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).

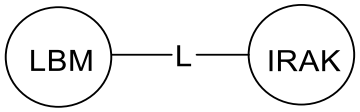
[0008] An ongoing need exists in the art for effective treatments for disease, especially hyperplasias and cancers, such as multiple myeloma. However, non-specific effects, and the inability to target and modulate certain classes of proteins altogether, such as transcription factors, remain as obstacles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

[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.

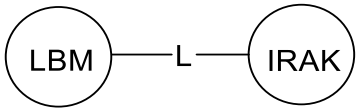
[0010] The present application further relates to targeted degradation of IRAK kinases through the use of bifunctional molecules, including bifunctional molecules that link a degradation inducing moiety to a ligand that binds IRAK kinases having the following general formula **I**:



I

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

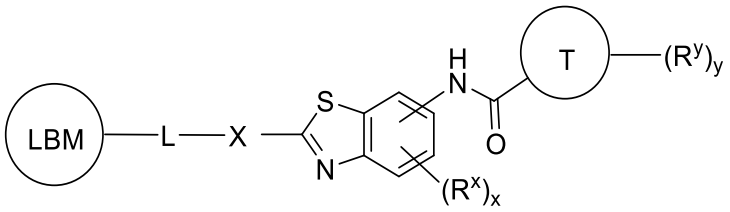
[0010a] In an aspect of the present disclosure, there is provided a compound of formula **I**:



I

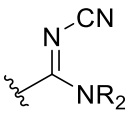
or a pharmaceutically acceptable salt thereof, wherein:

IRAK is an IRAK binding moiety capable of binding to IRAK4, said compound of formula **I** is a compound of formula **I-a-2**:



I-a-2

or a pharmaceutically acceptable salt thereof, wherein:

each R^x is independently hydrogen, 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, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-N^+(O^-)R_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-P(O)R_2$, $-SiR_3$, $-Si(OR)R_2$, or 

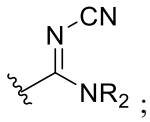
; or

two R^x 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;

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

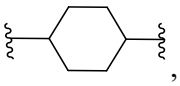
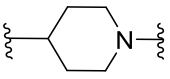
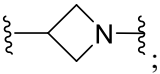
a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same carbon or 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 carbon or nitrogen, independently selected from nitrogen, oxygen, and sulfur;

each R^y is independently hydrogen, 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, $-C(O)NR_2$, $-C(S)NR_2$, -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 ;

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

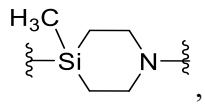
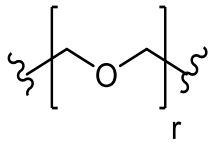
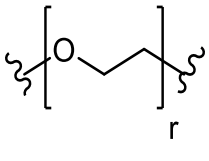
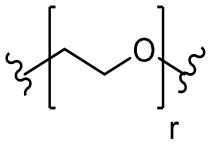
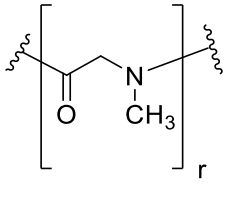
Ring T is selected from phenyl or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring T is further optionally substituted with 1-2 oxo groups;

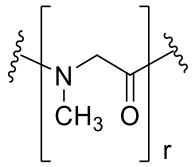
X is , , or ;

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

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

, , , , ,



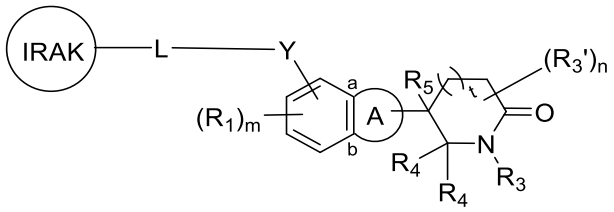
or ;

each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-12 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 4-12 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;

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

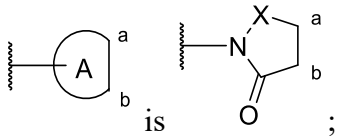
LBM is an IMiD-based cereblon E3 ubiquitin ligase binding moiety selected from:

(*i*)



I-oo-1

or a pharmaceutically acceptable salt thereof, and wherein:



is ;

Y is a bond;

X is C(O) or CH_2;

each R_1 is independently hydrogen, halogen, C_1-C_4 alkyl, or C_1-C_4 alkoxy;

R_3 is hydrogen;

two R_4, together with the carbon atom to which they are attached, form C(O);

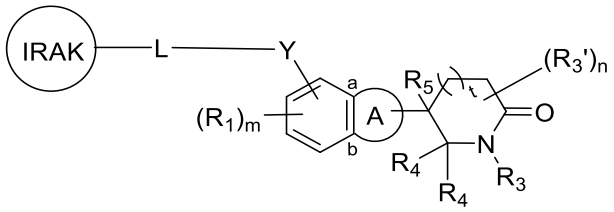
R_5 is hydrogen or C_1-C_3 alkyl;

t is 1;

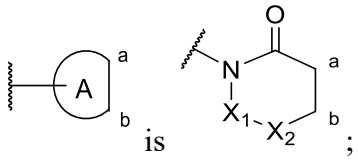
m is 0, 1, 2, 3, or 4; and

n is 0;

(*ii*)



I-oo-1



;

Y is a bond;

X_1-X_2 is C(H)═N, C(C_1-C_4 alkyl)═N, or C(C_1-C_4 haloalkyl);

each R_1 is independently hydrogen, halogen, -NH_2, -OH, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkoxy;

R_3 is hydrogen;

two R_4, together with the carbon atom to which they are attached, form C(O);

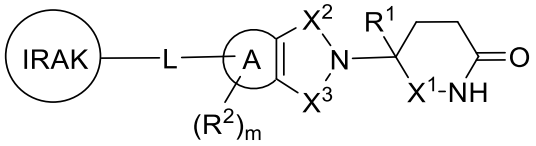
R_5 is hydrogen or C_1-C_3 alkyl;

t is 1;

m is 0, 1, 2 or 3; and

n is 0; or

(*iii*)



I-ccc-1

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is –C(O)–;

X^2 is –C(O)–;

X^3 is –CH_2– or –C(O)–;

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

each of R^2 is independently hydrogen, halogen, C_{1-4} aliphatic or $–OC_{1-4}$ aliphatic;

Ring A is fused 6-membered aryl containing 0-1 nitrogen atoms; and

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

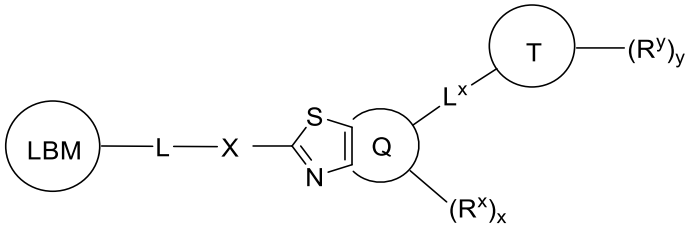
[0010b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0010c] In a further aspect of the present disclosure, there is provided a compound disclosed herein or a pharmaceutical composition thereof, for use in degrading IRAK4 protein kinase in a patient or biological sample.

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

[0010e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an IRAK4-mediated disorder, disease, or condition in a patient.

[0011] It has now been found that compounds of this present 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 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 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 present disclosure are also useful for the study of IRAK enzymes in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new IRAK inhibitors or IRAK degraders or other regulators of kinases, signaling pathways, and cytokine levels in vitro or in vivo.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

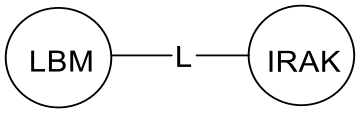
1. General Description of Certain Embodiments of the Invention:

[0015] 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. In some embodiments, a provided compound degrades IRAK4 and IMiD

CLAIMS

We claim:

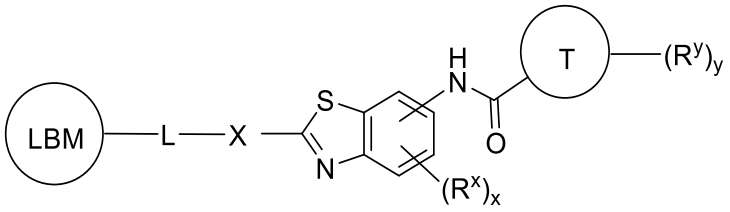
1. A compound of formula **I**:



I

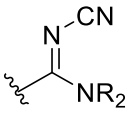
or a pharmaceutically acceptable salt thereof, wherein:

IRAK is an IRAK binding moiety capable of binding to IRAK4, said compound of formula **I** is a compound of formula **I-a-2**:



I-a-2

or a pharmaceutically acceptable salt thereof, wherein:

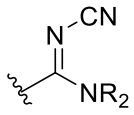
each R^x is independently hydrogen, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$,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

; or

two R^x 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;

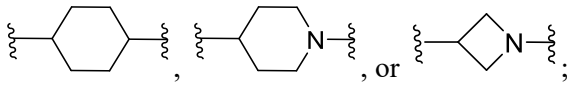
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

two R groups on the same carbon or 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 carbon or nitrogen, independently selected from nitrogen, oxygen, and sulfur;

each R^y is independently hydrogen, 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, $-C(O)NR_2$, $-C(S)NR_2$, -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 ;

