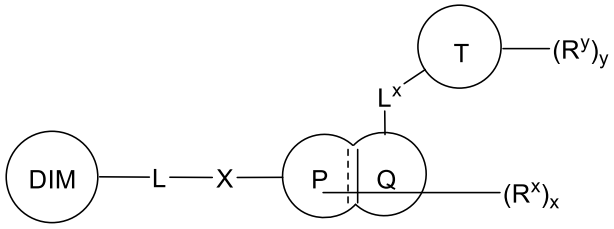
therapeutic agents that leverage E3 ligase mediated protein degradation to target cancer-associated proteins such as interleukin-1 receptor-associated kinases ("IRAK") hold promise as therapeutic agents. Accordingly, there remains a need to find compounds that are IRAK degraders useful as therapeutic agents.

SUMMARY

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



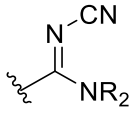
I-a

or a pharmaceutically acceptable salt thereof, wherein:

each R^x is independently hydrogen, R^z, halogen, -CN, and -OR;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated 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, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-SiR_3$, 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 P is a 5-membered heteroaryl ring having 1-3 heteroatoms

independently selected from nitrogen, oxygen, and sulfur;

Ring Q is benzo;

Ring T is selected from phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring T is further optionally substituted with 1-2 oxo groups;

L^x is -NHCO-;

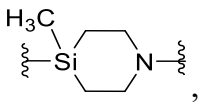
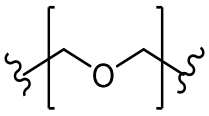
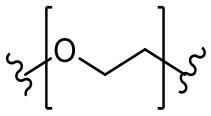
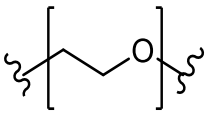
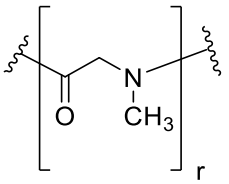
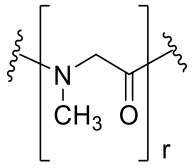
X is ;

 is a single or double bond;

x is 0, 1, or 2;

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

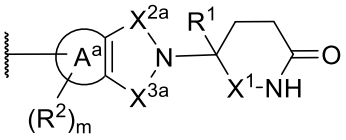
L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy-, -O-, -N(R)-, $–Si(R)_2–$, –Si(OH)(R)–, $–Si(OH)_2–$, –P(O)(OR)–, –P(O)(R)–, $–P(O)(NR_2)–$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -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 , 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, 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, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and

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

DIM is a degradation inducing moiety, wherein said degradation moiety is a cereblon E3 ubiquitin ligase binding moiety of formula **I-ccc-1**:



I-ccc-1

wherein:

X^1 is –C(O)–;

X^{2a} is –C(O)–;

X^{3a} 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^a is a fused ring selected from a 6-membered aryl containing 0-1 nitrogen atoms; and

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

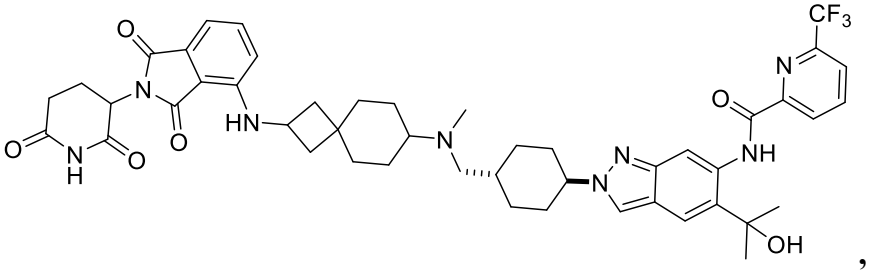
[0008b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

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

[0008d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating an IRAK-mediated disorder, disease, or condition in a patient, wherein the IRAK-mediated disorder, disease or condition is selected from the group consisting of a cancer, a neurodegenerative disease, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, a condition associated with organ transplantation, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T cell activation, a cardiovascular disorder, and a CNS disorder.

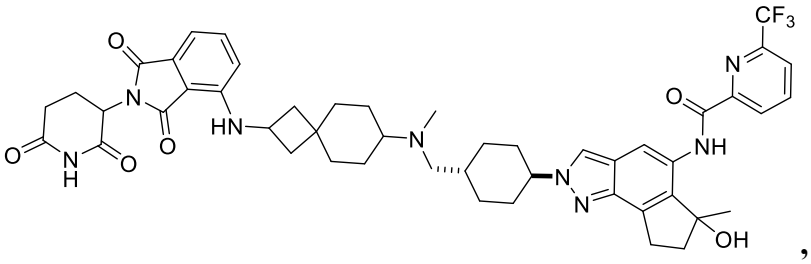
[0008e] In a further aspect of the present disclosure, there is provided a compound selected from any one of the following:

I-2



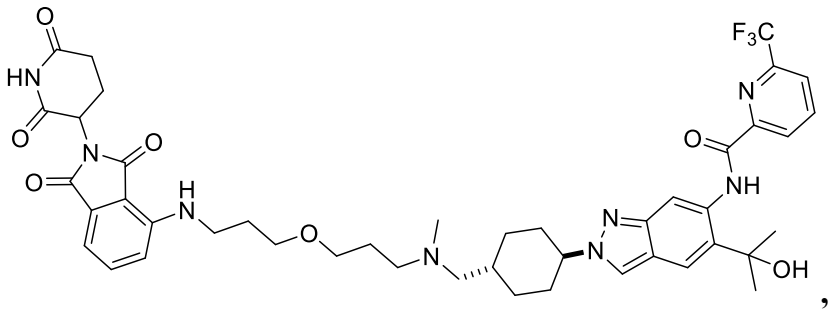
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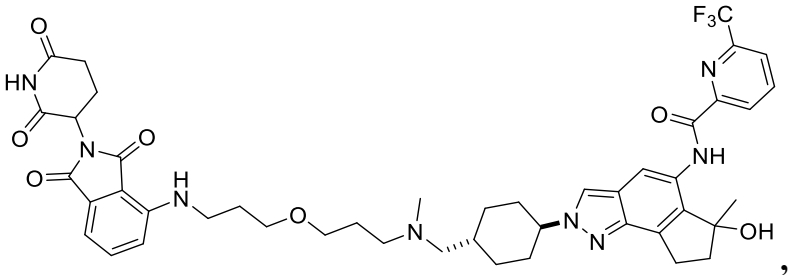
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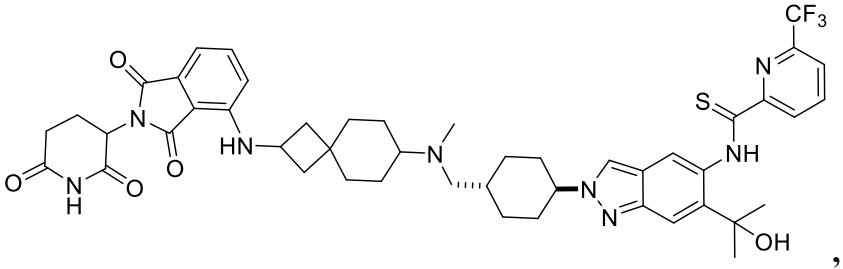
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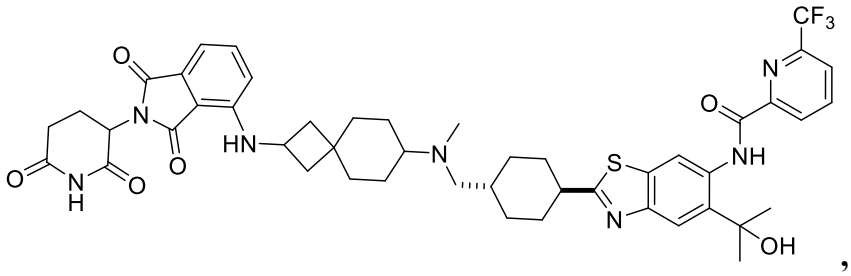
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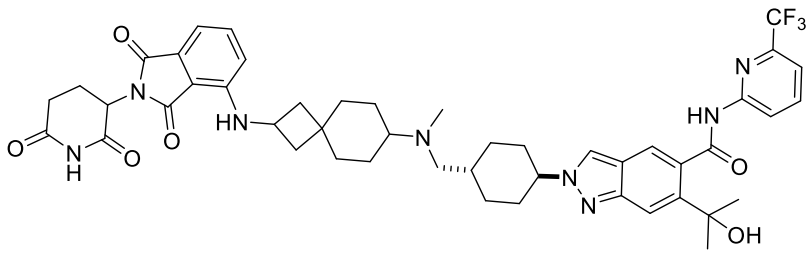
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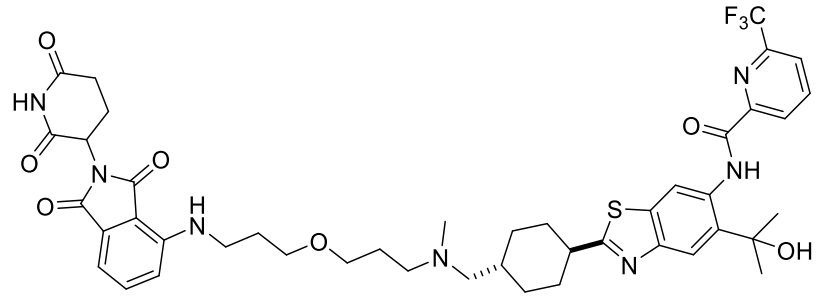
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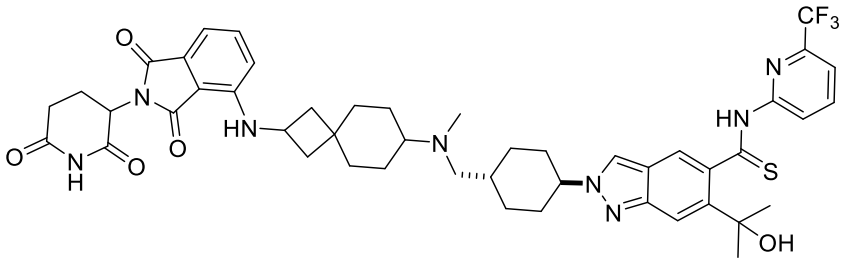
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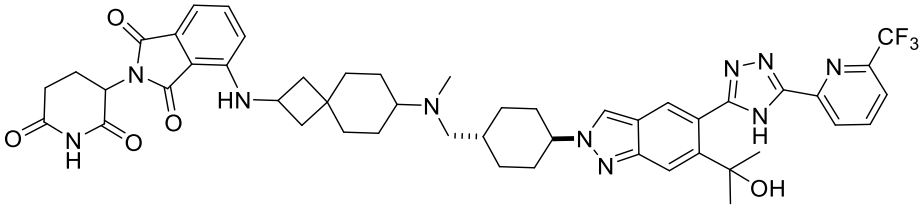
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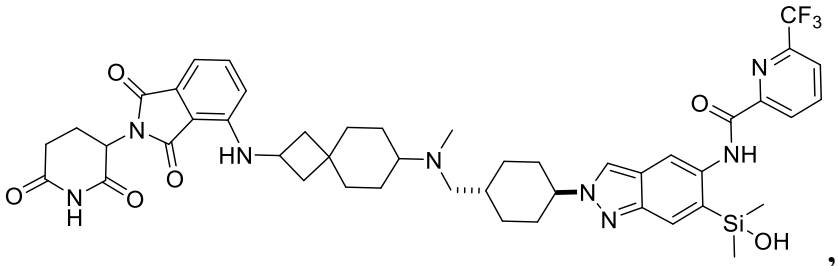
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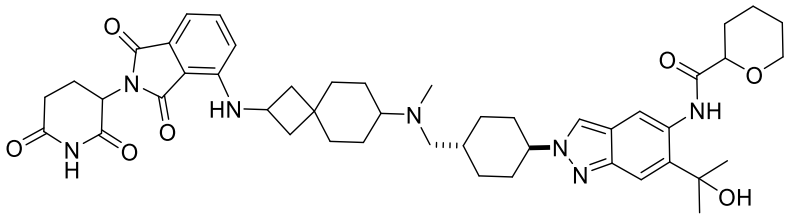
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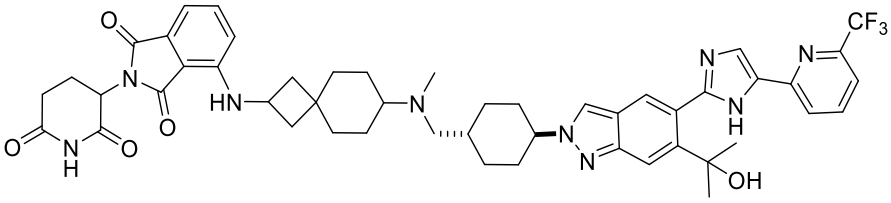
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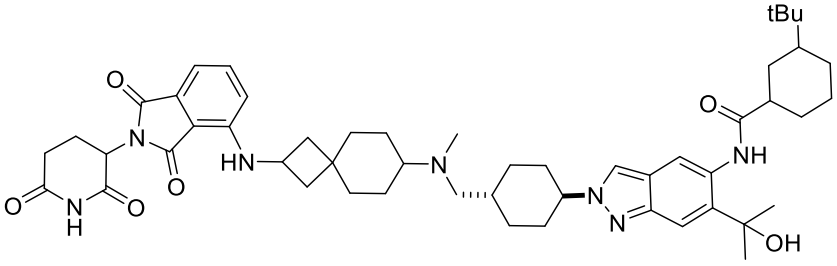
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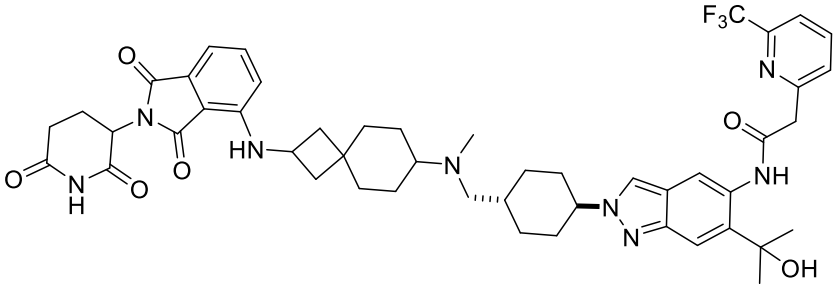
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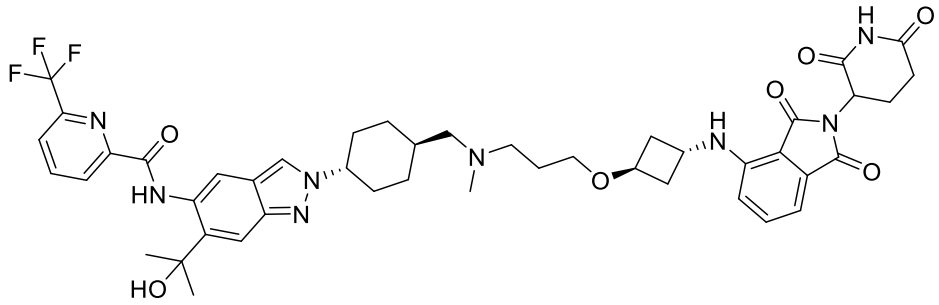
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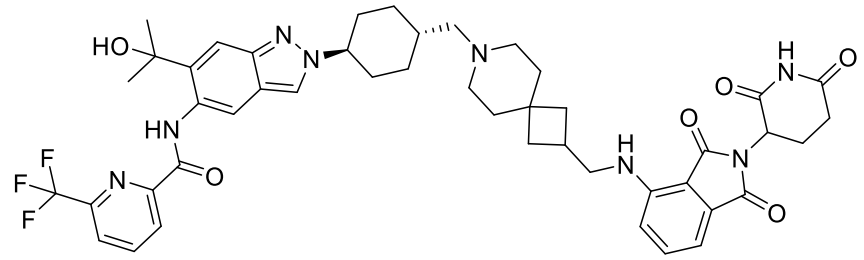
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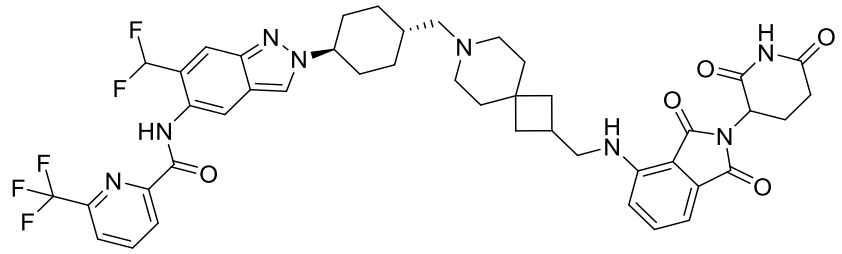
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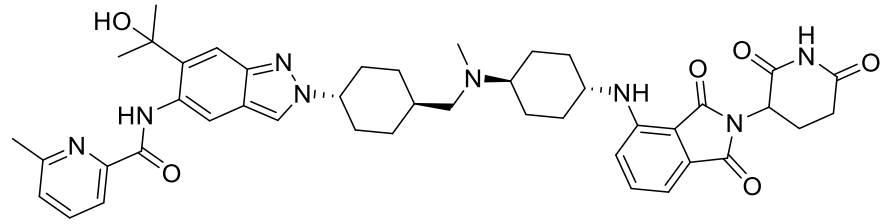
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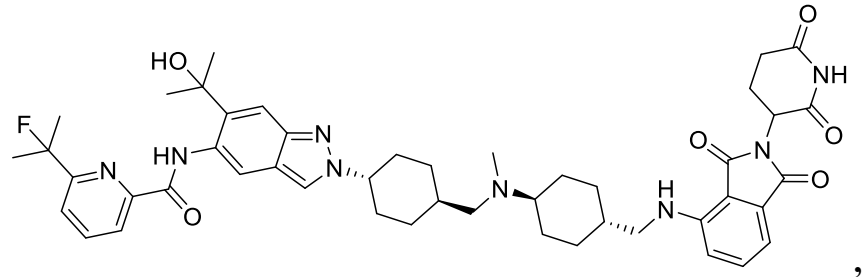
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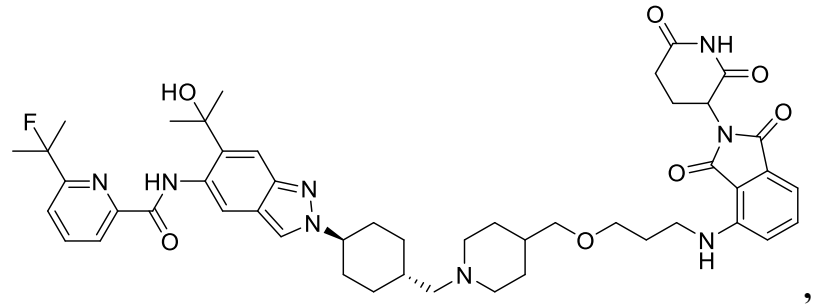
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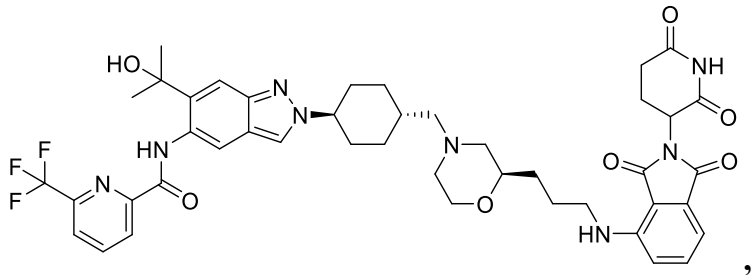
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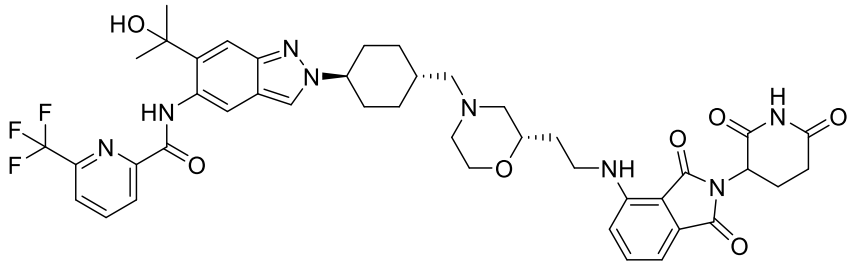
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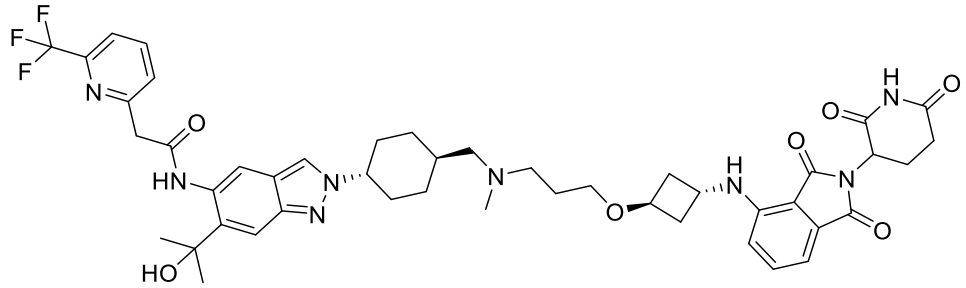
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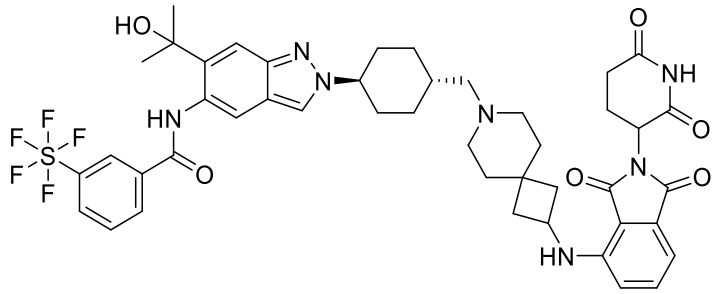
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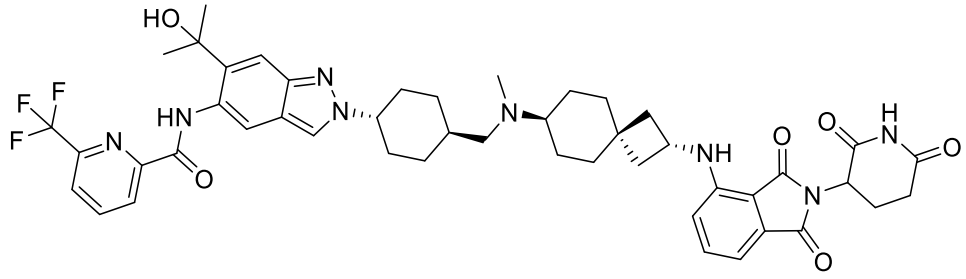
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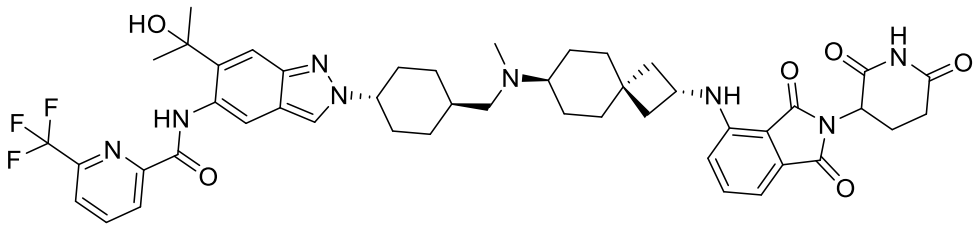
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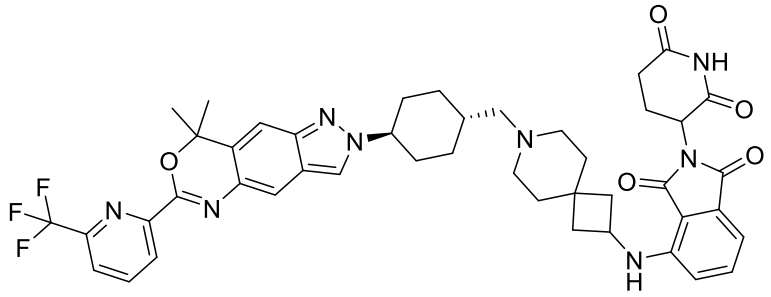
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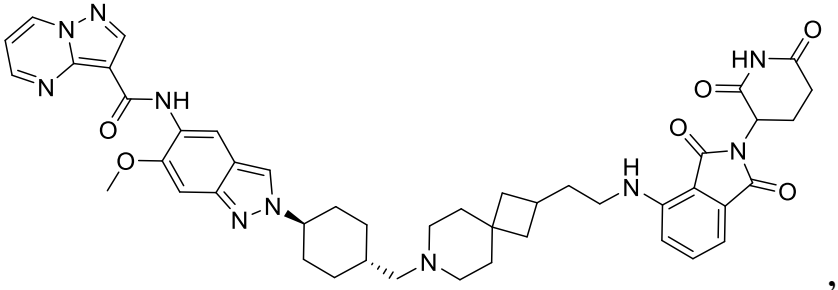
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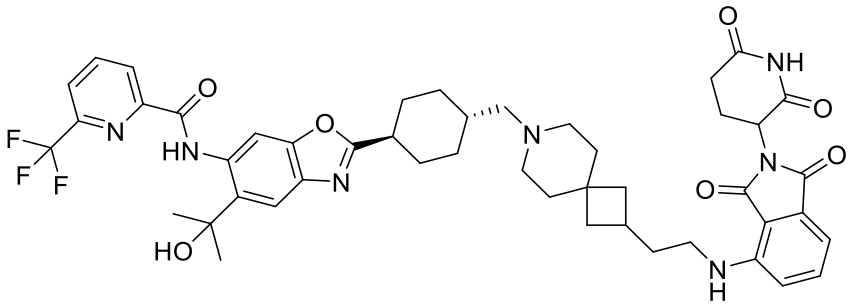
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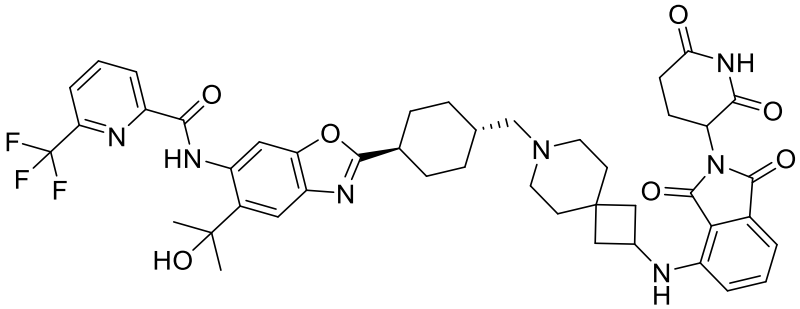
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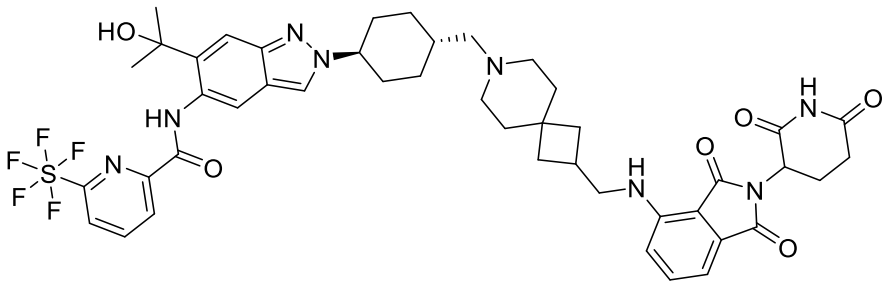
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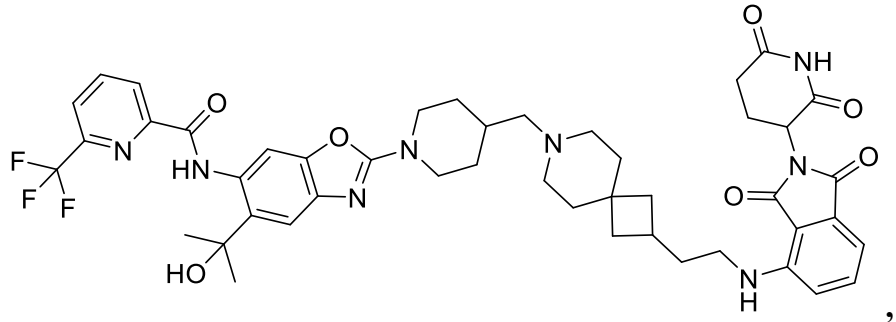
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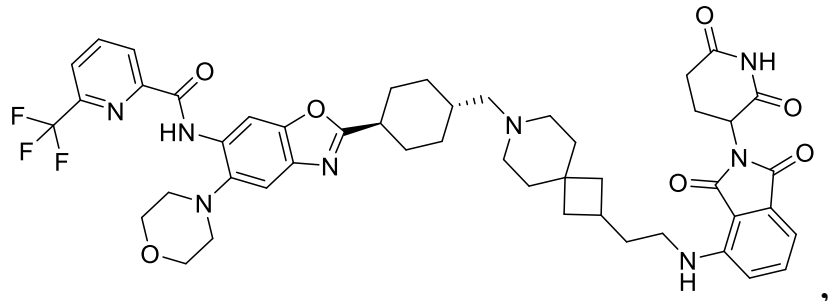
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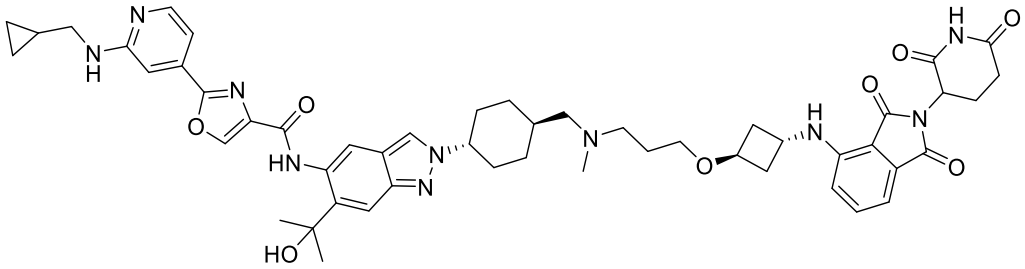
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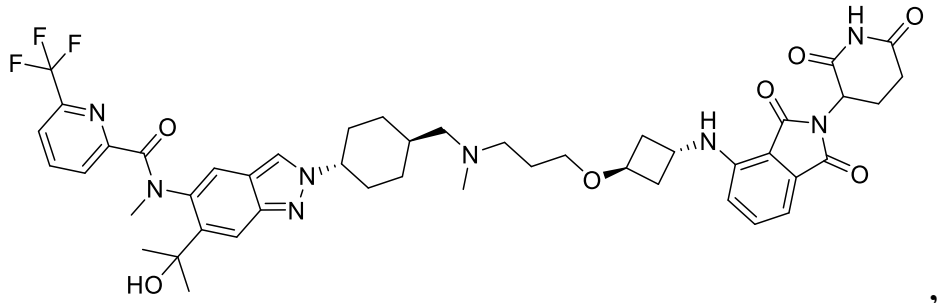
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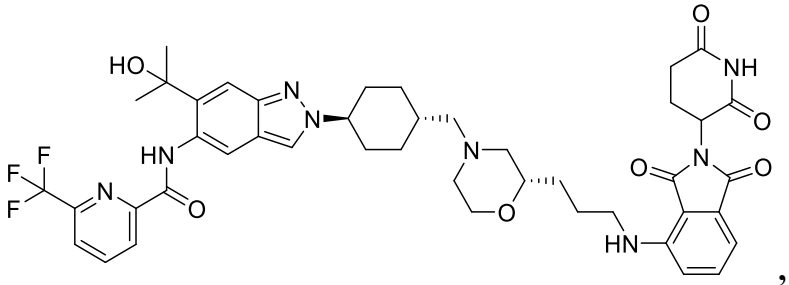
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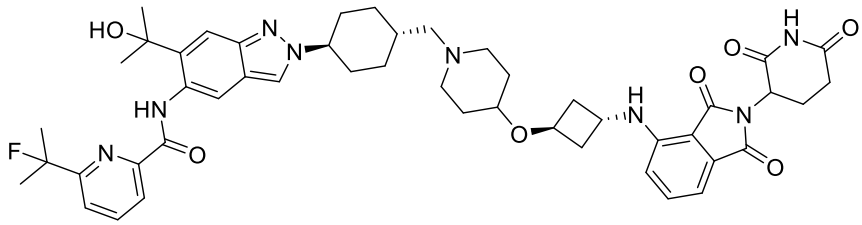
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I-233



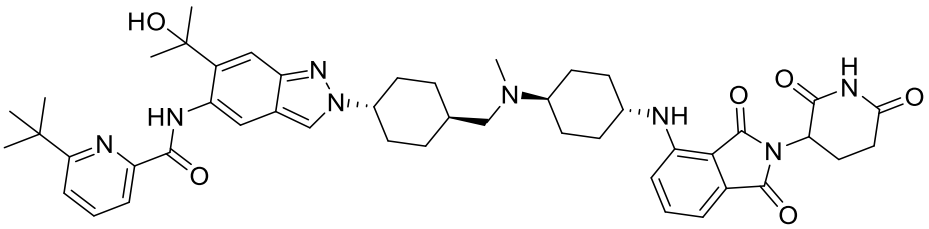
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I-234



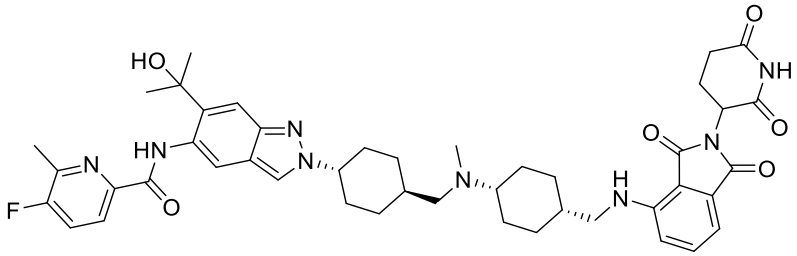
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I-236



