networks, modulation of cell surface receptors, ion channels, the secretory pathway, DNA repair and biogenesis of organelles.

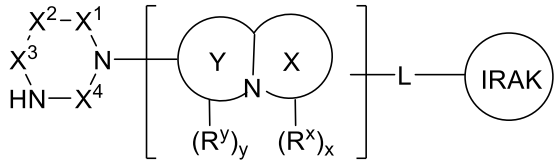
[0006] Aberrations in the process have recently been implicated in the pathogenesis of several diseases, both inherited and acquired. These diseases fall into two major groups: (a) those that result from loss of function with the resultant stabilization of certain proteins, and (b) those that result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

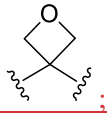


I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 and X^2 are independently a covalent bond, $-CR_2-$, -O-, $-CF_2-$,  ; or

X^1 and X^2 are -CR=CR-;

X^3 and X^4 are independently $-CH_2-$, -C(O)-, -C(S)-, or ;

Ring X and Ring Y are independently fused rings selected from a 5-6 membered saturated, partially unsaturated, or heteroaryl ring having 0-4 heteroatoms, in addition to the nitrogen already depicted in Ring X and Ring Y, independently selected from nitrogen, oxygen, and sulfur;

each R^x and R^y are independently selected from hydrogen, deuterium, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, $-C(S)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-Si(OR)R_2$, and $-SiR_3$;

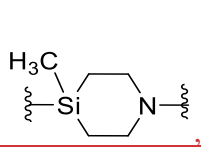
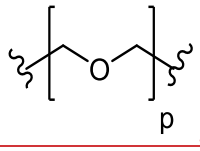
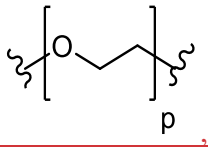
each R is independently selected from hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring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

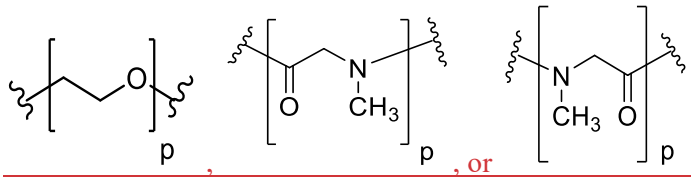
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the carbon or nitrogen, independently selected from nitrogen,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

each R^z is independently selected from 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;

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

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

L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by $-C(D)(H)-$, $-C(D)_2-$, -CRF-, $-CF_2-$, -Cy-, -O-, -N(R)-, $-Si(R)_2-$, $-Si(OH)(R)-$, $-Si(OH)_2-$, -P(O)(OR)-, -P(O)(R)-, $-P(O)(NR_2)-$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)C(O)O-, , , ,



, , or , 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, and sulfur;

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

IRAK is an IRAK binding moiety.

[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 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.

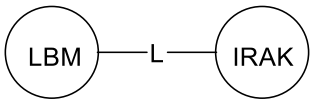
[0008e] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutical composition thereof, for use in therapy.

[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. 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.

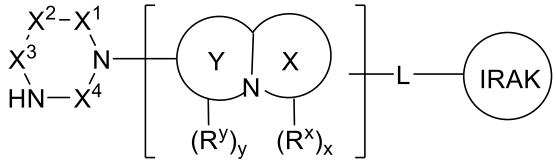
[0010] The present application further relates to bifunctional molecules, including bifunctional

molecules that link a cereblon-binding moiety to a ligand that binds IRAK kinases that are effective for the modulation of targeted ubiquitination. Such compounds have the general structure:



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, targeted degradation of IRAK kinases through the use of bifunctional molecules, including bifunctional molecules that link a cereblon-binding moiety to a ligand that binds IRAK kinases having the following general formula **I**:



I

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

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

[0013] 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:

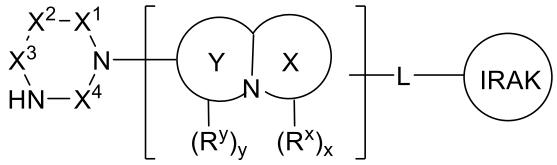
[0014] Compounds of the present invention, and compositions thereof, are useful as degraders and/or inhibitors of one or more IRAK protein kinases. In some embodiments, a provided compound degrades and/or inhibits IRAK-1/2/3/4.

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

CLAIMS

We claim:

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

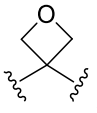


I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 and X^2 are independently a covalent bond, $-CR_2-$, $-O-$, $-CF_2-$,  ; or

X^1 and X^2 are $-CR=CR-$;

X^3 and X^4 are independently $-CH_2-$, $-C(O)-$, $-C(S)-$, or  ;

Ring X and Ring Y are independently fused rings selected from a 5-6 membered saturated, partially unsaturated, or heteroaryl ring having 0-4 heteroatoms, in addition to the nitrogen already depicted in Ring X and Ring Y, independently selected from nitrogen, oxygen, and sulfur;

each R^x and R^y are independently selected from hydrogen, deuterium, R^z, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-C(S)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-Si(OR)R_2$, and $-SiR_3$;

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:

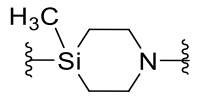
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the carbon or nitrogen, independently selected from nitrogen,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

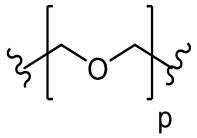
each R^z is independently selected from an optionally substituted group selected from C_{1-6} aliphatic, phenyl,

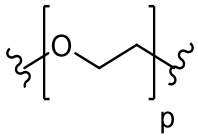
a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

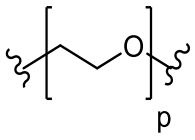
x is 0, 1, 2, 3 or 4; and

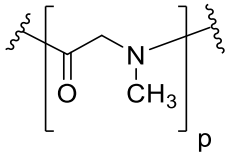
y is 0, 1, 2, 3 or 4;

