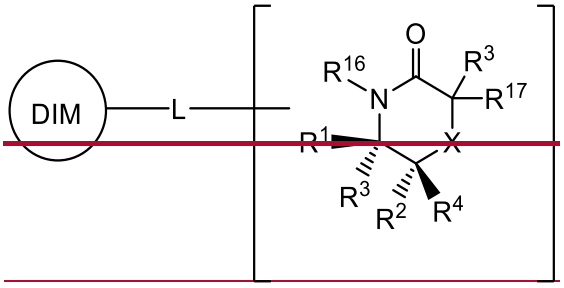
~~I-aaa-2~~



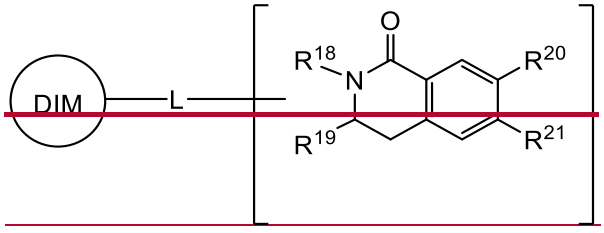
~~I-aaa-3~~



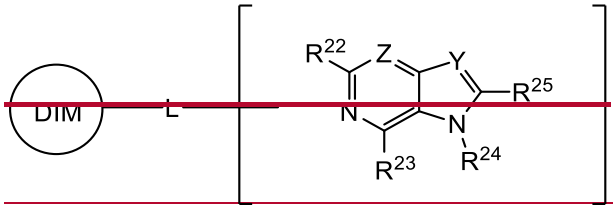
~~I-aaa-4~~



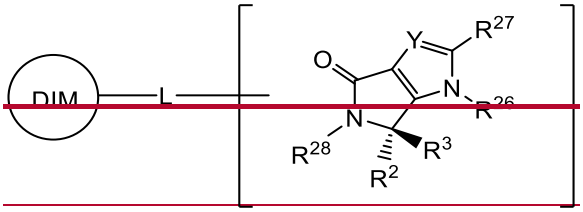
~~I-aaa-5~~



~~I-aaa-6~~



~~I-aaa-7~~



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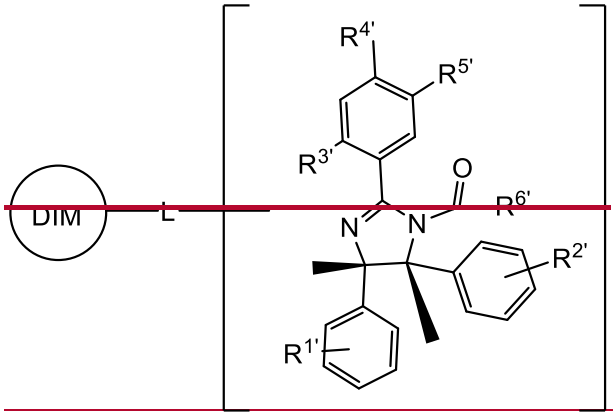
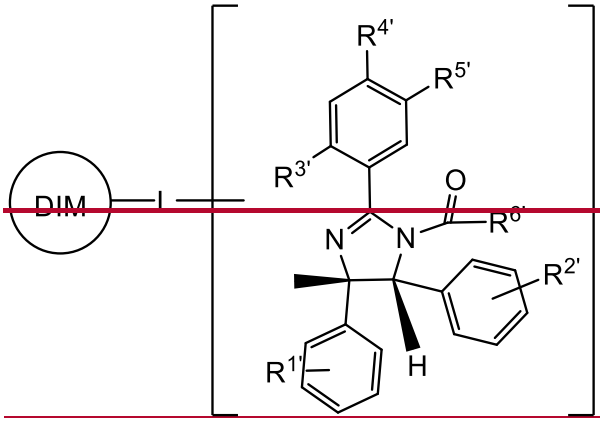
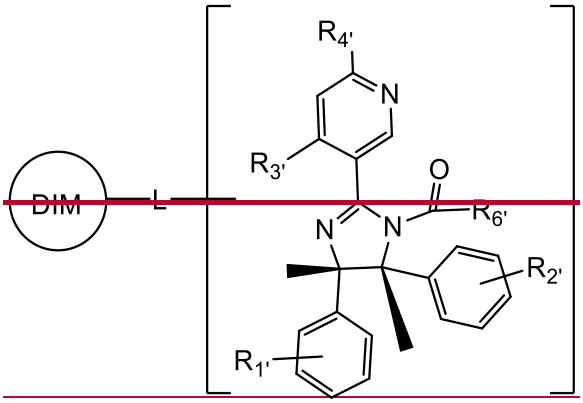


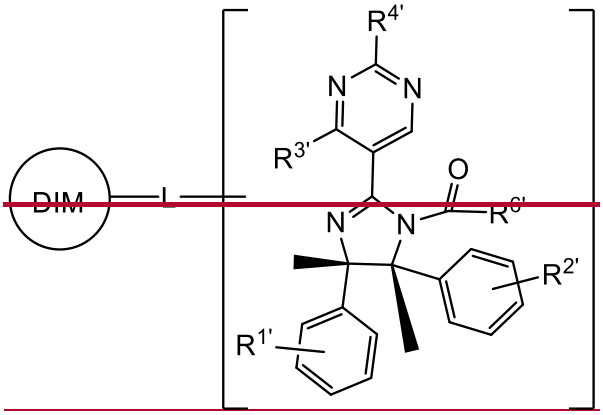
~~I-aaa-9~~



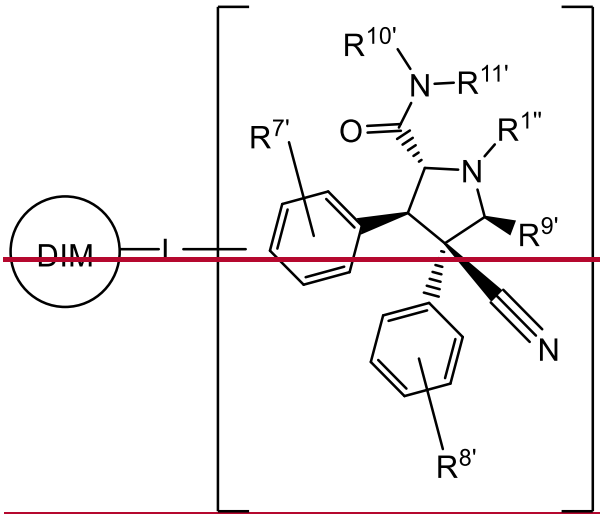
~~I-aaa-10~~



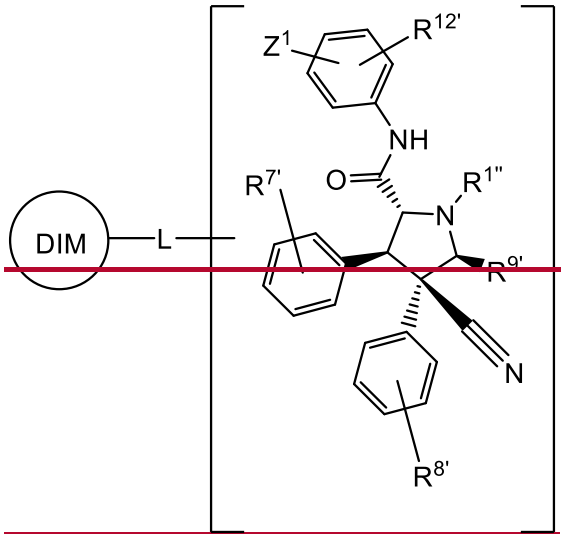
~~I-aaa-11~~



~~I-aaa-12~~



~~I-aaa-13~~



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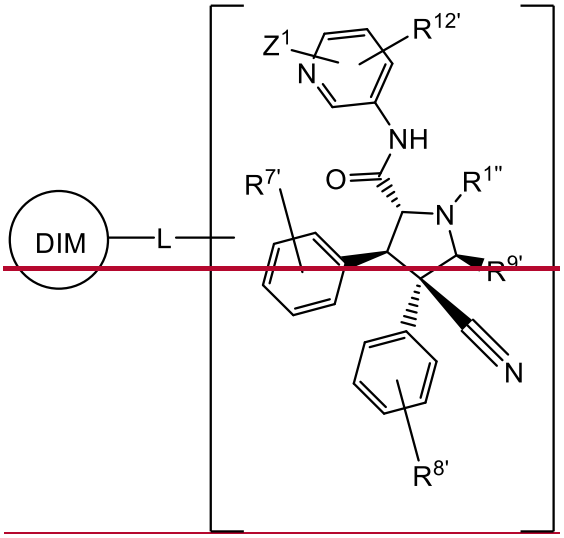
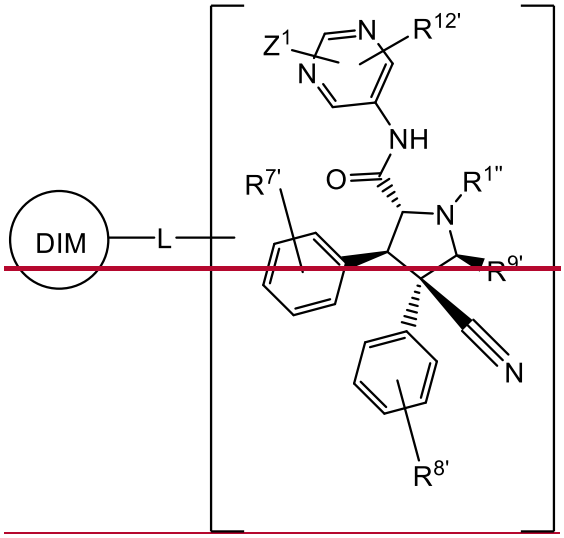


~~I-aaa-15~~



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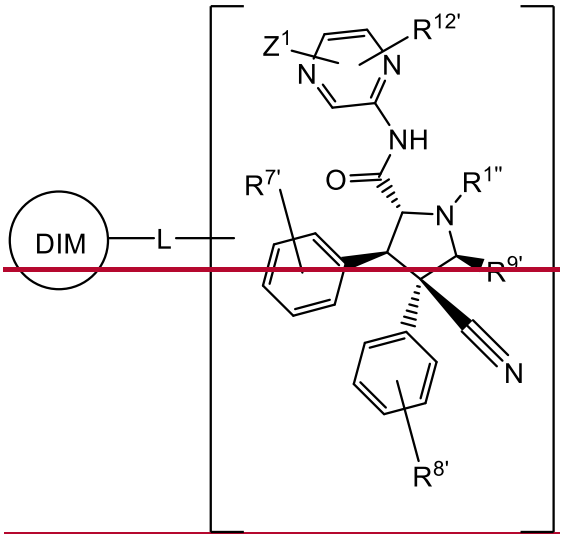

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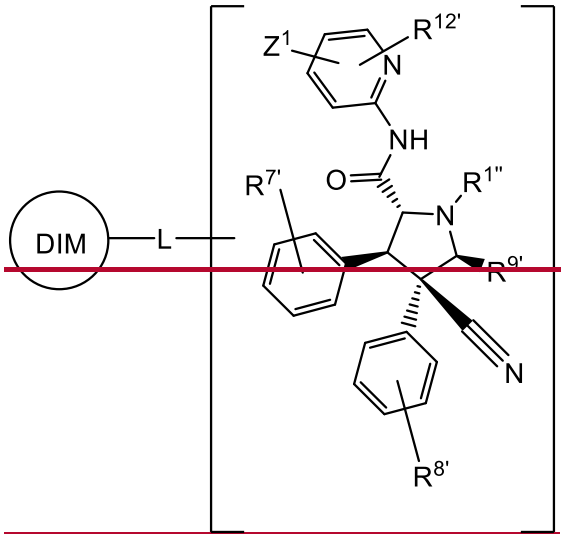