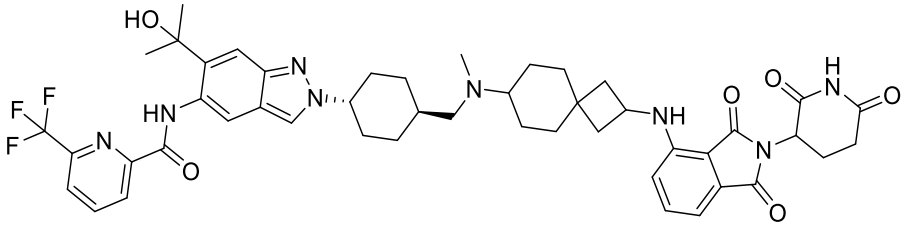
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I-237



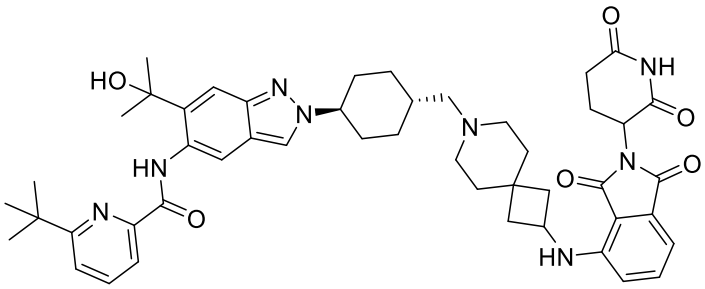
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I-238



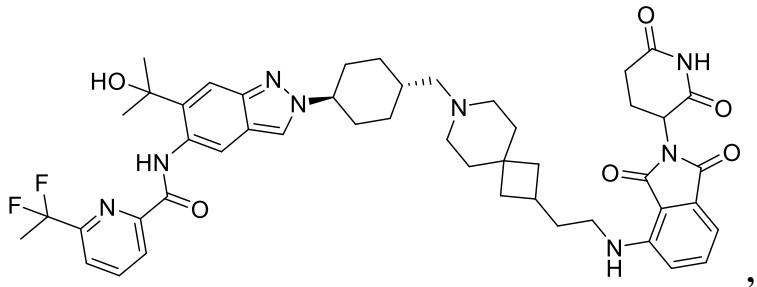
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I-249



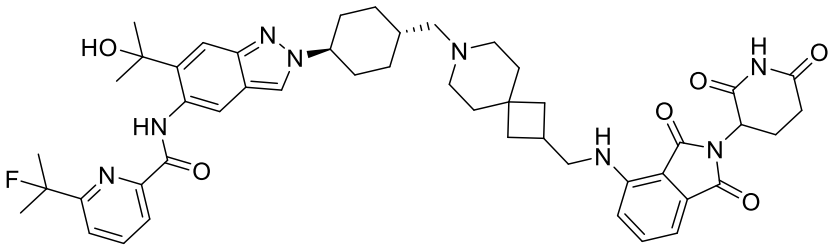
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I-250



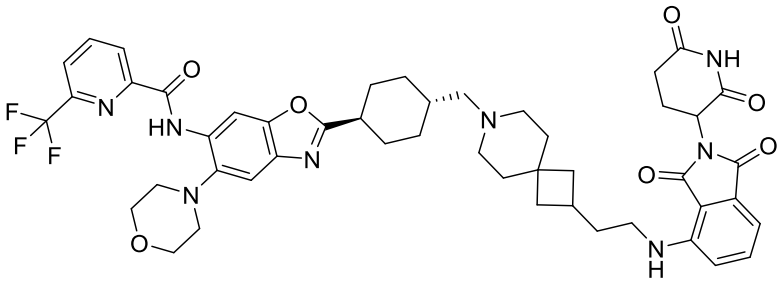
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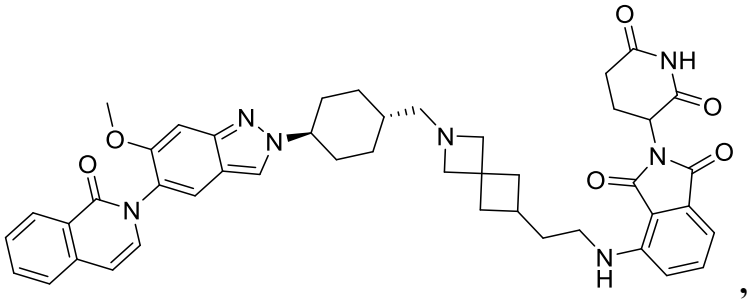
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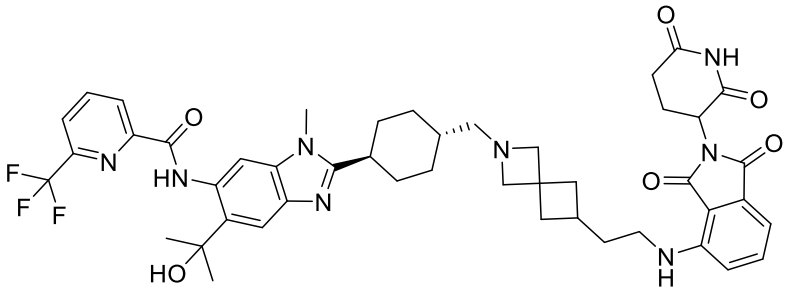
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I-286



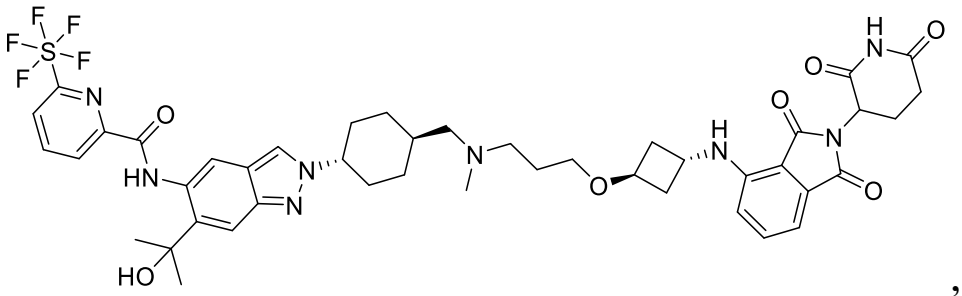
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I-287



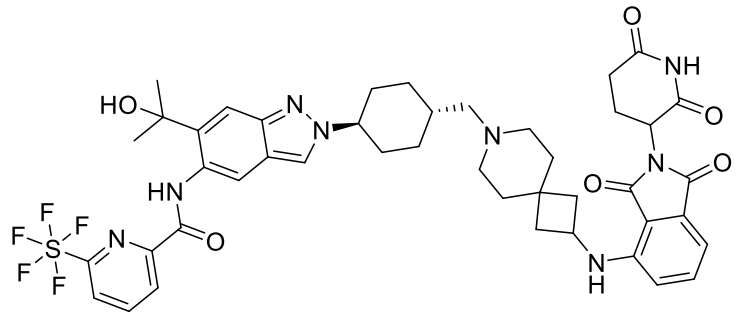
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I-290



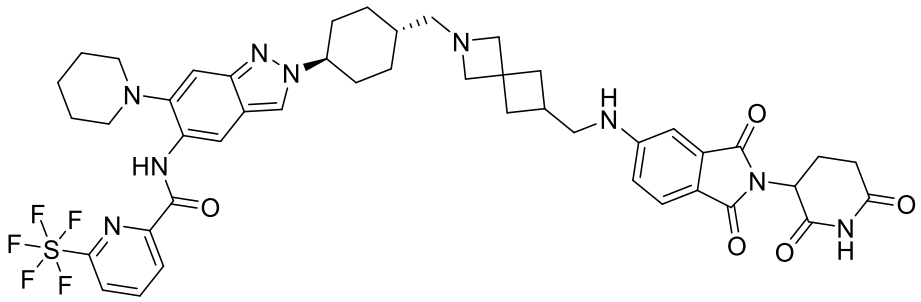
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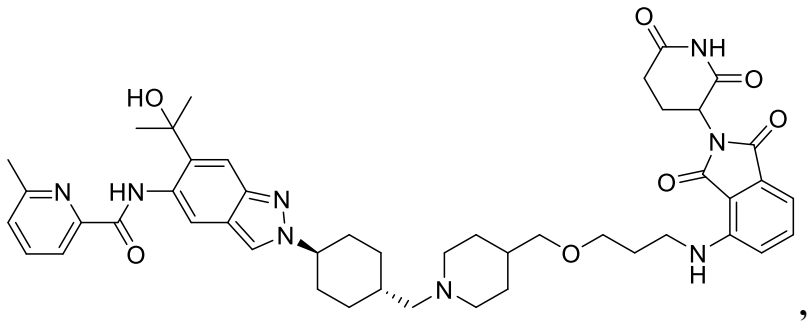
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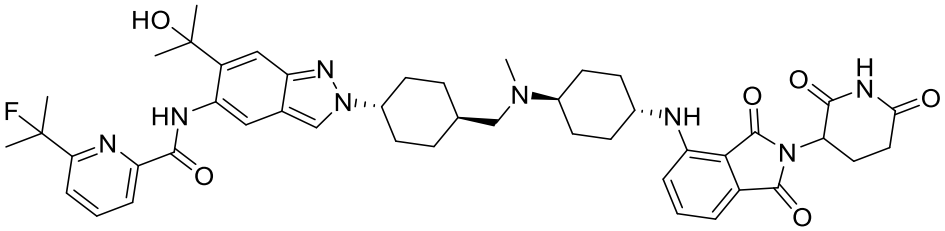
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I-304



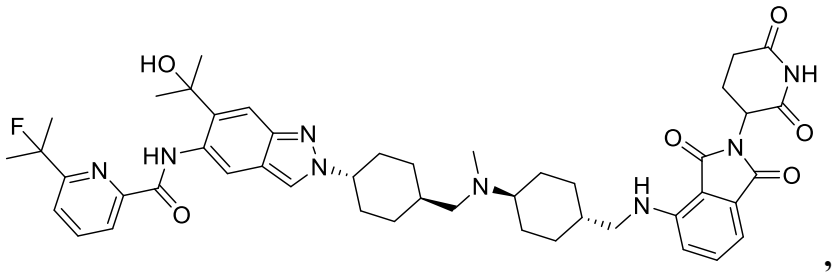
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I-306



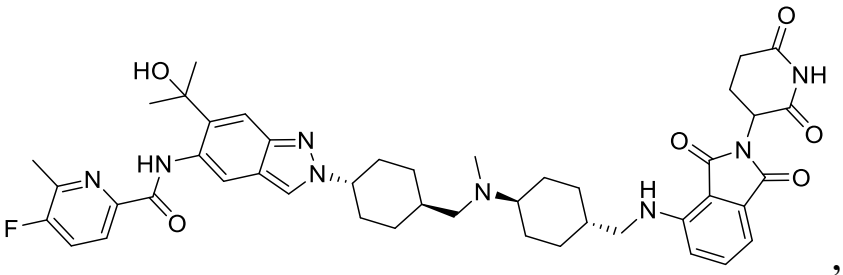
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I-307



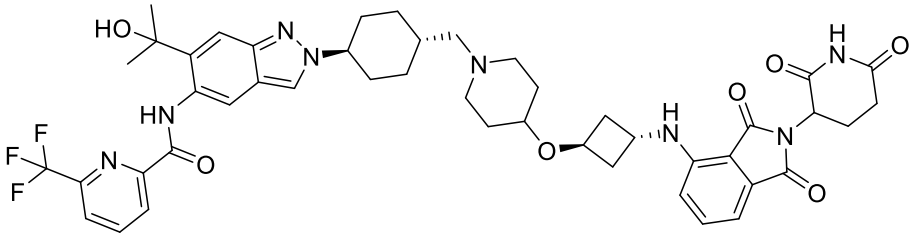
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I-308



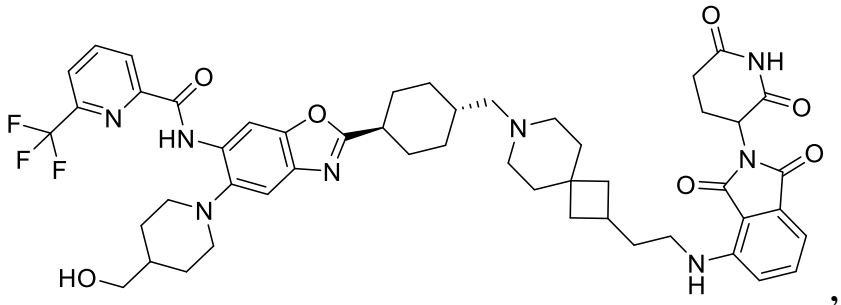
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I-312



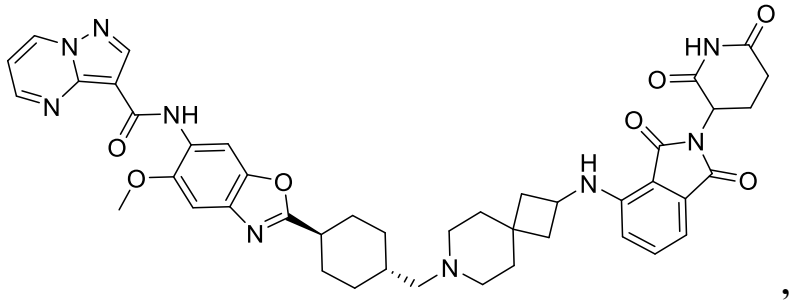
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I-314

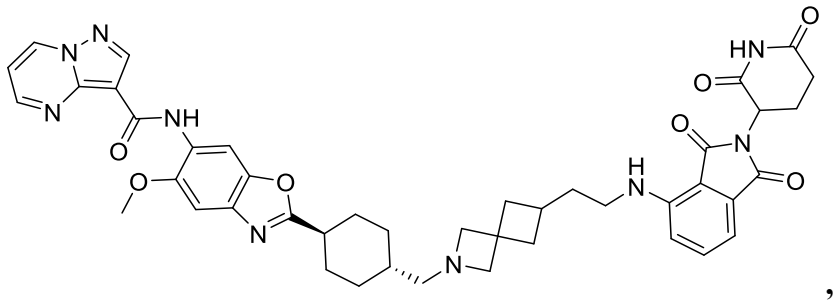


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I-321



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I-339 ,

or a pharmaceutically acceptable salt thereof.

[0008f] 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.

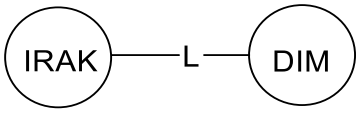
[0008g] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutical composition disclosed herein, for use in therapy.

[0008h] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating an IRAK-mediated disorder, disease, or condition in a patient, wherein the IRAK-mediated disorder, disease or condition is selected from the group consisting of a cancer, a neurodegenerative disease, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, a condition associated with organ transplantation, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T cell activation, a cardiovascular disorder, and a CNS disorder.

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

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

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



I

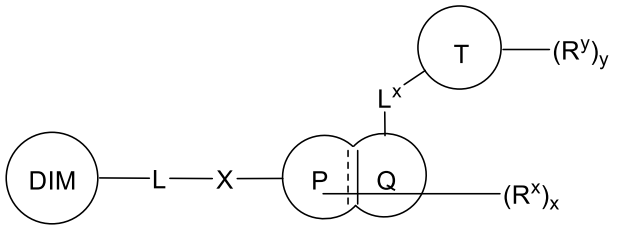
or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

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

CLAIMS

We claim:

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



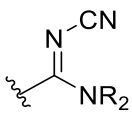
I-a

or a pharmaceutically acceptable salt thereof, wherein:

each R^x is independently hydrogen, R^z, halogen, -CN, and -OR;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated 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, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-SiR_3$, 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

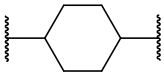
ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring P is a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring Q is benzo;

Ring T is selected from phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring T is further optionally substituted with 1-2 oxo groups;

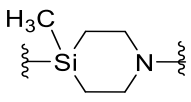
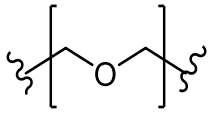
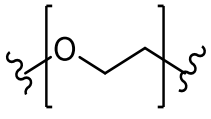
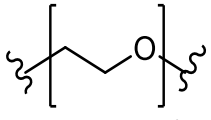
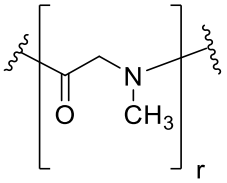
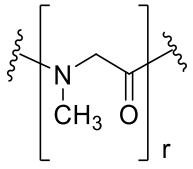
L^x is -NHCO-;

X is ;

---- is a single or double bond;

x is 0, 1, or 2;

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

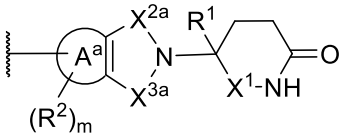
L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy-, -O-, -N(R)-, –$Si(R)_2$–, –Si(OH)(R)–, –$Si(OH)_2$–, –P(O)(OR)–, –P(O)(R)–, –P(O)(NR_2)–, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -N(R)$S(O)_2$-, -$S(O)_2$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, 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, an 8-10

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

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

DIM is a degradation inducing moiety, wherein said degradation moiety is a cereblon E3 ubiquitin ligase binding moiety of formula **I-ccc-1**:



I-ccc-1

wherein:

X^1 is –C(O)–;

X^{2a} is –C(O)–;

X^{3a} is $–CH_2–$ or –C(O)–;

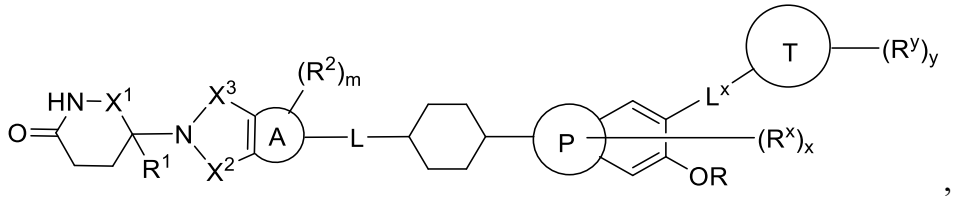
R^1 is hydrogen or C_{1-4} aliphatic;

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

Ring A^a is a fused ring selected from a 6-membered aryl containing 0-1 nitrogen atoms; and

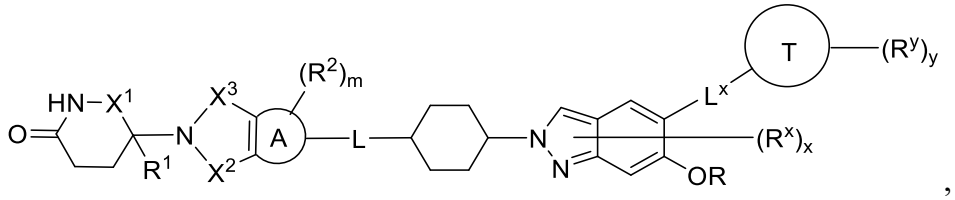
m is 0, 1, 2, 3 or 4.

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



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I-k-13



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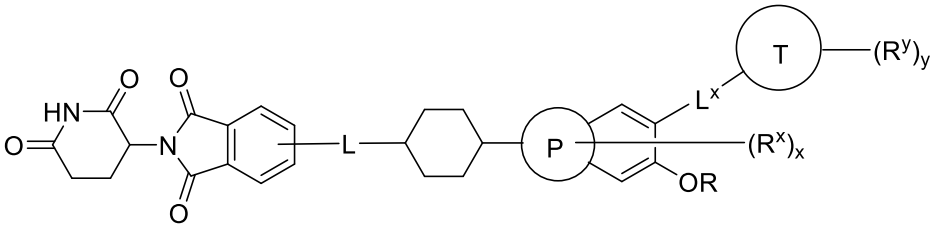
I-k-15

or a pharmaceutically acceptable salt thereof.

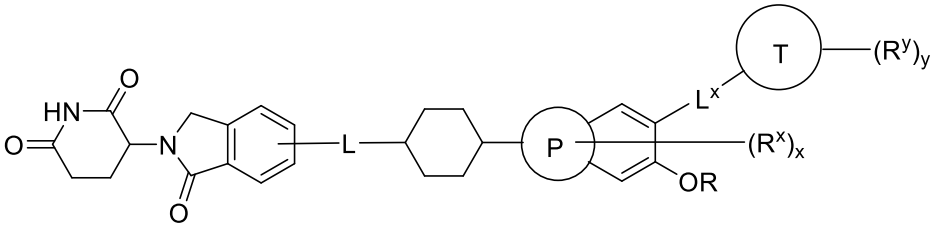
3. The compound of claim 1 or claim 2, wherein Ring A^a is a 6-membered aryl.

4. The compound of any one of claims 1-3, wherein Ring T is a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

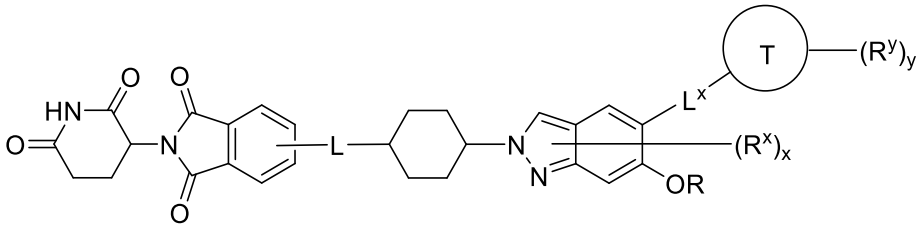
5. The compound of any one of claims 1-4, wherein said compound is any one of the following formulae:



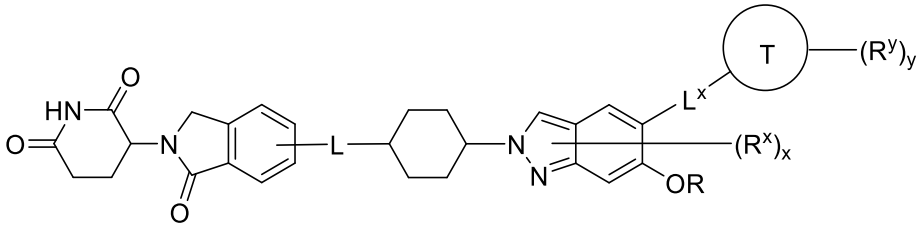
I-k-2



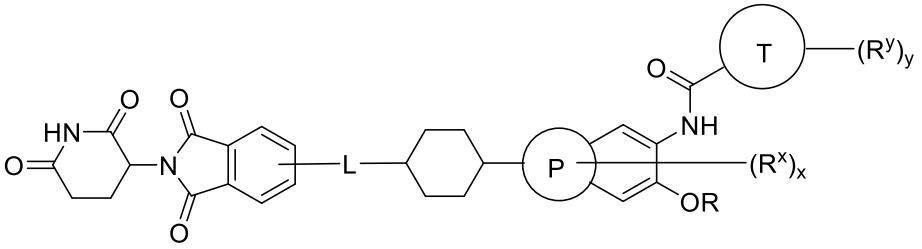
I-k-3



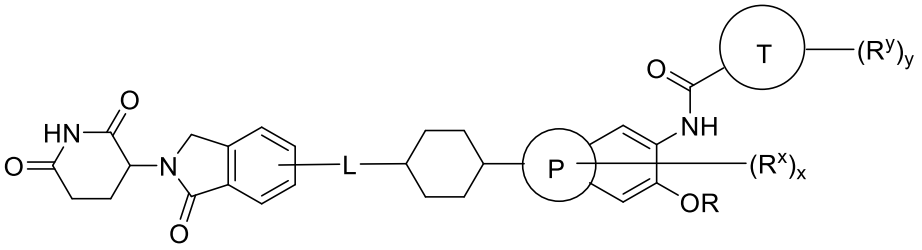
I-k-4



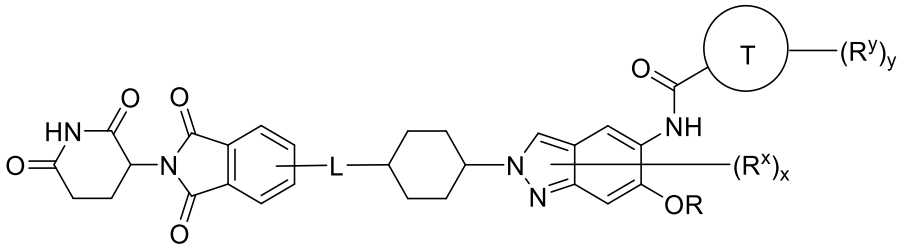
I-k-5



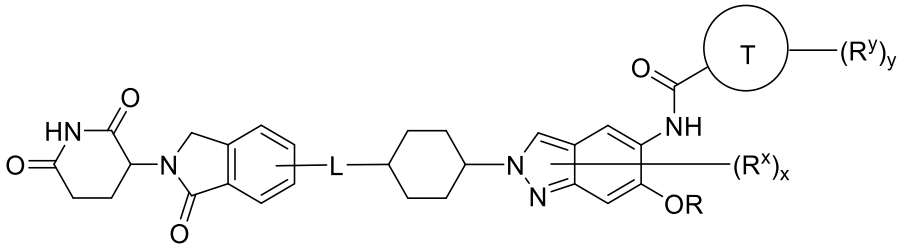
I-k-6



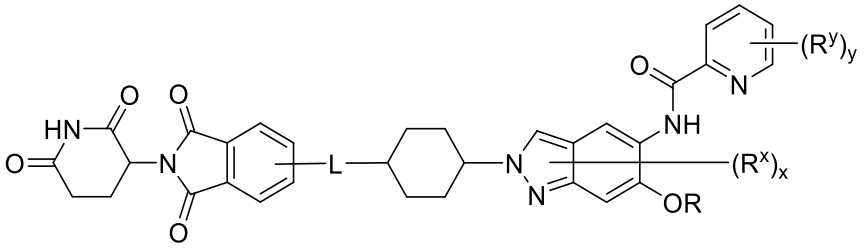
I-k-7



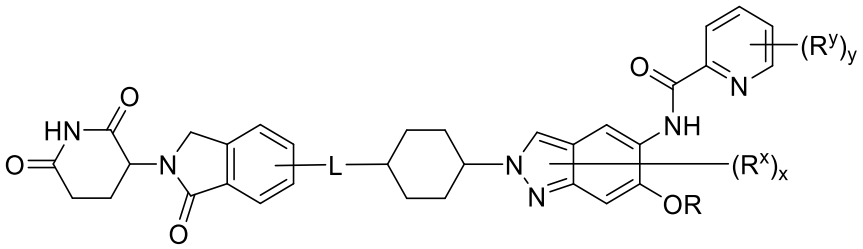
I-k-8



I-k-9

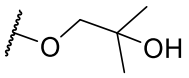
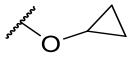
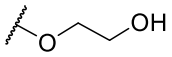
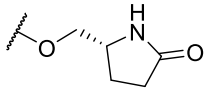
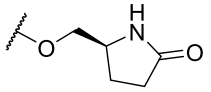


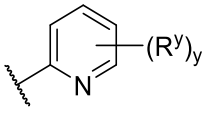
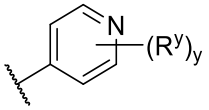
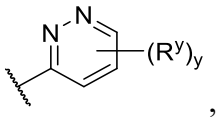
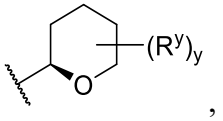
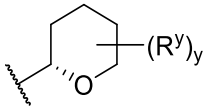
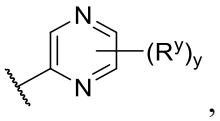
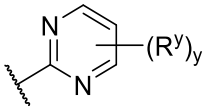
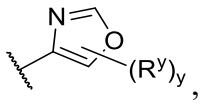
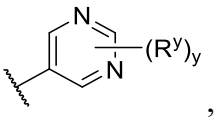
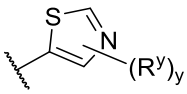
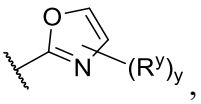
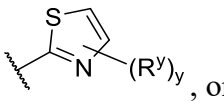
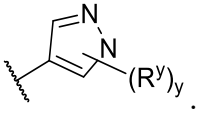
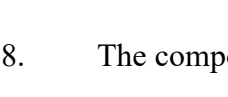
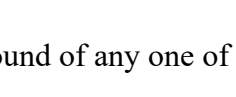
I-k-10



I-k-11

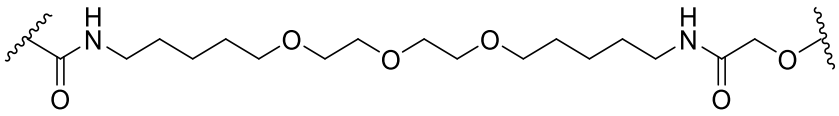
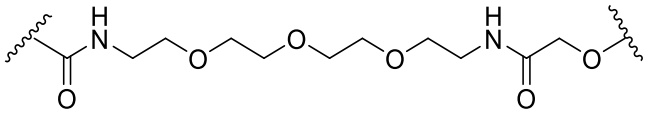
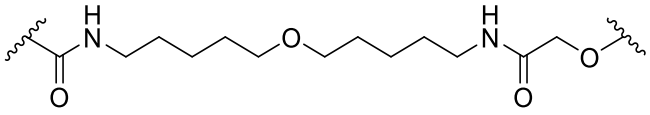
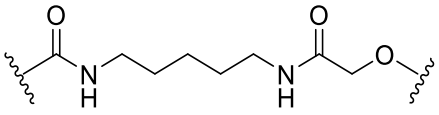
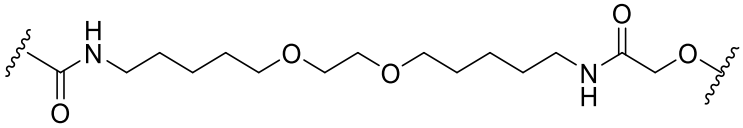
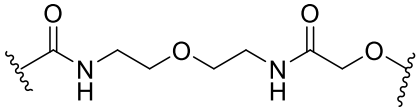
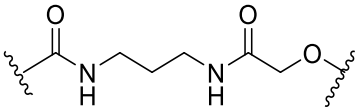
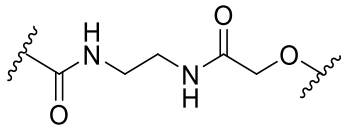
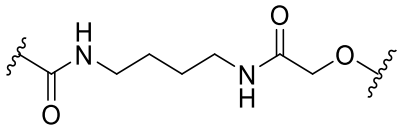
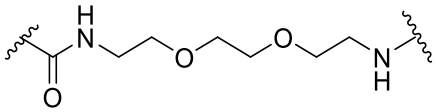
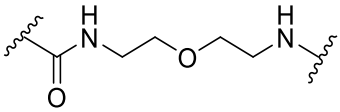
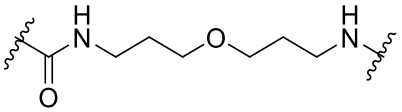
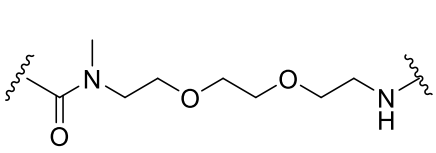
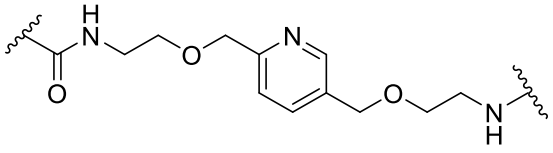
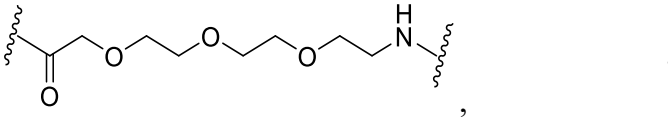
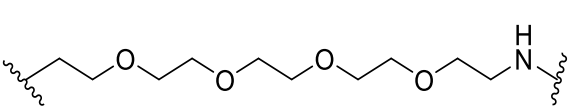
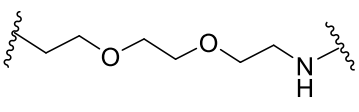
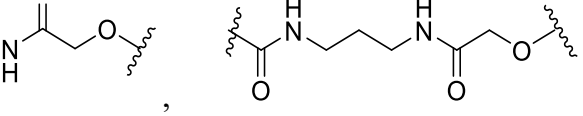
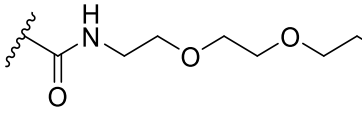
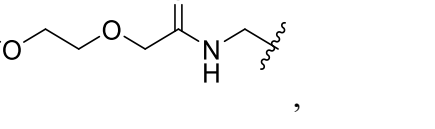
or a pharmaceutically acceptable salt thereof.

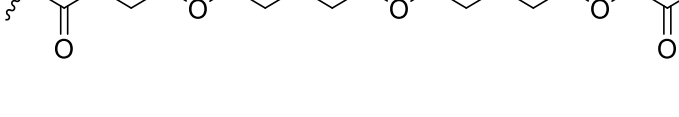
6. The compound of any one of claim 1-5, wherein R^x or OR is -OMe, -OEt, -OiPr, -OCF_2H, -OCF_3, , , ,  or .