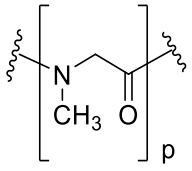
L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -C(D)(H)-, -C(D)$_2$-, -CRF-, -CF$_2$-, -Cy-, -O-, -N(R)-, -Si(R)$_2$-, -Si(OH)(R)-, -Si(OH)$_2$-, -P(O)(OR)-, -P(O)(R)-, -P(O)(NR$_2$)-,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

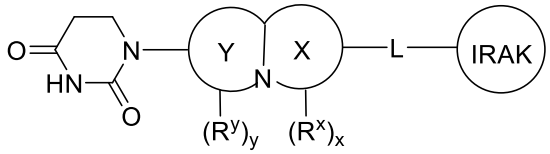
, wherein:

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

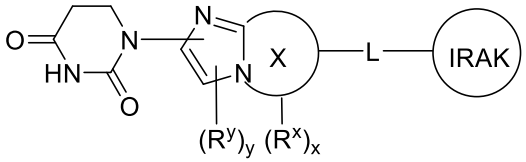
each p is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

IRAK is an IRAK binding moiety.

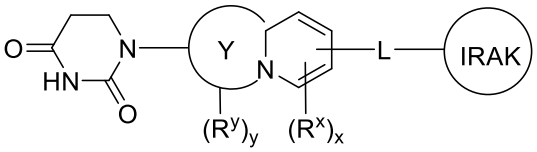
2. The compound of claim 1, wherein said compound is selected from any of the following formulae:



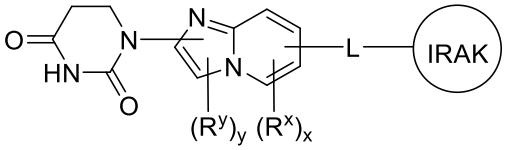
I-a-1



I-a-2



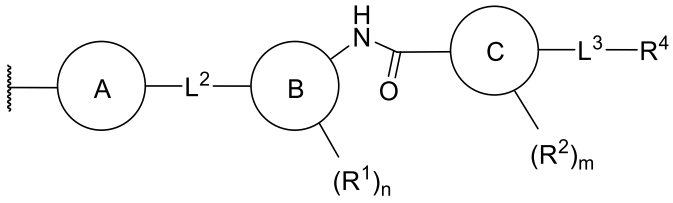
I-a-3



I-a-4

or a pharmaceutically acceptable salt thereof.

3. The compound of either claim 1 or claim 2, wherein the IRAK binding moiety is:



or a pharmaceutically acceptable salt thereof, wherein:

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

Ring B is phenyl, a 4-10 membered saturated or partially unsaturated mono- or bicyclic 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;

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

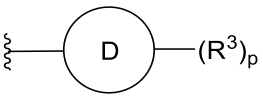
each of L^2 and L^3 is independently a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -$C(R)_2$-, -CH(R)-, -CF(R)-, -$C(F)_2$-, -N(R)-, -S-,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

each R^1 is independently hydrogen, deuterium, -R^5, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, -$P(O)(OR)_2$, -$P(O)(NR_2)_2$, -CFR_2, -$CF_2(R)$, -CF_3, -$CR_2(OR)$, -$CR_2(NR_2)$, -C(O)R, -C(O)OR, or -$C(O)NR_2$;

each R is independently hydrogen, deuterium, 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 atom are optionally taken together with their intervening atom to form an optionally substituted 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, 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^2 is independently hydrogen, deuterium, -R^5, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, -$P(O)(OR)_2$, -$P(O)(NR_2)_2$, -CFR_2, -$CF_2(R)$, -CF_3, -$CR_2(OR)$, -$CR_2(NR_2)$, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, -$OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, -$N(R)C(O)NR_2$, or -$N(R)S(O)_2R$;

R^4 is selected from 

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

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

each R^3 is independently hydrogen, deuterium, -R^5, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, -$P(O)(OR)_2$, -$P(O)(NR_2)_2$, -CFR_2, -$CF_2(R)$, -CF_3, -$CR_2(OR)$, -$CR_2(NR_2)$, -C(O)R, -C(O)OR, -$C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, -$OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, -$N(R)C(O)NR_2$, or –$N(R)S(O)_2R$;

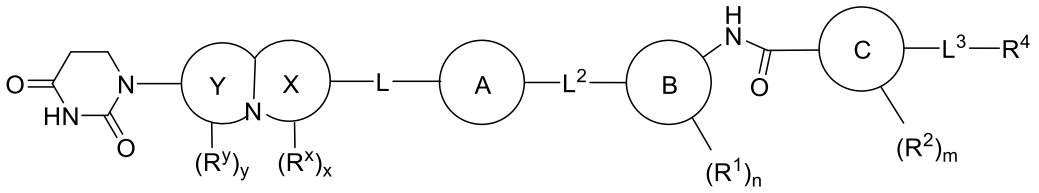
each R^5 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having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

each n is 0, 1, or 2;