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

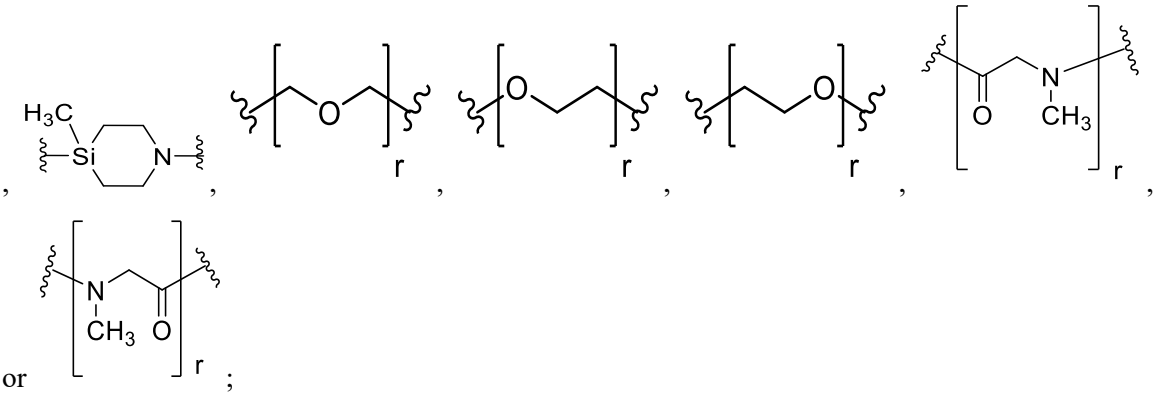
Ring T is selected from phenyl or a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring T is further optionally substituted with 1-2 oxo groups;

X is ;

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

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



or ;

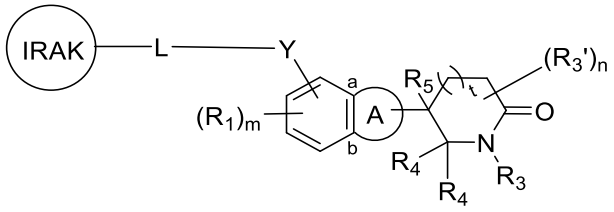
each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-12 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated 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 4-12 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;

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

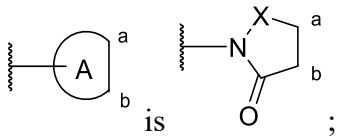
LBM is an IMiD-based cereblon E3 ubiquitin ligase binding moiety selected from:

(*i*)



I-oo-1

or a pharmaceutically acceptable salt thereof, and wherein:



;

Y is a bond;

X is C(O) or CH_2;

each R_1 is independently hydrogen, halogen, C_1-C_4 alkyl, or C_1-C_4 alkoxy;

R_3 is hydrogen;

two R_4, together with the carbon atom to which they are attached, form C(O);

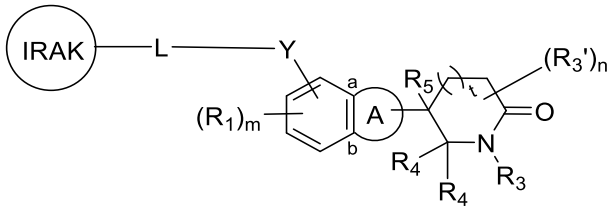
R_5 is hydrogen or C_1-C_3 alkyl;

t is 1;

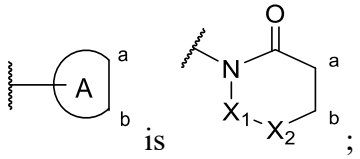
m is 0, 1, 2, 3, or 4; and

n is 0;

(*ii*)



I-oo-1



is ;

Y is a bond;

X_1-X_2 is C(H)═N, C(C_1-C_4 alkyl)═N, or C(C_1-C_4 haloalkyl);

each R_1 is independently hydrogen, halogen, -NH_2, -OH, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, or C_1-C_6 haloalkoxy;

R_3 is hydrogen;

two R_4, together with the carbon atom to which they are attached, form C(O);

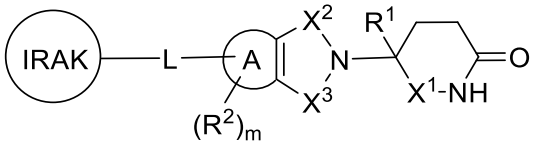
R_5 is hydrogen or C_1-C_3 alkyl;

t is 1;

m is 0, 1, 2 or 3; and

n is 0; or

(*iii*)



I-ccc-1

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is –C(O)–;

X^2 is –C(O)–;

X^3 is –CH_2– or –C(O)–;

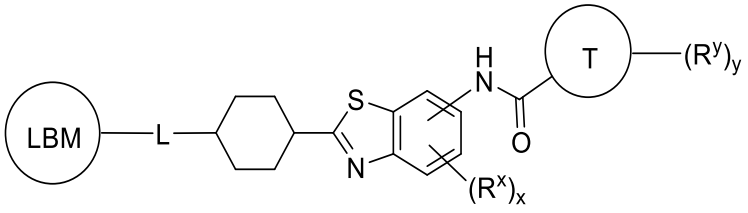
R^1 is hydrogen or C_{1-4} aliphatic;

each of R^2 is independently hydrogen, halogen, C_{1-4} aliphatic or –OC_{1-4} aliphatic;

Ring A is fused 6-membered aryl containing 0-1 nitrogen atoms; and

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

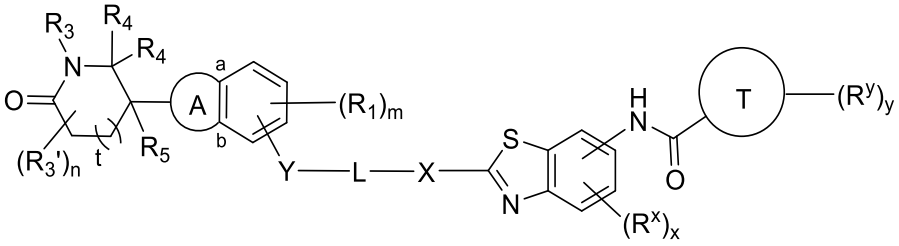
2. The compound of claim 1, wherein said compound is selected from:



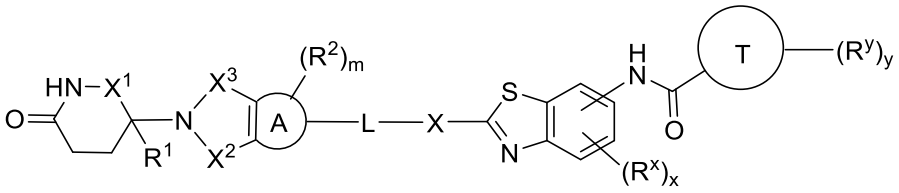
I-a-5

or a pharmaceutically acceptable salt thereof.

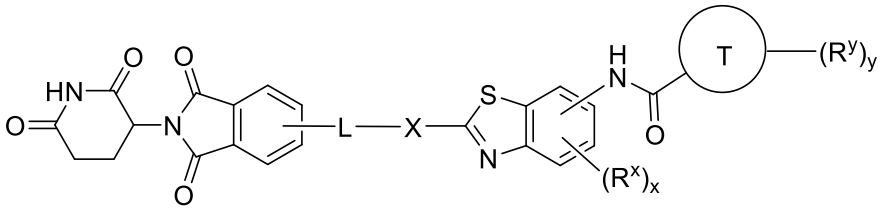
3. The compound of claim 1, wherein said compound is selected from any one of the following formulae:



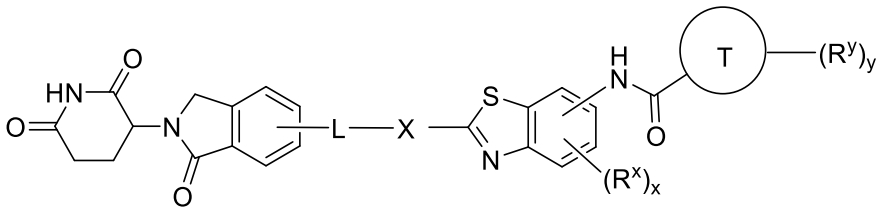
I-a-10



I-a-11



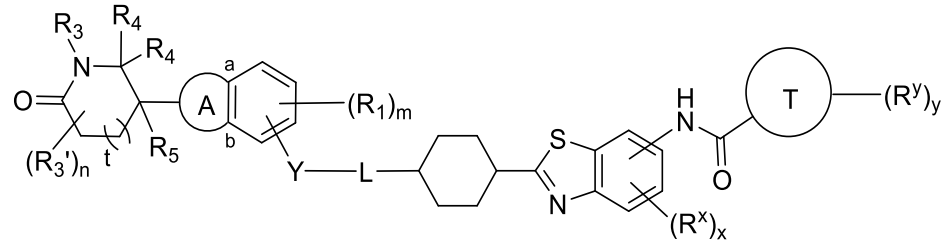
I-a-12



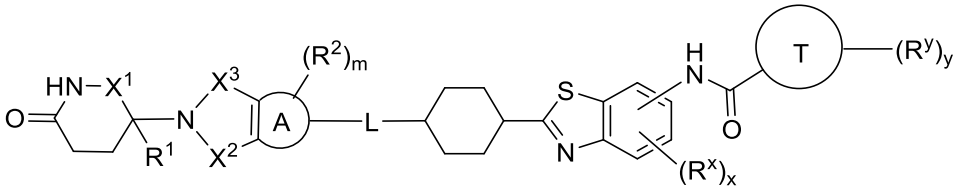
I-a-13

or a pharmaceutically acceptable salt thereof.