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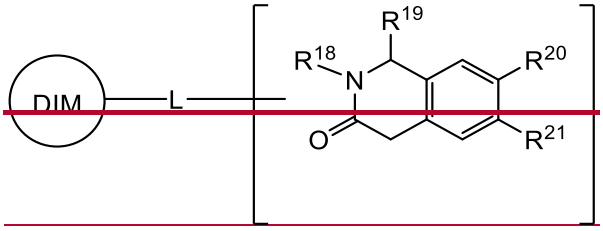

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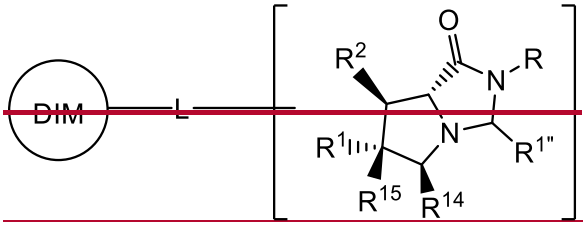


~~I-aaa-20~~

~~or a pharmaceutically acceptable salt thereof, wherein:~~

~~X is selected from $-CR_2-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, and $-NR-$;~~

~~each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:~~

~~two R groups on the same atom are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom from which they are attached, independently selected from nitrogen, oxygen, and sulfur.~~

~~Y and Z are independently selected from $-CR=$ and $-N=$;~~

~~Ring W is fused ring selected from benzo and a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;~~

~~R^1 and R^2 are independently an optionally substituted monocyclic or bicyclic ring selected from phenyl, a 5-10 membered aryl, and a 5-10 membered heteroaryl containing 1-4 heteroatoms independently~~

selected from nitrogen, oxygen, and sulfur;

R^3 and R^4 are independently selected from hydrogen and C_{1-6} alkyl;

R^5 is selected from an optionally substituted monocyclic or bicyclic ring selected from phenyl, a 5-10 membered aryl, and a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^6 is selected from hydrogen, -C(O)R, -C(O)OR, and -C(O)NR_2;

R^7 is selected from hydrogen and R^A;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^8 is selected from -C(O)R and R^A;

R^9 is a mono-, bis-, or tri-substituent on Ring W, wherein each of the substituents are independently selected from halogen and an optionally substituted C_{1-6} aliphatic;

R^{10} is selected from an optionally substituted monocyclic or bicyclic ring selected from phenyl, a 5-10 membered aryl, and a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{11} is -C(O)OR or -C(O)NR_2;

R^{12} and R^{13} are independently selected from hydrogen and R^A, or:

R^{12} and R^{13} are optionally taken together with their intervening atoms to form an optionally substituted 3-8 membered saturated, partially unsaturated, carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{14} is R^A;

R^{15} is -CN;

R^{16} is selected from R^A, -OR, $-(CR_2)_{0-6}$-C(O)R, $-(CR_2)_{0-6}$-C(O)OR, $-(CR_2)_{0-6}$-C(O)NR_2, $-(CR_2)_{0-6}$-S(O)$_2$R, $-(CR_2)_{0-6}$-N(R)S(O)$_2$R, $-(CR_2)_{0-6}$-S(O)$_2$$NR_2$;

R^{17} is selected from $-(CR_2)_{0-6}$-C(O)NR_2;

R^{18} and R^{19} are independently selected from hydrogen and R^A;

R^{20} and R^{21} are independently selected from hydrogen, R^A, halogen, and -OR, or:

R^{20} and R^{21} are optionally taken together with their intervening atoms to form a fused 5-7 membered partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a fused 5-6 membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{22}, R^{23}, R^{25}, and R^{27} are independently selected from hydrogen, R^A, halogen, -C(O)R, -C(O)OR, -C(O)NR_2, -NR_2, -OR, -S(O)R, -$S(O)_2R$, -$S(O)_2NR_2$;

R^{24}, R^{26}, and R^{28} are independently selected from hydrogen, R^A, -C(O)R, -C(O)OR, -C(O)NR_2, -S(O)R, -$S(O)_2R$, and -$S(O)_2NR_2$;

$R^{1'}$ and $R^{2'}$ are independently selected from halogen, -C≡CR, -CN, -CF_3, and -NO_2;

$R^{3'}$ is -OR;

$R^{4'}$, $R^{5'}$, $R^{6'}$ are independently selected from hydrogen, halogen, R^A, -CN, -CF_3, -NR_2, -OR, -SR, and -$S(O)_2R$;

$R^{7'}$ is a mono-, bis-, or tri-substituent, wherein each of the substituents are independenly selected from halogen;

$R^{8'}$ is a mono-, bis-, or tri-substituent, wherein each of the substituents are independently selected from hydrogen, halogen, R^A, -CN, -C≡CR, -NO_2, and -OR;

$R^{9'}$ is R^A;

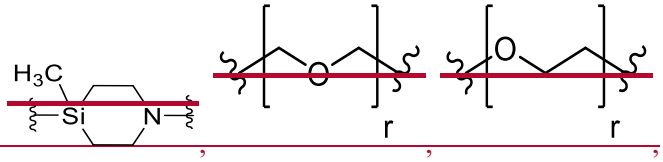
Z^1 is selected from hydrogen, halogen, and -OR;

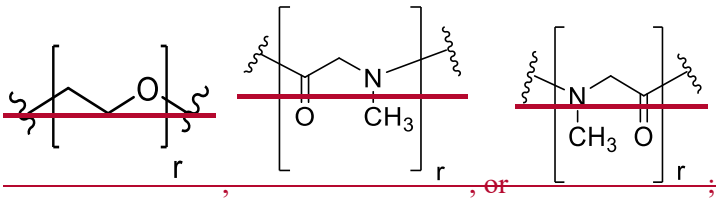
$R^{10'}$ and $R^{11'}$ are independently selected from hydrogen and R^A;

$R^{12'}$ is selected from -C(O)R, -C(O)OR, -C(O)NR_2, -OR, -$S(O)_2R$, -$S(O)_2NR_2$, and -S(O)R;

$R^{1''}$ is selected from hydrogen and R^A;

L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -C(D)(H)-, -$C(D)_2$-, -Cy-, -O-, -N(R)-, -$Si(R)_2$-, -Si(OH)(R)-, -$Si(OH)_2$-, -P(O)(OR)-, -P(O)(R)-, -P(O)(NR_2)-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -N(R)$S(O)_2$-, -$S(O)_2N(R)$-, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)C(O)O-,





, or ;

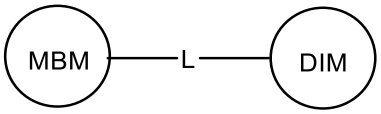
each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen,

~~oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;~~

~~r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and~~

~~DIM is a degradation moiety selected from an E3 ubiquitin ligase binding moiety (LBM), a lysine mimetic, and hydrogen.~~

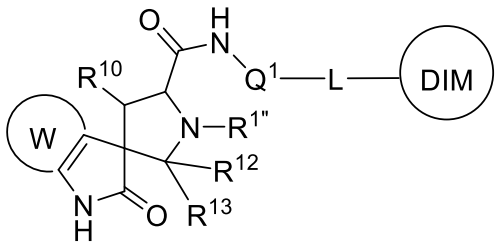
~~2~~1. A compound of formula **I**:



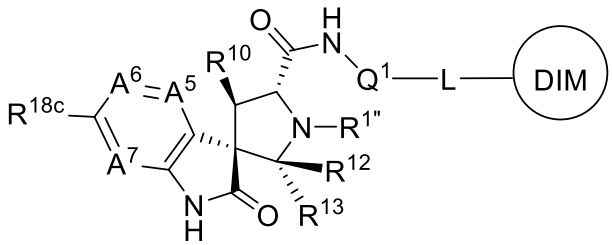
I

or a pharmaceutically acceptable salt thereof, wherein:

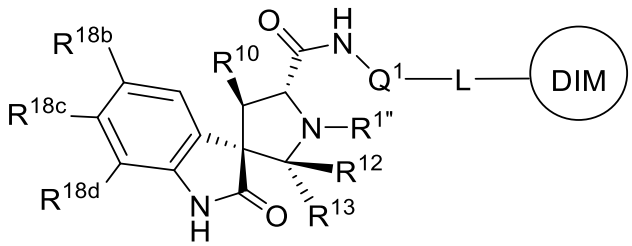
MBM is a MDM2 binding moiety capable of binding to MDM2 protein, said compound of formula **I** is a compound selected from formula:



I-bbb-1



I-bbb-2



I-bbb-3

or a pharmaceutically acceptable salt thereof, wherein:

$R^{1''}$ is selected from hydrogen and R^A;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7

membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^{10} is selected from an optionally substituted monocyclic or bicyclic ring selected from phenyl, a 5-10 membered aryl, and a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R_{12} and R_{13} are each independently selected from hydrogen and R^A, or:

R^{12} and R^{13} are optionally taken together with their intervening atoms to form an optionally substituted 4-8 membered saturated, partially unsaturated, carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

A^5 is selected from -C(R^{18a})= and -N=;

A^6 is selected from -C(R^{18b})= and -N=;

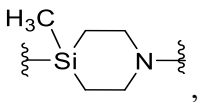
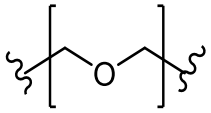
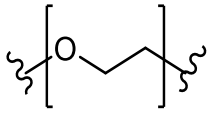
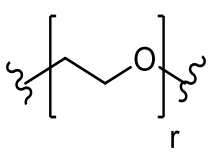
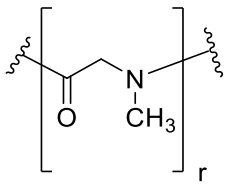
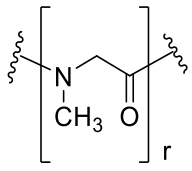
A^7 is selected from -C(R^{18d})= and -N=;

R^{18a}, R^{18b}, R^{18c}, and R^{18d} are each independently selected from hydrogen, halogen, R^A, and –OR;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring W is an optionally substituted fused ring selected from benzo and a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Q^1 is and optionally substituted bivalent group selected from alkylenyl, phenylenyl, heteroarylenyl, cycloalkylenyl, and heterocyclenyl;

L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by ~~–C(D)(H)–, –C(D)$_2$–,~~ –Cy-, -O-, -N(R)-, –Si(R)$_2$–, –Si(OH)(R)–, –Si(OH)$_2$–, –P(O)(OR)–, –P(O)(R)–, –P(O)(NR$_2$)–, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)$_2$-, -N(R)S(O)$_2$-, -S(O)$_2$N(R)-, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, –N(R)C(O)O-,  ,  ,  ,  ,  , or  ;

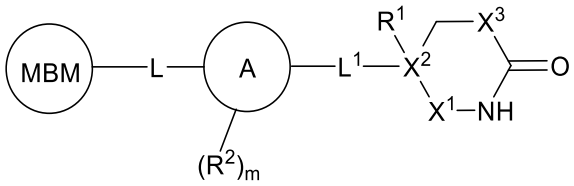
each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

DIM is a degradation moiety selected from an E3 ubiquitin ligase binding moiety (LBM), a lysine mimetic, and hydrogen.

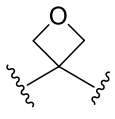
23. The compound of ~~either~~ claim 1 ~~or claim 2~~, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety, a VHL E3 ubiquitin ligase binding moiety, an IAP E3 ubiquitin ligase binding moiety, or an MDM2 E3 ubiquitin ligase binding moiety.