7. The compound of any one of claims 1-6, wherein Ring T is phenyl, , , , , , , , , , , , , , , , , , or .

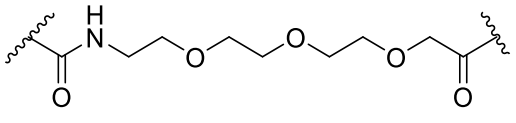
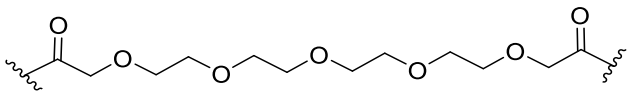
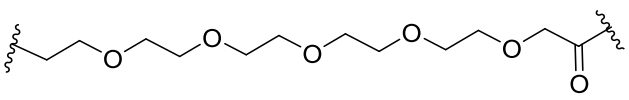
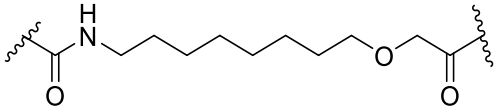
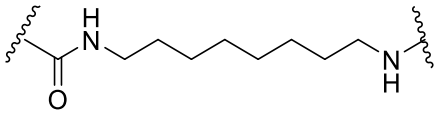
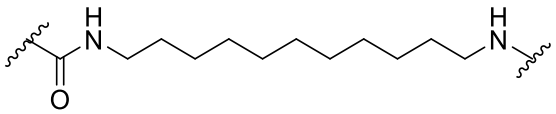
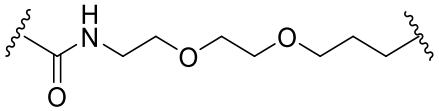
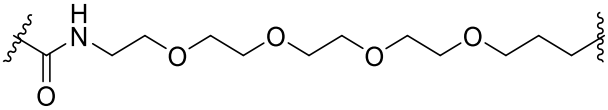
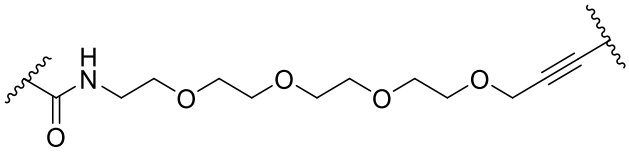
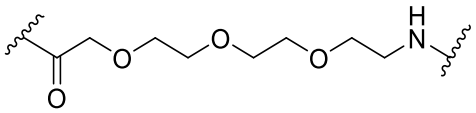
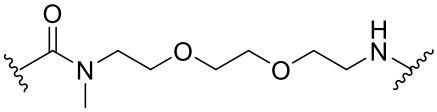
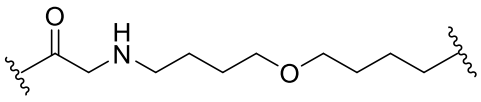
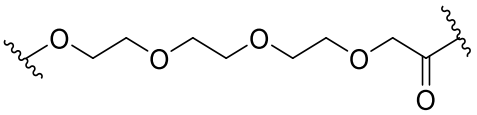
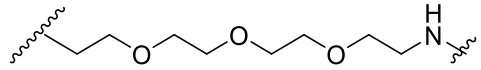
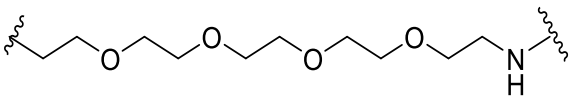
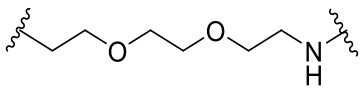
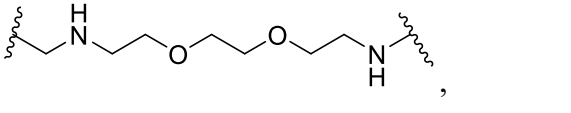
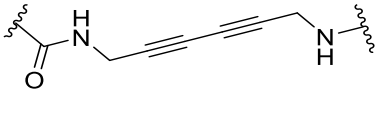
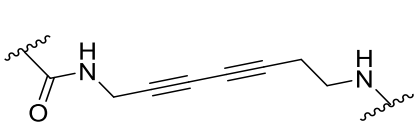
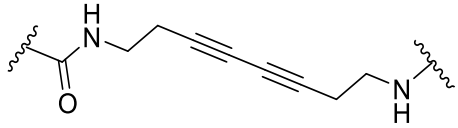
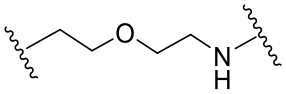
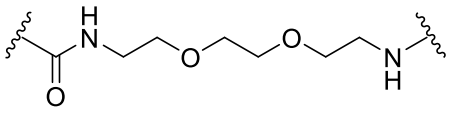
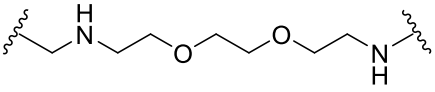
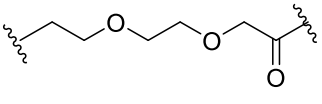
8. The compound of any one of claims 1-7, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{1-30} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy-, -O-, -N(R)-, –$Si(R)_2$–, –Si(OH)(R)–, –$Si(OH)_2$–, –P(O)(OR)–, –P(O)(R)–, –$P(O)(NR_2)$–, -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)-, or –N(R)C(O)O-.

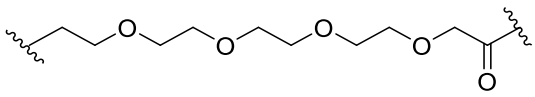
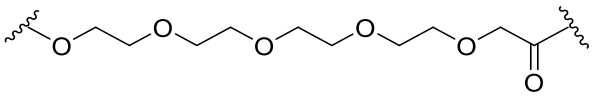
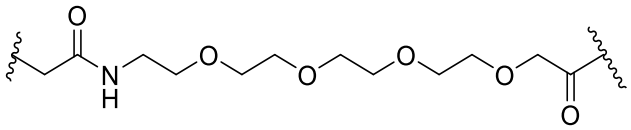
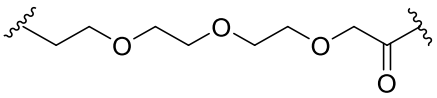
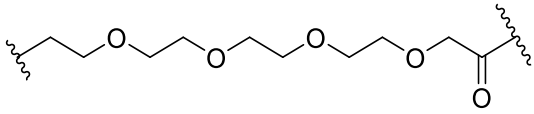
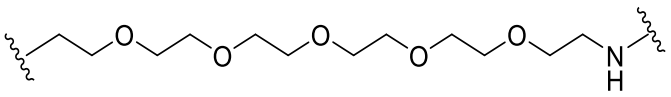
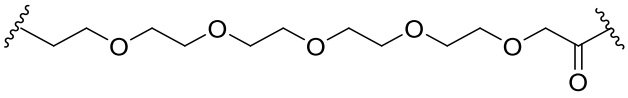
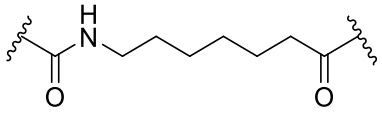
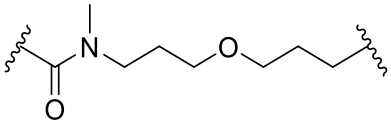
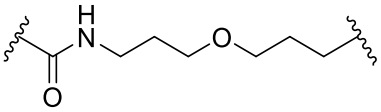
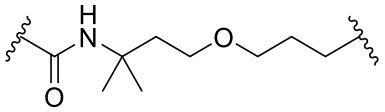
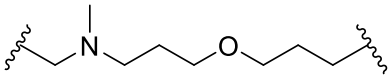
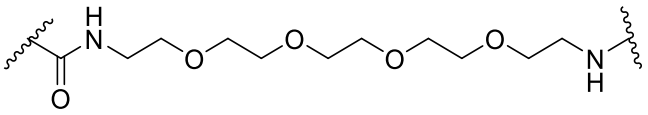
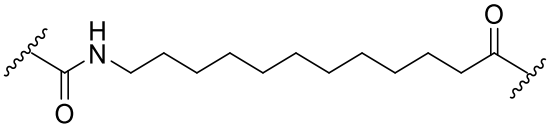
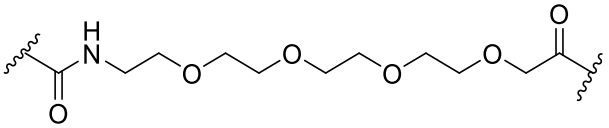
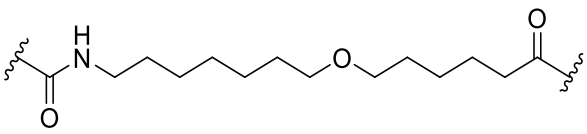
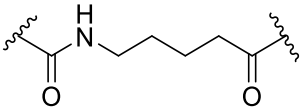
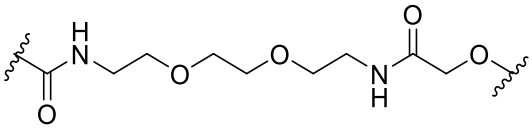
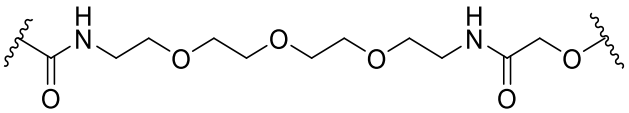
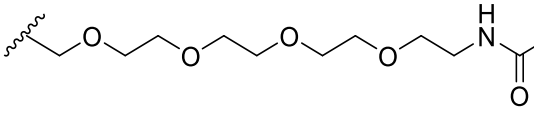
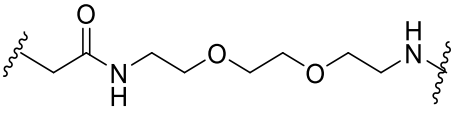
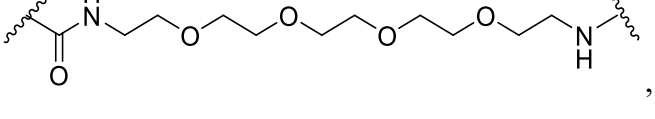
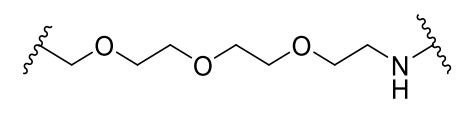
9. The compound of any one of claims 1-8, wherein L is


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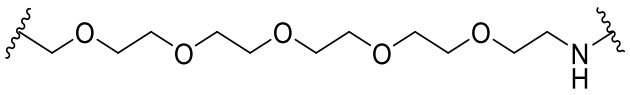
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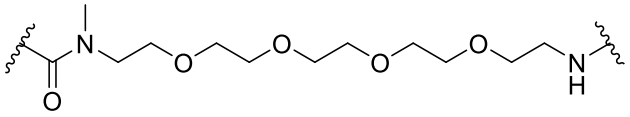
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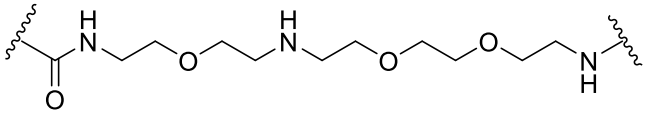

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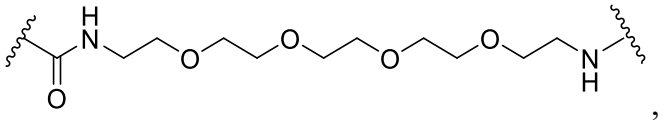
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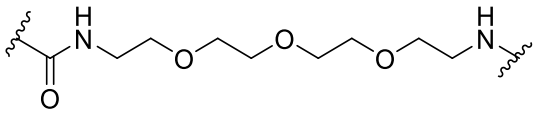
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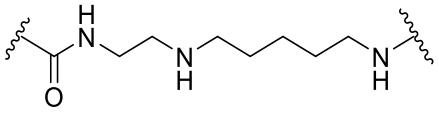

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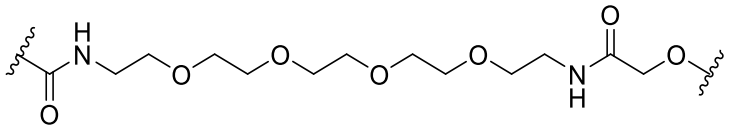

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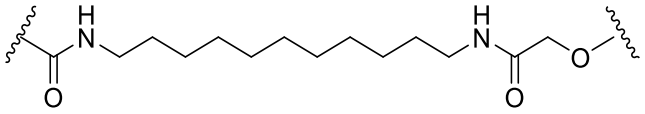

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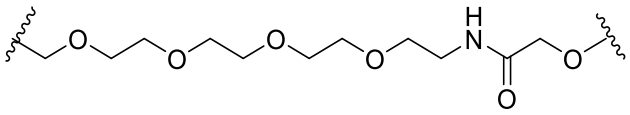

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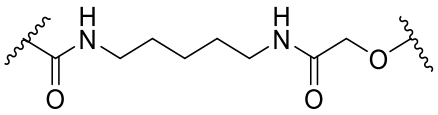

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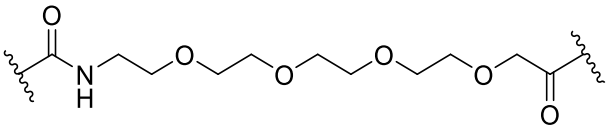

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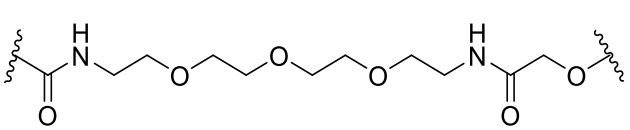

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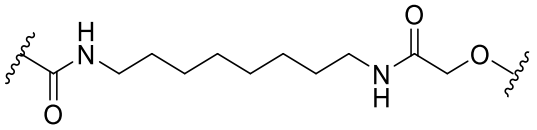

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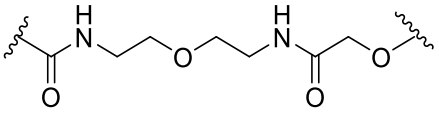

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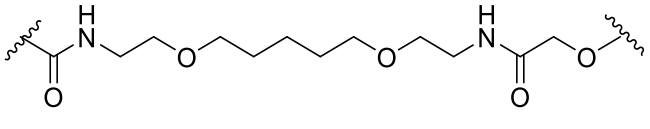

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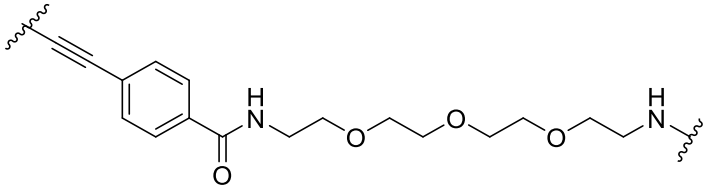

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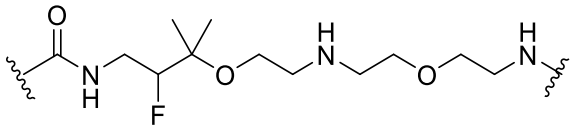
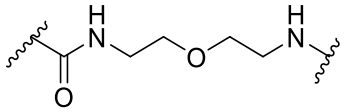
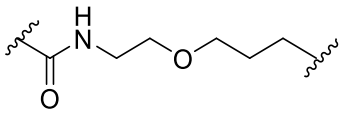
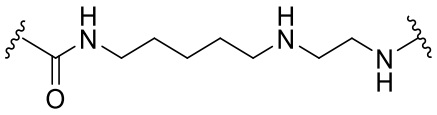
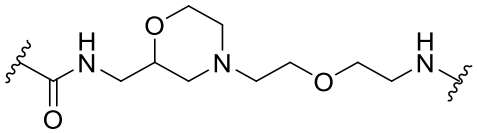
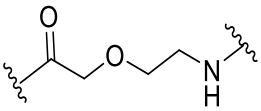
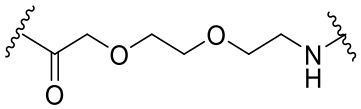
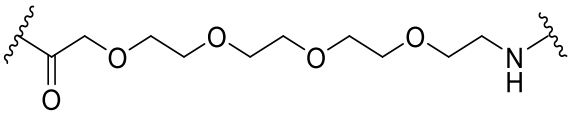
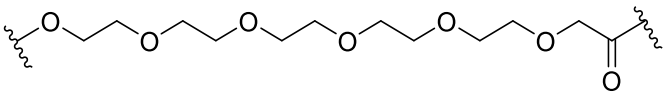
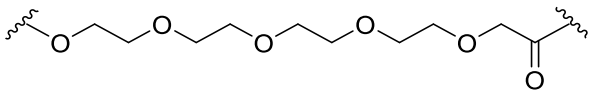
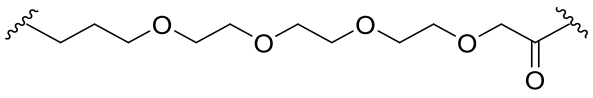
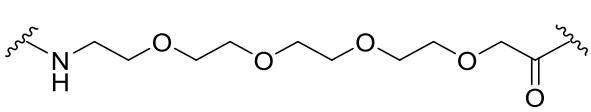
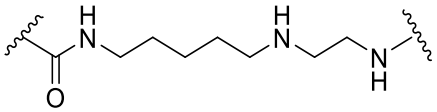
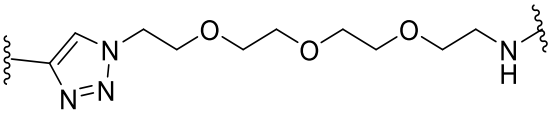

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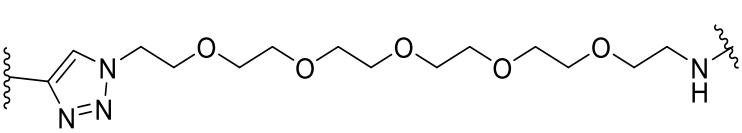
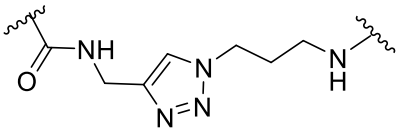
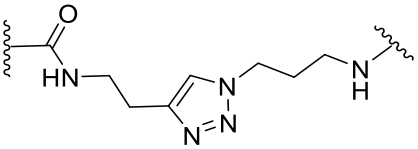
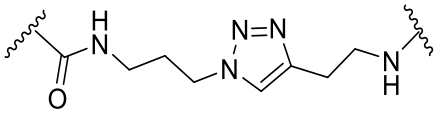
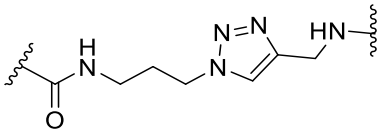
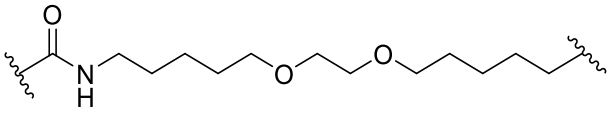

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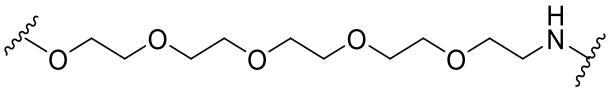
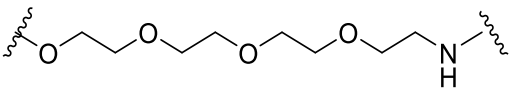
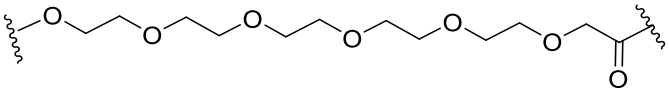
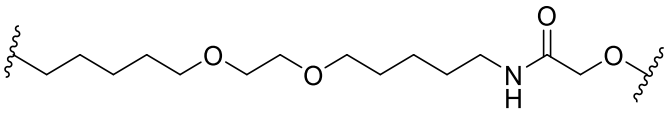
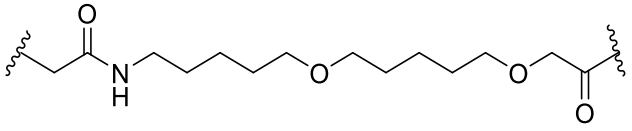
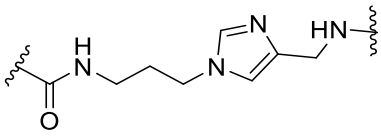
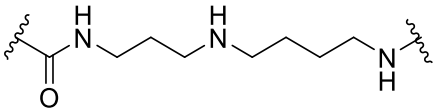
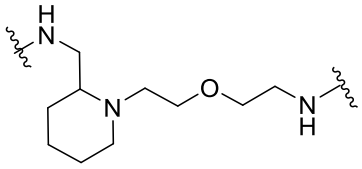
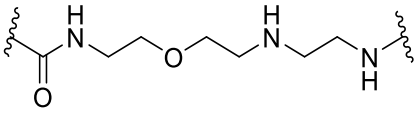
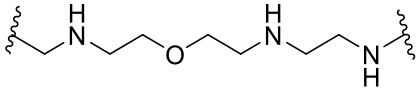
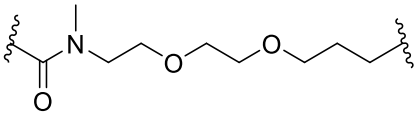
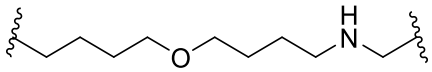
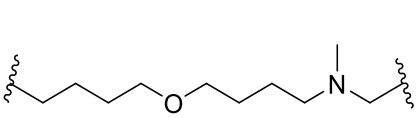

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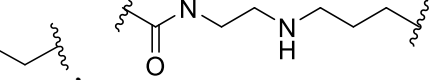
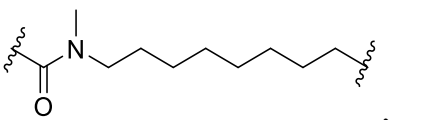

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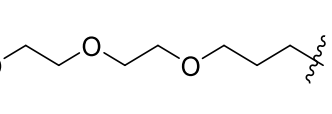
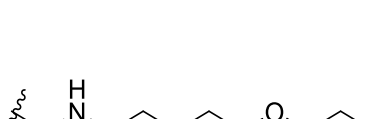
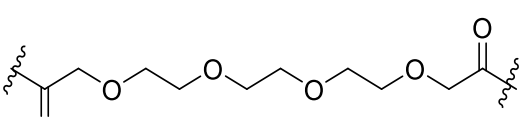
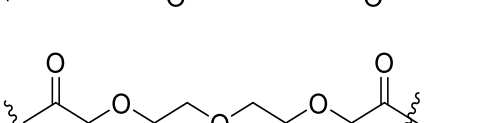
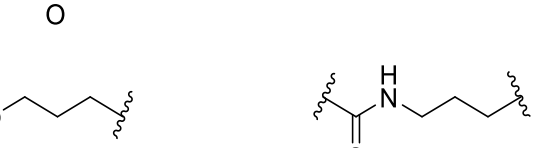
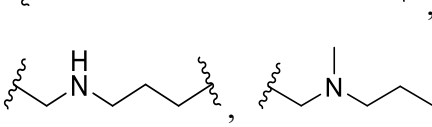
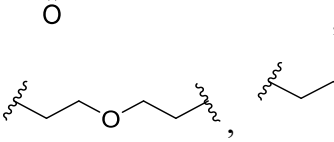
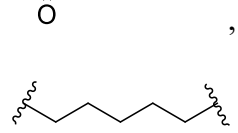

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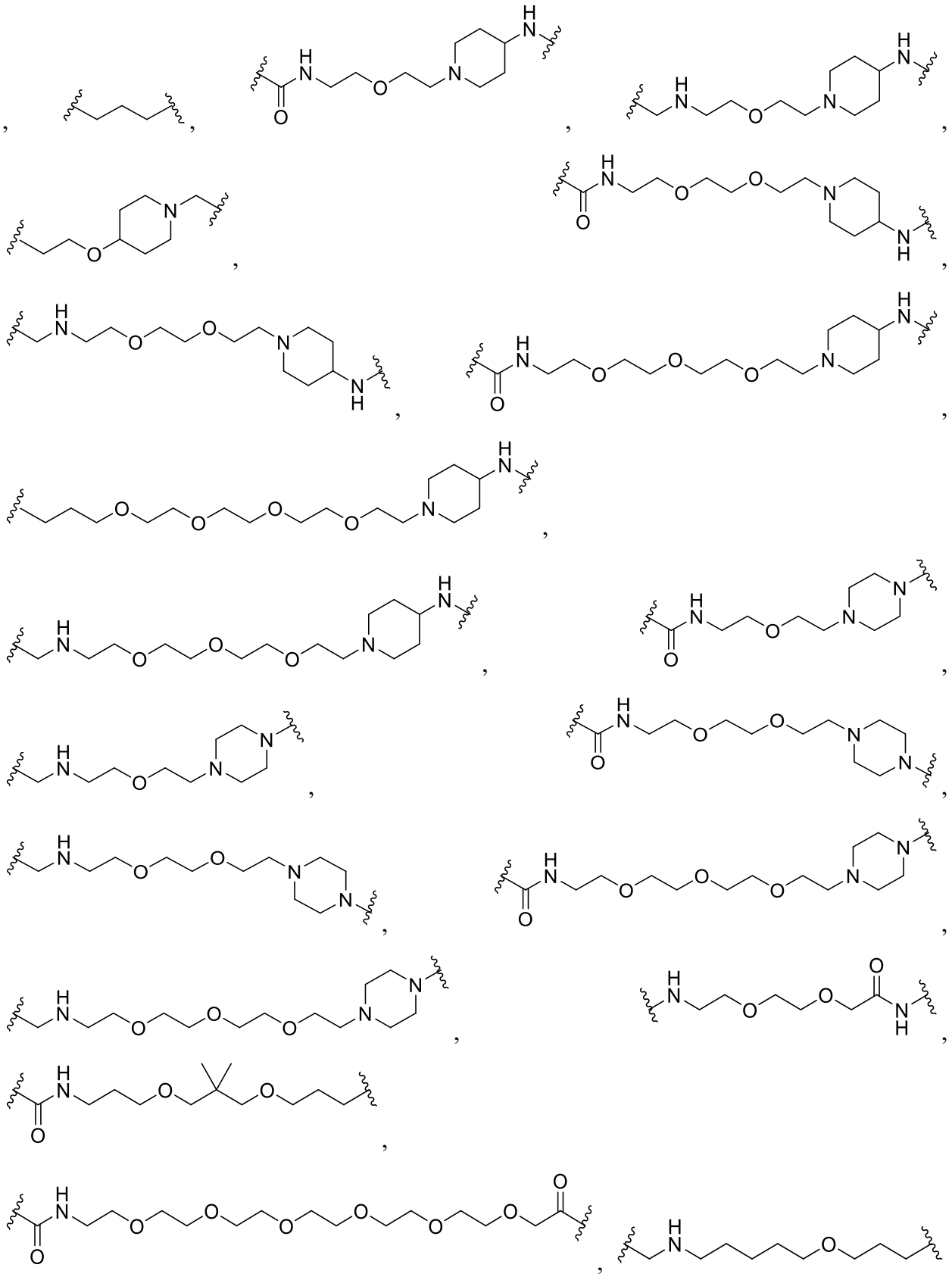
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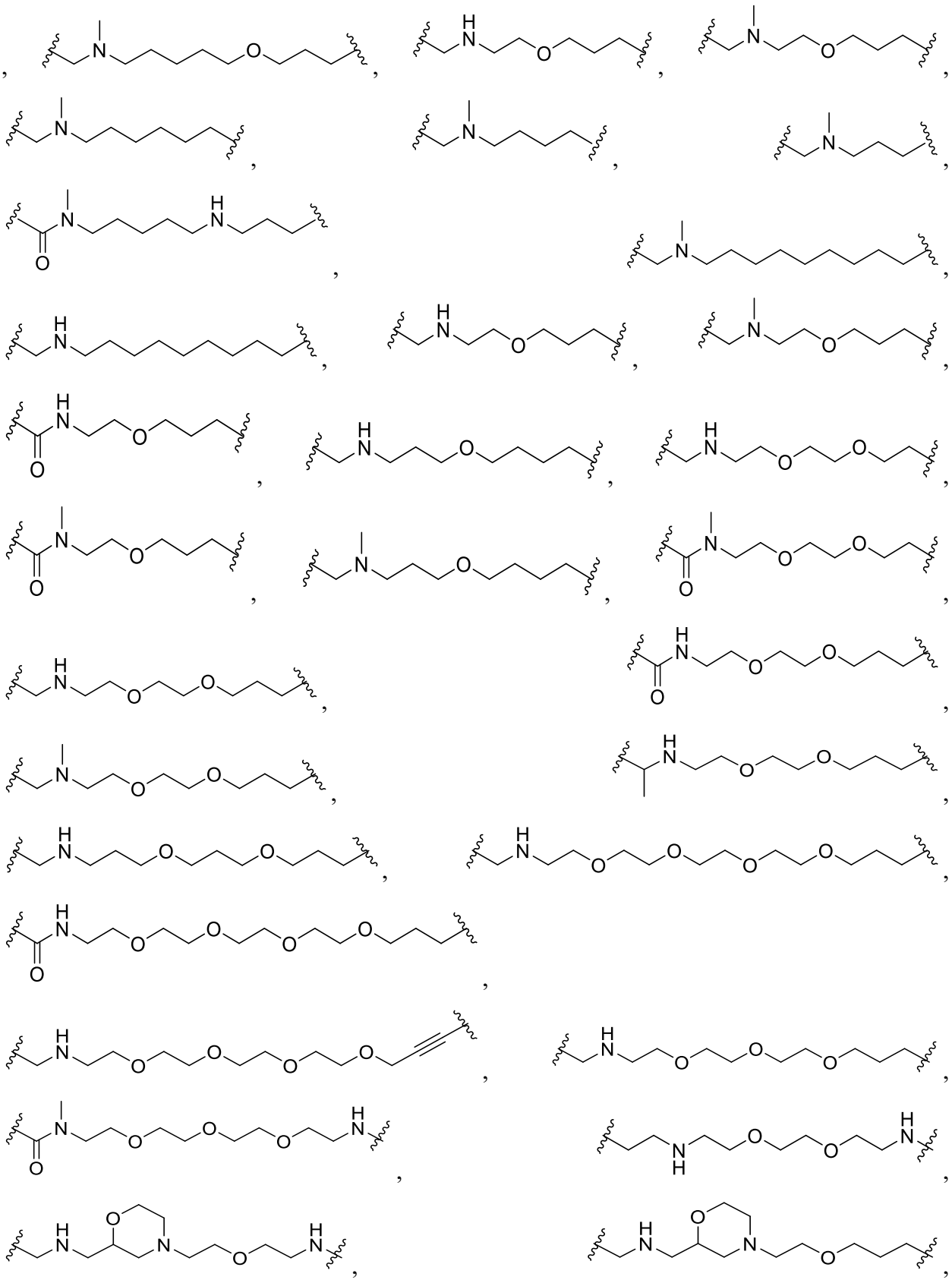

