

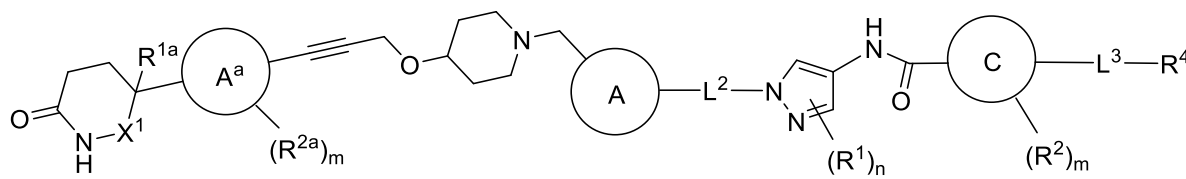
remain as obstacles to the development of effective anti-cancer agents. As such, small molecule therapeutic agents that leverage E3 ligase mediated protein degradation to target cancer-associated proteins such as interleukin-1 receptor-associated kinases (“IRAK”) hold promise as therapeutic agents. Accordingly, there remains a need to find compounds that are IRAK degraders useful as therapeutic agents.

SUMMARY OF THE INVENTION

[0009] The present application relates novel bifunctional compounds, which function to recruit IRAK kinases 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 IRAK kinases, which are 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 IRAK kinases, 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 IRAK kinases. 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., multiple myeloma.

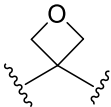
[0010] The present application further relates to targeted degradation of IRAK kinases through the use of bifunctional molecules, including bifunctional molecules that link a cereblon-binding moiety to a ligand that binds IRAK kinases.

[0010a] In an aspect of the present disclosure, there is provided a compound of formula **II-f-5**:



II-f-5

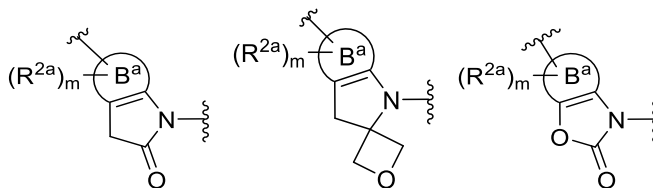
or a pharmaceutically acceptable salt thereof, wherein:

X¹ is a bivalent moiety selected from a covalent bond, -CH₂-, -C(O)-, -C(S)-, and ;

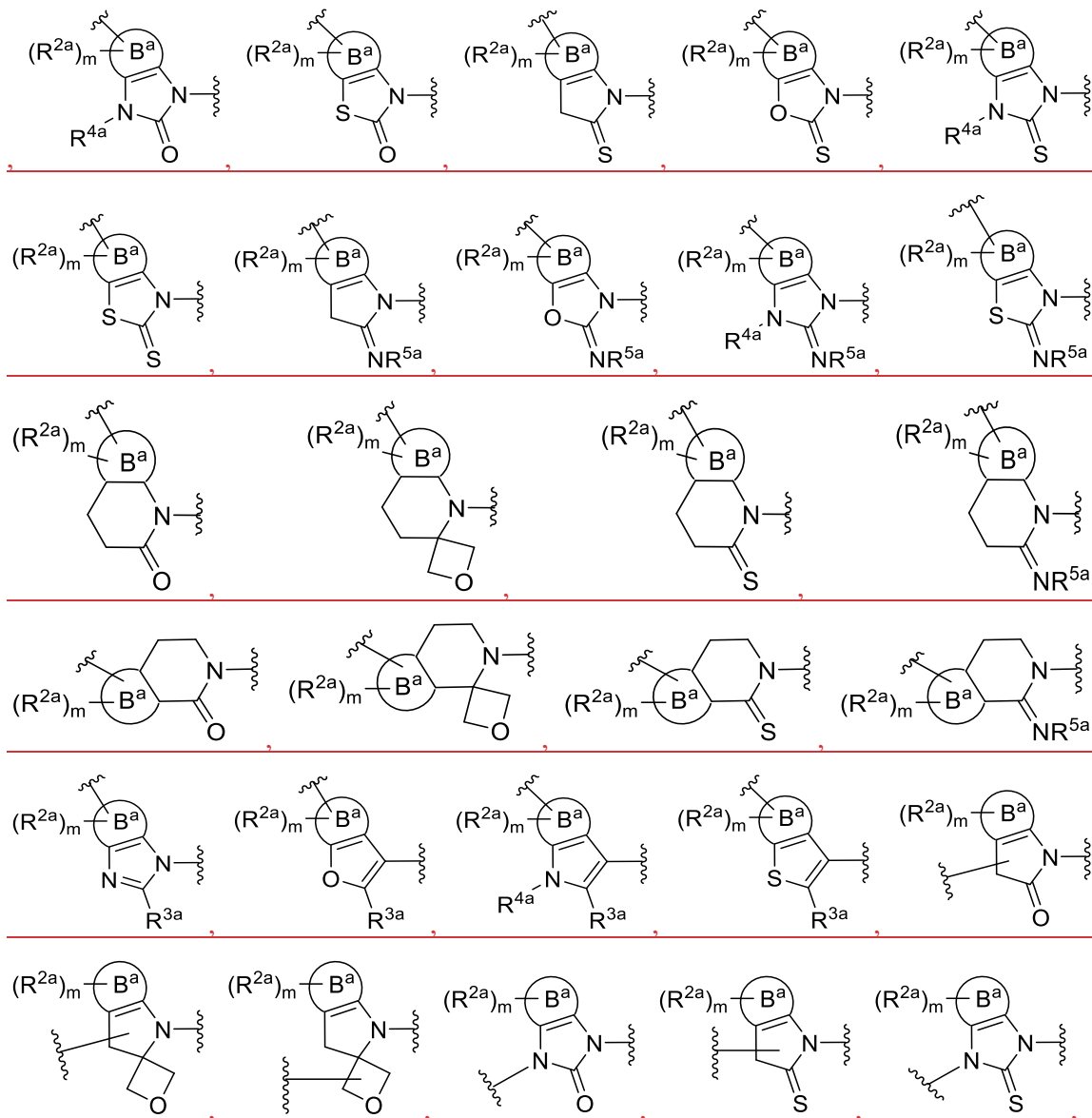
R^{1a} is hydrogen, halogen, -CN, -OR, -SR, -S(O)R, -S(O)₂R, -N(R)₂, -Si(R)₃, or an optionally substituted

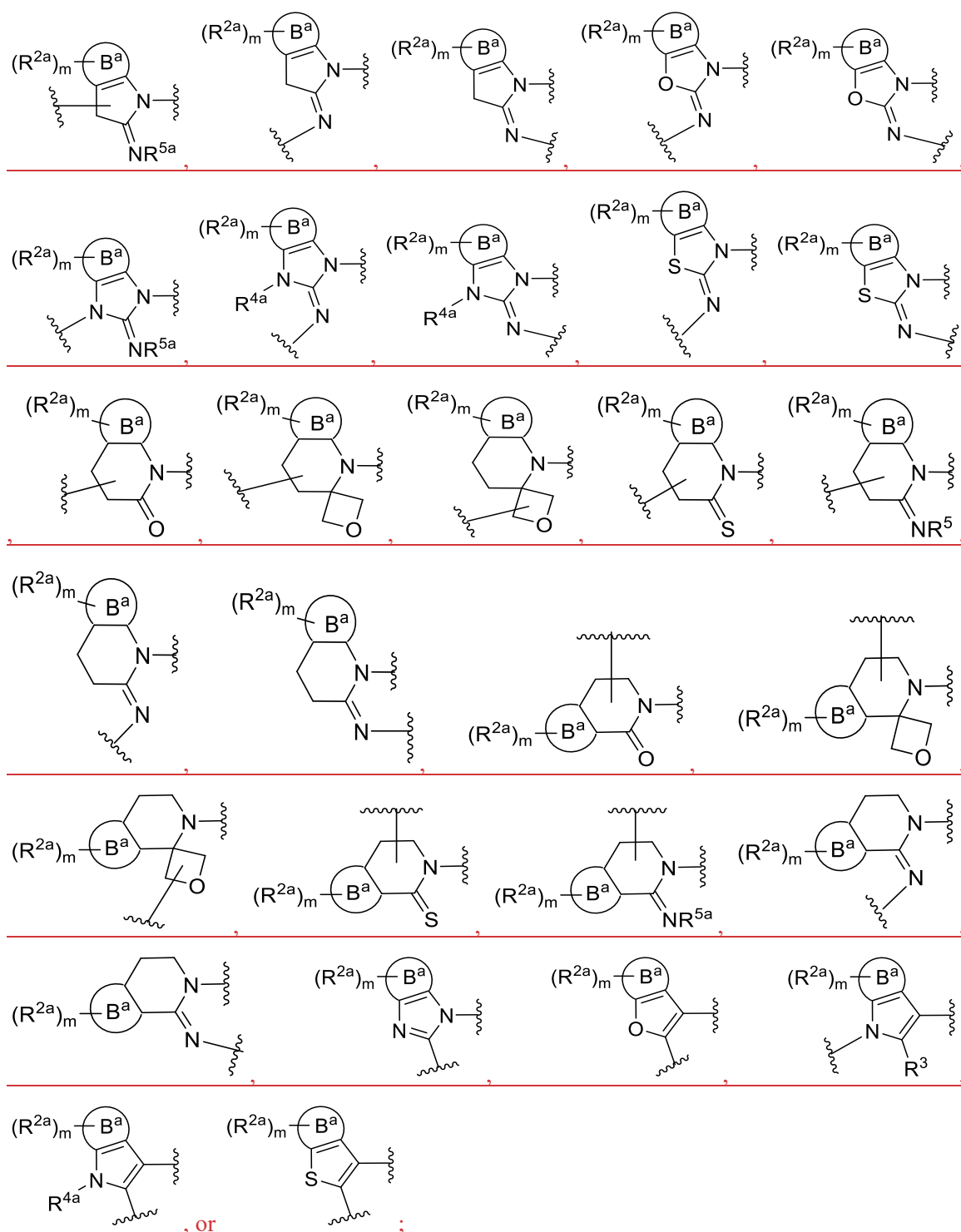
C₁₋₄ aliphatic;

each R^{2a} is independently hydrogen, R^{6a} , halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, or -N(R)S(O)₂R;



Ring A^a is a bicyclic or tricyclic ring selected from





Ring B^a is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5 to 7-membered partially saturated carbocyclyl, 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur;

R^{3a} is selected from hydrogen, halogen, -OR, -N(R)₂, or -SR;

each R^{4a} is independently hydrogen, R^{6a}, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, or -N(R)S(O)₂R;

R^{5a} is hydrogen, C₁₋₄ aliphatic, or -CN;

each R^{6a} is independently an optionally substituted group selected from C₁₋₆ 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;

Ring A is a 4-10 membered saturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring C is phenyl, or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

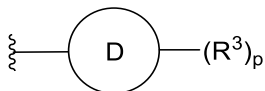
each of L² and L³ is independently a covalent bond or a C₁₋₃ bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -C(R)₂-, -CH(R)-, -C(F)₂-, -N(R)-, -S-, -S(O)₂- or -CR=CR-;

each R¹ is independently hydrogen, R⁵, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -S(O)(NR)₂, -P(O)(OR)₂, -P(O)(NR₂)₂, -CFR₂, -CF₂(R), -CF₃, -CR₂(OR), -CR₂(NR₂), -C(O)R, -C(O)OR, or -C(O)NR₂;

each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ 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 atom are optionally taken together with their intervening atom to form an optionally substituted 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spirocyclic, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R² is independently hydrogen, R⁵, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -S(O)(NR)₂, -P(O)(OR)₂, -P(O)(NR₂)₂, -CF₂(R), -CF₃, -CR₂(OR), -CR₂(NR₂), -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, or -N(R)S(O)₂R;



R^4 is selected from _____, hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic or a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring D is phenyl, a 4-10 membered saturated or partially unsaturated monocyclic or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^3 is independently hydrogen, R^5 , halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -S(O)(NR)R, -P(O)(OR)₂, -P(O)(NR₂)₂, -CF₂(R), -CF₃, -CR₂(OR), -CR₂(NR₂), -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, or -N(R)S(O)₂R;

each R^5 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;

n is 0, 1, or 2;

each m is independently 0, 1, 2, 3 or 4; and

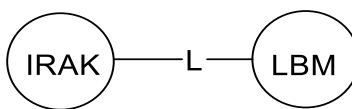
p is 0, 1, 2, 3 or 4.

[0010b] 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.

[0010c] 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 autoimmune disease, an inflammatory disorder, or an immunodeficiency disorder in a patient.

[0010d] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutical composition thereof, for use in therapy.

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



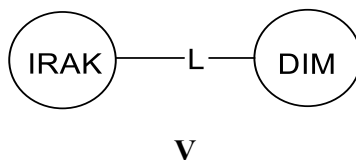
I

3d

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

[0012] It has also now been found that compounds of this ~~invention~~present disclosure, and pharmaceutically acceptable compositions thereof, are effective as degraders of IRAK kinases. Such compounds

have the general formula **V**:



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

[0013] Compounds of the present ~~invention~~present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of signaling pathways implicating IRAK kinases. Such diseases, disorders, or conditions include those described herein.

[0014] Compounds provided by this ~~invention~~present disclosure are also useful for the study of IRAK enzymes in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new IRAK inhibitors or IRAK degraders or other regulators of kinases, signaling pathways, and cytokine levels in vitro or in vivo.

BRIEF DESCRIPTION OF THE FIGURES

[0015] FIG. 1 is an image showing a western blot of degrader **I-30** in OCI-LY10 at 24 h.

[0016] FIG. 2 is an image of a dose response curve for IKAK4 (% control)(y-axis) versus degrader **I-30** concentration (μM) (x-axis) for OCI-LY10 and TMD8 cell lines and in vitro degradation results (DC_{90} , μM).

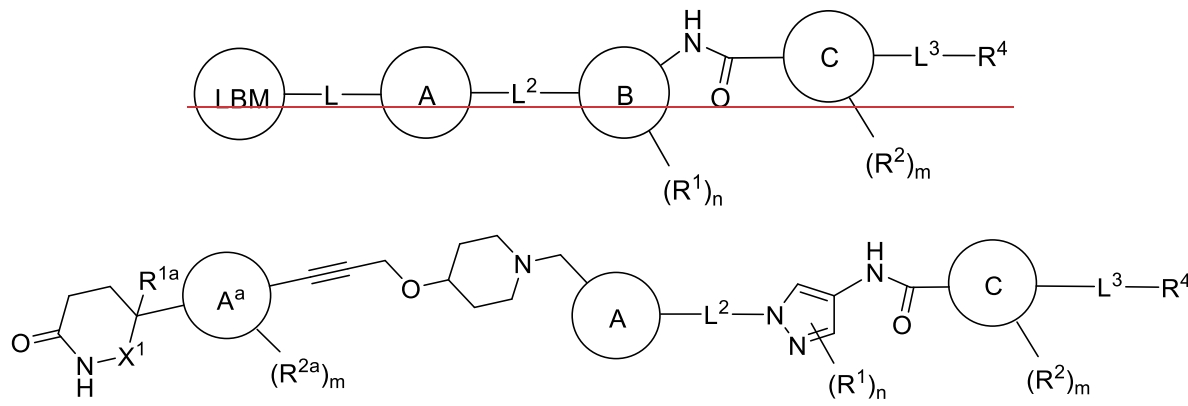
[0017] FIG. 3 is an image of a deep TMT proteomics scatterplot in OCI-LY10 at 8h showing Log2 FC 10 nM degrader **I-30** in DMSO (y-axis) and Log2 FC 10 nM degrader in DMSO Rep1 (x-axis).

