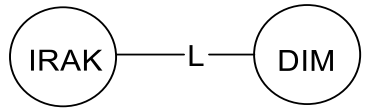
therapeutic agents that leverage E3 ligase mediated protein degradation to target cancer-associated proteins such as interleukin-1 receptor-associated kinases ("IRAK") hold promise as therapeutic agents. Accordingly, there remains a need to find compounds that are IRAK degraders useful as therapeutic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

SUMMARY ~~OF THE INVENTION~~

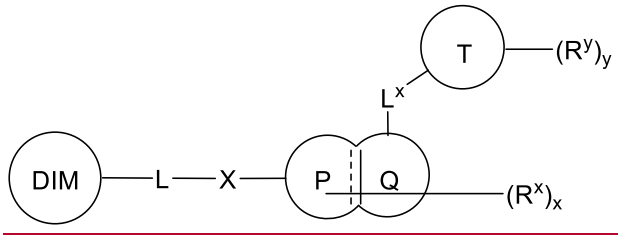
[0008a] In an aspect of the present disclosure, there is provided a compound of formula **I**:



I

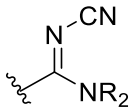
or a pharmaceutically acceptable salt thereof, wherein:

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



I''-a

or a pharmaceutically acceptable salt thereof, wherein:

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

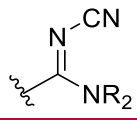
; or

two R^x groups are optionally taken together to form an optionally substituted 5-6 membered partially unsaturated or aryl fused ring having 0-3 heteroatoms independently

selected from nitrogen, oxygen, or sulfur, or a 3-5 membered saturated or partially unsaturated carbocyclic or heterocyclic spiro fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur,

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

two R groups on the same atom are optionally taken together with their intervening atoms to form a 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spiro, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^y is independently hydrogen, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CFR_2$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, $-C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-SiR_3$, $-SF_5$, or 

; or

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

each R^z is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-9 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, or spirocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring P and Ring Q are fused rings independently selected from benzo, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms

independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring P and Ring Q are independently and optionally substituted with 1-2 oxo groups;

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

L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with $-Cy^x-$, -O-, -S-, -C(O)-, -C(S)-, $-CR_2-$, -CRF-, $-CF_2-$, -NR-, -N=CR-, -CR=CR-, or $-S(O)_2-$, wherein R of $-CR_2-$, -CRF-, -NR-, -N=CR-, or -CR=CR- can combine with R^x or R^y to form a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

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

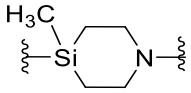
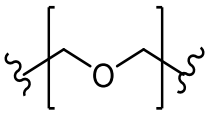
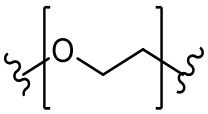
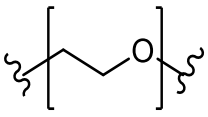
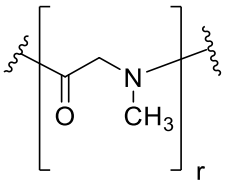
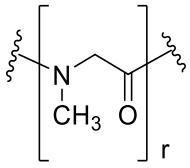
X is a covalent bond or a 4-6 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

---- is a single or double bond;

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

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

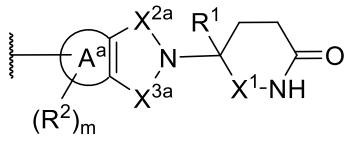
L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by –Cy-, -O-, -N(R)-, $–Si(R)_2–$, –Si(OH)(R)–, $–Si(OH)_2–$, –P(O)(OR)–, –P(O)(R)–, $–P(O)(NR_2)–$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -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, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and

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.

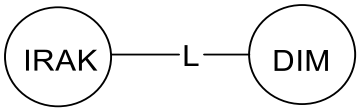
[0008c] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutical composition disclosed herein, for use in therapy.

[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 degrading and/or inhibiting an IRAK protein kinase in a patient or biological sample, wherein the compound or pharamaceutical composition is to be administered to said patient, or said biological sample is contacted with said compound or pharmaceutical composition.

[0008e] In a further 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.

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

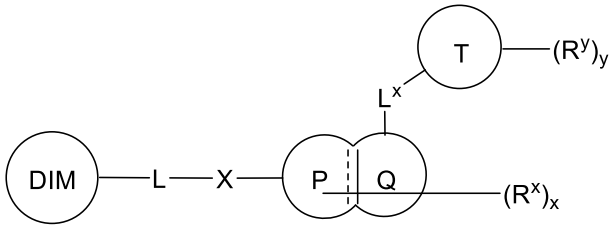
[0010] The present application further relates to targeted degradation of IRAK kinases through the use of bifunctional molecules, including bifunctional molecules that link a degradation inducing moiety to a ligand that binds IRAK kinases having the following general formula **I**:



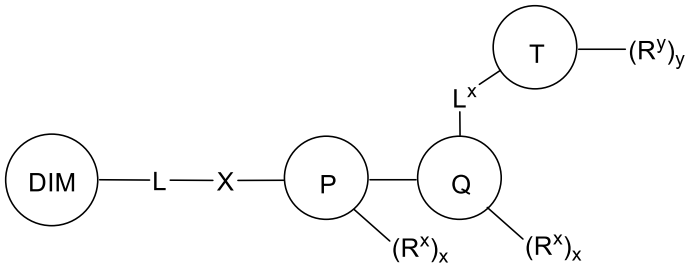
I

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

[0011] It has now been found that compounds of this ~~invention~~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**:



I-a



I-b

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

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

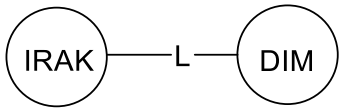
[0013] Compounds provided by this ~~invention~~ present disclosure are also useful for the study of IRAK enzymes in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new IRAK inhibitors or IRAK degraders or other regulators of kinases, signaling pathways, and cytokine levels in vitro or in vivo.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Certain Embodiments of the Invention:

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

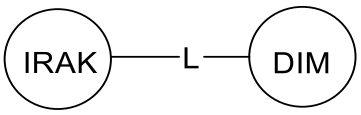
[0015] In certain embodiments, the present invention provides a compound of formula **I**:



CLAIMS

We claim:

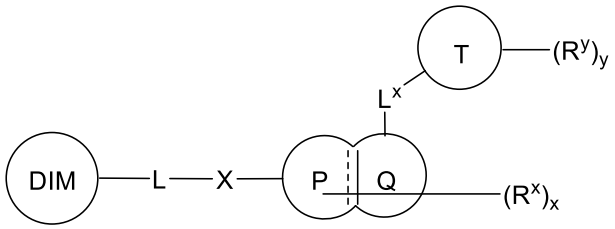
1. A compound of formula **I**:



I

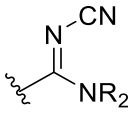
or a pharmaceutically acceptable salt thereof, wherein:

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



I″-a

or a pharmaceutically acceptable salt thereof, wherein:

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

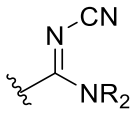
; or

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

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

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

two R groups on the same atom are optionally taken together with their intervening atoms to form a 4-11 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, spiro, or heteroaryl ring having 0-3 heteroatoms, in addition to the atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^y is independently hydrogen~~, deuterium~~, R^z, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -CFR_2, -CF_2R, -CF_3, -$CR_2(OR)$, -$CR_2(NR_2)$, -C(O)R, -C(O)OR, -$C(O)NR_2$, -$C(S)NR_2$, -C(O)N(R)OR, -OC(O)R, -$OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, -$N(R)C(O)NR_2$, -$N(R)S(O)_2R$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -SiR_3, -SF_5, or  ; or

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

each R^z is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-9 membered saturated or partially unsaturated carbocyclic or heterocyclic monocyclic, bicyclic, bridged bicyclic, or spirocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring P and Ring Q are ~~optionally~~ fused rings independently selected from ~~phenyl or~~ benzo, a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ring P and Ring Q are independently and optionally substituted with 1-2 oxo groups;

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

L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -Cy^x-, -O-, -S-, -C(O)-, -C(S)-, -CR_2-, -CRF-, -CF_2-, -NR-, -N=CR-, -CR=CR-, or -$S(O)_2$-, wherein R of -CR_2-, -CRF-, -NR-, -N=CR-, or -CR=CR- can combine with R^x or R^y to form a 4-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

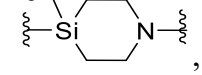
-Cy^x- is an optionally substituted ring selected from a 3-5 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5 membered heteroaryl ring having 1-4 heteroatoms independently selected from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

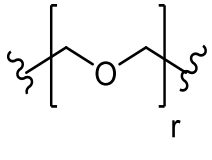
X is a covalent bond or a 4-6 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

---- is a single or double bond;

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

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

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

, 

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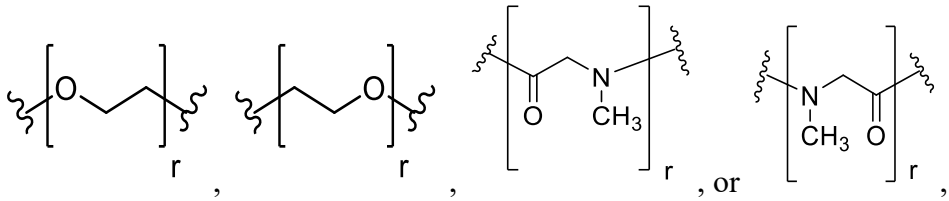
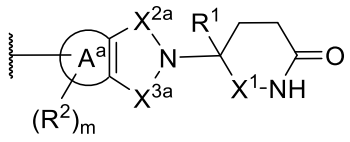


, or , wherein

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

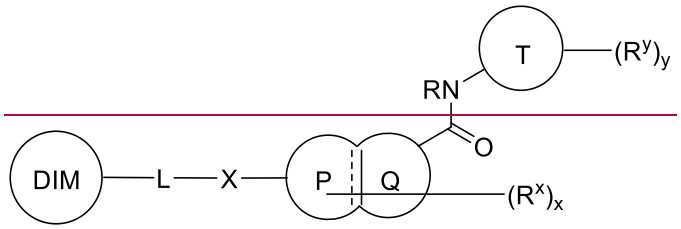
R^1 is hydrogen or C_{1-4} aliphatic;

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

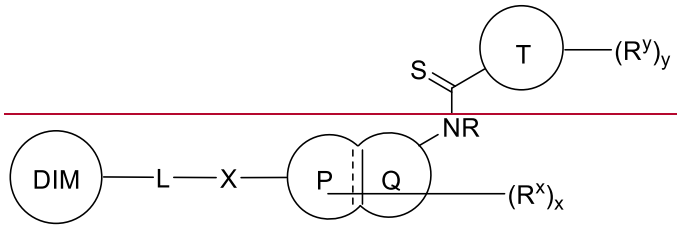
Ring A^a is a fused ring selected from a 6-membered aryl containing 0-1 nitrogen atoms; and

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

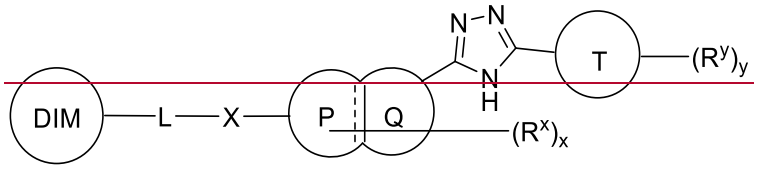
~~2. The compound of claim 1, wherein said compound is any one of formulae I-c-1, I-c-2, I-c-3, I-c-4, I-c-5, I-c-6, I-c-7, I-d-1, I-d-2, I-d-3, I-d-4, I-e-1, I-f-1, I-f-2, I-f-3, I-g-1, I-h-1, or I-h-2:~~



