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.

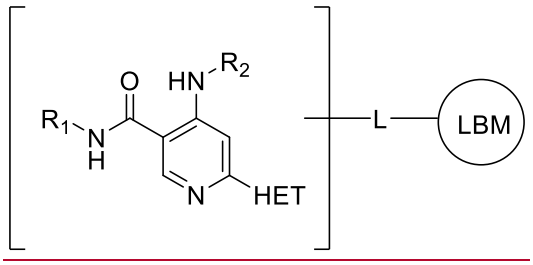
[0006] Aberrations in the process have recently been implicated in the pathogenesis of several diseases, both inherited and acquired. These diseases fall into two major groups: (a) those that result from loss of function with the resultant stabilization of certain proteins, and (b) those that result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

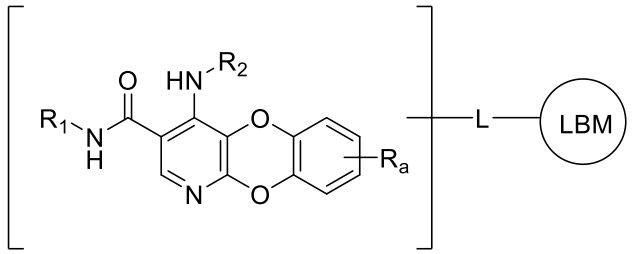
[0008] An ongoing need exists in the art for effective treatments for disease, especially hyperplasias and cancers, such as multiple myeloma. However, non-specific effects, and the inability to target and modulate certain classes of proteins altogether, such as transcription factors, remain as obstacles 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 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~~

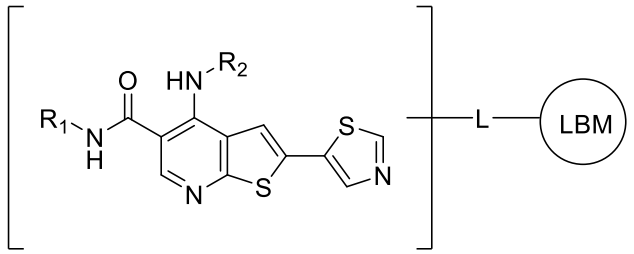
[0008a] In an aspect of the present disclosure, there is provided a compound of formula:



I-b-1



I-b-2



I-b-3

or a pharmaceutically acceptable salt thereof, wherein:

HET is a heteroaryl selected from indolyl, pyrrolo[1,2-b]pyridazine, pyrrolo[2,3-b]pyridinyl, pyrrolo[2,3-d]pyrimidinyl, pyrazolo[3,4-d]pyrimidinyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, imidazo[4,5-b]pyridinyl, and purinyl, wherein said heteroaryl is substituted with R_a and R_b;

R_a is H, F, Cl, Br, —CN, —OH, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-4}hydroxyalkyl, C_{1-4} alkoxy, —NH_2, —NH(C_{1-4} alkyl), —N(C_{1-4} alkyl)$_2$, —NH(C_{1-4} hydroxyalkyl), —NH(C_{1-4} fluoroalkyl), —NH(C_{1-6} hydroxy-fluoroalkyl), —CH_2NHC(O)(C_{1-6} alkyl), —CH_2NHC(O)(C_{1-6}hydroxyalkyl), —CH_2NHC(O)NH(C_{1-6} alkyl), —CH_2NHC(O)NHCH$_2$(phenyl), —CH_2NHC(O)N(C_{1-4} alkyl)$_2$, —CH_2NHC(O)O(C_{1-4} alkyl), —CH_2NHC(O)(C_{3-6} cycloalkyl), —CH_2NHC(O)(tetrahydrofuranyl), —CH_2NHC(O)CH_2(C_{3-6} cycloalkyl), —CH_2NHC(O)CH_2(tetrahydropyranyl), —CH_2NHC(O)CH_2(phenyl), —NHC(O)(C_{1-4} alkyl), pyrrolidinyl, hydroxypyrrolidinyl, or pyridazinyl;

R_b is H or —NH_2;

R_1 is:

(i) C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} fluoroalkyl, C_{1-6} hydroxyalkyl, C_{1-8} hydroxy-fluoroalkyl, —(C_{1-6} alkylenyl)O(C_{1-4} alkyl), —(C_{1-6} alkylenyl)O(C_{1-4}fluoroalkyl),

—(C_{1-6} fluoroalkylenyl)O(C_{1-4} alkyl), —(C_{1-6}fluoroalkylenyl)O(C_{1-4} deuteroalkyl), —(C_{1-6} fluoroalkylenyl)O(C_{1-4}fluoroalkyl), —(C_{1-4} fluoroalkylenyl)C(C_{3-6} cycloalkyl)$_2$(OH), —(C_{1-4}alkylenyl)NHC(O)(C_{1-4} alkylenyl)OC(O)(C_{1-3} alkyl), —(C_{1-6}alkylenyl)NHS(O)$_2$(C_{1-4} alkyl), —(C_{1-6} alkylenyl)P(O)(C_{1-4} alkoxy)$_2$, —(C_{1-6} fluoroalkylenyl)NH(C_{1-4} alkyl), —(C_{1-6} alkylenyl)C(O)NH(C_{1-4} alkyl), —(C_{1-6} fluoroalkylenyl)C(O)NH(C_{1-4} alkyl), —(C_{1-6}fluoroalkylenyl)C(O)NH(C_{1-4} hydroxyalkyl), or —(C_{1-6}fluoroalkylenyl)OP(O)(OH)$_2$;

(ii) —(C_{1-3} alkylenyl)R_x, —(C_{1-3} fluoroalkylenyl)R_x, —(C_{1-3}alkylenyl)C(O)R_x, —(C_{1-3} alkylenyl)C(O)NHR_x, —(C_{1-3}fluoroalkylenyl)C(O)R_x, or —CH_2CF=(tetrahydropyranyl), wherein R_x is a cyclic group selected from C_{3-6} cycloalkyl, 1-dioxidothiomorpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, and morpholinyl, wherein each cyclic group is substituted with zero to 3 substituents independently selected from F, —OH, —CH_3, —$C(CH_2)_2OH$, —OCH_3, —$C(O)CH_2CN$, —$S(O)_2CH_3$, —$S(O)_2NH_2$, —NHC(O)CH_3, —$N(S(O)_2CH_3)_2$, oxetanyl, and morpholinyl;

(iii) C_{3-6} cycloalkyl or C_{4-6} cycloalkenyl, each substituted with zero to 3 substituents independently selected from F, —OH, —CN, C_{1-3}alkyl, C_{1-3} alkoxy, —S(C_{1-3} alkyl), —NO_2, —$S(O)_2$(C_{1-3} alkyl), C_{1-4}hydroxyalkyl, —C(C_{1-3} alkyl)(OH)(C_{3-6} cycloalkyl), —CH_2C(O)NH(C_{1-3} alkyl), —NHC(O)(C_{1-3} alkyl), —NHC(O)(C_{1-4}hydroxyalkyl), —C(O)NH(C_{1-3} alkyl), —C(O)NH(C_{1-3} deuteroalkyl), —C(O)NH(C_{3-6} cycloalkyl), —NHC(O)O(C_{1-3} alkyl), and —$NHS(O)_2$(C_{1-3}alkyl); or

(iv) tetrahydropyranyl or piperidinyl, each substituted with zero to 1 substituent selected from —OH, C_{1-3} alkyl, C_{1-3} fluoroalkyl, C_{1-4} hydroxyalkyl, and C_{1-3}alkoxy;

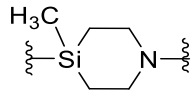
R_2 is:

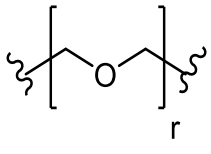
(i) C_{1-7} alkyl or C_{2-6} alkenyl, each substituted with zero to three substituents independently selected from F, —OH, and —CN; —(C_{1-4} alkylenyl)O(C_{1-4} alkyl), —(C_{1-4} alkylenyl)O(C_{1-4} fluoroalkyl), —(C_{1-6} alkylenyl)NH_2, —(C_{1-6} alkylenyl)S(O)$_2$(C_{1-3} alkyl), —(C_{1-6}fluoroalkylenyl)NH(C_{1-3} alkyl), or —(C_{1-6} alkylenyl)NHC(O)(C_{1-4}fluoroalkyl);

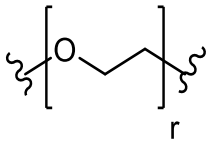
(ii) —(C_{1-4} alkylenyl)R_y wherein R_y is C_{3-6} cycloalkyl, azetidinyl, oxetanyl,

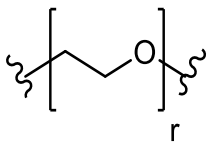
tetrahydropyranyl, or morpholinyl, each substituted with zero to 2 substituents independently selected from F, —OH, and C_{1-3} alkyl;

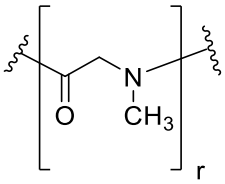
(iii) C_{3-6} cycloalkyl, azetidinyl, oxetanyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, or tetrahydropyranyl, each substituted with zero to 3 substituents independently selected from F, —OH, C_{1-3}alkyl, C_{1-3} hydroxyalkyl, —C(O)(C_{1-3} alkyl), —C(O)(C_{1-3} fluoroalkyl), —C(O)(C_{1-3} cyanoalkyl), —C(O)O(C_{1-3} alkyl), —C(O)NH_2, —C(O)NH(C_{1-3} alkyl), —NH_2, —NH(C_{1-3} alkyl), —NH(C_{1-3} fluoroalkyl), —NH(oxetanyl), —NHC(O)(C_{1-3} alkyl), —NHC(O)(C_{1-3} fluoroalkyl), —NHC(O)(C_{3-6} cycloalkyl), and —S(O)$_2$(C_{1-3} alkyl);

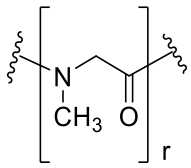
L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-4 methylene units of L are independently replaced by –Cy-, -O-, -N(R)-, –Si(R)$_2$–, –Si(OH)(R)–, –Si(OH)$_2$–, –P(O)(OR)–, –P(O)(R)–, –P(O)(NR$_2$)–, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)$_2$-, -N(R)S(O)$_2$-, -S(O)$_2$N(R)-, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, –N(R)C(O)O-, 

, 

, 

, 

, 

, or 

, wherein

each –Cy– is independently a 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

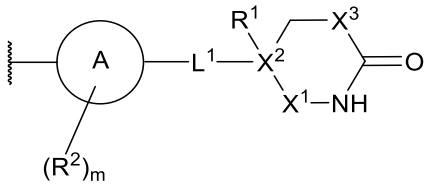
each R is independently selected from hydrogen, C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom are optionally taken together with their intervening atoms to form a 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, 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;

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

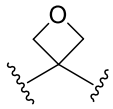
LBM is:

(i)



I-aa

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  ;

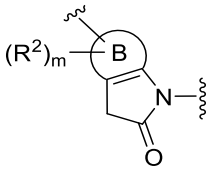
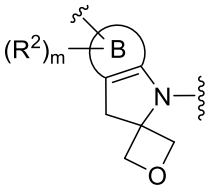
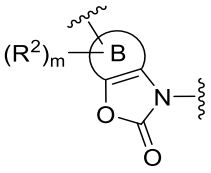
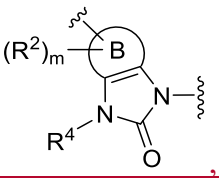
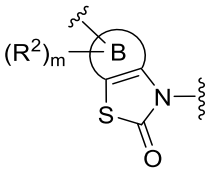
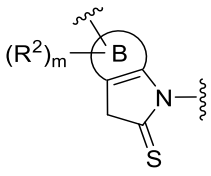
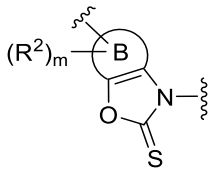
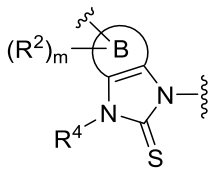
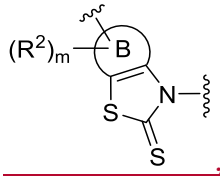
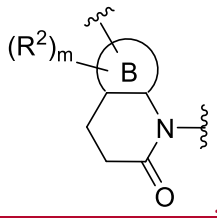
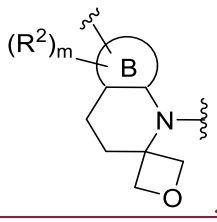
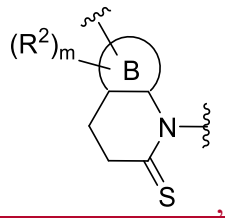
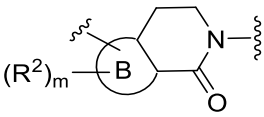
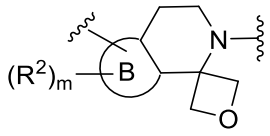
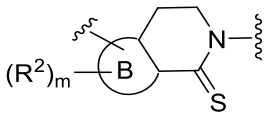
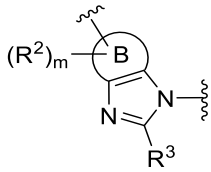
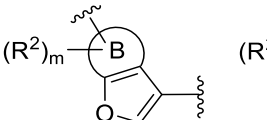
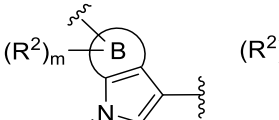
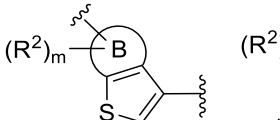
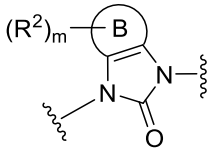
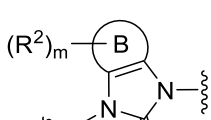
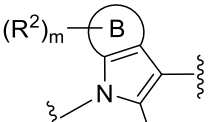
X^2 is a carbon atom or silicon atom;

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

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

each R^2 is independently hydrogen, 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, $-N(R)C(O)N(R)_2$, -

$NP(O)R_2$, $-N(R)P(O)(OR)_2$, $-N(R)P(O)(OR)(NR_2)$, $-N(R)P(O)(NR_2)_2$, or $-N(R)S(O)_2R$;

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

Ring B is 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 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;

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 –$N(R)S(O)_2R$;

each R^6 is independently 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;

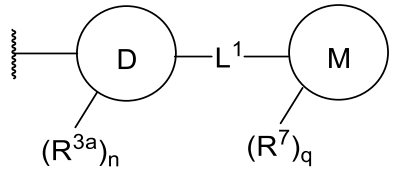
L^1 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -$C(R)_2$-, -CH(R)-, -$C(F)_2$-, -N(R)-, -S-, -$S(O)_2$- or -(C)=CH-;

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

each R is independently selected from hydrogen, 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:

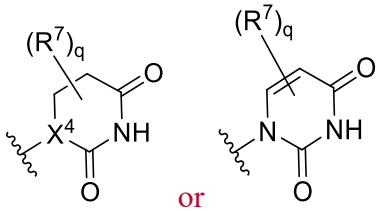
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur, or

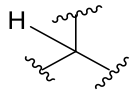
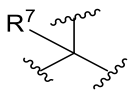
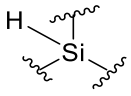
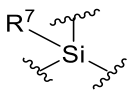
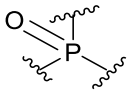
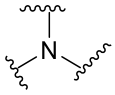
(ii)



I-nn

or a pharmaceutically acceptable salt thereof, wherein:

Ring M is selected from  or ;

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

each R is independently selected from hydrogen, 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, 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, $-N(R)C(O)NR_2$, $-NP(O)R_2$, $-N(R)P(O)(OR)_2$, $-N(R)P(O)(OR)NR_2$, $-N(R)P(O)(NR_2)_2$, or $–N(R)S(O)_2R$;

each R^6 is independently 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, 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 C_{1-4} aliphatic;

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.

[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 and/or inhibiting an IRAK4 protein kinase in a patient or biological sample.

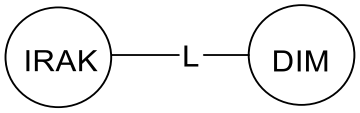
[0008d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an IRAK4-mediated disorder, disease, or condition in a patient.

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

[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.

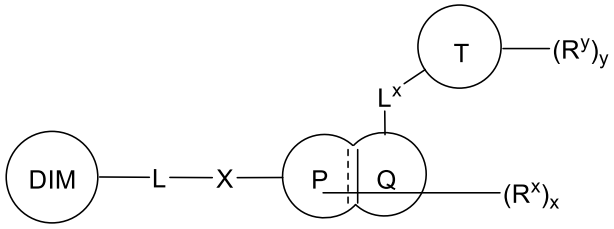
[0010] The present application further relates to targeted degradation of IRAK kinases through the use of bifunctional molecules, including bifunctional molecules that link a degradation inducing moiety to a ligand that binds IRAK kinases having the following general formula **I**:



I

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

[0011] It has now been found that compounds of this ~~invention~~disclosure, and pharmaceutically acceptable compositions thereof, are effective for the modulation of targeted ubiquitination. Such compounds have the formula **I-a**:



I-a

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

[0012] The present ~~invention~~disclosure further relates to bifunctional compounds that not only degrade IRAK, but also degrade IMiD substrates, such as Ikaros, Aiolos, or Ikaros and Aiolos.

[0013] 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 IRAK kinases. Such diseases, disorders, or conditions include those described herein.

[0014] Compounds provided by this ~~invention~~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.

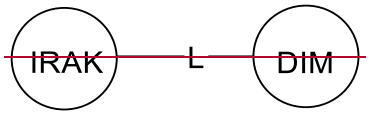
DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Certain Embodiments of the Invention:

CLAIMS

We claim:

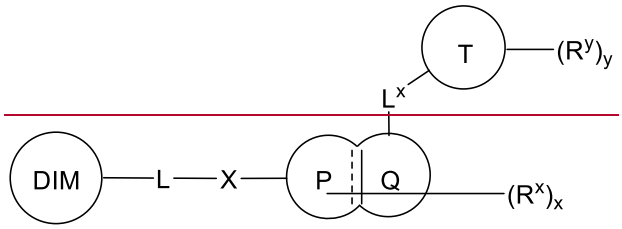
1. A compound of formula I:



I

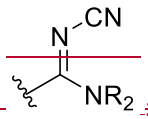
or a pharmaceutically acceptable salt thereof, wherein:

IRAK is an IRAK binding moiety capable of binding to IRAK4, said compound of formula I is a compound of formula I-a:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

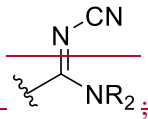
each R^* is independently hydrogen, deuterium, $R^{\neq}$, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $N(R)S(O)_2R$, $N^+(O^-)R_2$, $-OP(O)R_2$, $OP(O)(OR)_2$, $OP(O)(OR)NR_2$, $OP(O)(NR_2)_2$, $P(O)R_2$, SiR_3, $Si(OR)R_2$, or 

; or

two R^* groups are optionally taken together to form an optionally substituted 5-6 membered partially unsaturated or aryl fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-5 membered saturated or partially unsaturated carbocyclic or heterocyclic spiro fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur,

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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 atoms to form a 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, 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 R^y is independently hydrogen, deuterium, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-SiR_3$, $-SF_5$, or  ; or

a single R^y and a single R^x are optionally taken together with their intervening atoms to form a 8-20 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic or bicyclic ring having 1-10 heteroatoms, independently selected from nitrogen, oxygen, and sulfur;

each R^z is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-9 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, or spirocyclic 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 P and Ring Q are fused rings independently selected from benzo, a 4-7 membered saturated or partially unsaturated 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, wherein Ring P and Ring Q are independently and optionally substituted with 1-2 oxo groups;

Ring T is selected from phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-9 membered mono- or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring T is further optionally substituted with 1-2 oxo groups;

L^x 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 $-Cy^x-$, -O-, -S-, -C(O)-, -C(S)-, $-CR_2-$, -CRF-, $-CF_2-$, -NR-, -N=CR-, -CR=CR-, or $-S(O)_2-$, wherein R of $-CR_2-$

~~, -CRF-, -NR-, -N=CR-, or -CR=CR- can combine with R^{x} or R^{y} to form a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;~~

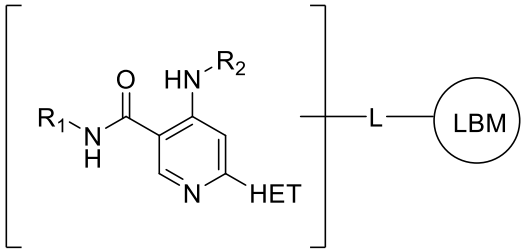
~~Cy^{x} is an optionally substituted ring selected from a 3-5 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Cy^{x} is optionally substituted with 1-2 oxo groups;~~

~~X is a covalent bond or a 4-6 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;~~

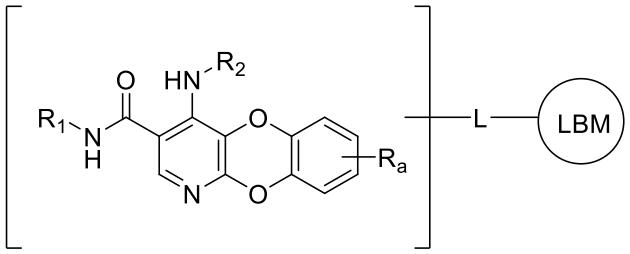
~~==== is a single or double bond;~~

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

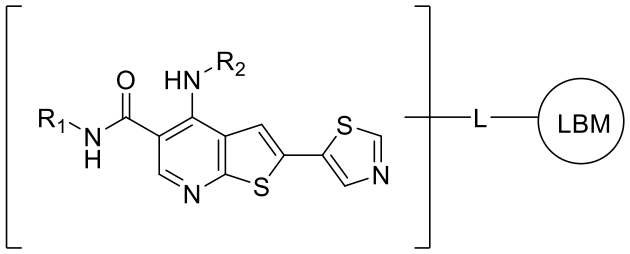
~~y is 0, 1, 2, 3 or 4;~~



I-b-1



I-b-2



I-b-3

or a pharmaceutically acceptable salt thereof, wherein:

HET is a heteroaryl selected from indolyl, pyrrolo[1,2-b]pyridazine, pyrrolo[2,3-b]pyridinyl, pyrrolo[2,3-d]pyrimidinyl, pyrazolo[3,4-d]pyrimidinyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, imidazo[4,5-b]pyridinyl, and purinyl, wherein said heteroaryl is substituted with R_a and R_b;

R_a is H, F, Cl, Br, —CN, —OH, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-4}hydroxyalkyl, C_{1-4} alkoxy, —NH_2, —$NH(C_{1-4}$ alkyl), —$N(C_{1-4}$ alkyl)$_2$, —$NH(C_{1-4}$ hydroxyalkyl), —$NH(C_{1-4}$ fluoroalkyl), —$NH(C_{1-6}$ hydroxy-fluoroalkyl), —$CH_2NHC(O)(C_{1-6}$ alkyl), —$CH_2NHC(O)(C_{1-6}$hydroxyalkyl), —$CH_2NHC(O)NH(C_{1-6}$ alkyl), —$CH_2NHC(O)NHCH_2$(phenyl), —$CH_2NHC(O)N(C_{1-4}$ alkyl)$_2$, —$CH_2NHC(O)O(C_{1-4}$ alkyl), —$CH_2NHC(O)(C_{3-6}$ cycloalkyl), —$CH_2NHC(O)$(tetrahydrofuranyl), —$CH_2NHC(O)CH_2(C_{3-6}$ cycloalkyl), —$CH_2NHC(O)CH_2$(tetrahydropyranyl), —$CH_2NHC(O)CH_2$(phenyl), —$NHC(O)(C_{1-4}$ alkyl), pyrrolidinyl, hydroxypyrrolidinyl, or pyridazinyl;

R_b is H or —NH_2;

R_1 is:

(i) C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} fluoroalkyl, C_{1-6} hydroxyalkyl, C_{1-8} hydroxy-fluoroalkyl, —(C_{1-6} alkylenyl)O(C_{1-4} alkyl), —(C_{1-6} alkylenyl)O(C_{1-4}fluoroalkyl), —(C_{1-6} fluoroalkylenyl)O(C_{1-4} alkyl), —(C_{1-6}fluoroalkylenyl)O(C_{1-4} deuteroalkyl), —(C_{1-6} fluoroalkylenyl)O(C_{1-4}fluoroalkyl), —(C_{1-4} fluoroalkylenyl)C(C_{3-6} cycloalkyl)$_2$(OH), —(C_{1-4}alkylenyl)NHC(O)(C_{1-4} alkylenyl)OC(O)(C_{1-3} alkyl), —(C_{1-6}alkylenyl)NHS(O)$_2$(C_{1-4} alkyl), —(C_{1-6} alkylenyl)P(O)(C_{1-4} alkoxy)$_2$, —(C_{1-6} fluoroalkylenyl)NH(C_{1-4} alkyl), —(C_{1-6} alkylenyl)C(O)NH(C_{1-4} alkyl), —(C_{1-6} fluoroalkylenyl)C(O)NH(C_{1-4} alkyl), —(C_{1-6}fluoroalkylenyl)C(O)NH(C_{1-4} hydroxyalkyl), or —(C_{1-6}fluoroalkylenyl)OP(O)(OH)$_2$;