[0018] FIG. 4 includes graphical images showing the decrease of IRAK4 at 24h with count (y-axis) versus IRAK (MFI) (x-axis) using several concentrations of degrader **I-30** (A); the time dependent induction of apoptosis with 50 nM degrader **I-30** showing IRAK4 (% control) (left y-axis) and cleaved CASP3 (% control) (right y-axis) versus time (h) (x-axis) (B); the inhibition of cell proliferation at 72 h showing count (y-axis) versus Ki67 (MFI) (x-axis) at several concentrations of degrader **I-30** (C); and the induction of apoptosis is mechanism specific showing cleaved CASP3 (% control) (y-axis) for degrader **I-30** and inactive (x-axis) at several concentrations respectively (D).

CLAIMS

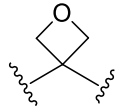
We claim:

1. A compound of ~~Formula II-f-5'~~:



II-f-5'

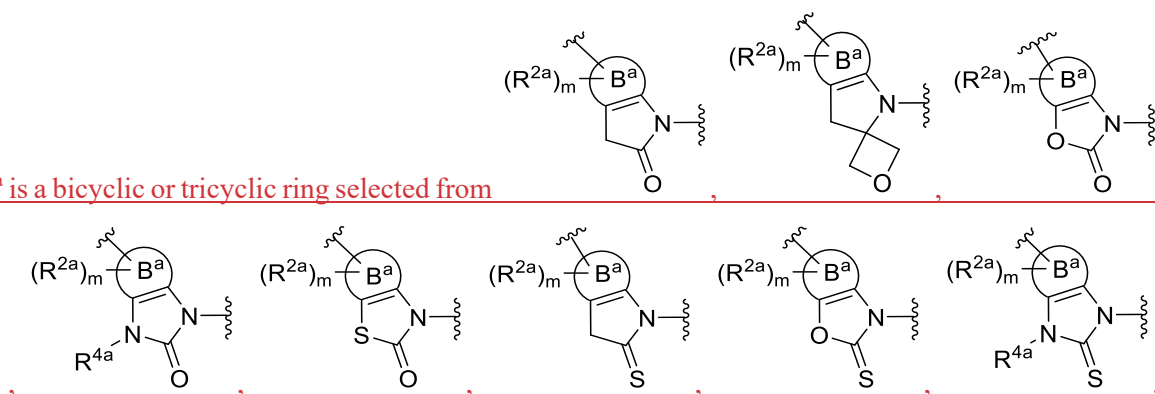
or a pharmaceutically acceptable salt thereof, wherein:

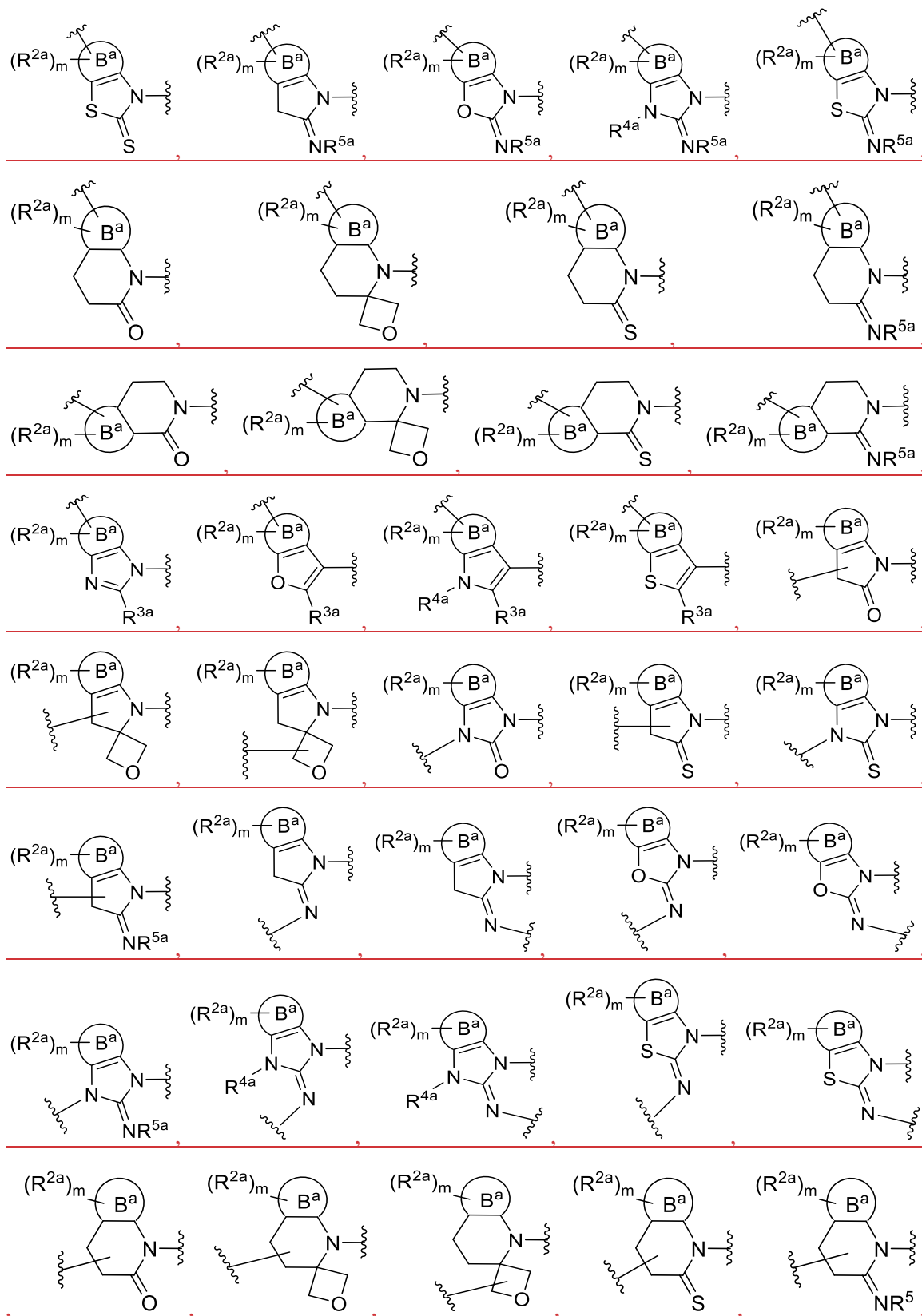
X^1 is a bivalent moiety selected from a covalent bond, $-CH_2-$, $-C(O)-$, $-C(S)-$, and ;

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

each R^{2a} is independently hydrogen, R^{6a} , 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 $-N(R)S(O)_2R$;

Ring A^a is a bicyclic or tricyclic ring selected from





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

Ring C is phenyl, ~~a 4-7 membered saturated or partially unsaturated carbocyclic ring or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur,~~ or a 5-6-10 membered monocyclic or bicyclic heteroaryl ring having 1-4-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

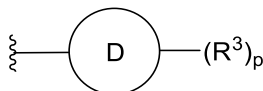
each of L² and L³ is independently a covalent bond or a C₁₋₃ bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -C(R)₂-, -CH(R)-, -C(F)₂-, -N(R)-, -S-, -S(O)₂- or -CR=CR-;

each R¹ is independently hydrogen, ~~deuterium,~~ —R⁵, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -S(O)(NR)R, -P(O)(OR)₂, -P(O)(NR₂)₂, -CFR₂, -CF₂(R), -CF₃, -CR₂(OR), -CR₂(NR₂), -C(O)R, -C(O)OR, or -C(O)NR₂, ~~or two R¹ on the same carbon together form =O or =S;~~

each R is independently hydrogen, ~~deuterium,~~ or an optionally substituted group selected from C₁₋₆ 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 atom are optionally taken together with their intervening atom to form an optionally substituted 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, ~~spirocyclic~~ spiro, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R² is independently hydrogen, ~~deuterium,~~ —R⁵, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -S(O)(NR)R, -P(O)(OR)₂, -P(O)(NR₂)₂, -CF₂(R), -CF₃, -CR₂(OR), -CR₂(NR₂), -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, or —N(R)S(O)₂R, ~~or two R² on the same carbon together form =O or =S;~~



R⁴ is selected from ~~hydrogen or~~ hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic or a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring D is phenyl, a 4-10 membered saturated or partially unsaturated ~~monocyclicmono-~~ or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^3 is independently hydrogen, ~~deuterium,~~ $-R^5$, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)(NR)R$, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, or ~~$-N(R)S(O)_2R$, or two R^3 on the same carbon together form $=O$ or $=S$;~~

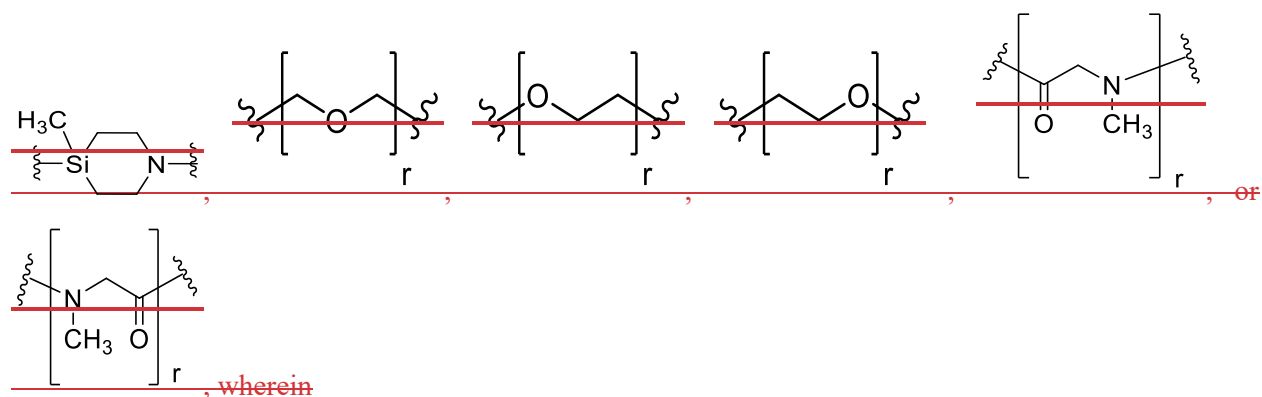
each R^5 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having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

~~each~~ n is 0, 1, or 2;

each m is independently 0, 1, 2, 3 or 4; and

~~each~~ p is 0, 1, 2, 3 or 4;

~~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 $-C(D)(H)-$, $-C(D)_2-$, $-Cy-$, $-O-$, $-N(R)-$, $-Si(R)_2-$, $-Si(OH)(R)-$, $-Si(OH)_2-$, $-P(O)(OR)-$, $-P(O)(R)-$, $-P(O)(NR_2)-$, $-S-$, $-OC(O)-$, $-C(O)O-$, $-C(O)-$, $-S(O)-$, $-S(O)_2-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, $-N(R)C(O)-$, $-C(O)N(R)-$, $-OC(O)N(R)-$, $-N(R)C(O)O-$,~~



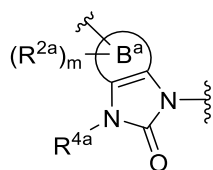
~~each $-Cy-$ is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic-arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro-carbocyclylenyl, an 8-10 membered bicyclic saturated 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, or sulfur, and wherein r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

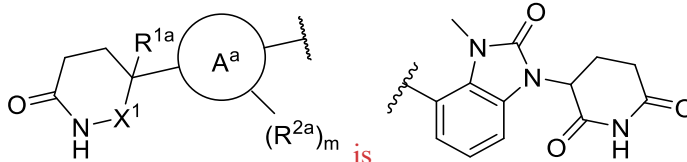
LBM is a ligase binding moiety,

wherein the compound of formula **H'** is not compound **I-99** or **I-100** in **Table 1A**.

2. The compound of claim 1, wherein X^1 is $-C(O)-$, R^{1a} is hydrogen, m of $(R^{2a})_m$ is 0, Ring A^a is



, Ring B^a is a fused 6-membered aryl, and R^{4a} is a C_{1-6} aliphatic.

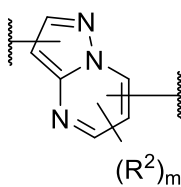


3. The compound of claim 1, wherein is

4. The compound of claim 1, wherein Ring A is a 4-6 membered saturated monocyclic carbocyclic or heterocyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

5. The compound of claim 1, wherein Ring A is cyclohexyl.

6. The compound of claim 1, wherein Ring C is a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.



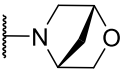
7. The compound of claim 1, wherein Ring C is

8. The compound of claim 1, wherein L^2 and L^3 are covalent bonds.

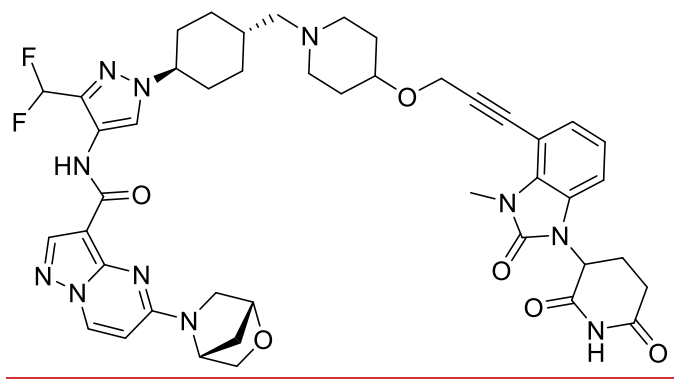
9. The compound of claim 1, wherein n is 1 and R¹ is hydrogen, R⁵, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -CFR₂, -CF₂(R), -CF₃, -CR₂(OR), -CR₂(NR₂), -C(O)R, -C(O)OR, or -C(O)NR₂.