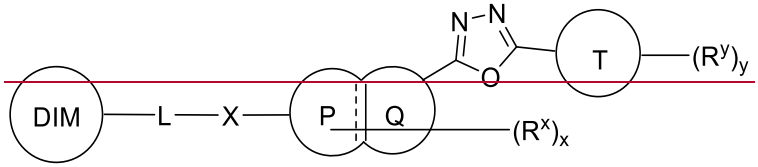
~~I-c-1~~



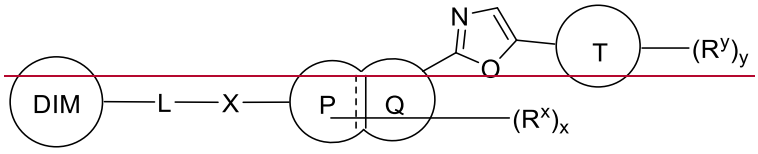
~~I-c-2~~



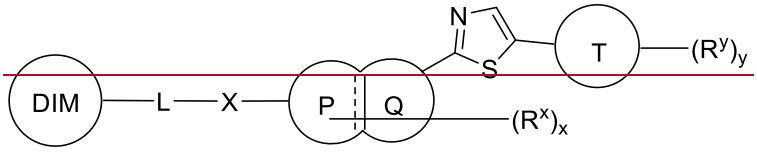
~~I-c-3~~



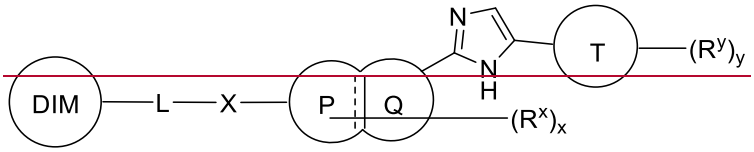
~~I-c-4~~



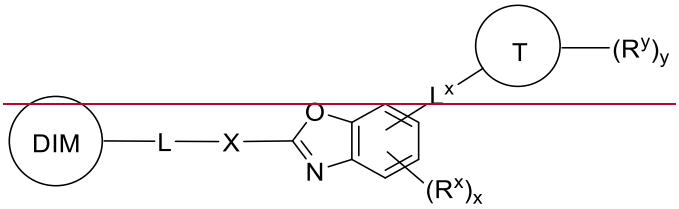
~~I-c-5~~



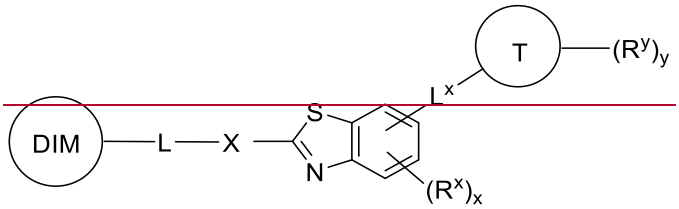
~~I-c-6~~



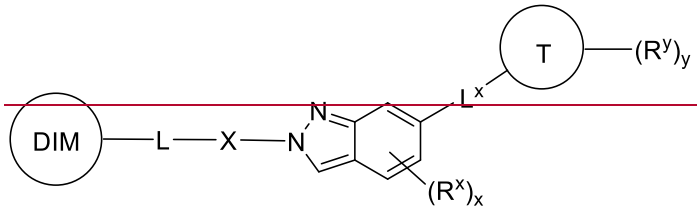
~~I-c-7~~



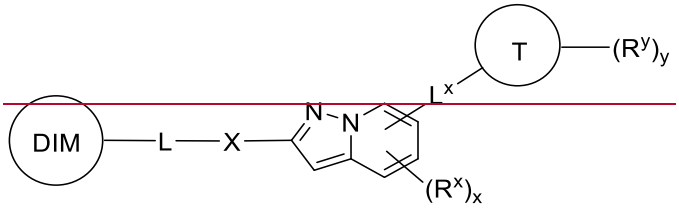
~~I-d-1~~



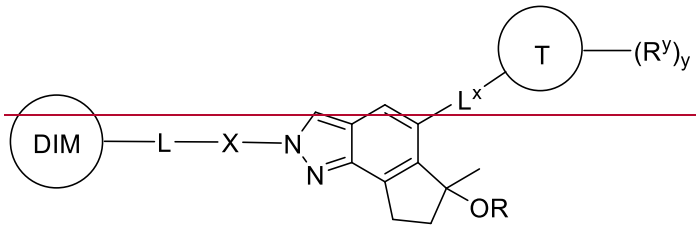
~~I-d-2~~



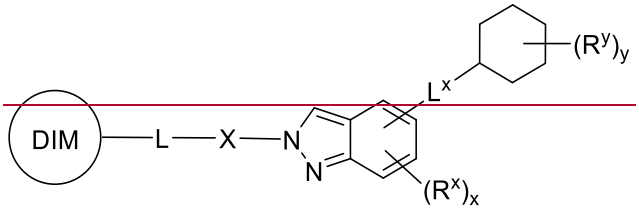
~~I-d-3~~



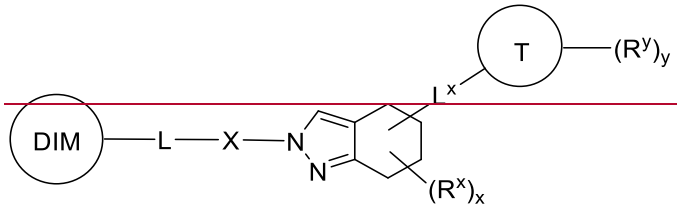
~~I-d-4~~



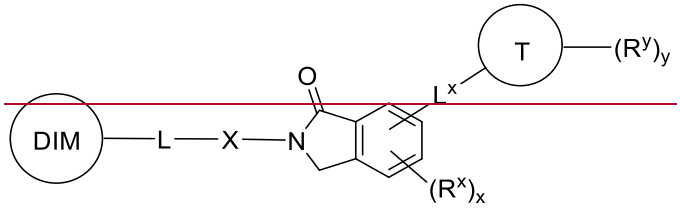
~~I-e-1~~



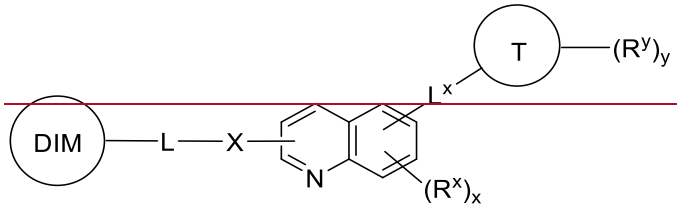
~~I-f-1~~



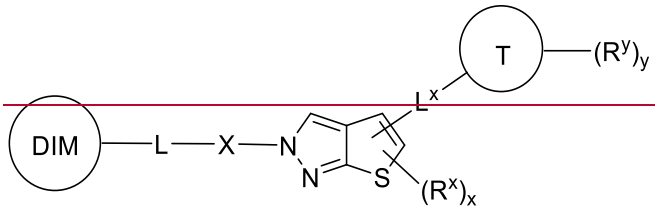
~~I-f-2~~



~~I-f-3~~



~~I-g-1~~

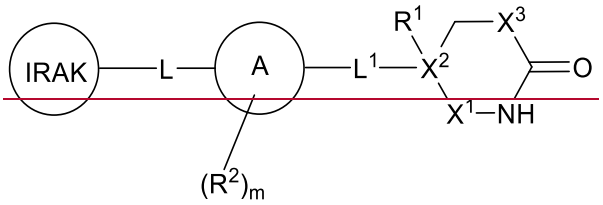