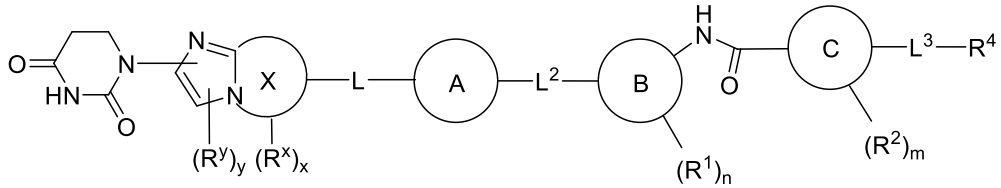
each m is 0, 1, 2, 3 or 4; and

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

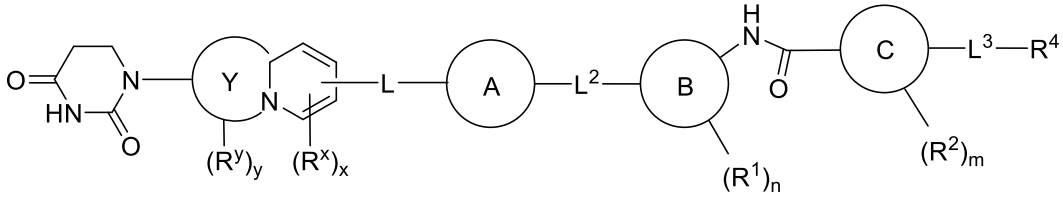
4. The compound of claim 3, wherein said compound is one of the following formulae:



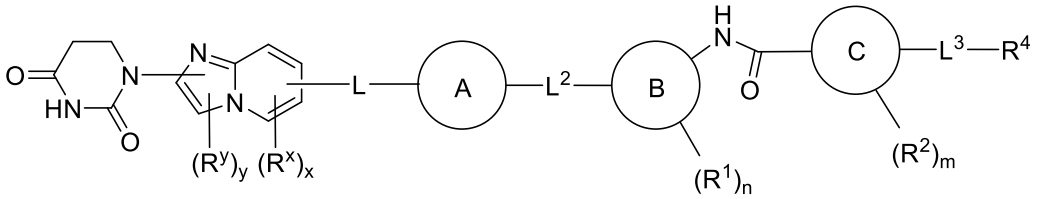
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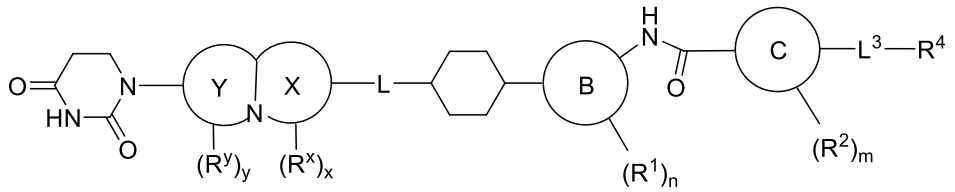
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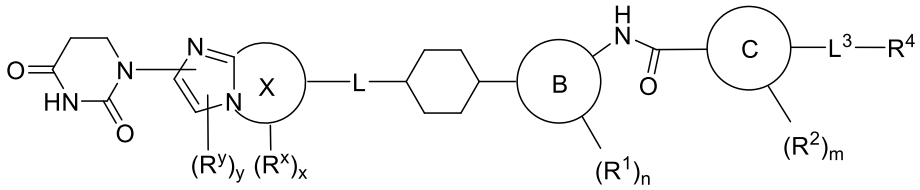
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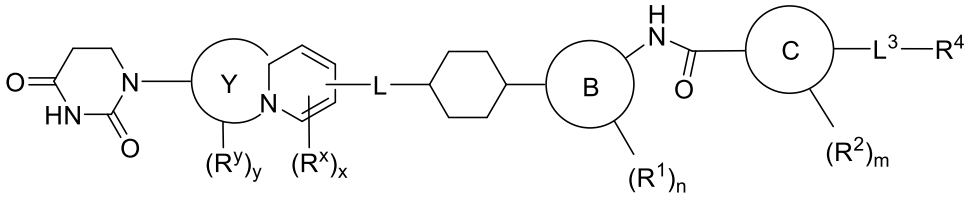
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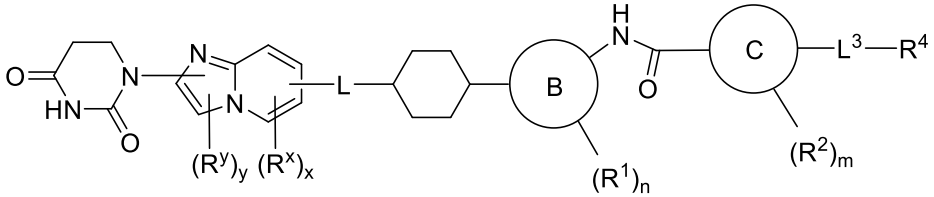
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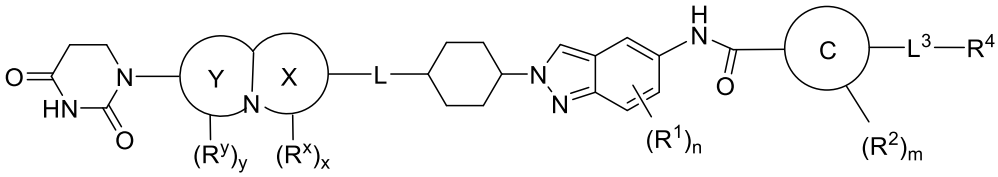
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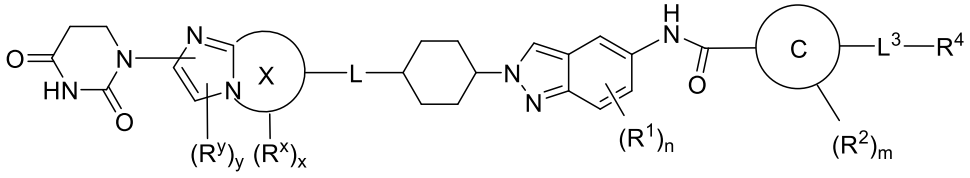
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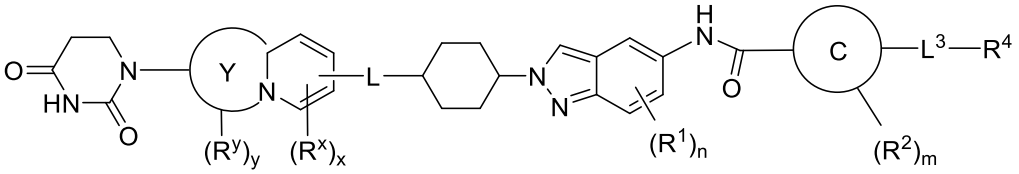
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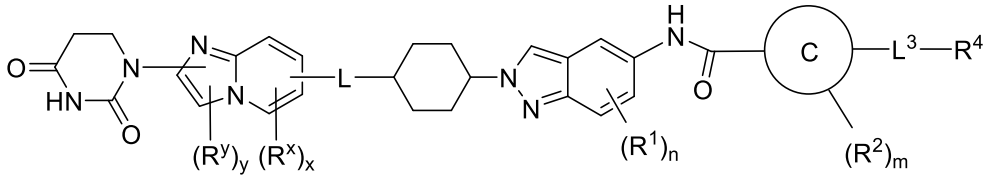