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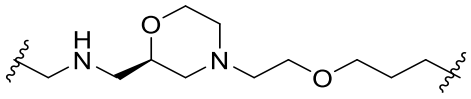
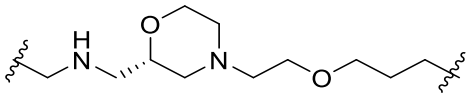
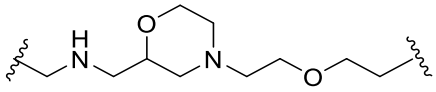
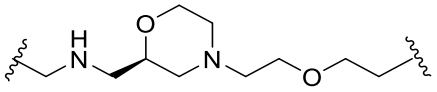
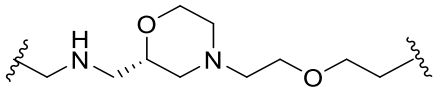
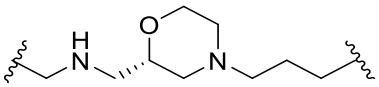
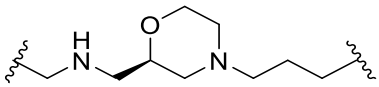
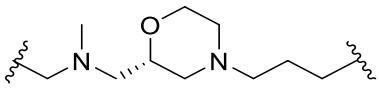
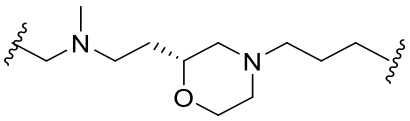
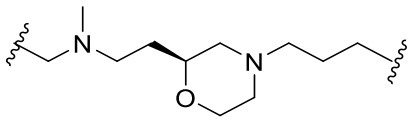
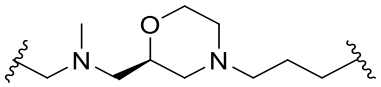
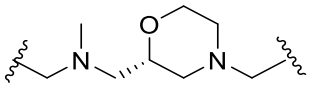
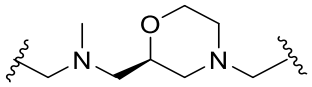
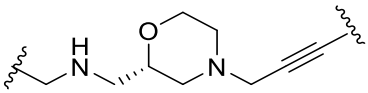
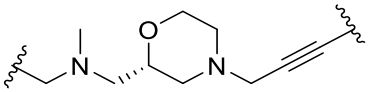
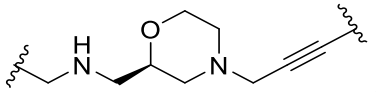
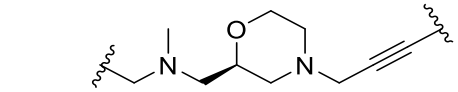
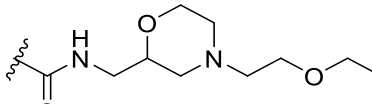
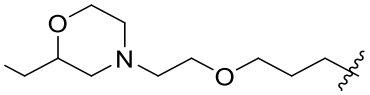
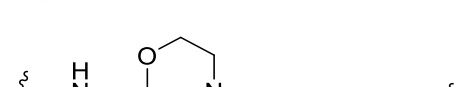
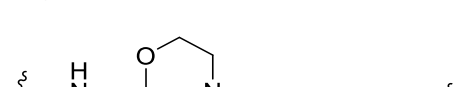
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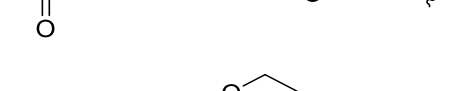
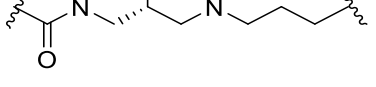
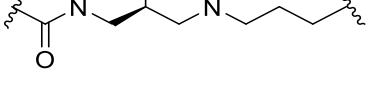
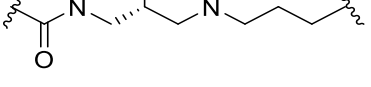
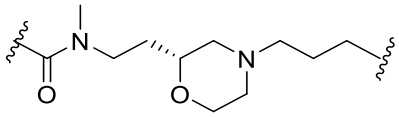
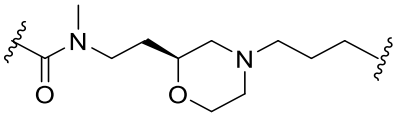
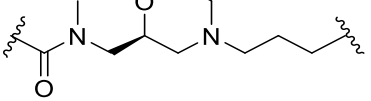
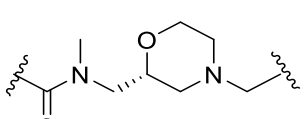
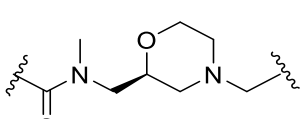
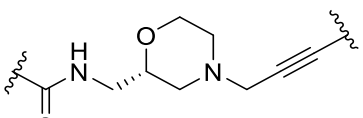
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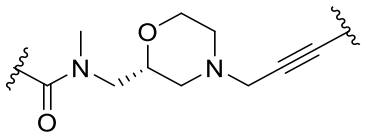
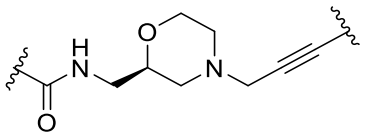
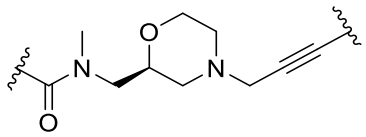
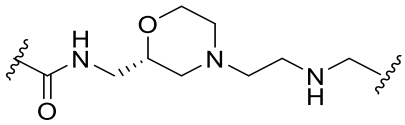
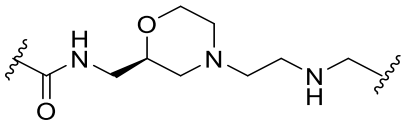
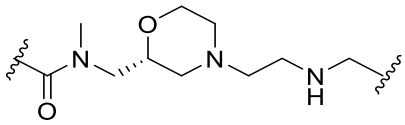
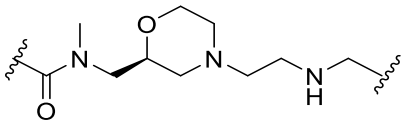
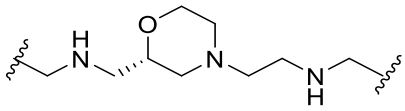
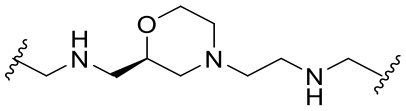
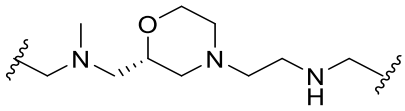
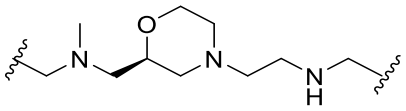
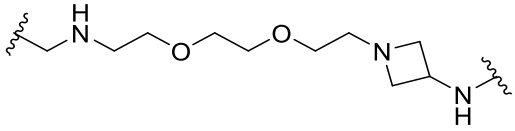
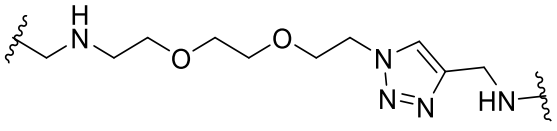
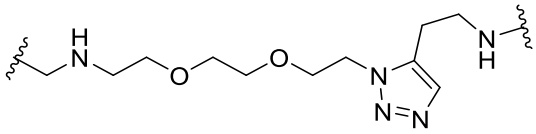
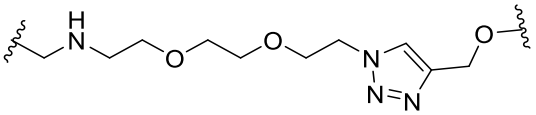
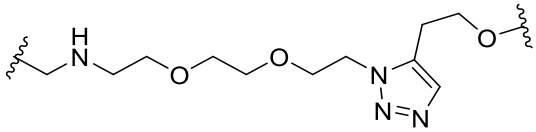
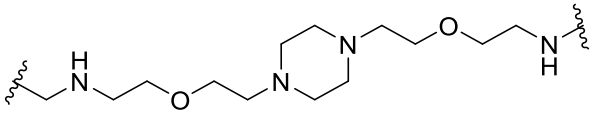
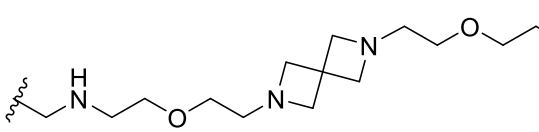
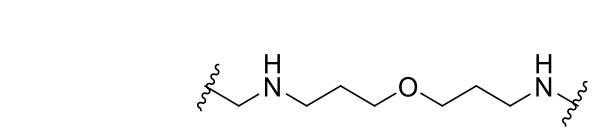
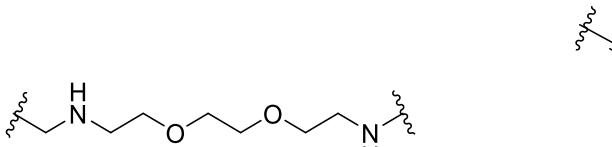
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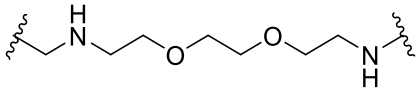
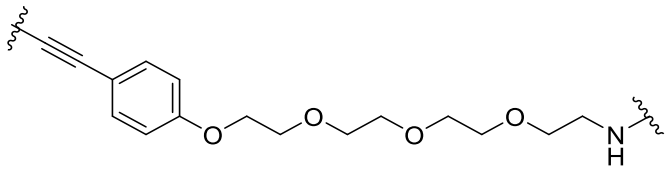
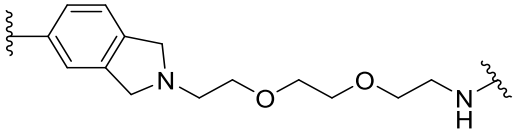
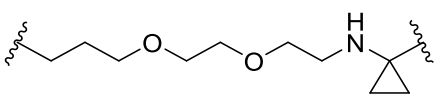


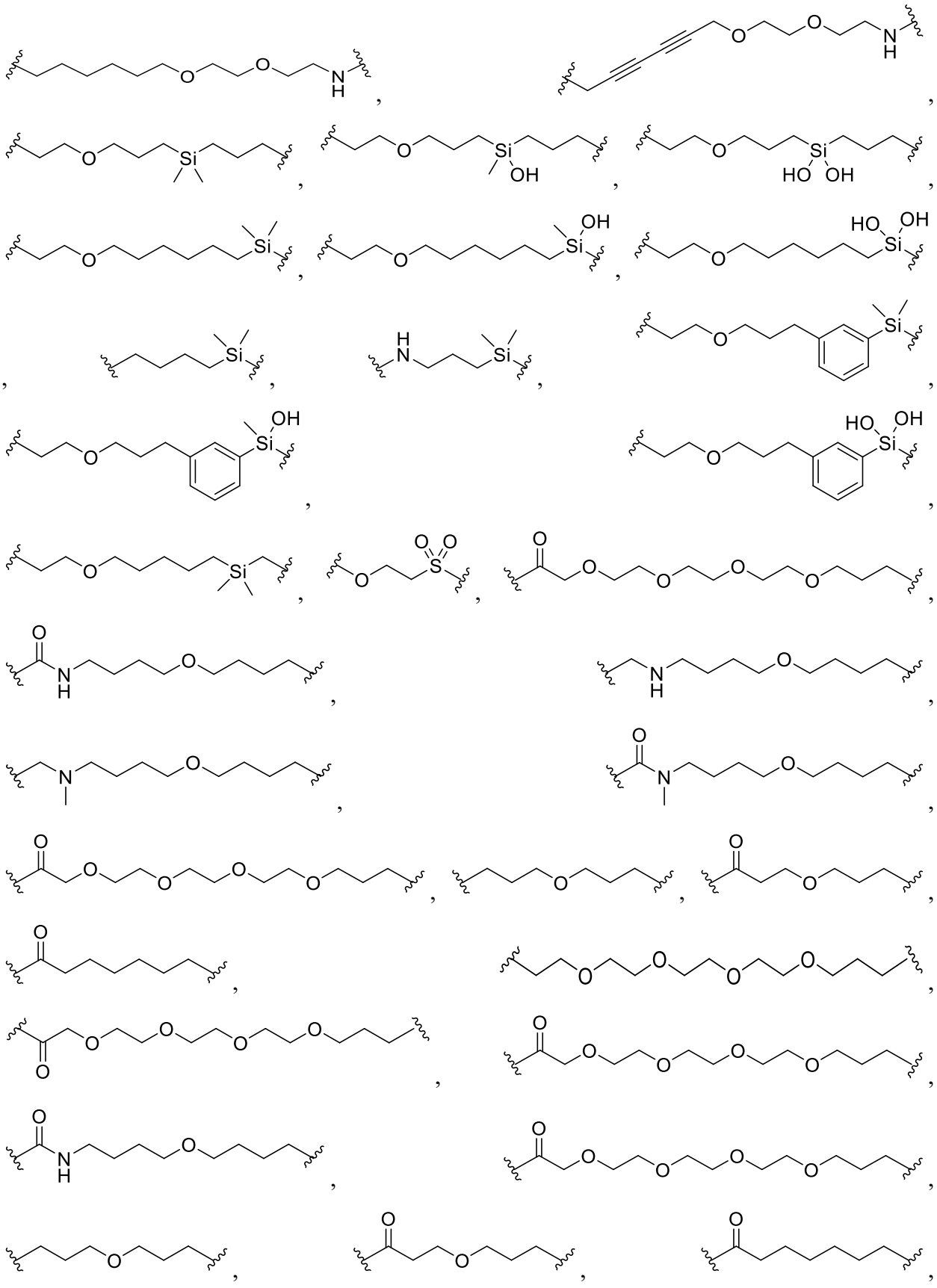


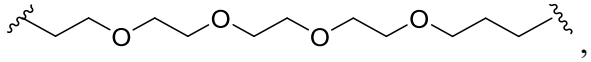
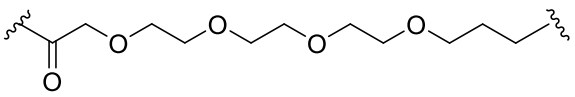
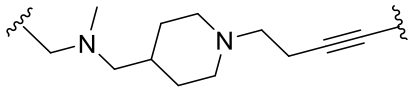
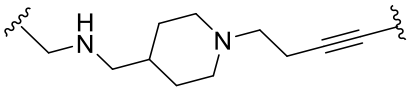
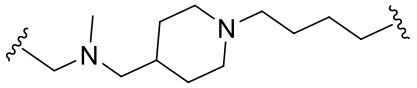
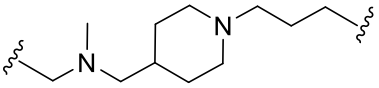
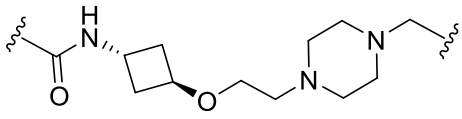
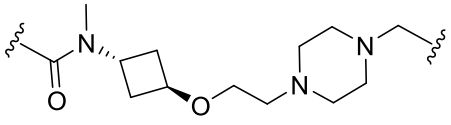
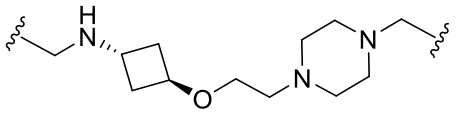
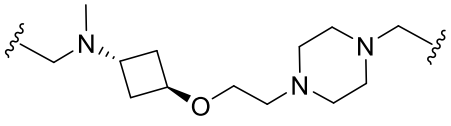
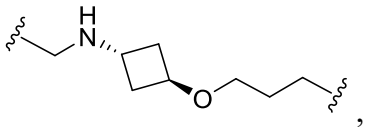
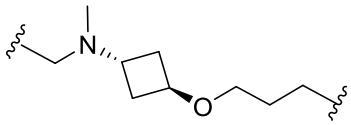
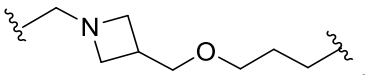
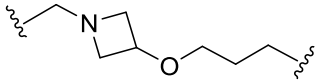
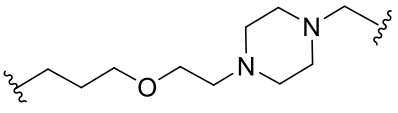
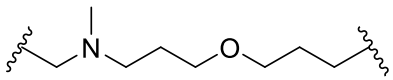
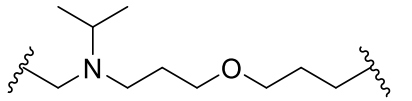
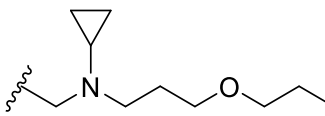
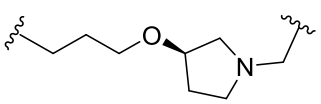
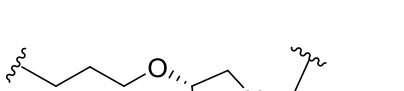
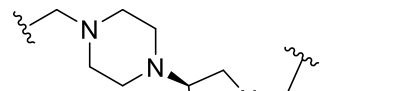
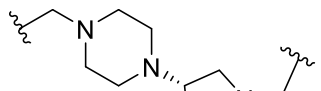
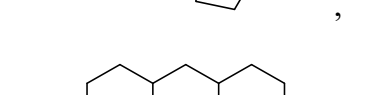
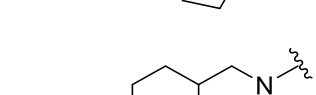
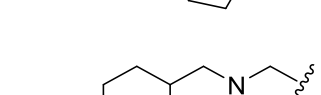

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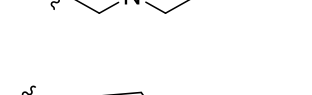
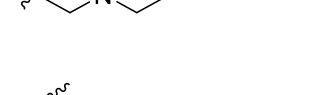
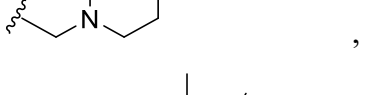
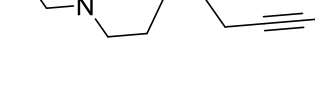
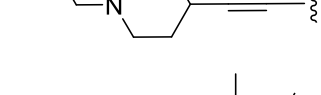
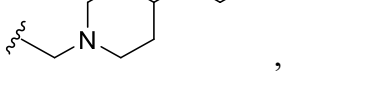
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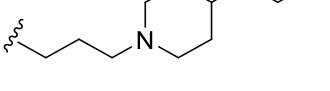

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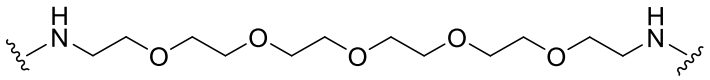
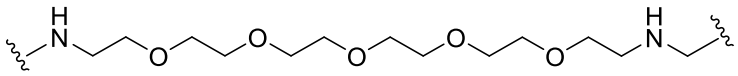
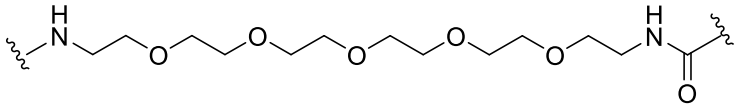
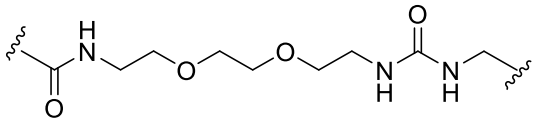
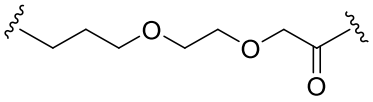
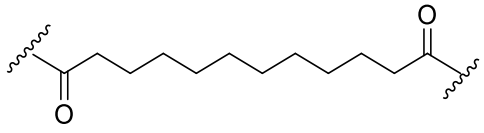
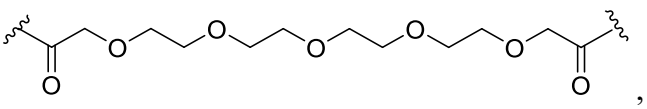
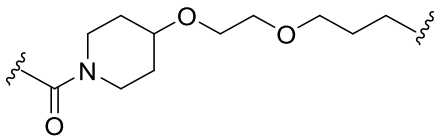
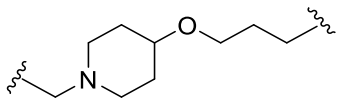
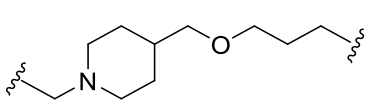
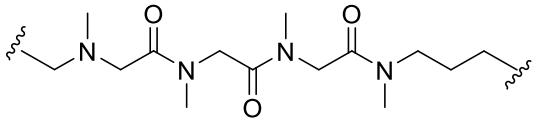
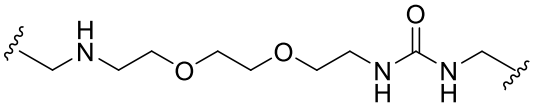
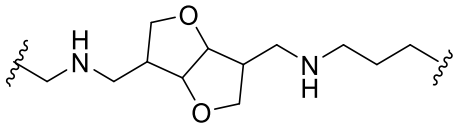
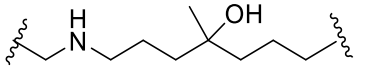
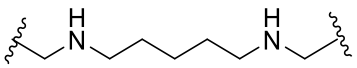
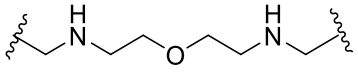
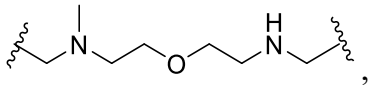
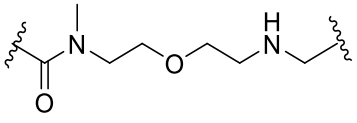
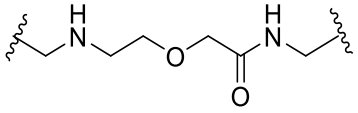
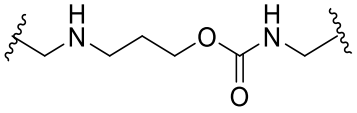
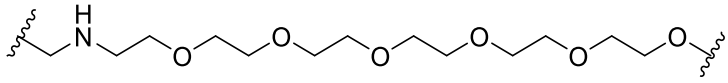
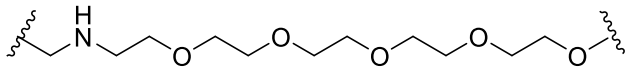
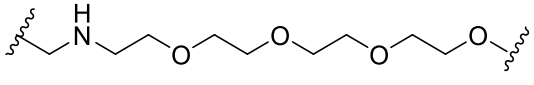
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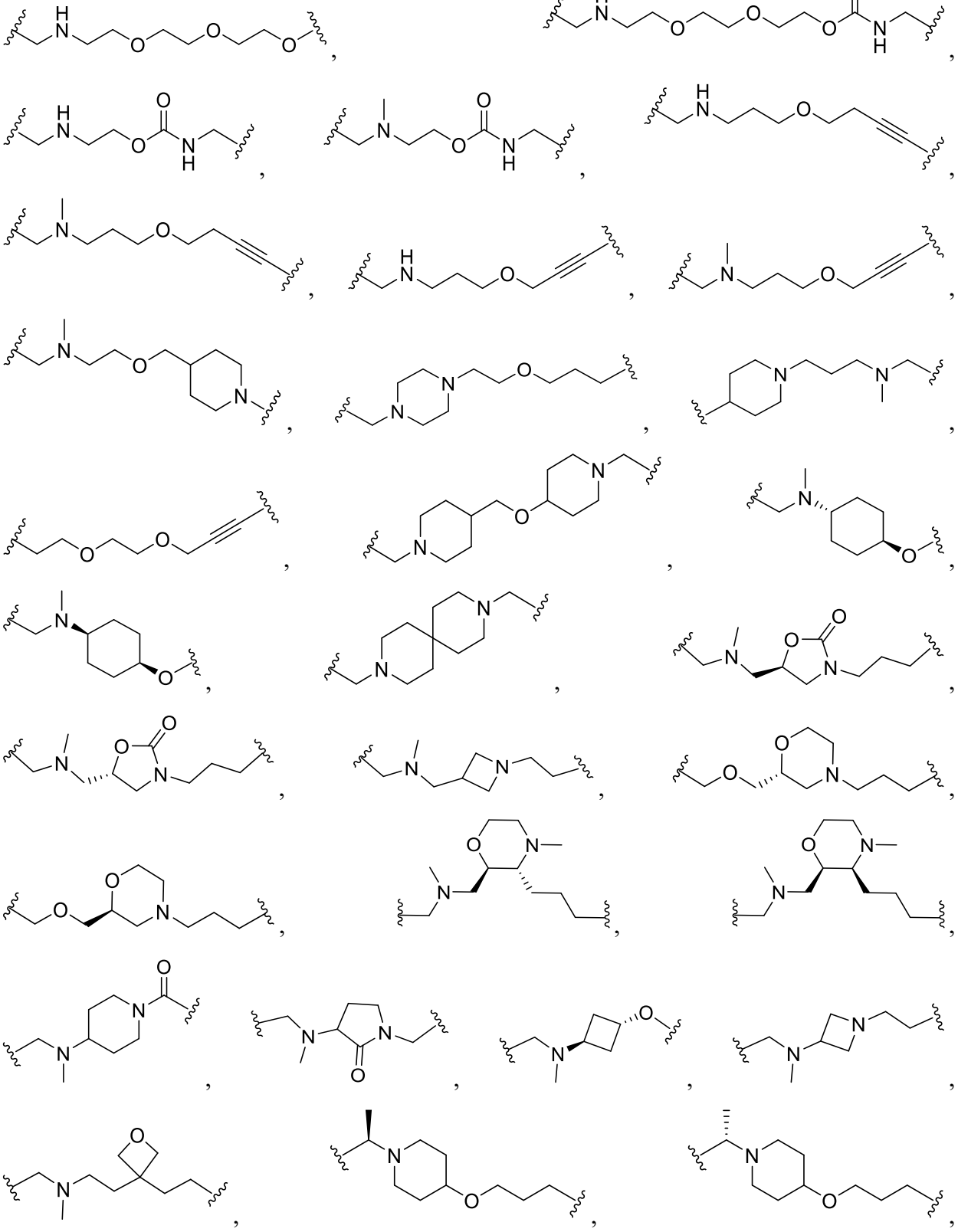
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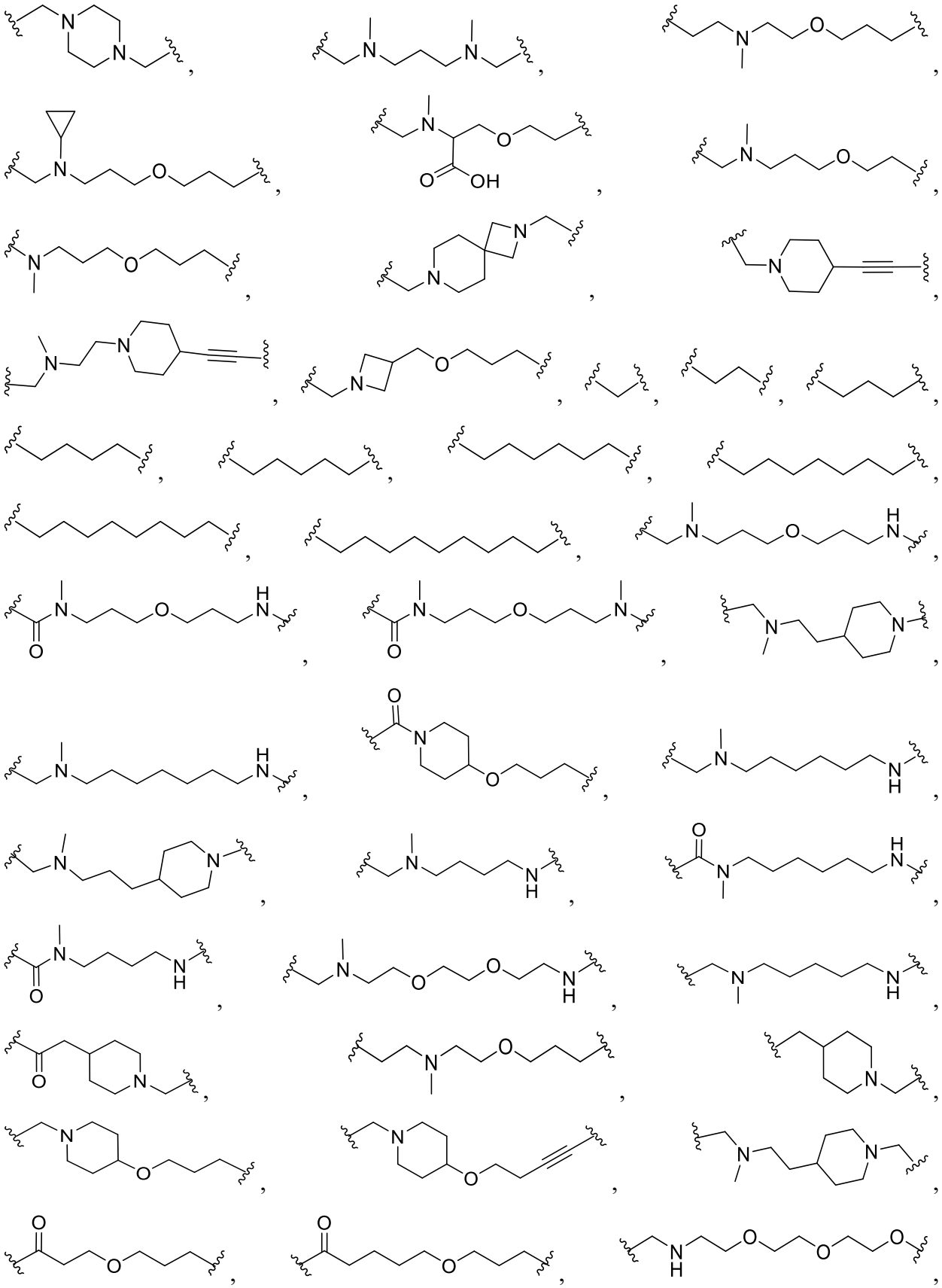
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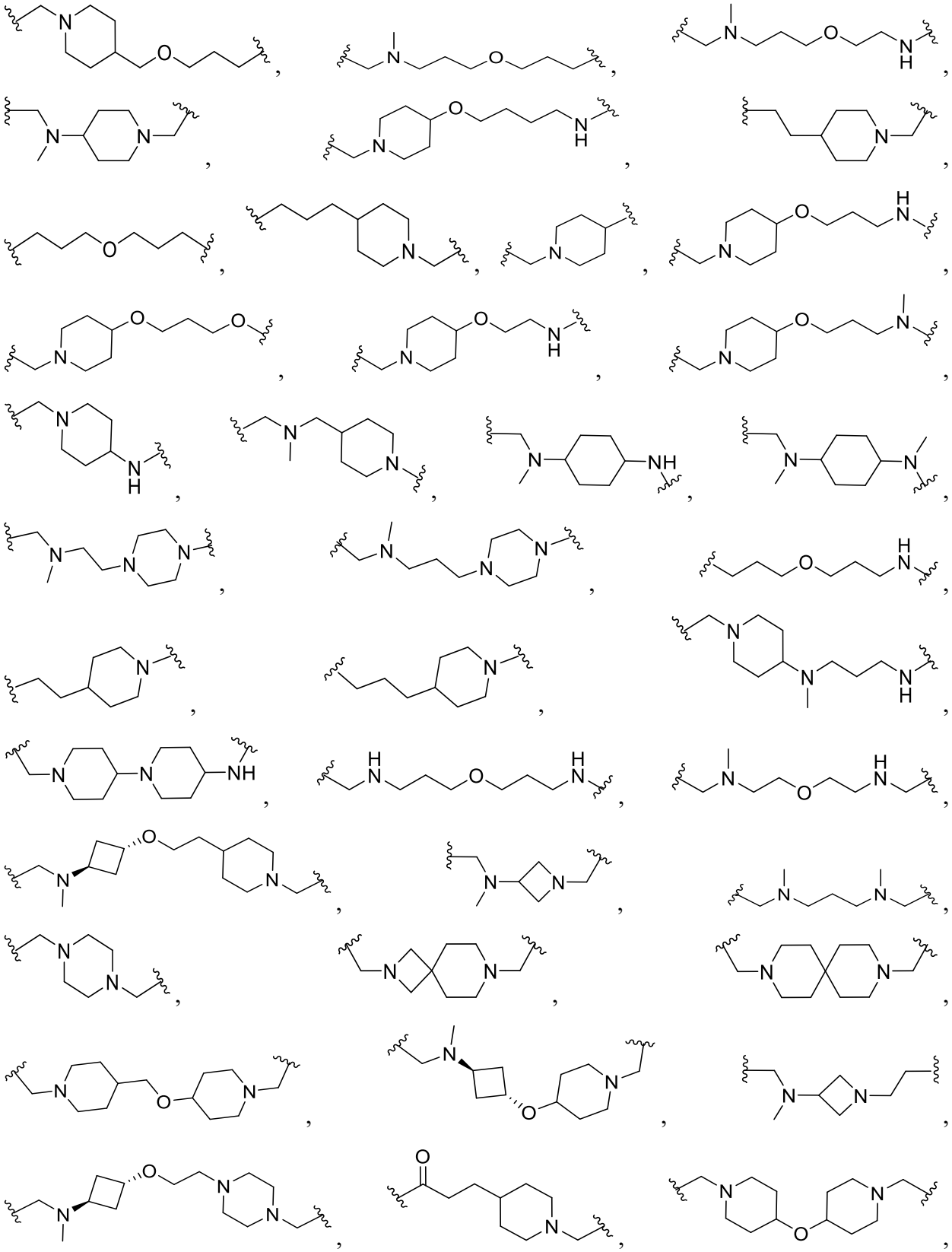
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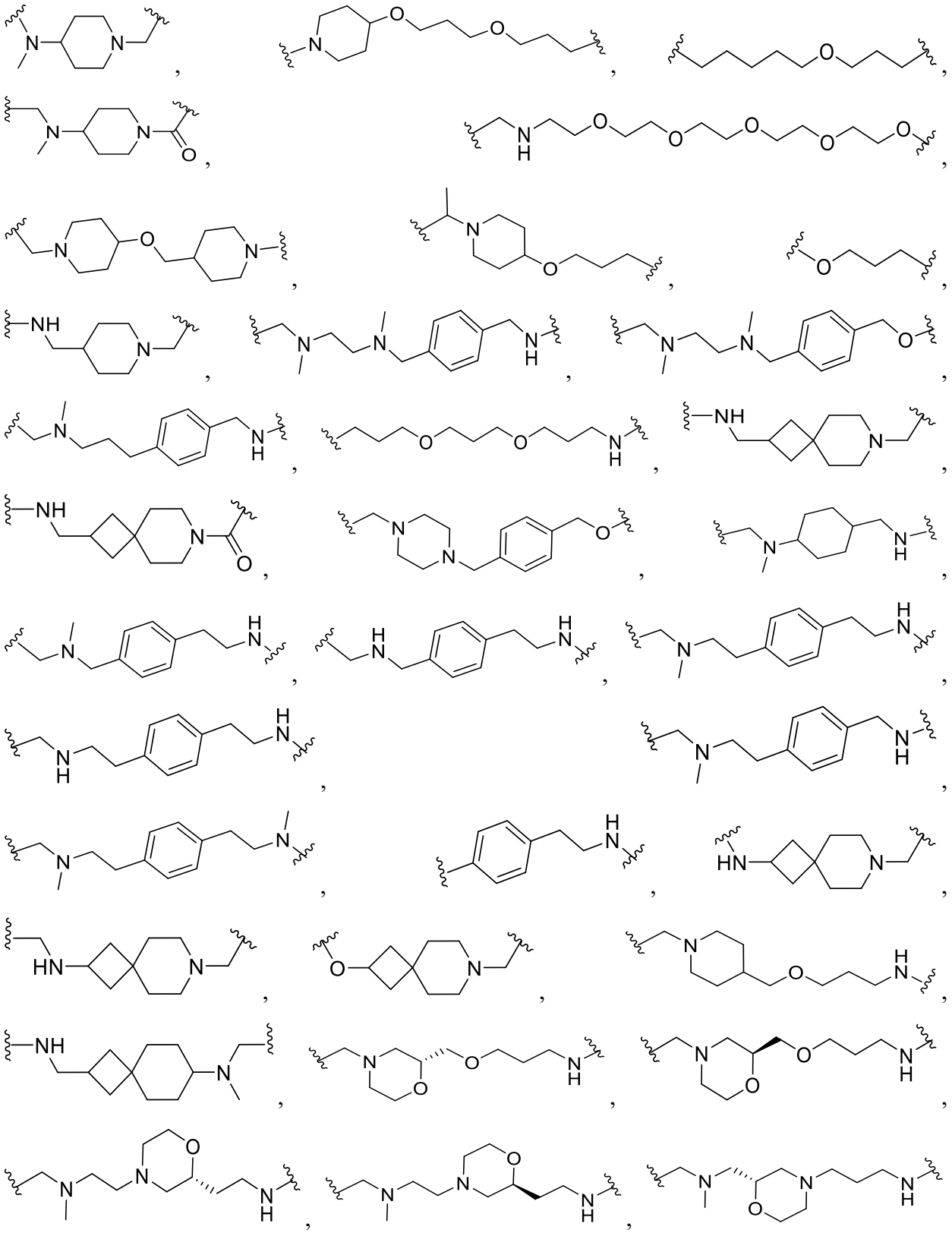
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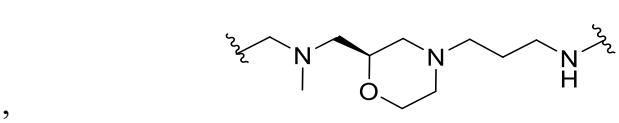
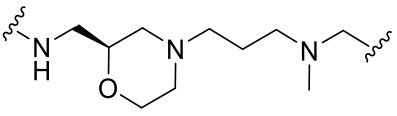
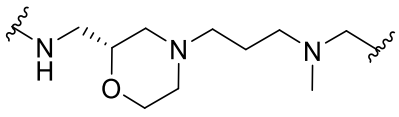
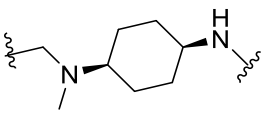
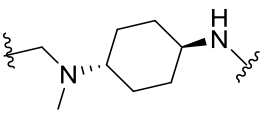
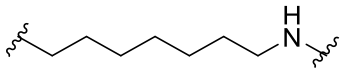
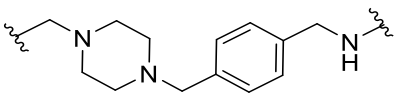
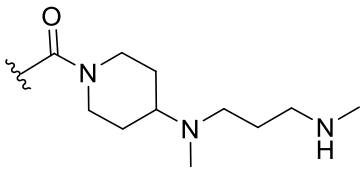
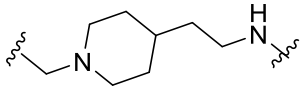
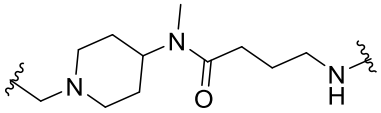
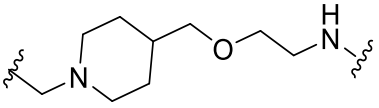
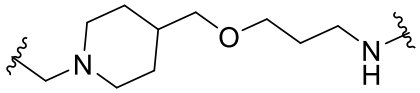
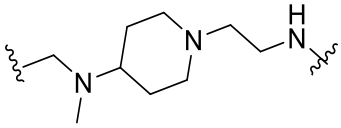
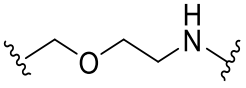
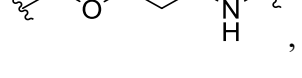
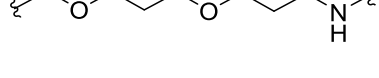
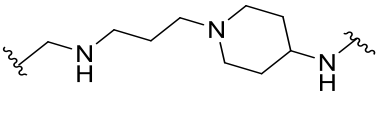
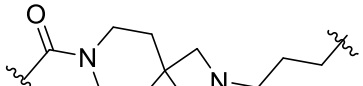
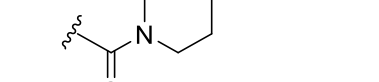
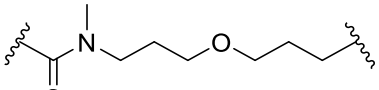
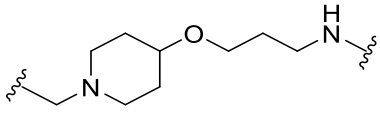
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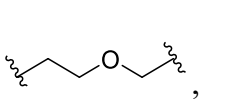
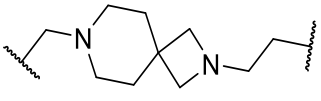
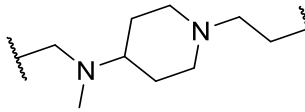
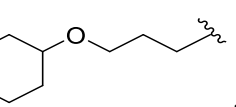
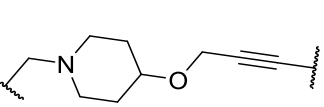
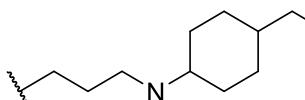
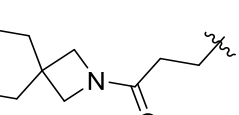
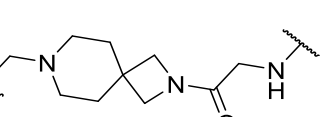
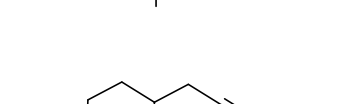
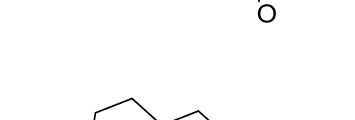
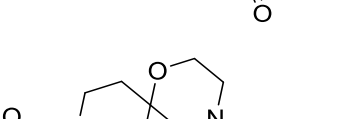