~~I-g-2~~

~~or a pharmaceutically acceptable salt thereof.~~

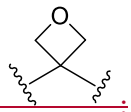
~~3. The compound of claim 1 or claim 2, wherein the DIM is a ligase binding moiety (LBM), lysine mimetic, or hydrogen atom.~~

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



~~**I-aa**~~

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

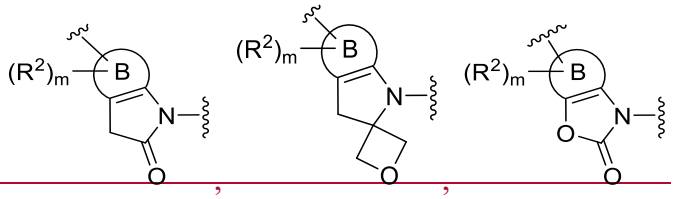
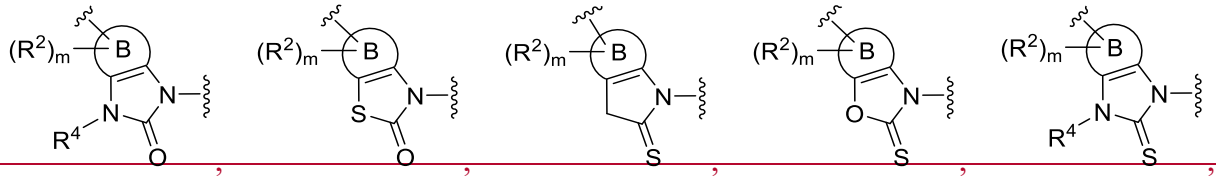
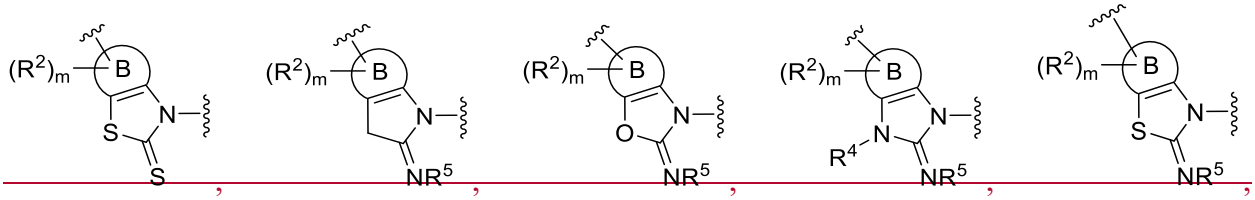
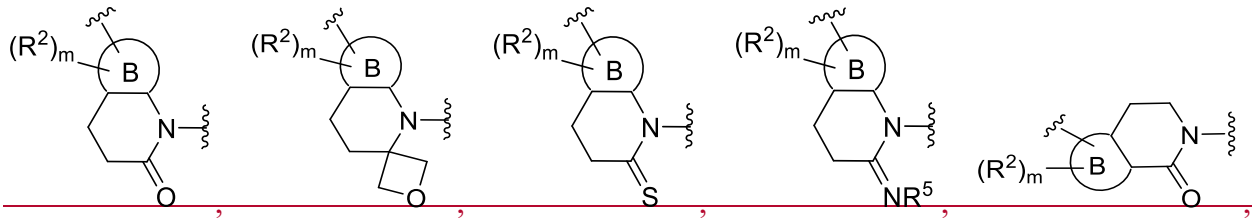
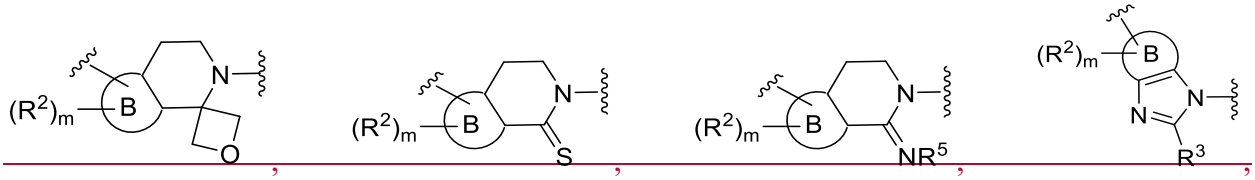
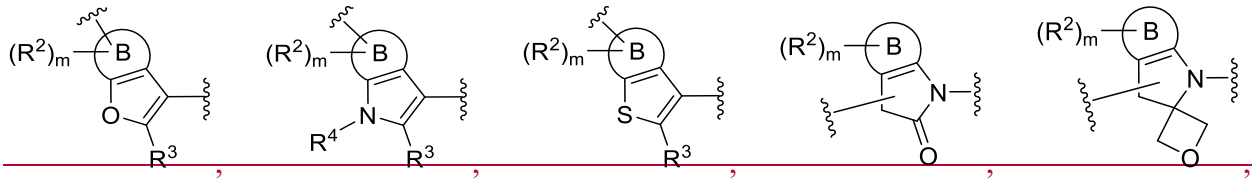
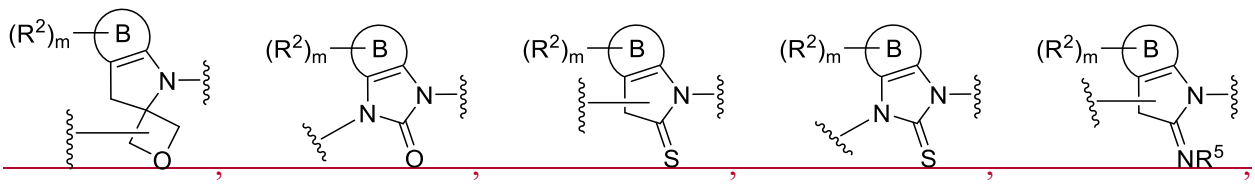
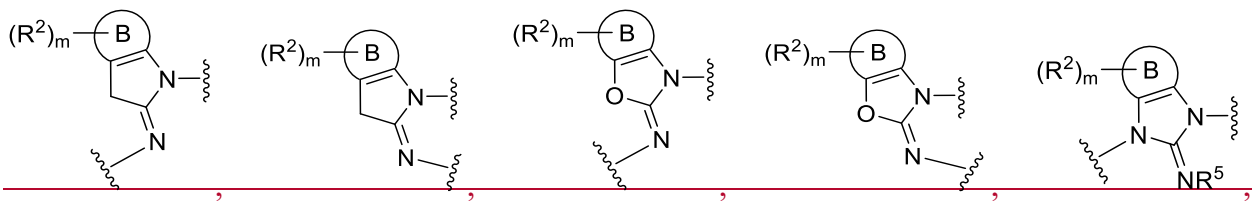
~~X^1 is a bivalent moiety selected from a covalent bond, CH_2, $CHCF_3$, SO_2, S(O), P(O)R, P(O)OR, $P(O)NR_2$, C(O), C(S), or~~  ~~;~~