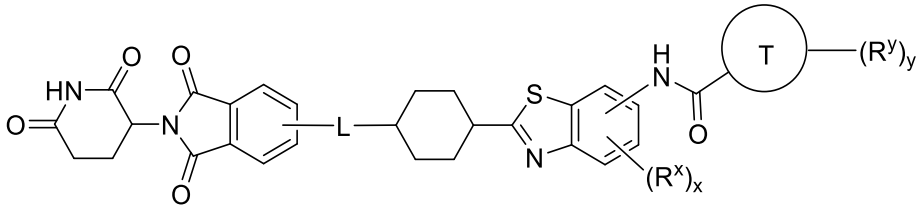
4. The compound of claim 2, wherein said compound is selected from any one of the following formulae:



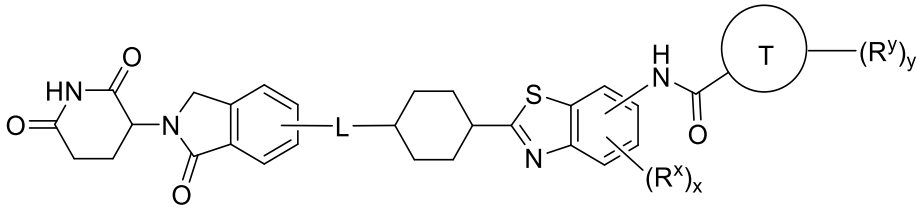
I-a-26



I-a-27



I-a-28



I-a-29

or a pharmaceutically acceptable salt thereof.

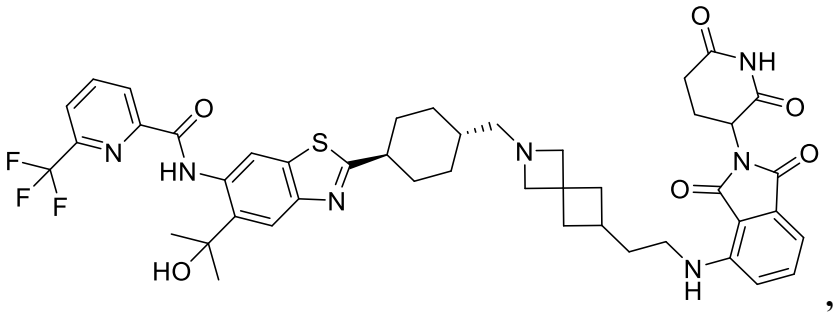
5. The compound of any one of claims 1-4, wherein R^x is hydrogen, R^z, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -CFR_2, -CF_2R, -CF_3, -$CR_2(OR)$, -$CR_2(NR_2)$, -C(O)R, -C(O)OR, -$C(O)NR_2$, -$C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, -$OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, -$N(R)C(O)NR_2$, or -$N(R)S(O)_2R$.

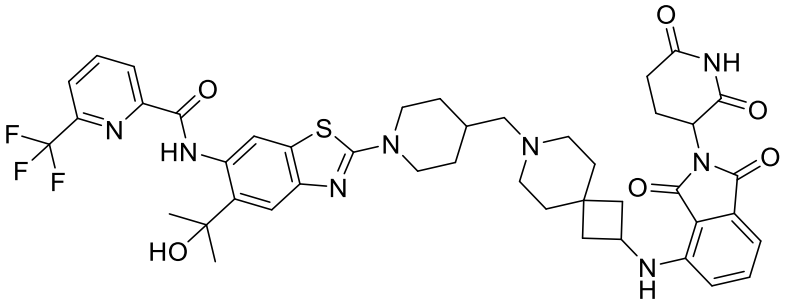
6. The compound of any one of claims 1-5, wherein R^y is hydrogen, R^z, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -CFR_2, -CF_2R, -CF_3, -$CR_2(OR)$, -$CR_2(NR_2)$, -C(O)R, -C(O)OR, -$C(O)NR_2$, -$C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, -$OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, -$N(R)C(O)NR_2$, or -$N(R)S(O)_2R$.

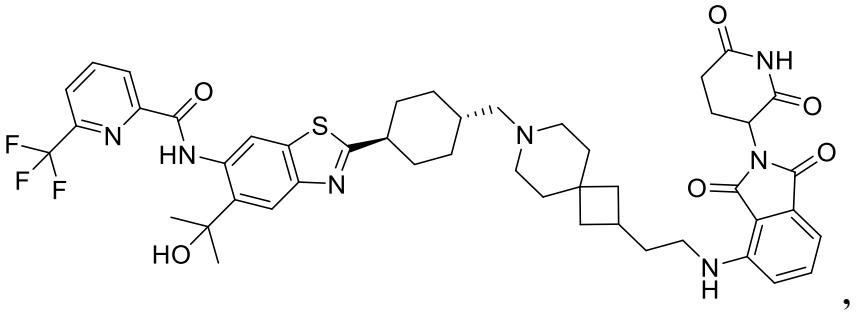
7. The compound of any one of claims 1-6, wherein Ring T is a 5-10 membered monocyclic or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

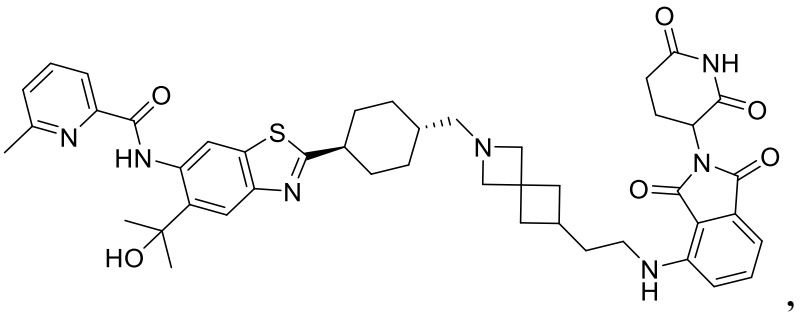
8. The compound of any one of claims 1-7, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -N(R)-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -N(R)$S(O)_2$-, -$S(O)_2$N(R)-,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

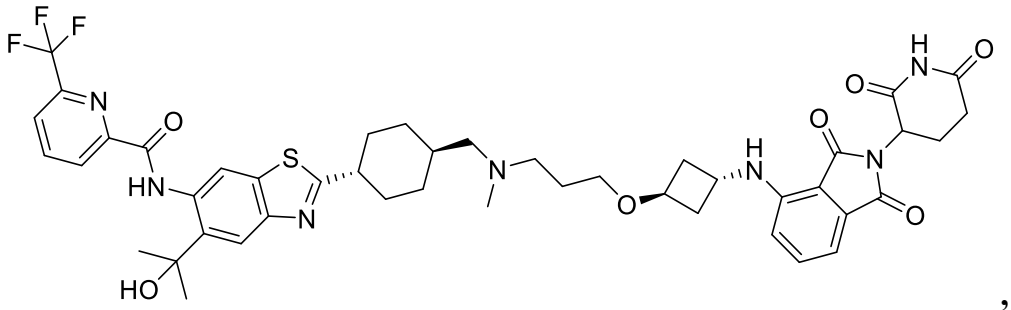
9. The compound of any of one of claims 1-8, wherein said compound is selected from:

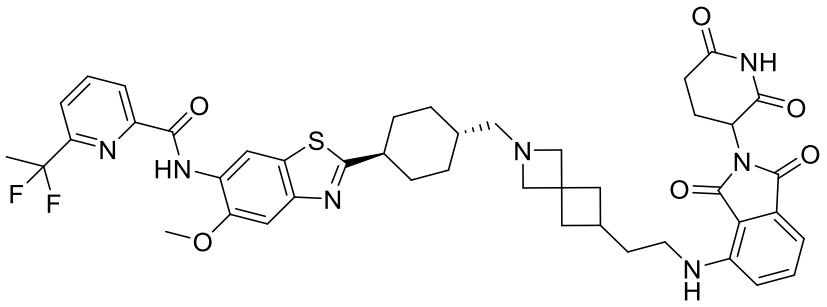
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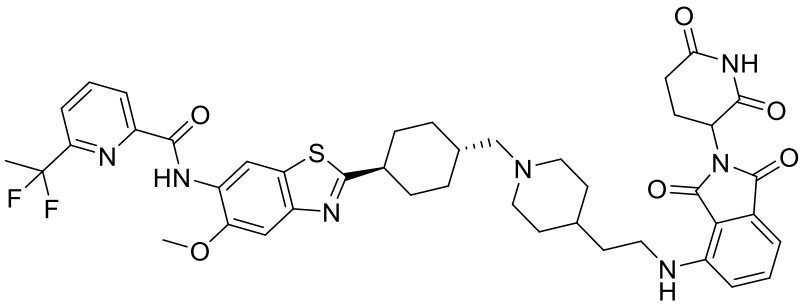
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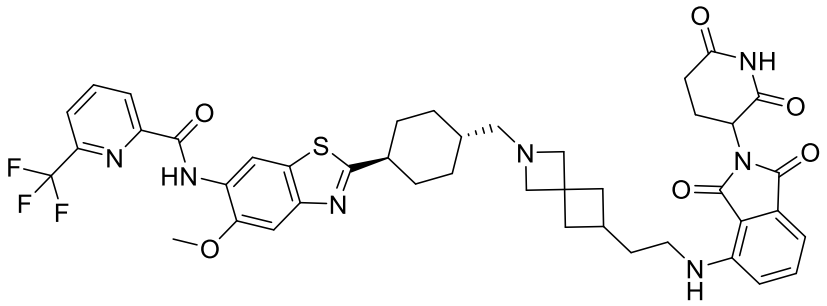
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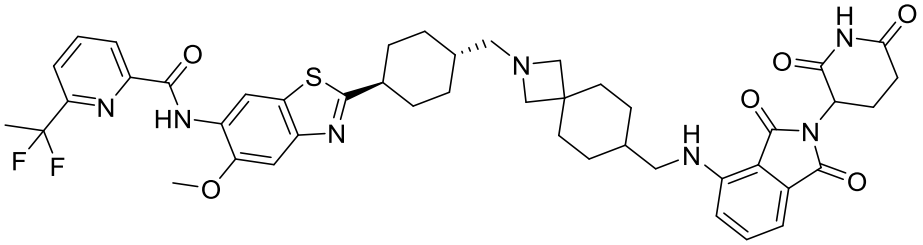
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I-7 ,