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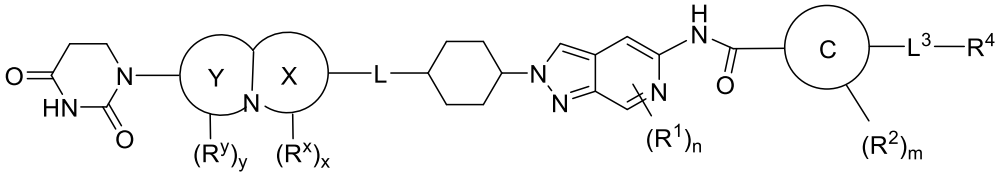
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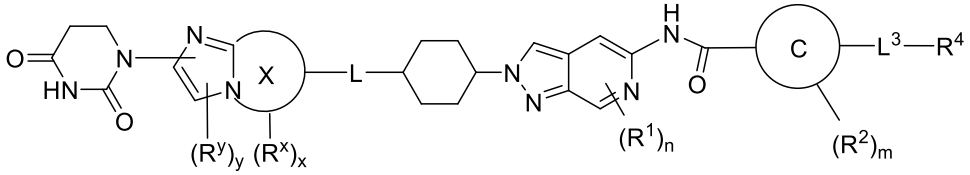
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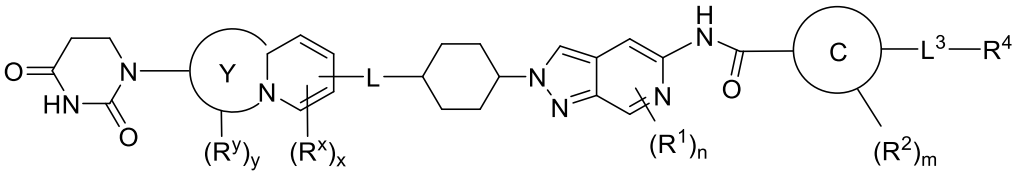
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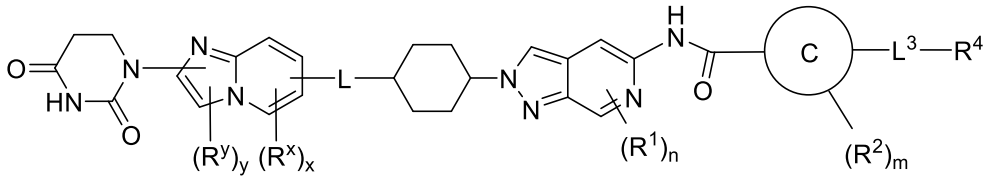
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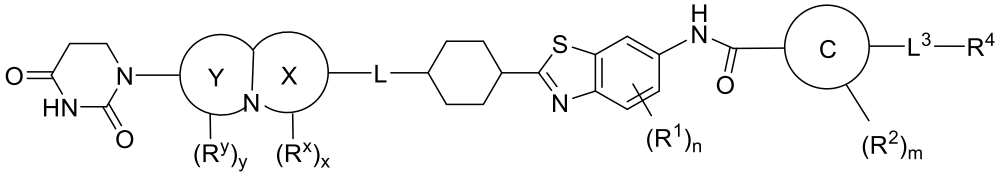
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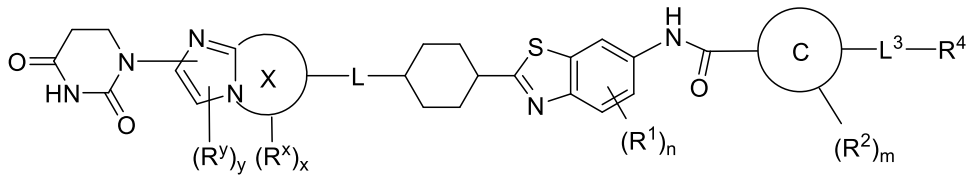
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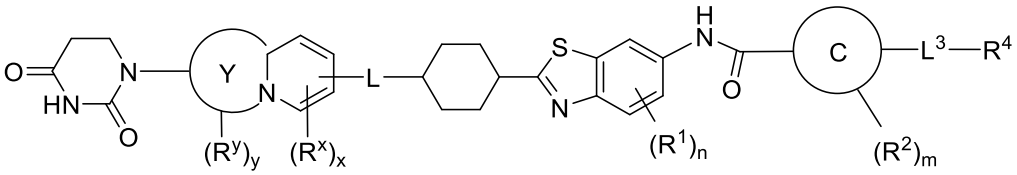
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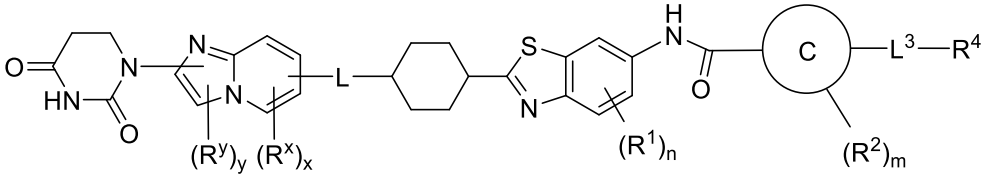