34. The compound of claim 23, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety and said compound is of formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

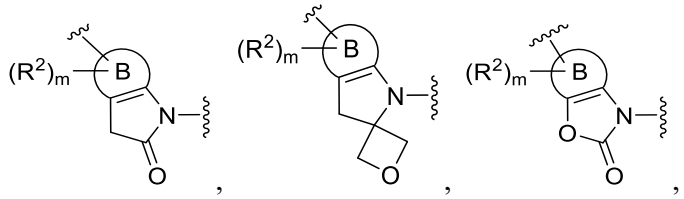
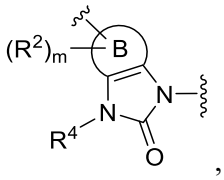
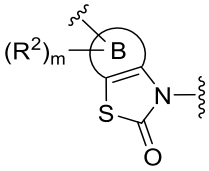
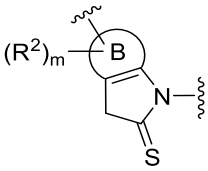
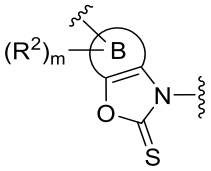
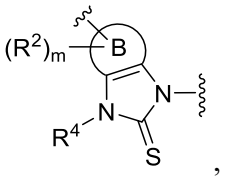
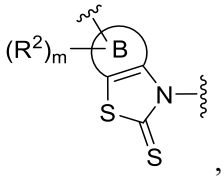
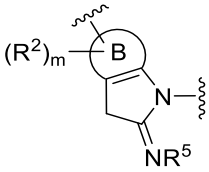
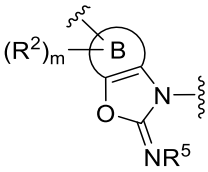
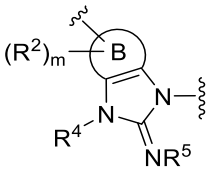
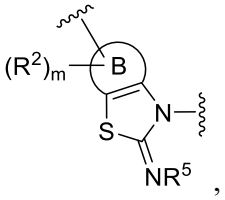
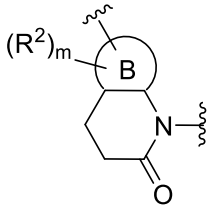
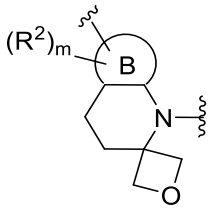
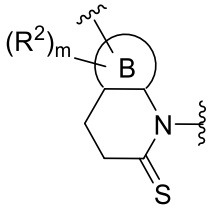
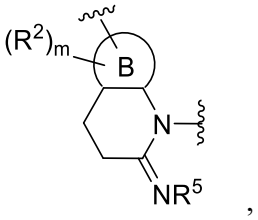
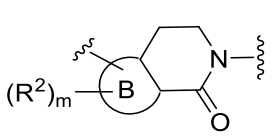
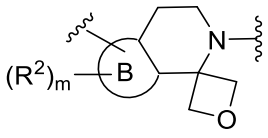
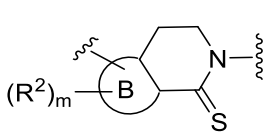
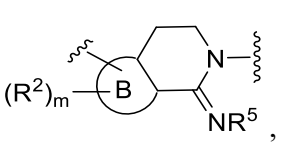
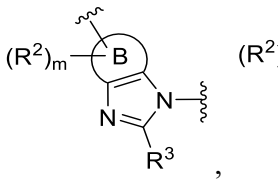
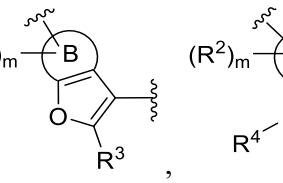
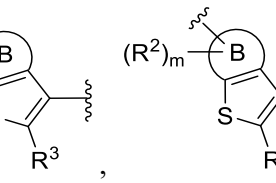
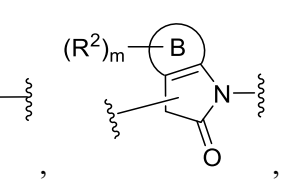
X^1 is a bivalent moiety selected from a covalent bond, $–CH_2–$, $–CHCF_3–$, $–SO_2–$, –S(O)–, –P(O)R–, –P(O)OR–, $–P(O)NR_2–$, –C(O)–, –C(S)–, or  ;

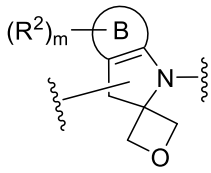
X^2 is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from $–CR_2–$, –NR–, –O–, –S–, or $–Si(R_2)–$;

R^1 is hydrogen~~, deuterium~~, halogen, –CN, –OR, –SR, –S(O)R, –$S(O)_2$R, –$N(R)_2$, –$P(O)(OR)_2$, –$P(O)(NR_2)OR$, –$P(O)(NR_2)_2$, –$Si(OH)_2R$, –$Si(OH)(R)_2$, –$Si(R)_3$, or an optionally substituted C_{1-4} aliphatic;

each R^2 is independently hydrogen~~, deuterium~~, –R^6, halogen, –CN, –NO_2, –OR, -SR, -$N(R)_2$, -$Si(R)_3$, -$S(O)_2R$, -$S(O)_2N(R)_2$, -S(O)R, -C(O)R, -C(O)OR, –$C(O)N(R)_2$, -$C(O)N(R)OR$, -$C(R)_2N(R)C(O)R$, -$C(R)_2N(R)C(O)N(R)_2$, -OC(O)R, -$OC(O)N(R)_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)(NR_2)$, -$OP(O)(NR_2)_2$-, -N(R)C(O)OR, -N(R)C(O)R, -$N(R)C(O)N(R)_2$, –N(R)$S(O)_2$R, -$NP(O)R_2$, -N(R)$P(O)(OR)_2$, -N(R)$P(O)(OR)(NR_2)$, -N(R)$P(O)(NR_2)_2$, or –N(R)$S(O)_2$R;

Ring A is a bi- or tricyclic ring selected from  , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , ,  , , ,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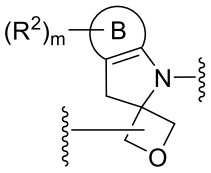
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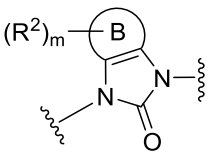
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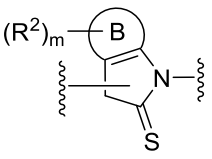
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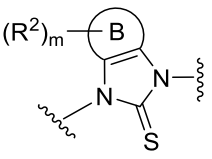
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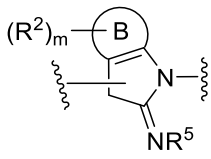
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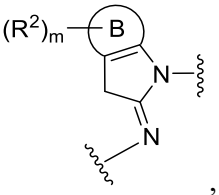
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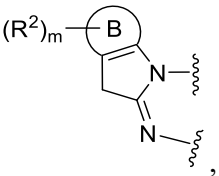
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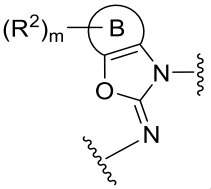
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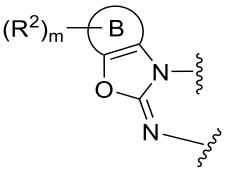
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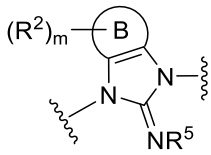
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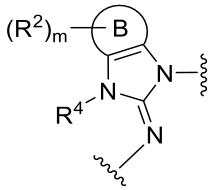
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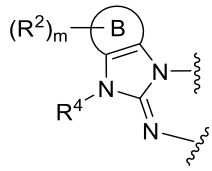
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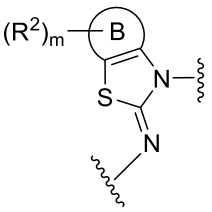
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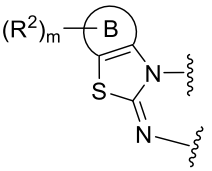
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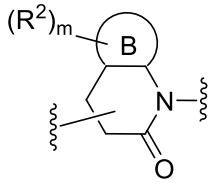
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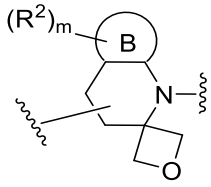
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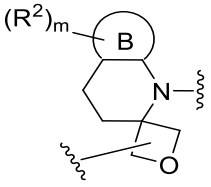
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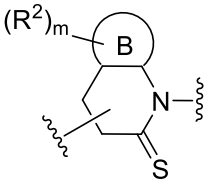
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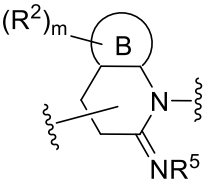
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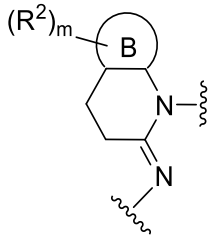
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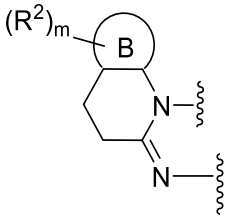
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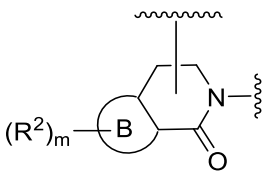
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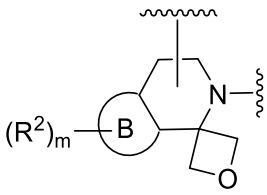
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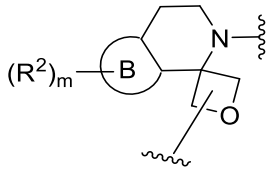
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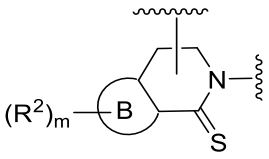
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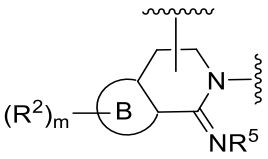
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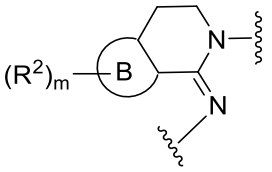
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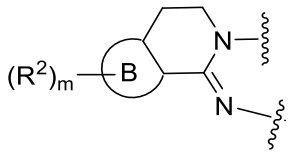
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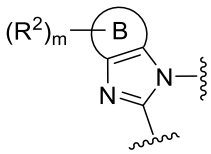
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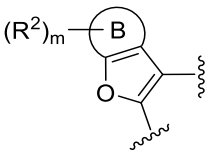
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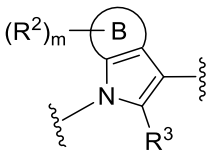
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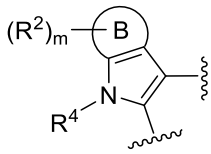
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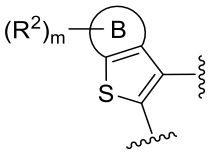

, wherein

Ring B is a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, and sulfur, and 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

R^3 is selected from hydrogen, halogen, –OR, $–N(R)_2$, or –SR;

each R^4 is independently hydrogen, $–R^6$, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $–N(R)S(O)_2R$;

R^5 is hydrogen, C_{1-4} aliphatic, or –CN;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

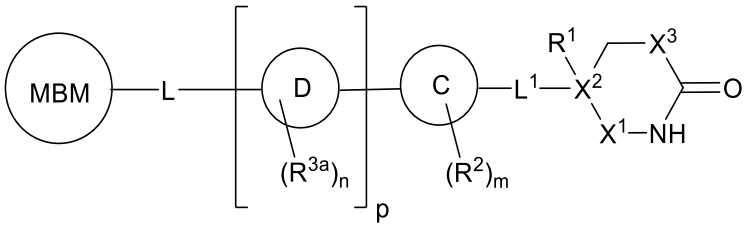
L^1 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, $-S(O)_2-$ or -(C)=CH-;

m is 0, 1, 2, 3 or 4;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

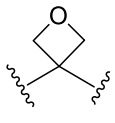
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

45. The compound of claim 23, wherein LBM is a cereblon E3 ligase binding moiety and said compound is of formula **I-d**:



I-d

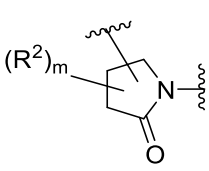
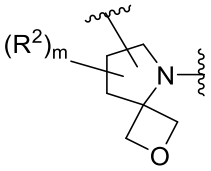
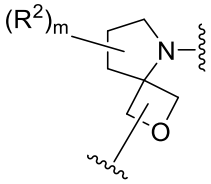
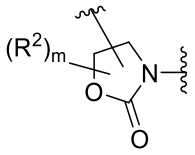
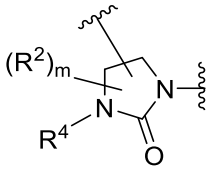
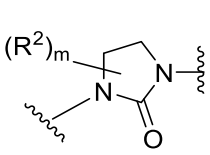
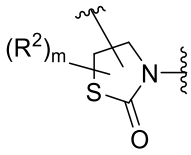
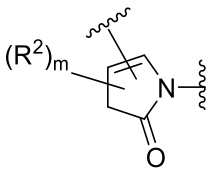
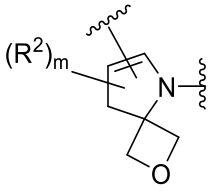
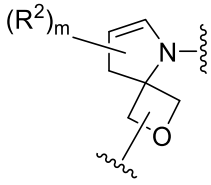
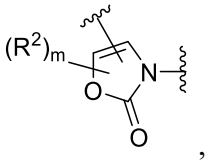
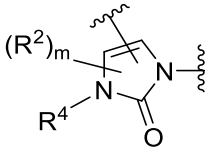
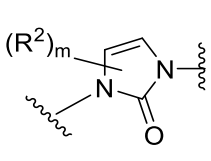
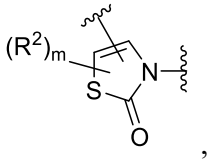
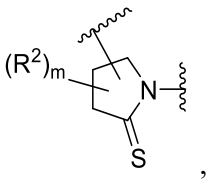
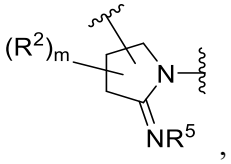
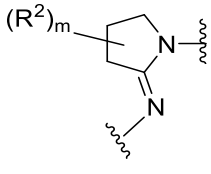
or a pharmaceutically acceptable salt thereof, wherein:

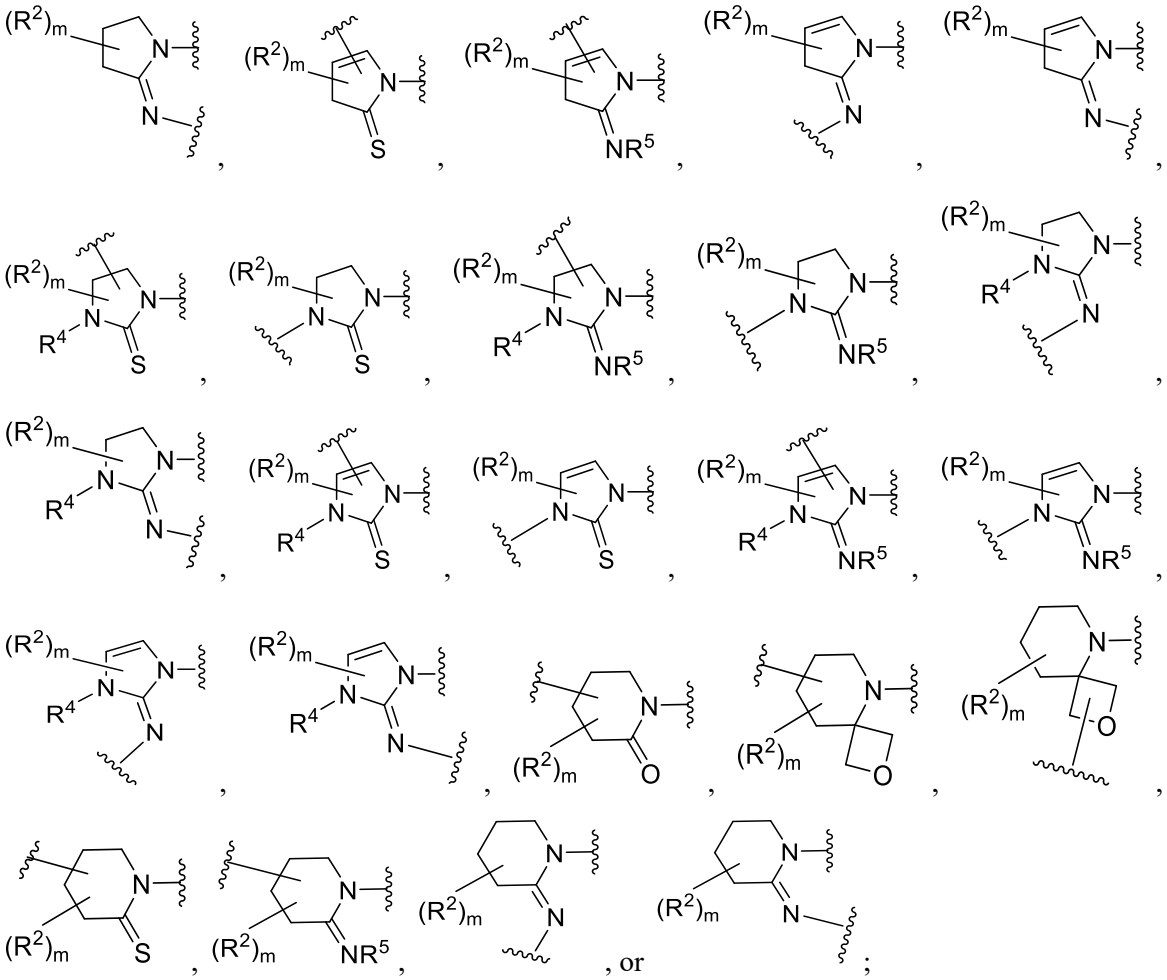
X^1 is a bivalent moiety selected from a covalent bond, $–CH_2–$, $–CHCF_3–$, $–SO_2–$, –S(O) –, –P(O)R–, –P(O)OR–, $–P(O)NR_2–$, –C(O)–, –C(S)–, or  ;

X^2 is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from $–CR_2–$, –NR–, –O–, –S–, or $–Si(R_2)–$;

R^1 is hydrogen~~, deuterium~~, halogen, –CN, –OR, –SR, –S(O)R, $–S(O)_2R$, $–NR_2$, $–P(O)(OR)_2$, $–P(O)(NR_2)OR$, $–P(O)(NR_2)_2$, $–Si(OH)_2R$, $–Si(OH)(R)_2$, $–Si(R)_3$, or an optionally substituted C_{1-4} aliphatic;

Ring C is a monocyclic or bicyclic ring selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .



each of R^2 and R^{3a} is independently hydrogen~~, deuterium~~, $–R^6$, halogen, –CN, $–NO_2$, –OR, -SR, $-N(R)_2$, $-Si(R)_3$, $-S(O)_2R$, $-S(O)_2N(R)_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)N(R)_2$, -C(O)N(R)OR, $-C(R)_2N(R)C(O)R$, $-C(R)_2N(R)C(O)N(R)_2$, $-OC(O)R$, $-OC(O)N(R)_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)(NR_2)$, $-OP(O)(NR_2)_2$-, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)N(R)_2$, $–N(R)S(O)_2R$, $-NP(O)R_2$, $-N(R)P(O)(OR)_2$, $-N(R)P(O)(OR)(NR_2)$, $-N(R)P(O)(NR_2)_2$, or $–N(R)S(O)_2R$;

Ring D is selected from a 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

each R^4 is independently hydrogen, $–R^6$, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, $-N(R)C(O)OR$, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $–N(R)S(O)_2R$;

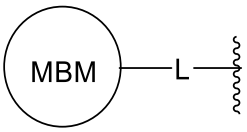
R^5 is hydrogen, C_{1-4} aliphatic, or –CN;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^1 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, $-S(O)_2-$ or -(C)=CH-;

m is 0, 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

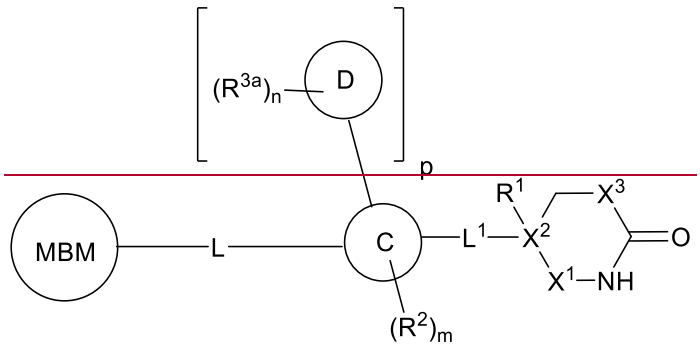
p is 0 or 1, wherein when p is 0, the bond connecting Ring C and Ring D is connected to 

; and

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

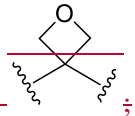
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

~~6. The compound of claim 3, wherein LBM is a cereblon E3 ligase binding moiety and said compound is of formula I-f:~~



~~I-f~~

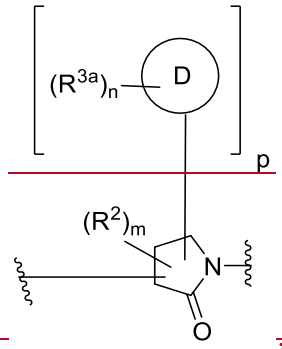
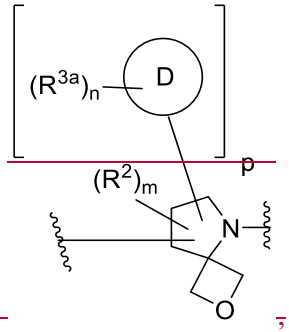
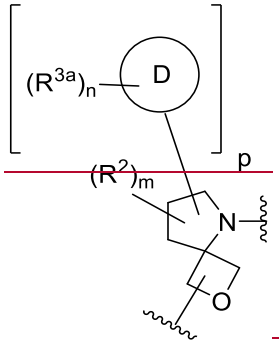
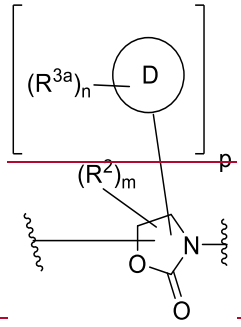
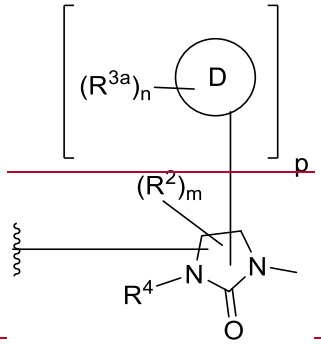
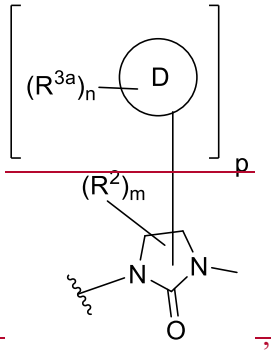
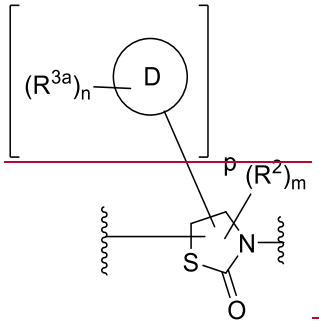
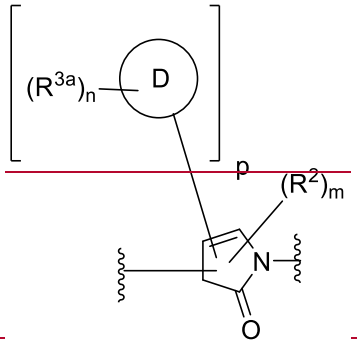
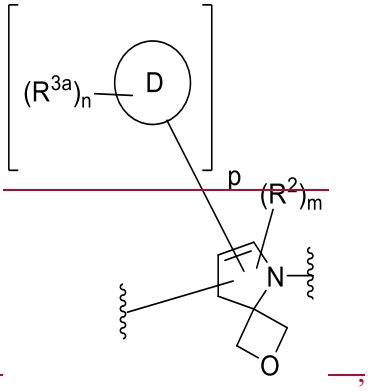
~~or a pharmaceutically acceptable salt thereof, wherein:~~