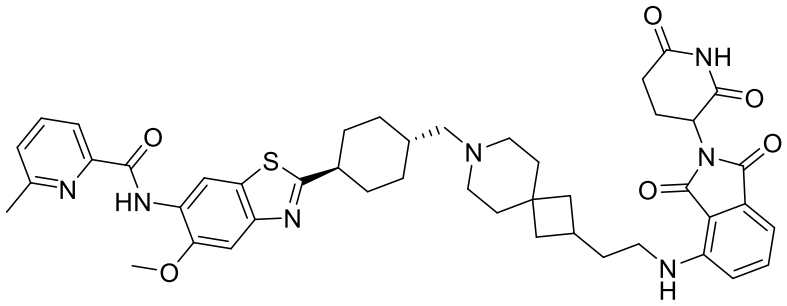
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I-10 ,

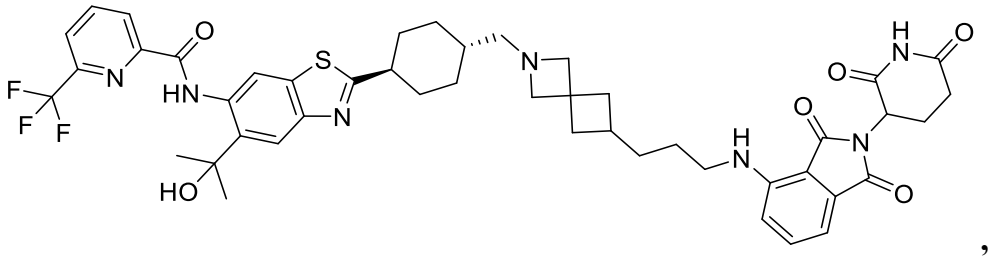
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I-12



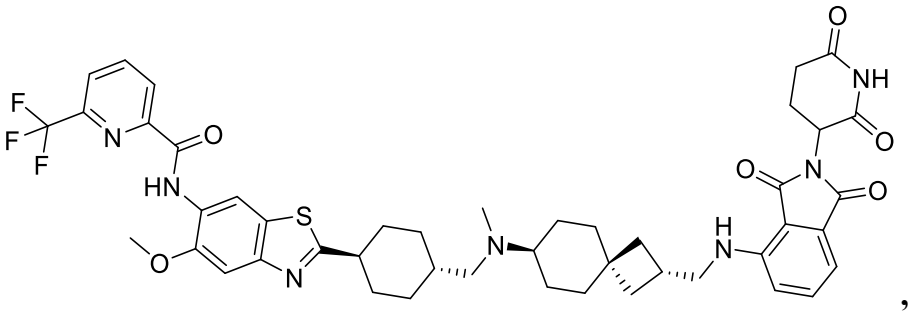
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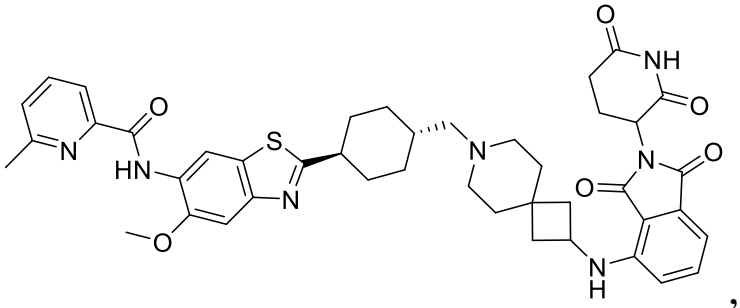
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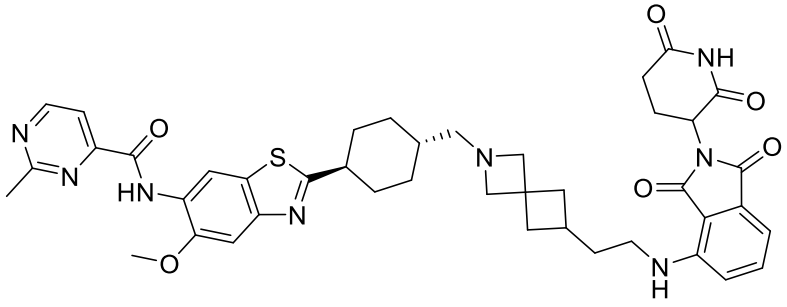
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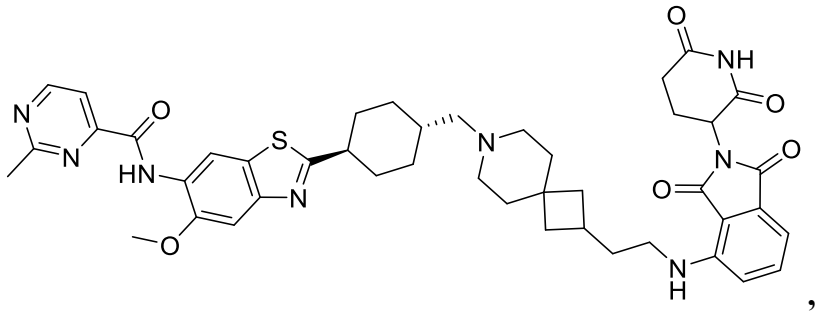
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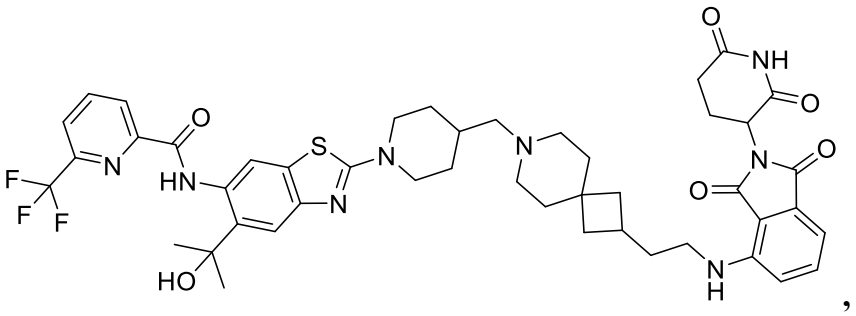
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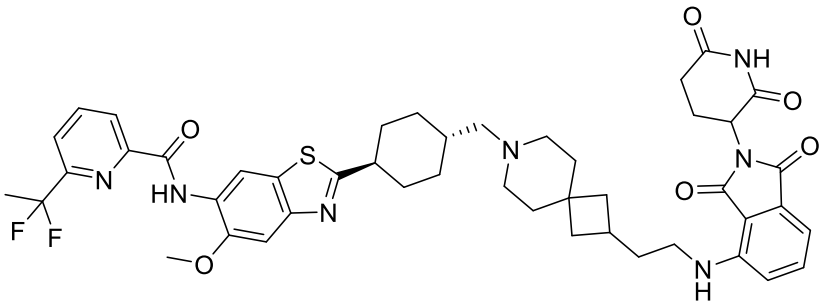
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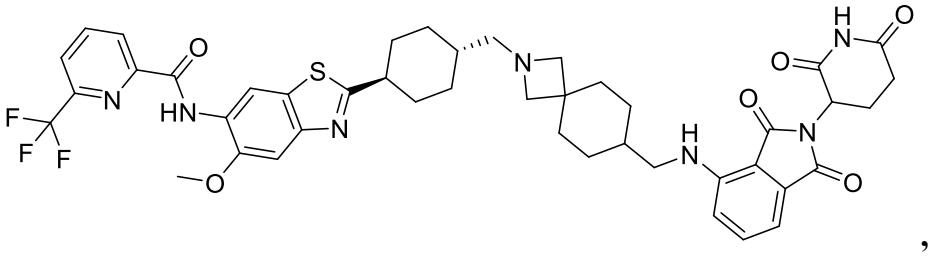
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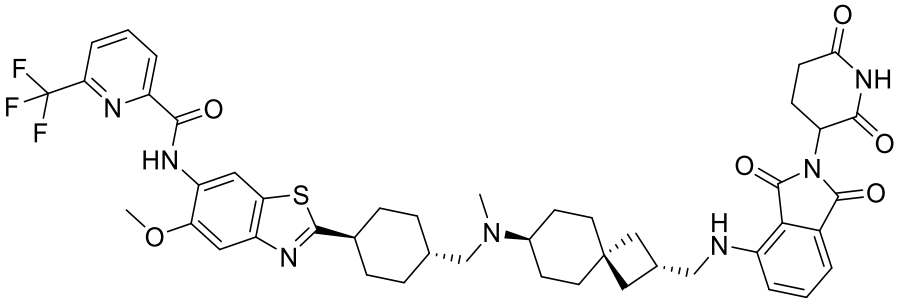
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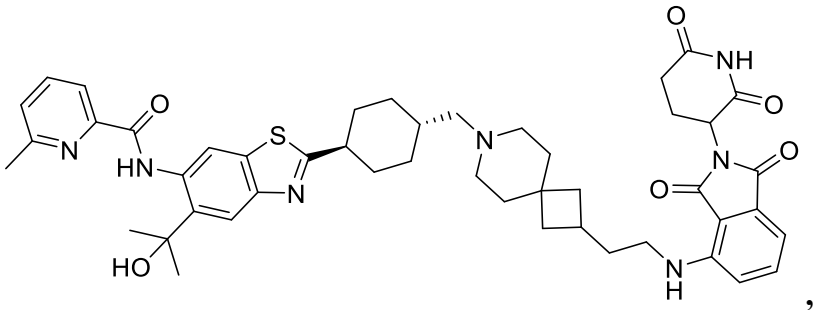
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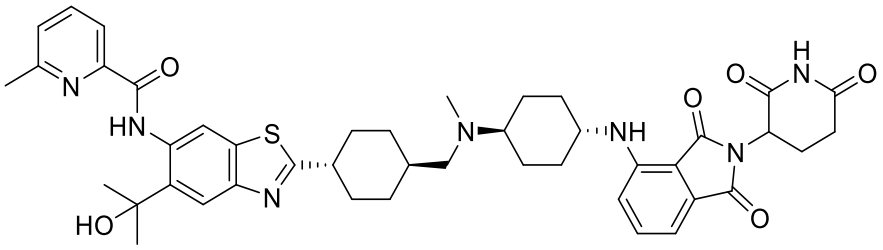
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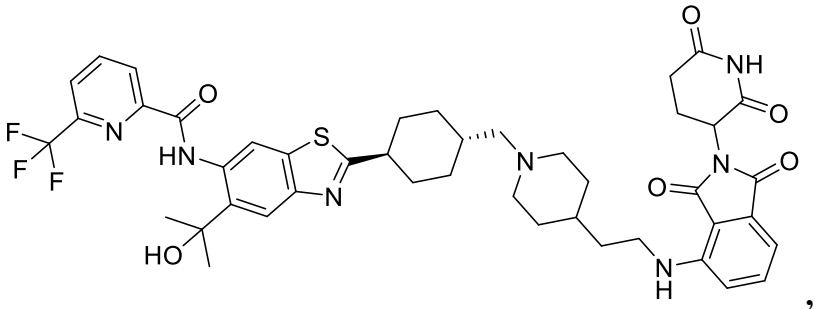
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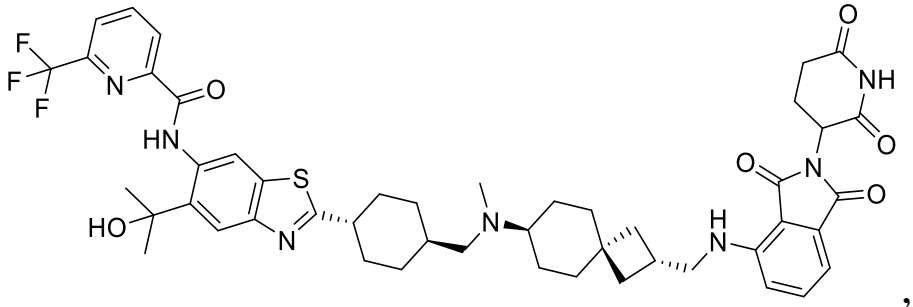
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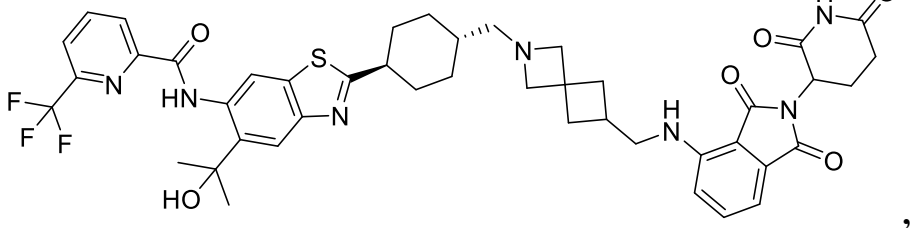
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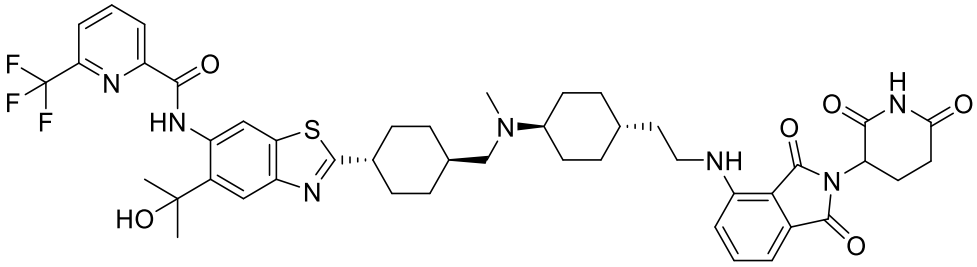
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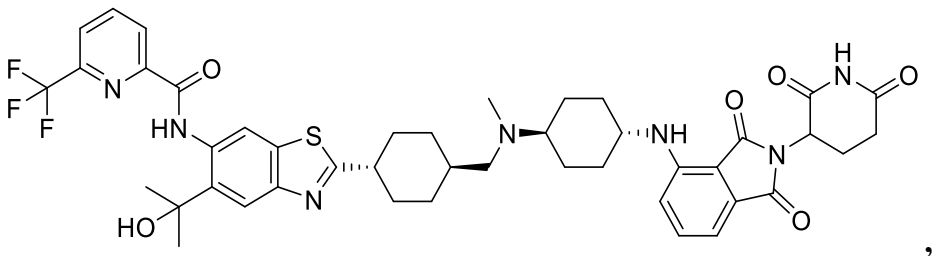