(ii) —(C_{1-3} alkylenyl)R_x, —(C_{1-3} fluoroalkylenyl)R_x, —(C_{1-3}alkylenyl)C(O)R_x, —(C_{1-3} alkylenyl)C(O)NHR_x, —(C_{1-3}fluoroalkylenyl)C(O)R_x, or —CH_2CF=(tetrahydropyranyl), wherein R_x is a cyclic group selected from C_{3-6} cycloalkyl, 1-dioxidothiomorpholinyl, piperidinyl, piperazinyl, pyrrolidinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, and morpholinyl, wherein each cyclic group is substituted with zero to 3 substituents independently selected from F, —OH, —CH_3, —$C(CH_2)_2$OH, —OCH_3, —$C(O)CH_2CN$, —$S(O)_2CH_3$, —$S(O)_2NH_2$, —$NHC(O)CH_3$, —$N(S(O)_2CH_3)_2$, oxetanyl, and morpholinyl;

(iii) C_{3-6} cycloalkyl or C_{4-6} cycloalkenyl, each substituted with zero to 3 substituents independently selected from F, —OH, —CN, C_{1-3}alkyl, C_{1-3} alkoxy, —$S(C_{1-3}$ alkyl), —NO_2, —$S(O)_2(C_{1-3}$ alkyl), C_{1-4}hydroxyalkyl, —$C(C_{1-3}$ alkyl)(OH)(C_{3-6} cycloalkyl), —$CH_2C(O)NH(C_{1-3}$ alkyl), —$NHC(O)(C_{1-3}$ alkyl), —$NHC(O)(C_{1-4}$hydroxyalkyl), —

C(O)NH(C_{1-3} alkyl), —C(O)NH(C_{1-3} deuteroalkyl), —C(O)NH(C_{3-6} cycloalkyl), —NHC(O)O(C_{1-3} alkyl), and —NHS(O)$_2$(C_{1-3}alkyl); or

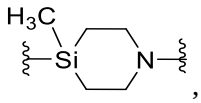
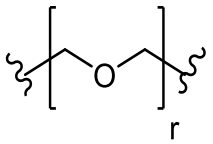
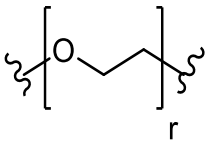
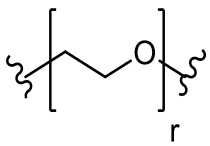
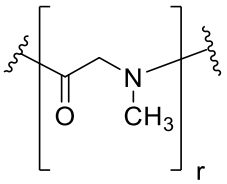
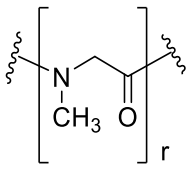
(iv) tetrahydropyranyl or piperidinyl, each substituted with zero to 1 substituent selected from —OH, C_{1-3} alkyl, C_{1-3} fluoroalkyl, C_{1-4} hydroxyalkyl, and C_{1-3}alkoxy;

R_2 is:

(i) C_{1-7} alkyl or C_{2-6} alkenyl, each substituted with zero to three substituents independently selected from F, —OH, and —CN; —(C_{1-4} alkylenyl)O(C_{1-4} alkyl), —(C_{1-4} alkylenyl)O(C_{1-4} fluoroalkyl), —(C_{1-6} alkylenyl)NH$_2$, —(C_{1-6} alkylenyl)S(O)$_2$(C_{1-3} alkyl), —(C_{1-6}fluoroalkylenyl)NH(C_{1-3} alkyl), or —(C_{1-6} alkylenyl)NHC(O)(C_{1-4}fluoroalkyl);

(ii) —(C_{1-4} alkylenyl)R_y wherein R_y is C_{3-6} cycloalkyl, azetidinyl, oxetanyl, tetrahydropyranyl, or morpholinyl, each substituted with zero to 2 substituents independently selected from F, —OH, and C_{1-3} alkyl;

(iii) C_{3-6} cycloalkyl, azetidinyl, oxetanyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, or tetrahydropyranyl, each substituted with zero to 3 substituents independently selected from F, —OH, C_{1-3}alkyl, C_{1-3} hydroxyalkyl, —C(O)(C_{1-3} alkyl), —C(O)(C_{1-3} fluoroalkyl), —C(O)(C_{1-3} cyanoalkyl), —C(O)O(C_{1-3} alkyl), —C(O)NH$_2$, —C(O)NH(C_{1-3} alkyl), —NH$_2$, —NH(C_{1-3} alkyl), —NH(C_{1-3} fluoroalkyl), —NH(oxetanyl), —NHC(O)(C_{1-3} alkyl), —NHC(O)(C_{1-3} fluoroalkyl), —NHC(O)(C_{3-6} cycloalkyl), and —S(O)$_2$(C_{1-3} alkyl);

L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-46 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  , wherein

each –Cy– is independently ~~a~~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

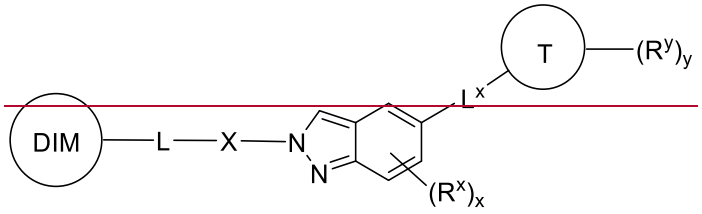
each R is independently selected from hydrogen, C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same atom are optionally taken together with their intervening atoms to form a 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, 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;

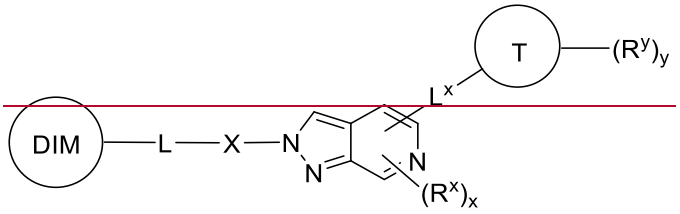
r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

~~DIM is a degradation inducing moiety.~~

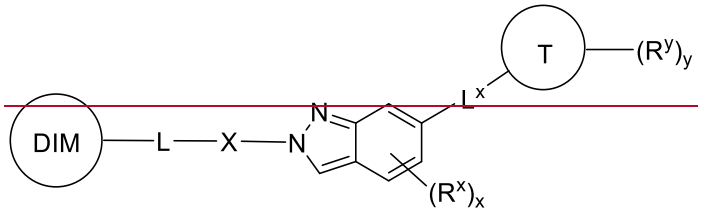
~~2. The compound of claim 1, wherein said compound is any one of the following formulae:~~



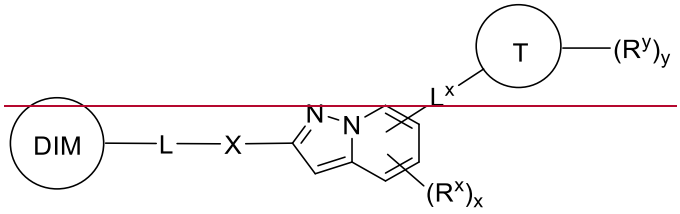
~~I-d-1~~



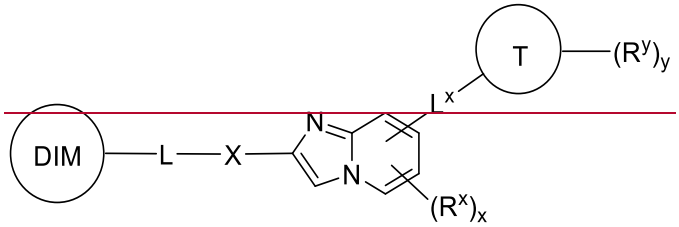
~~I-d-2~~



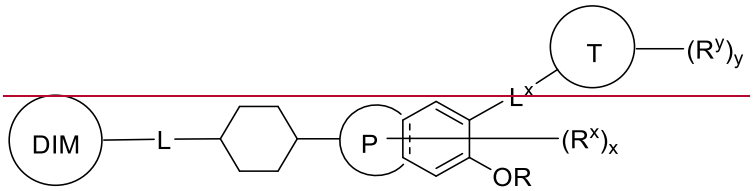
~~I-d-3~~



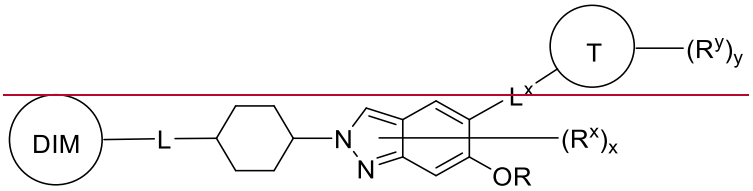
~~I-d-4~~



~~I-d-5~~



~~I-d-6~~



~~I-d-7~~

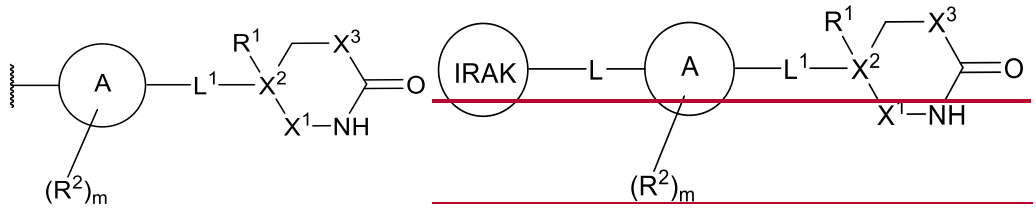
~~or a pharmaceutically acceptable salt thereof.~~

~~3. The compound of claim 1 or claim 2, wherein the DIM is a ligase binding moiety (LBM), lysine mimetic, or hydrogen atom.~~

~~4. The compound of claim 3, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety and said compound is of formula **I-aa**:~~

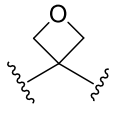
LBM is:

(i)



I-aa

or a pharmaceutically acceptable salt thereof, wherein:

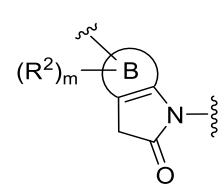
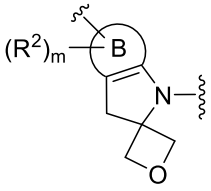
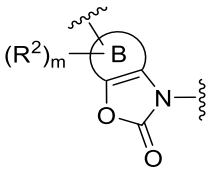
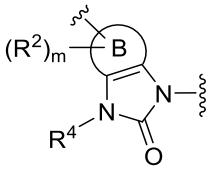
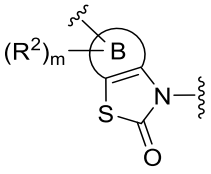
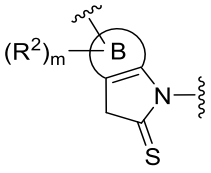
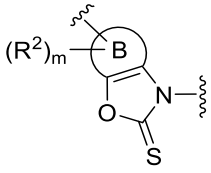
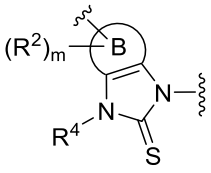
X^1 is a bivalent moiety selected from a covalent bond, $–CH_2–$, $–CHCF_3–$, $–SO_2–$, –S(O) –, –P(O)R–, –P(O)OR–, $–P(O)NR_2–$, –C(O)–, –C(S)–, or  ;

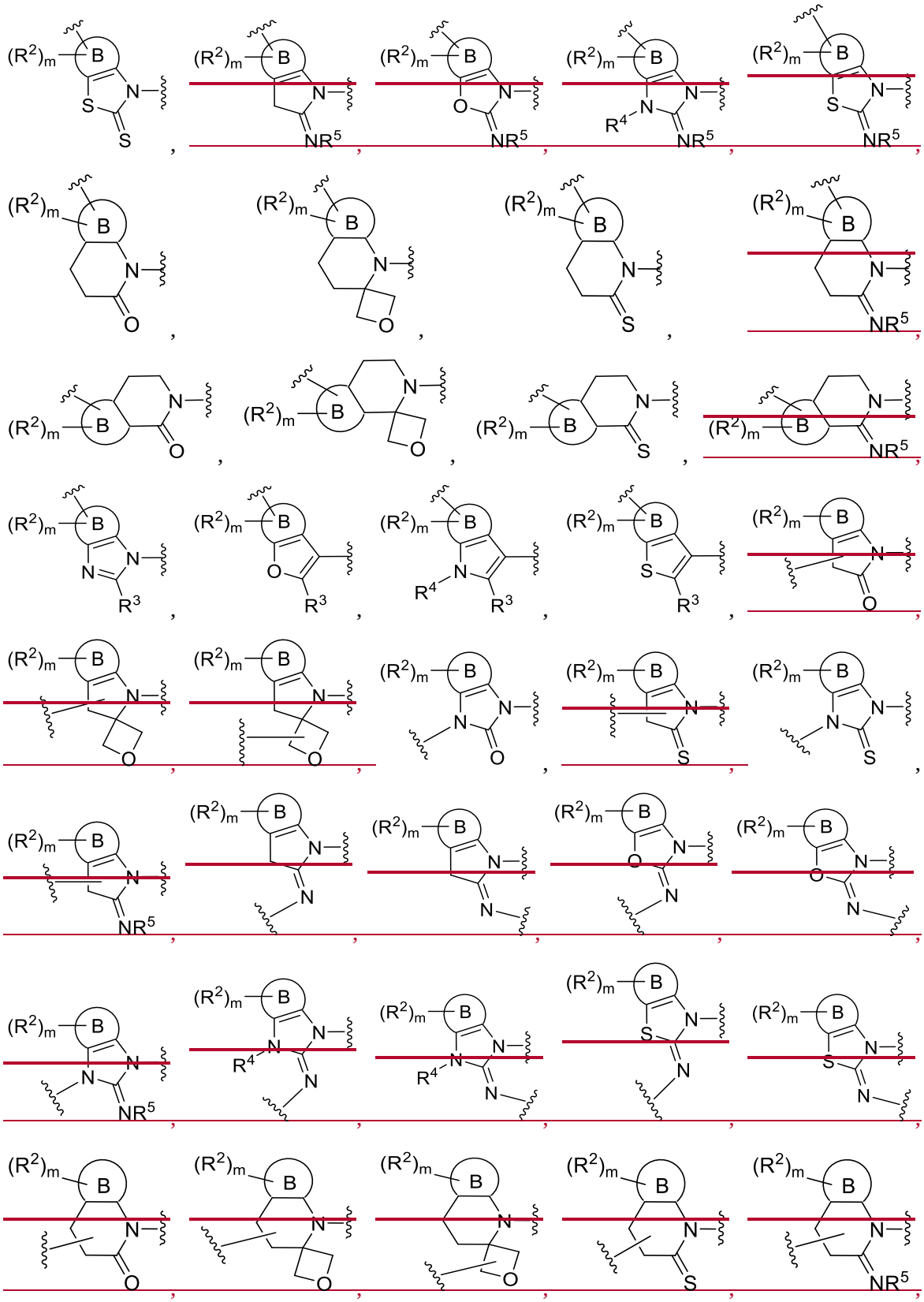
X^2 is a carbon atom or silicon atom;

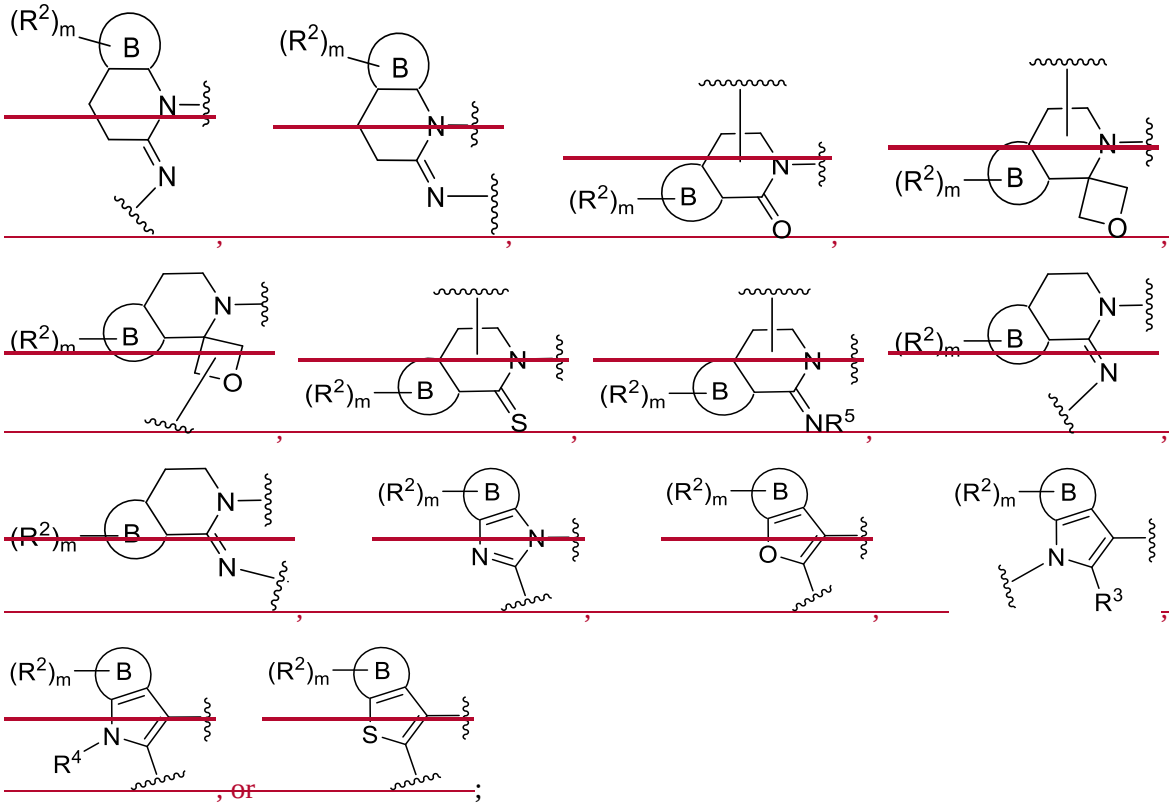
X^3 is a bivalent moiety selected from $–CR_2–$, –NR–, –O–, –S–, or $–Si(R_2)–$;

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^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 $–N(R)S(O)_2R$;

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





Ring B is 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 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;

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 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;

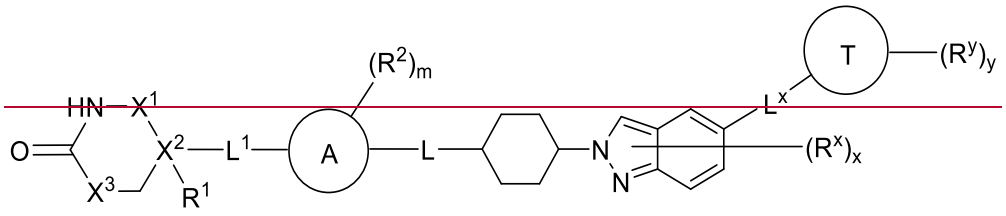
L^1 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, -S-, $-S(O)_2-$ or -(C)=CH-;

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

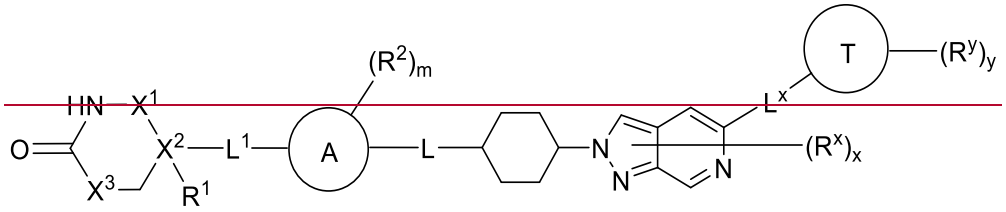
each R is independently ~~hydrogen, or an optionally substituted group~~ selected from hydrogen, C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring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

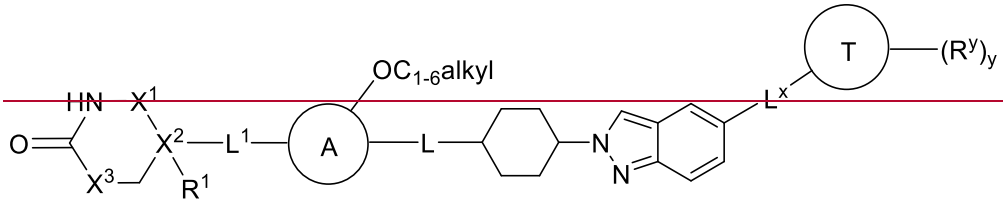
~~5. The compound of claim 4, wherein said compound is any one of the following formulae:~~



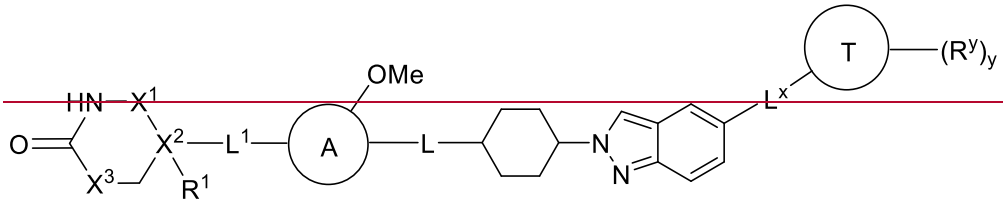
~~I-e-1~~



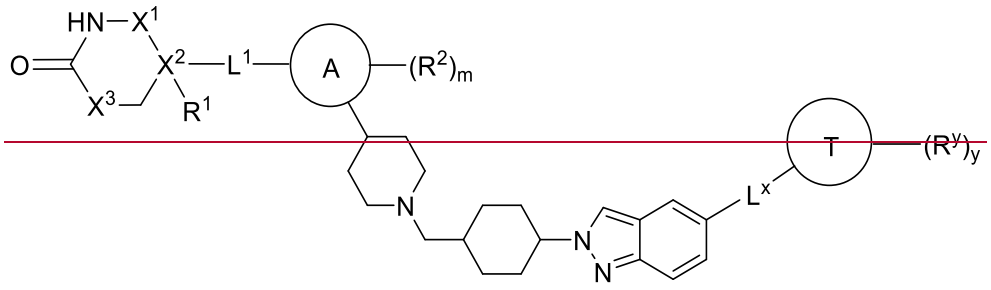
~~I-e-2~~



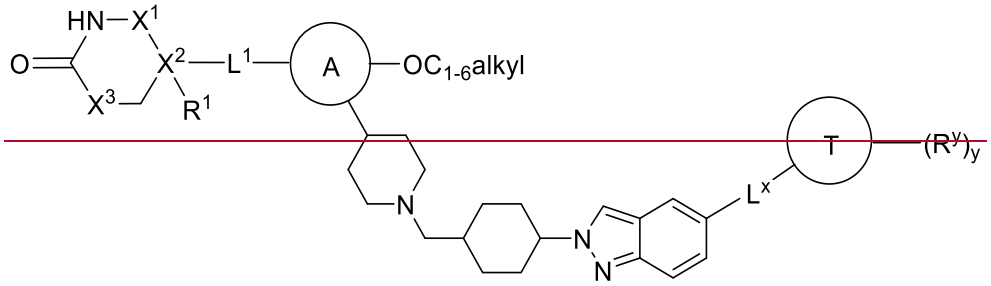
~~I-f-1~~



~~I-f-2~~



~~I-f-3~~



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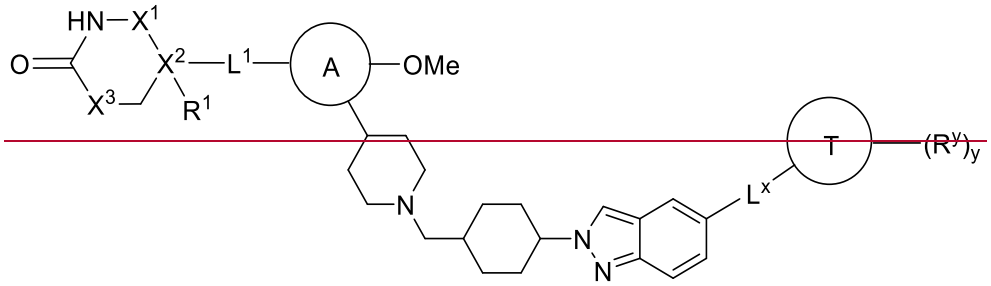
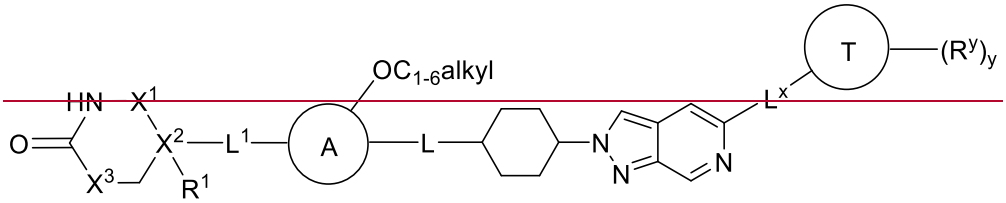
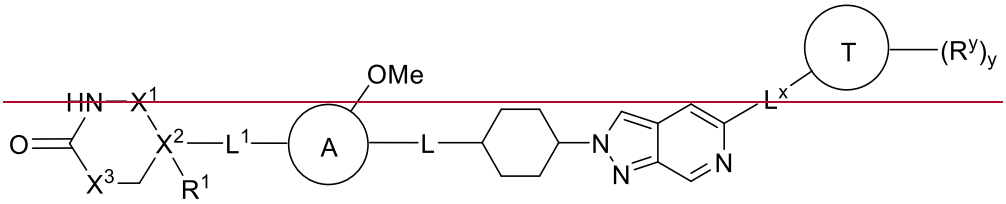