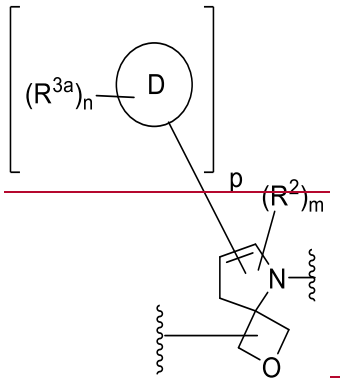
~~X^1 is a bivalent moiety selected from a covalent bond, CH_2, $CHCF_3$, SO_2, S(O), P(O)R, P(O)OR, $P(O)NR_2$, C(O), C(S), or~~  ~~;~~

~~X^2 is a carbon atom or silicon atom;~~

~~X^3 is a bivalent moiety selected from CR_2, NR, O, S, or $Si(R_2)$;~~

~~R^1 is hydrogen, deuterium, halogen, –CN, –OR, –SR, –S(O)R, $–S(O)_2R$, $–NR_2$, $–P(O)(OR)_2$, $–P(O)(NR_2)OR$, $–P(O)(NR_2)_2$, $–Si(OH)_2R$, $–Si(OH)(R)_2$, $–Si(R)_3$, or an optionally substituted C_{1-4} aliphatic;~~

~~Ring C is a monocyclic or bicyclic ring selected from~~  ,  ,  ,  ,  ,  ,  ,  ,  ,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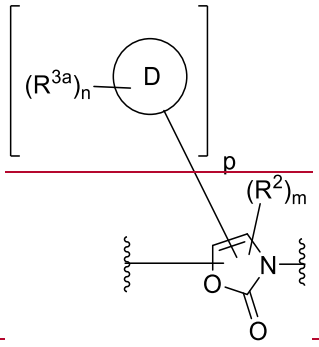
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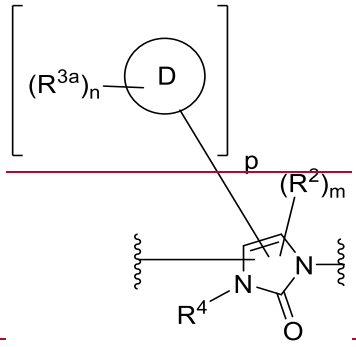
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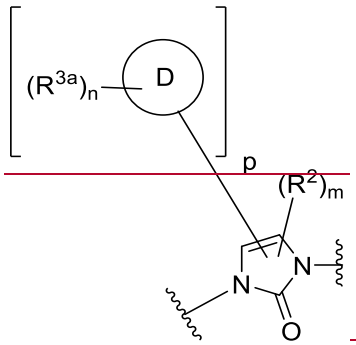
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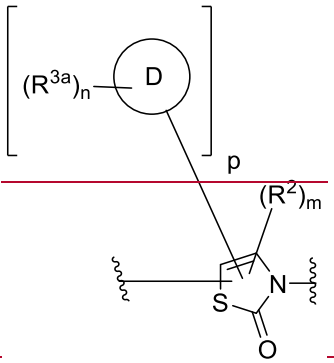
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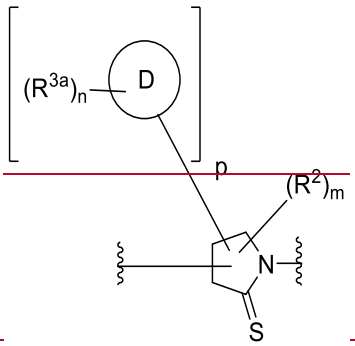
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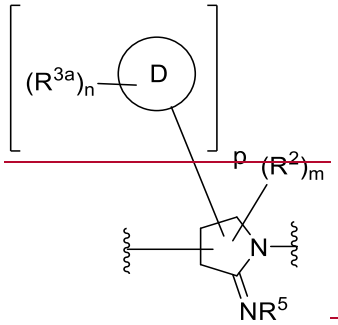
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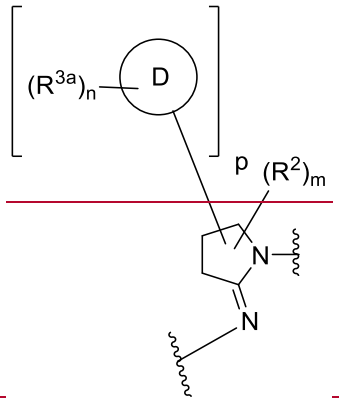
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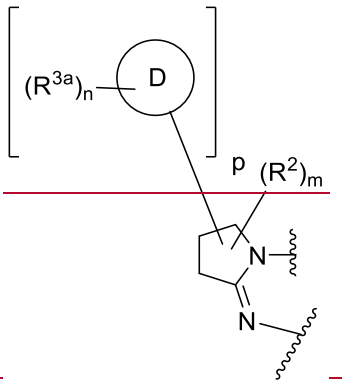
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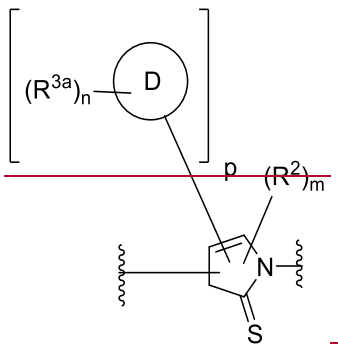
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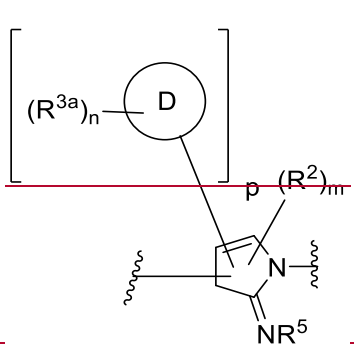
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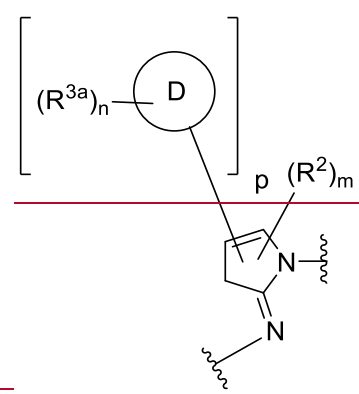
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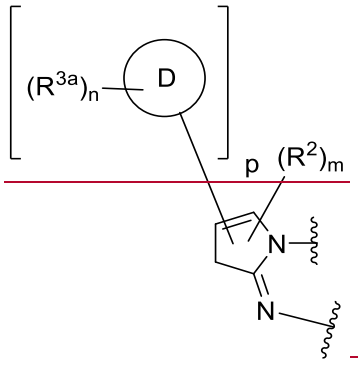
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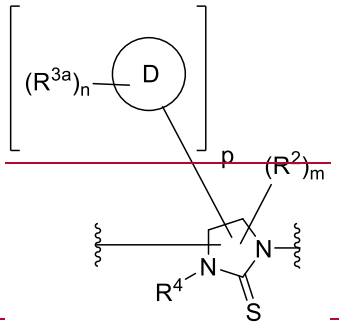
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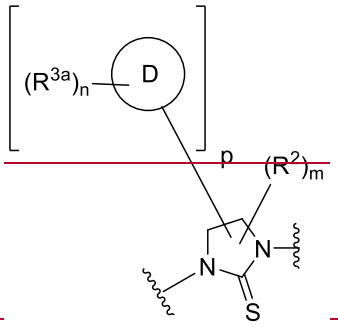
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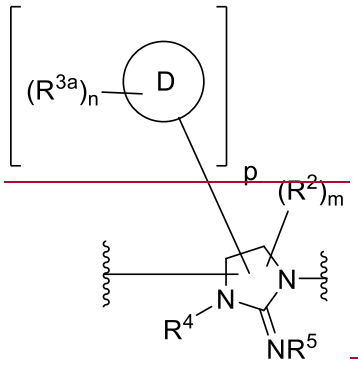
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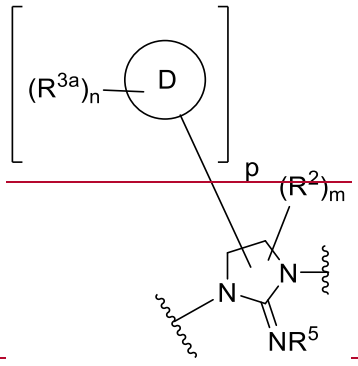
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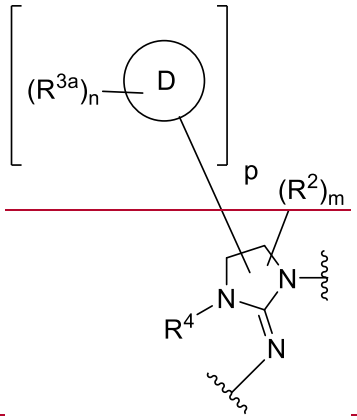
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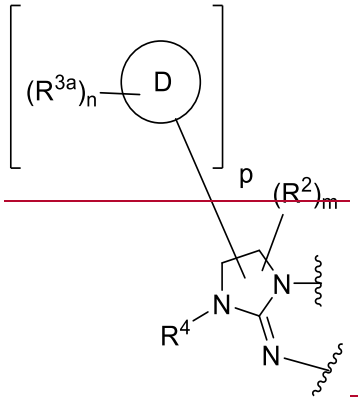
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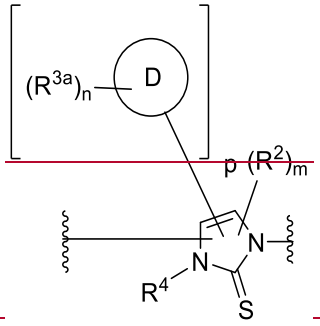
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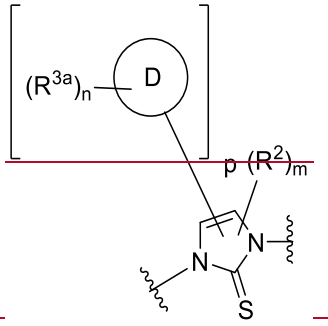
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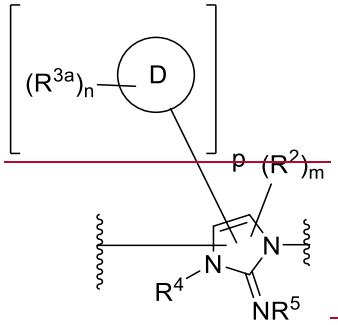
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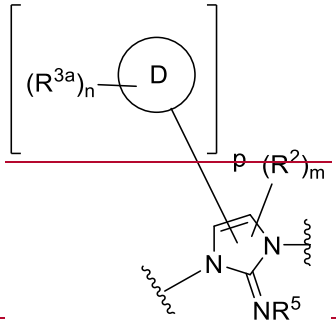
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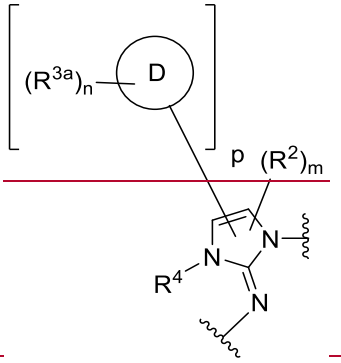
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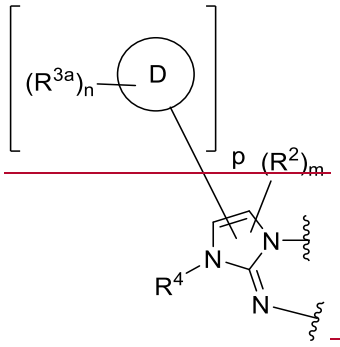