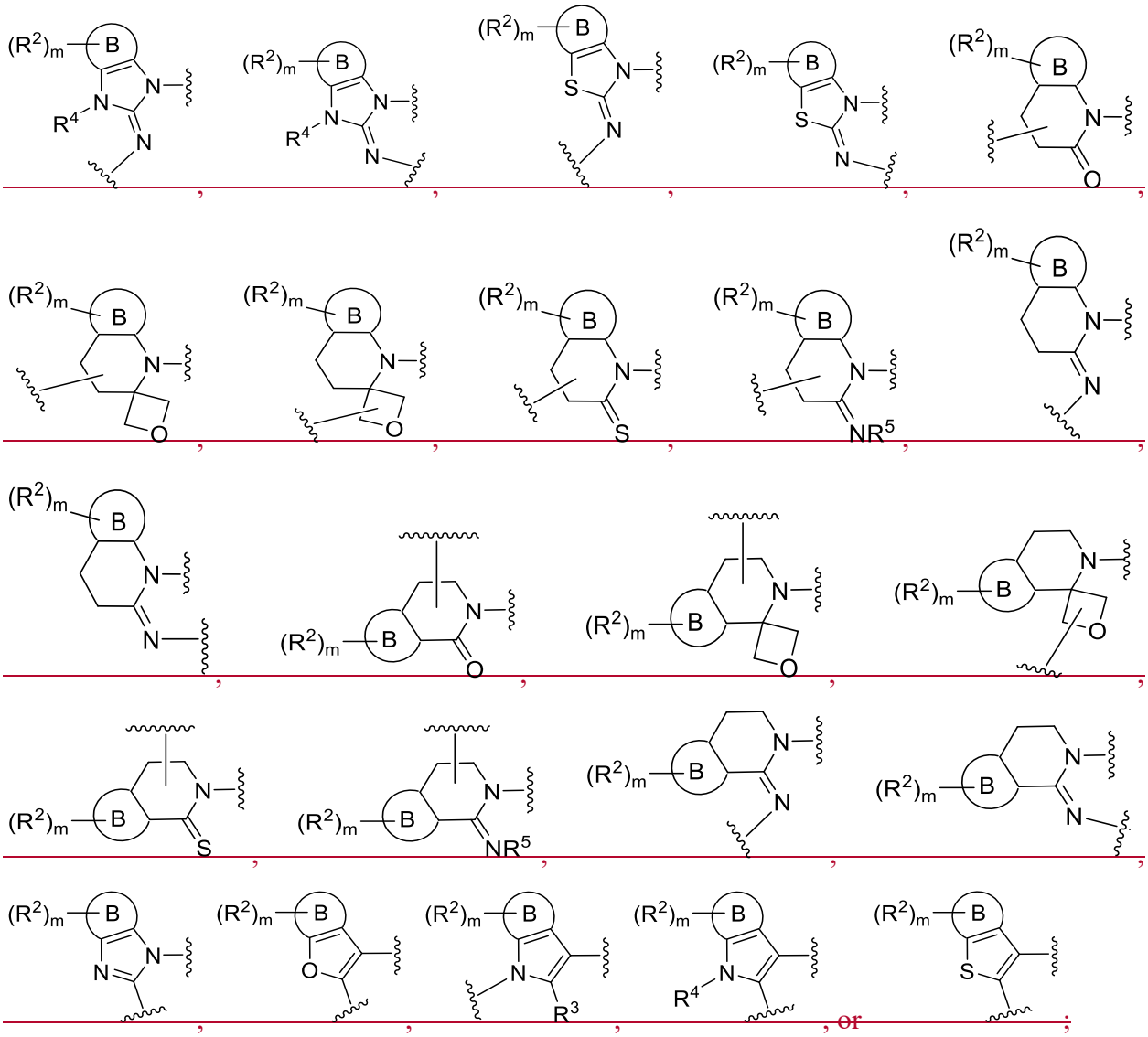
~~X^2 is a carbon atom or silicon atom;~~