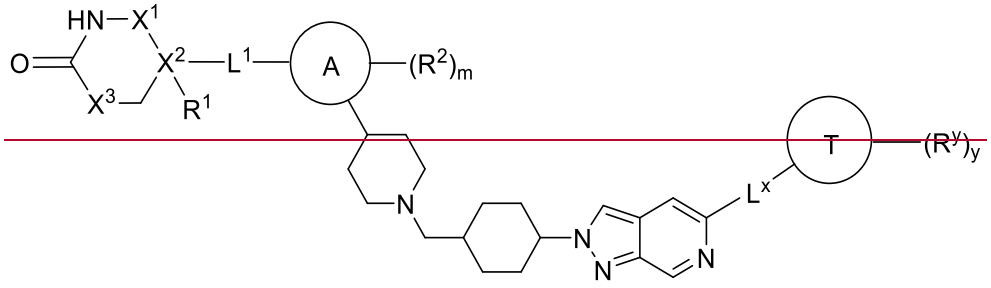
~~I-f-5~~



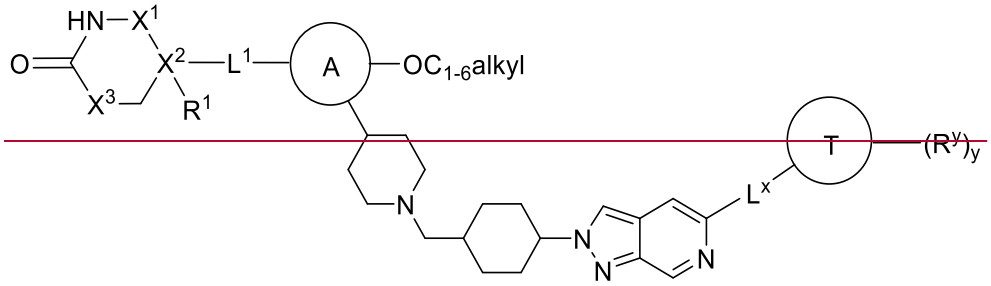
~~I-f-6~~



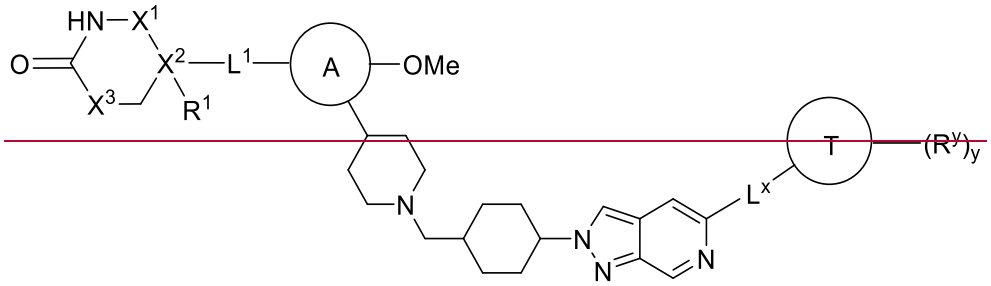
~~I-f-7~~



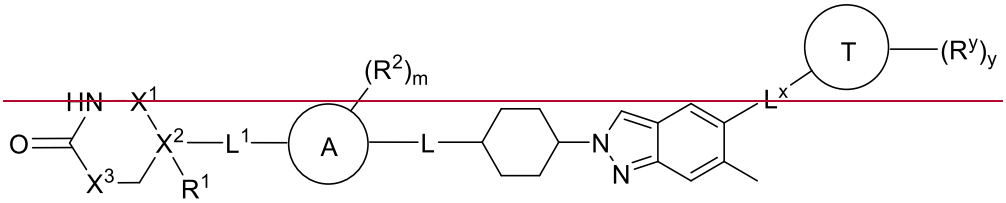
~~I-f-8~~



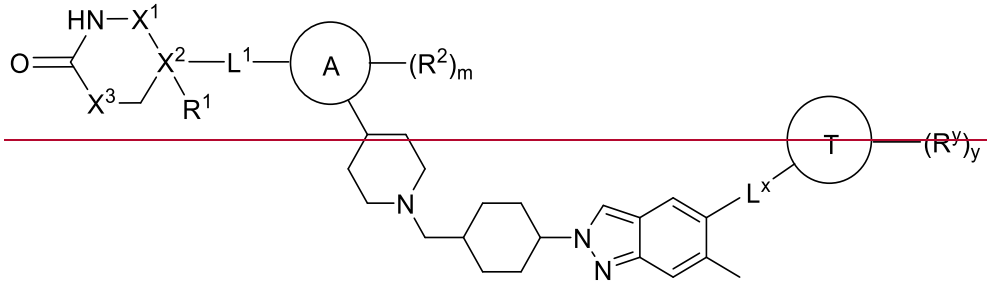
~~I-f-9~~



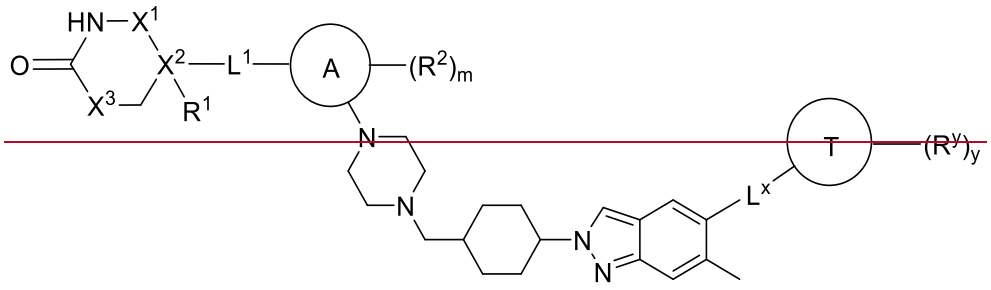
~~I-f-10~~



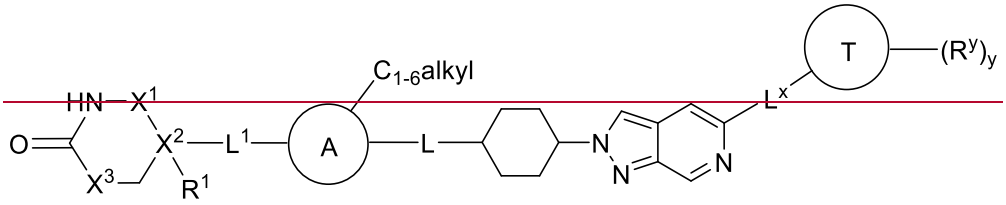
~~I-f-11~~



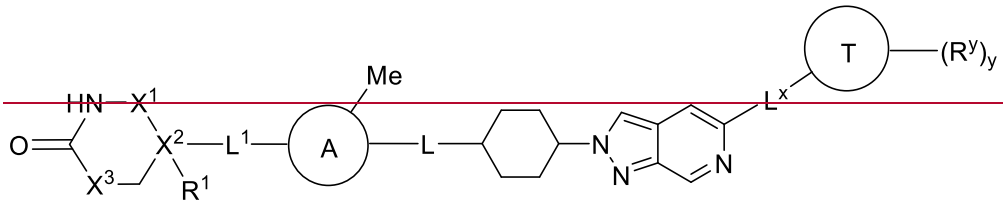
~~I-f-12~~



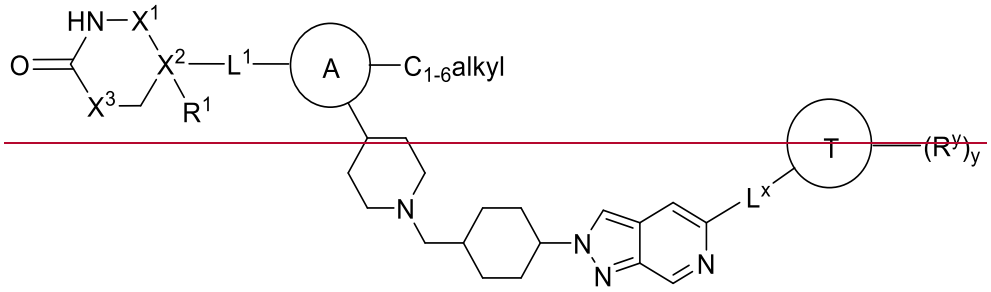
~~I-f-13~~



~~I-f-14~~



~~I-f-15~~



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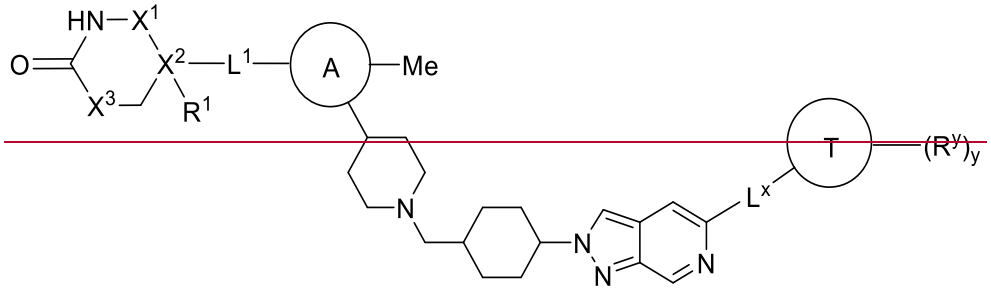
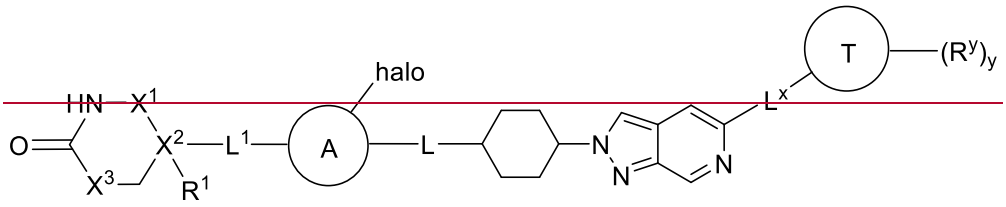
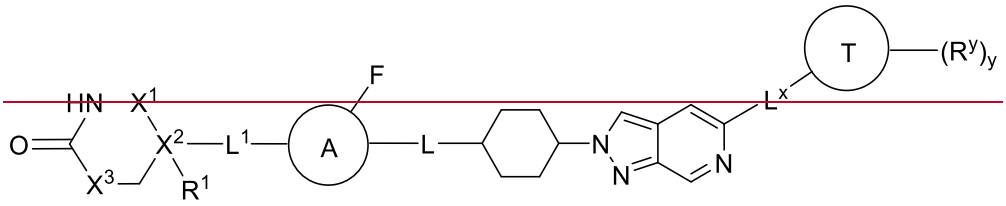


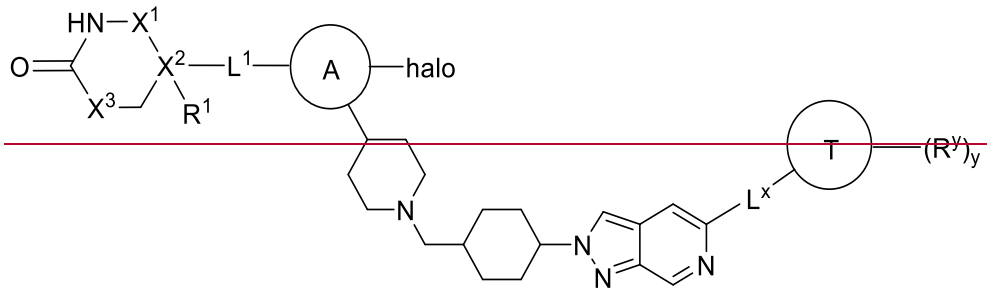
~~I-f-17~~



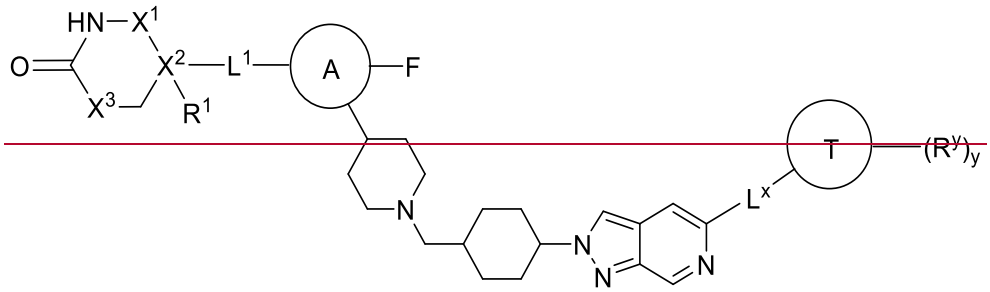
~~I f 18~~



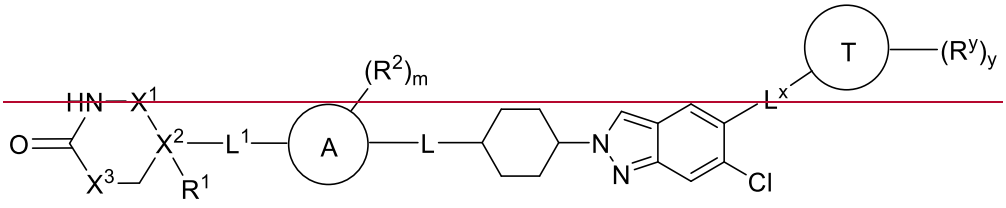
~~I f 19~~



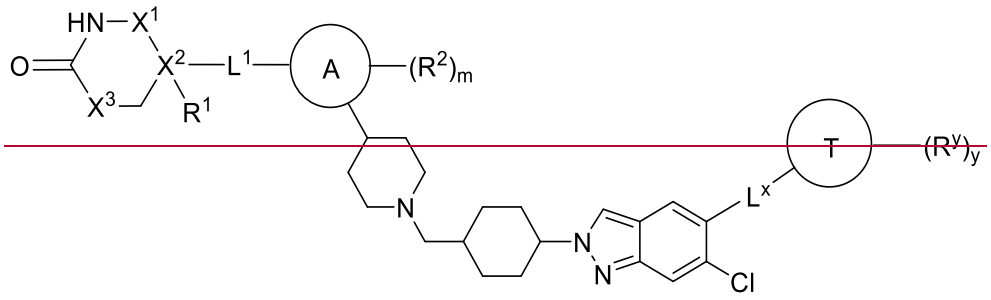
~~I f 20~~



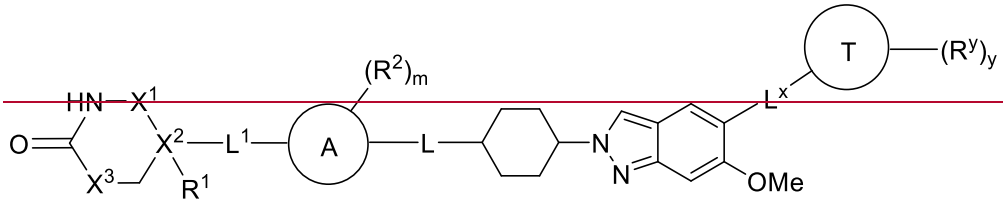
~~I f 21~~



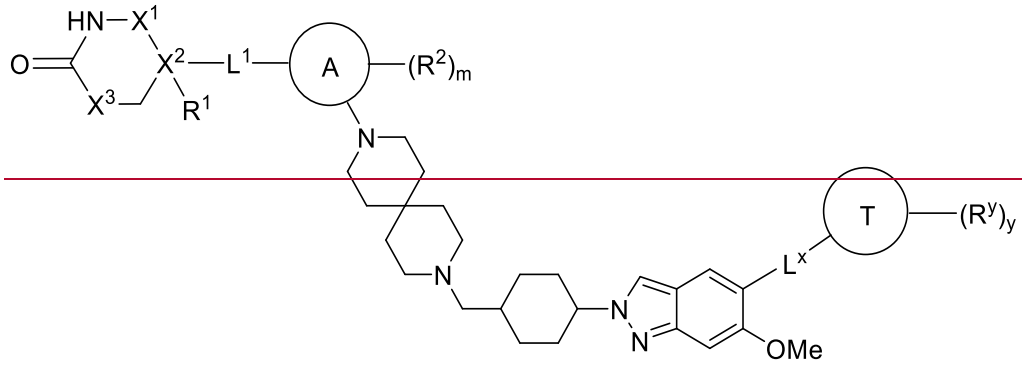
~~I f 22~~



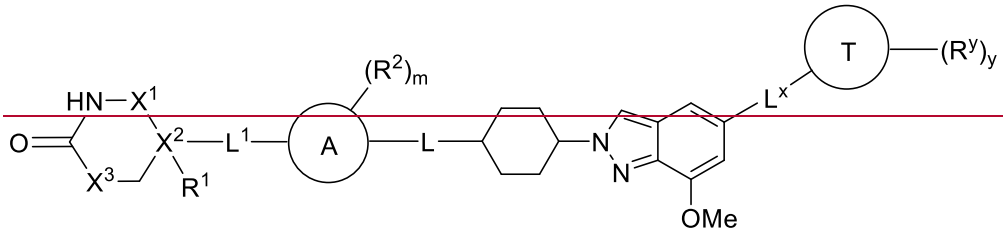
~~I f 23~~



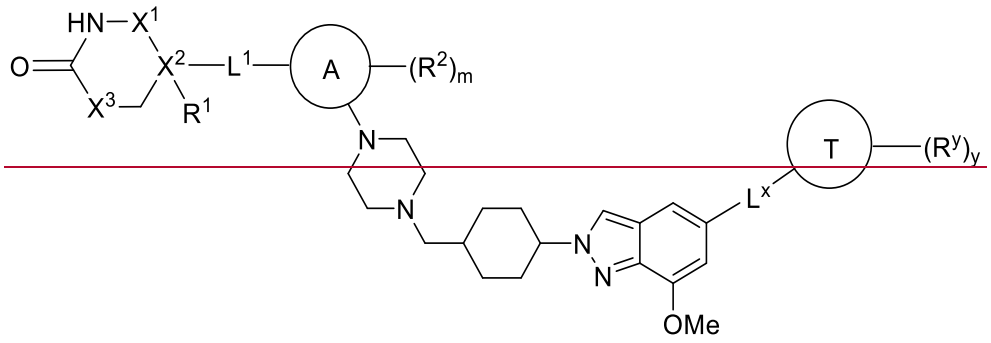
~~I f 24~~



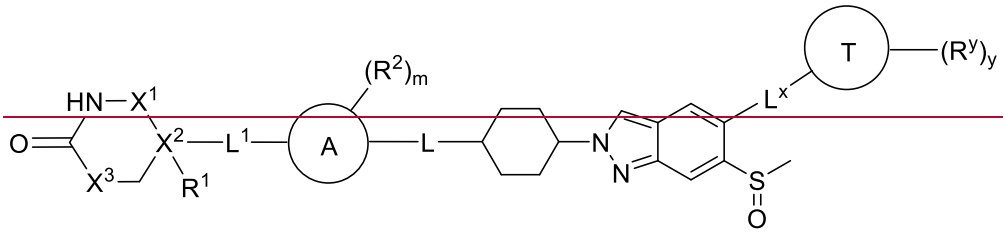
~~I f 25~~



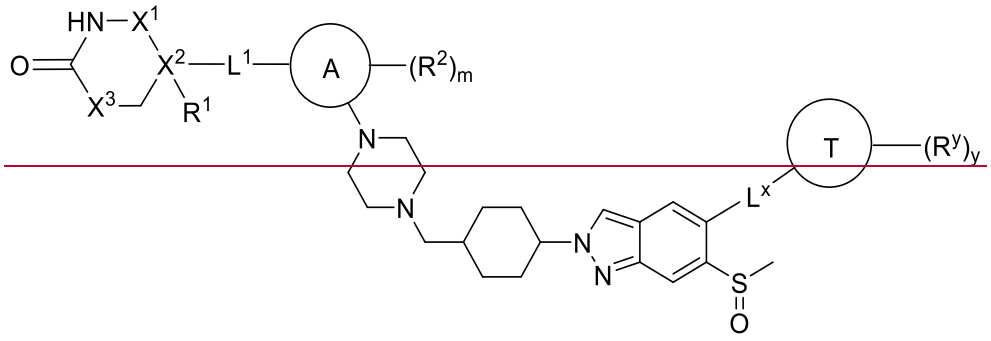
~~I f 26~~



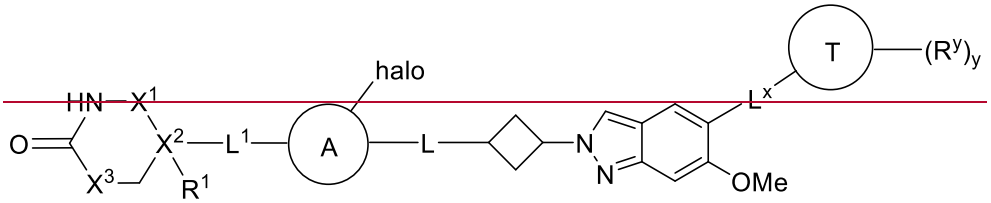
~~I f 27~~



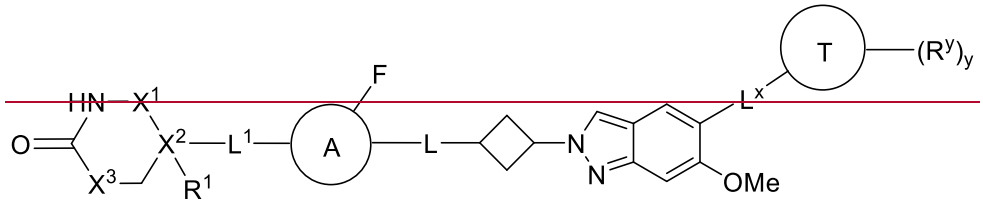
~~I f 28~~



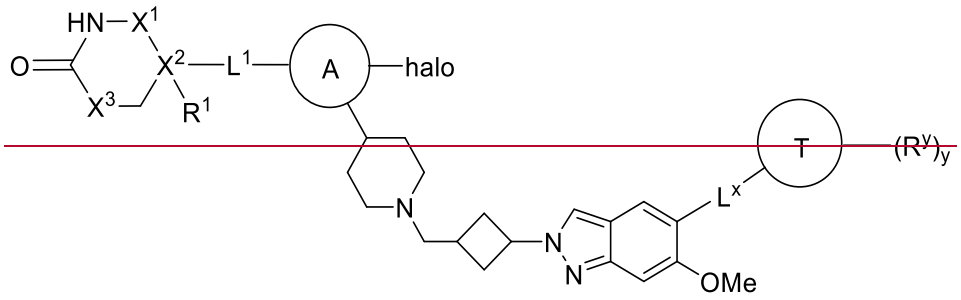
~~I f 29~~



~~I f 30~~



~~I f 31~~



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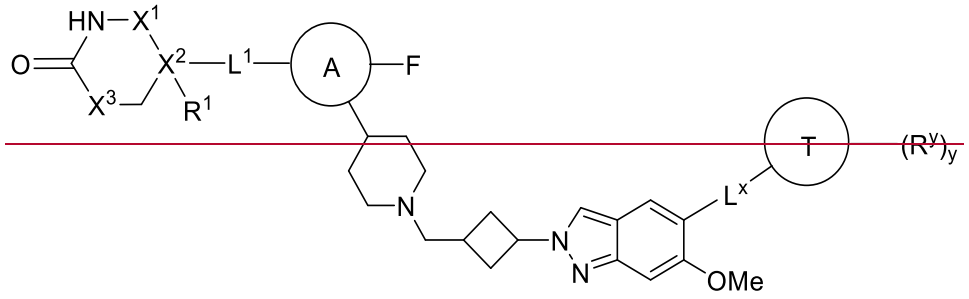
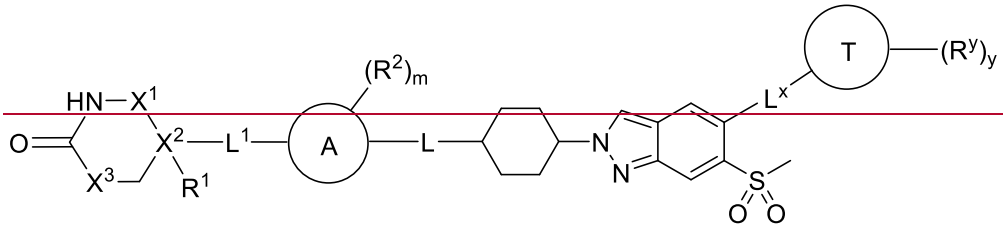
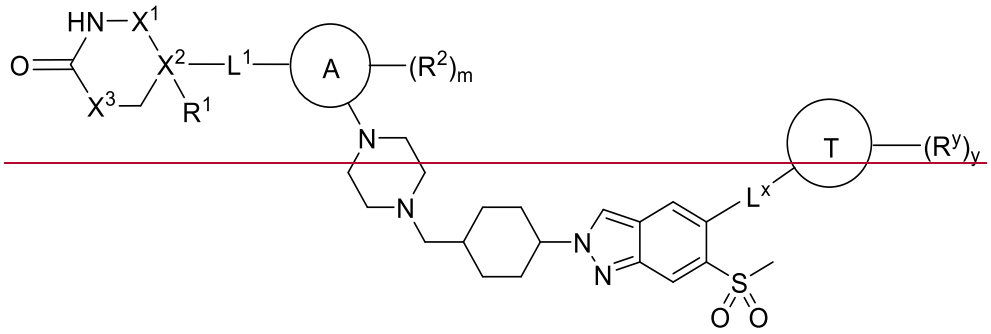