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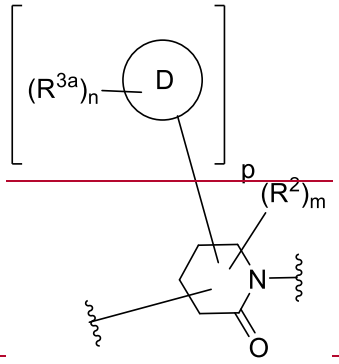

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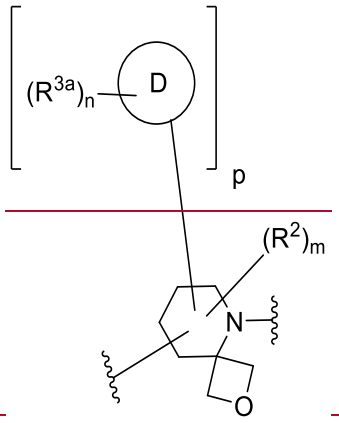

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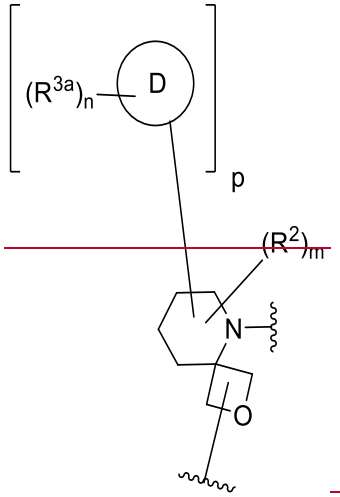

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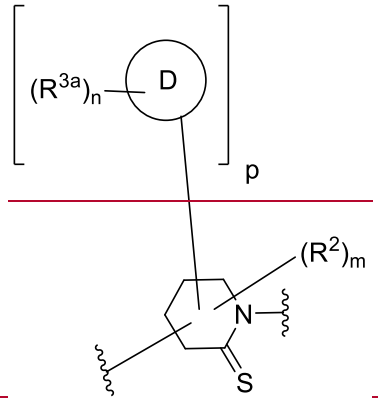

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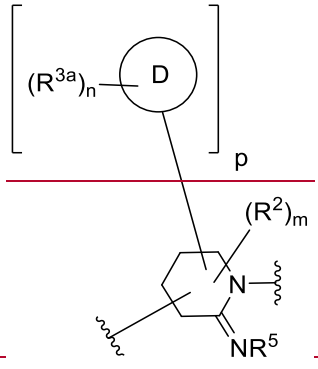

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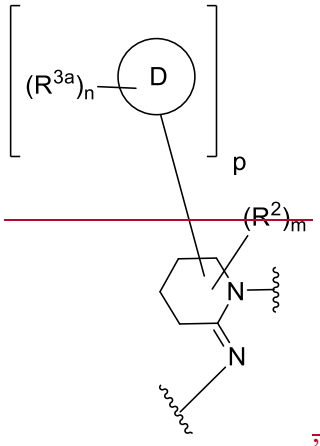
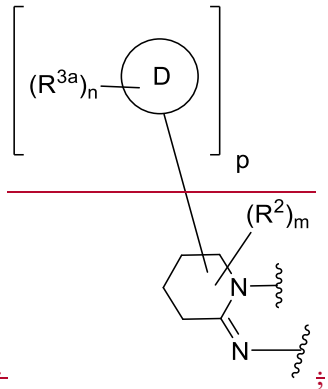




~~, or~~

~~each or R^2 and R^{3a} is independently hydrogen, deuterium, R^6, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-N(R)_2$, $-Si(R)_3$, $-S(O)_2R$, $-S(O)_2N(R)_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, $-C(O)N(R)OR$, $-C(R)_2N(R)C(O)R$, $-C(R)_2N(R)C(O)N(R)_2$, $-OC(O)R$, $-OC(O)N(R)_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)(NR_2)$, $-OP(O)(NR_2)_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)N(R)_2$, $-N(R)S(O)_2R$, $-NP(O)R_2$, $-N(R)P(O)(OR)_2$, $-N(R)P(O)(OR)(NR_2)$, $-N(R)P(O)(NR_2)_2$, or $-N(R)S(O)_2R$;~~

~~Ring D is selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;~~

~~each R^4 is independently hydrogen, R^6, halogen, CN, NO_2, OR, SR, NR_2, $S(O)_2R$, $S(O)_2NR_2$, S(O)R, C(O)R, C(O)OR, $C(O)NR_2$, C(O)N(R)OR, OC(O)R, $OC(O)NR_2$, N(R)C(O)OR, N(R)C(O)R, $N(R)C(O)NR_2$, or $N(R)S(O)_2R$;~~

~~R^5 is hydrogen, C_{1-4} aliphatic, or CN;~~

~~each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;~~

~~L^1 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, $-S(O)_2-$ or -(C)=CH-;~~

~~m is 0, 1, 2, 3 or 4;~~

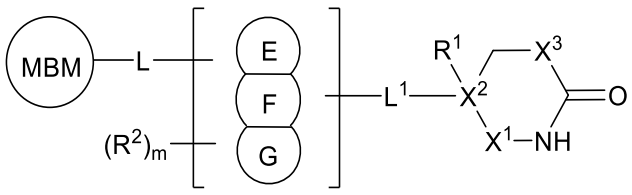
~~n is 0, 1, 2, 3 or 4;~~

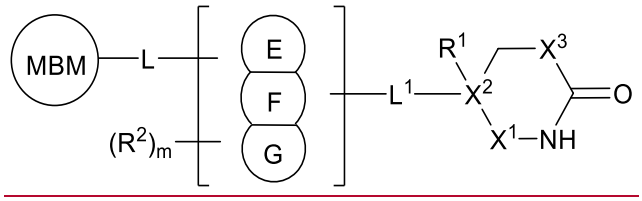
~~p is 0 or 1; and~~

~~each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:~~

~~two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.~~

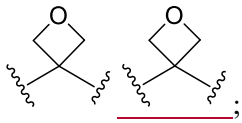
~~7~~5. The compound of claim ~~1~~2, wherein LBM is a cereblon E3 ligase binding moiety and said compound is of formula **I-h**:





I-h

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is a bivalent moiety selected from a covalent bond, $–CH_2–$, $–CHCF_3–$, $–SO_2–$, –S(O) –, –P(O)R–, –P(O)OR–, $–P(O)NR_2–$, –C(O)–, –C(S)–, or  ;

X^2 is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from $–CR_2–$, –NR–, –O–, –S–, or $–Si(R_2)–$;

R^1 is hydrogen~~, deuterium~~, halogen, –CN, –OR, –SR, –S(O)R, $–S(O)_2R$, $–N(R)_2$, $–P(O)(OR)_2$, $–P(O)(NR_2)OR$, $–P(O)(NR_2)_2$, $–Si(OH)_2R$, $–Si(OH)(R)_2$, $-Si(R)_3$, or an optionally substituted C_{1-4} aliphatic;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

each R^2 is independently hydrogen~~, deuterium~~, $–R^6$, halogen, –CN, $–NO_2$, –OR, -SR, $-N(R)_2$, $-Si(R)_3$, $-S(O)_2R$, $-S(O)_2N(R)_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)N(R)_2$, -C(O)N(R)OR, $-C(R)_2N(R)C(O)R$, $-C(R)_2N(R)C(O)N(R)_2$, -OC(O)R, $-OC(O)N(R)_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)(NR_2)$, $-OP(O)(NR_2)_2$-, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)N(R)_2$, $–N(R)S(O)_2R$, $-NP(O)R_2$, $-N(R)P(O)(OR)_2$, $-N(R)P(O)(OR)(NR_2)$, $-N(R)P(O)(NR_2)_2$, or $–N(R)S(O)_2R$;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

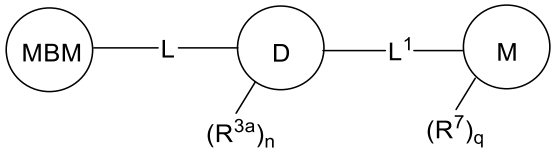
each of Ring E, Ring F, and Ring G is independently a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or

sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl ring with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur, , wherein each of Ring E, Ring F, and Ring G is independently and optionally further substituted with 1-2 oxo groups;

L^1 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, $-S(O)_2-$ or -(C)=CH-; and

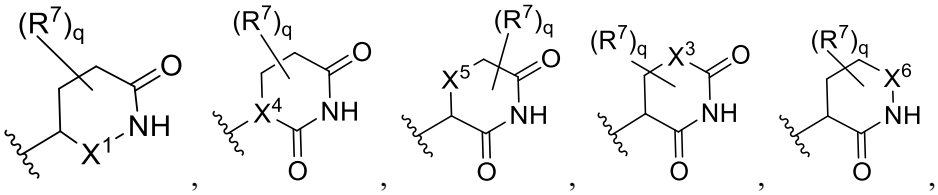
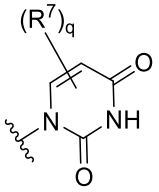
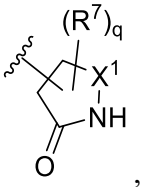
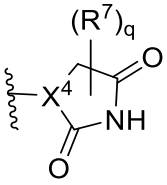
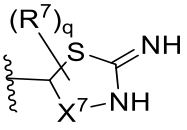
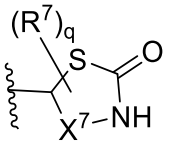
m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

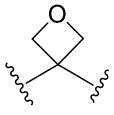
68. The compound of claim 21, wherein LBM is a cereblon E3 ligase binding moiety and said compound is a compound of formula **I-ii**:



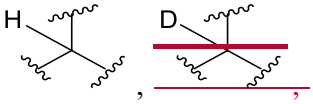
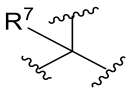
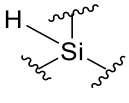
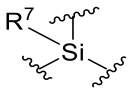
I-ii

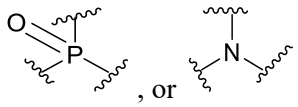
or a pharmaceutically acceptable salt thereof, wherein:

Ring M is selected from  , , , , ,  ,  ,  ,  , or  ;

each of X^1, X^6, and X^7 is independently a bivalent moiety selected from a covalent bond, $–CH_2–$, $–CHCF_3–$, $–SO_2–$, –S(O) –, –P(O)R–, –P(O)OR–, $–P(O)NR_2–$, –C(O)–, –C(S)–, or  ;

each of X^3 and X^5 is independently a bivalent moiety selected from a covalent bond, $–CR_2–$, –NR–, –O–, –S–, or $–SiR_2–$;

X^4 is a trivalent moiety selected from  ,  ,  ,  ,



, or ;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

each R^{3a} is independently hydrogen, ~~deuterium,~~ R^6, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, $-C(R)_2N(R)C(O)R$, $-C(R)_2N(R)C(O)N(R)_2$, -OC(O)R, $-OC(O)N(R)_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$-, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $–N(R)S(O)_2R$, $-NP(O)R_2$, $-N(R)P(O)(OR)_2$, $-N(R)P(O)(OR)NR_2$, $-N(R)P(O)(NR_2)_2$, or $–N(R)S(O)_2R$;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^7 is independently hydrogen~~, deuterium~~, halogen, –CN, –OR, –SR, –S(O)R, $–S(O)_2R$, $–NR_2$, $–P(O)(OR)_2$, $–P(O)(NR_2)OR$, $–P(O)(NR_2)_2$, $–Si(OH)R_2$, $–Si(OH)_2R$, $–SiR_3$, or an optionally substituted C_{1-4} aliphatic; or