10. The compound of claim 1, wherein n is 1 and R¹ is -CHF₂.

11. The compound of claim 1, wherein R⁴ is an optionally substituted group selected from C₁₋₆ aliphatic or a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

12. The compound of claim 1, wherein R⁴ is .

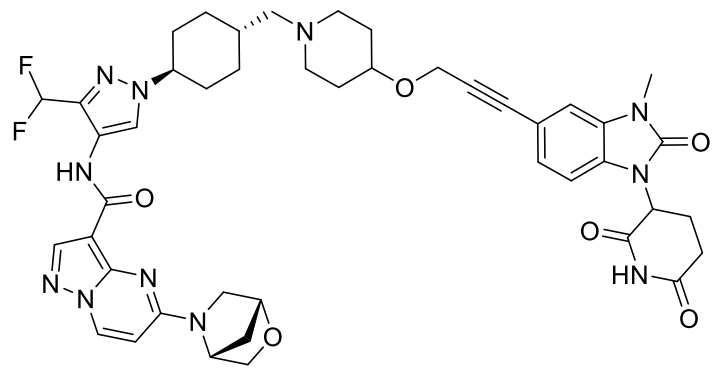
13. The compound of claim 1, wherein said compound is



I-417

or a pharmaceutically acceptable salt thereof.

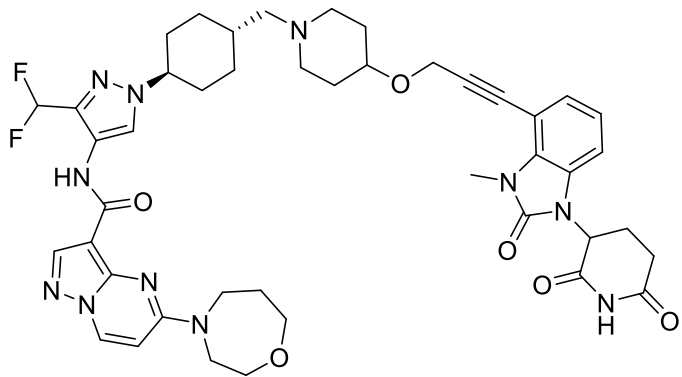
14. The compound of claim 1, wherein said compound is



I-483

or a pharmaceutically acceptable salt thereof.

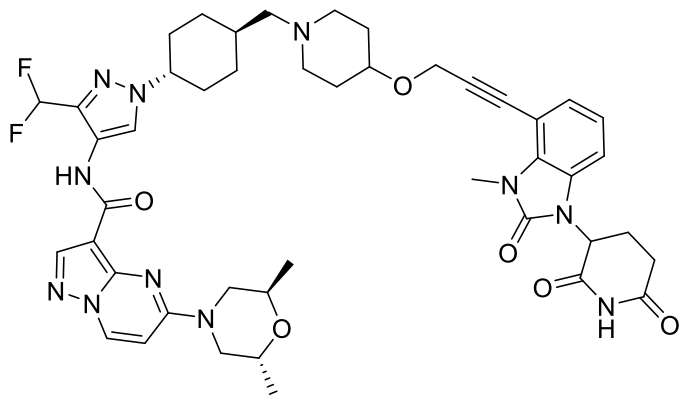
15. The compound of claim 1, wherein said compound is



I-522

or a pharmaceutically acceptable salt thereof.

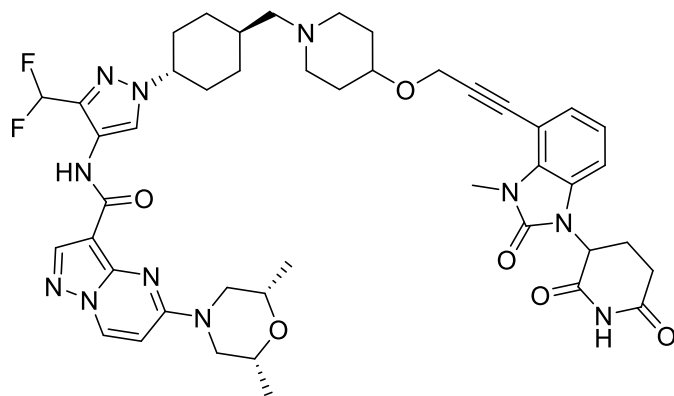
16. The compound of claim 1, wherein said compound is



I-527

or a pharmaceutically acceptable salt thereof.

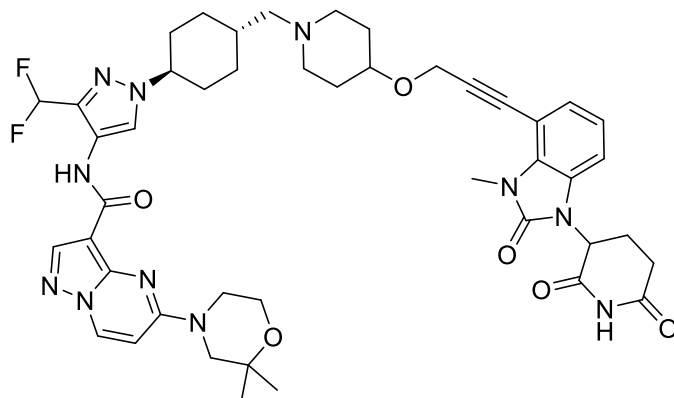
17. The compound of claim 1, wherein said compound is



I-531

or a pharmaceutically acceptable salt thereof.

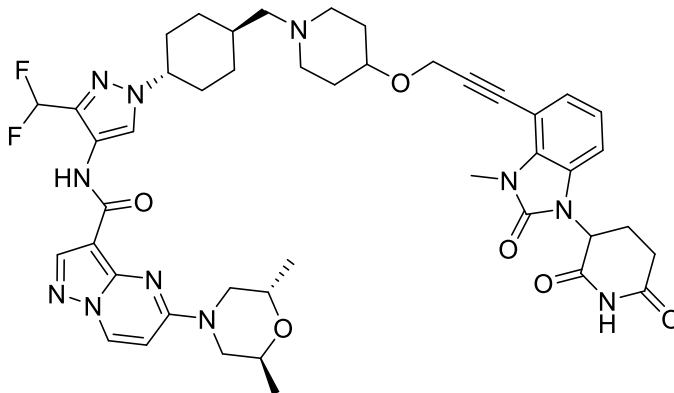
18. The compound of claim 1, wherein said compound is



I-533

or a pharmaceutically acceptable salt thereof.

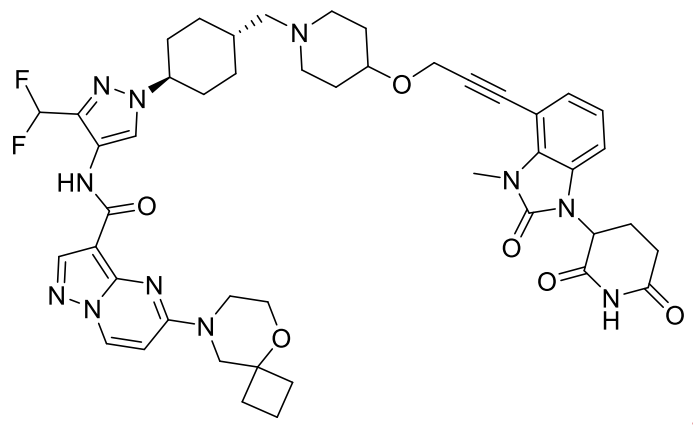
19. The compound of claim 1, wherein said compound is



I-536

or a pharmaceutically acceptable salt thereof.

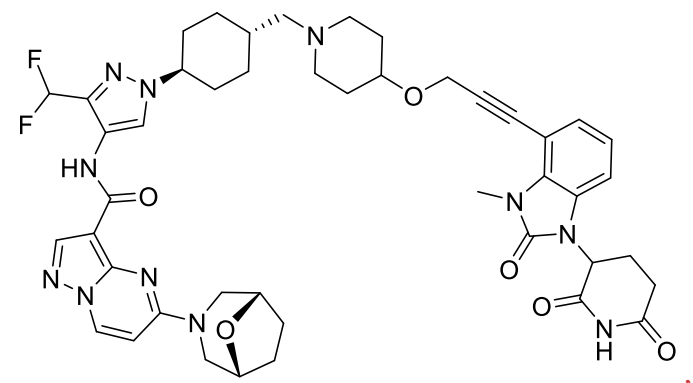
20. The compound of claim 1, wherein said compound is



I-541

or a pharmaceutically acceptable salt thereof.

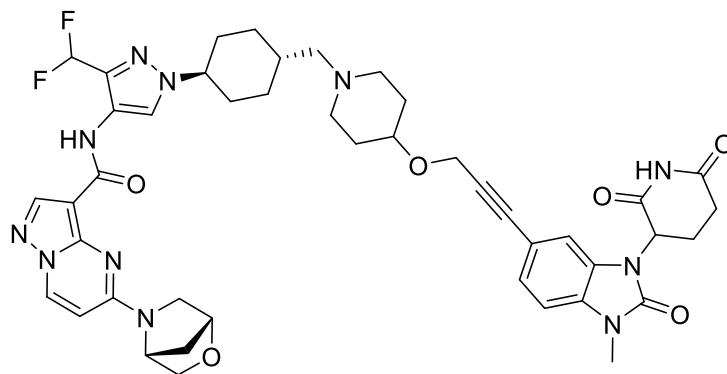
21. The compound of claim 1, wherein said compound is



I-547

or a pharmaceutically acceptable salt thereof.

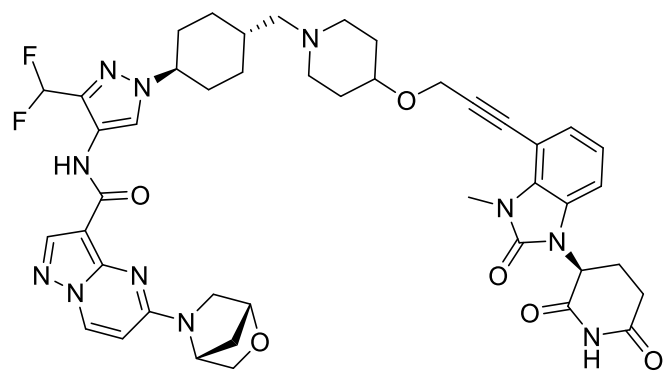
22. The compound of claim 1, wherein said compound is



I-548

or a pharmaceutically acceptable salt thereof.

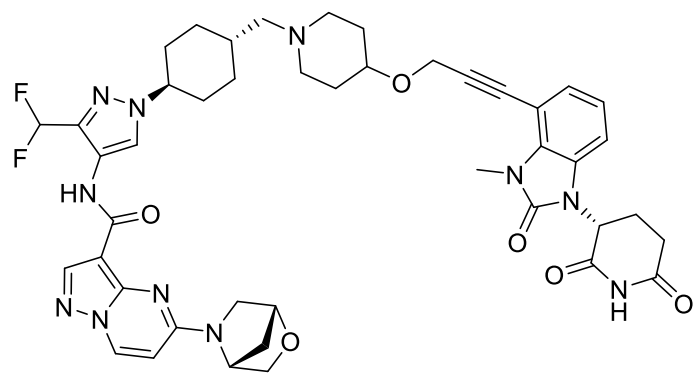
23. The compound of claim 1, wherein said compound is



I-560

or a pharmaceutically acceptable salt thereof.

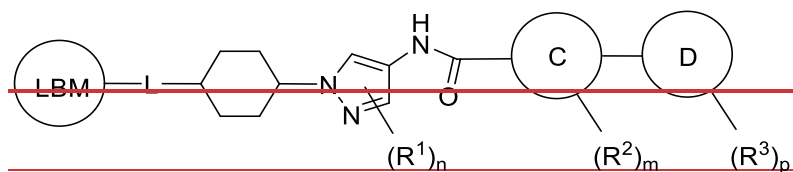
24. The compound of claim 1, wherein said compound is



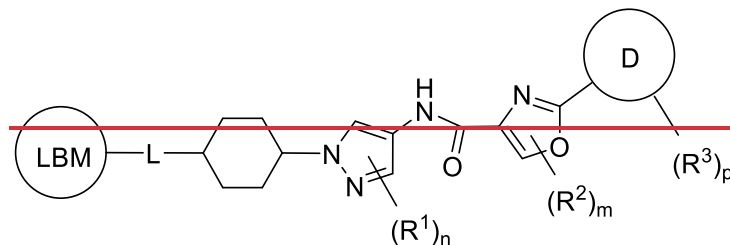
I-561

or a pharmaceutically acceptable salt thereof.

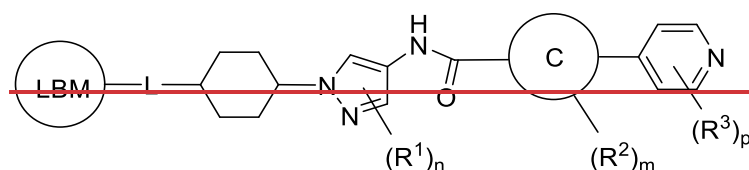
2. ~~The compound according to claim 1, wherein said compound is formula H-a, H-b, H-c, or H-d:~~



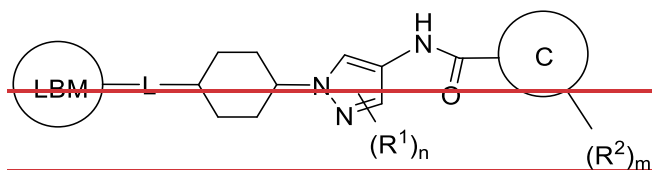
H-a



H-b



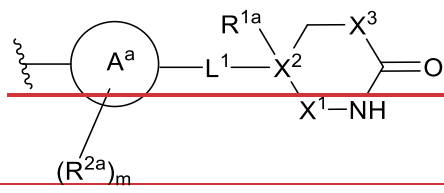
H-c



H-d

or a pharmaceutically acceptable salt thereof.