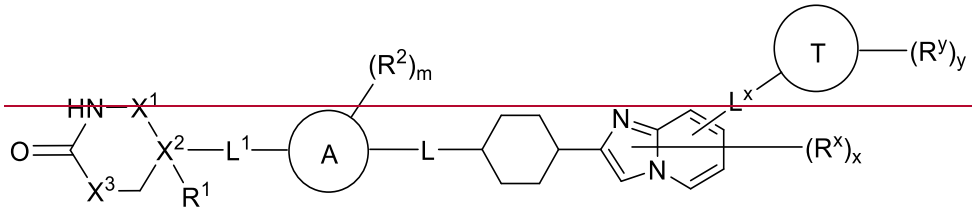
~~I f 33~~



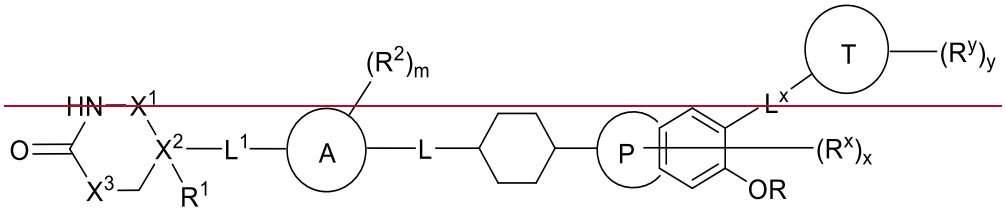
~~I f 34~~



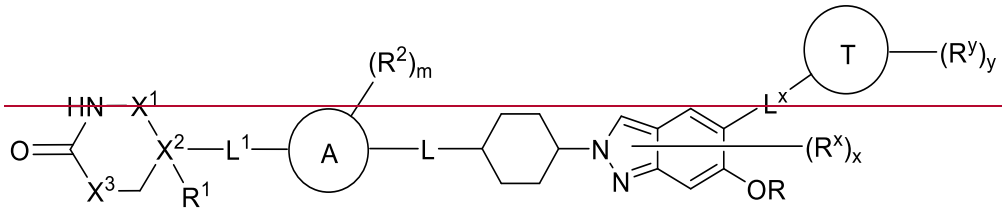
~~I f 35~~



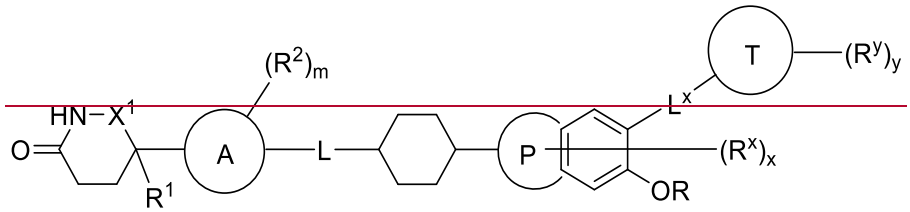
~~I-e-3~~



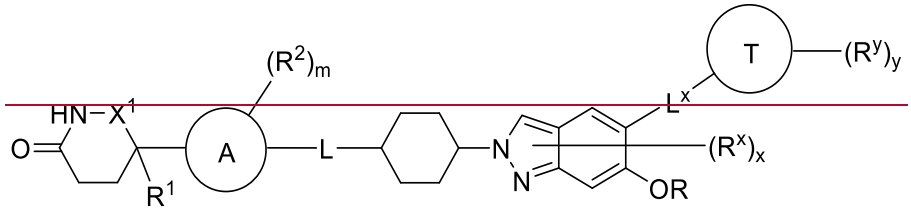
~~I-e-4~~



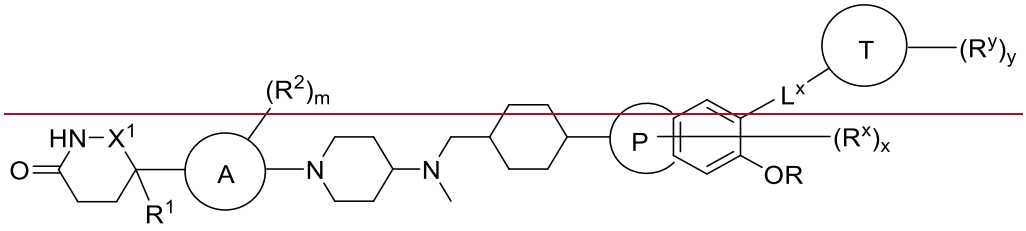
~~I-e-5~~



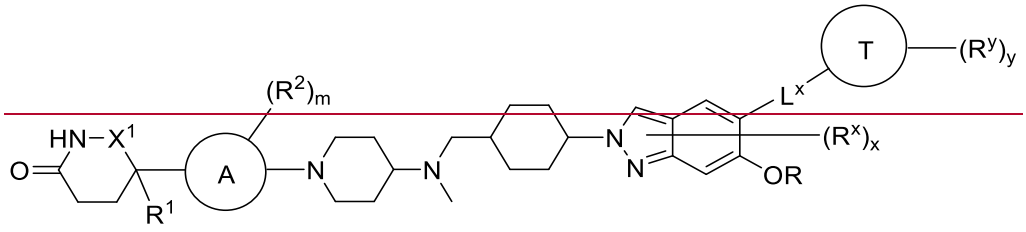
~~I-e-6~~



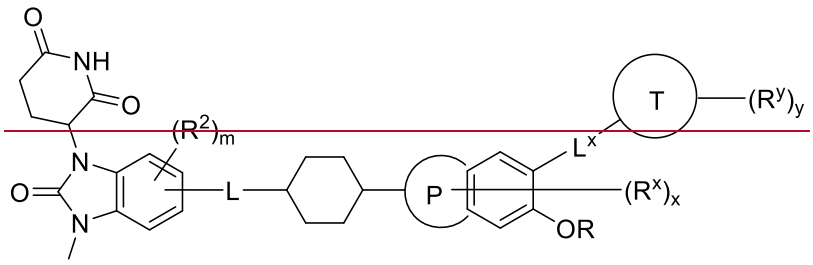
~~I-e-7~~



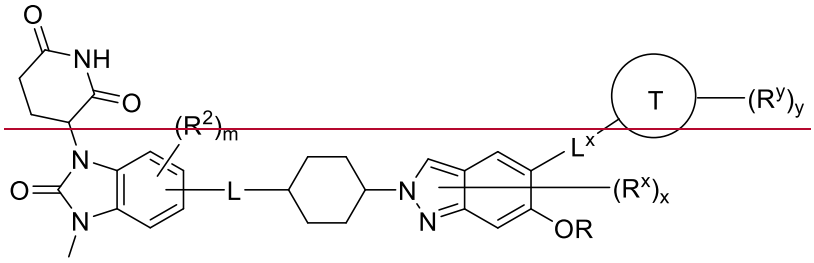
~~I-e-8~~



~~I-e-9~~



~~I-e-10~~

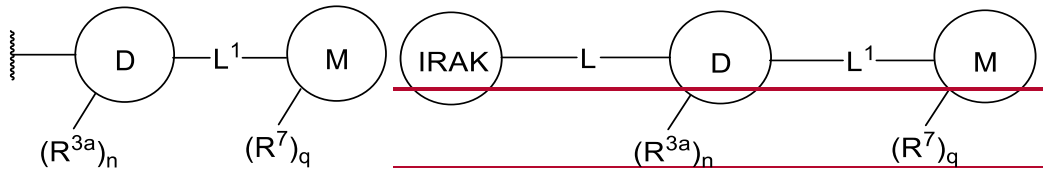


~~I-e-11~~

~~or a pharmaceutically acceptable salt thereof.~~

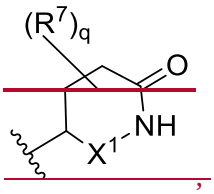
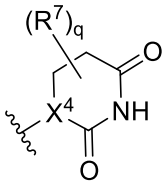
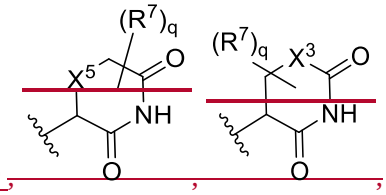
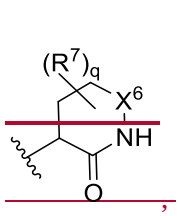
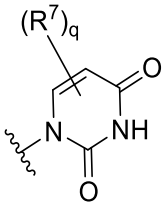
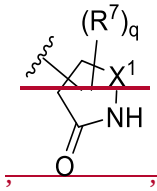
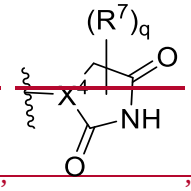
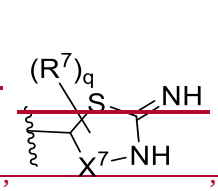
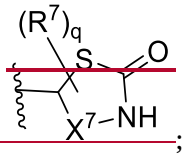
~~6. The compound of claim 3, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety and said compound is of formula **I-nn**:~~

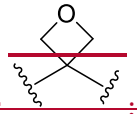
(ii)



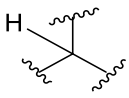
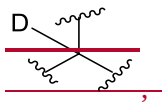
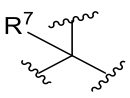
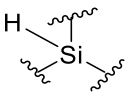
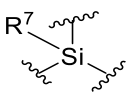
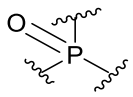
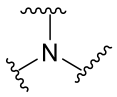
I-nn

or a pharmaceutically acceptable salt thereof, wherein:

Ring M~~E~~ is selected from  ,  , or  ,  ,  ,  ,  ,  , 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 selected from 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.

2. The compound of claim 1, wherein HET is a heteroaryl selected from indolyl, pyrrolo[1,2-b]pyridazine, pyrrolo[2,3-d]pyrimidinyl, pyrazolo[3,4-b]pyridinyl, pyrazolo[3,4-d]pyrimidinyl, and imidazo[4,5-b]pyridinyl.

3. The compound of claim 1 or claim 2, wherein R_a is H, F, Cl, —CN, —OH, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-4}hydroxyalkyl, or C_{1-4} alkoxy.

4. The compound of any one of claims 1-3, wherein R_b is H.

5. The compound of any one of claims 1-4, wherein R_1 is:

(i) C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} fluoroalkyl, C_{1-6} hydroxyalkyl, or C_{1-8} hydroxy-fluoroalkyl;

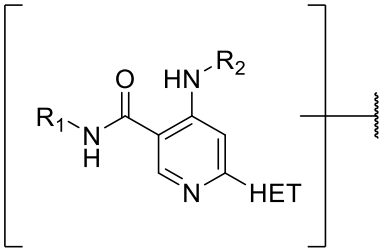
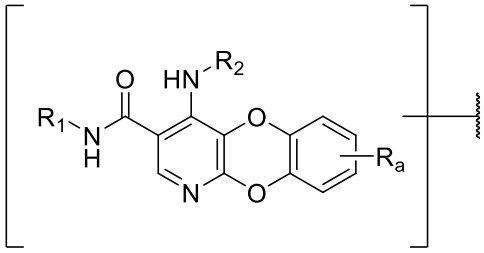
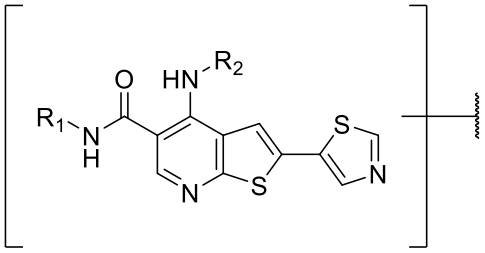
(ii) C_{3-6} cycloalkyl substituted with zero to 3 substituents independently selected from F, —OH, —CN, C_{1-3}alkyl, and C_{1-3} alkoxy;

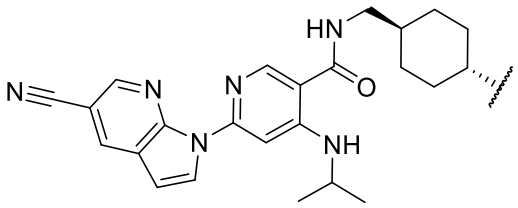
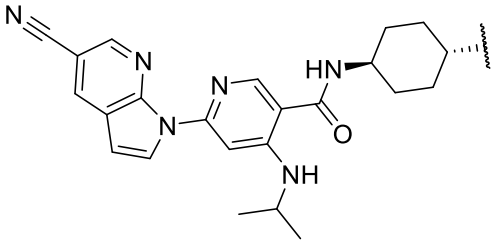
(iii) tetrahydropyranyl or piperidinyl, each substituted with zero to 1 substituent selected from —OH, C_{1-3} alkyl, C_{1-3} fluoroalkyl, C_{1-4} hydroxyalkyl, and C_{1-3}alkoxy.

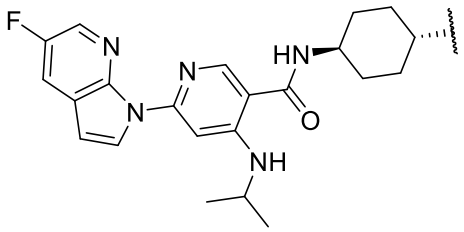
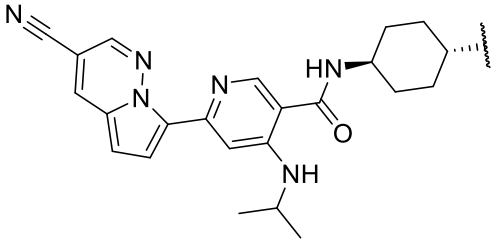
6. The compound of any one of claims 1-5, wherein R_2 is:

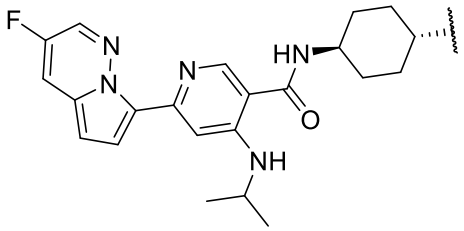
(i) C_{1-7} alkyl substituted with zero to three substituents independently selected from F, —OH, and —CN; or

(ii) C_{3-6} cycloalkyl, azetidinyl, oxetanyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, or tetrahydropyranyl, each substituted with zero to 3 substituents independently selected from F, —OH, C_{1-3}alkyl, and C_{1-3} hydroxyalkyl.

7. The compound of any one of claims 1-6, wherein  ,  , or  is:

 ,  ,

 ,  ,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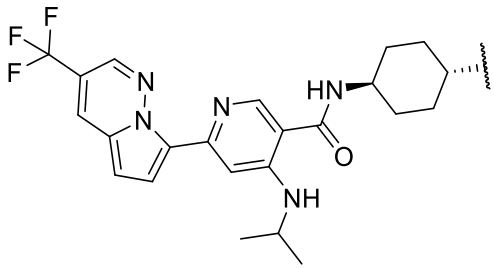
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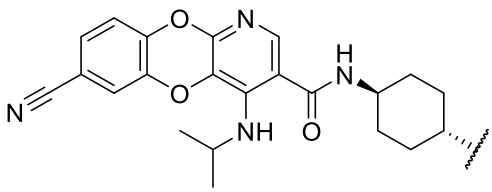
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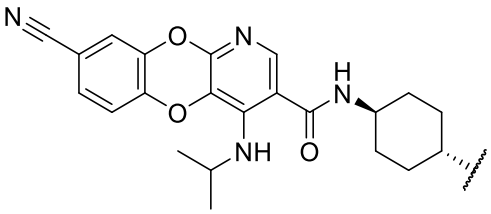
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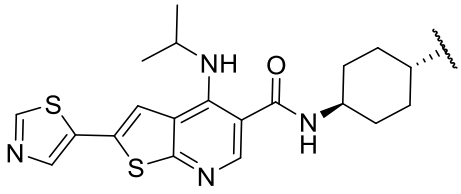
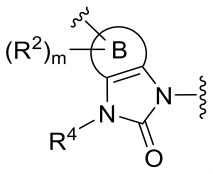
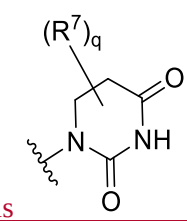

.

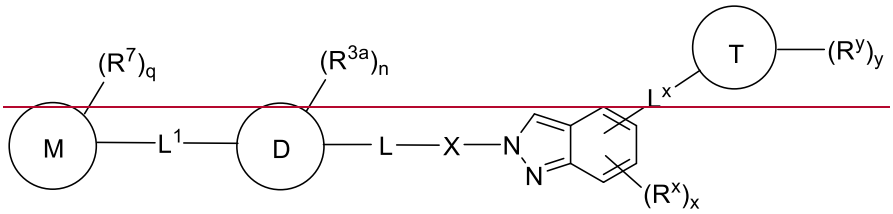
8. The compound of any one of claims 1-7, wherein Ring A is  .

9. The compound of any one of claims 1-8, wherein Ring B is a fused 6-membered aryl.

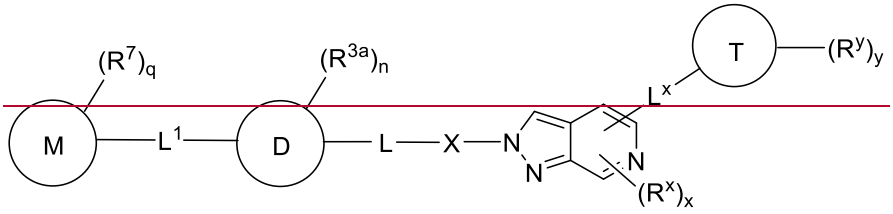
10. The compound of any one of claims 1-9, wherein Ring M is  .

11. The compound of any one of claims 1-10, wherein Ring D is a 6 to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

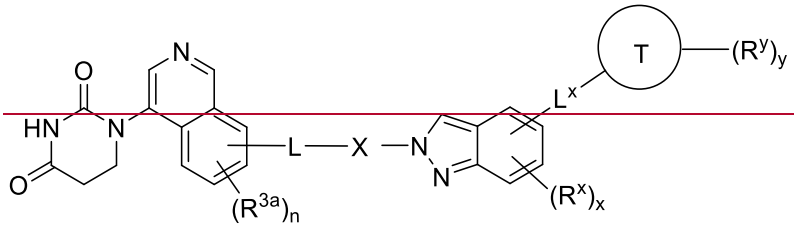
~~7. The compound of claim 6, wherein said compound is any one of the following formulae:~~



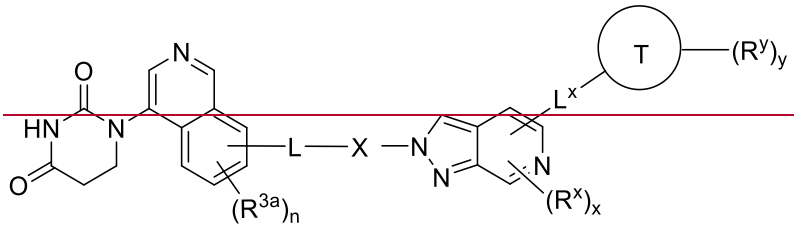
~~I e-12~~



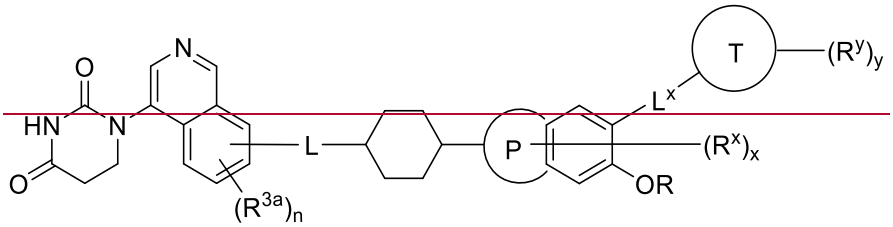
~~I e-13~~



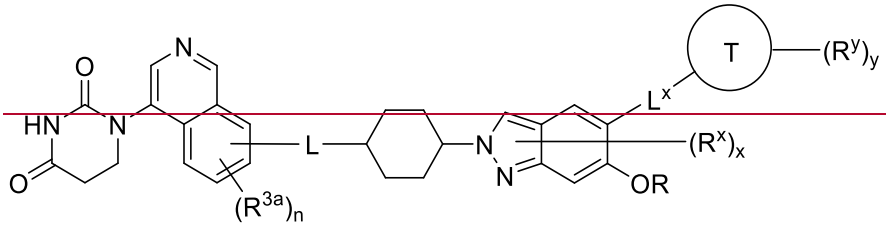
~~I e-14~~



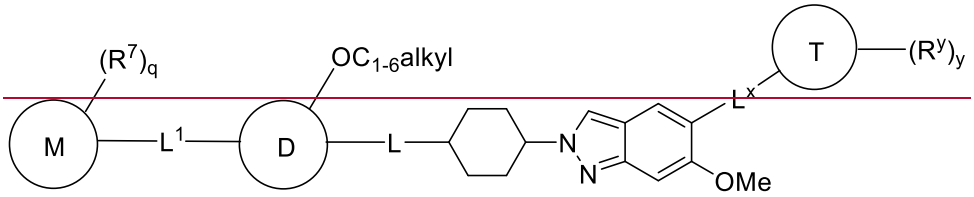
~~I e-15~~



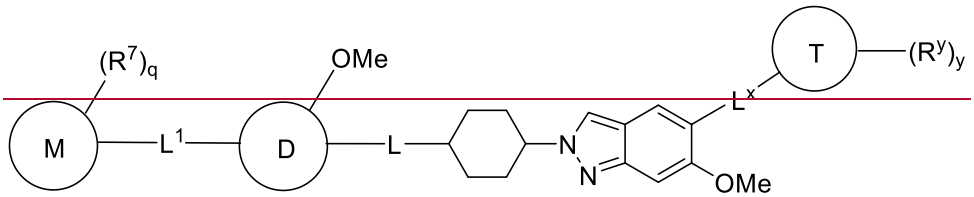
~~I e-16~~



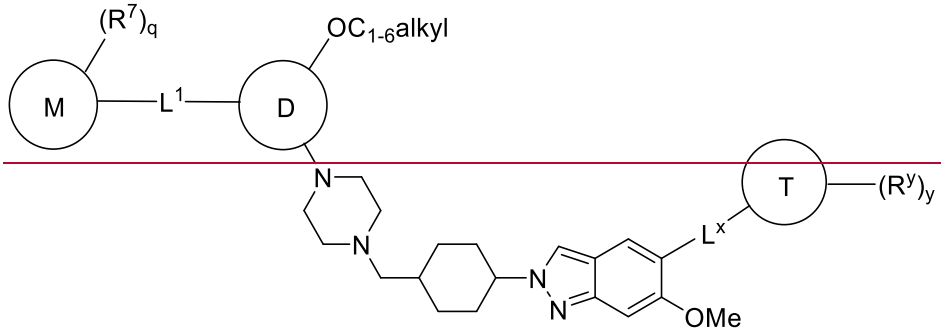
~~I-e-17~~



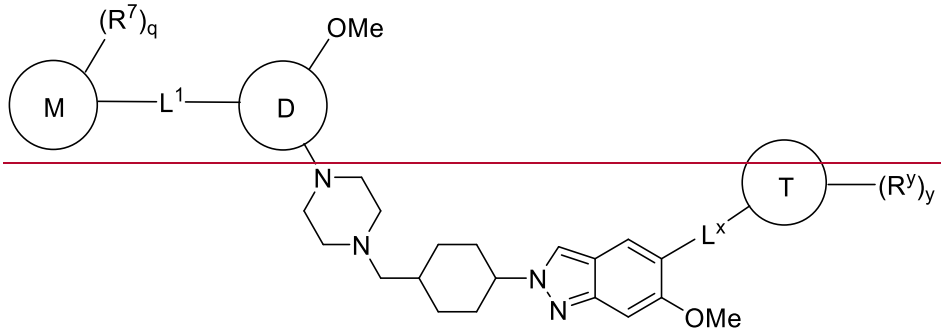
~~I-e-18~~



~~I-e-19~~



~~I-e-20~~

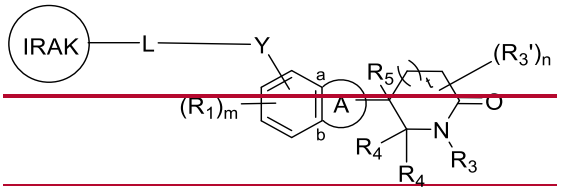


~~I-e-21~~

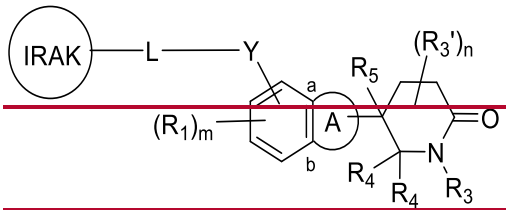
~~or a pharmaceutically acceptable salt thereof.~~