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

~~R^1 is hydrogen, deuterium, halogen, CN, OR, SR, S(O)R, $S(O)_2R$, $N(R)_2$, $P(O)(OR)_2$, $P(O)(NR_2)OR$, $P(O)(NR_2)_2$, $Si(OH)_2R$, $Si(OH)(R)_2$, $Si(R)_3$, or an optionally substituted C_{1-4} aliphatic;~~

~~each R^2 is independently hydrogen, deuterium, R^6, halogen, CN, NO_2, OR, SR, $N(R)_2$, $Si(R)_3$, $S(O)_2R$, $S(O)_2N(R)_2$, S(O)R, C(O)R, C(O)OR, $C(O)N(R)_2$, C(O)N(R)OR, $C(R)_2N(R)C(O)R$, $C(R)_2N(R)C(O)N(R)_2$, OC(O)R, $OC(O)N(R)_2$, $OP(O)R_2$, $OP(O)(OR)_2$, $OP(O)(OR)(NR_2)$, $OP(O)(NR_2)_2$, N(R)C(O)OR, N(R)C(O)R, $N(R)C(O)N(R)_2$, $N(R)S(O)_2R$, $NP(O)R_2$, N(R)P(O)(OR)2, N(R)P(O)(OR)(NR2), $N(R)P(O)(NR_2)_2$, or $N(R)S(O)_2R$;~~

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



Ring B is a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

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

each R^4 is independently hydrogen, R^6, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR,

~~$C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;~~

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

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

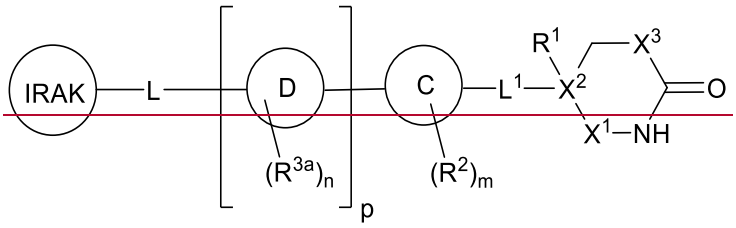
~~L^1 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with $-O-$, $-C(O)-$, $-C(S)-$, $-C(R)_2-$, $-CH(R)-$, $-C(F)_2-$, $-N(R)-$, $-S-$, $-S(O)_2-$ or $-(C)=CH-$;~~

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

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

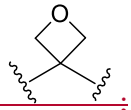
~~two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.~~

~~5. The compound of claim 3, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety and said compound is of formula **I-dd**:~~



~~**I-dd**~~

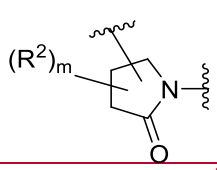
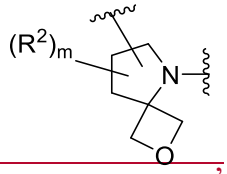
~~or a pharmaceutically acceptable salt thereof, wherein:~~

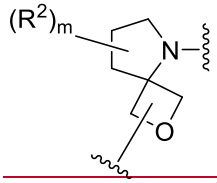
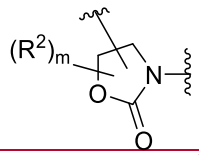
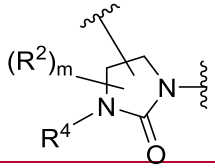
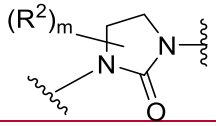
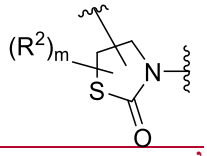
~~X^1 is a bivalent moiety selected from a covalent bond, CH_2, $CHCF_3$, SO_2, S(O), P(O)R, P(O)OR, $P(O)NR_2$, C(O), C(S), or~~  ~~;~~

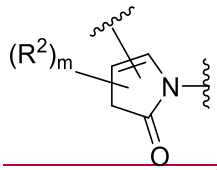
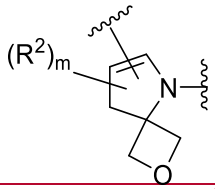
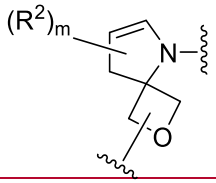
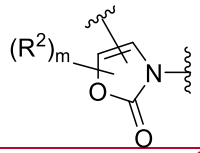
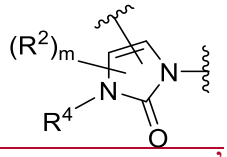
~~X^2 is a carbon atom or silicon atom;~~