3. ~~The compound according to either of claim 1 or claim 2, wherein LBM is cereblon E3 ubiquitin~~



ligase binding moiety ~~(R^{2a})_m~~ ; wherein:

~~X¹ is a bivalent moiety selected from a covalent bond, CH₂, C(O), C(S), or~~

~~X² is a carbon atom or silicon atom;~~

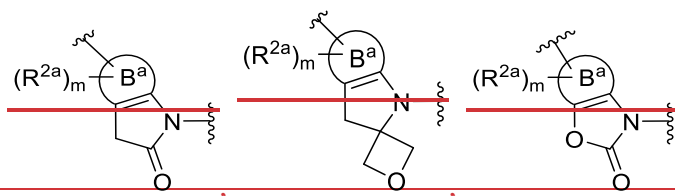


~~X³ is a bivalent moiety selected from CH₂ or Si(R₂);~~

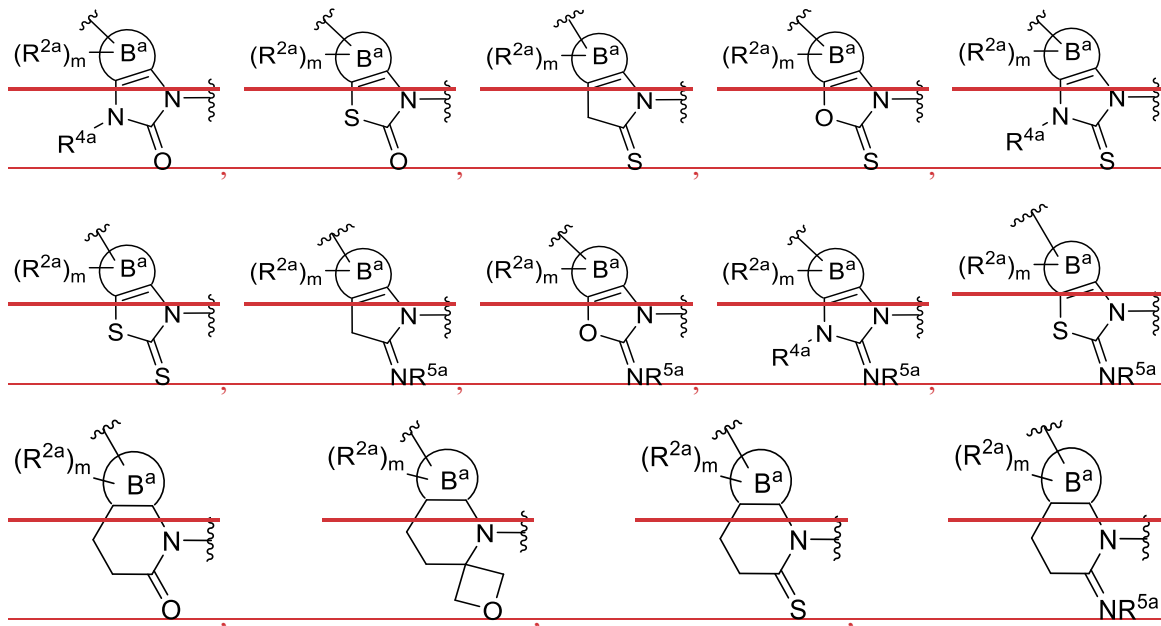
~~each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms 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;~~

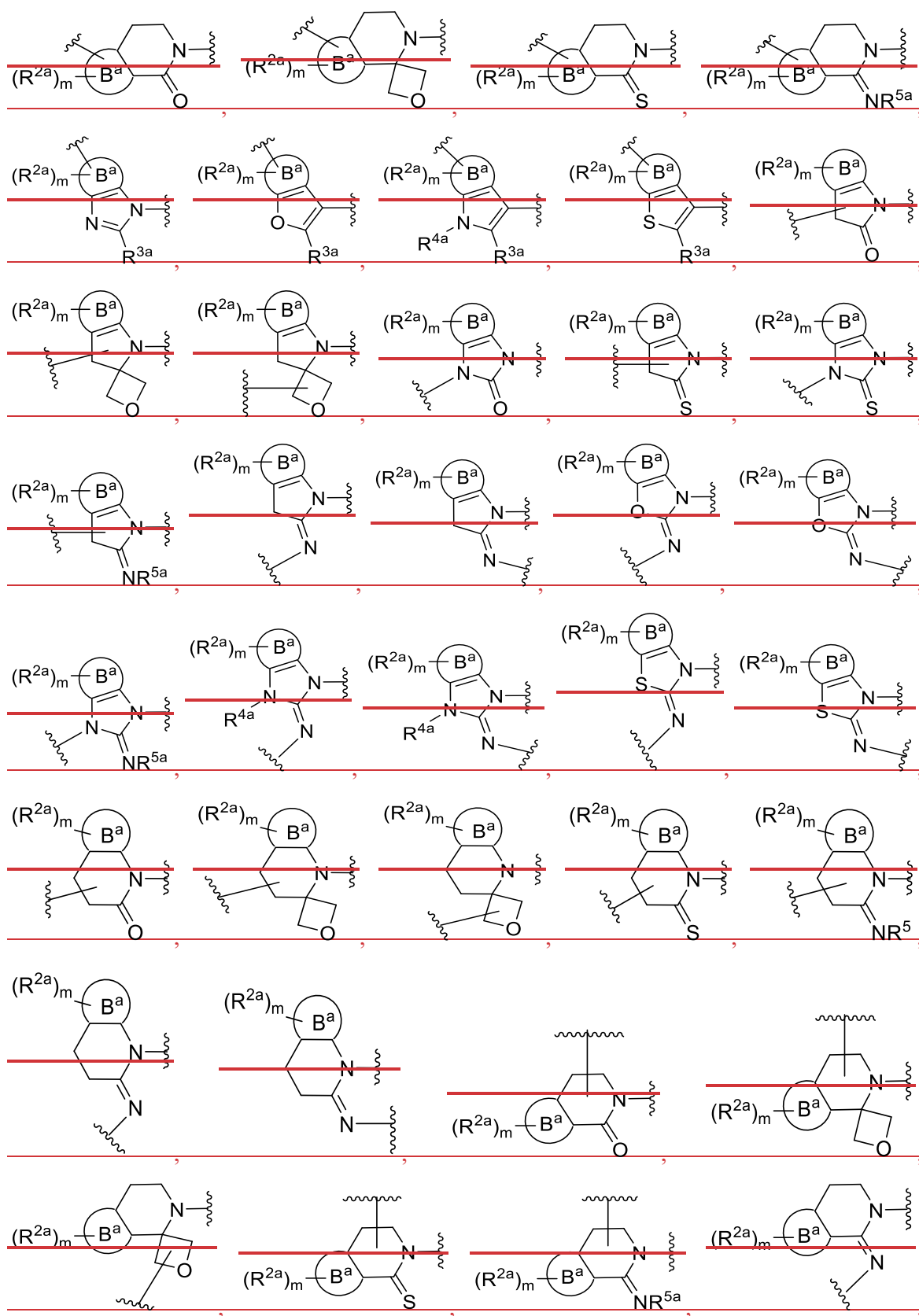
~~R^{1a} is hydrogen, deuterium, halogen, CN, OR, SR, S(O)R, S(O)₂R, N(R)₂, Si(R)₃, or an optionally substituted C₁₋₄ aliphatic;~~

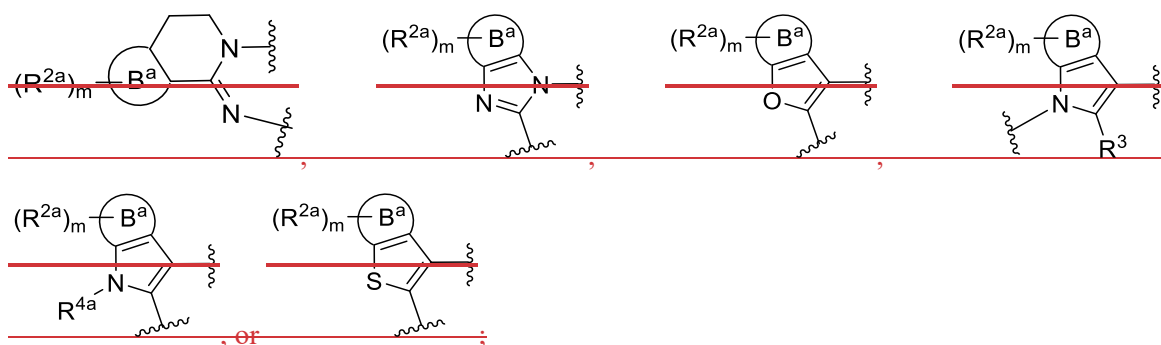
~~each R^{2a} is independently hydrogen, deuterium, R^{6a}, halogen, CN, NO₂, OR, SR, NR₂, Si(R)₃, S(O)₂R, S(O)₂NR₂, S(O)R, C(O)R, C(O)OR, C(O)NR₂, C(O)N(R)OR, OC(O)R, OC(O)NR₂, N(R)C(O)OR, N(R)C(O)R, N(R)C(O)NR₂, or N(R)S(O)₂R;~~



~~Ring A^a is a bi- or tricyclic ring selected from~~







Ring B^a is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5 to 7-membered partially saturated carbocyclyl, 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur;

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

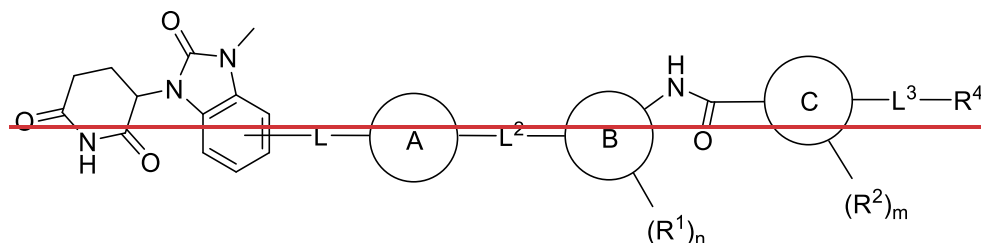
each R^{4a} is independently hydrogen, R^{6a} , halogen, CN, NO_2 , OR, SR, NR_2 , $S(O)_2R$, $S(O)_2NR_2$, $S(O)R$, $C(O)R$, $C(O)OR$, $C(O)NR_2$, $C(O)N(R)OR$, $OC(O)R$, $OC(O)NR_2$, $N(R)C(O)OR$, $N(R)C(O)R$, $N(R)C(O)NR_2$, or $N(R)S(O)_2R$;

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

each R^{6a} 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 independently a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 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 $CR=CR$; and m is 0, 1, 2, 3 or 4.

4. The compound according to any one of claim 1-3, wherein said compound is any one of formula H-h, H-i, H-j, H-k, or H-l:

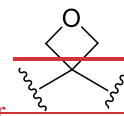


H-h



~~5. The compound according to either of claim 1 or claim 2, wherein LBM is E3 ubiquitin ligase~~





X^1 is a bivalent moiety selected from a covalent bond, CH_2 , C(O) , C(S) , or

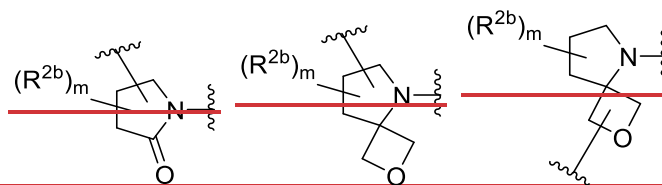
X^2 is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from CH_2 or $\text{Si(R}_2\text{)}$;

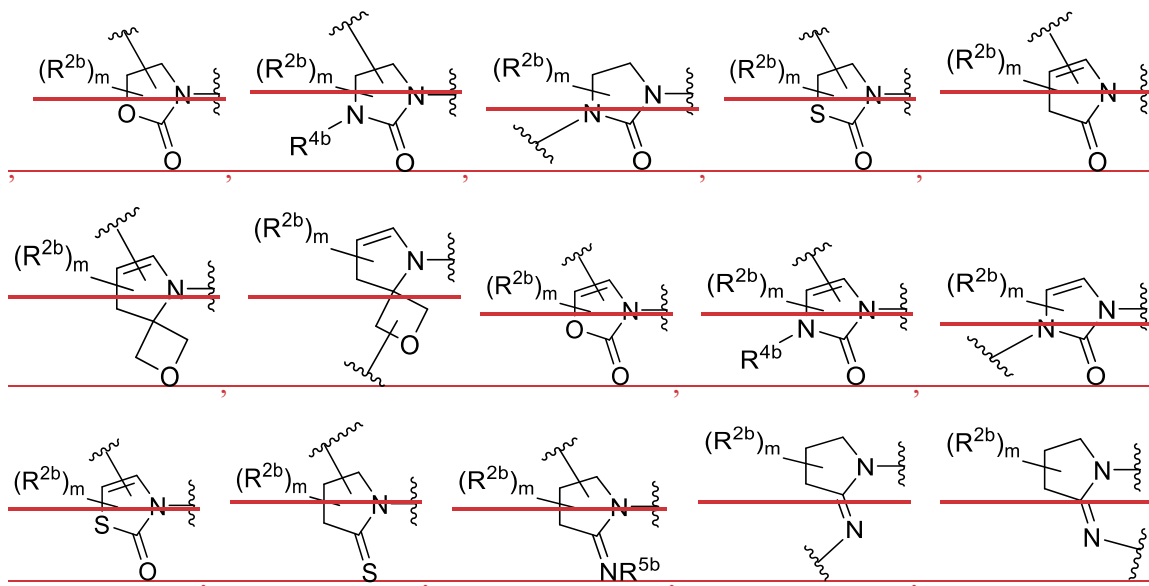
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

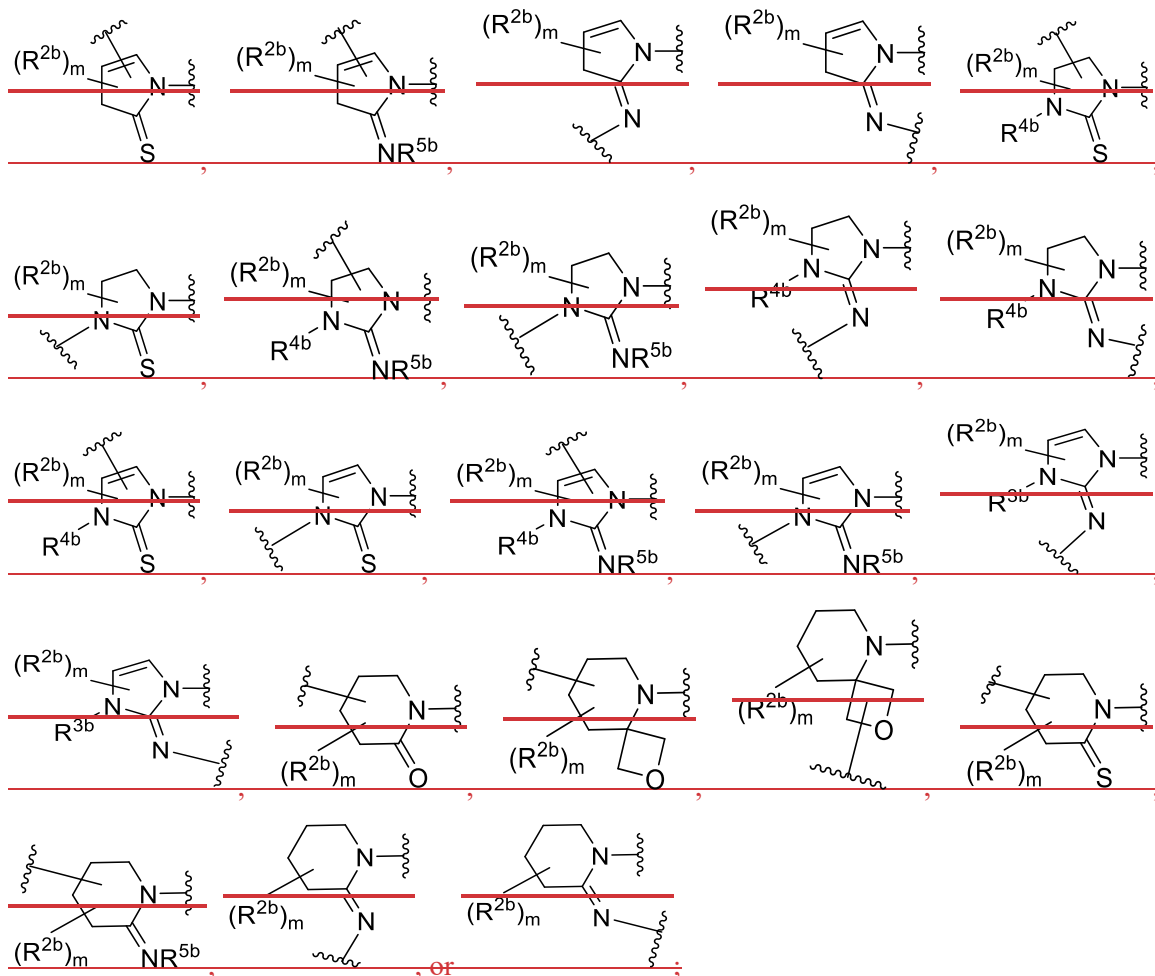
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