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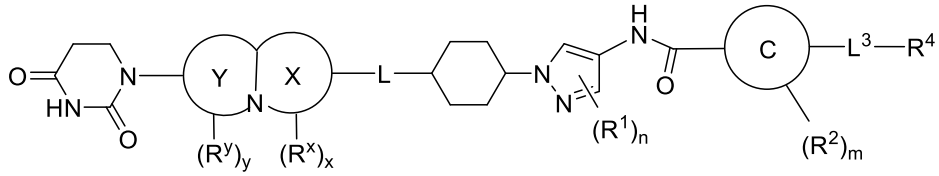
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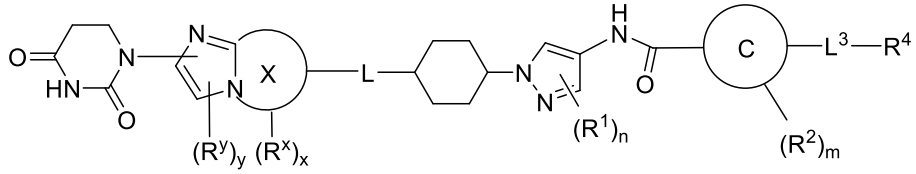
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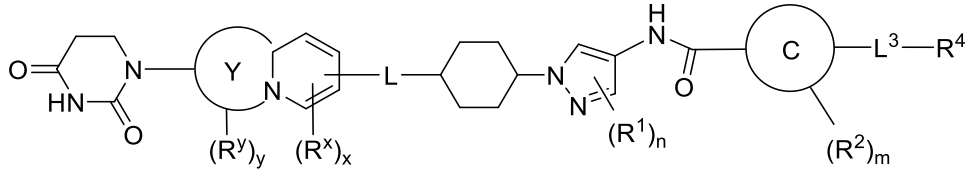
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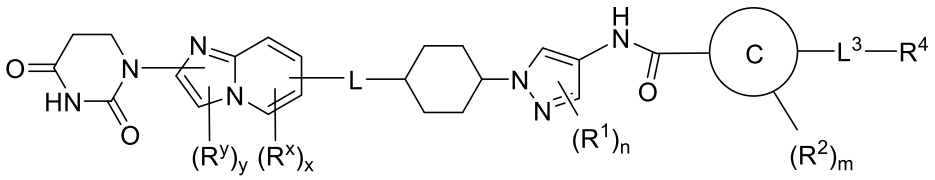
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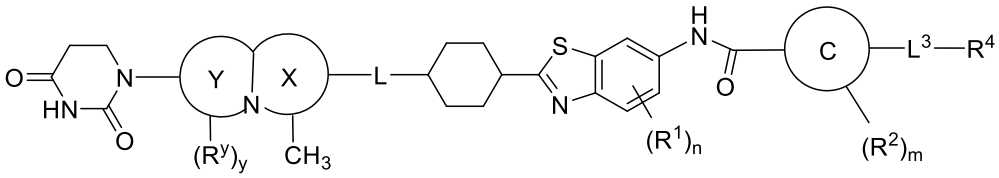
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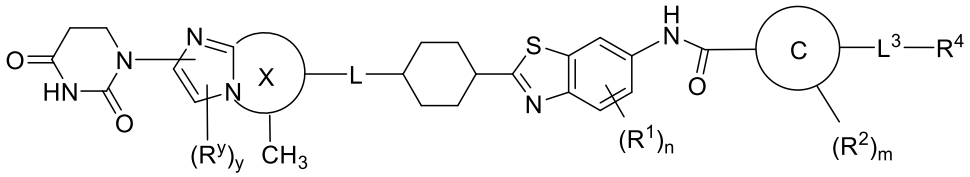
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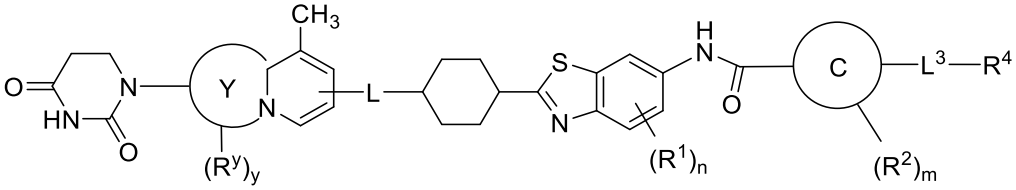
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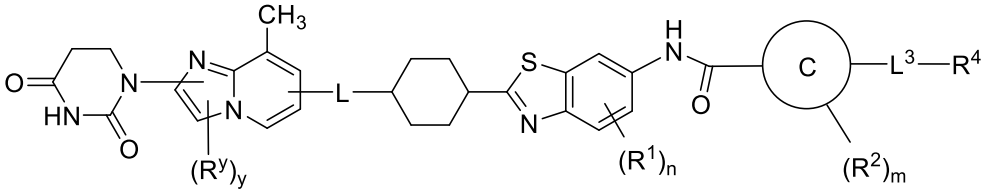