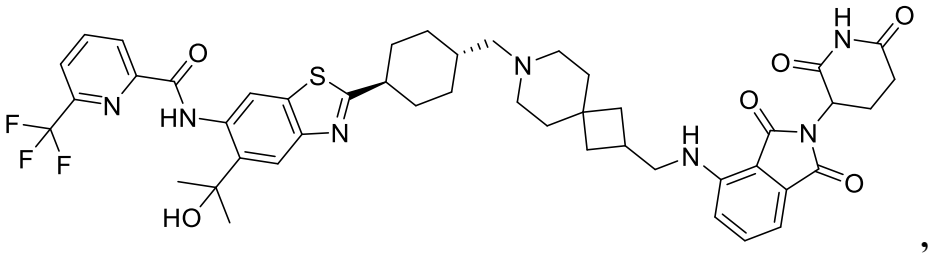
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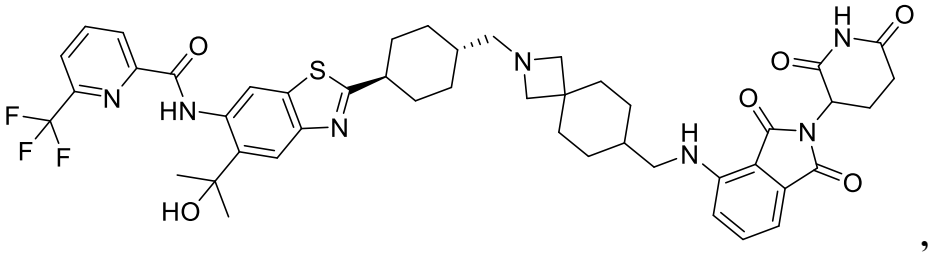
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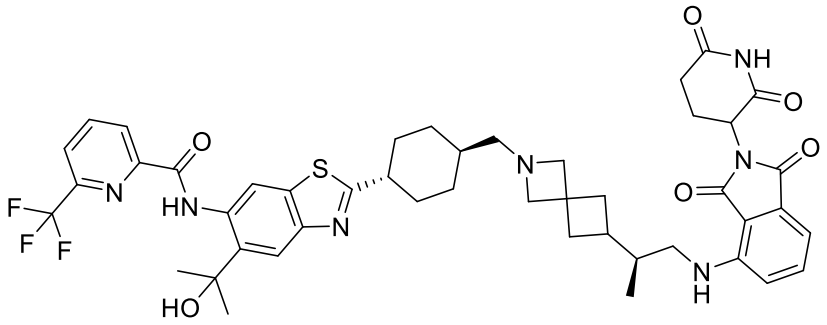


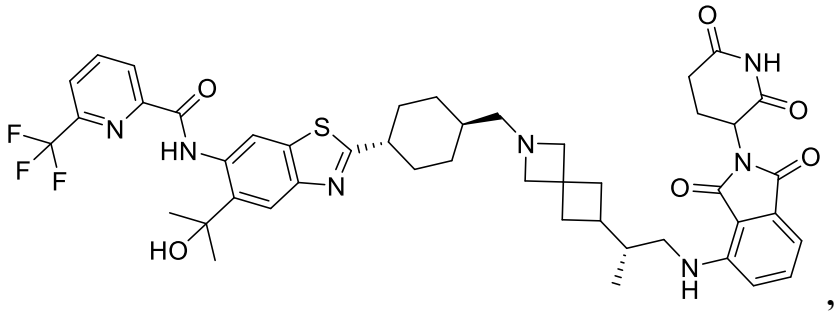
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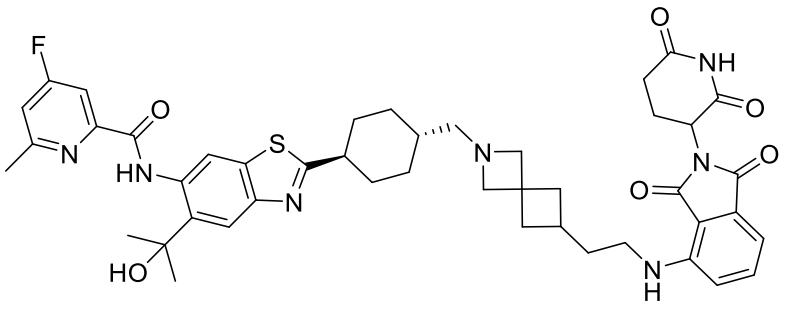
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I-29 ,