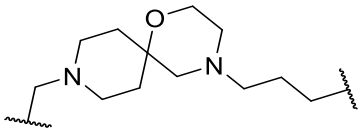
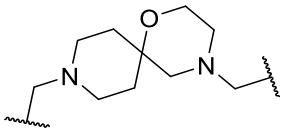
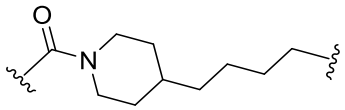
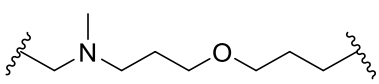
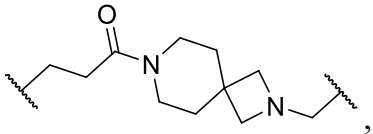
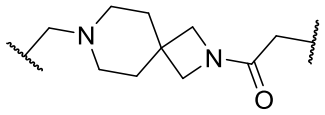
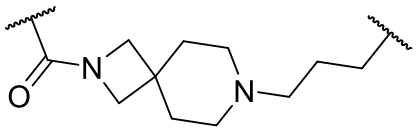
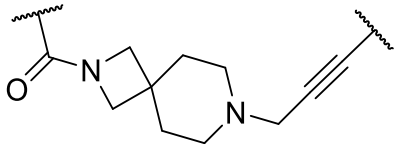
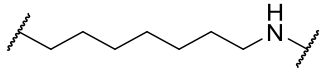
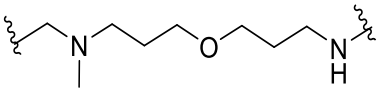
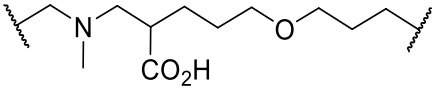
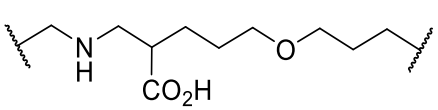
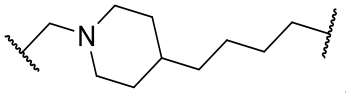
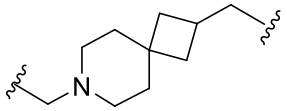
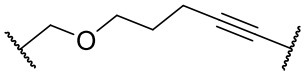
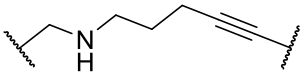
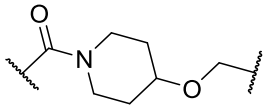
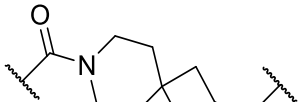
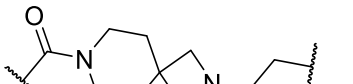
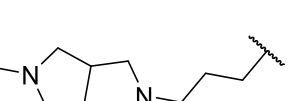
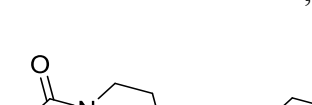
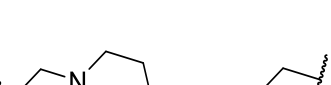
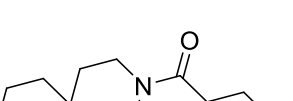
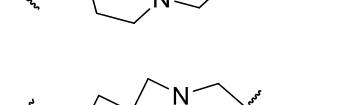
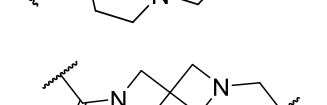


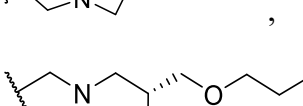
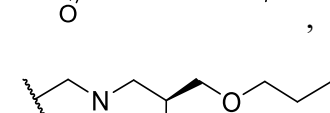
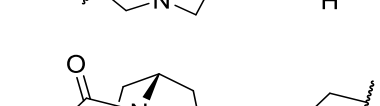
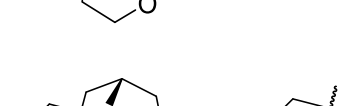
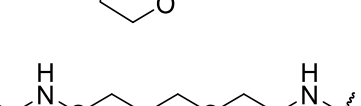
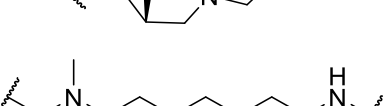
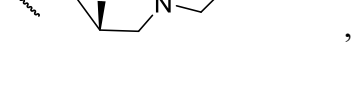
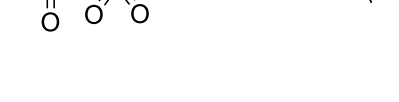





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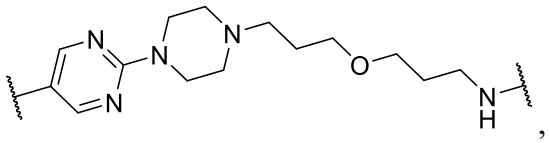
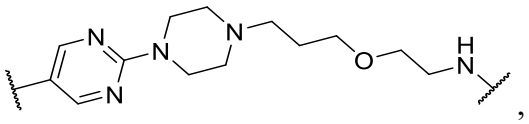
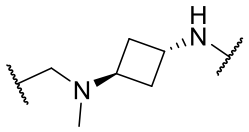
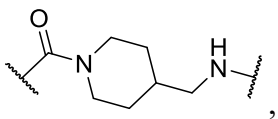
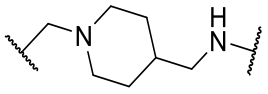
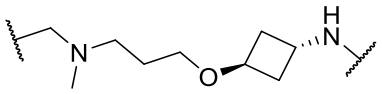
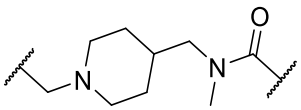
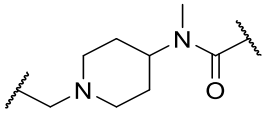
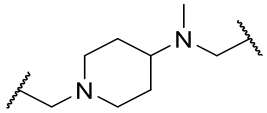
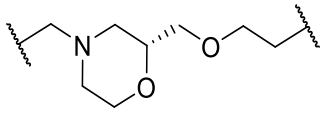
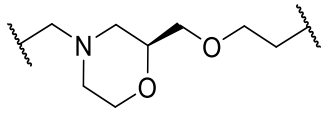
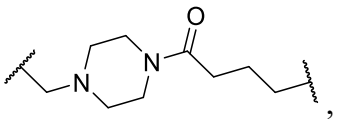
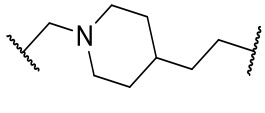
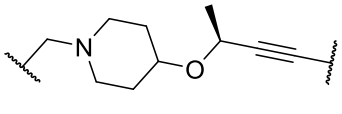
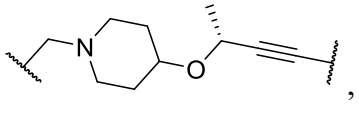
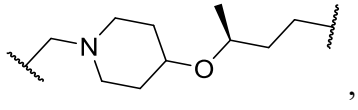
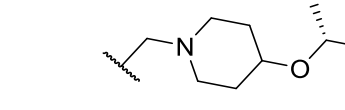
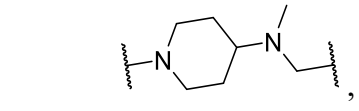
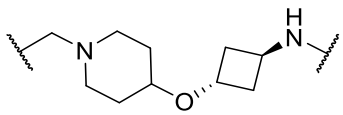
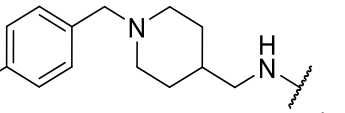
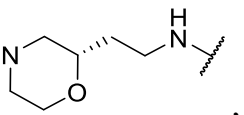
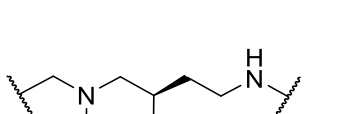
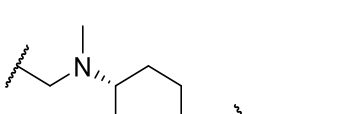
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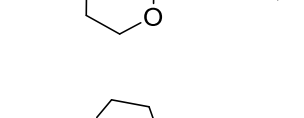
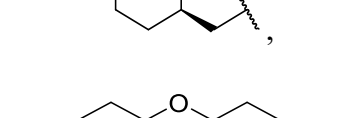
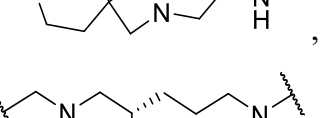
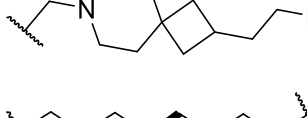
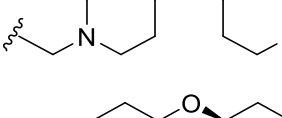
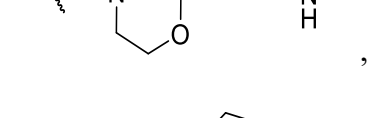
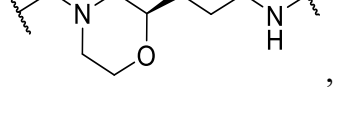
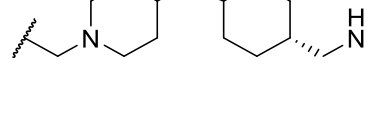
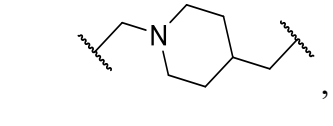
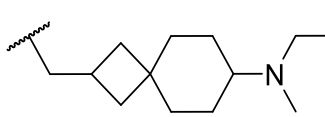
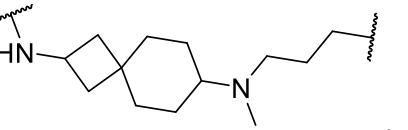
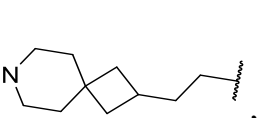
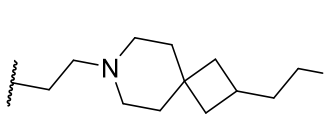
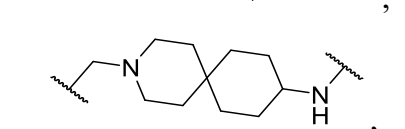
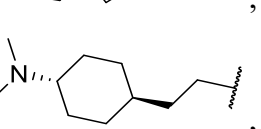
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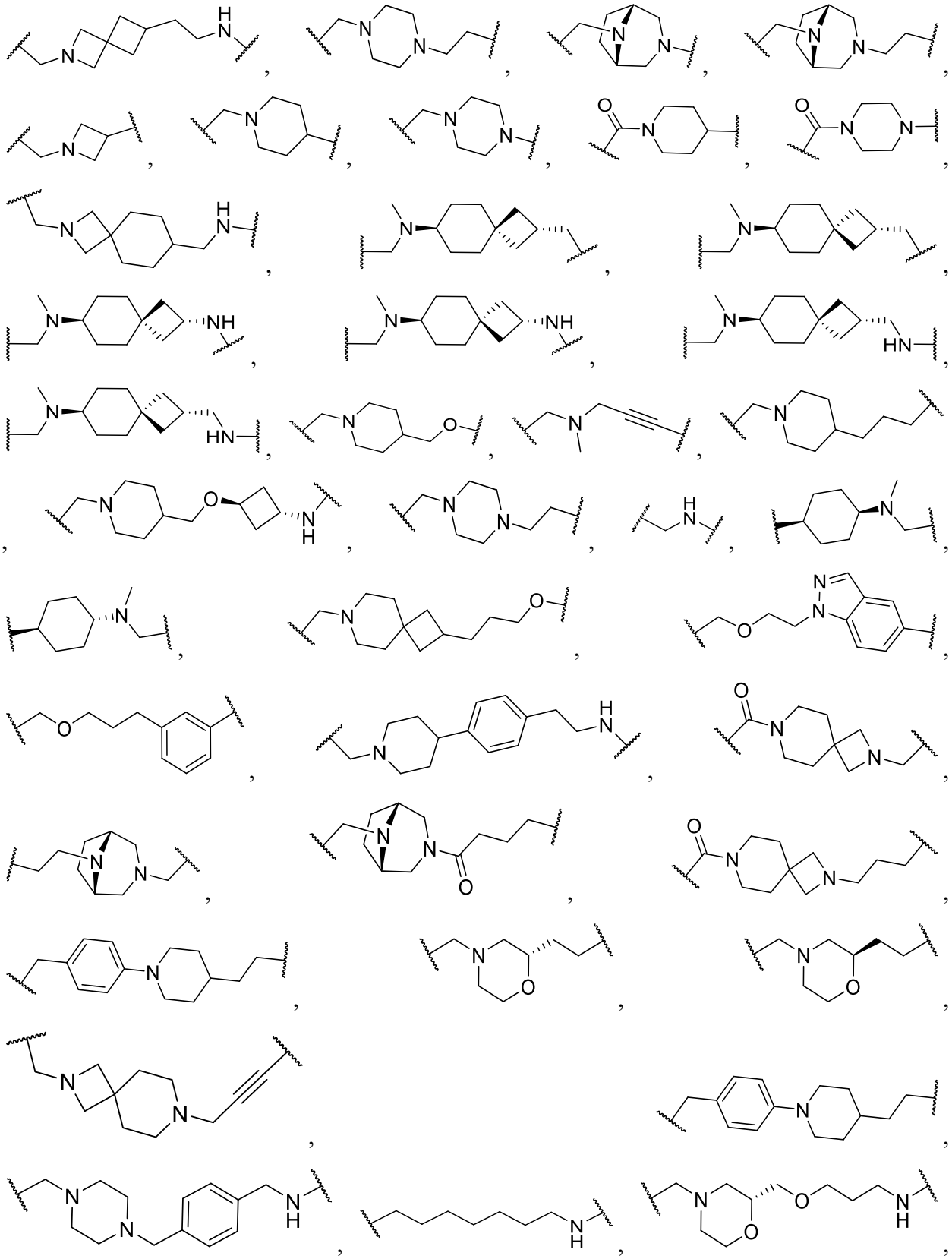

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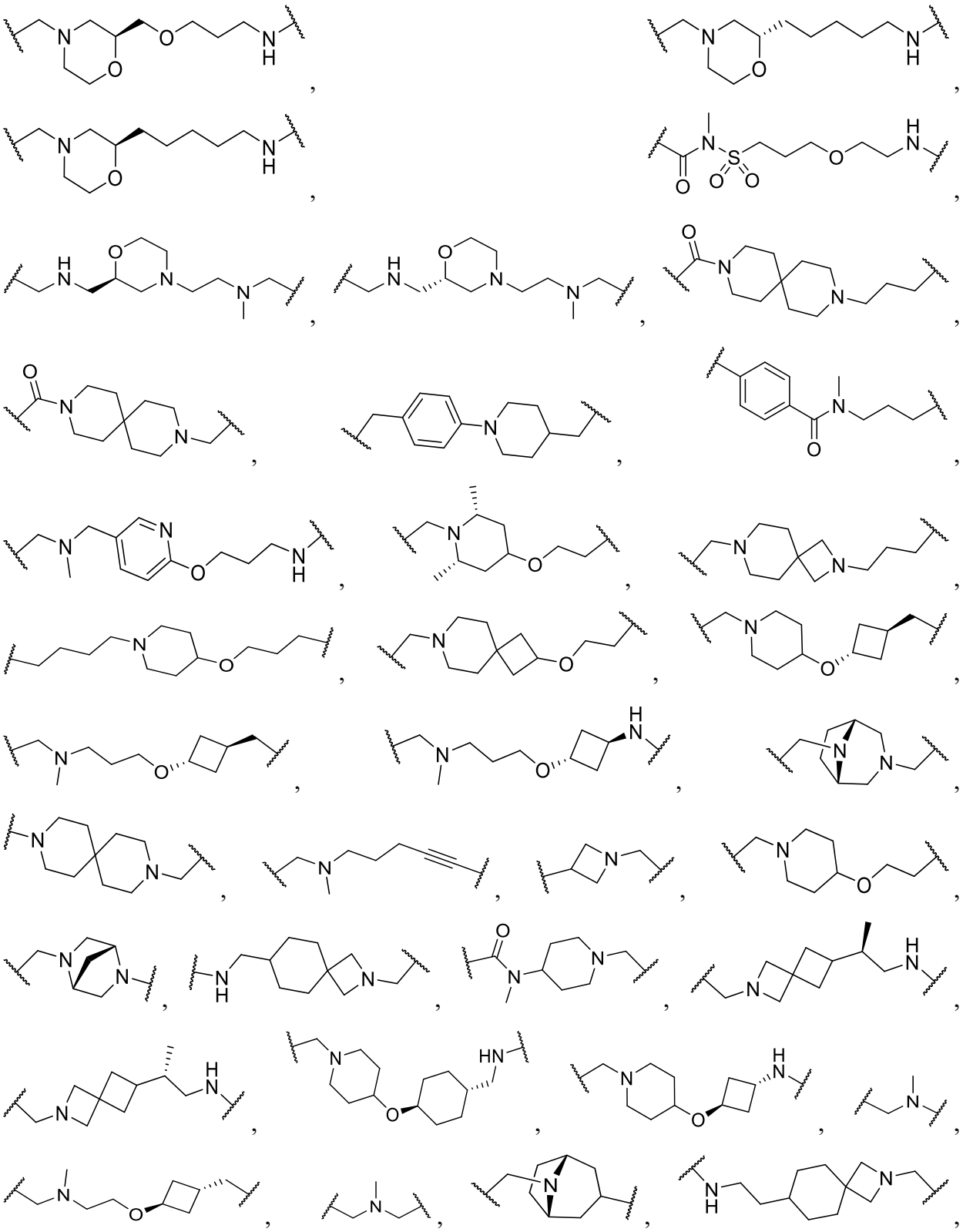
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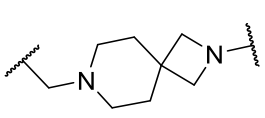
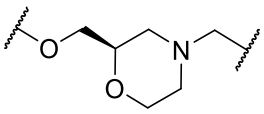
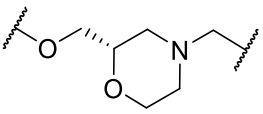
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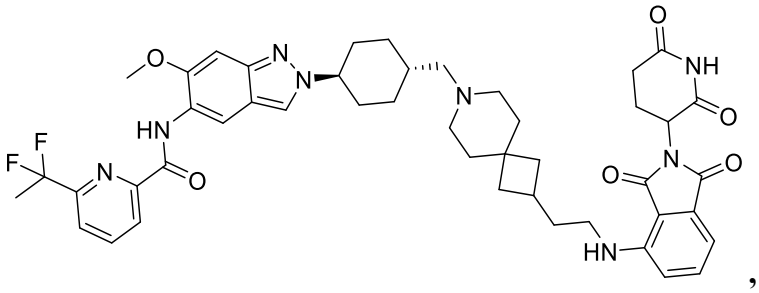





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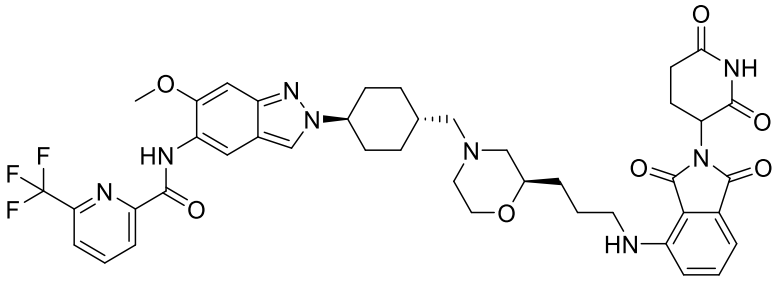
10. The compound of any of one of claims 1-9, wherein said compound is selected from any one of the following compounds:

I-63



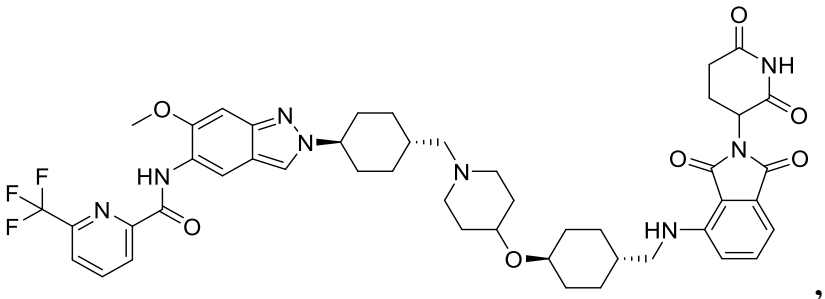
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I-68



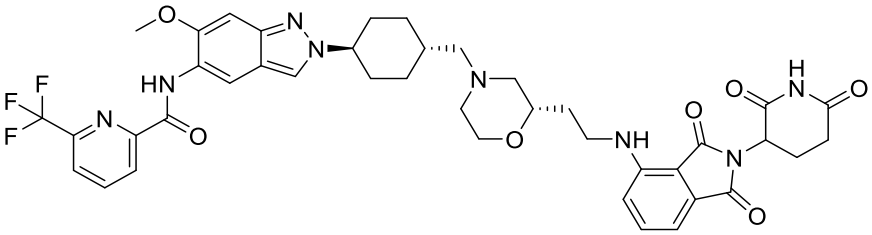
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I-69



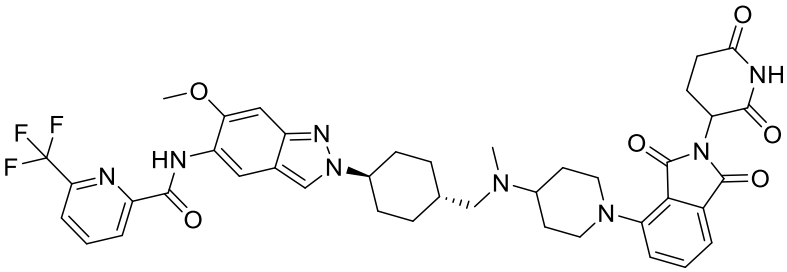
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I-71



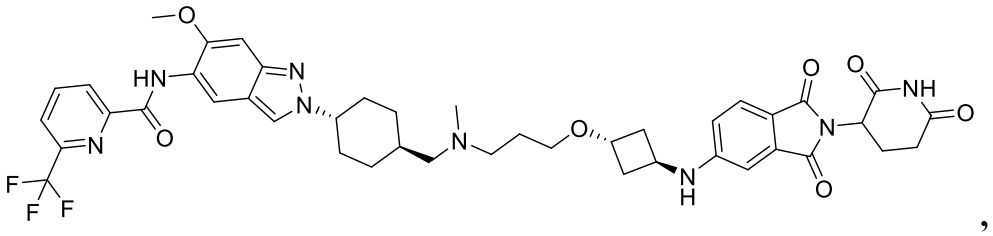
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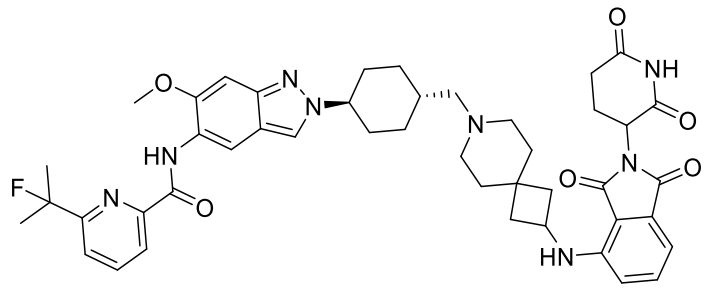
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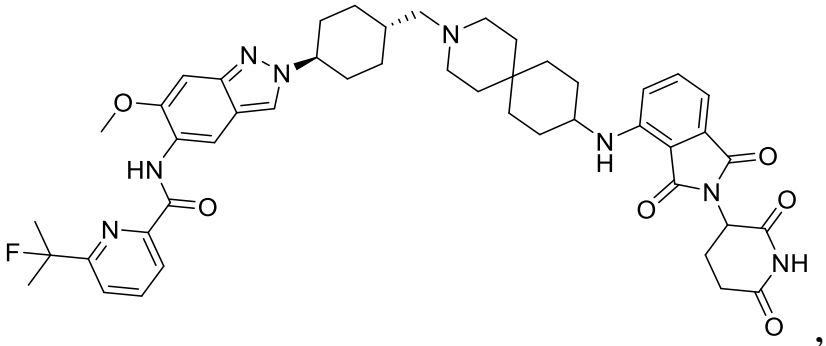
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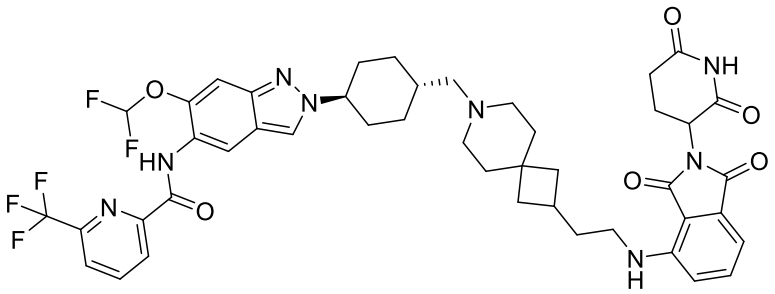
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I-88



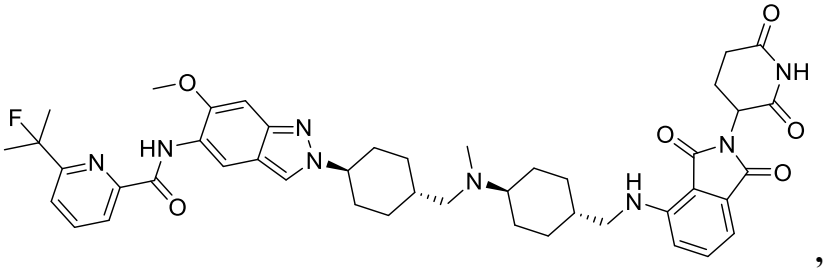
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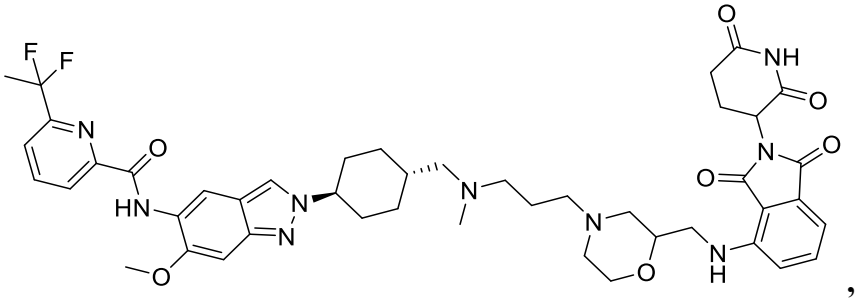
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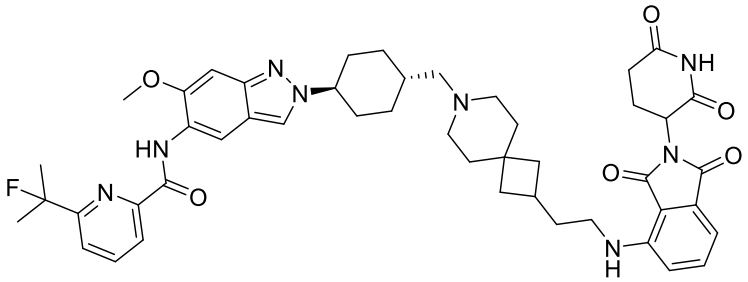
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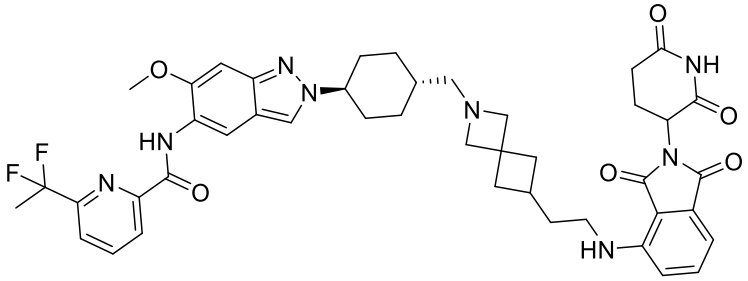
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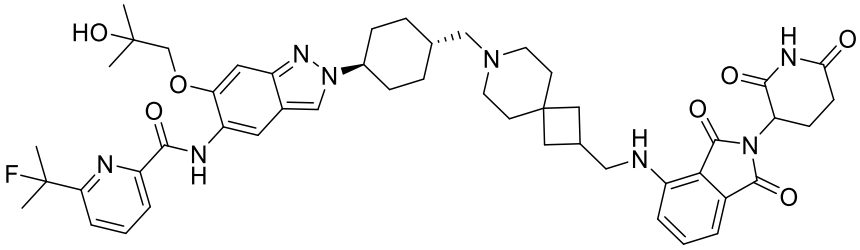
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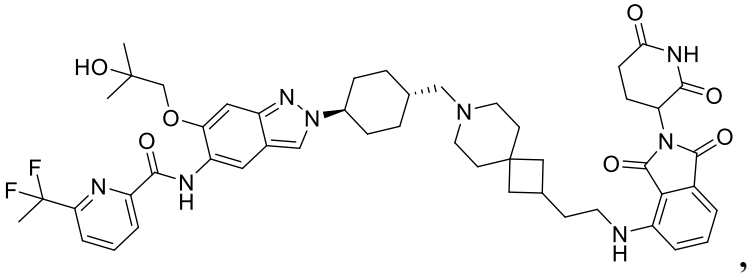
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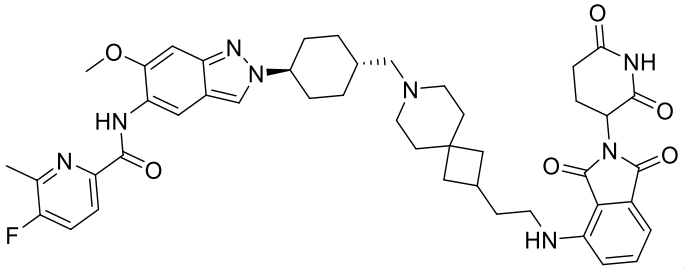
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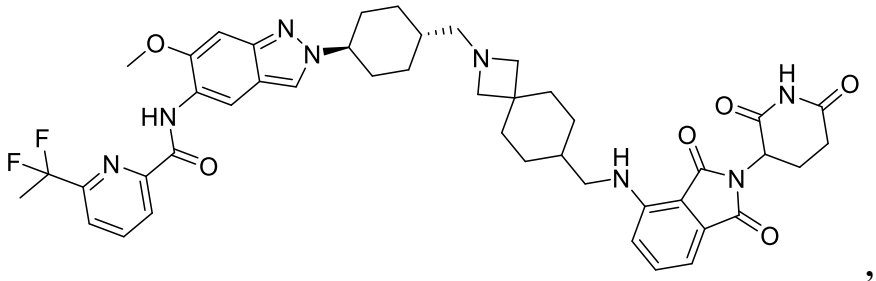
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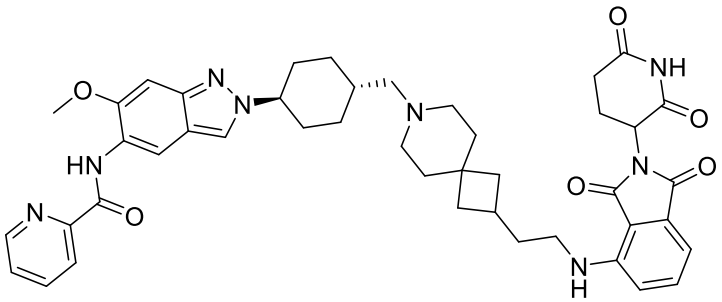
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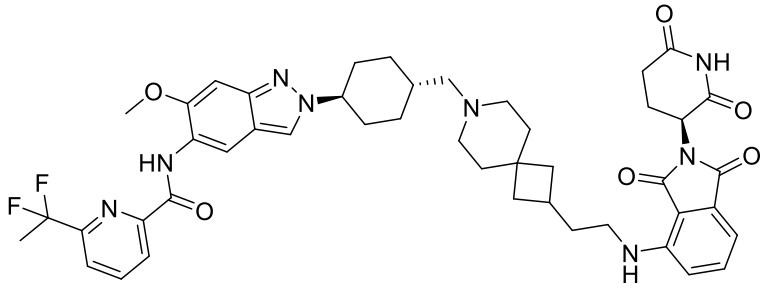
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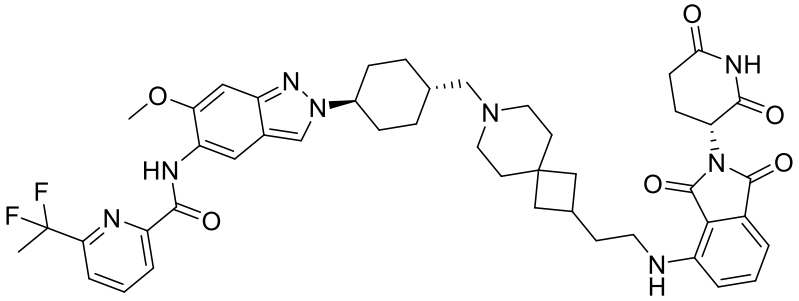
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I-128