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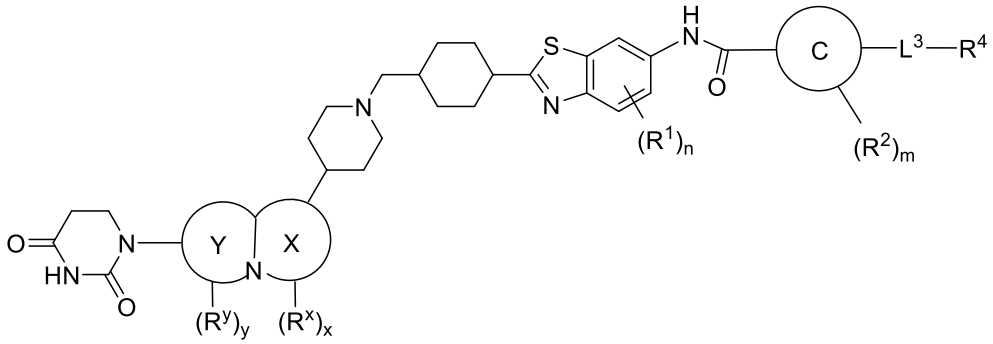
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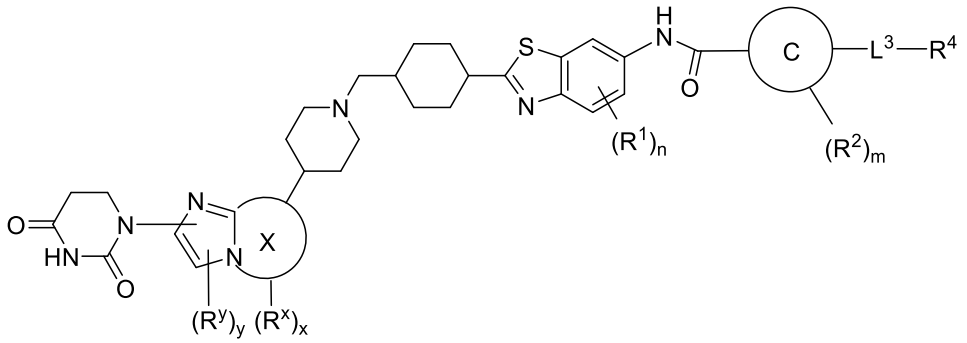
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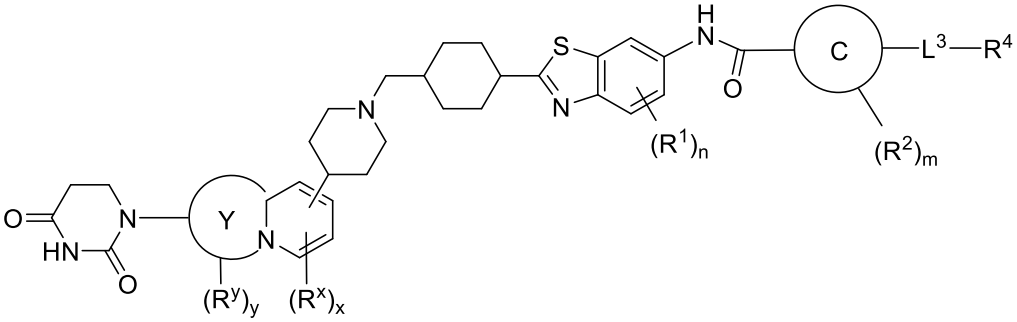
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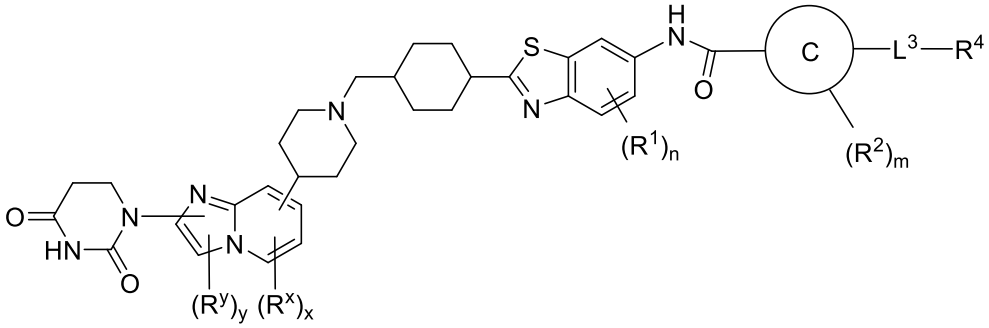
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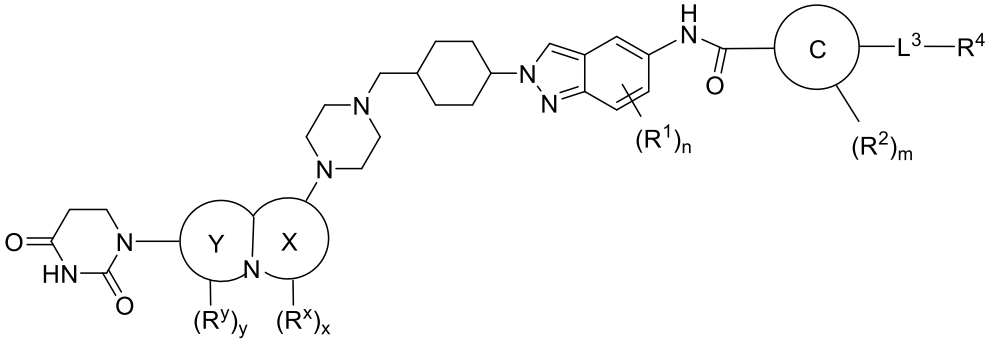
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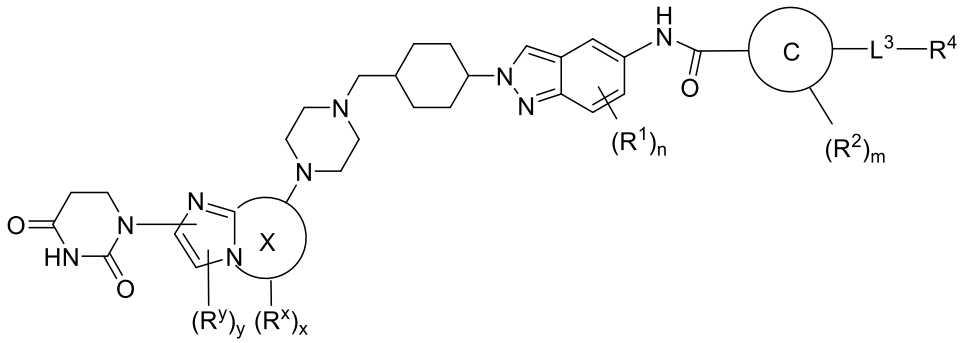
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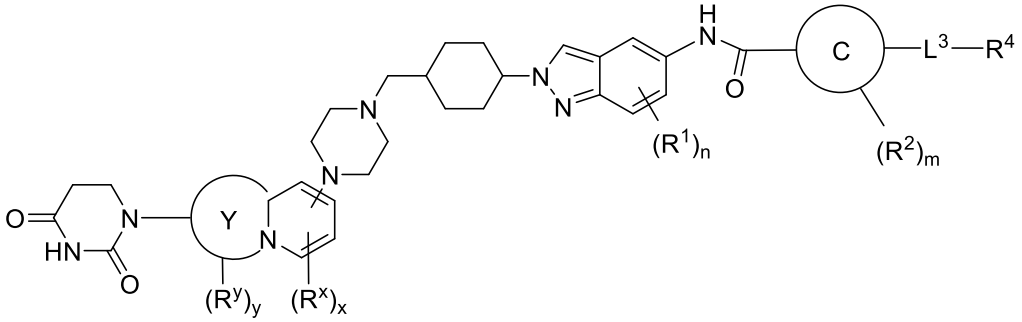
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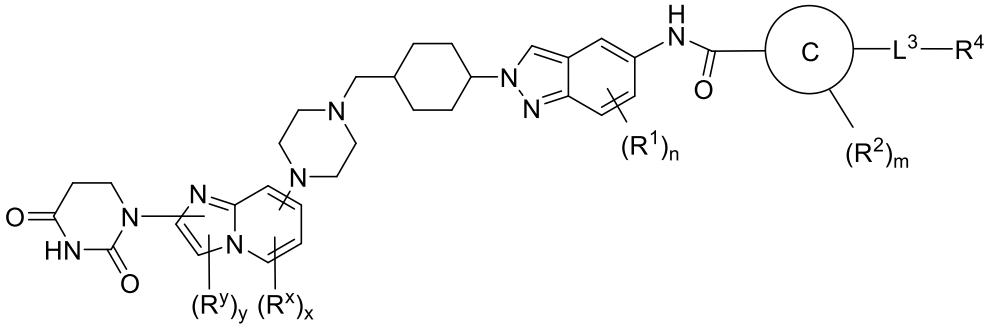
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I-aa-34