R^{1b} is hydrogen, deuterium, halogen, CN, OR, SR, S(O)R , $\text{S(O)}_2\text{R}$, N(R)_2 , Si(R)_3 , or an optionally substituted C_{1-4} aliphatic;



Ring A^b is a mono or bicyclic ring selected from





each R^{2b} is independently hydrogen, R^{6b} , 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 $N(R)S(O)_2R$;

Ring B^b is selected from a 6-membered aryl containing 0-2 nitrogen atoms or a 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur;

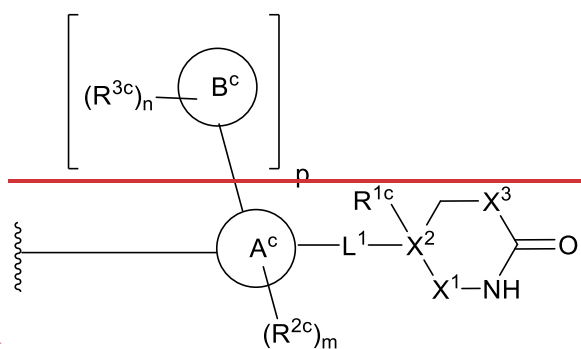
each of R^{3b} and R^{4b} is independently hydrogen, R^{6b} , halogen, CN, NO_2 , OR, SR, NR_2 , $S(O)_2R$, $S(O)_2NR_2$, $S(O)R$, $C(O)R$, $C(O)OR$, $C(O)NR_2$, $C(O)N(R)OR$, $OC(O)R$, $OC(O)NR_2$, $N(R)C(O)OR$, $N(R)C(O)R$, $N(R)C(O)NR_2$, or $N(R)S(O)_2R$;

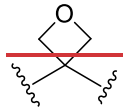
R^{5b} is hydrogen, C_{1-4} aliphatic, or CN;

each R^{6b} 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 independently a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 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 $CR=CR$;
 m is 0, 1, or 2;
 n is 0, 1, 2, 3, or 4; and
 p is 0 or 1.

6. ~~The compound according to either of claim 1 or claim 2, wherein LBM is E3 ubiquitin ligase~~



X^1 is a bivalent moiety selected from a covalent bond, CH_2 , $C(O)$, $C(S)$, or ;

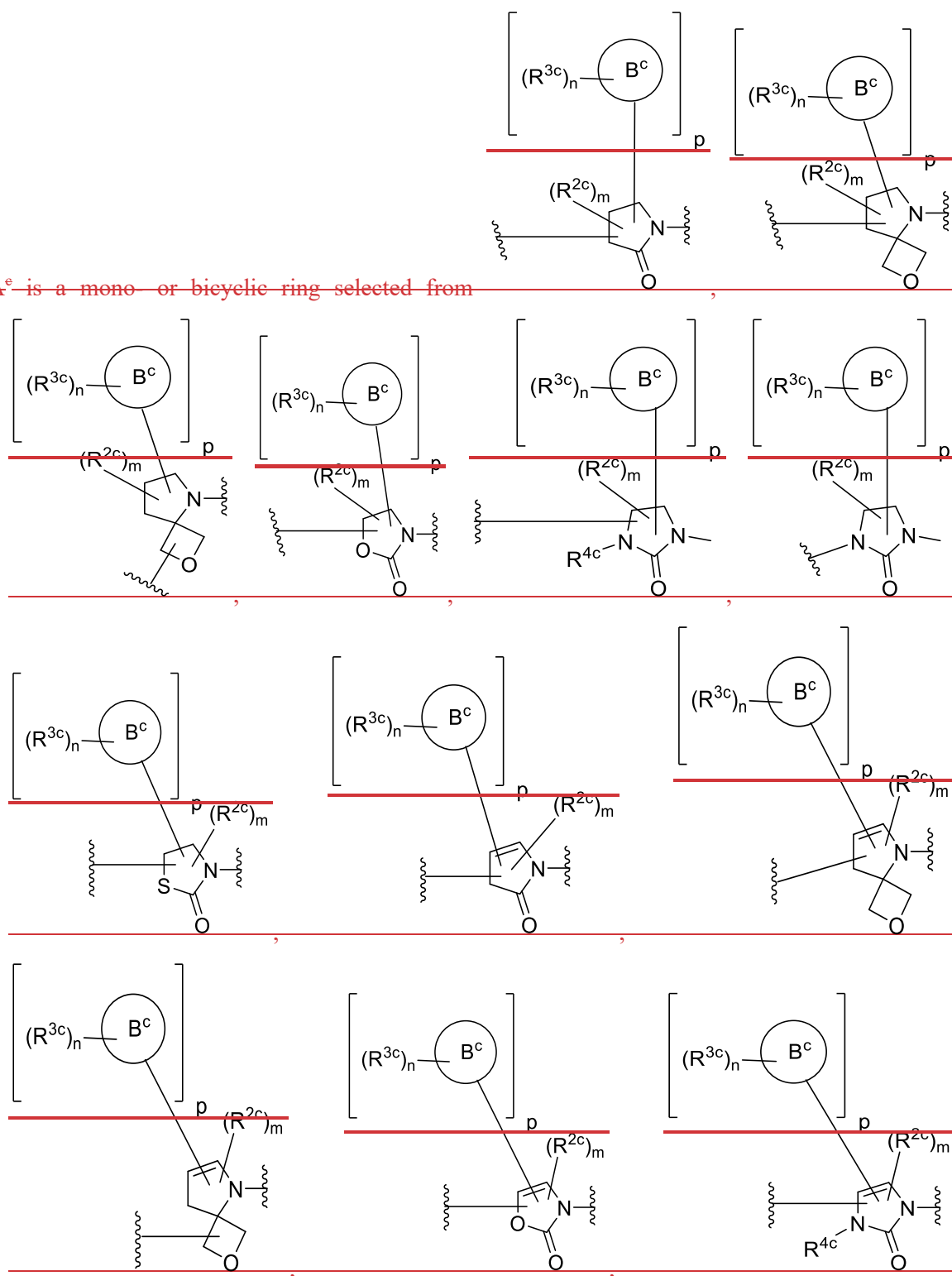
X^2 is a carbon atom or silicon atom;

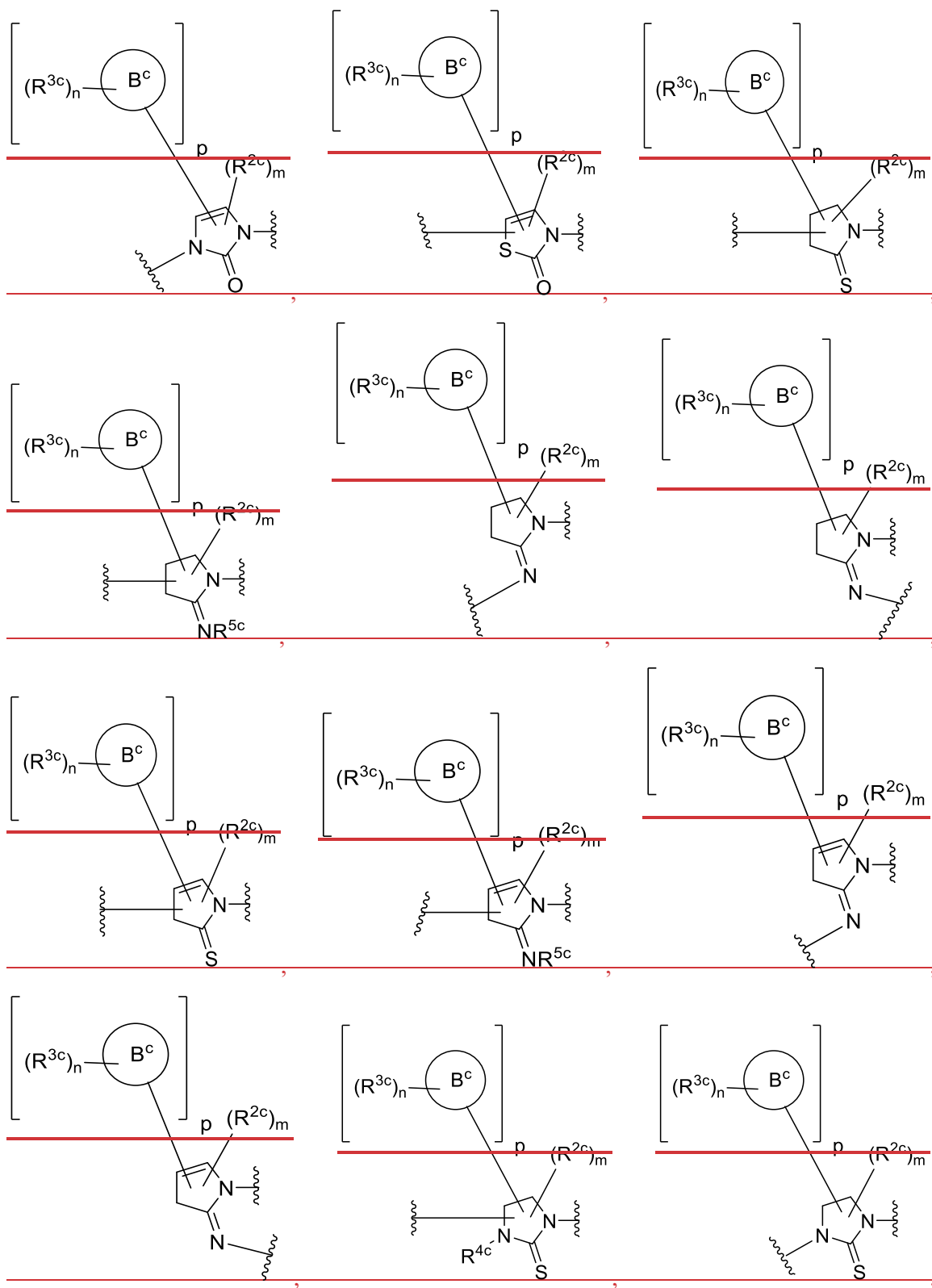
X^3 is a bivalent moiety selected from CH_2 or $Si(R)_2$;

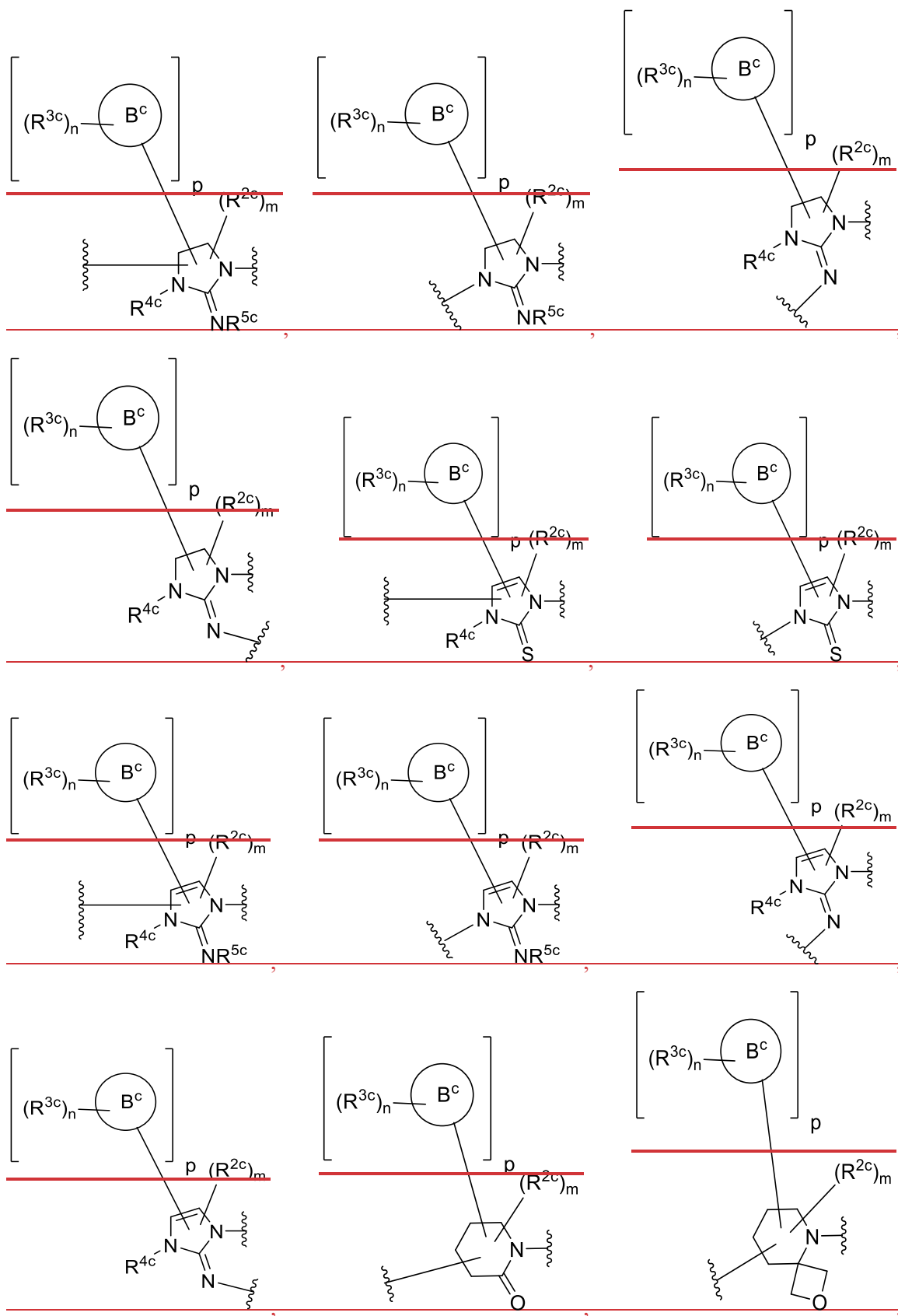
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