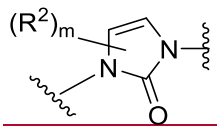
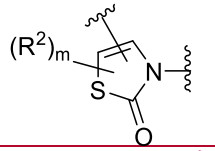
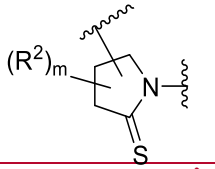
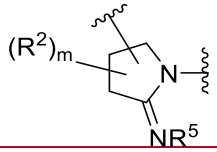
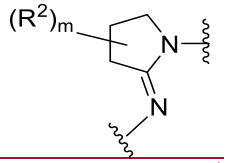
~~X^3 is a bivalent moiety selected from CR_2, NR, O, S, or $Si(R_2)$;~~

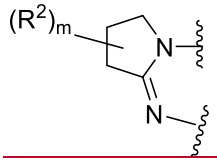
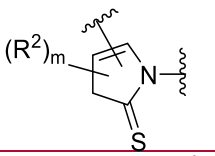
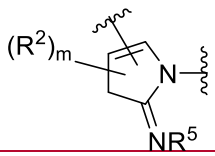
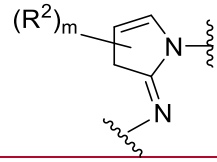
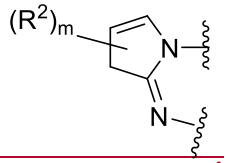
~~R^1 is hydrogen, deuterium, halogen, CN, OR, SR, S(O)R, $S(O)_2R$, NR_2, $P(O)(OR)_2$, $P(O)(NR_2)OR$, $P(O)(NR_2)_2$, $Si(OH)_2R$, $Si(OH)(R)_2$, $Si(R)_3$, or an optionally substituted C_{1-4} aliphatic;~~

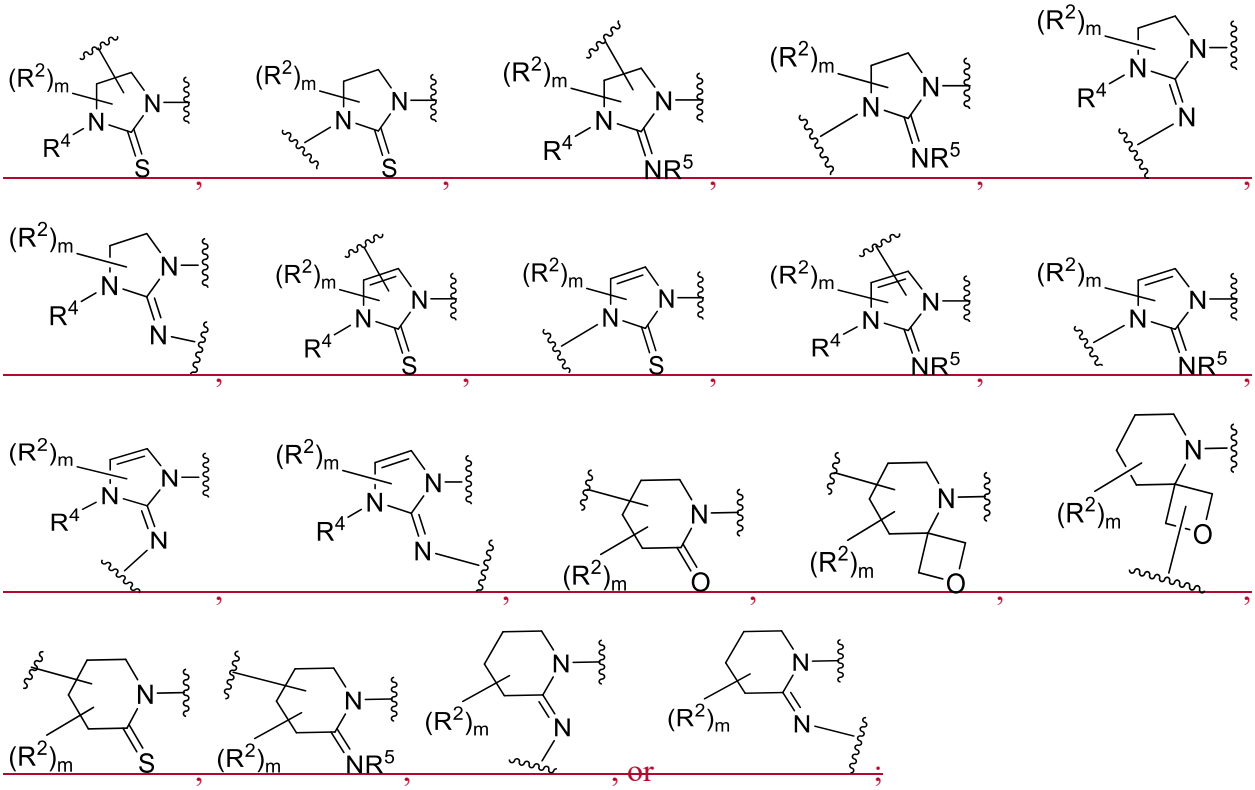
~~Ring C is a mono- or bicyclic ring selected from~~   ~~,~~

 ~~,~~  ~~,~~  ~~,~~  ~~,~~  ~~,~~

 ~~,~~  ~~,~~  ~~,~~  ~~,~~  ~~,~~

 ~~,~~  ~~,~~  ~~,~~  ~~,~~  ~~,~~

 ~~,~~  ~~,~~  ~~,~~  ~~,~~  ~~,~~



each of R^2 and R^{3a} is independently hydrogen, deuterium, R^6, halogen, CN, NO_2, OR, SR, $N(R)_2$, $Si(R)_3$, $S(O)_2R$, $S(O)_2N(R)_2$, S(O)R, C(O)R, C(O)OR, $C(O)N(R)_2$, C(O)N(R)OR, $C(R)_2N(R)C(O)R$, $C(R)_2N(R)C(O)N(R)_2$, OC(O)R, $OC(O)N(R)_2$, $OP(O)R_2$, $OP(O)(OR)_2$, $OP(O)(OR)(NR_2)$, $OP(O)(NR_2)_2$, N(R)C(O)OR, N(R)C(O)R, $N(R)C(O)N(R)_2$, $N(R)S(O)_2R$, $NP(O)R_2$, $N(R)P(O)(OR)_2$, $N(R)P(O)(OR)(NR_2)$, $N(R)P(O)(NR_2)_2$, or $N(R)S(O)_2R$;