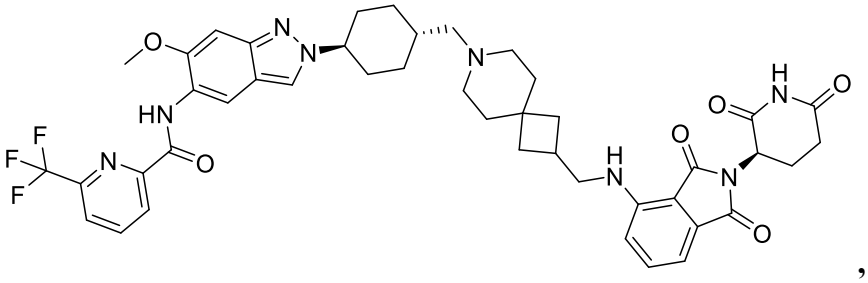
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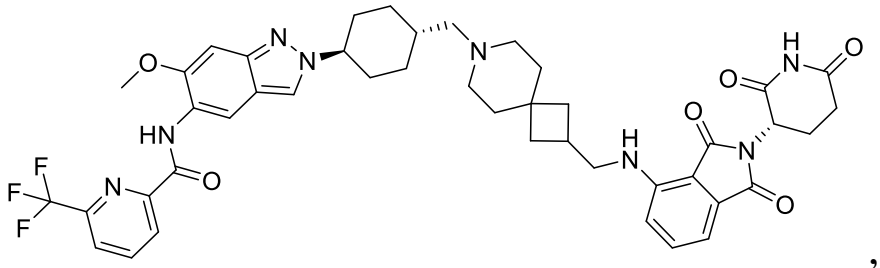
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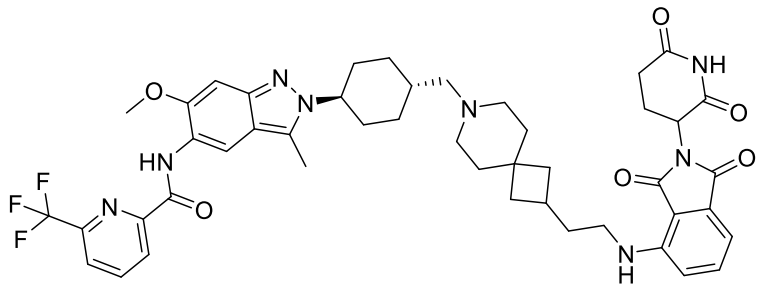
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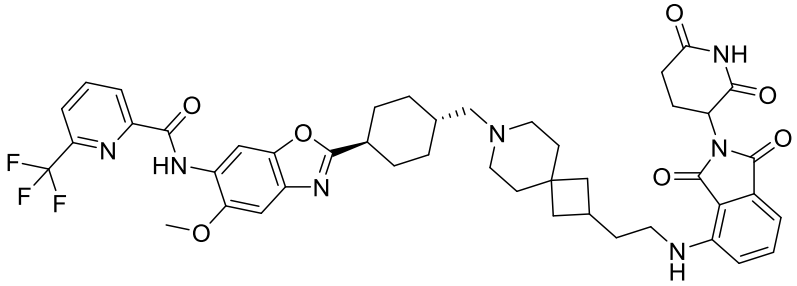
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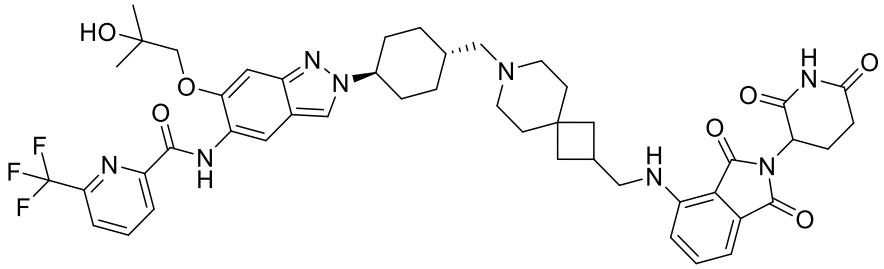
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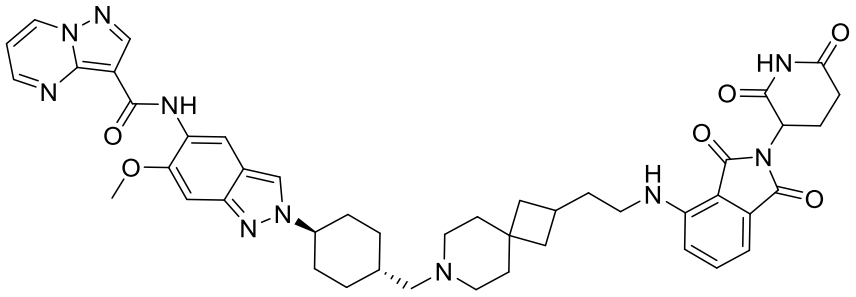
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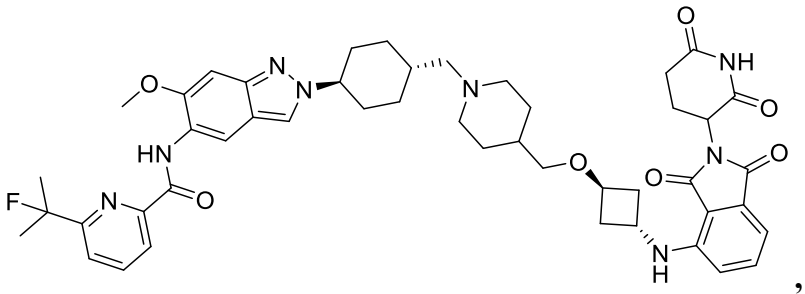
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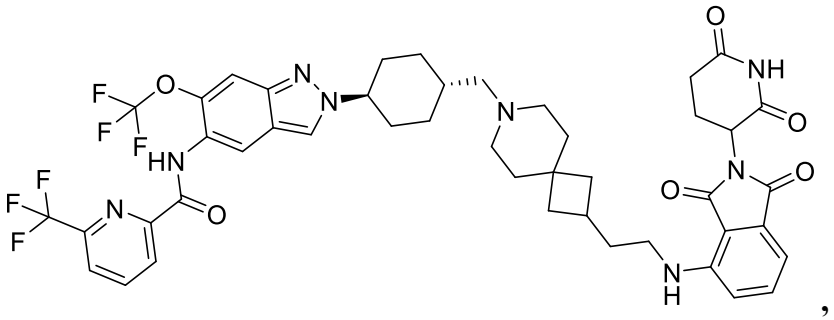
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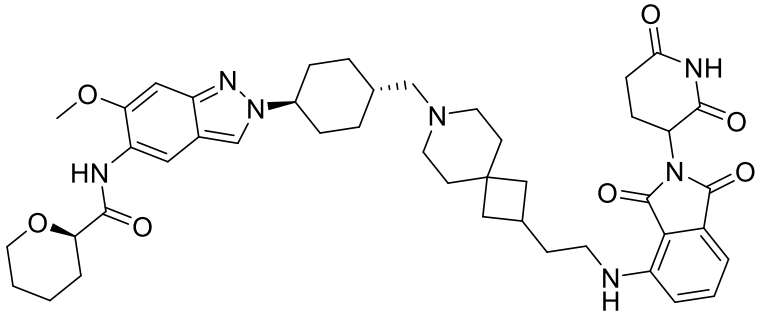
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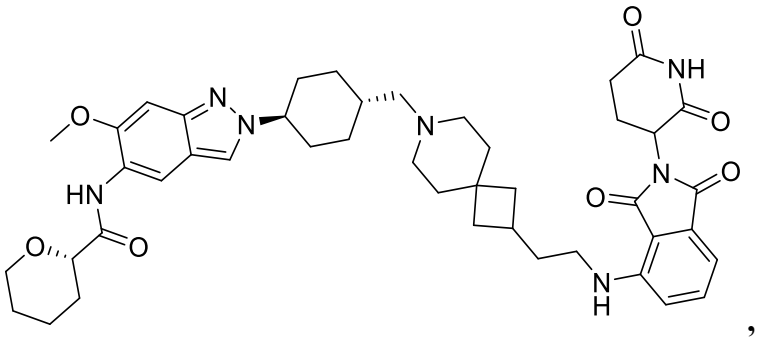
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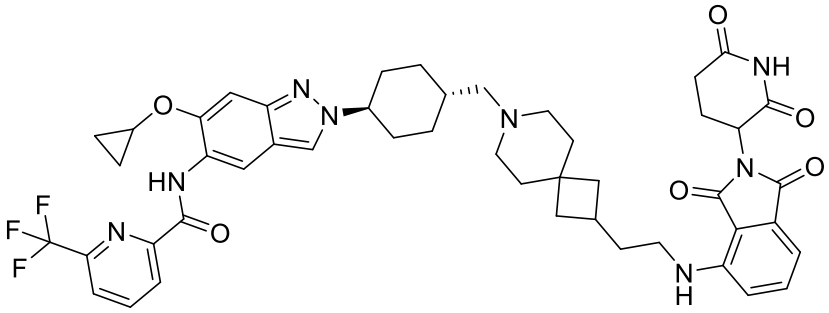
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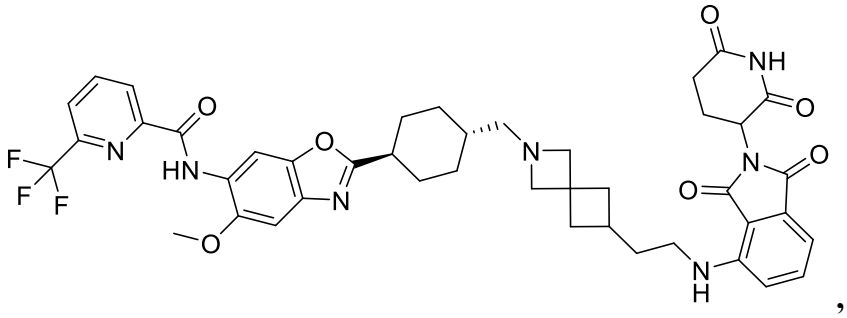
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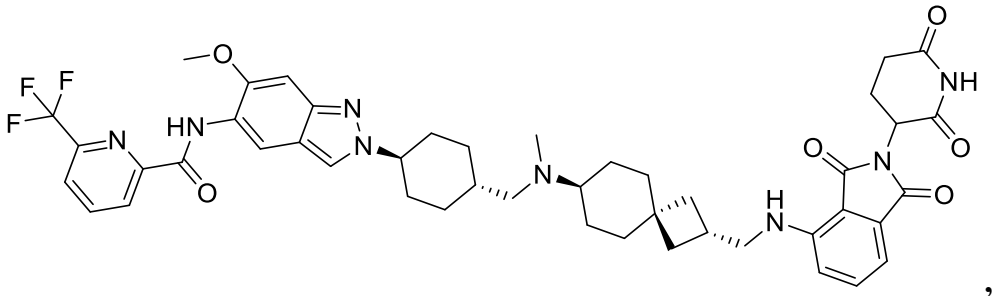
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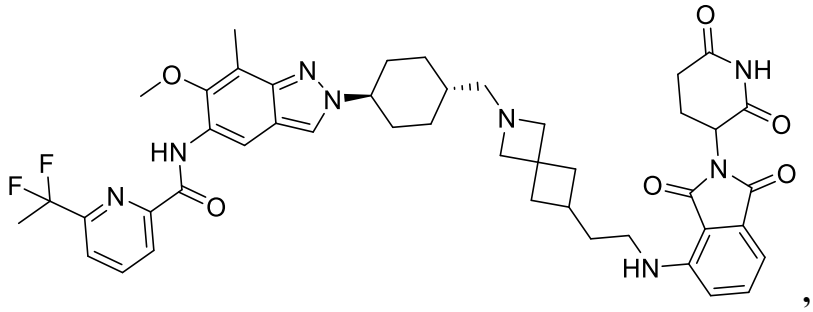
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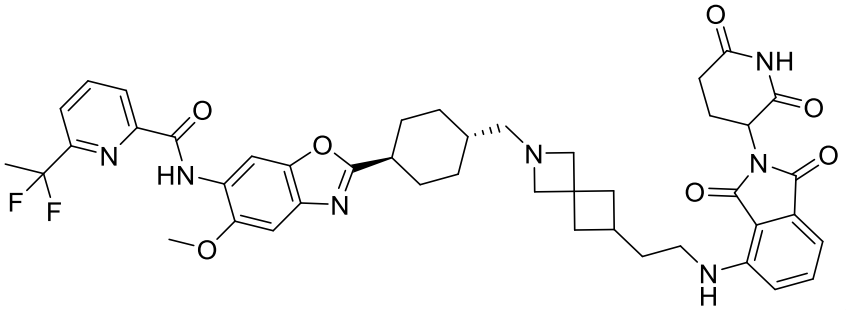
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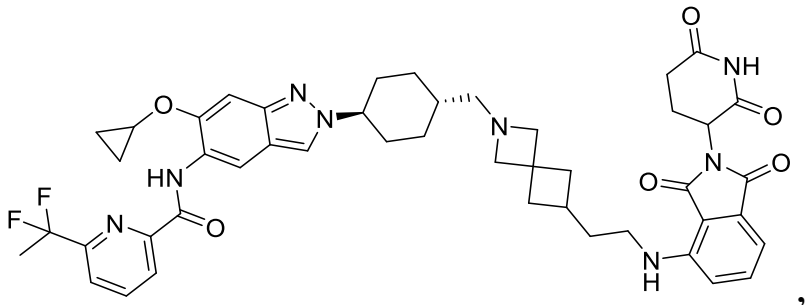
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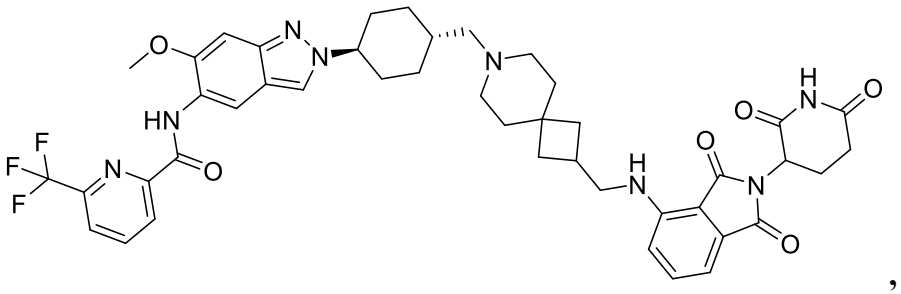
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I-200



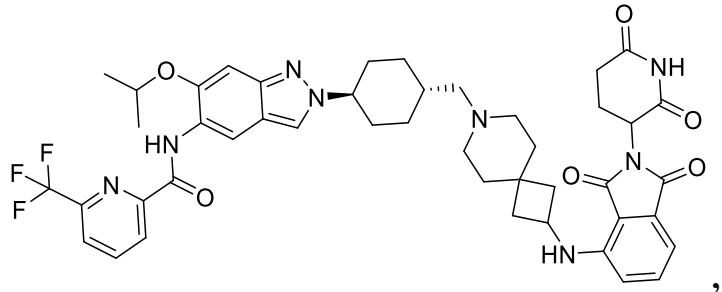
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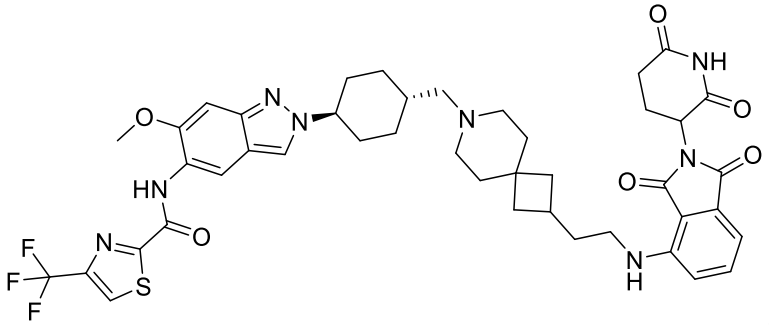
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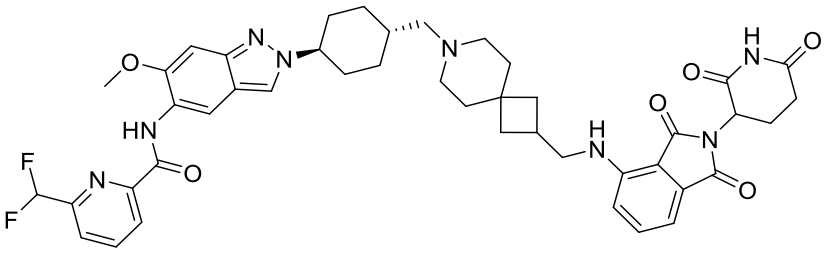
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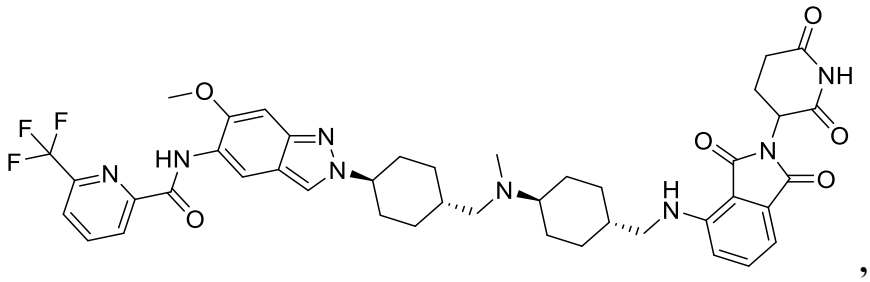
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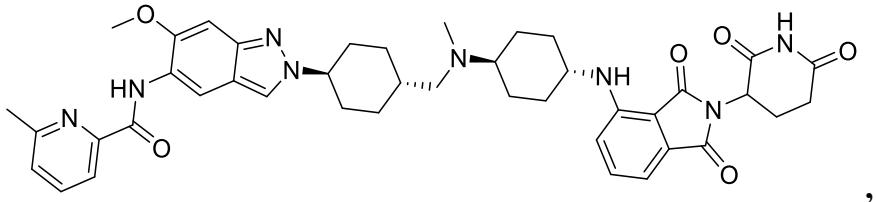
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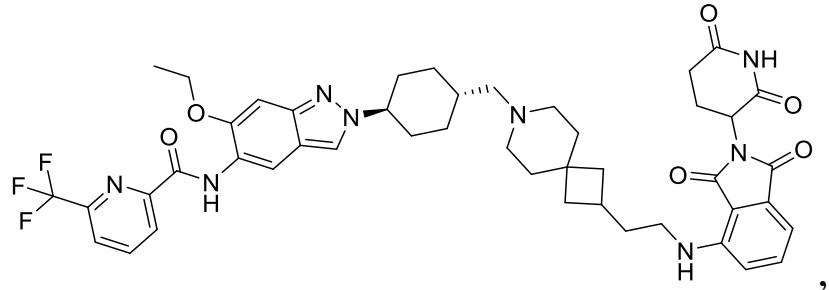
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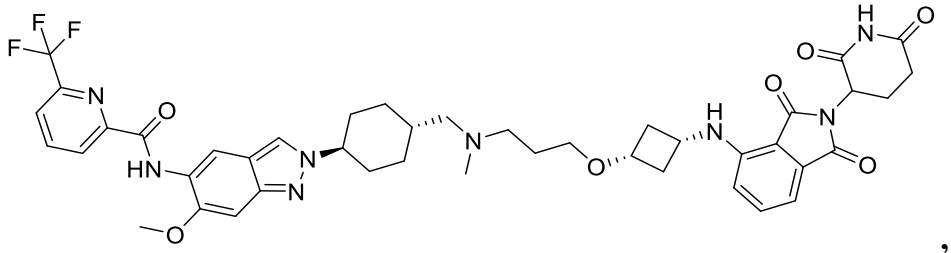
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I-212