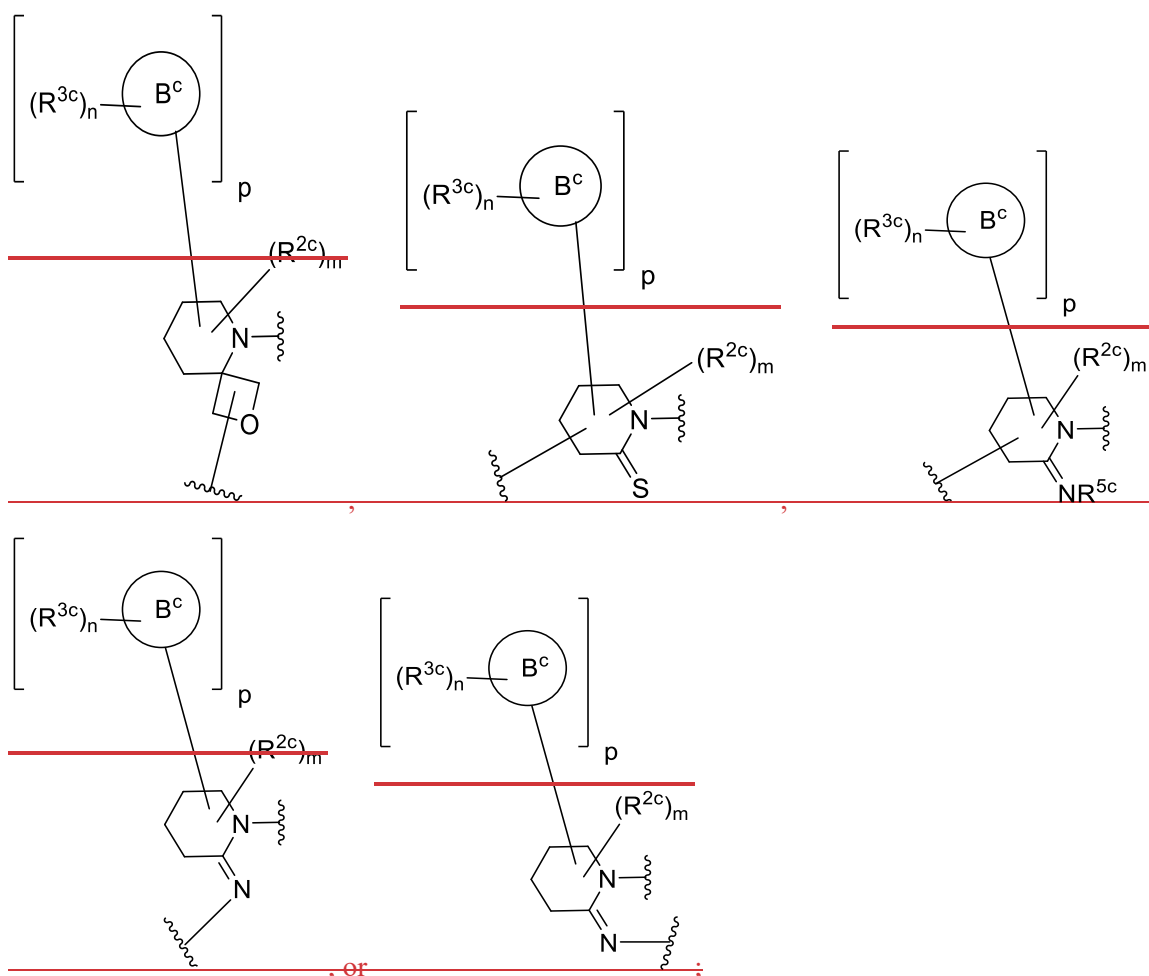
R^{1e} is hydrogen, deuterium, halogen, CN , OR , SR , $S(O)R$, $S(O)_2R$, $N(R)_2$, $Si(R)_3$, or an optionally substituted C_{1-4} aliphatic;

Ring A^e is a mono or bicyclic ring selected from









each R^{2e} is independently hydrogen, R^{6e} , 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 $N(R)S(O)_2R$;

Ring B^e is selected from a 6-membered aryl containing 0-2 nitrogen atoms or a 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur;

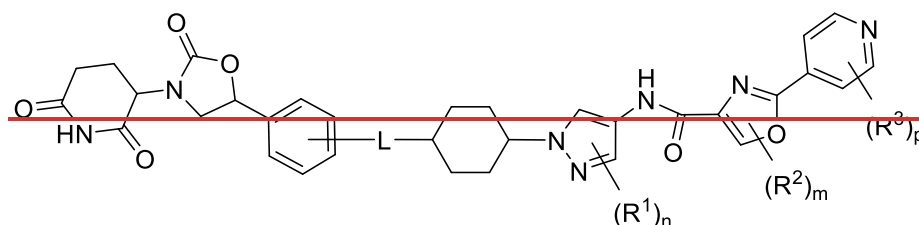
each of R^{3e} and R^{4e} is independently hydrogen, R^{6e} , halogen, CN, NO_2 , OR, SR, NR_2 , $S(O)_2R$, $S(O)_2NR_2$, $S(O)R$, $C(O)R$, $C(O)OR$, $C(O)NR_2$, $C(O)N(R)OR$, $OC(O)R$, $OC(O)NR_2$, $N(R)C(O)OR$, $N(R)C(O)R$, $N(R)C(O)NR_2$, or $N(R)S(O)_2R$;

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

each R^{6e} 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 independently a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 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 $CR=CR$;
 m is 0, 1, or 2;
 n is 0, 1, 2, 3, or 4; and
 p is 0 or 1.

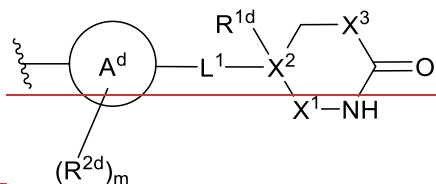
7. ~~The compound of claim 5, wherein said compound is of formula **H-m**:~~



H-m

or a pharmaceutically acceptable salt thereof.

8. ~~The compound according to either of claim 1 or claim 2, wherein LBM is E3 ubiquitin ligase~~



binding moiety

, wherein:

X^1 is a bivalent moiety selected from a covalent bond, CH_2 , $C(O)$, $C(S)$, or

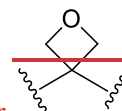
X^2 is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from CH_2 or $Si(R)_2$;

R^{1d} is hydrogen, deuterium, halogen, CN, OR, SR, $S(O)R$, $S(O)_2R$, $N(R)_2$, $Si(R)_3$, 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:

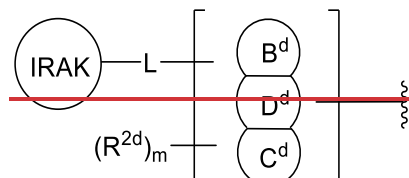
two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7



~~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^{2d} is independently hydrogen, R^{3d} , halogen, CN, NO_2 , OR, SR, $N(R)_2$, $Si(R)_3$, $S(O)_2R$, $S(O)_2N(R)_2$, $S(O)R$, $C(O)R$, $C(O)OR$, $C(O)N(R)_2$, $C(O)N(R)OR$, $C(R)_2N(R)C(O)R$, $C(R)_2N(R)C(O)N(R)_2$, $OC(O)R$, $OC(O)N(R)_2$, $N(R)C(O)OR$, $N(R)C(O)R$, $N(R)C(O)N(R)_2$, or $N(R)S(O)_2R$, or two R^{2d} on the same carbon together form $=O$ or $=S$;~~

~~each R^{3d} 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;~~



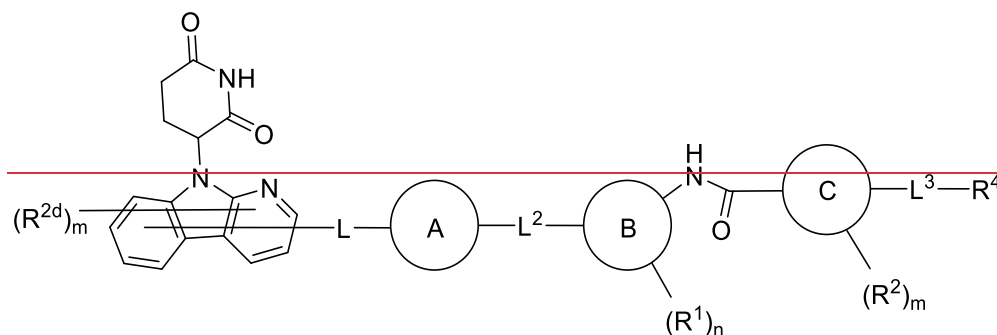
~~Ring A^d is a triicyclic ring selected from _____, wherein~~

~~each of Ring B^d , Ring C^d , and Ring D^d is independently a fused ring selected from 6-membered aryl containing 0-3 nitrogens, 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 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur; and~~

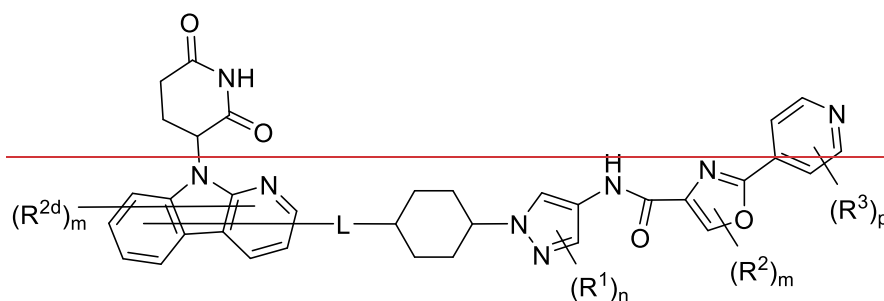
~~L^1 is independently a covalent bond or a C_{1-3} -bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with O , $C(O)$, $C(S)$, $C(R)_2$, $CH(R)$, $C(F)_2$, $N(R)$, S , $S(O)_2$ or $CR=CR$; and~~

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

~~9. The compound of claim 8, wherein said compound is of formula **H-r** or **H-s**:~~



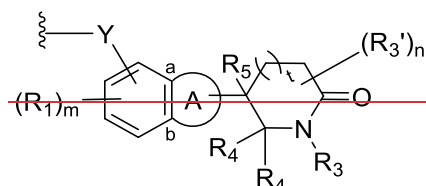
~~H-r~~



~~H-s~~

or a pharmaceutically acceptable salt thereof.

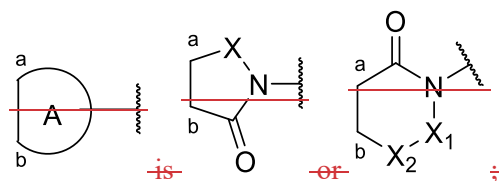
10. ~~The compound according to either of claim 1 or claim 2, wherein LBM is cereblon E3 ubiquitin~~



~~ligase binding moiety~~

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

~~wherein:~~



~~Y is a bond, Y₁, O, NH, NR₂, C(O)O, OC(O), C(O)NR₂', NR₂'C(O), Y₁-O, Y₁-NH, Y₁-NR₂, Y₁-C(O), Y₁-C(O)O, Y₁-OC(O), Y₁-C(O)NR₂', or Y₁-NR₂'C(O), wherein Y₁ is C₁₋₆ alkylene, C₂₋₆ alkenylene, or C₂₋₆ alkynylene;~~

~~X is C(O) or C(R₃)₂;~~

~~X₁-X₂ is C(R₃)=N or C(R₃)₂-C(R₃)₂;~~

~~each R₁ is independently halogen, nitro, NH₂, OH, C(O)OH, C₁₋₆ alkyl, or C₁₋₆ alkoxy;~~

~~R₂ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₈ cycloalkyl, 3 to 8 membered heterocycloalkyl, C(O)-C₁₋₆ alkyl, C(O)-C₂₋₆ alkenyl, C(O)-C₃₋₈ cycloalkyl, or C(O)-3 to 8 membered heterocycloalkyl, and R₂ is optionally substituted with one or more of halogen, N(R₆)₂, NHC(O)R₆, NHC(O)OR₆, OR₆, C₃₋₈ cycloalkyl, 3 to 8 membered heterocycloalkyl, C₆₋₁₀ aryl, or 5 to 10 membered heteroaryl, wherein each of the C₃₋₈ cycloalkyl, 3 to 8 membered heterocycloalkyl, C₆₋₁₀ aryl or 5 to 10 membered heteroaryl is optionally further substituted with one or more of halogen, NH₂, CN, nitro, OH, C(O)OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkoxy;~~

~~R₂' is H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₈ cycloalkyl, or 3- to 8-membered heterocycloalkyl, and R₂', when not being H, is optionally substituted with one or more of halogen, N(R_a)₂, NHC(O)R_a, NHC(O)OR_a, OR_b, C₃₋₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein each of the C₃₋₈ cycloalkyl, 3- to 8-membered heterocycloalkyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more of halogen, NH₂, CN, nitro, OH, C(O)OH, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or C₁₋₆ haloalkoxy;~~

~~each R₃ is independently H or C₁₋₃ alkyl optionally substituted with C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;~~

~~each R₃' is independently C₁₋₃ alkyl;~~

~~each R₄ is independently H or C₁₋₃ alkyl; or two R₄, together with the carbon atom to which they are attached, form C(O), a C₃₋₆ carbocycle, or a 4-, 5-, or 6-membered heterocycle comprising 1 or 2 heteroatoms selected from N and O;~~