R^7 and X^1 or X^3 are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, carbocyclic ring or heterocyclic ring having 1-3 heteroatoms, independently selected from boron, nitrogen, oxygen, silicon, or sulfur;

two R^7 groups on the same carbon are optionally taken together with their intervening atoms to form a 3-6 membered spiro fused ring or a 4-7 membered heterocyclic ring having 1-2 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur;

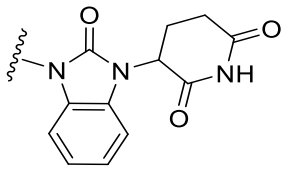
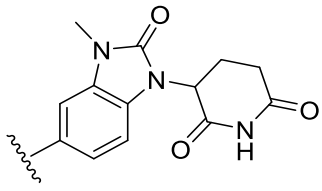
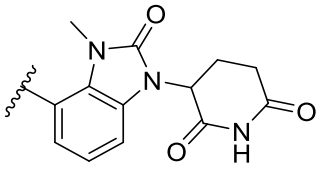
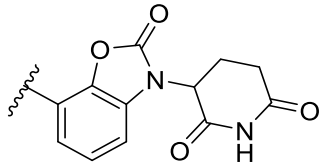
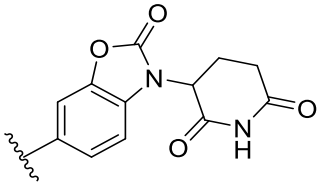
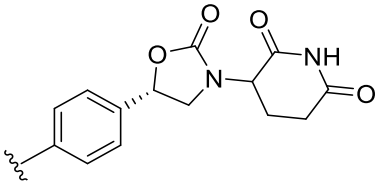
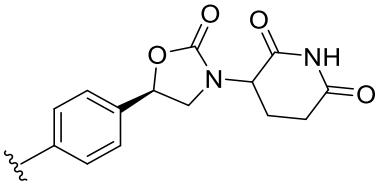
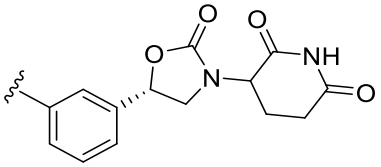
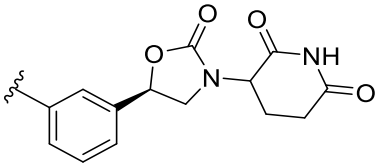
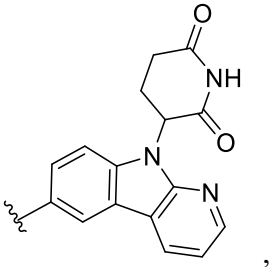
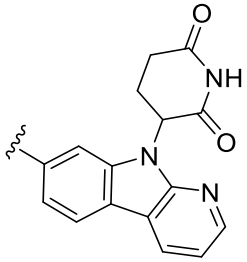
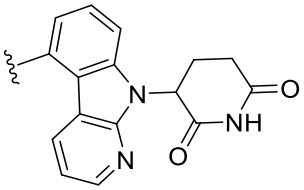
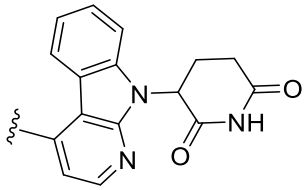
two R^7 groups on adjacent carbon atoms are optionally taken together with their intervening atoms to form a 3-7 membered saturated, partially unsaturated, carbocyclic ring or heterocyclic ring having 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or a 7-13 membered saturated, partially unsaturated, bridged heterocyclic ring, or a spiro heterocyclic ring having 1-3 heteroatoms, independently selected from boron, nitrogen, oxygen, silicon, or sulfur;

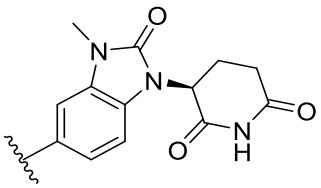
Ring D is selected from 6 to 10-membered aryl or heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

L^1 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -$C(R)_2$-, -CH(R)-, -$C(F)_2$-, -N(R)-, -S-, -$S(O)_2$- or -(C)=CH-;

n is 0, 1, 2, 3, or 4; and

q is 0, 1, 2, 3, or 4.

79. The compound of any one of claims 2-63-8, wherein the cereblon E3 ubiquitin ligase binding moiety is selected from:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,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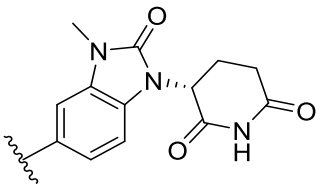
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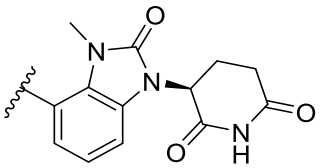
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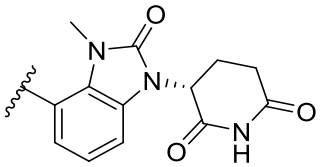
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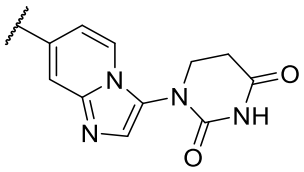
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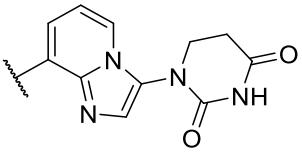
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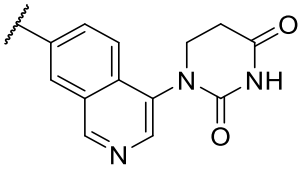
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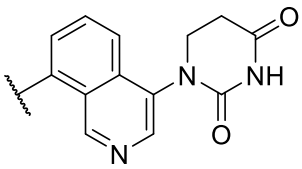
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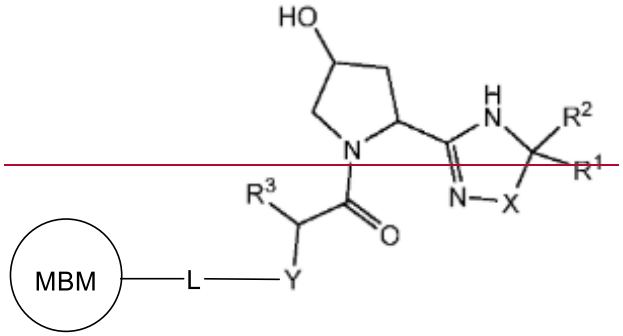
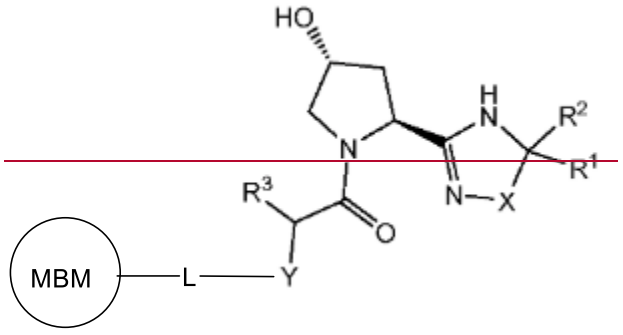
~~10. The compound of claim 3, wherein LBM is a VHL E3 ubiquitin ligase binding moiety and said compound is selected from any of the following formulae:~~

~~(*i*)~~



~~I-aa-1~~

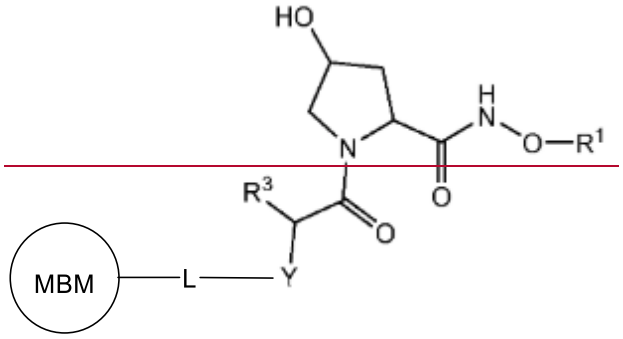


~~I-aa-2~~

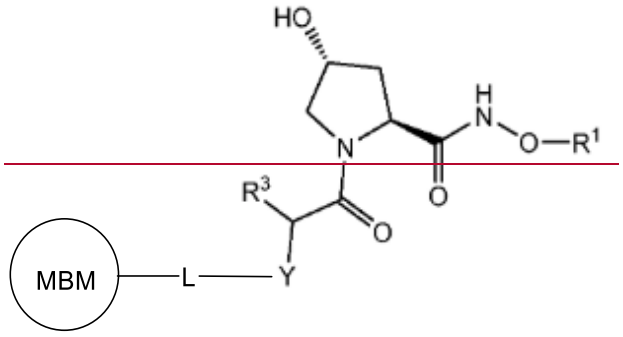
~~or a pharmaceutically acceptable salt thereof, wherein each of the variables R^1, R^2, R^3, X, and Y is as defined~~

~~and described in WO 2019/084026, the entirety of each of which is herein incorporated by reference; and~~

~~(*ii*)~~

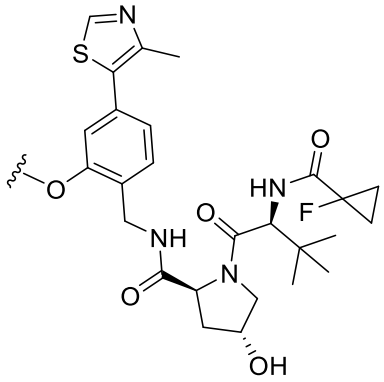


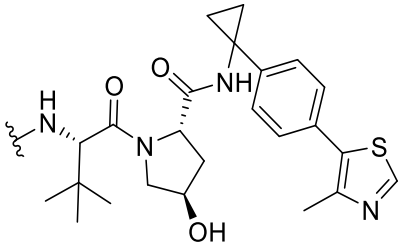
~~I-bb-1~~



~~I-bb-2~~

~~or a pharmaceutically acceptable salt thereof, wherein each of the variables R^1, R^3, and Y is as defined and described in WO 2019/084030, the entirety of each of which is herein incorporated by reference.~~

~~11~~8. The compound of claim 2~~3 or claim 10~~, wherein VHL E3 ubiquitin ligase binding moiety is selected from 

, 

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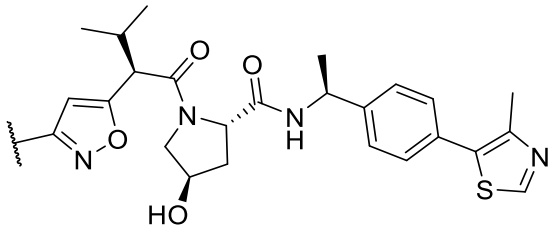
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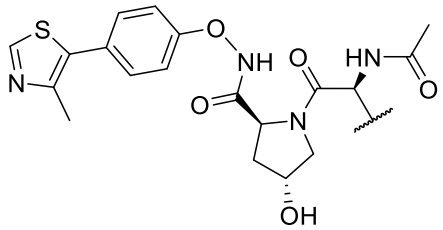
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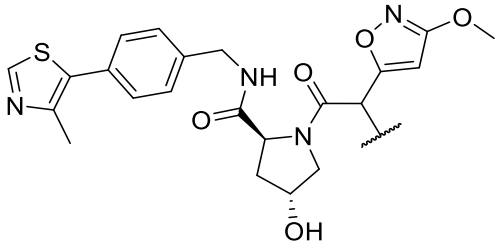
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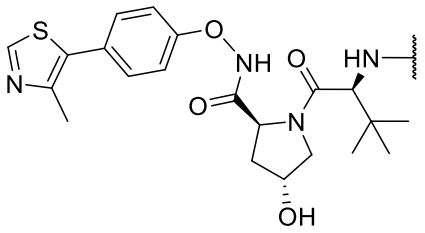
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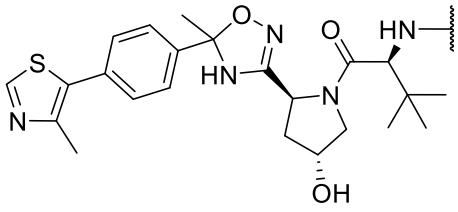
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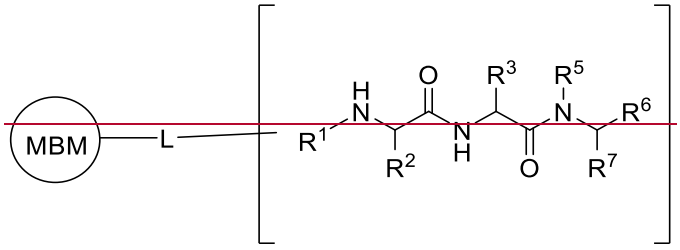
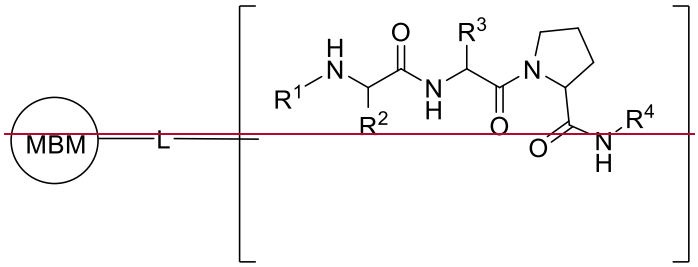
~~12. The compound of claim 3, wherein LBM is a IAP E3 ubiquitin ligase binding moiety and said compound is selected from any of the following formulae:~~