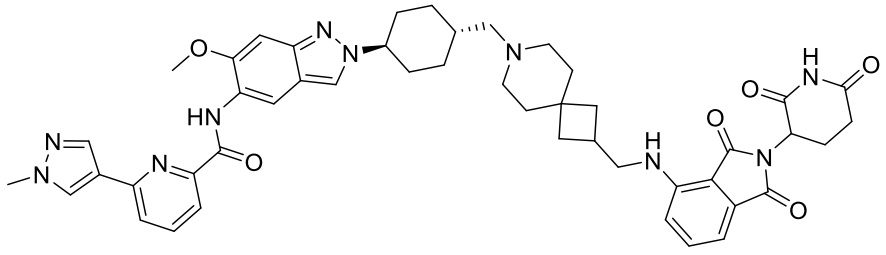
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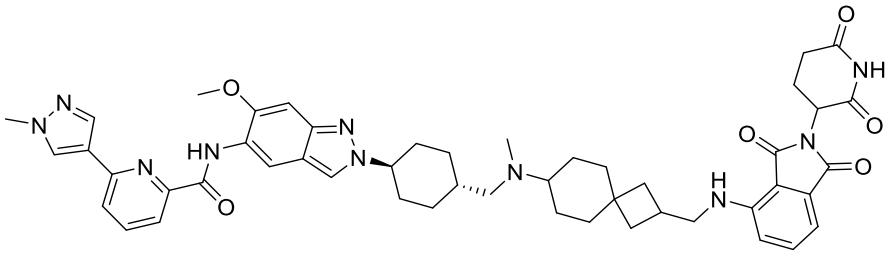
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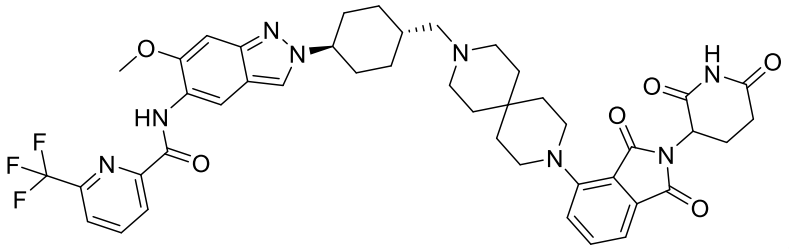
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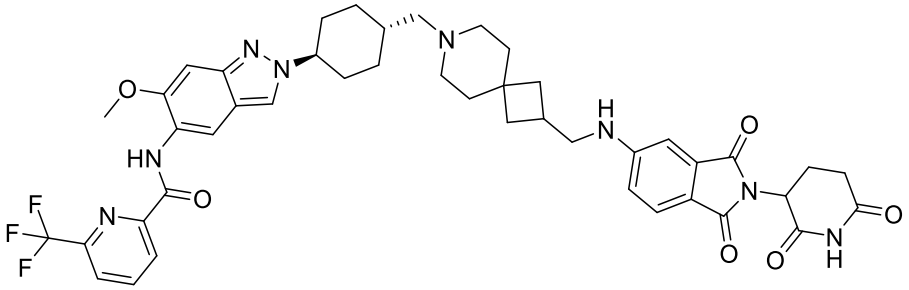
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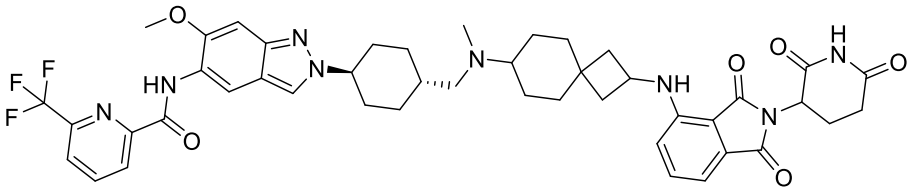
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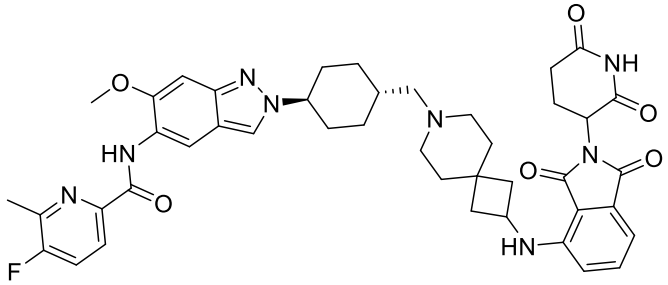
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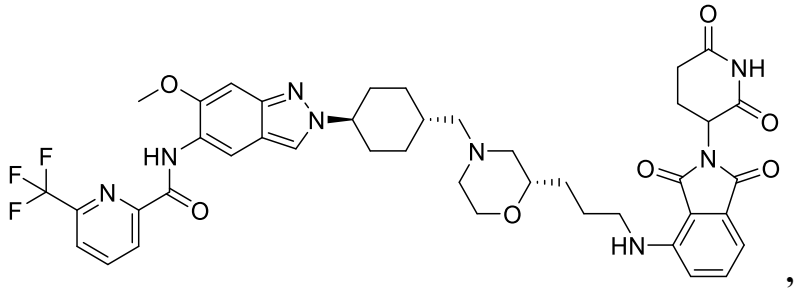
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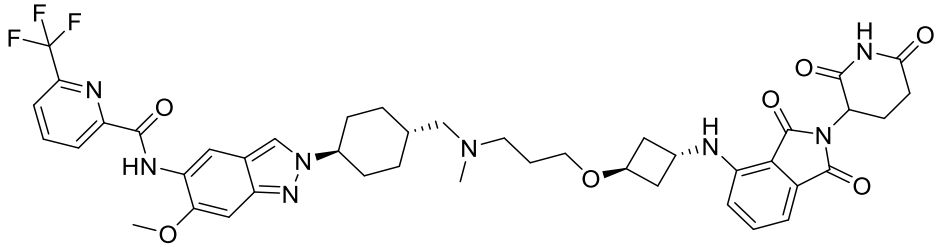
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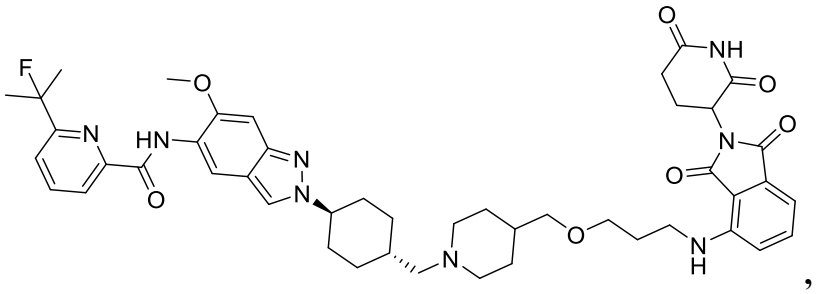
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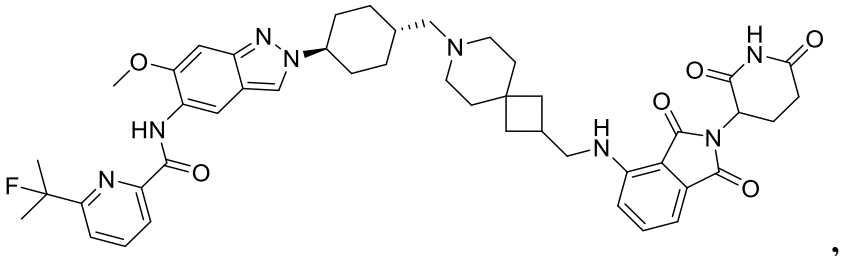
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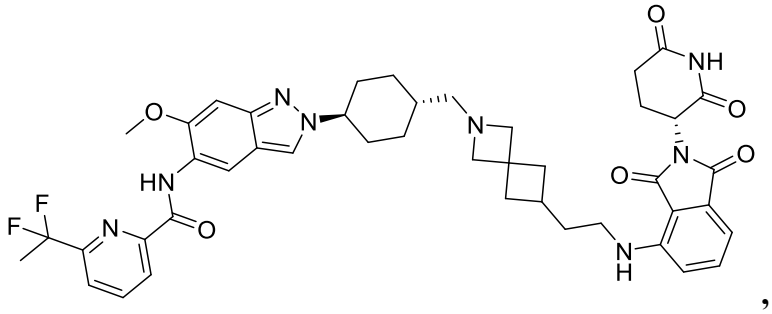
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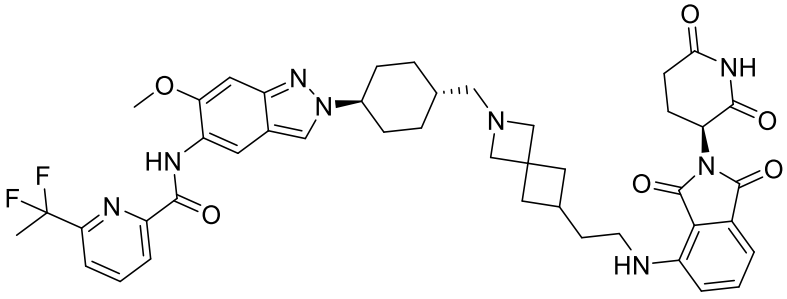
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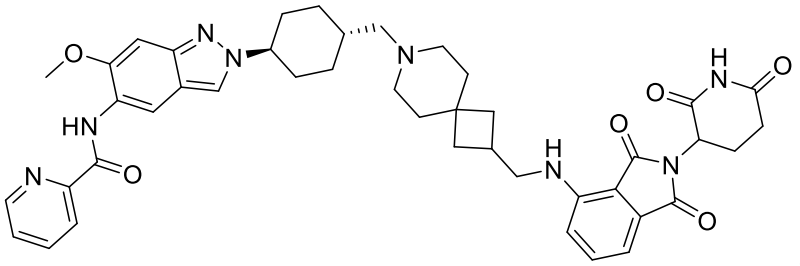
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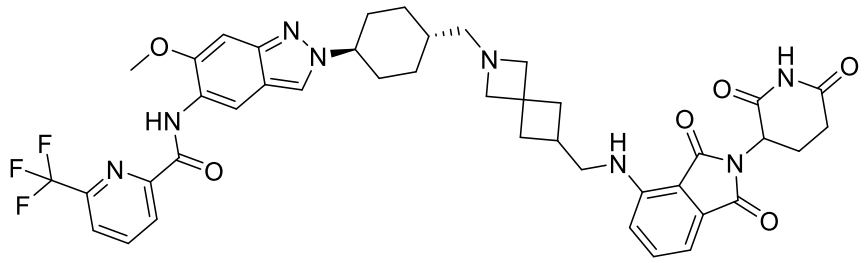
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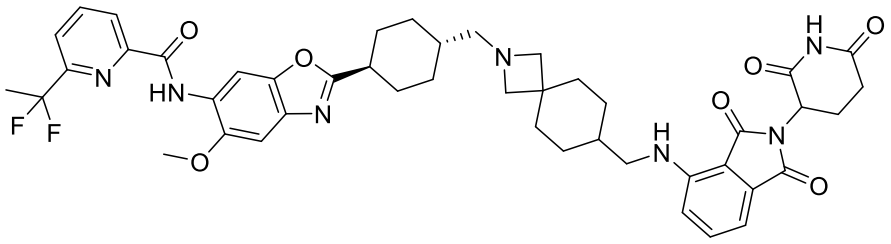
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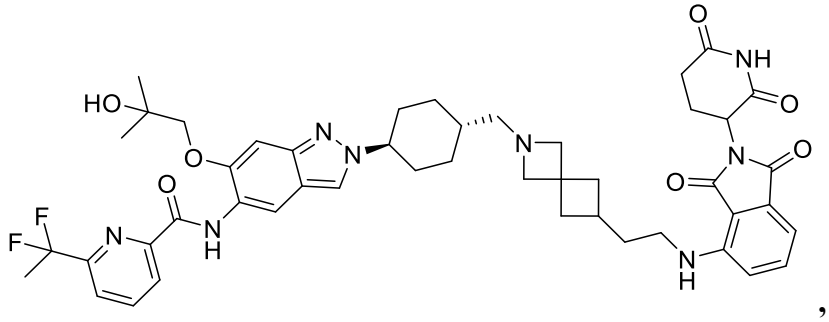
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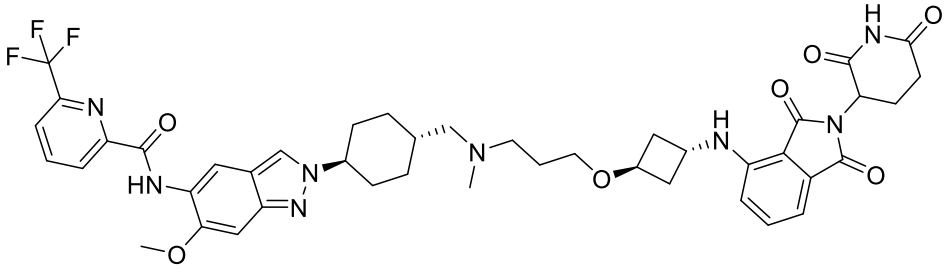
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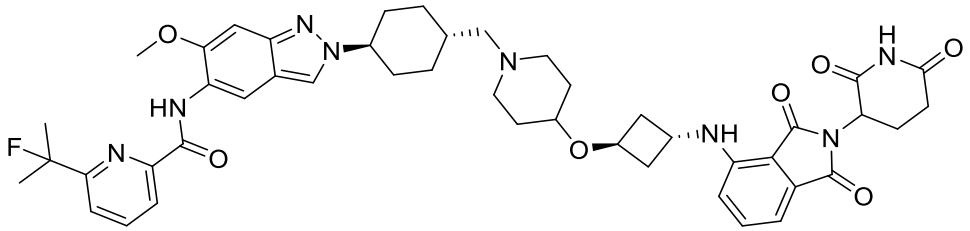
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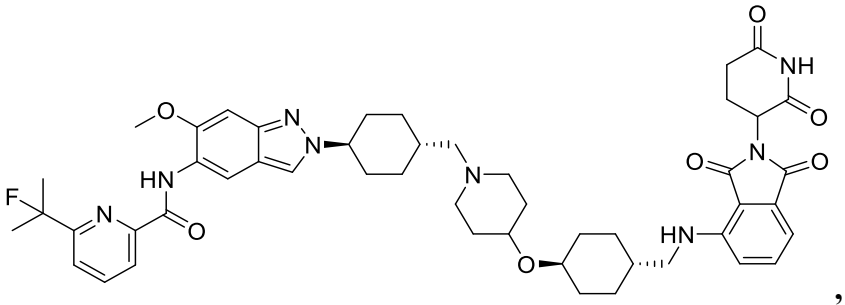
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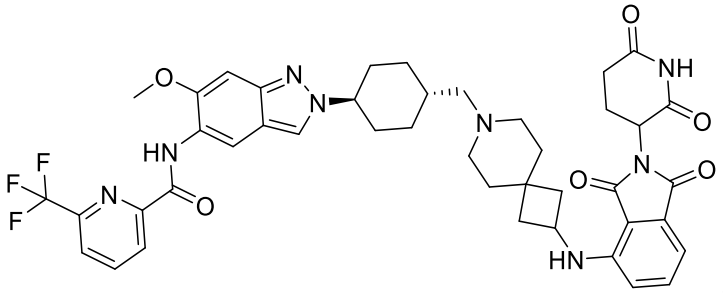
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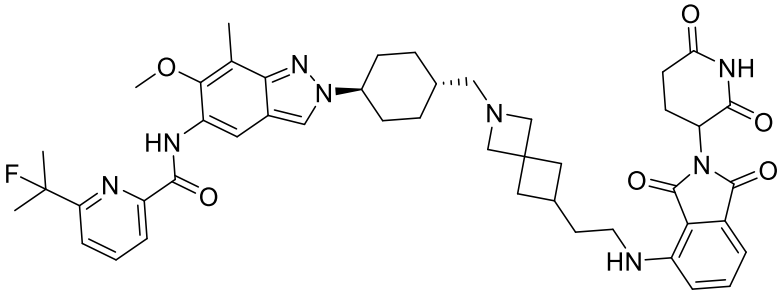
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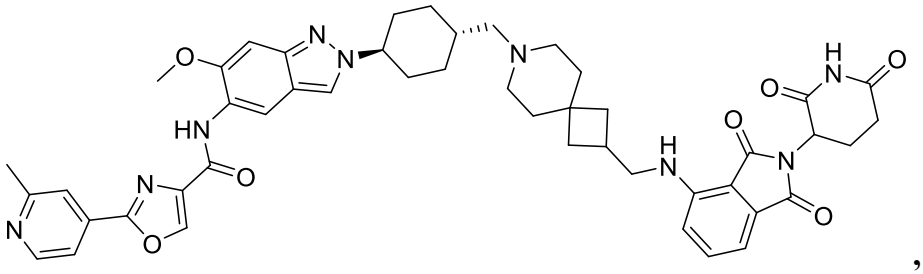
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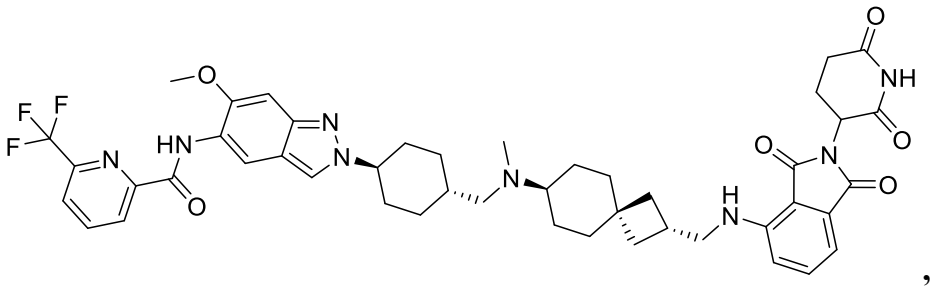
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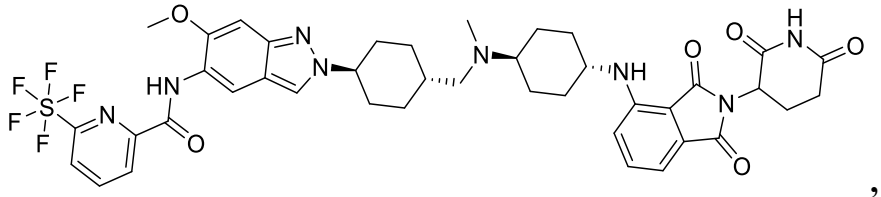
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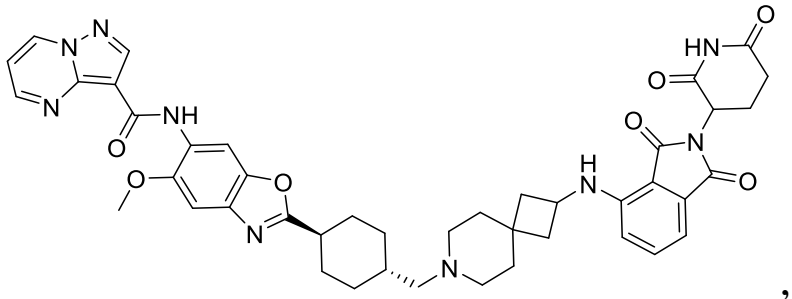
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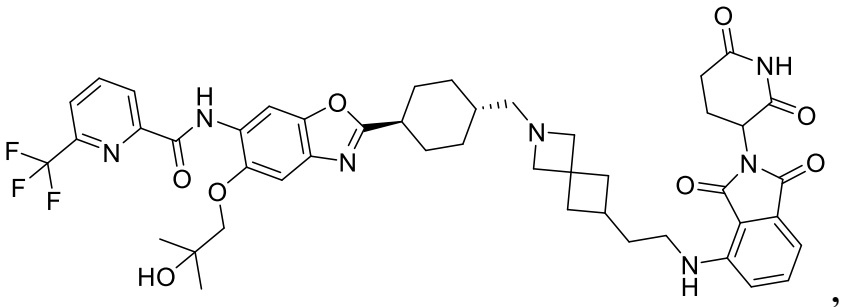
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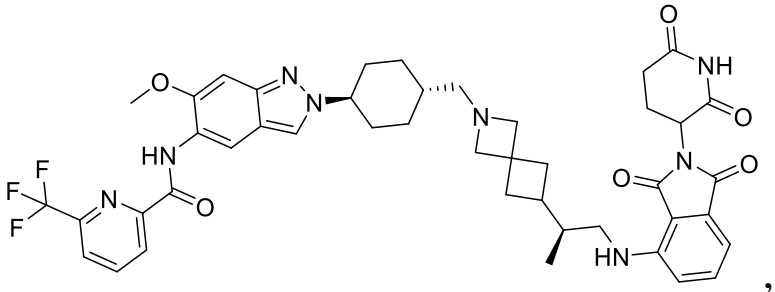
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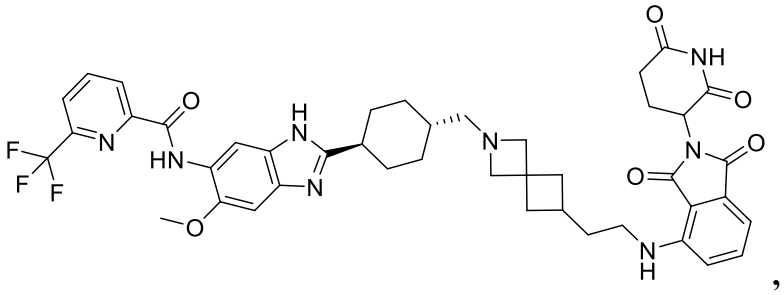
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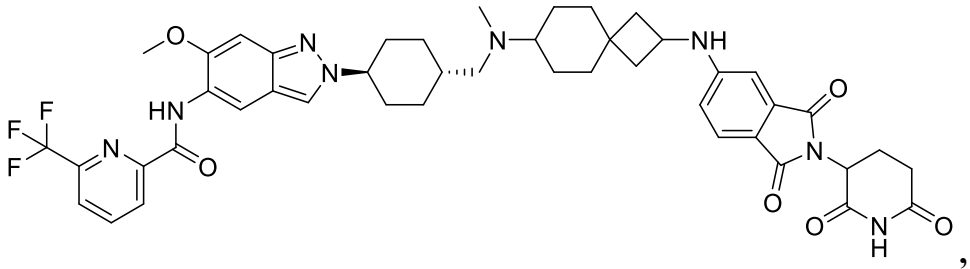
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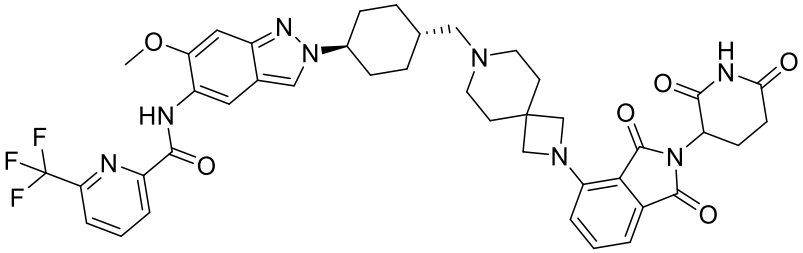
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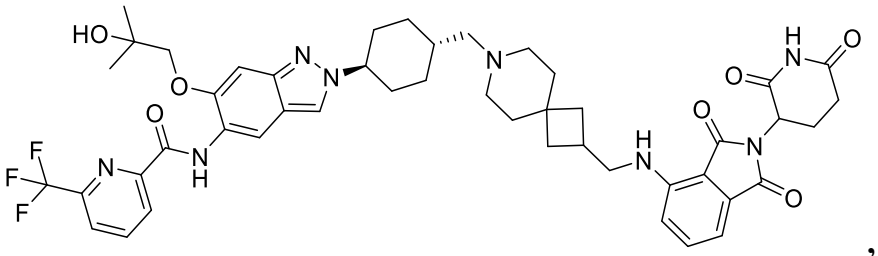
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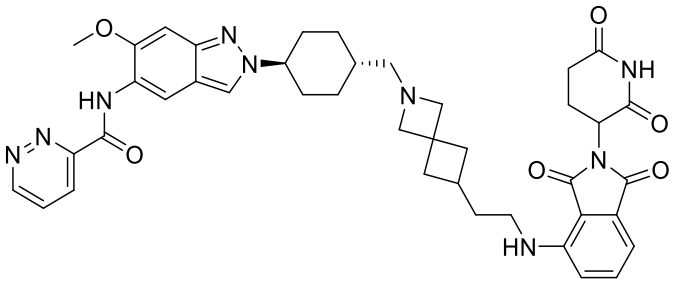
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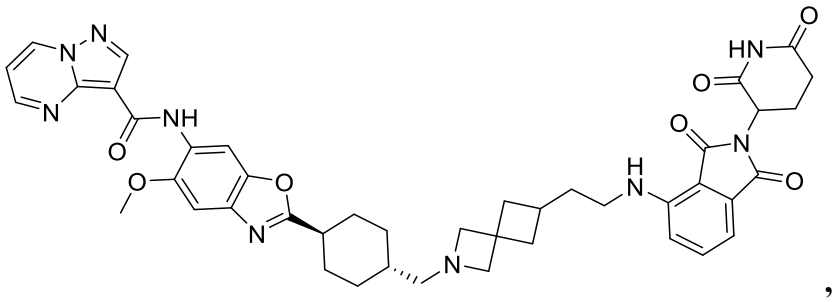
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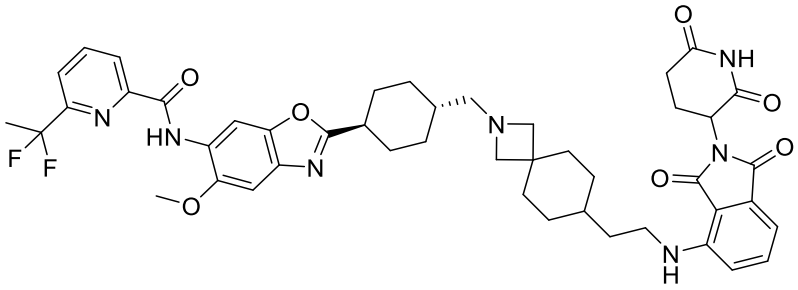
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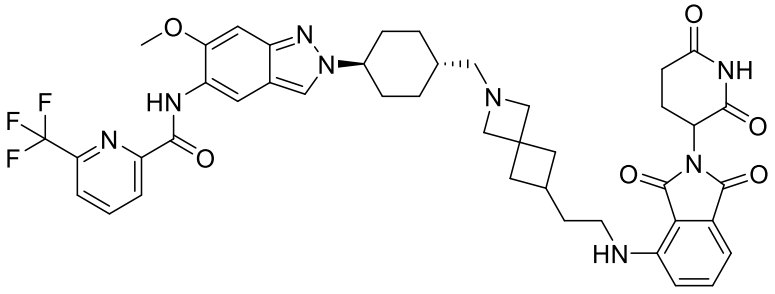
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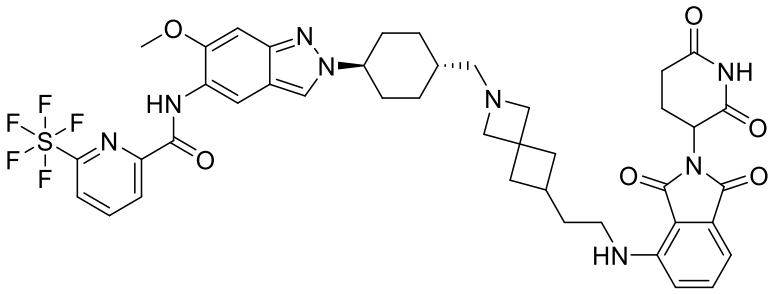
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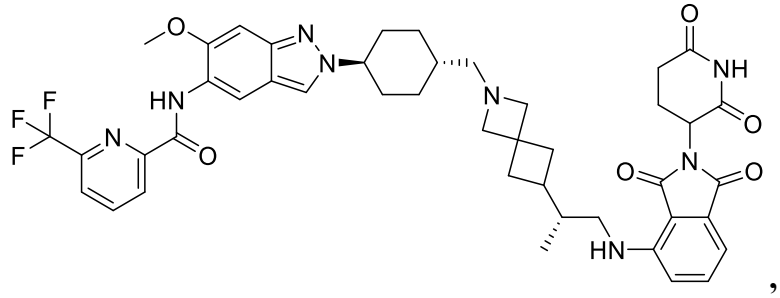
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or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound of any one of claims 1-10, and a

pharmaceutically acceptable carrier, adjuvant, or vehicle.

12. A compound of any one of claims 1-10, or a pharmaceutical composition of claim 11, for use in therapy.

13. Use of a compound of any one of claims 1-10, or a pharmaceutical composition of claim 11, in the manufacture of a medicament for treating an IRAK-mediated disorder, disease, or condition in a patient, wherein the IRAK-mediated disorder, disease or condition is selected from the group consisting of a cancer, a neurodegenerative disease, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, a condition associated with organ transplantation, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T cell activation, a cardiovascular disorder, and a CNS disorder.

14. The use of claim 13, wherein the cancer or proliferative disorder is selected from the group consisting of a benign or malignant tumor, solid tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastoma, neuroblastoma, multiple myeloma, gastrointestinal cancer, colon carcinoma, colorectal adenoma, a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphoma, Hodgkin's or Non-Hodgkin's lymphoma, a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, primary cutaneous T-cell lymphoma, smoldering or indolent multiple myeloma, and a hematological malignancy selected from_leukemia, diffuse large B-cell lymphoma (DLBCL), ABC DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström's macroglobulinemia (WM), splenic marginal zone lymphoma, multiple

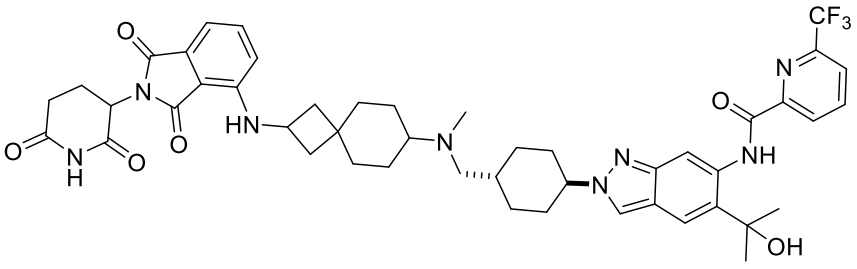
myeloma, plasmacytoma, or intravascular large B-cell lymphoma.

15. The use of claim 13, wherein the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia, and a neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity, hypoxia, epilepsy, treatment of diabetes, metabolic syndrome, obesity, organ transplantation and graft versus host disease.

16. The use of claim 13, wherein the inflammatory disorder is selected from the group consisting of ocular allergy, conjunctivitis, keratoconjunctivitis sicca, vernal conjunctivitis; allergic rhinitis, hemolytic anemia, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia or another inflammatory disease in which autoimmune reactions are implicated or which have an autoimmune component or etiology, systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, ulcerative colitis, Crohn's disease or another autoimmune inflammatory bowel disease, irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, optionally including idiopathic nephrotic syndrome or minal change nephropathy), chronic granulomatous disease, endometriosis, leptospiriosis renal disease, glaucoma, retinal disease, aging, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hyperchlolesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ecodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic, non-allergic, mild, moderate, severe, bronchitic, or exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, silica induced diseases, COPD

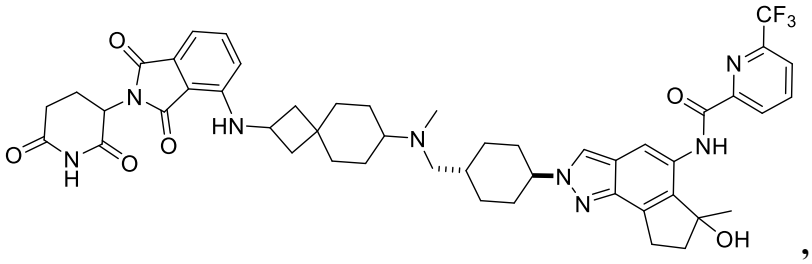
(reduction of damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression), pulmonary disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, Type 2 diabetes, appendicitis, atopic dermatitis, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, vaginitis, vasculitis, vulvitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, Cryopyrin Associated Periodic Syndrome (CAPS), and osteoarthritis.

17. A compound selected from any one of the following:

I-2 

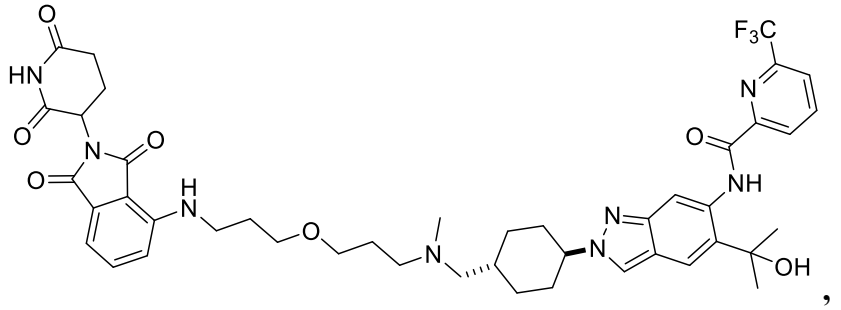
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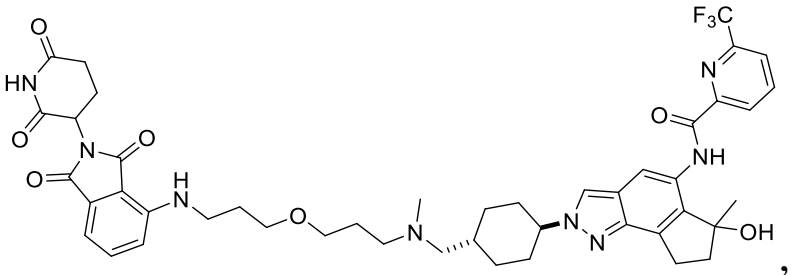
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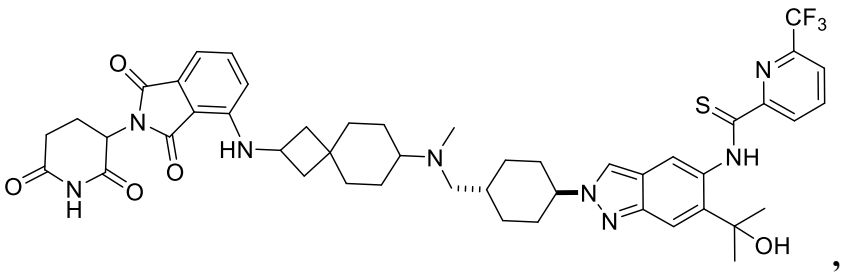
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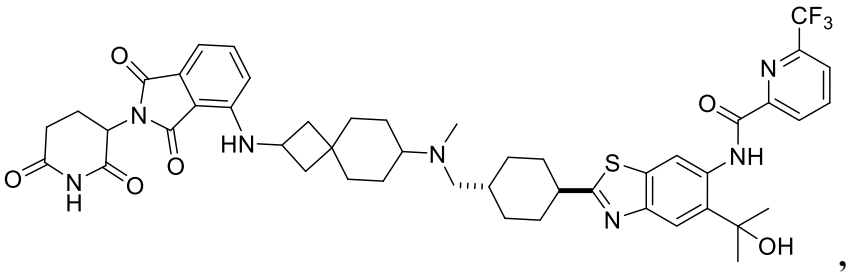
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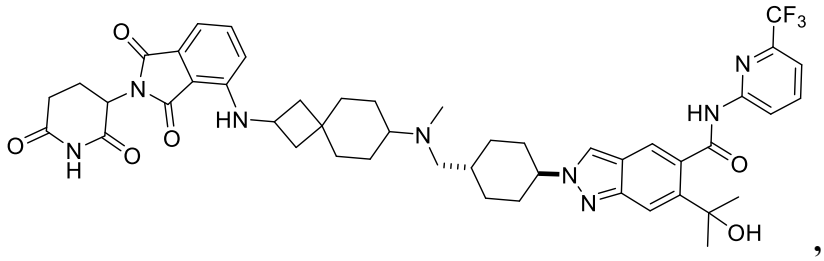
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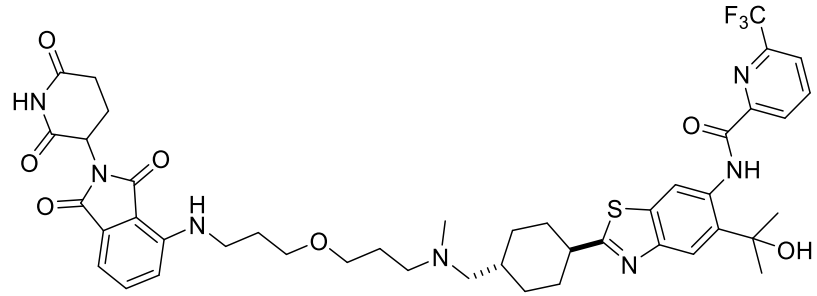
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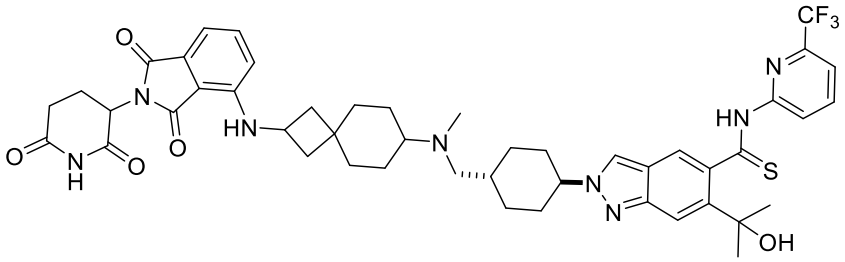
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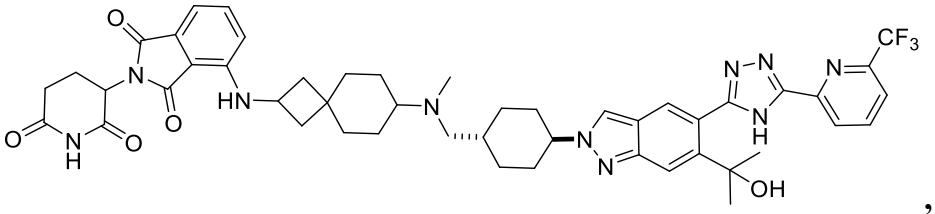
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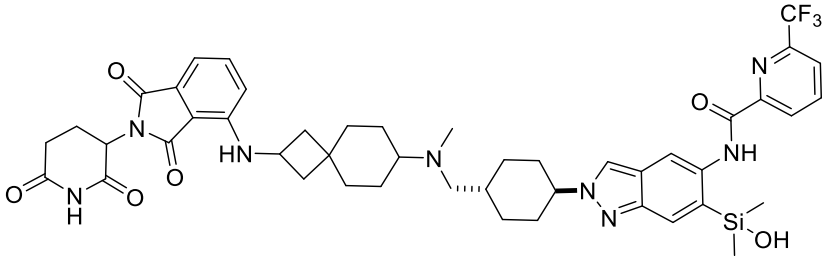
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I-22



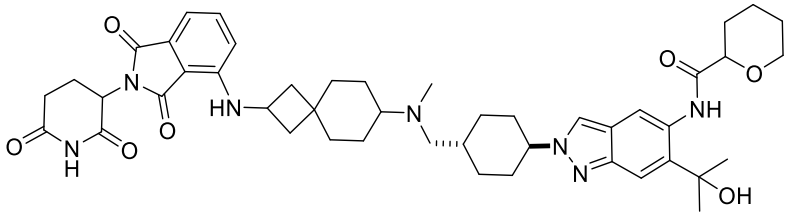
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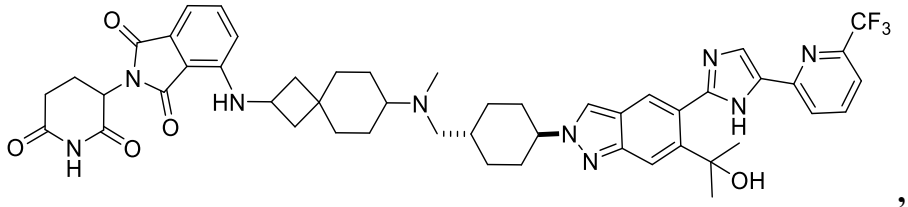
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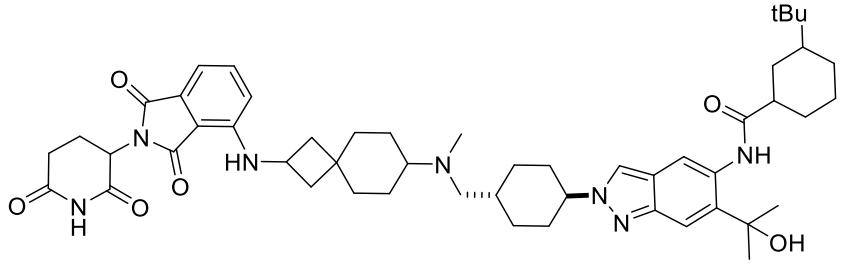
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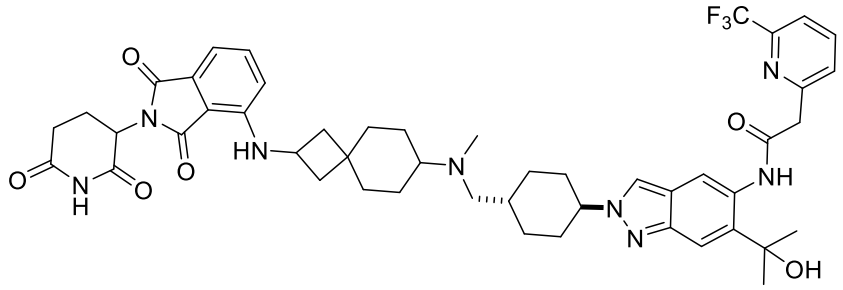
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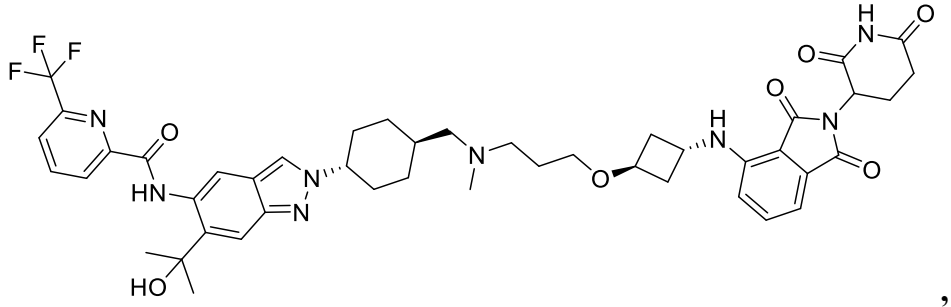
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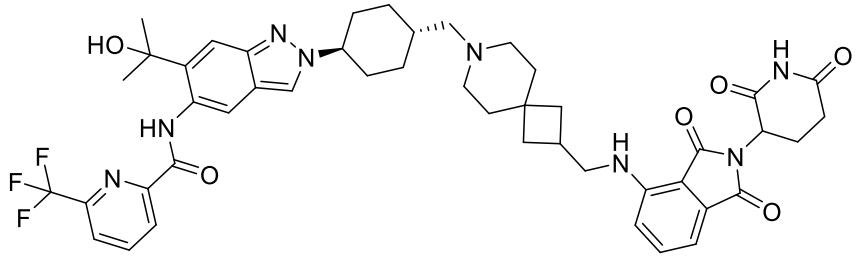
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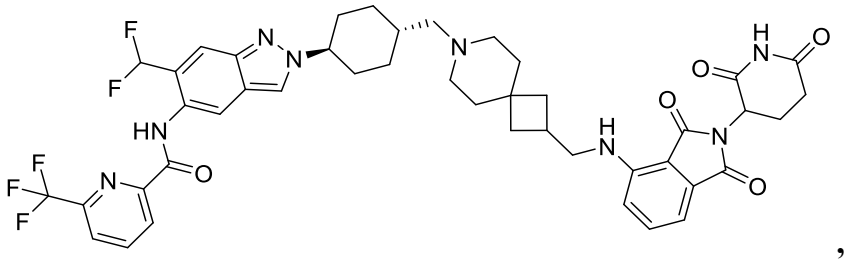
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I-42