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

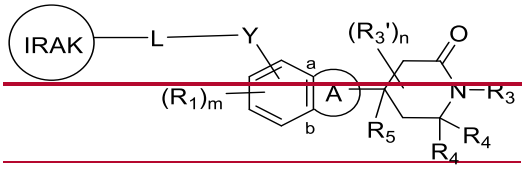
~~(*i*)~~



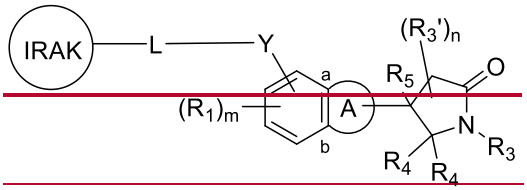
~~I oo-1~~



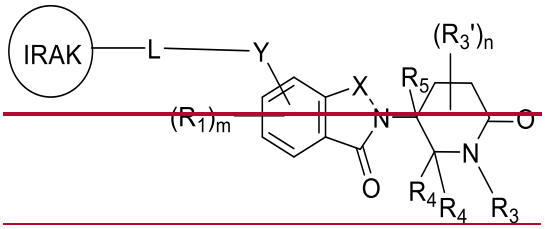
~~I oo-2~~



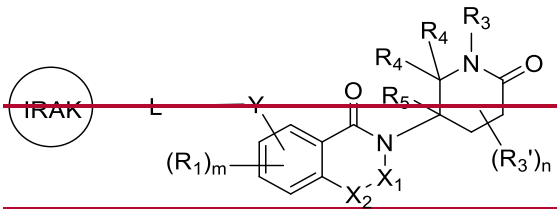
~~I oo-3~~



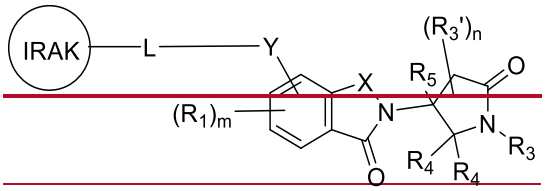
~~I oo-4~~



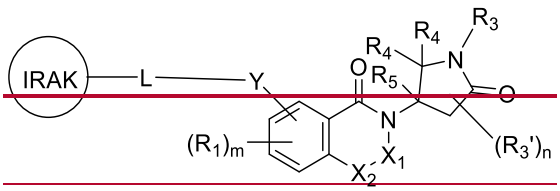
~~I oo-5~~



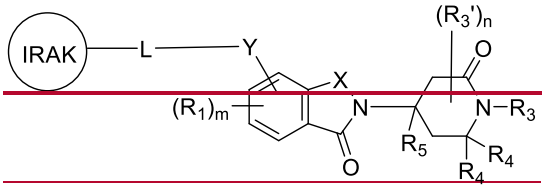
~~I oo-6~~



~~I oo-7~~



~~I oo-8~~



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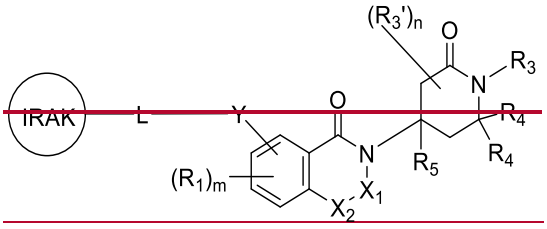
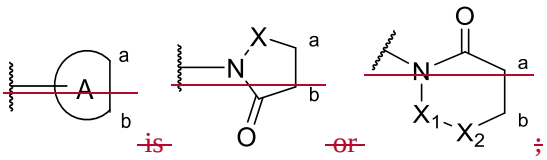


~~I oo-10~~

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



is or ;

Y is a bond, Y_1, O, NH, NR_2, C(O)O, OC(O), C(O)NR_2', NR_2'C(O), Y_1—O, Y_1—NH, Y_1—NR_2, Y_1—C(O), Y_1—C(O)O, Y_1—OC(O), Y_1—C(O)NR_2', or Y_1—NR_2'C(O), wherein Y_1 is C_1-C_6 alkylene, C_2-C_6 alkenylene, or C_2-C_6 alkynylene;

X is C(O) or $C(R_3)_2$;

X_1-X_2 is $C(R_3)$=N or $C(R_3)_2$—$C(R_3)_2$;

each R_1 is independently halogen, nitro, NH_2, OH, C(O)OH, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

R_2 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C(O)—C_1-C_6 alkyl, C(O)—C_2-C_6 alkenyl, C(O)—C_3-C_8 cycloalkyl, or C(O) 3- to 8-membered heterocycloalkyl, and R_2 is optionally substituted with one or more of halogen, $N(R_a)_2$, $NHC(O)R_a$, $NHC(O)OR_a$, OR_b, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each of the C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6-C_{10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more of halogen, NH_2, CN, nitro, OH, C(O)OH, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkoxy;

R_2' is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, or 3- to 8-membered heterocycloalkyl, and R_2', 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, C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein each of the C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6-C_{10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more of halogen, NH_2, CN, nitro, OH, C(O)OH, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkoxy;

each R_3 is independently H or C_1-C_3 alkyl optionally substituted with C_6-C_{10} aryl or 5- to 10-membered heteroaryl;

each R_3' is independently C_1-C_3 alkyl;

each R_4 is independently H or C_1-C_3 alkyl; or two R_4, together with the carbon atom to which they are attached, form C(O), a C_3-C_6 carbocycle, or a 4-, 5-, or 6-membered heterocycle comprising 1 or 2 heteroatoms selected from N and O;

R_5 is H, C_1-C_3 alkyl, F, or Cl;

each R_a independently is H or C_1-C_6 alkyl;

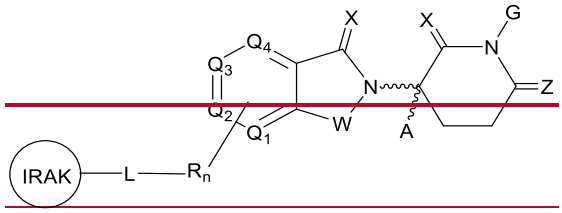
R_b is H or tosyl;

t is 0 or 1;

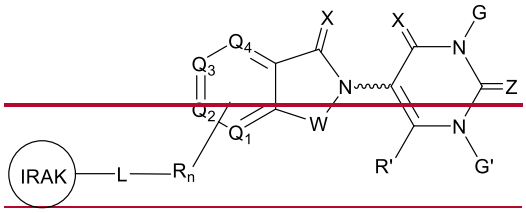
m is 0, 1, 2 or 3; and

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

~~(*ii*)~~



~~I pp-1~~



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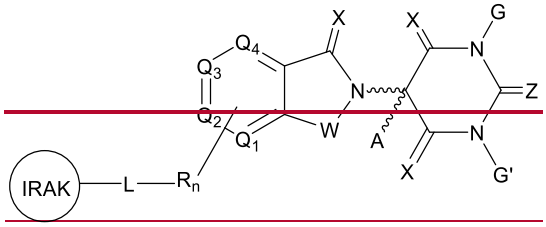

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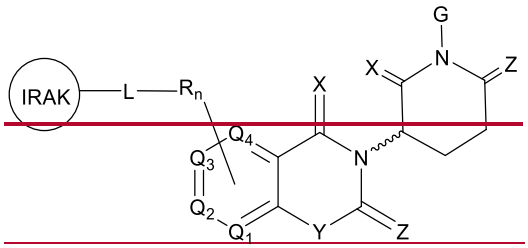

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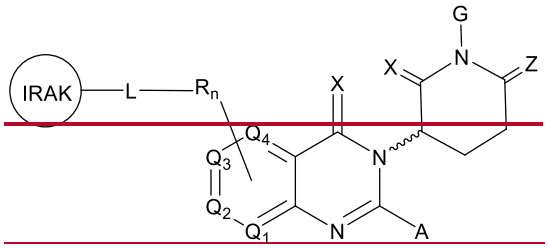

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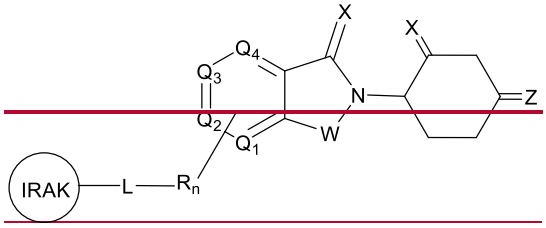
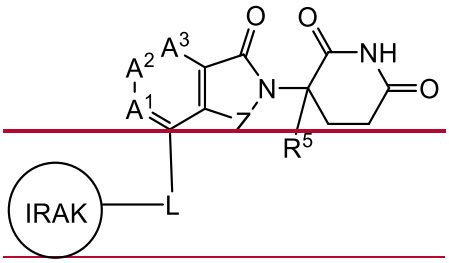


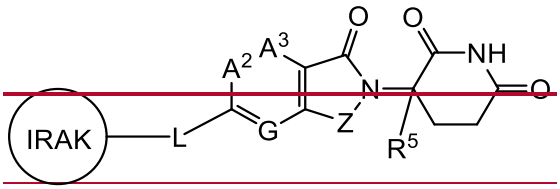
~~I pp-6~~

~~or a pharmaceutically acceptable salt thereof, and wherein each of the variables A, G, G', Q_1, Q_2, Q_3, Q_4, R, R', W, X, Y, Z, ····, and n is as defined and described in WO 2016/197114 and US 2018/0147202;~~

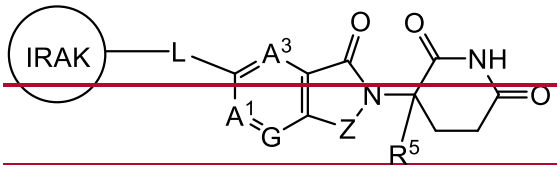
~~(*iii*)~~



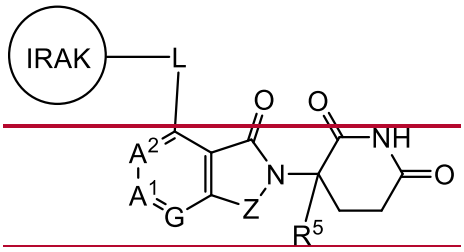
~~I zz-1~~



~~I-zz-2~~



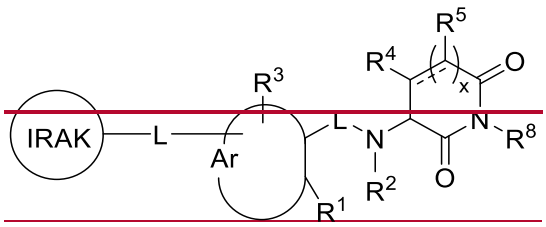
~~I-zz-3~~



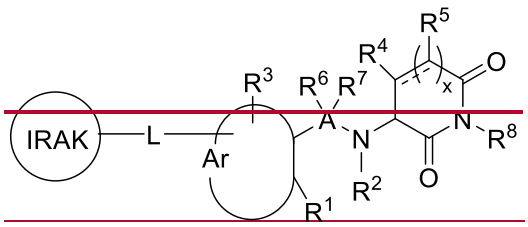
~~I-zz-4~~

~~or a pharmaceutically acceptable salt thereof, and wherein each of the variables A^1, A^2, A^3, R^5, G and Z is as defined and described in WO 2017/176958;~~

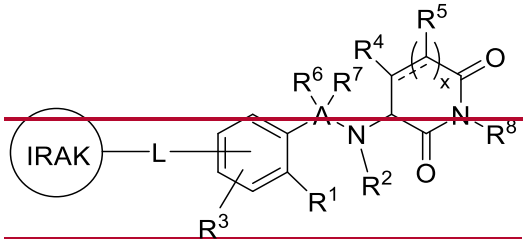
~~(*iv*)~~



~~I-tt-1~~



~~I-tt-2~~



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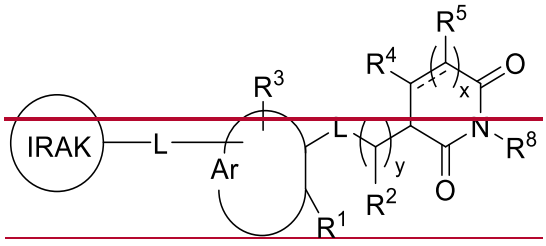
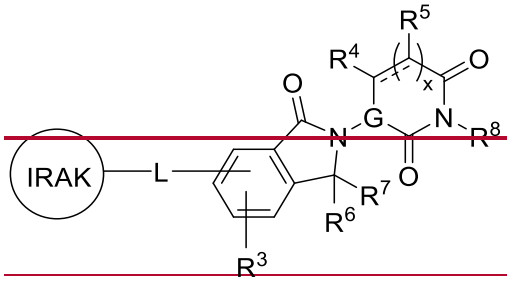
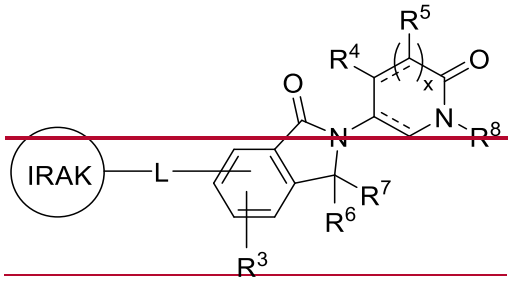


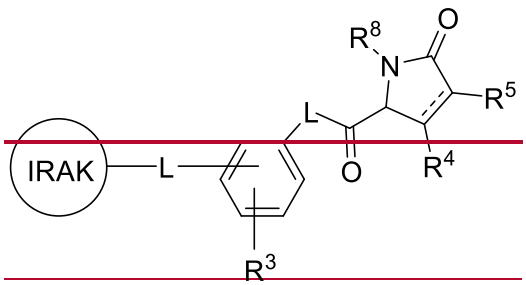
~~I-tt-4~~



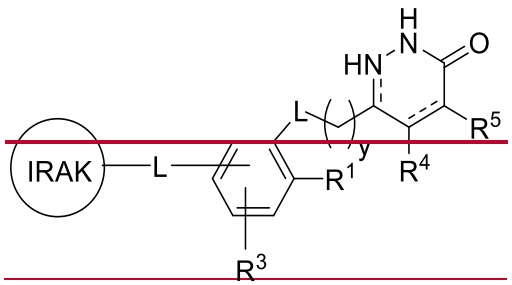
~~I-tt-5~~



~~I-tt-6~~



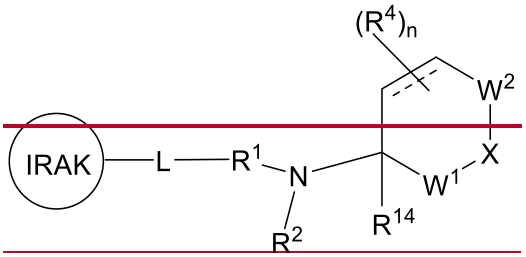
~~I-tt-7~~



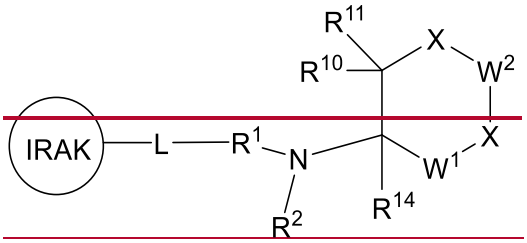
~~I-tt-8~~

~~or a pharmaceutically acceptable salt thereof, and wherein each of the variables Ar, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, A, L, x, y, and ═══ is as described and defined in WO 2017/161119;~~

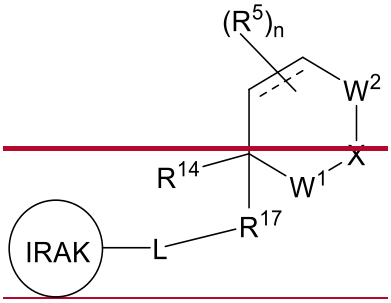
~~(v)~~



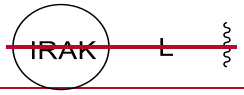
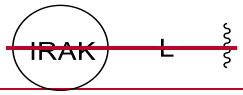
~~I-qq-1~~



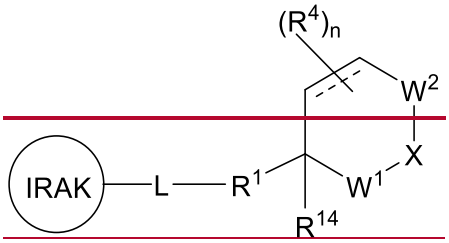
~~I-qq-2~~



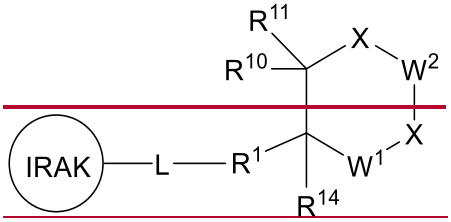
~~I-qq-3~~

~~or a pharmaceutically acceptable salt thereof, wherein each of the variables R^1, R^2, R^4, R^5, R^{10}, R^{11}, R^{14}, R^{17}, W^1, W^2, X, ═══, and n is as defined in WO 2017/197051, and wherein~~  ~~is attached to R^1, the ring formed by combining R^1 and R^2, or R^{17} at the site of attachment of R^{12} as defined in WO 2017/197051 such that~~  ~~takes the place of the R^{12} substituent;~~

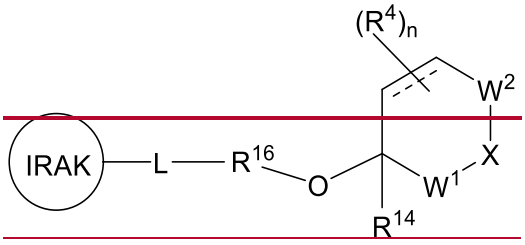
~~(*vi*)~~



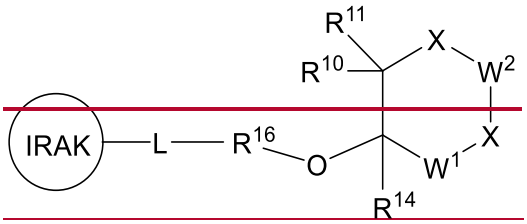
~~I-rr-1~~



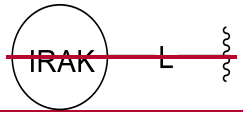
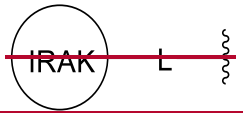
~~I-rr-2~~



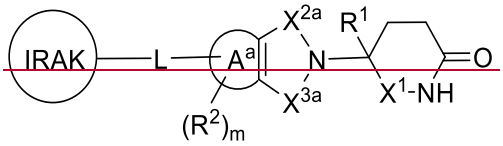
~~I-rr-3~~



I-rr-4

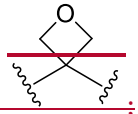
or a pharmaceutically acceptable salt thereof, wherein each of the variables R^1, R^4, R^{10}, R^{11}, R^{14}, R^{16}, W^1, W^2, X, ═══, and n is as defined in WO 2018/237026, and wherein  is attached to R^1 or R^{16} at the site of attachment of R^{12} as defined in WO 2018/237026, such that  takes the place of the R^{12} substituent; or

(v)



I-ccc-1

or a pharmaceutically acceptable salt thereof, wherein:

each of X^1, X^{2a}, and X^{3a} is independently a bivalent moiety selected from a covalent bond, CH_2, C(O), C(S), or  ;

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

each of R^2 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 $N(R)S(O)_2R$;

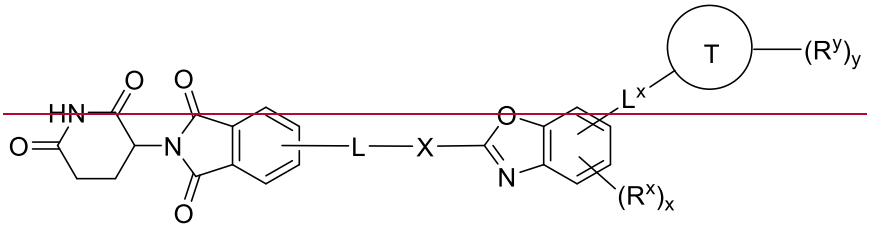
Ring A^a is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5- to 7-membered partially saturated carbocyclyl, 5- to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 5-membered heteroaryl with 1-3 heteroatoms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

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

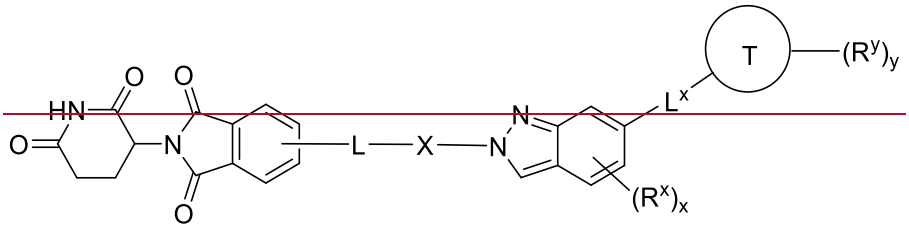
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

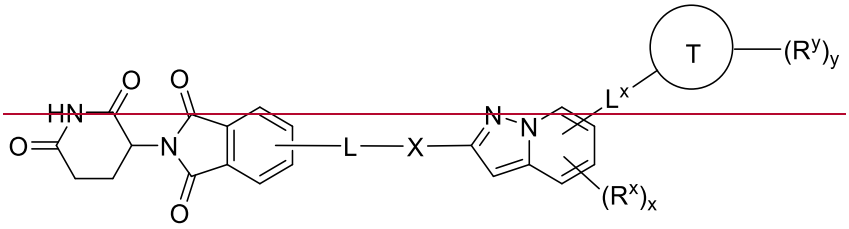
9. The compound of claim 8, wherein said compound is any one of the following formulae:



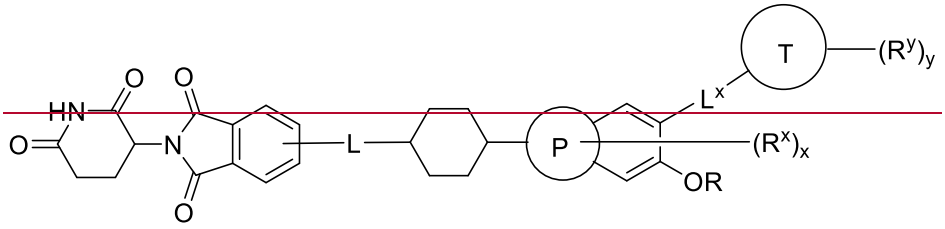
I j-1



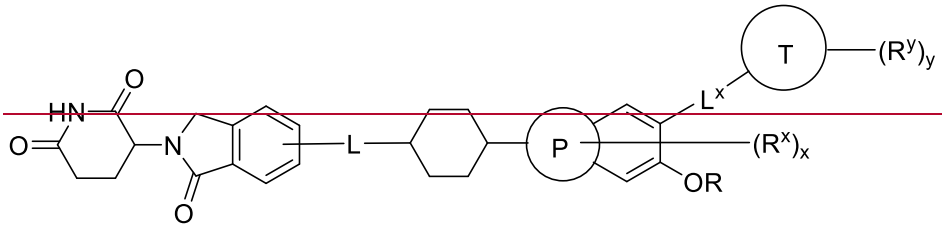
I j-3



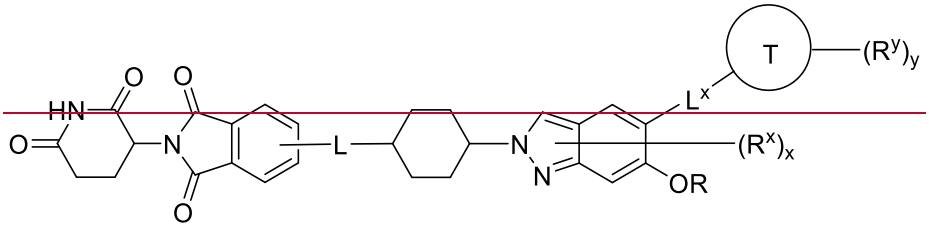
I j-4



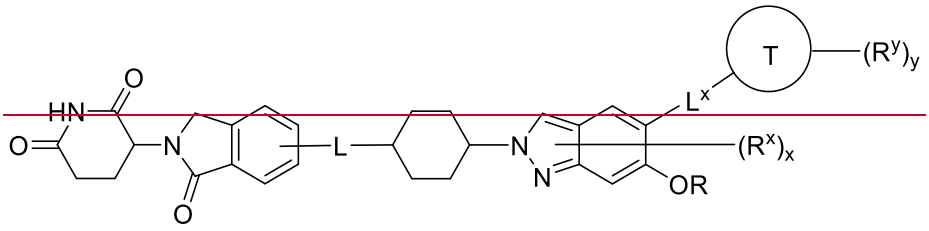
I k-2



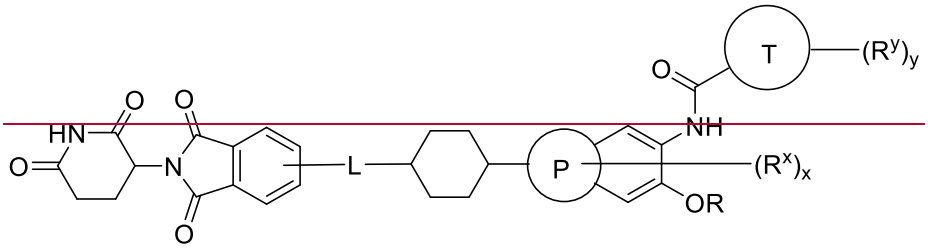
~~I k-3~~



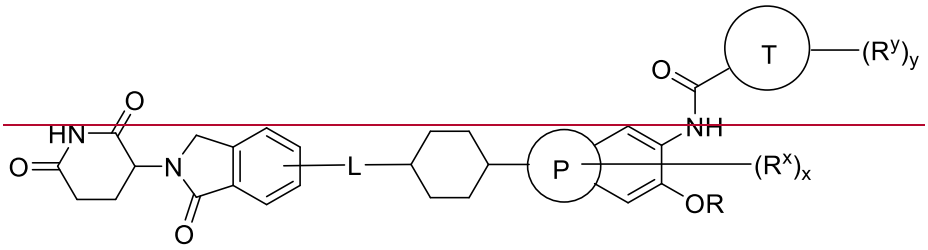
~~I k-4~~



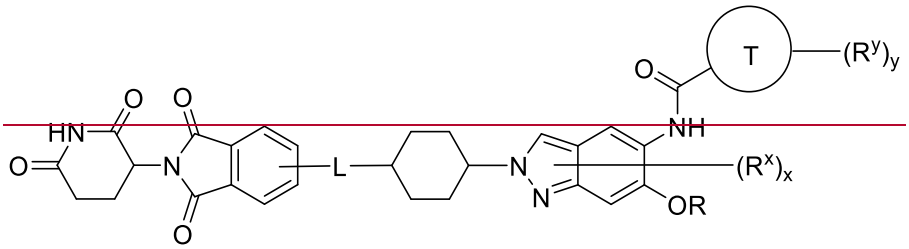
~~I k-5~~



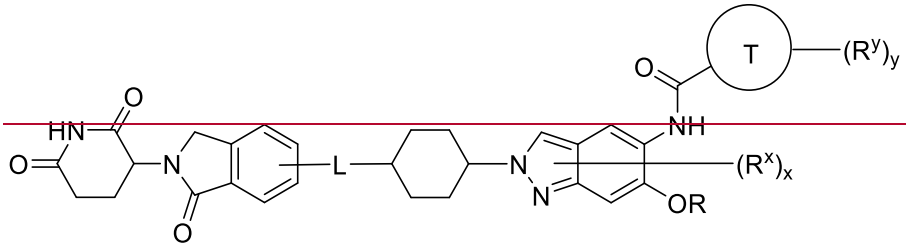
~~I k-6~~



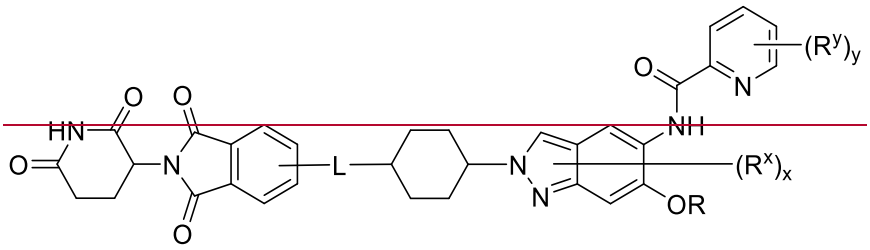
~~I k-7~~



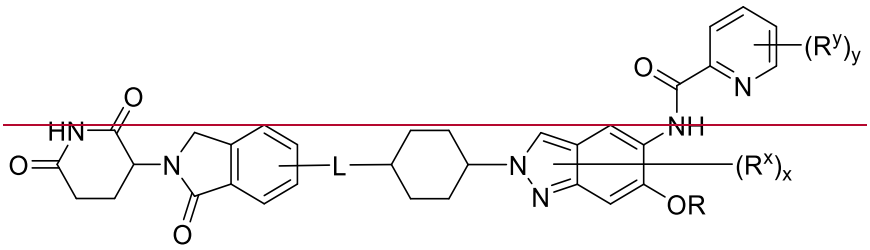
~~I k-8~~



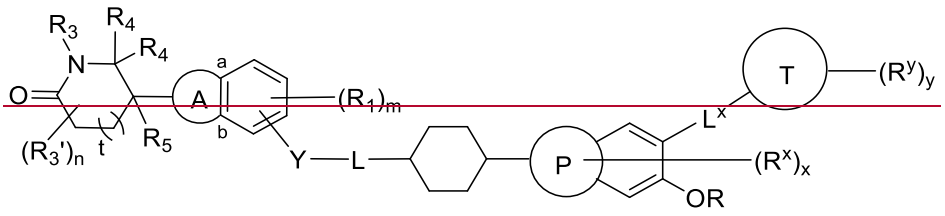
~~I k-9~~



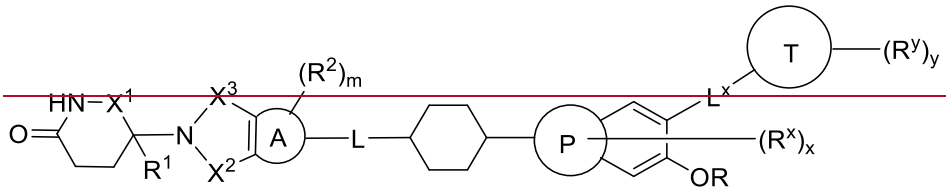
~~I k-10~~



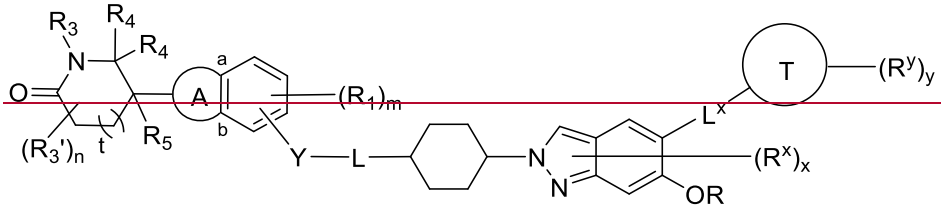
~~I k-11~~



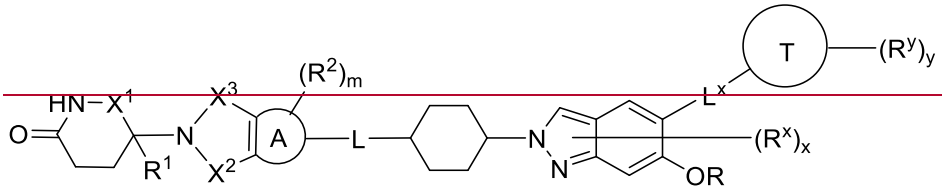
~~I k-12~~



~~I k-13~~



~~I k-14~~

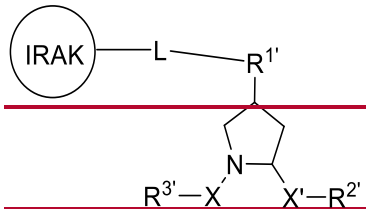


~~I k-15~~

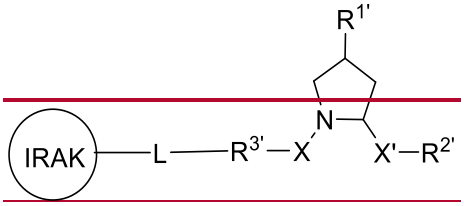
~~or a pharmaceutically acceptable salt thereof.~~

~~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:~~

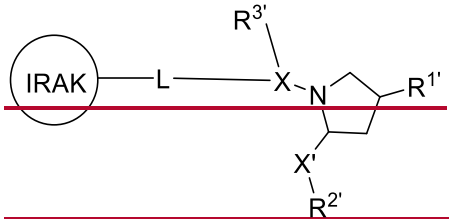
~~(i)~~



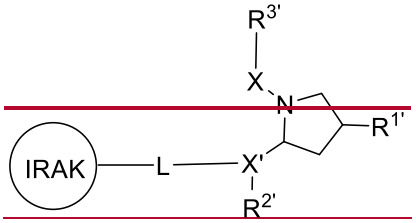
~~I ww-1~~



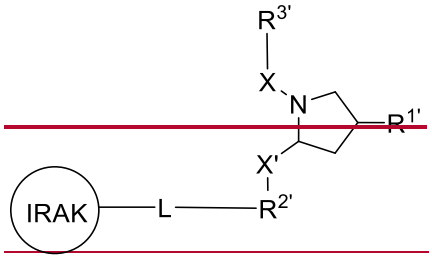
~~I ww-2~~



~~I ww-3~~



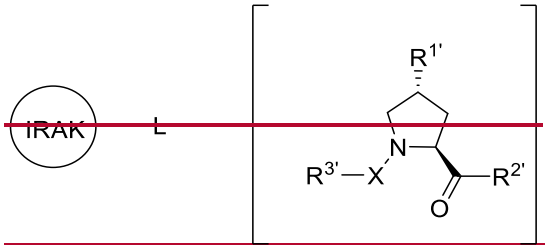
~~I ww-4~~



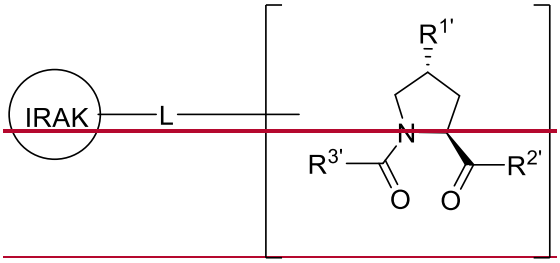
~~I-ww-5~~

~~or a pharmaceutically acceptable salt thereof, and wherein each of the variables $R^{1'}$, $R^{2'}$, $R^{3'}$, X, and X' is as defined and described in WO 2013/106643 and US 2014/0356322;~~

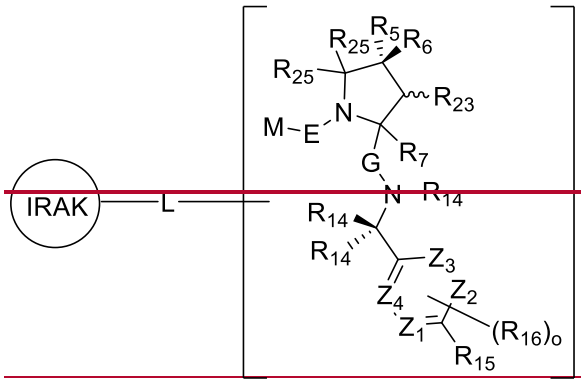
~~*(ii)*~~



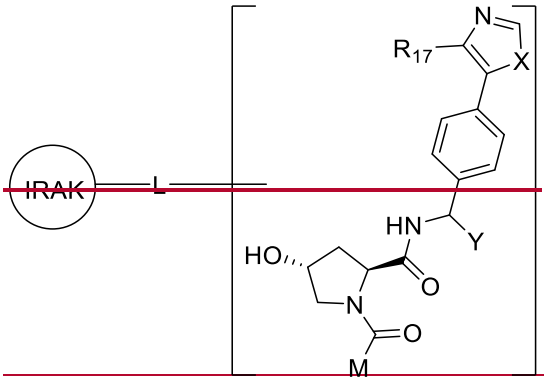
~~I-xx-1~~



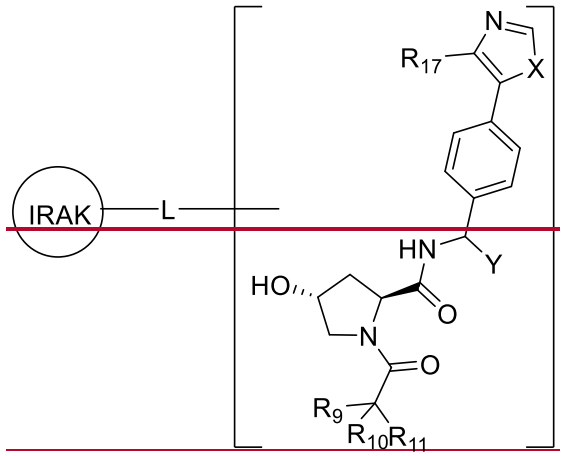
~~I-xx-2~~

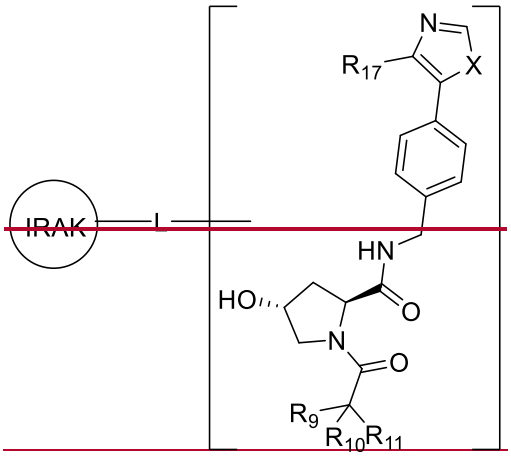


~~I-xx-3~~



~~I-xx-4~~

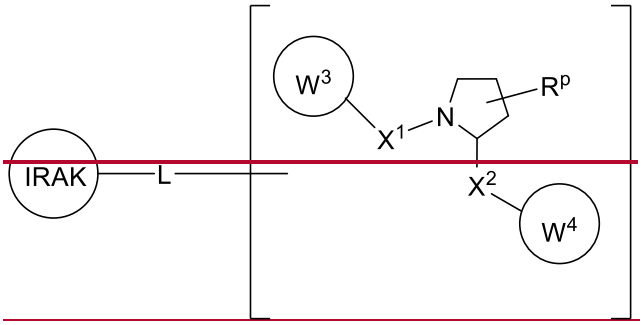




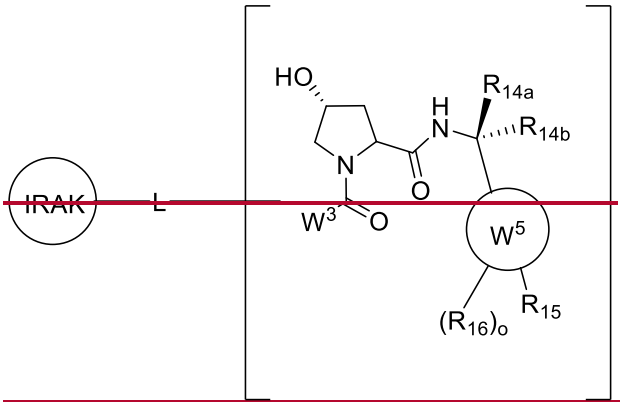
~~I xx-5~~ ~~I xx-6~~

~~or a pharmaceutically acceptable salt thereof, and wherein each of the variables $R^{1'}$, $R^{2'}$, $R^{3'}$, R_5, R_6, R_7, R_9, R_{10}, R_{11}, R_{14}, R_{15}, R_{16}, R_{17}, R_{23}, R_{25}, E, G, M, X, X', Y, Z_1, Z_2, Z_3, Z_4, and o is as defined and described in WO 2016/149668 and US 2016/0272639; or~~

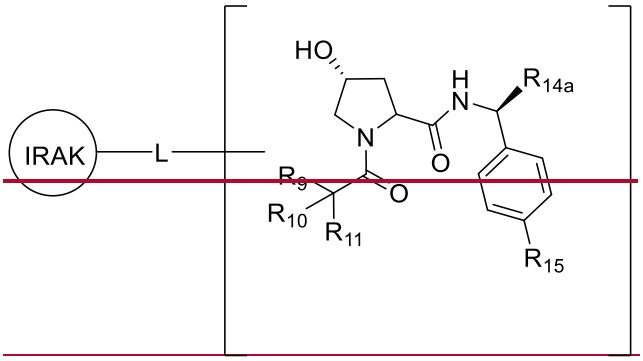
~~*(iii)*~~



~~I yy-1~~



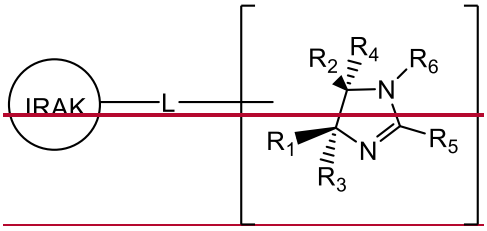
~~I yy-2~~



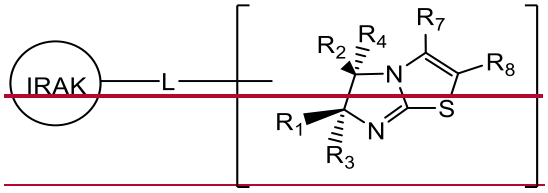
~~I yy-3~~

~~or a pharmaceutically acceptable salt thereof, and wherein each of the variables R^p, R_9, R_{10}, R_{11}, R_{14a}, R_{14b}, R_{15}, R_{16}, W^3, W^4, W^5, X^1, X^2, and o is as defined and described in WO 2016/118666 and US 2016/0214972.~~

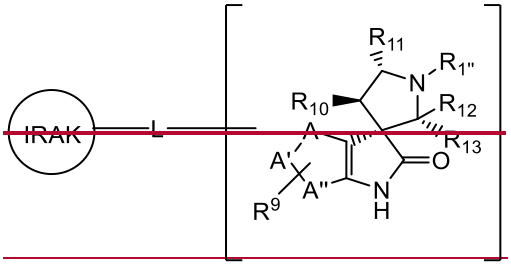
~~11. The compound of claim 3, wherein LBM is a MDM2 E3 ubiquitin ligase binding moiety and said compound is selected from any of the following formulae:~~