~~R₅ is H, C₁₋₃ alkyl, F, or Cl;~~

~~each R_a independently is H or C₁₋₆ alkyl;~~

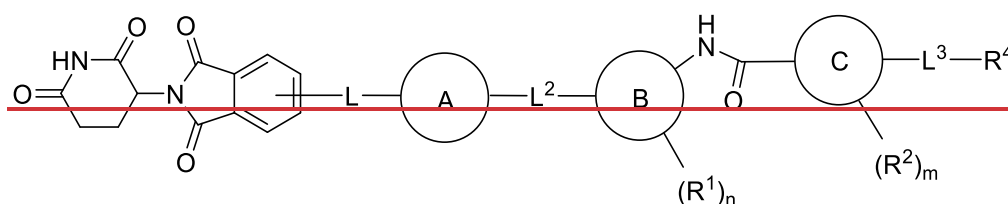
~~R_b is H or tosyl;~~

~~t is 0 or 1;~~

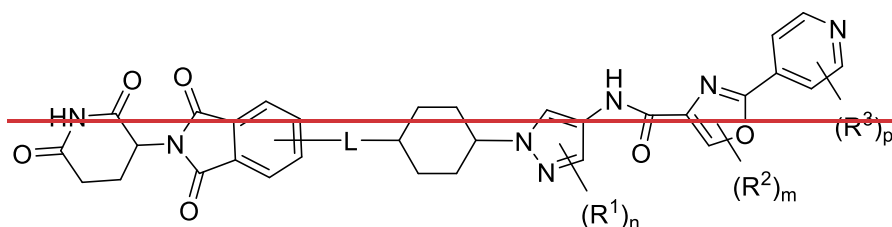
~~m is 0, 1, 2 or 3; and~~

~~n is 0, 1 or 2.~~

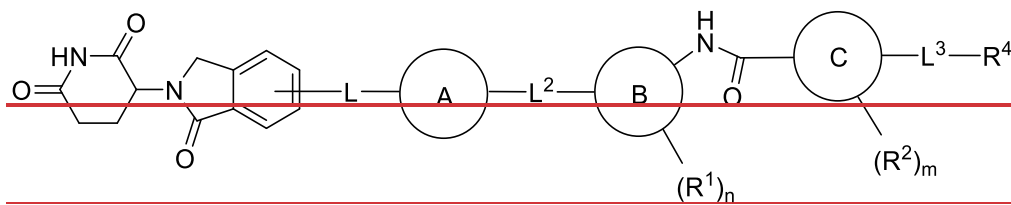
11. — The compound of claim 10, wherein said compound is of formula **H-n**, **H-o**, **H-p**, or **H-q**:



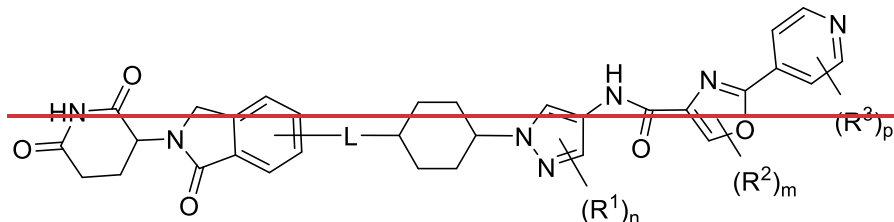
H-n



H-o



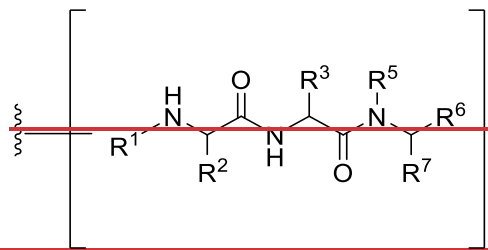
H-p



H-q

or a pharmaceutically acceptable salt thereof.

12. — The compound according to either of claim 1 or claim 2, wherein LBM is IAP E3 ubiquitin ligase



binding moiety, or a pharmaceutically acceptable salt thereof,

wherein:

R¹ is selected from hydrogen or alkyl;

R² is selected from hydrogen or alkyl;

R³ is selected from hydrogen, alkyl, cycloalkyl and heterocycloalkyl;

R⁵ and R⁶ are independently selected from hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or

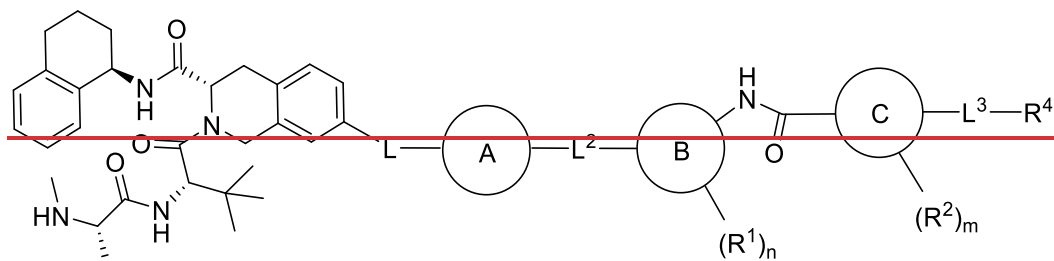
R⁵ and R⁶ are taken together to form a pyrrolidine or a piperidine ring further optionally fused to 1-2 cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings, each of which can then be further fused to another cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring, or

R³ and R⁵ are taken together to form a 5-8 membered ring further optionally fused to 1-2 cycloalkyl, heterocycloalkyl, aryl or heteroaryl ring;

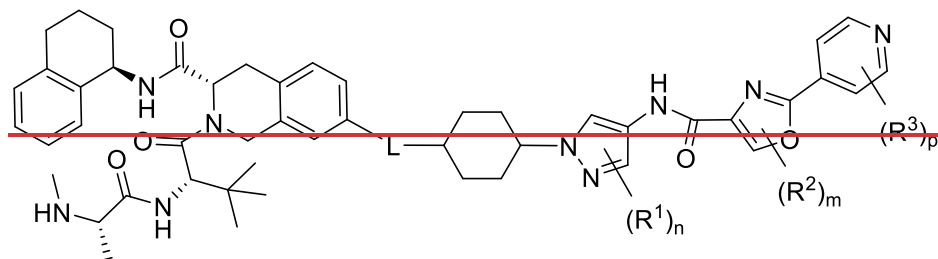
R⁷ is selected from cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, each one further optionally substituted with 1-3 substituents selected from halogen, alkyl, haloalkyl, hydroxyl, alkoxy, cyano, (hetero)cycloalkyl or (hetero)aryl, or R⁷ is C(O)NHR⁴; and

R^4 is selected from alkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, further optionally substituted with 1-3 substituents selected from halogen, alkyl, haloalkyl, hydroxyl, alkoxy, cyano, (hetero)cycloalkyl or (hetero)aryl, or R^7 is $C(O)NHR^4$.

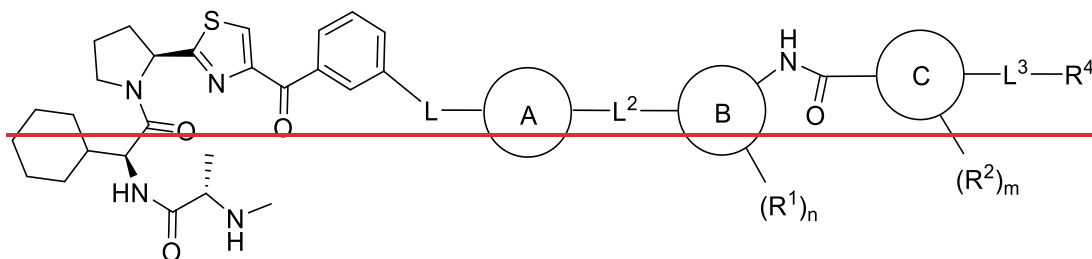
13. The compound of claim 12, wherein said compound is of formula **H-vv**, **H-ww**, **H-zz**, or **H-aaa**:



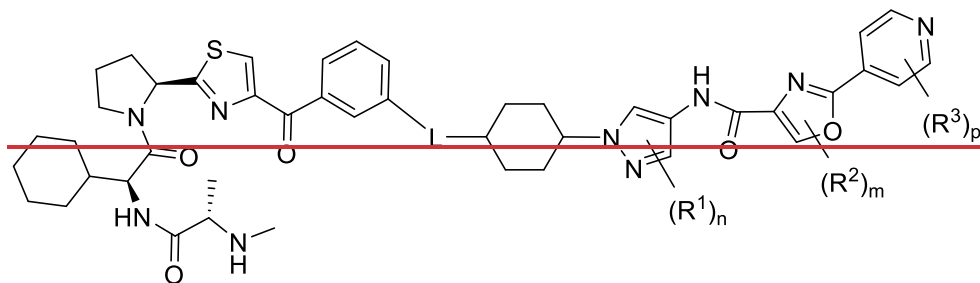
H-vv



H-ww



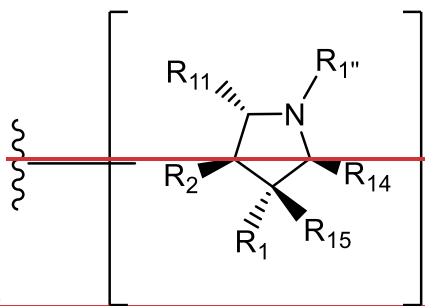
H-zz



H-aaa

or a pharmaceutically acceptable salt thereof.

14. ~~The compound according to either of claim 1 or claim 2, wherein LBM is a MDM2 E3 ligase~~



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

~~R₁ and R₂ are independently selected from the group consisting of an aryl or heteroaryl group, a heteroaryl group having one or two heteroatoms independently selected from sulfur or nitrogen, wherein the aryl or heteroaryl group can be mono-cyclic or bi-cyclic, or unsubstituted or substituted with one to three substituents independently selected from the group consisting of: halogen, CN, C₁₋₆ alkyl group, C₃₋₆ cycloalkyl, OH, alkoxy with 1 to 6 carbons, fluorine substituted alkoxy with 1-6 carbons, sulfoxide with 1-6 carbons, sulfone with 1-6 carbons, ketone with 2-6 carbons, amides with 2-6 carbons, and dialkyl amine with 2-6 carbons;~~

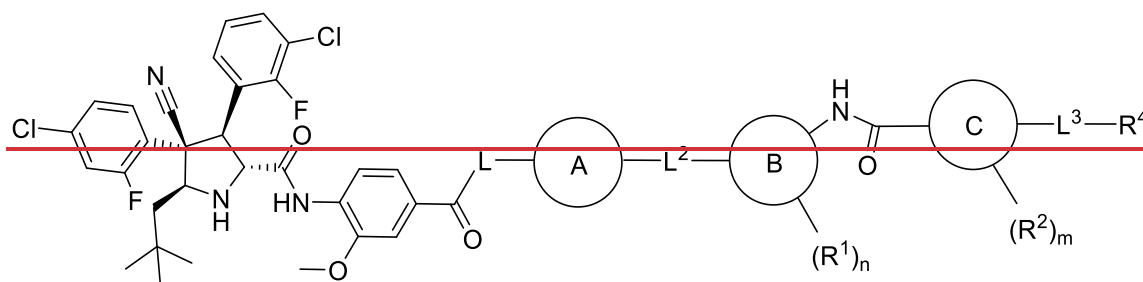
~~R₁₁ is C(O)N(R^h)(Rⁱ), wherein R^h and Rⁱ are selected from groups consisting of the following: H, C1 to C6 alkyl, alkoxy substituted alkyl, sulfone substituted alkyl, aryl, hetero aryl, mono-, bis- or tri-substituted aryl or hetero-aryl, alkyl carboxylic acid, heteroaryl carboxylic acid, alkyl carboxylic acid, fluorine substituted alkyl carboxylic acid, aryl substituted cycloalkyl, hetero-aryl substituted cycloalkyl; wherein R^h and Rⁱ are independently selected from the group consisting of H, connected to form a ring, 4-hydroxycyclohexane; mono- and di-hydroxy substituted alkyl (C₃₋₆); 3-hydroxycyclobutane; phenyl-4-carboxylic acid, and substituted phenyl-4-carboxylic acid;~~

~~R₁₄ is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocycle, substituted heterocycle, cycloalkyl, substituted cycloalkyl, cycloalkenyl and substituted cycloalkenyl;~~

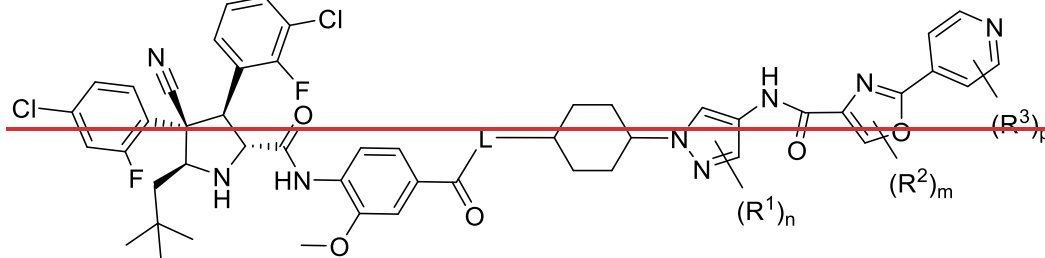
~~R₁₅ is CN;~~

~~R₁₂ is selected from the group consisting of alkyl, aryl substituted alkyl, alkoxy substituted alkyl, cycloalkyl, aryl substituted cycloalkyl, and alkoxy substituted cycloalkyl.~~

15. ~~The compound of claim 14, wherein said compound is of formula II-xx or II-yy:~~



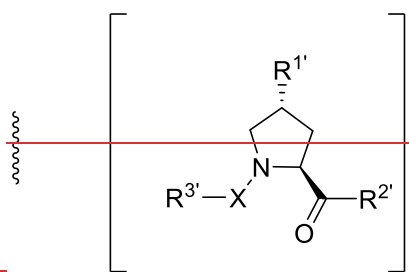
H-xx



H-yy

or a pharmaceutically acceptable salt thereof.

16. — The compound according to either of claim 1 or claim 2, wherein LBM is VHL E3-ubiquitin ligase



binding moiety—, or a pharmaceutically acceptable salt thereof, wherein:

$R^{1'}$ is an optionally substituted C_{1-6} alkyl group, an optionally substituted $(CH_2)_nOH$, an optionally substituted $(CH_2)_nSH$, an optionally substituted $(CH_2)_nO(C_{1-6}alkyl)$ group, an optionally substituted $(CH_2)_nWCOCW$ (C_{0-6}) alkyl group containing an epoxide moiety WCOCW where each W is independently H or a C_{1-3} alkyl group, an optionally substituted $(CH_2)_nCOOH$, an optionally substituted $(CH_2)_nC(O)(C_{1-6}alkyl)$, an optionally substituted $(CH_2)_nNHC(O)R_1$, an optionally substituted $(CH_2)_nC(O)NR_1R_2$, an optionally substituted $(CH_2)_nOC(O)NR_1R_2$, $(CH_2O)_nH$, an optionally substituted $(CH_2)_nOC(O)(C_{1-6}alkyl)$, an optionally substituted $(CH_2)_nC(O)O(C_{1-6}alkyl)$, an optionally substituted $(CH_2)_nCOOH$, an optionally substituted $(OCH_2)_nO(C_{1-6}alkyl)$, an optionally substituted $(CH_2O)_nC(O)(C_{1-6}alkyl)$, an optionally substituted $(OCH_2)_nNHC(O)R_1$, an optionally substituted $(CH_2O)_nC(O)NR_1R_2$, $(CH_2CH_2O)_nH$, an optionally substituted $(CH_2CH_2O)_nCOOH$, an optionally substituted $(OCH_2CH_2O)_n(C_{1-6}alkyl)$.