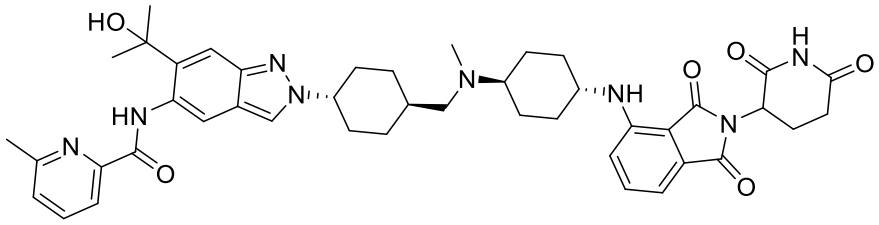
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I-46



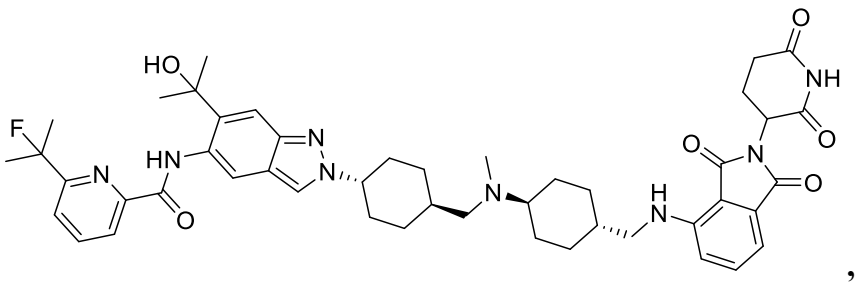
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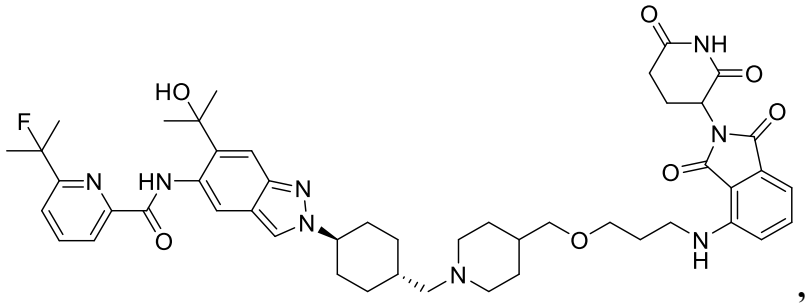
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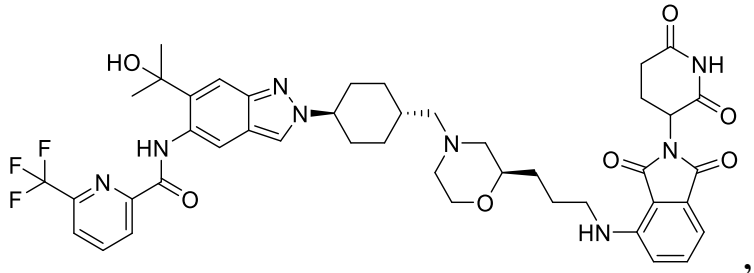
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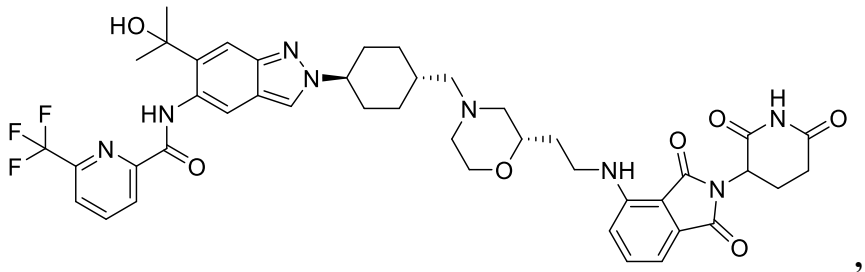
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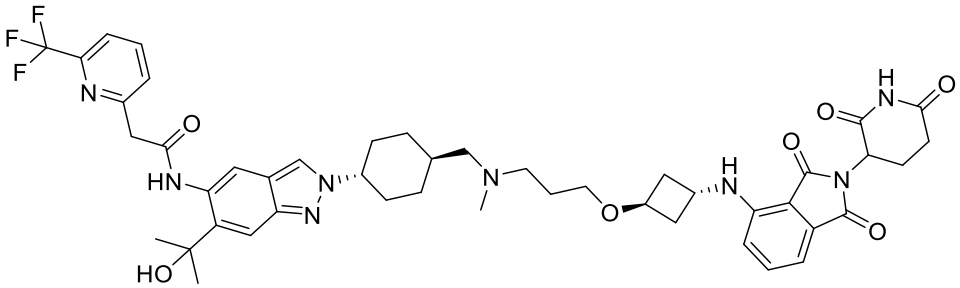
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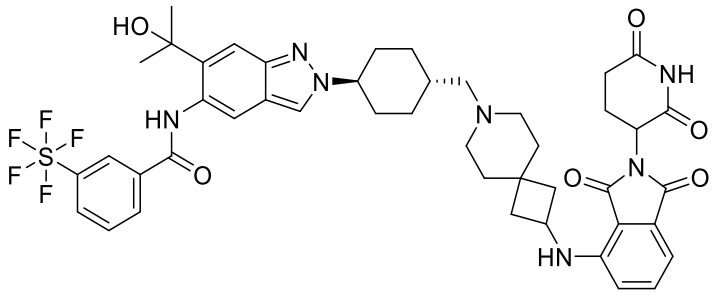
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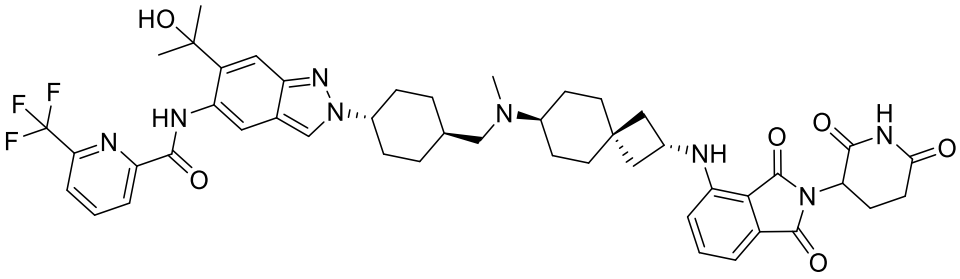
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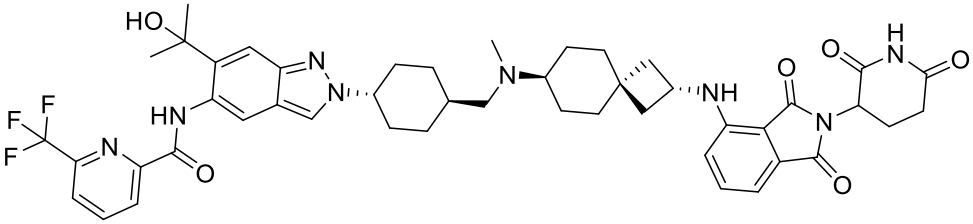
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I-124



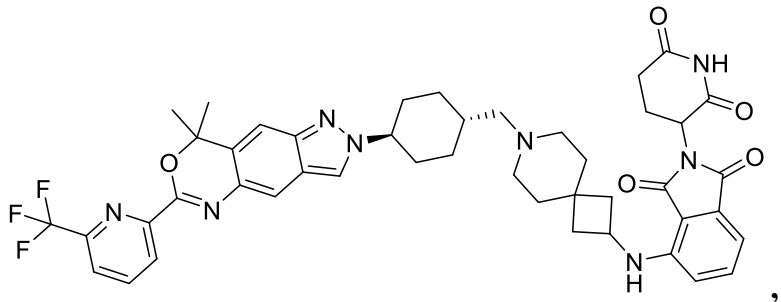
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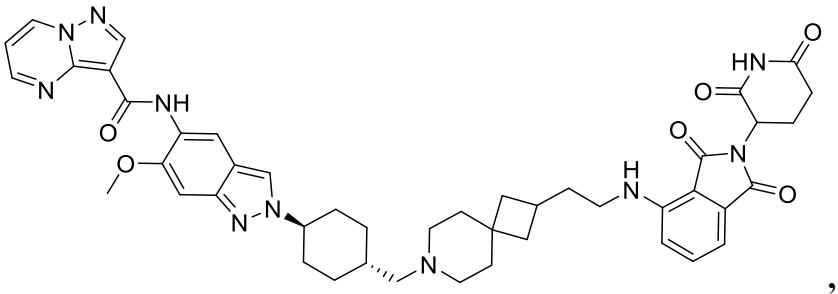
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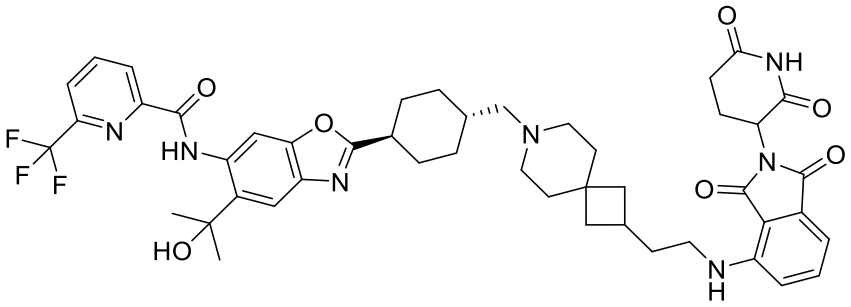
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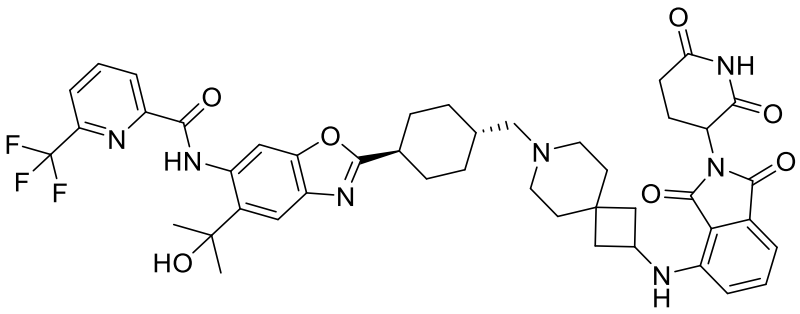
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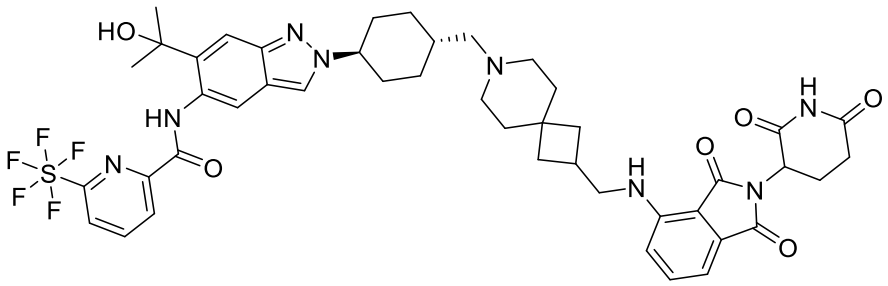
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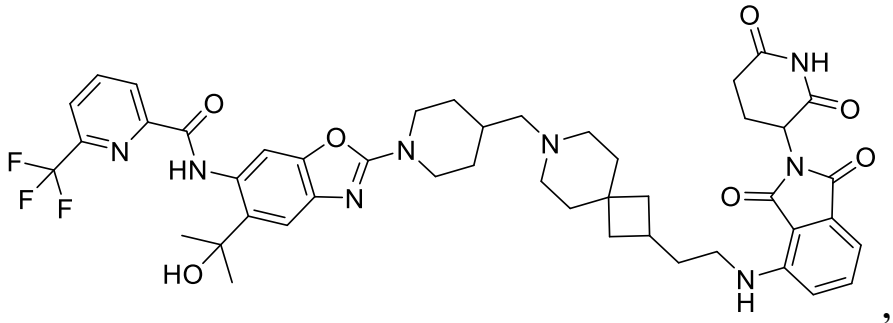
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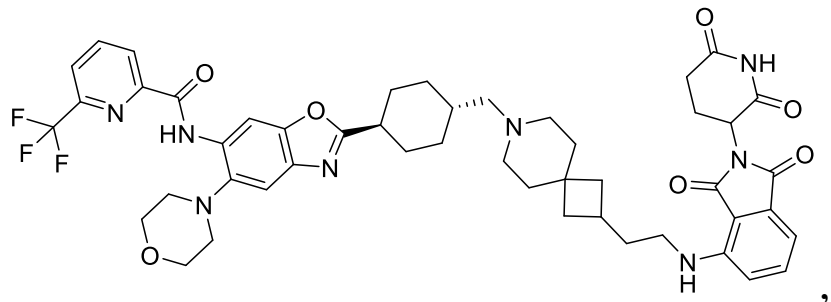
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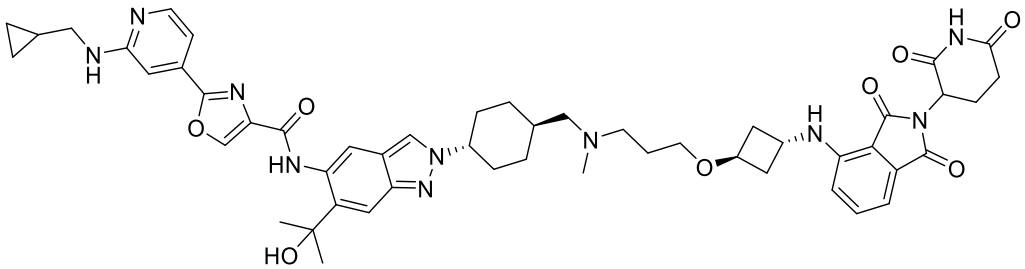
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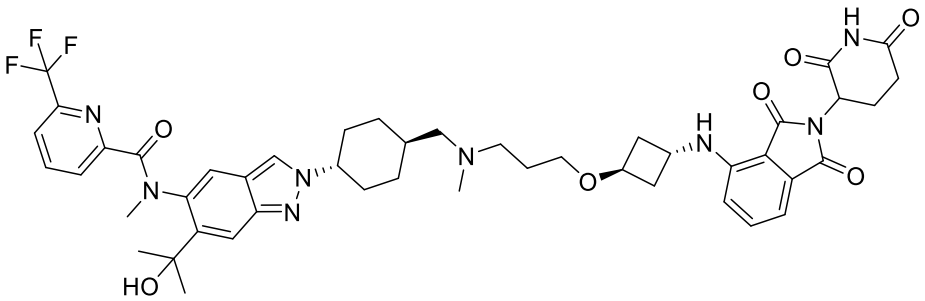
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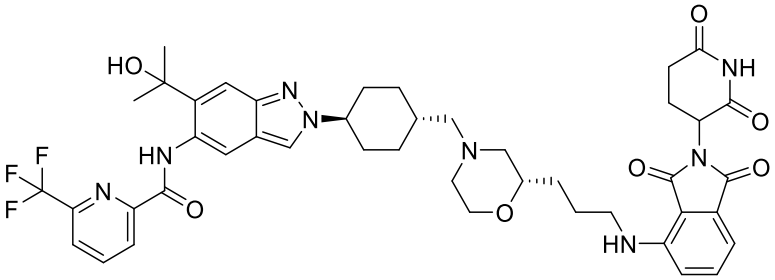
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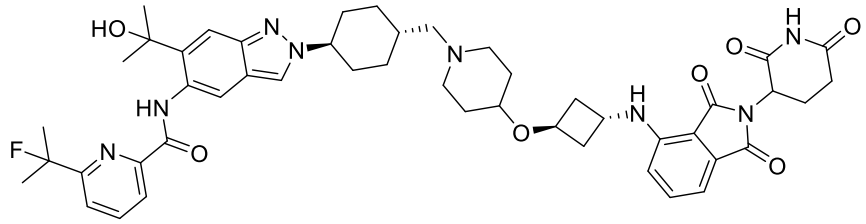
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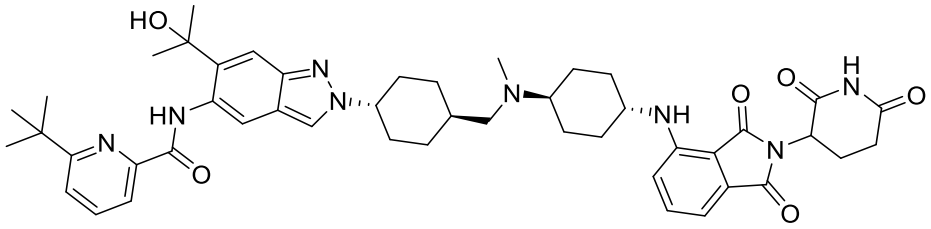
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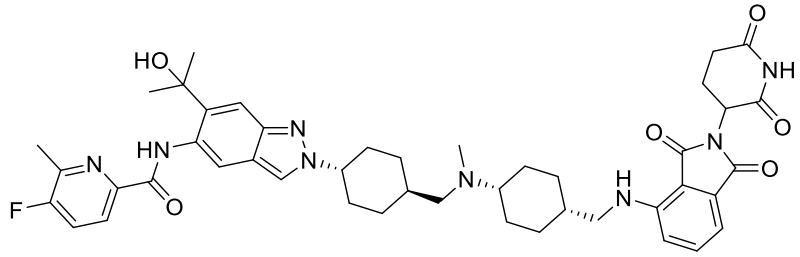
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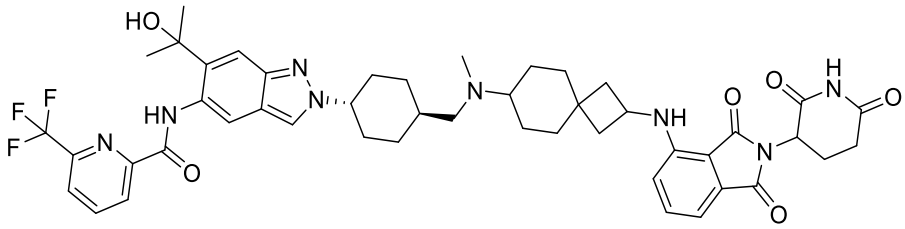
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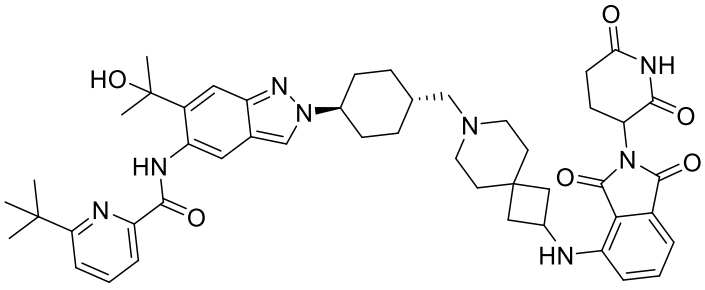
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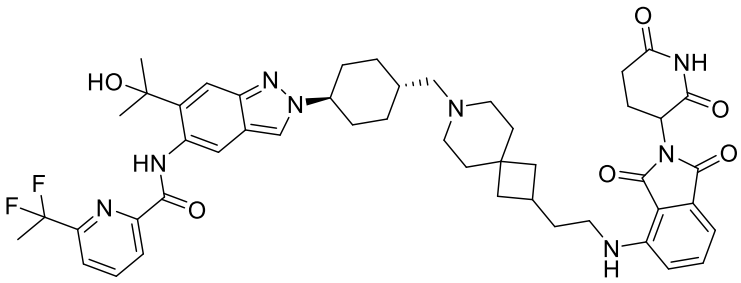
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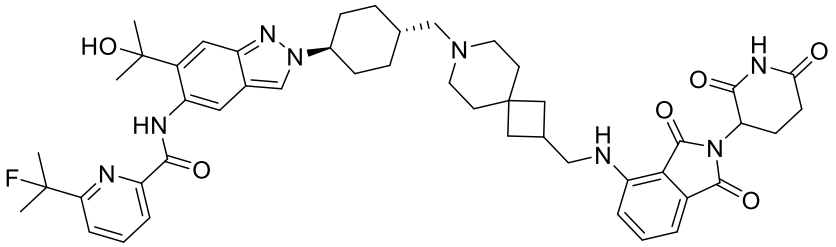
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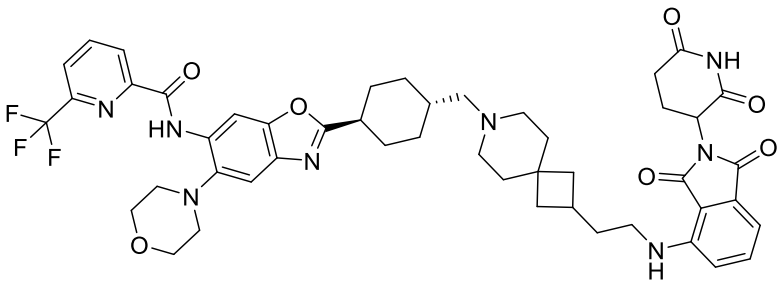
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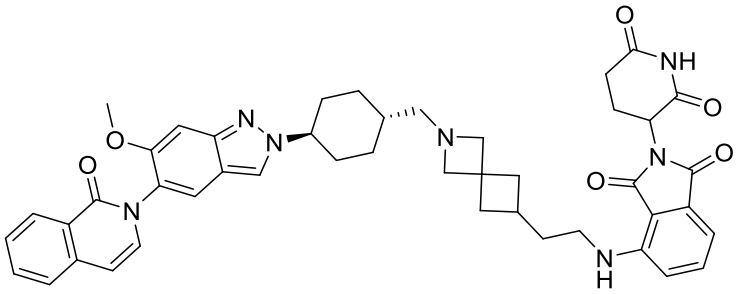
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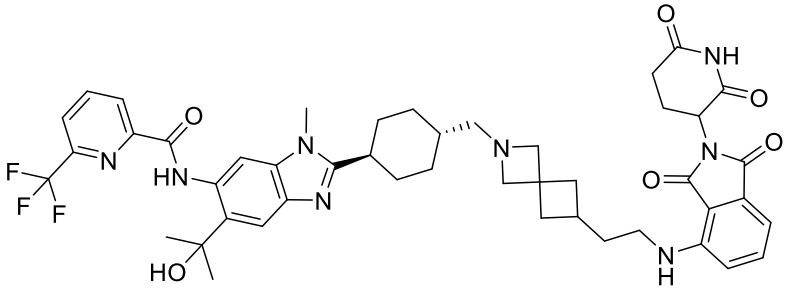
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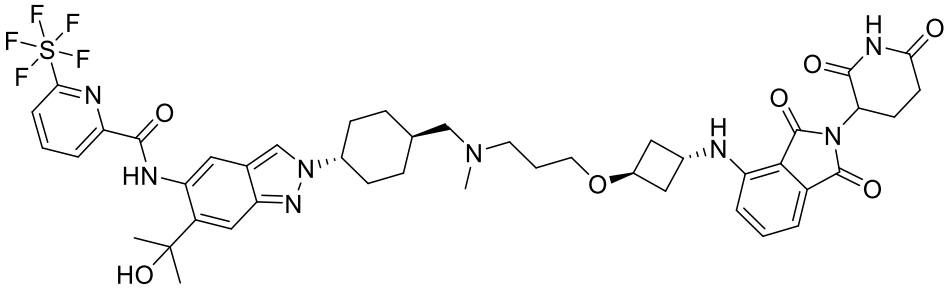
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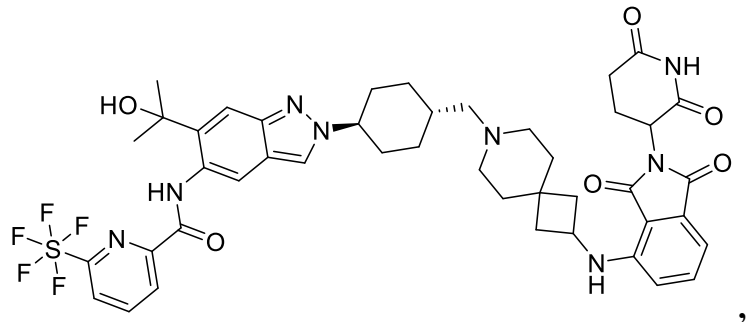
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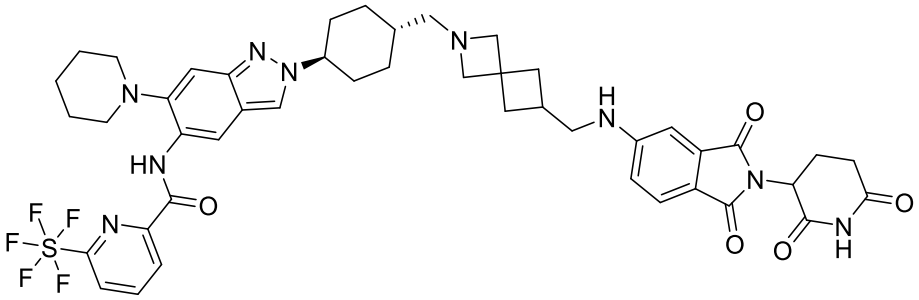
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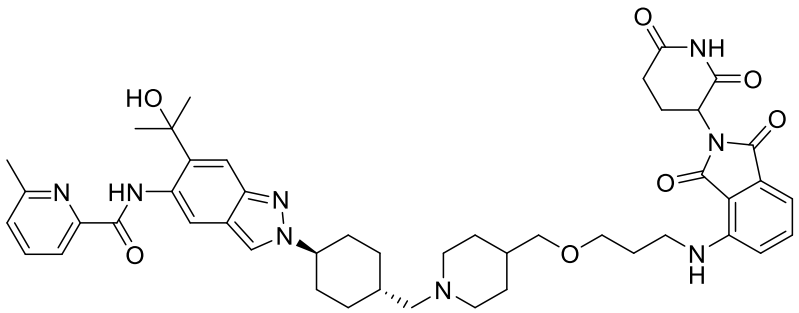
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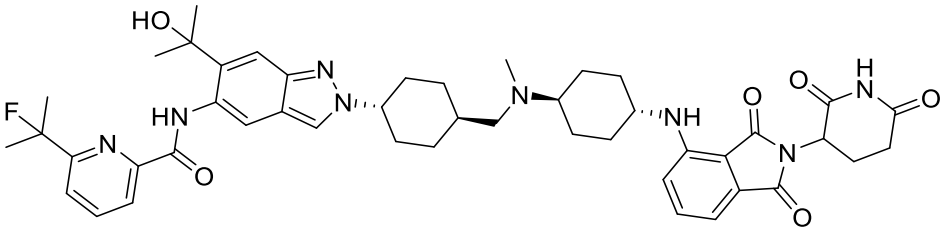
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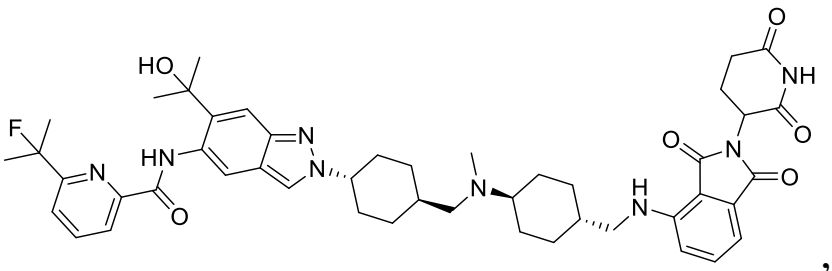
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I-306



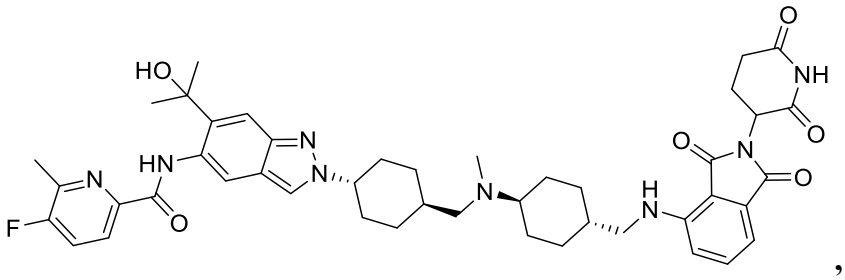
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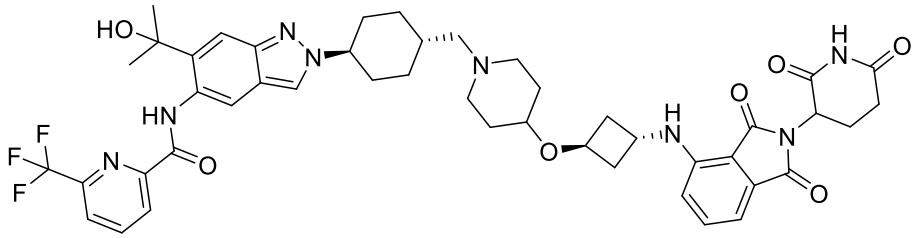
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I-308



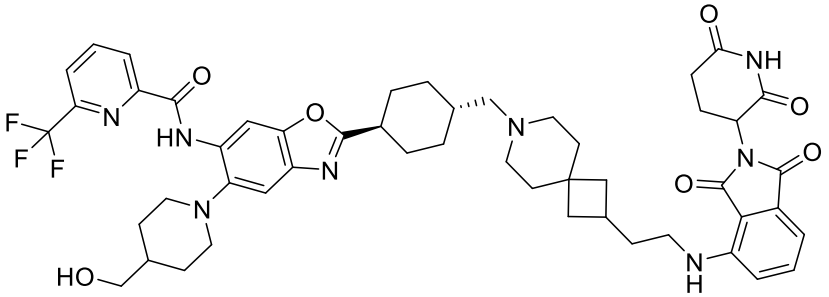
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I-312



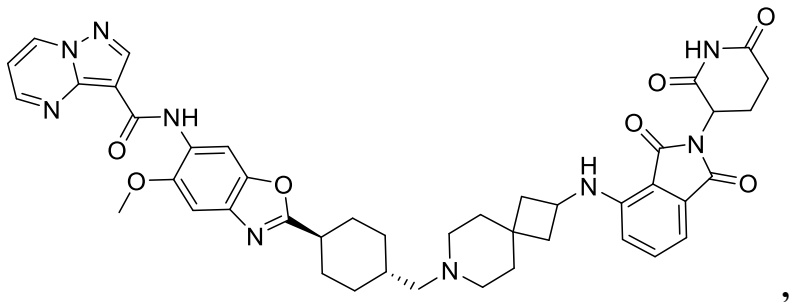
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I-314



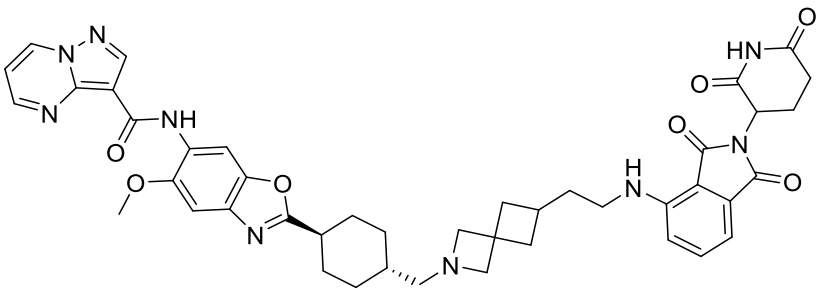
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I-321



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or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a compound of claim 17, and a

pharmaceutically acceptable carrier, adjuvant, or vehicle.

19. A compound of claim 17, or a pharmaceutical composition of claim 18, for use in therapy.

20. Use of a compound of claim 17, or a pharmaceutical composition of claim 18, in the manufacture of a medicament for treating an IRAK-mediated disorder, disease, or condition in a patient, wherein the IRAK-mediated disorder, disease or condition is selected from the group consisting of a cancer, a neurodegenerative disease, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, a condition associated with organ transplantation, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T cell activation, a cardiovascular disorder, and a CNS disorder.

21. The use of claim 20, wherein the cancer or proliferative disorder is selected from the group consisting of a benign or malignant tumor, solid tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastoma, neuroblastoma, multiple myeloma, gastrointestinal cancer, colon carcinoma, colorectal adenoma, a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphoma, Hodgkin’s or Non-Hodgkin’s lymphoma, a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, primary cutaneous T-cell lymphoma, smoldering or indolent multiple myeloma, and a hematological malignancy selected from_leukemia, diffuse large B-cell lymphoma (DLBCL), ABC DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström’s macroglobulinemia (WM), splenic marginal zone lymphoma, multiple myeloma, plasmacytoma, or intravascular large B-cell lymphoma.

22. The use of claim 20, wherein the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia, and a neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity, hypoxia, epilepsy, treatment of diabetes, metabolic syndrome, obesity, organ transplantation and graft versus host disease.

23. The use of claim 20, wherein the inflammatory disorder is selected from the group consisting of ocular allergy, conjunctivitis, keratoconjunctivitis sicca, vernal conjunctivitis; allergic rhinitis, hemolytic anemia, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia or another inflammatory disease in which autoimmune reactions are implicated or which have an autoimmune component or etiology, systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, ulcerative colitis, Crohn's disease or another autoimmune inflammatory bowel disease, irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, nephritis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, optionally including idiopathic nephrotic syndrome or minal change nephropathy), chronic granulomatous disease, endometriosis, leptospiriosis renal disease, glaucoma, retinal disease, aging, headache, pain, complex regional pain syndrome, cardiac hypertrophy, muscle wasting, catabolic disorders, obesity, fetal growth retardation, hyperchlolesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ecodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic, non-allergic, mild, moderate, severe, bronchitic, or exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, silica induced diseases, COPD (reduction of damage, airways inflammation, bronchial hyperreactivity, remodeling or disease

progression), pulmonary disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, myasthenia gravis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, Type 2 diabetes, appendicitis, atopic dermatitis, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, vaginitis, vasculitis, vulvitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, Cryopyrin Associated Periodic Syndrome (CAPS), and osteoarthritis.