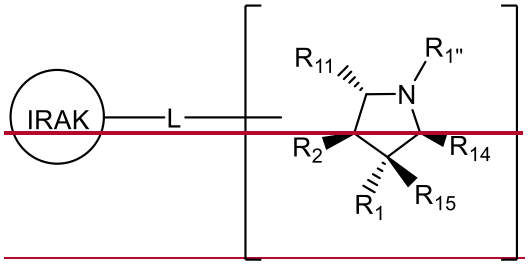
~~I aaa-1~~



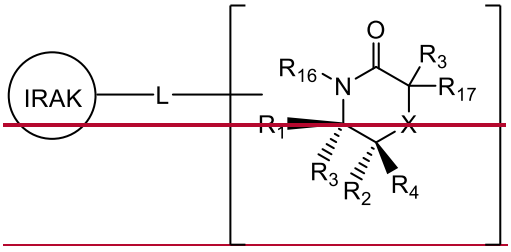
~~I aaa-2~~

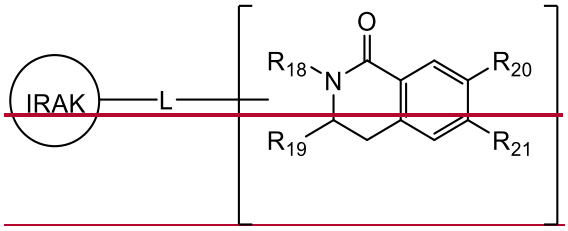


~~I aaa-3~~

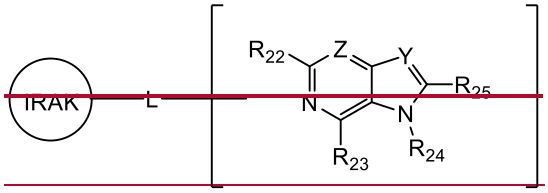


~~I aaa-4~~

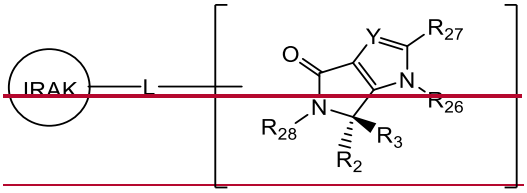




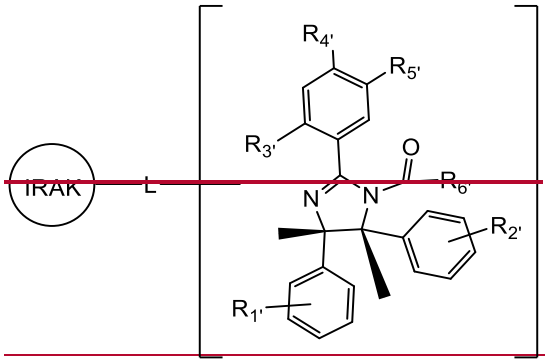
~~I-aaa-5~~



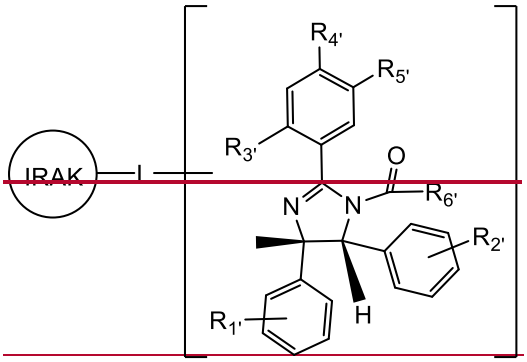
~~I-aaa-6~~



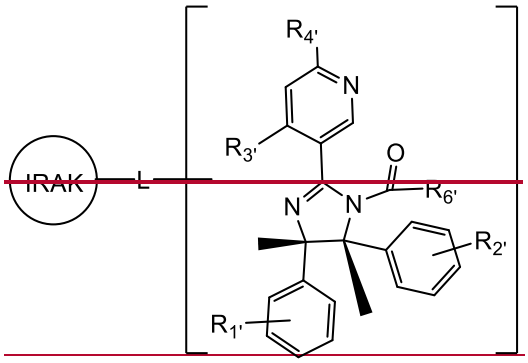
~~I-aaa-7~~



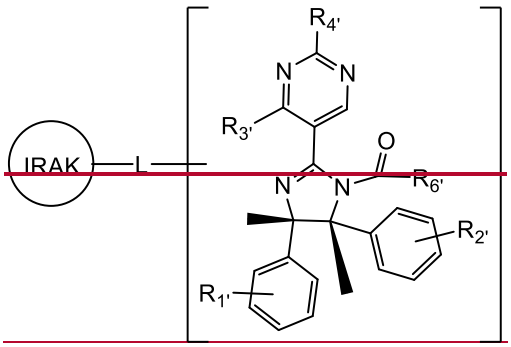
~~I-aaa-8~~



~~I-aaa-9~~

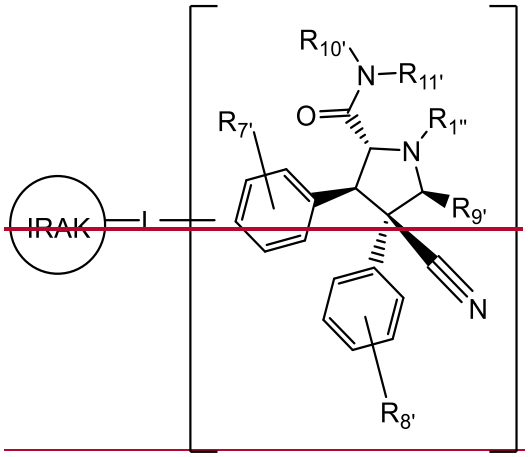


~~I-aaa-10~~

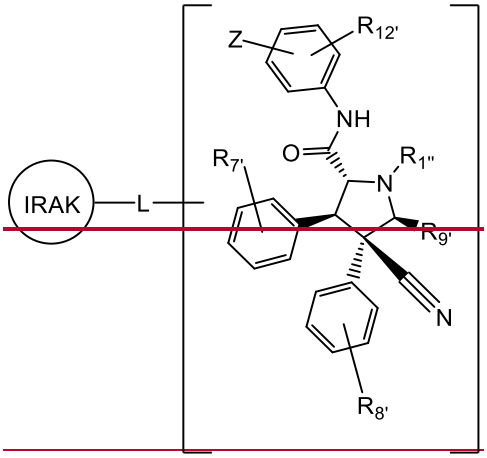


~~I-aaa-11~~

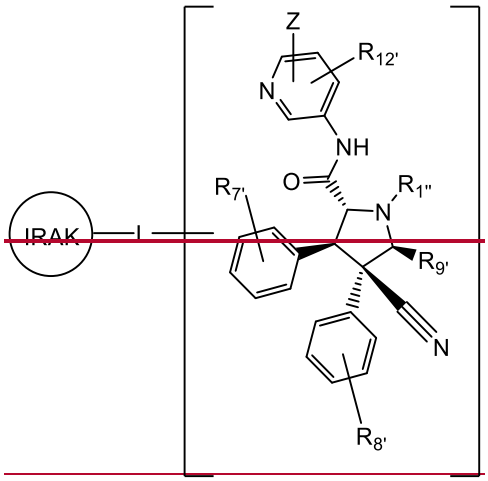
~~I-aaa-12~~



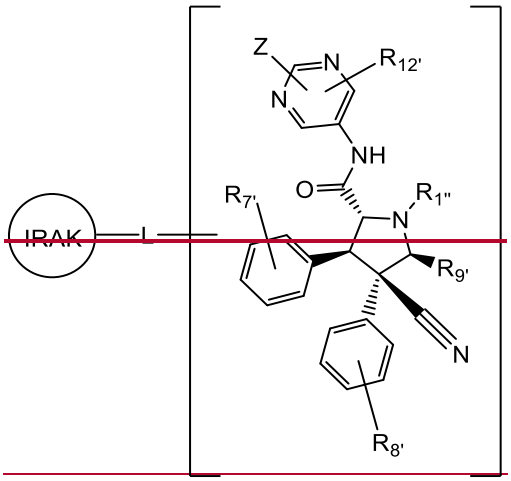
~~I aaa 13~~



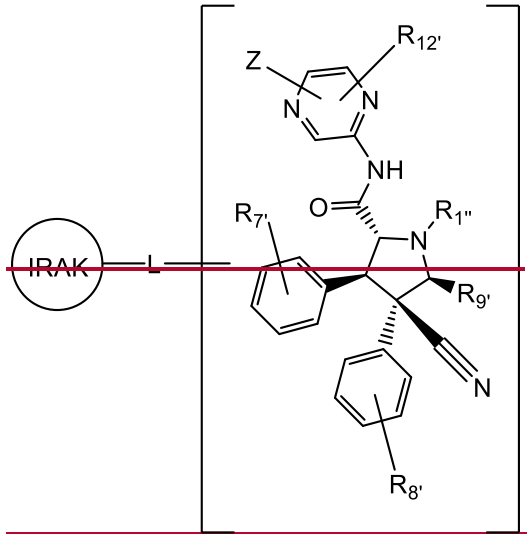
~~I aaa 14~~



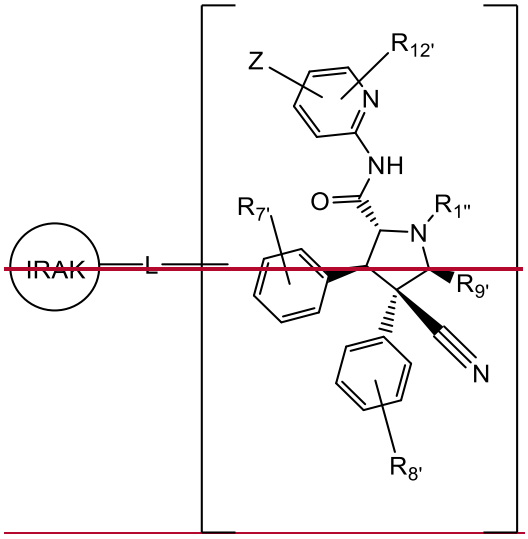
~~I aaa 15~~



~~I aaa 16~~



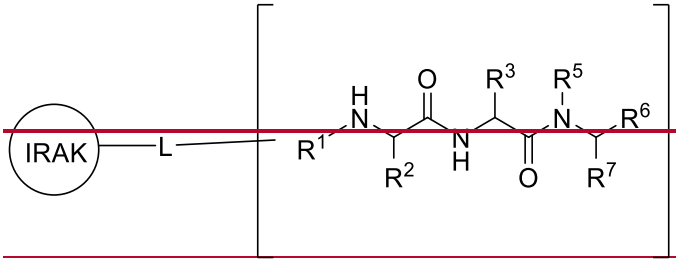
~~I aaa-17~~



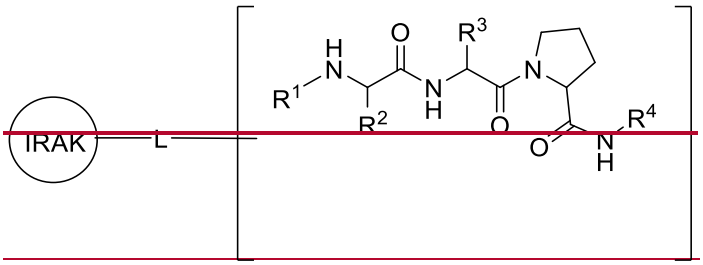
~~I aaa-18~~

~~or a pharmaceutically acceptable salt thereof, and wherein each of the variables R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, $R_{1'}$, $R_{2'}$, $R_{3'}$, $R_{4'}$, $R_{5'}$, $R_{6'}$, $R_{7'}$, $R_{8'}$, $R_{9'}$, $R_{10'}$, $R_{11'}$, $R_{12'}$, $R_{1''}$, A, A', A'', X, Y, and Z is as defined and described in WO 2017/011371 and US 2017/0008904.~~

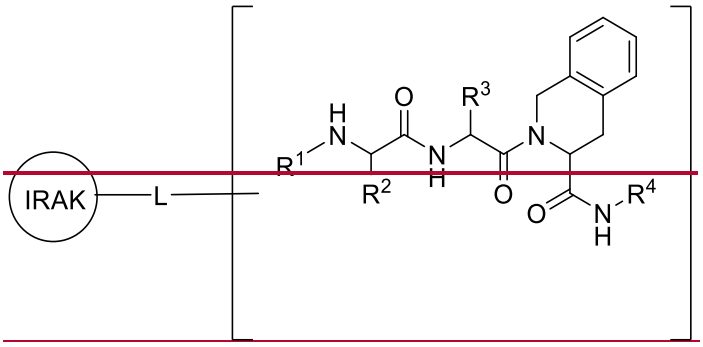
~~12. The compound of claim 3, wherein LBM is a IAP E3 ubiquitin ligase binding moiety and said compound is selected from any of the following formulae:~~



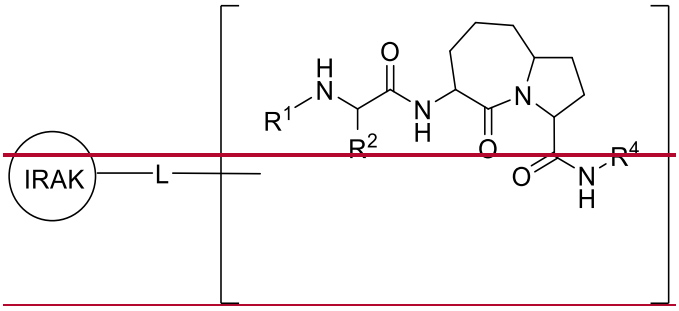
~~I bbb-1~~



~~I bbb-2~~



~~I-bbb-3~~

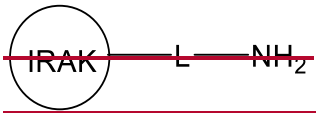


~~I-bbb-4~~

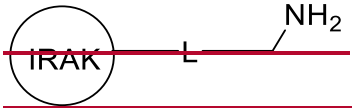
~~or a pharmaceutically acceptable salt thereof, and wherein each of the variables R^1, R^2, R^3, R^4, R^5, R^6, and R^7, is as defined and described in WO 2017/011590 and US 2017/0037004.~~

~~13. The compound of claim 3, wherein DIM is a lysine mimetic and said compound is selected from any one of the following formulae:~~

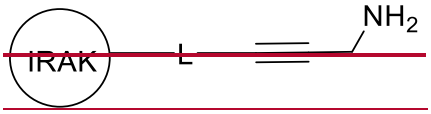
~~(*i*)~~



~~I-kkk-1~~



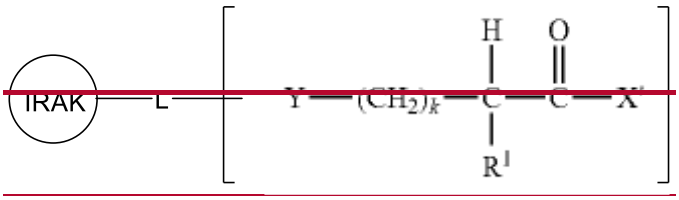
~~I-kkk-2~~



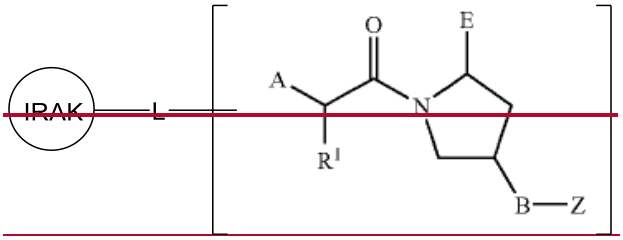
~~I-kkk-3~~

~~or a pharmaceutically acceptable salt thereof; and~~

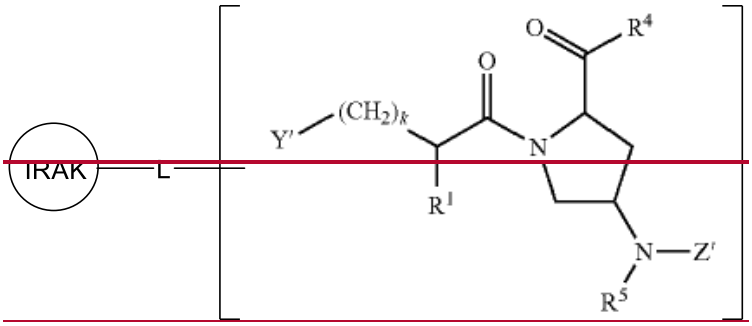
(ii)



I-III-1



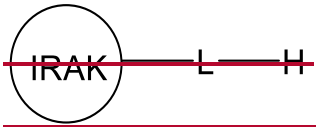
I-III-2



I-III-3

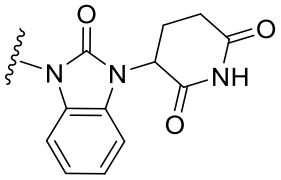
or a pharmaceutically acceptable salt thereof, wherein each of the variables R^1, R^4, R^5, A, B, E, Y, Y′, Z, Z′, and k are as defined and described in U.S. Pat. No. 7,622,496.

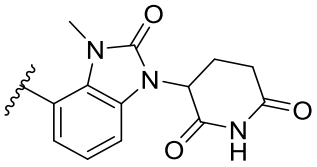
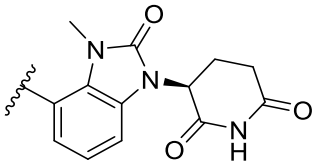
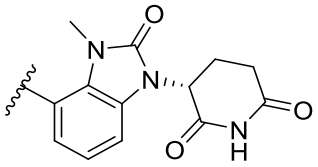
14. The compound of claim 3, wherein DIM is a hydrogen atom and said compound is formula **I-mmm**:

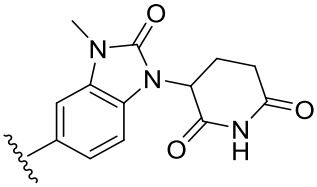
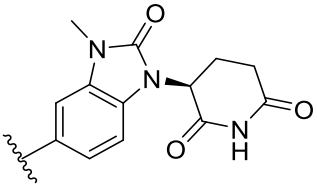
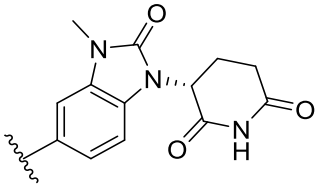


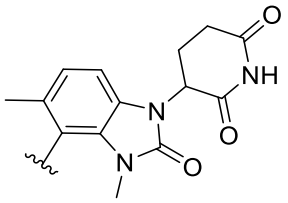
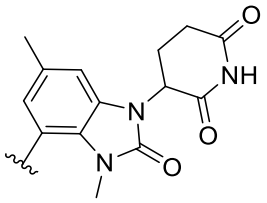
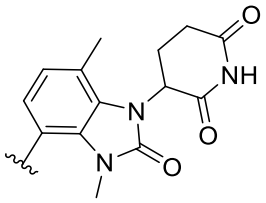
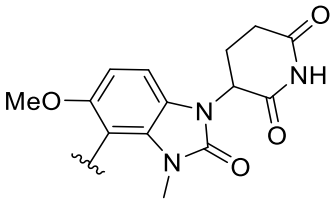
I-mmm

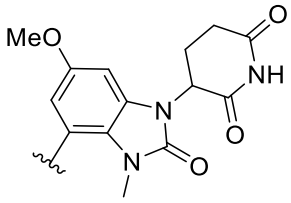
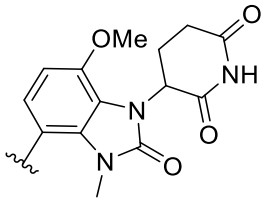
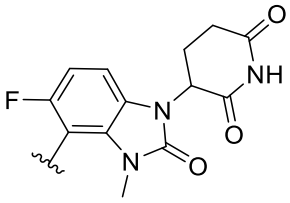
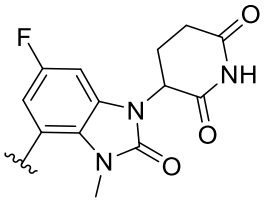
or a pharmaceutically acceptable salt thereof.

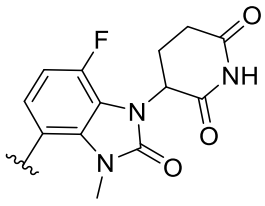
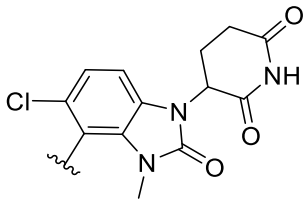
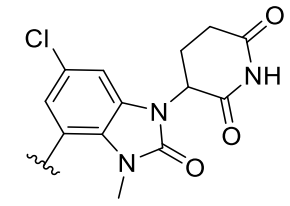
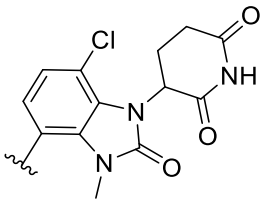
12. The compound of any one of claims 1-11, wherein LBM is  ,

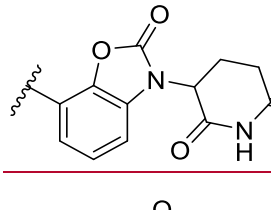
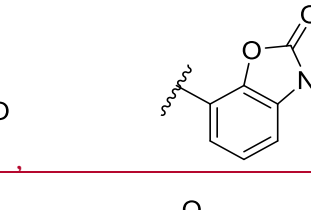
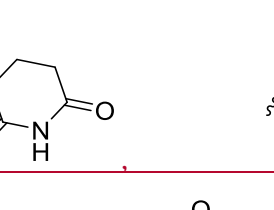
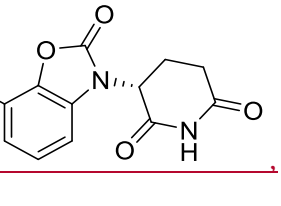
 ,  ,  ,

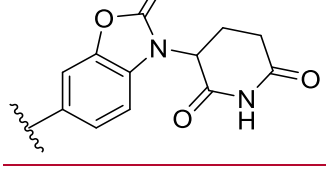
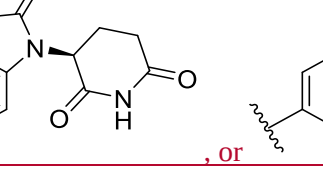
 ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,

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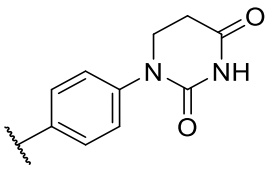
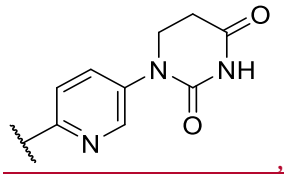
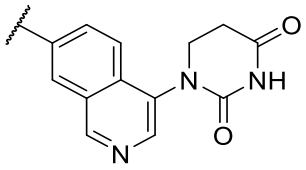
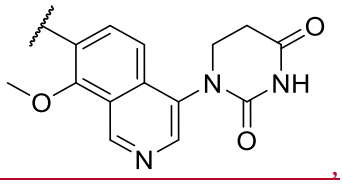
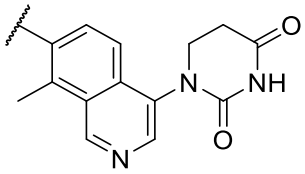
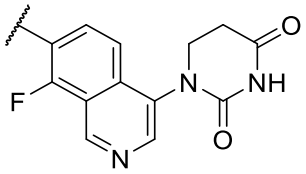
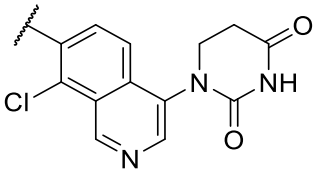
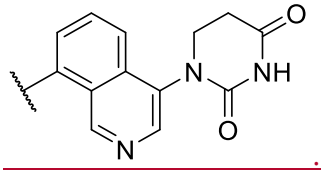
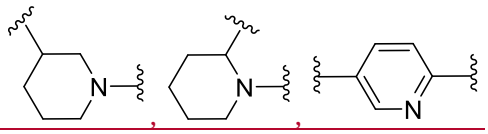
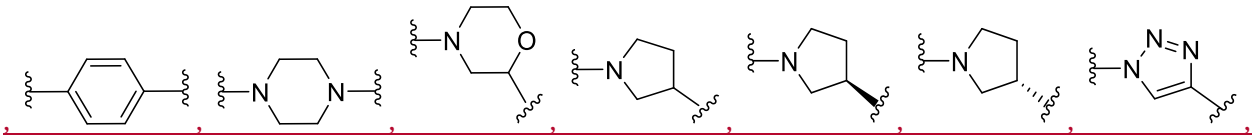
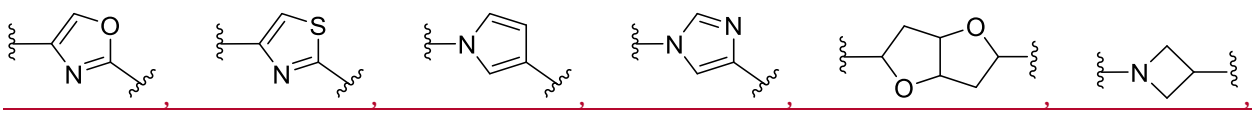
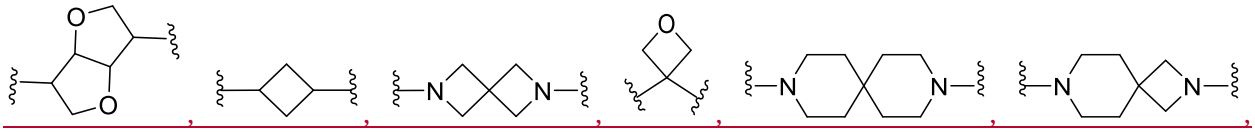
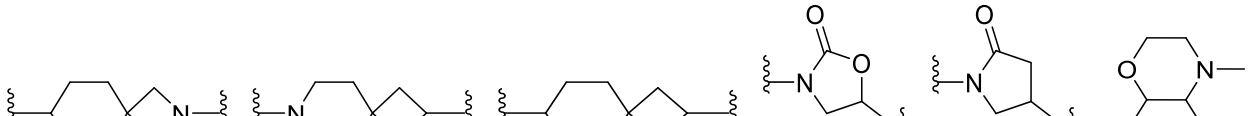
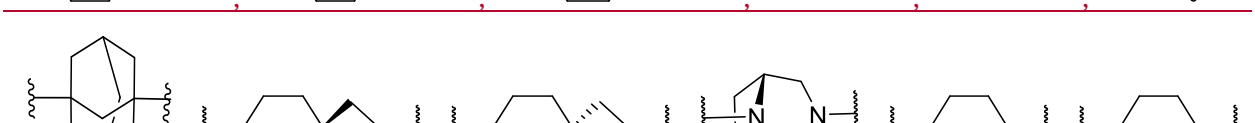
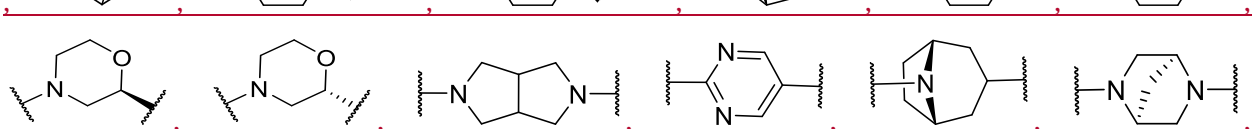
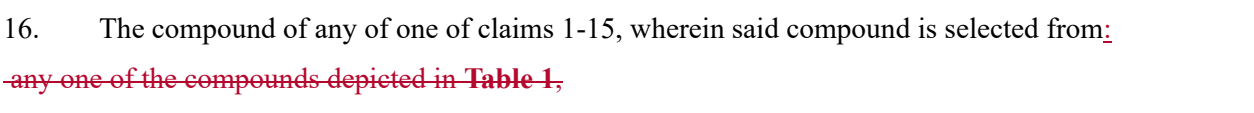
13. The compound of any one of claims 1-12, wherein LBM is  ,  ,  ,  ,  ,  ,  , or  .

1415. The compound according to any one of claims 1-14, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{1-30} hydrocarbon chain, wherein 0-46 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)-, or –N(R)C(O)O–~~-, wherein:~~

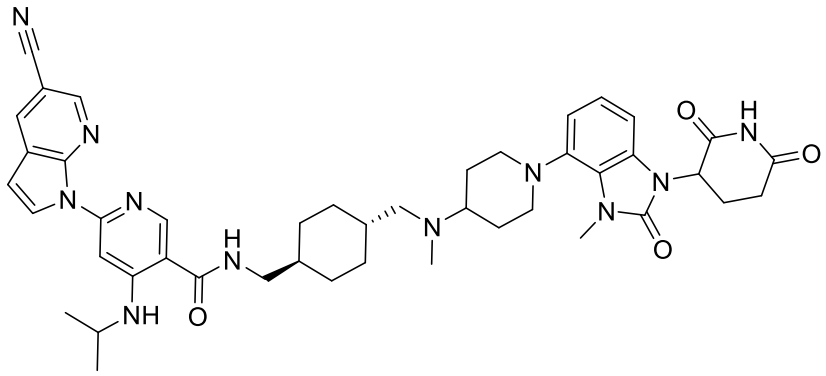
~~each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated 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~~.