C_6alkyl), an optionally substituted $(\text{CH}_2\text{CH}_2\text{O})_n\text{C}(\text{O})\text{C}_1\text{--C}_6\text{alkyl}$, an optionally substituted $(\text{OCH}_2\text{CH}_2)_n\text{NHC}(\text{O})\text{R}_1$, an optionally substituted $(\text{CH}_2\text{CH}_2\text{O})_n\text{C}(\text{O})\text{NR}_1\text{R}_2$, an optionally substituted SO_2R_5 , an optionally substituted $\text{S}(\text{O})\text{R}_5$, NO_2 , CN , or halogen;

R_1 and R_2 are each independently H or a $\text{C}_1\text{--C}_6\text{alkyl}$ group which may be optionally substituted with one or two hydroxyl groups or up to three halogen groups;

R_5 is a $\text{C}_1\text{--C}_6\text{alkyl}$ group, an optionally substituted aryl, heteroaryl or heterocycle group or a $(\text{CH}_2)_m\text{NR}_1\text{R}_2$ group;

X and X' are each independently $\text{C}=\text{O}$, $\text{C}=\text{S}$, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$;

R is an optionally substituted $(\text{CH}_2)_n(\text{C}=\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{alkyl}$ group, an optionally substituted $(\text{CH}_2)_n(\text{C}=\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{NR}_{1N}\text{R}_{2N}$ group, an optionally substituted $(\text{CH}_2)_n(\text{C}=\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{Aryl}$, an optionally substituted $(\text{CH}_2)_n(\text{C}=\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{heteroaryl}$, an optionally substituted $(\text{CH}_2)_n(\text{C}=\text{O})_u\text{NR}_1(\text{SO}_2)_w\text{heterocycle}$, an optionally substituted $\text{NR}^+(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{alkyl}$, an optionally substituted $\text{NR}^+(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{NR}_{1N}\text{R}_{2N}$, an optionally substituted $\text{NR}^+(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{NR}_1\text{C}(\text{O})\text{R}_{1N}$, an optionally substituted $\text{NR}^+(\text{CH}_2)_n(\text{C}=\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{aryl}$, an optionally substituted $\text{NR}^+(\text{CH}_2)_n(\text{C}=\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{heteroaryl}$ or an optionally substituted $\text{NR}^+(\text{CH}_2)_n(\text{C}=\text{O})_u\text{NR}_1(\text{SO}_2)_w\text{heterocycle}$, an optionally substituted $\text{X}^{\text{R}2' }\text{alkyl}$ group; an optionally substituted $\text{X}^{\text{R}2' }\text{aryl}$ group; an optionally substituted $\text{X}^{\text{R}2' }\text{heteroaryl}$ group; an optionally substituted $\text{X}^{\text{R}2' }\text{heterocycle}$ group;

$\text{R}^{3' }$ is an optionally substituted alkyl, an optionally substituted $(\text{CH}_2)_n(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{alkyl}$, an optionally substituted $(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{NR}_{1N}\text{R}_{2N}$, an optionally substituted $(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{NR}_1\text{C}(\text{O})\text{R}_{1N}$, an optionally substituted $(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{Aryl}$, an optionally substituted $(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{heteroaryl}$, an optionally substituted $(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{heterocycle}$, an optionally substituted $\text{NR}^+(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{alkyl}$, an optionally substituted $\text{NR}^+(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{NR}_{1N}\text{R}_{2N}$, an optionally substituted $\text{NR}^+(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{NR}_1\text{C}(\text{O})\text{R}_{1N}$, an optionally substituted $\text{NR}^+(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{Aryl}$, an optionally substituted $\text{NR}^+(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{heteroaryl}$, an optionally substituted $\text{NR}^+(\text{CH}_2)_n\text{C}(\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{heterocycle}$, an optionally substituted $\text{O}(\text{CH}_2)_n(\text{C}=\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{alkyl}$, an optionally substituted $\text{O}(\text{CH}_2)_n(\text{C}=\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{NR}_{1N}\text{R}_{2N}$, an optionally substituted $\text{O}(\text{CH}_2)_n(\text{C}=\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{NR}_1\text{C}(\text{O})\text{R}_{1N}$, an optionally substituted $\text{O}(\text{CH}_2)_n(\text{C}=\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{Aryl}$, an optionally substituted $\text{O}(\text{CH}_2)_n(\text{C}=\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{heteroaryl}$ or an optionally substituted $\text{O}(\text{CH}_2)_n(\text{C}=\text{O})_u(\text{NR}_1)_v(\text{SO}_2)_w\text{heterocycle}$; $(\text{CH}_2)_n(\text{V})_n\text{--}(\text{CH}_2)_n(\text{V})_n\text{--alkyl}$ group, an optionally substituted $(\text{CH}_2)_n(\text{V})_n\text{--}(\text{CH}_2)_n(\text{V})_n\text{--aryl}$ group, an optionally substituted $(\text{CH}_2)_n(\text{V})_n\text{--}(\text{CH}_2)_n(\text{V})_n\text{--heteroaryl}$ group, an optionally substituted

~~(CH₂)_n-(V)_n-(CH₂)_n-(V)_n-heterocycle group, an optionally substituted -(CH₂)_n-N(R₁)-(C=O)_m-
(V)_n-alkyl group, an optionally substituted -(CH₂)_n-N(R₁)-(C=O)_m-(V)_n-aryl group, an optionally
substituted -(CH₂)_n-N(R₁)-(C=O)_m-(V)_n-heteroaryl group, an optionally substituted -(CH₂)_n-
N(R₁)-(C=O)_m-(V)_n-heterocycle group, an optionally substituted -X^{R3'}-alkyl group, an optionally
substituted -X^{R3'}-aryl group, an optionally substituted -X^{R3'}-heteroaryl group, an optionally
substituted -X^{R3'}-heterocycle group, wherein R_{1N} and R_{2N} are each independently H, C₁-C₆ alkyl
which is optionally substituted with one or two hydroxyl groups and up to three halogen groups or
an optionally substituted -(CH₂)_n-aryl, -(CH₂)_n-heteroaryl or -(CH₂)_n-heterocycle group;~~

~~V is O, S or NR₁;~~

~~R₁ is the same as above;~~

~~R₁⁺ and R₁⁻ are each independently H or a C₁-C₃ alkyl group;~~

~~X^{R2'} and X^{R3'} are each independently an optionally substituted -(CH₂)_n, -(CH₂)_n-CH(X_v)=CH(X_v), -(CH₂)_n-
CH=CH-, (CH₂CH₂O)_n or a C₃-C₆ cycloalkyl group, where X_v is H, a halo or a C₁-C₃ alkyl group
which is optionally substituted;~~

~~each m is independently 0, 1, 2, 3, 4, 5, 6;~~

~~each m' is independently 0 or 1;~~

~~each n is independently 0, 1, 2, 3, 4, 5, 6;~~

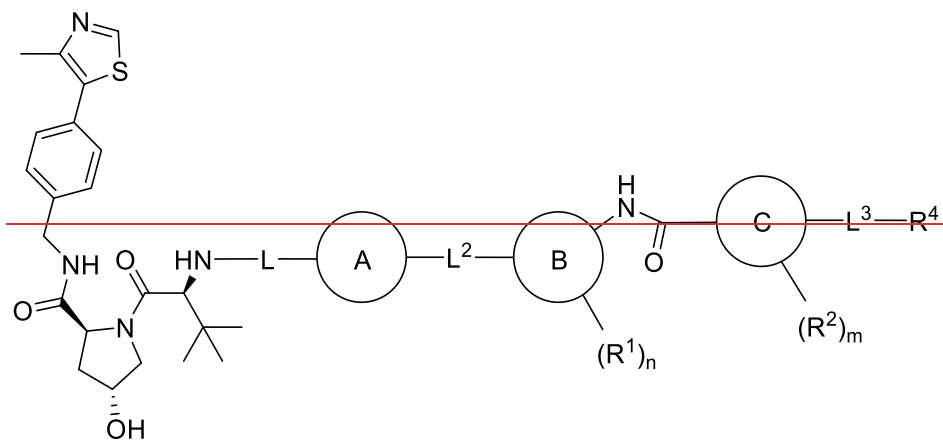
~~each n' is independently 0 or 1;~~

~~each u is independently 0 or 1;~~

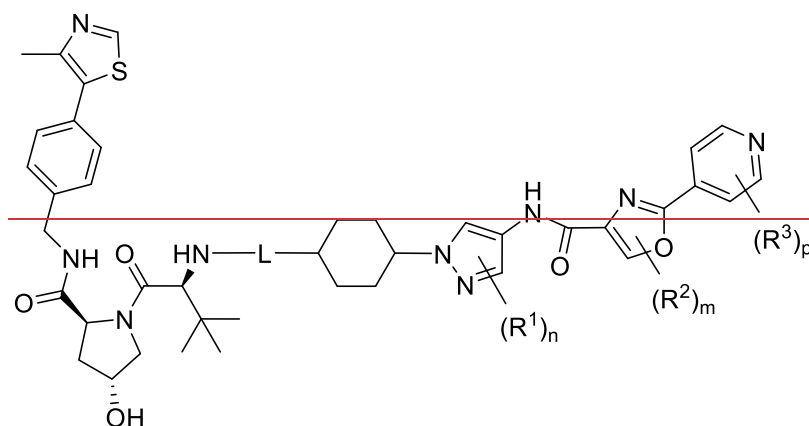
~~each v is independently 0 or 1; and~~

~~each w is independently 0 or 1.~~

17. The compound of claim 16, wherein said compound is of formula **II-bbb** or **II-ccc**:



II-bbb



H-eee

or a pharmaceutically acceptable salt thereof.

18. ~~The compound according to any one of claims 1-17, wherein L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C₁₋₅₀ hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by Cy, O, N(R), 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, wherein 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, or sulfur.~~

19. ~~The compound of any one of claims 1-18, wherein said compound is selected from any one of those depicted in Table 1, or a pharmaceutically acceptable salt thereof.~~

2025. A pharmaceutical composition comprising a compound of claim 1 ~~according any of one claims 1-19~~, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

~~21. — A method of degrading and/or inhibiting an IRAK protein kinase in a patient or biological sample comprising administering to said patient, or contacting said biological sample with a compound according to any one of claims 1-19, or a pharmaceutical composition thereof.~~

~~22. — The method of claim 21, wherein the IRAK protein kinase is an IRAK-4 protein kinase.~~

~~23. — The method of claim 21, wherein the IRAK protein kinase is an IRAK-1, IRAK-2, or IRAK-3 protein kinase.~~

~~24. — A method of treating an IRAK-mediated disorder, disease, or condition in a patient comprising administering to said patient a compound according to any of one claims claims 1-19, or a pharmaceutical composition thereof.~~

~~2526. Use of a compound of claim 1, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an autoimmune disease, an inflammatory disorder, or an immunodeficiency disorder in a patientThe method of claim 24, wherein the IRAK-mediated disorder, disease or condition is selected from the group consisting of a cancer, a neurodegenerative disease, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, a condition associated with organ transplantation, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T-cell activation, a cardiovascular disorder, and a CNS disorder.~~

~~26. — The method of claim 25, wherein the cancer or proliferative disorder is selected from the group consisting of a benign or malignant tumor, solid tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastoma, neuroblastoma, multiple myeloma, gastrointestinal cancer, colon carcinoma, colorectal adenoma, a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma, lymphoma, Hodgkin's or Non-Hodgkin's lymphoma, a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, an IL-1 driven disorder, a MyD88 driven disorder, smoldering or~~

~~indolent multiple myeloma, and a hematological malignancy selected from leukemia, diffuse large B-cell lymphoma (DLBCL), ABC DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström's macroglobulinemia (WM), splenic marginal zone lymphoma, multiple myeloma, plasmacytoma, or intravascular large B-cell lymphoma.~~

~~27. The method of claim 26, wherein the MyD88 driven disorder is selected from the group consisting of ABC DLBCL, Waldenström's macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T cell lymphoma, and chronic lymphocytic leukemia.~~

~~28. The method of claim 26, wherein the IL-1 driven disorder is smoldering or indolent multiple myeloma.~~

~~29. The method of claim 25, wherein the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia, and a neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity, hypoxia, epilepsy, treatment of diabetes, metabolic syndrome, obesity, organ transplantation and graft versus host disease.~~

~~3027. The method use of claim 2526, wherein the inflammatory disease or disorder is selected from the group consisting of ocular allergy, conjunctivitis, keratoconjunctivitis sicca, vernal conjunctivitis, allergic rhinitis, hemolytic anemia, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia or another inflammatory disease in which autoimmune reactions are implicated or which have an autoimmune component or etiology, systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, ulcerative colitis, Crohn's disease or another autoimmune inflammatory bowel disease, irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, endocrine ophthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, optionally including idiopathic nephrotic syndrome or minimal change~~

nephropathy), chronic granulomatous disease, endometriosis, leptospirosis renal disease, glaucoma, retinal disease, aging, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hypercholesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ectodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic, non-allergic, mild, moderate, severe, bronchitic, or exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, silica induced diseases, COPD (reduction of damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression), pulmonary disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, Type 2 diabetes, appendicitis, atopic dermatitis, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, vaginitis, vasculitis, vulvitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angitis, urticaria, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile~~Juvenile~~ rheumatoid arthritis, cryopyrin associated periodic syndrome, adult onset Still's disease, macrophage activation syndrome, Cryopyrin Associated Periodic Syndrome (CAPS), primary and secondary hemophagocytic lymphohistiocytosis, familial Mediterranean fever, NLRP12 autoinflammatory syndrome, or osteoarthritis.

28. The use of claim 26, wherein the disease or disorder is ocular allergy, conjunctivitis, keratoconjunctivitis sicca, vernal conjunctivitis, allergic rhinitis, chronic rhinosinusitis with nasal polyps (CRSwNP), hemolytic anemia, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, eosinophilia, hypereosinophilia, Loffler's syndrome, eosinophilic pneumonia, tropical eosinophilia, bronchopulmonary aspergillosis, polyarteritis nodosa, Churg-Strauss syndrome, eosinophilic granuloma, eosinophilic asthma, eosinophilic COPD, psoriasis, generalized pustular psoriasis, psoriasis vulgaris,

contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis, herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus, erythematosus, systemic lupus erythematosus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acne vulgaris, hidradenitis suppurativa, Sweet Syndrome, pyoderma gangrenosum, allergic conditions of the skin, acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, cryopyrin associated periodic syndrome, adult onset Still's disease, macrophage activation syndrome, primary and secondary hemophagocytic lymphohistiocytosis, familial Mediterranean fever, NLRP12 autoinflammatory syndrome.

29. A compound of claim 1, or a pharmaceutical composition thereof, for use in therapy.