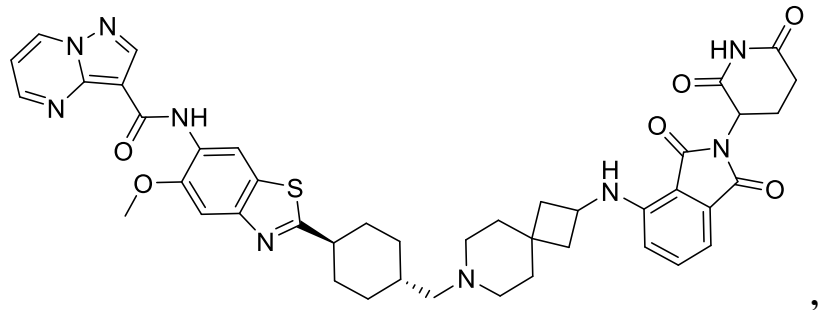
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I-31 ,

I-32 ,

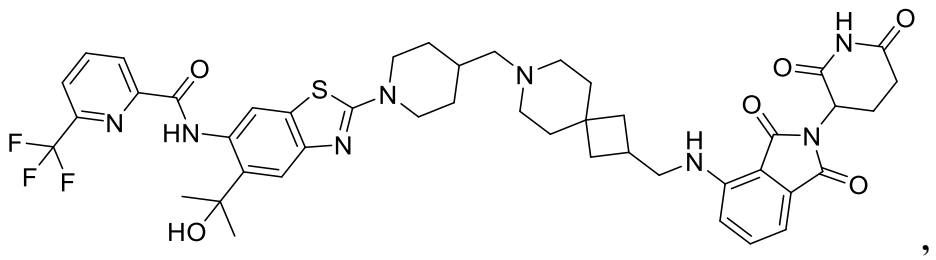
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I-34



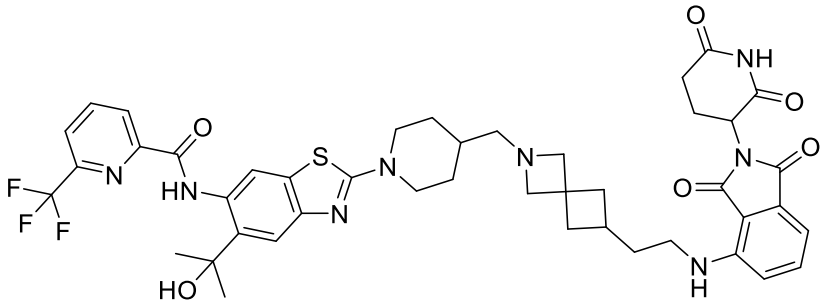
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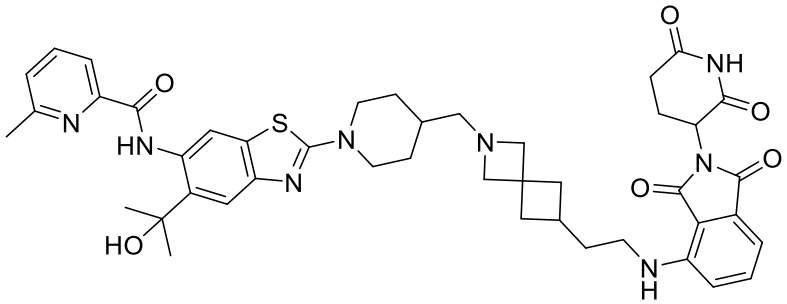
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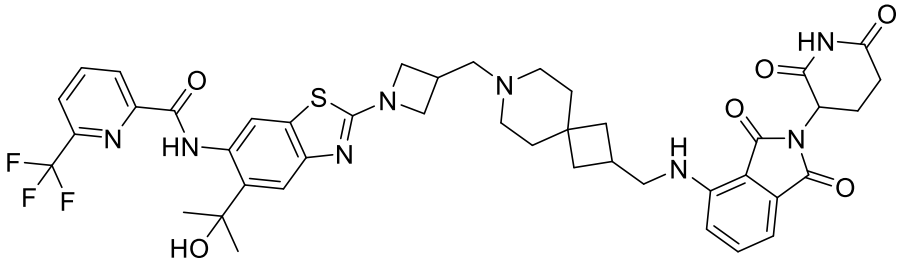
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I-37



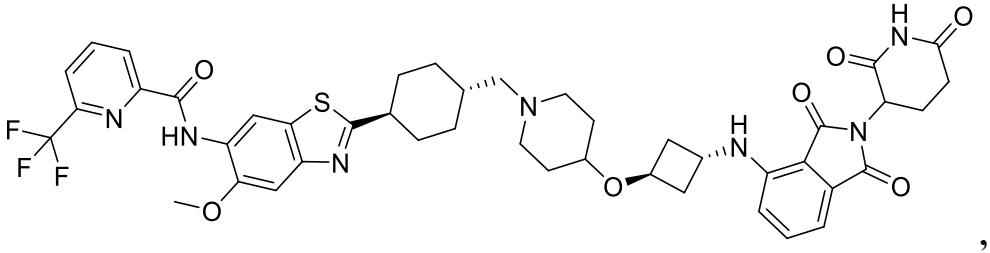
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I-38



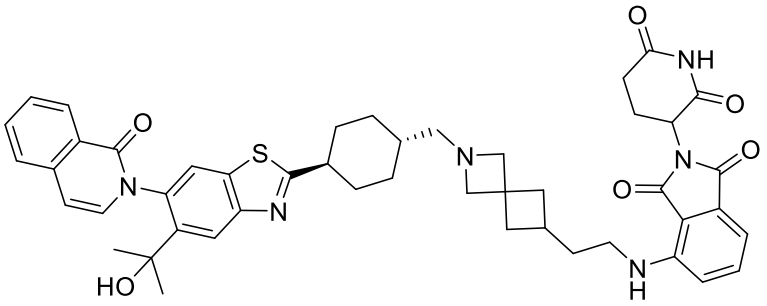
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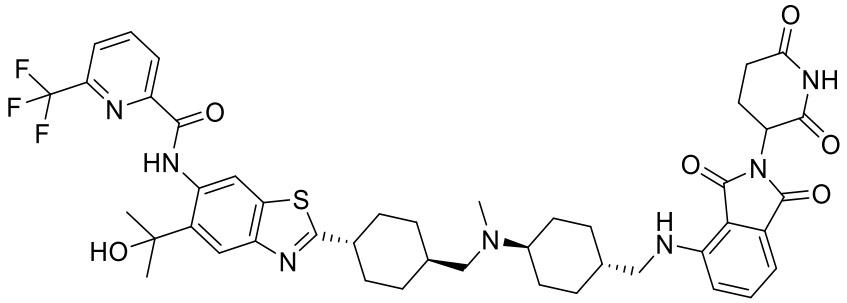
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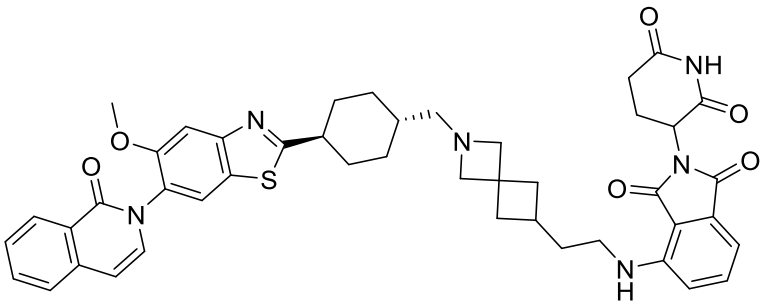
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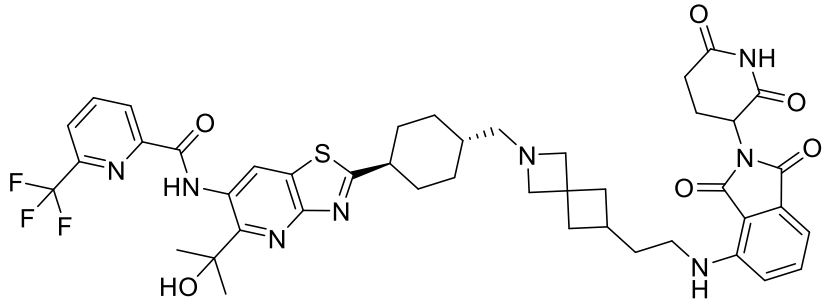
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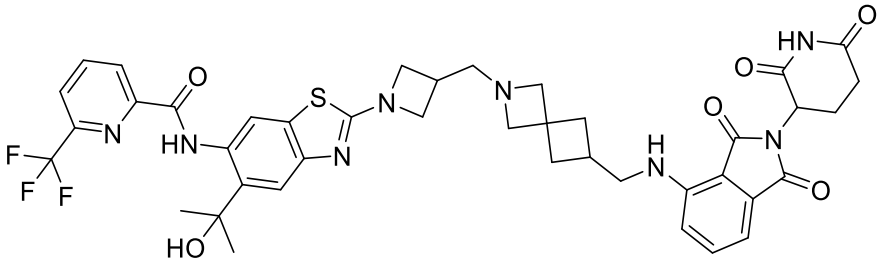
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I-43