15. The compound of any one of claim 1-12, wherein –Cy– is  ,  ,  ,  ,  ,  ,  ,  ,  , , , , or .

16. The compound of any of one of claims 1-15, wherein said compound is selected from:

~~any one of the compounds depicted in **Table 1**,~~

I-84



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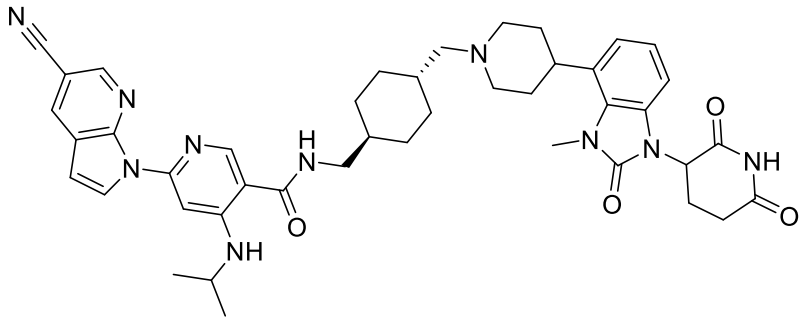

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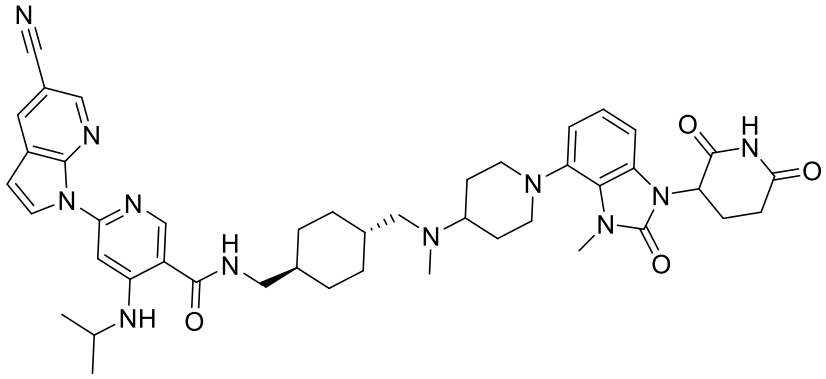

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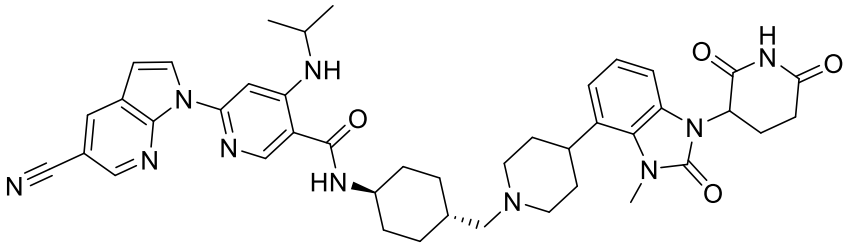

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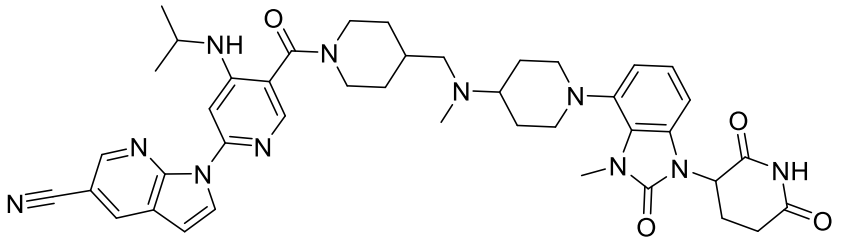

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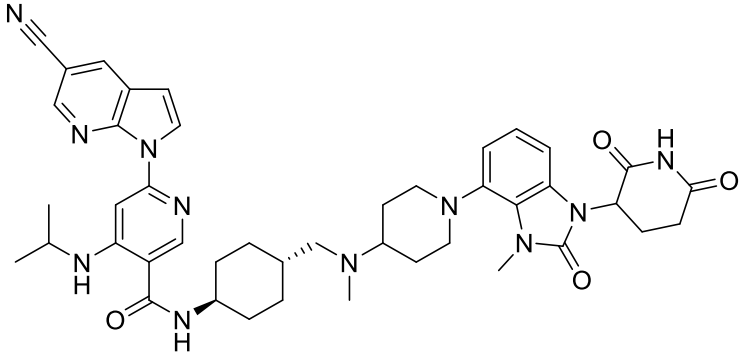

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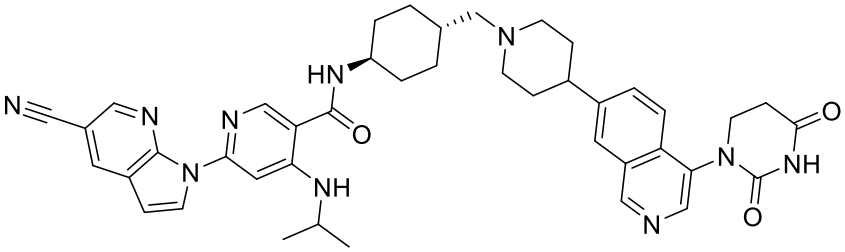

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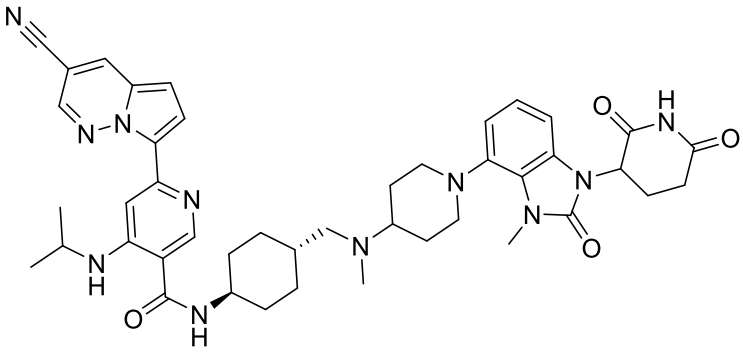

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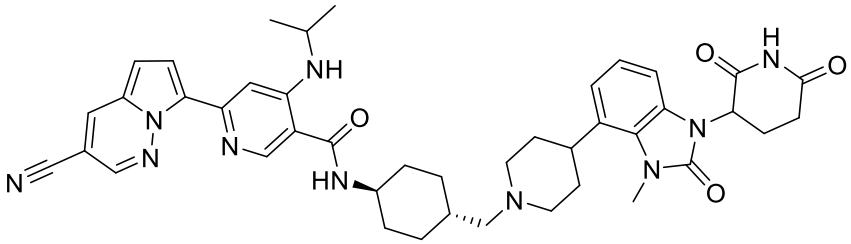

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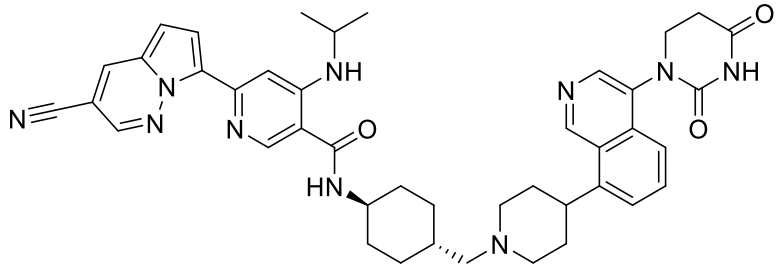

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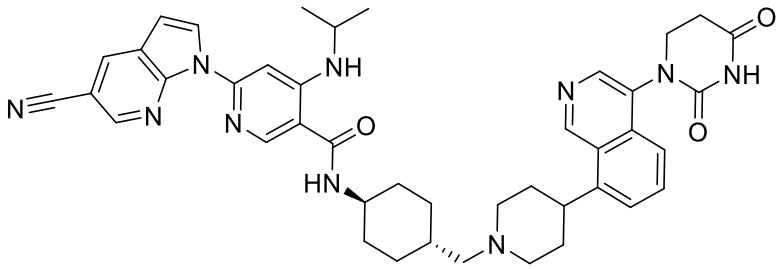

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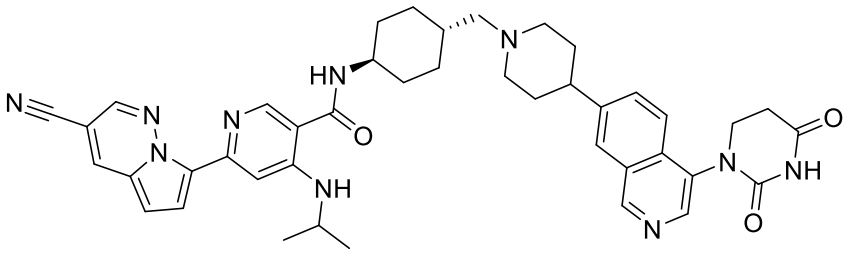

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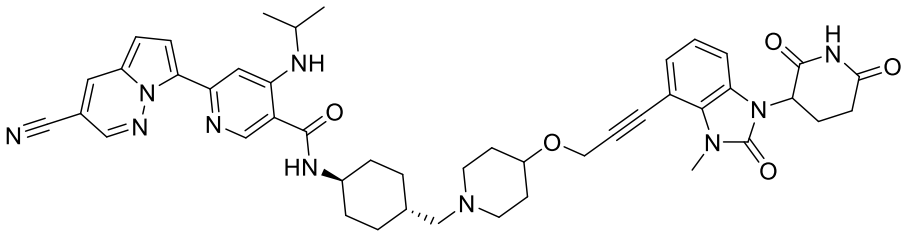

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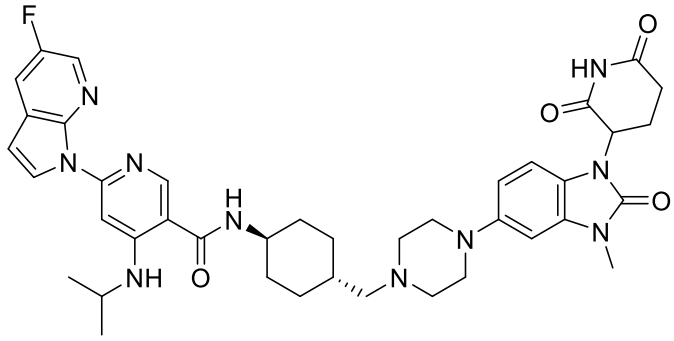

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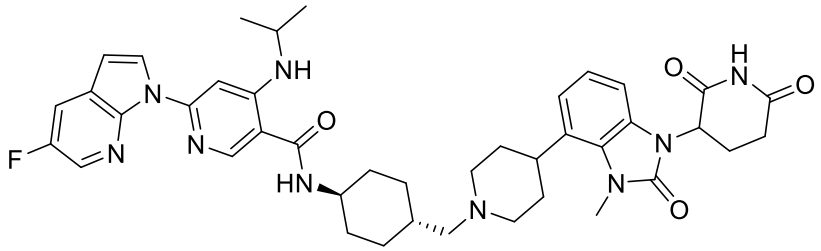

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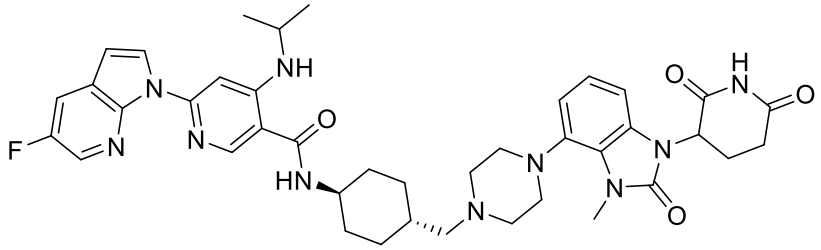

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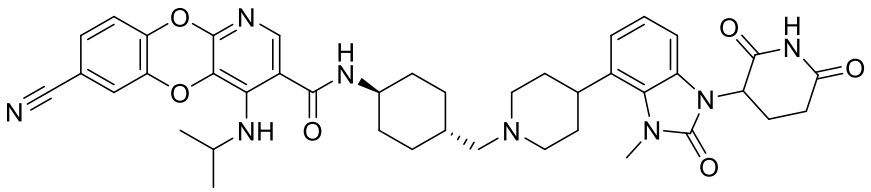

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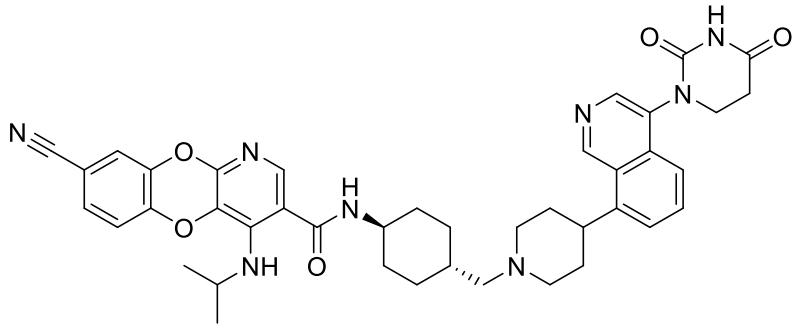

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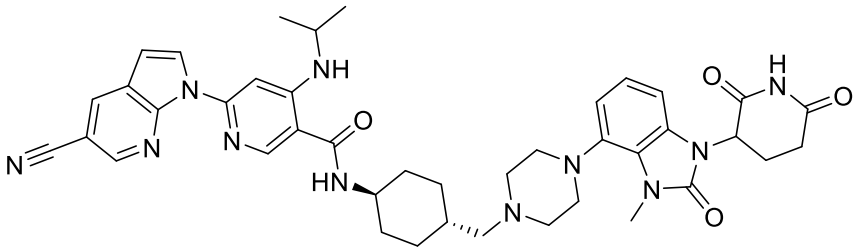

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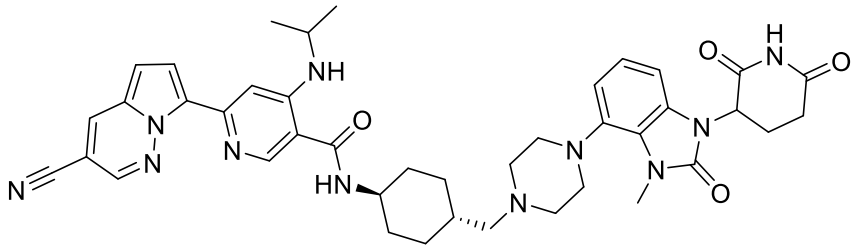

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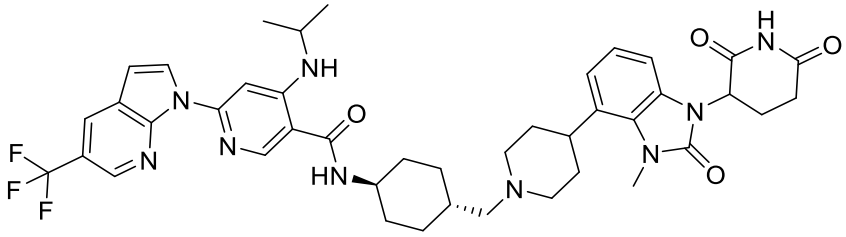

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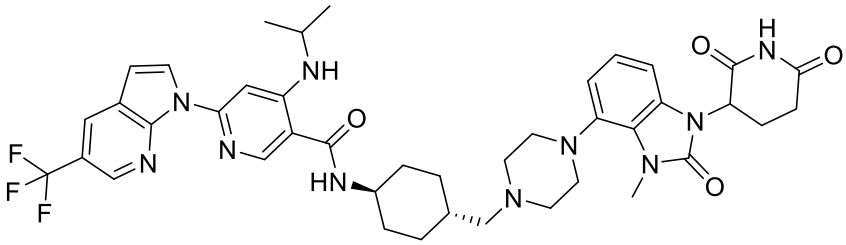

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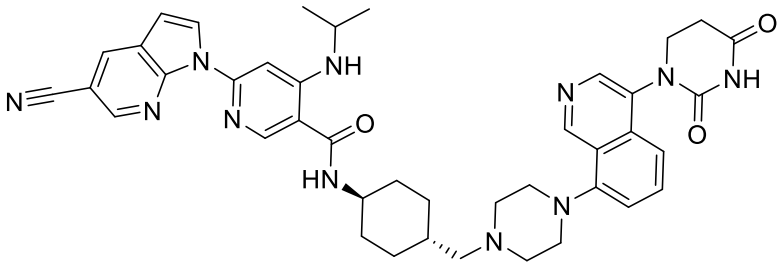

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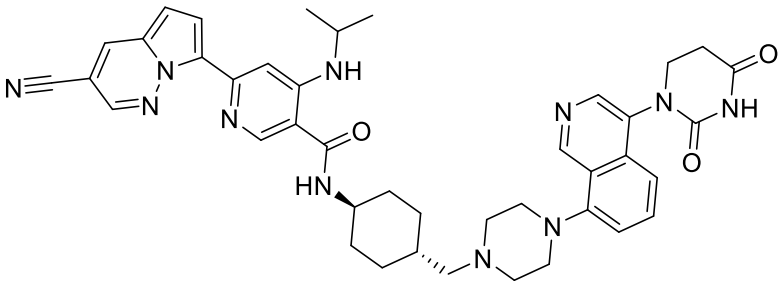

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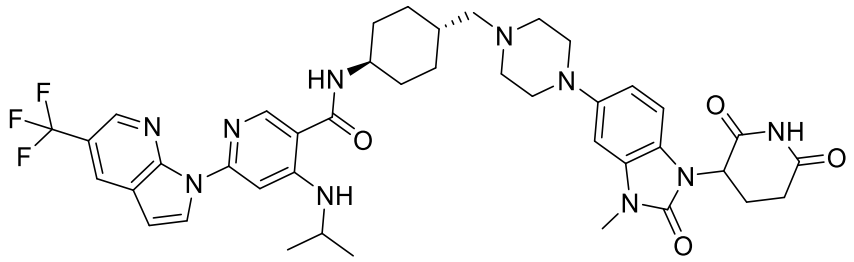

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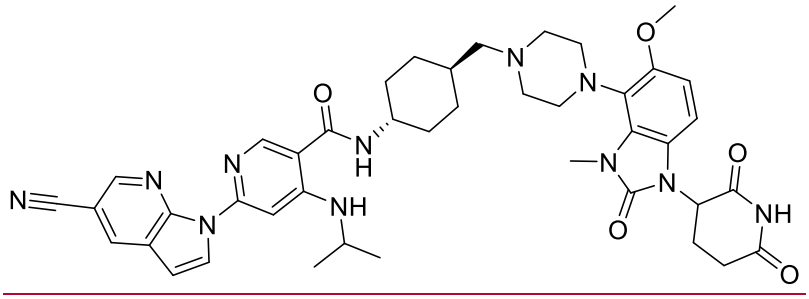

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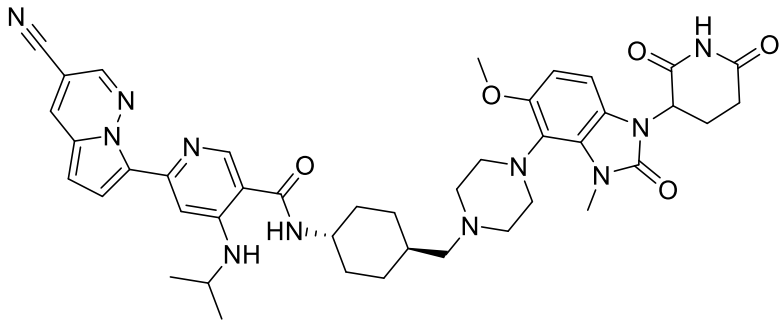
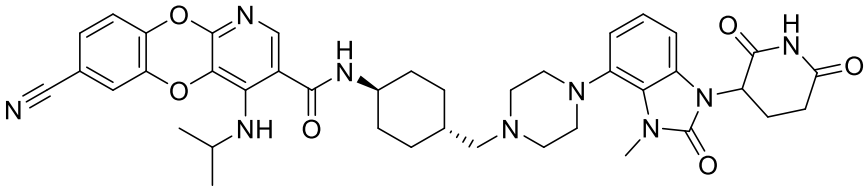
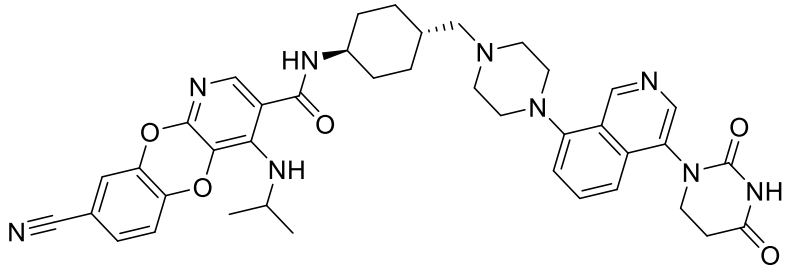
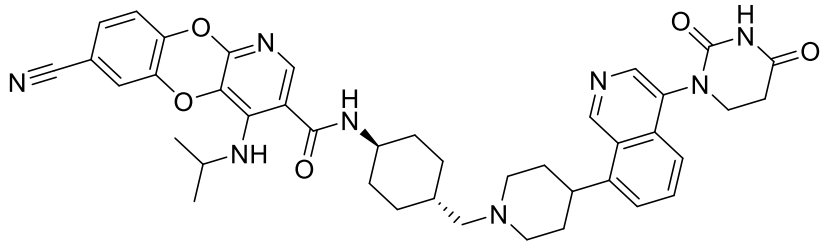


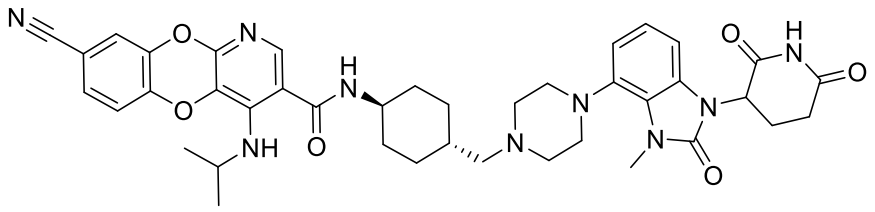
I-407

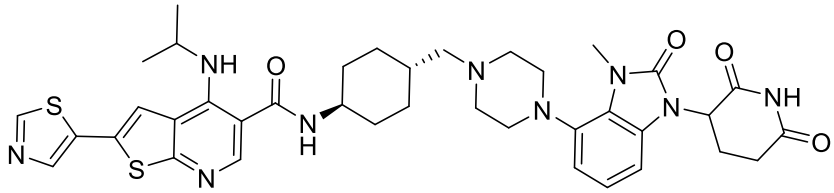


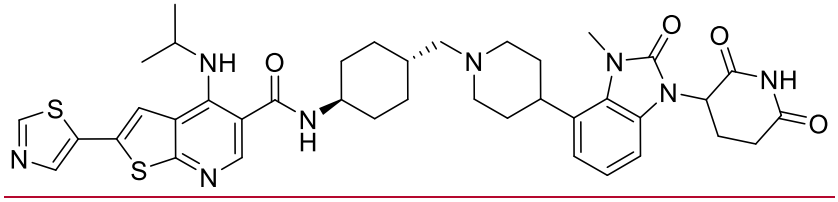
I-408

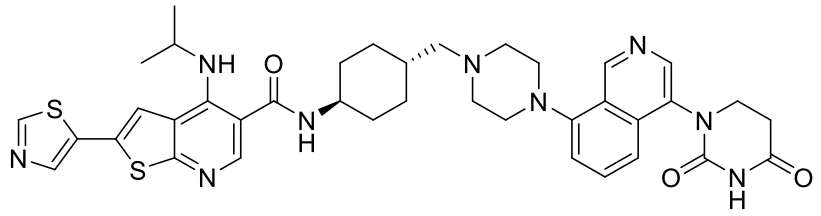


I-409 

I-410 

I-416 

I-417 

I-418 

or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising a compound of any one of claims 1-16, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

18. ~~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~~A compound of any one of claims 1-16, or a pharmaceutical composition thereof, for use in degrading and/or inhibiting an IRAK4 protein kinase in a patient or biological sample.

19. Use of~~A method of treating an IRAK-mediated disorder, disease, or condition in a patient comprising administering to said patient~~ a compound of any one of claims 1-16, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an IRAK4-mediated disorder, disease, or condition in a patient.

20. The use~~method~~ of claim 19, wherein the IRAK4~~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.

21. The use~~method~~ of claim 20, 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.

22. The method of claim 20, wherein the inflammatory 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 granulamatosis, 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 opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, ~~uveitis (~~anterior uveitis,~~and~~ posterior uveitis~~)~~, 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 minal change nephropathy)~~, chronic granulomatous disease, endometriosis, leptospiriosis renal disease, glaucoma, retinal disease, aging, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hyperchlolesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ecodermal 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 angiitis, 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 rheumatoid arthritis, Cryopyrin Associated Periodic Syndrome (CAPS), and osteoarthritis.

23. A compound of any one of claims 1-16, or a pharmaceutical composition thereof, for use in therapy.

~~23. Use of a compound of any one of claims 1-16 or a pharmaceutical composition thereof in the manufacture of a medicament for degrading and/or inhibiting an IRAK protein kinase in a patient or biological sample.~~

~~24. Use of a compound of any one of claims 1-16 or a pharmaceutical composition thereof in the manufacture of a medicament for treating an IRAK-mediated disorder, disease, or condition in a patient.~~

~~25. The use 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 use 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 use of claim 25, wherein the inflammatory 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 granulamatosis, 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 opthalmopathy, 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 minal change nephropathy), chronic granulomatous disease, endometriosis, leptospiriosis renal disease, glaucoma, retinal disease, aging, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hyperchlolesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ecodermal 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 angiitis, 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 rheumatoid arthritis, Cryopyrin Associated Periodic Syndrome (CAPS), and osteoarthritis.~~