I-aa-35



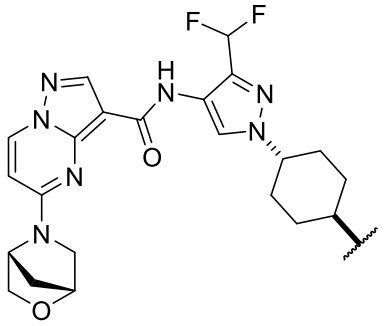
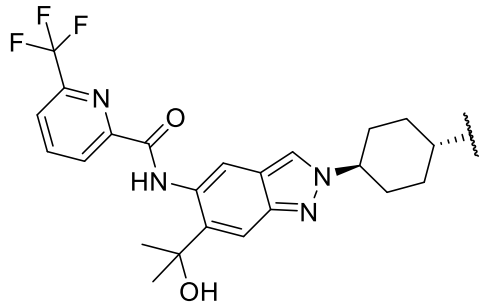
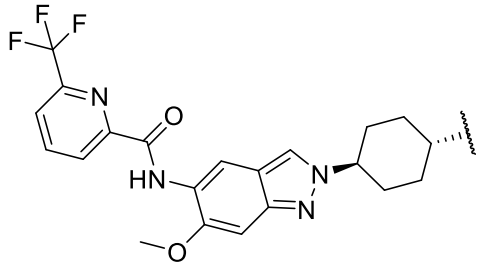
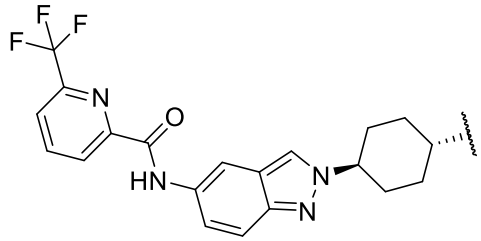
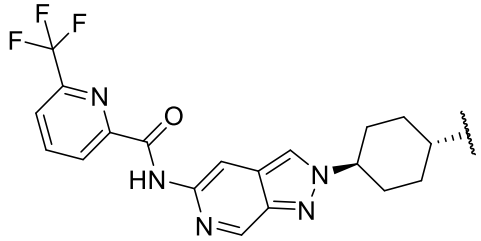
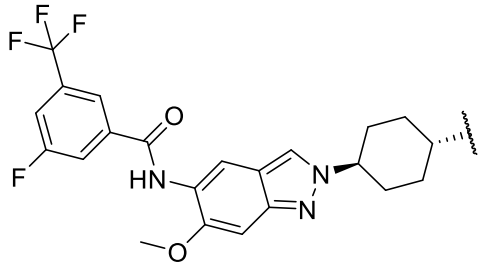
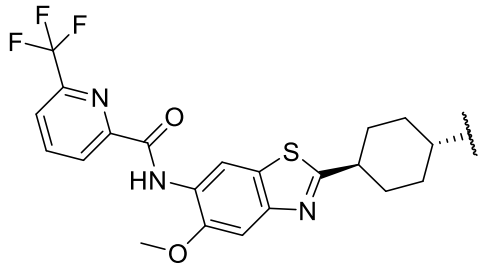
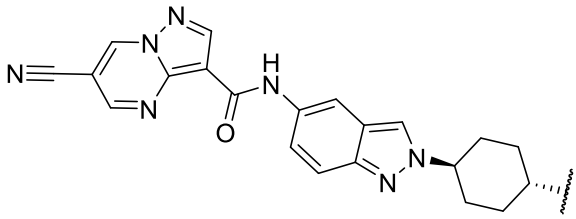
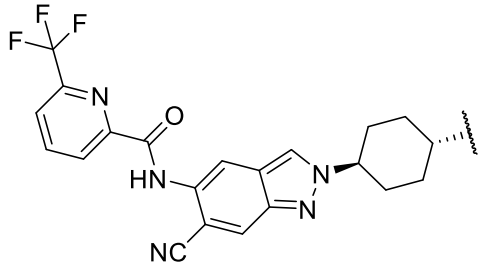
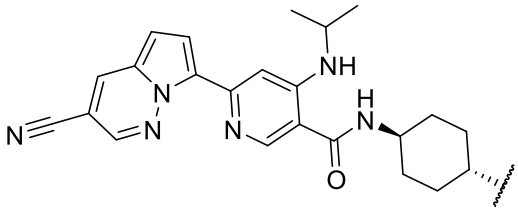
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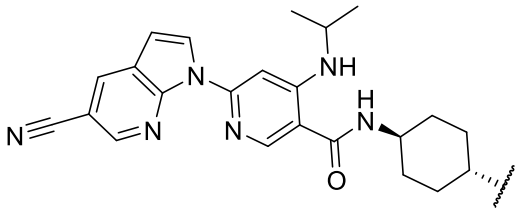
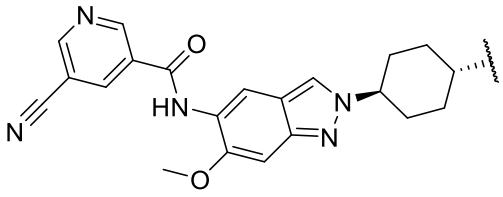
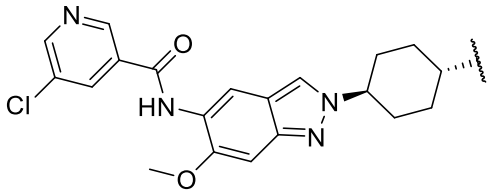
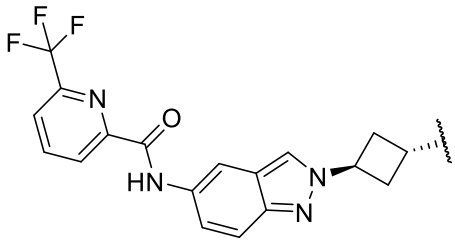
or a pharmaceutically acceptable salt thereof.

5. The compound of either claim 3, wherein Ring B is a 5-9 membered mono- or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

6. The compound of any one of claims 3-5, wherein Ring C is phenyl or a 6-10 membered mono- or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

7. The compound of claim 1 or claim 2, wherein the IRAK binding moiety is


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8. The compound of any one of claims 1-7, wherein L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy-, -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -NRS$(O)_2$-, -$S(O)_2$NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, or –NRC(O)O-.

9. The compound of any one of claims 1-8, wherein said compound is selected from any one of the compounds depicted in **Table 1**, or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound of any one of claims 1-9, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

11. The pharmaceutical composition of claim 10, further comprising an additional therapeutic agent.

12. A compound of any one of claims 1-9, or a pharmaceutical composition thereof, for use in ~~A method of~~ degrading IRAK4 protein kinase in a patient or biological sample ~~comprising administering to said patient, or contacting said biological sample with a compound of any one of claims 1-9, or a pharmaceutical composition thereof~~.

~~13. A method of treating an IRAK4 mediated disorder, disease, or condition in a patient comprising administering to said patient a compound of any one of claims 1-9, or a pharmaceutical composition thereof.~~

~~14. The method of claim 13, further comprising administration of an additional therapeutic agent.~~

~~15. The method of claim 13, wherein the IRAK4-mediated disorder, disease or condition is selected from 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.~~

~~16. The method of claim 13, wherein the IRAK4-mediated disorder, disease or condition is selected from a MyD88 driven disorder.~~

~~17. The method of claim 16, wherein the MyD88 driven disorder is selected from ABC DLBCL, Waldenström's macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma, and chronic lymphocytic leukemia.~~

~~18~~13. Use of a compound of any one of claims 1-9, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an IRAK4-mediated disorder, disease, or condition in a patient.

~~19~~14. The use of claim ~~18~~13, wherein the compound, or the pharmaceutical composition thereof, is to be administered, and ~~further comprising treating the patient with~~ an additional therapeutic agent is to be further administered.

~~20~~15. The use of claim ~~18~~13, wherein the IRAK4-mediated disorder, disease or condition is selected from 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~~16. The use of claim ~~18~~13, wherein the IRAK4-mediated disorder, disease or condition is selected from a MyD88 driven disorder.

~~22~~17. The use of claim ~~21~~16, wherein the MyD88 driven disorder is selected from ABC DLBCL,

Waldenström's macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma, and chronic lymphocytic leukemia.

18. A compound of any one of claims 1-9, or a pharmaceutical composition thereof, for use in therapy.