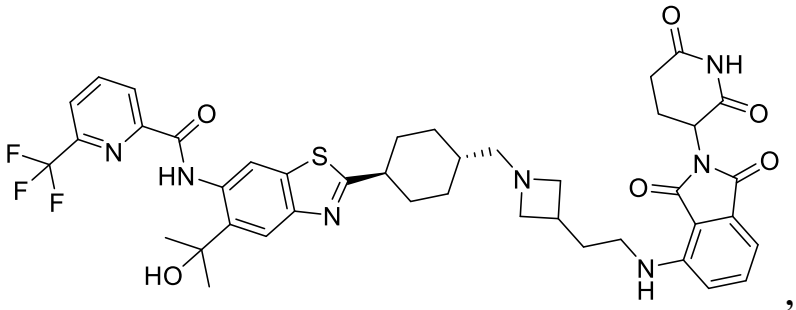
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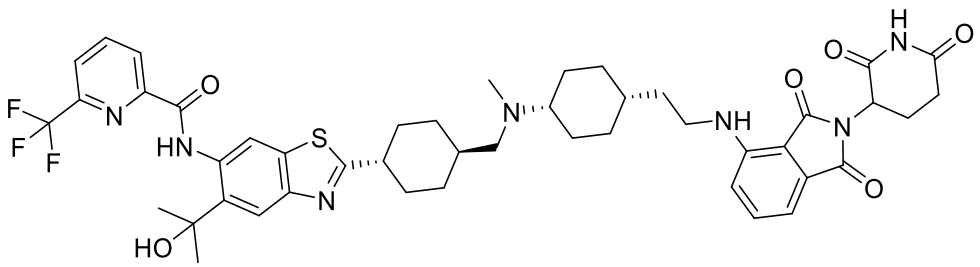
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I-45



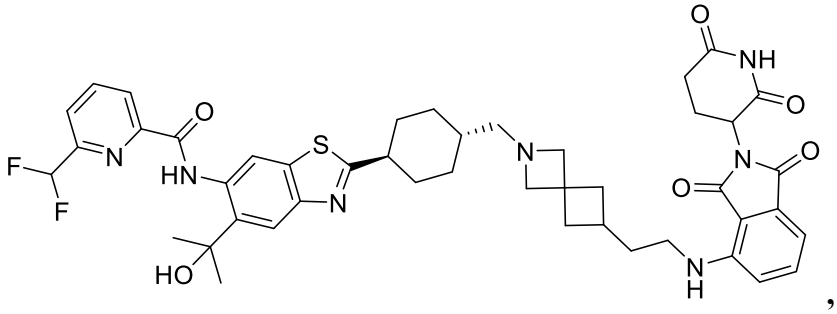
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I-46



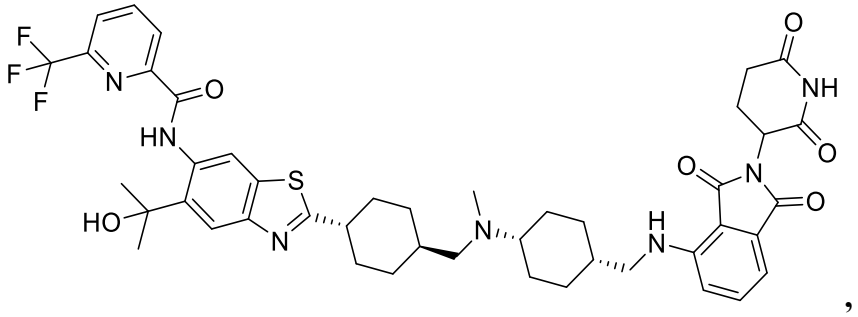
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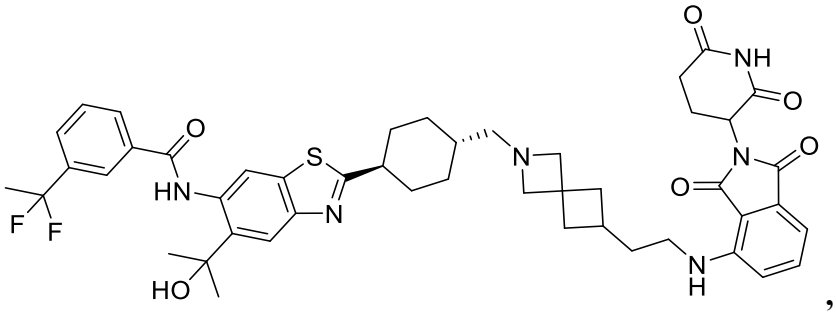
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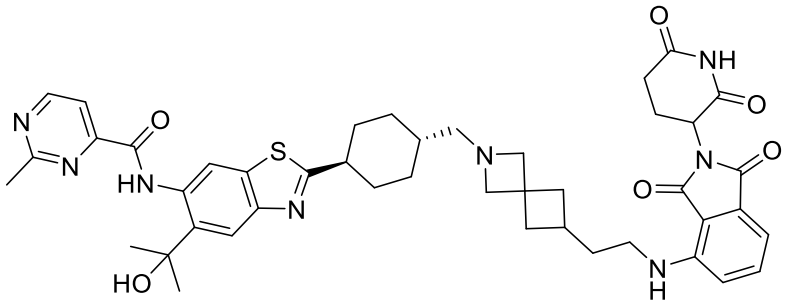
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I-50



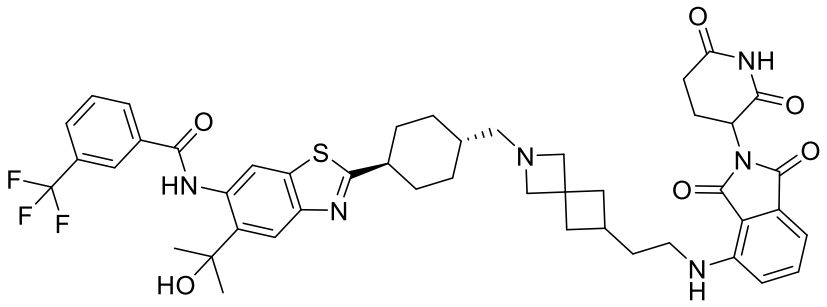
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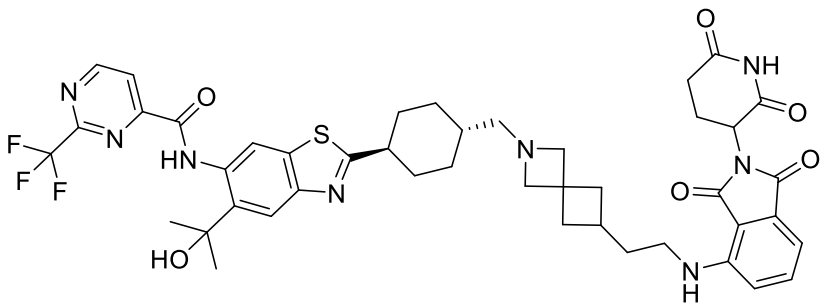
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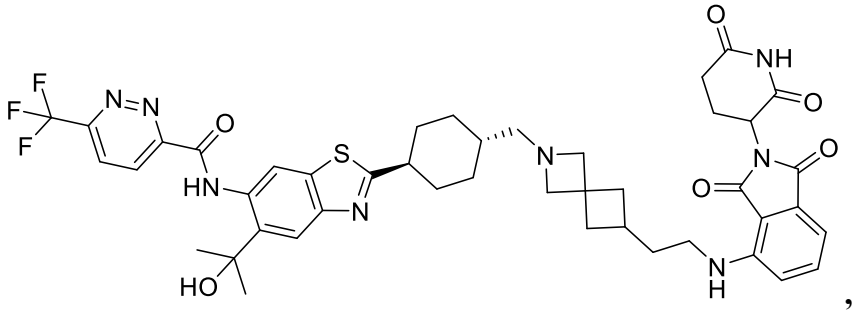
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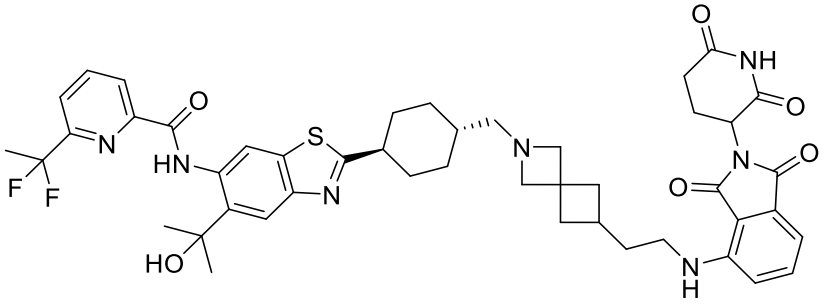
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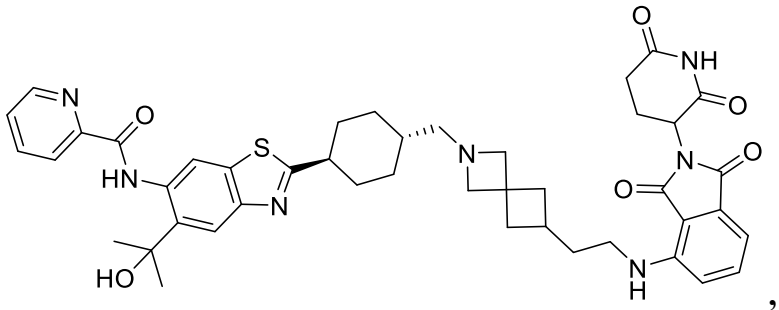
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I-56



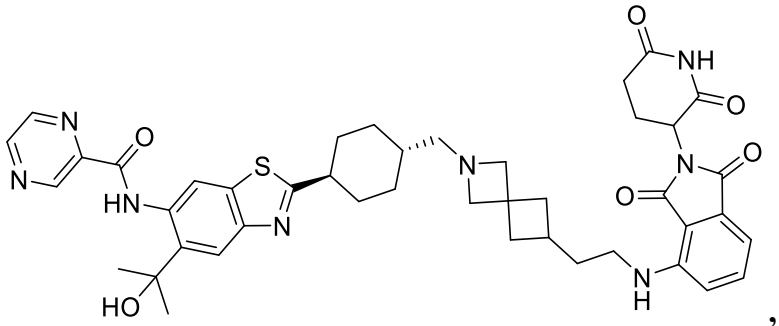
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I-57