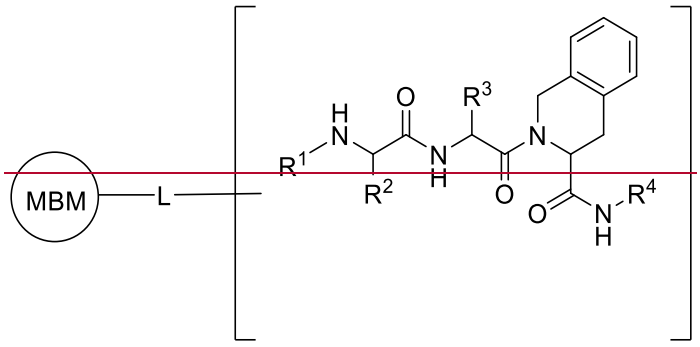
~~*(i)*~~



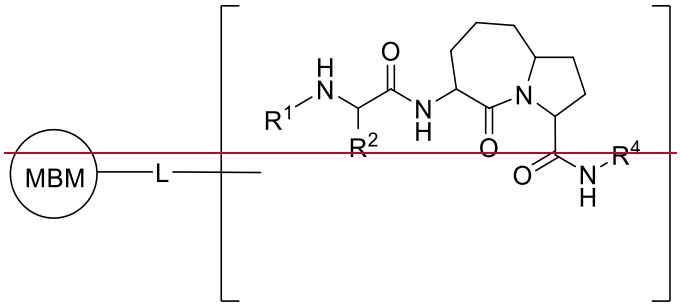
~~I-u-1~~



~~I-u-2~~



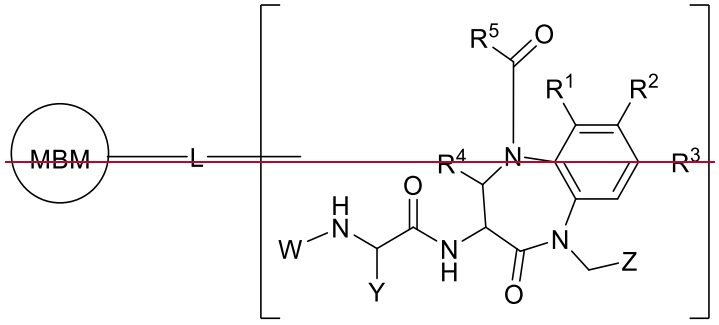
~~I-u-3~~



~~I-u-4~~

~~or a pharmaceutically acceptable salt thereof, wherein each of the variables R^1, R^2, R^3, R^4, R^5, R^6, and R^7, is as defined and described in WO 2017/011590 and US 2007/037004; and~~

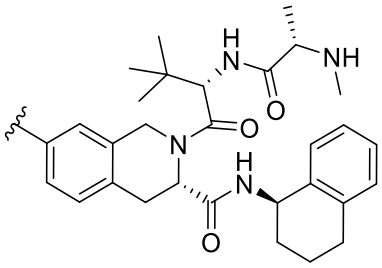
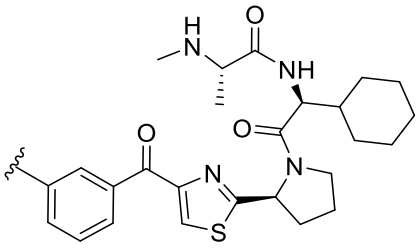
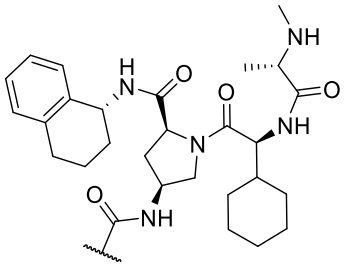
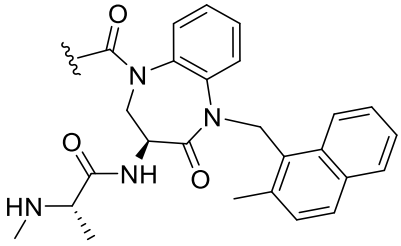
~~(*ii*)~~

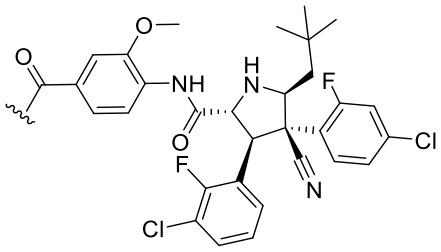
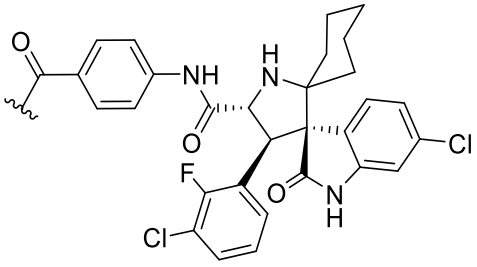
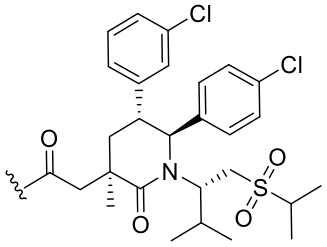
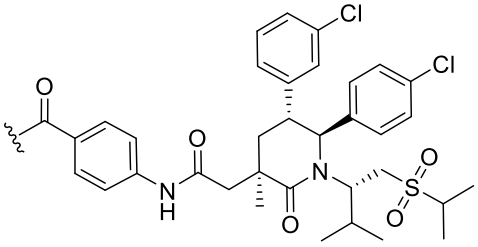
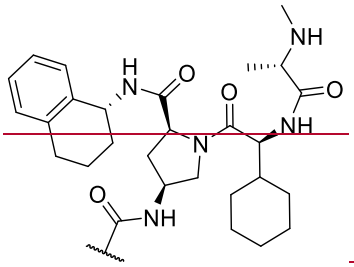
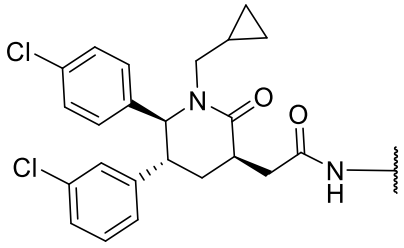
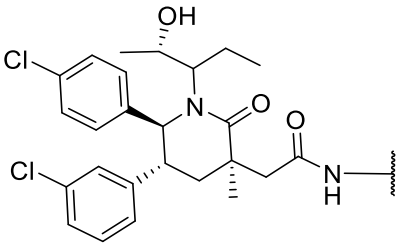
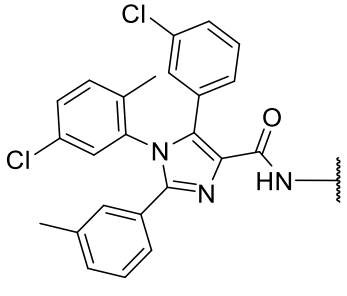


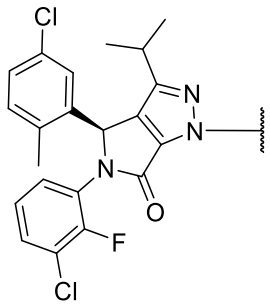
~~I-v~~

~~or a pharmaceutically acceptable salt thereof, wherein each of the variables W, Y, Z, R^1, R^2, R^3, R^4, and R^5 is as described and defined in WO 2014/044622, US 2015/0225449, WO 2015/071393, and US 2016/0272596.~~

~~139~~. The compound of claim 23 ~~or claim 12~~, wherein the IAP E3 ubiquitin ligase binding moiety is

selected from  ,  ,  , and  .

~~14~~10. The compound of claim ~~3~~2, wherein the MDM2 E3 ubiquitin ligase binding moiety is selected from  ,  ,  ,  ,  ,  ,  ,  , and



11~~15~~. The compound of any one of claims 1-10~~14~~, wherein said compound is selected from any one of the compounds depicted in **Table 1**, or a pharmaceutically acceptable salt thereof.

12~~16~~. A pharmaceutical composition comprising a compound of any one of claims 1-11~~claim 15~~, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

13~~17~~. The pharmaceutical composition of claim 12~~16~~, further comprising an additional therapeutic agent.

14~~18~~. A compound of any one of claims 1-11 or a pharmaceutical composition thereof, for use in~~method of~~ degrading MDM2 protein in a patient or biological sample~~ comprising administering to said patient, or contacting said biological sample with a compound of any one of claims 1-15, or a pharmaceutical composition thereof~~.

15. A compound of any one of claims 1-11 or a pharmaceutical composition thereof, for use in therapy.

~~19~~16. ~~A~~ Use of a compound of any one of claims 1-11 or a pharmaceutical composition thereof, in the manufacture of a medicament for~~method of~~ treating an MDM2-mediated disorder, disease, or condition in a patient~~ comprising administering to said patient a compound of any one of claims 1-15, or a pharmaceutical composition thereof~~.

~~20. The method of claim 19, further comprising administration of an additional therapeutic agent.~~

~~21~~17. ~~A method of treating a patient, the method comprising administering to the patient a therapeutically effective amount~~Use of a compound of any one of claims 1-11~~15,~~ or a pharmaceutical composition thereof, in the manufacture of a medicament for treating a patient in need~~pharmaceutically acceptable salt~~ thereof, wherein the patient has cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative

disorder, sepsis, or a viral infection.

1822. The use of~~method~~ claim 1721, wherein the patient has cancer.

1923. The use~~method~~ of claim 1822, wherein the cancer is selected from adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic

urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway ghoma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

2024. The use~~method~~ of claim 1823, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT- midline carcinoma, multiple myeloma, small cell lung cancer (SCLC), neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.

~~25. The method of any one of claims 21-24, further comprising administration of an additional therapeutic agent.~~

~~26. Use of a compound of any one of claims 1-15 in the manufacture of a medicament for treating an MDM2-mediated disorder, disease, or condition in a patient.~~

~~27. The use of claim 26, further comprising an additional therapeutic agent.~~

~~28. The use of claim 26, wherein the MDM2-mediated disorder, disease, or condition is cancer.~~

29. The use of claim 28, wherein the cancer is selected from adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogeous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer,

osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma periotonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway ghoma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor..

30. The use of claim 29, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT- midline carcinoma, multiple myeloma, small cell lung cancer (SCLC), neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.