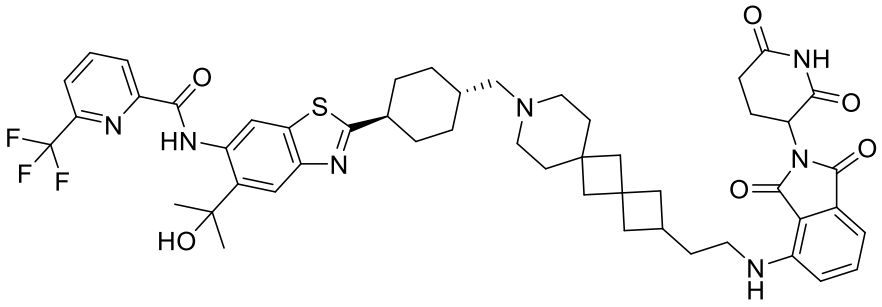
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I-58



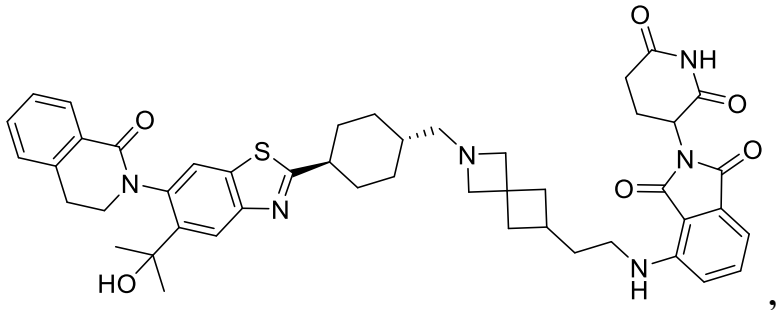
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I-59



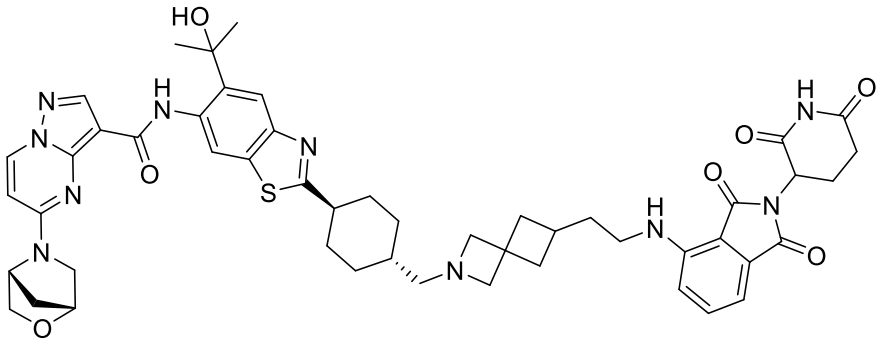
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I-60



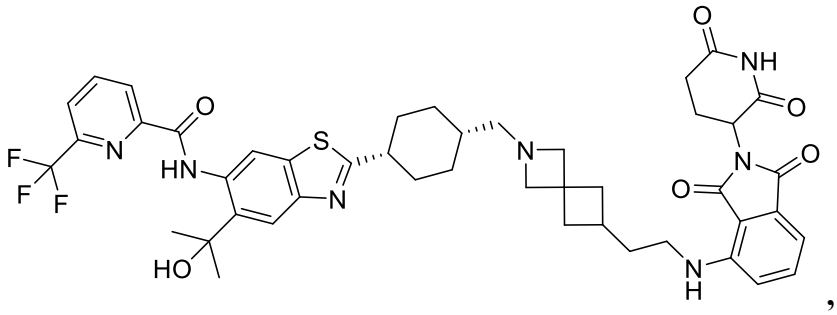
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I-61



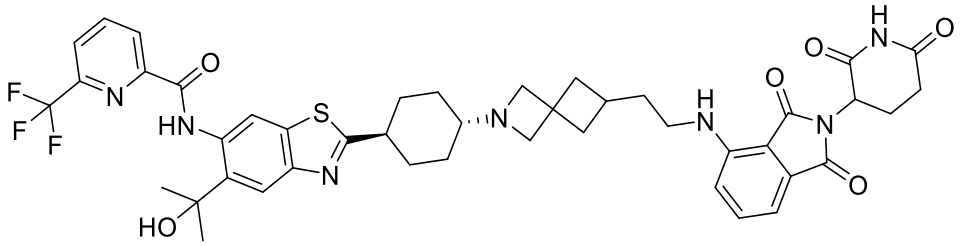
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I-62



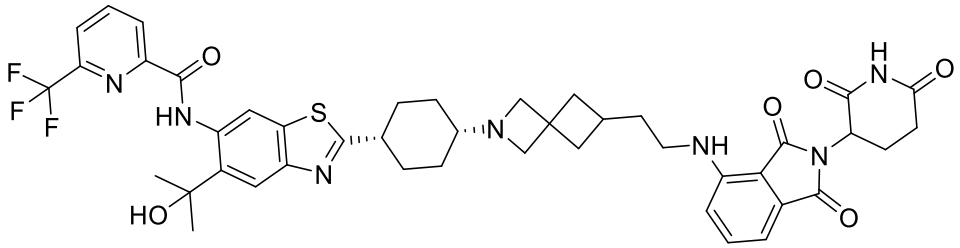
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I-63



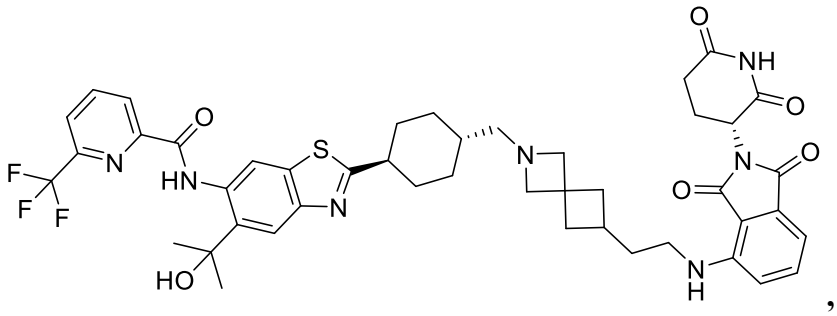
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I-64



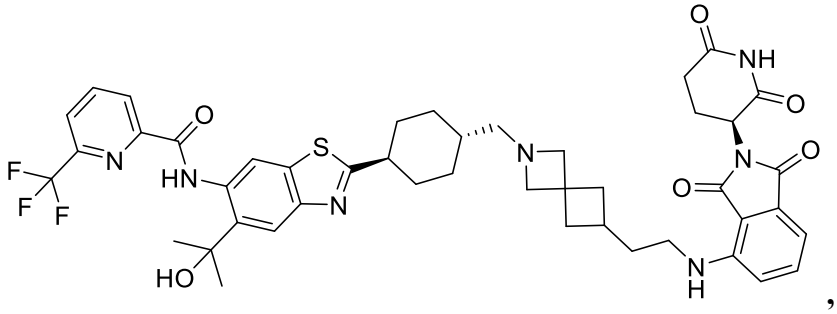
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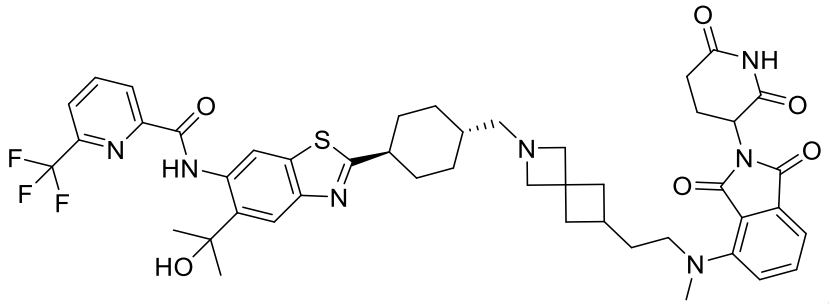


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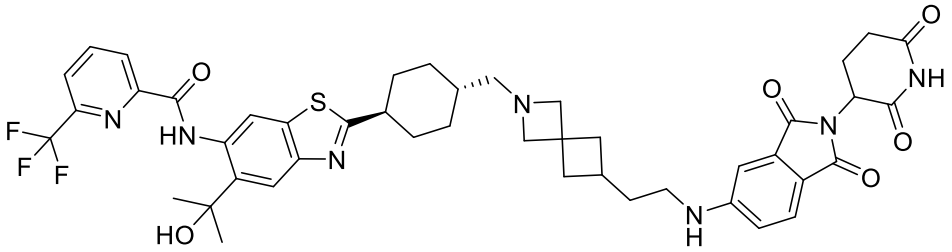
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or a pharmaceutically acceptable salt thereof.

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

11. The pharmaceutical composition according to 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 degrading IRAK4 protein kinase in a patient or biological sample.

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

14. 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.

15. The use of claim 14, wherein the compound or pharmaceutical composition thereof is to be administered to the patient, and wherein an additional therapeutic agent is to be further administered.

16. The use of claim 14, wherein the IRAK4-mediated disorder, disease or condition is a cancer or proliferative disorder selected from 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, and intravascular large B-cell lymphoma.

17. The use 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.