Ring D is selected from a 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

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

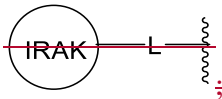
~~R^5 is hydrogen, C_{1-4} aliphatic, or –CN;~~

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

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

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

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

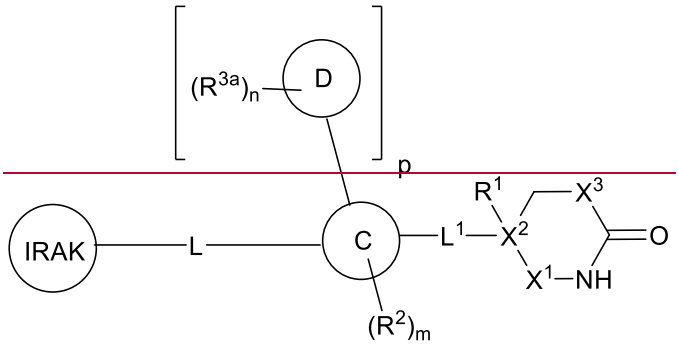
~~p is 0 or 1, wherein when p is 0, the bond connecting Ring C and Ring D is connected to~~ 

~~; and~~

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

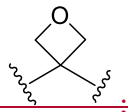
~~two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.~~

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



~~I-ff~~

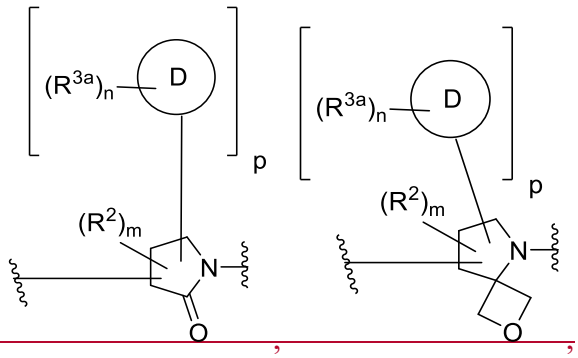
~~or a pharmaceutically acceptable salt thereof, wherein:~~

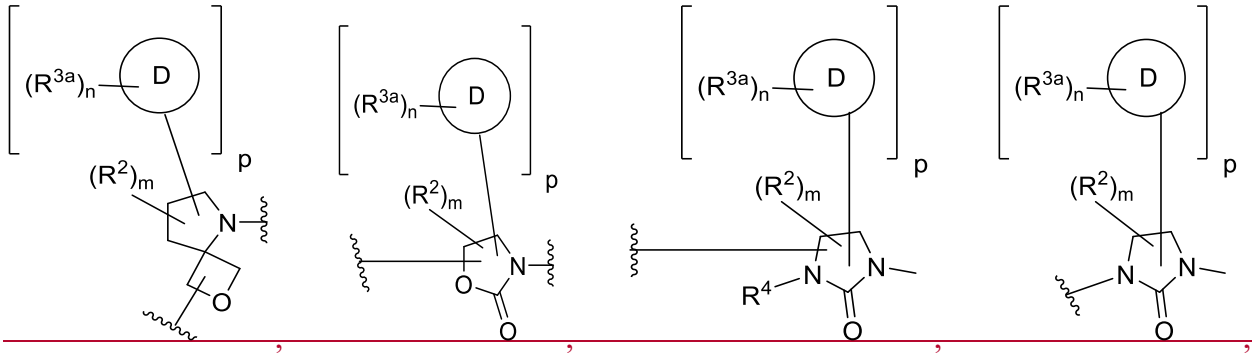
~~X^1 is a bivalent moiety selected from a covalent bond, CH_2, $CHCF_3$, SO_2, S(O), P(O)R, P(O)OR, P(O)NR_2, C(O), C(S), or~~  ~~;~~

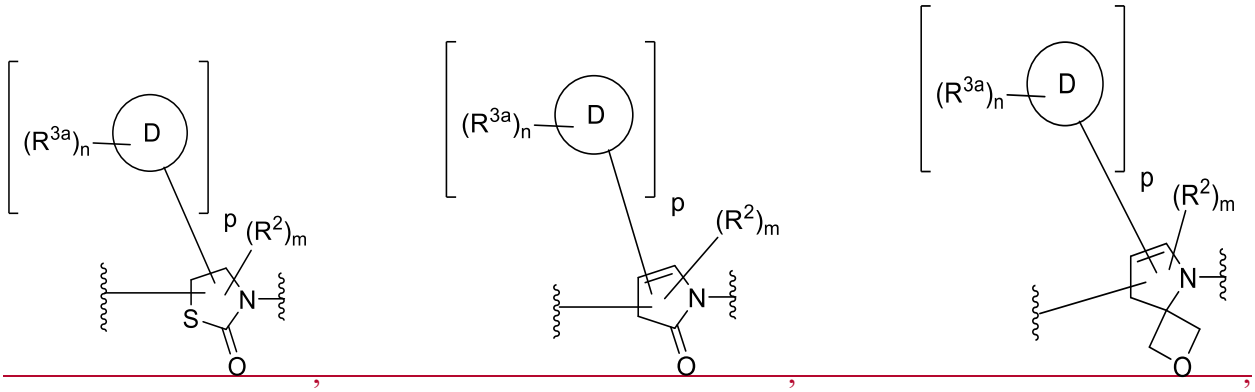
~~X^2 is a carbon atom or silicon atom;~~

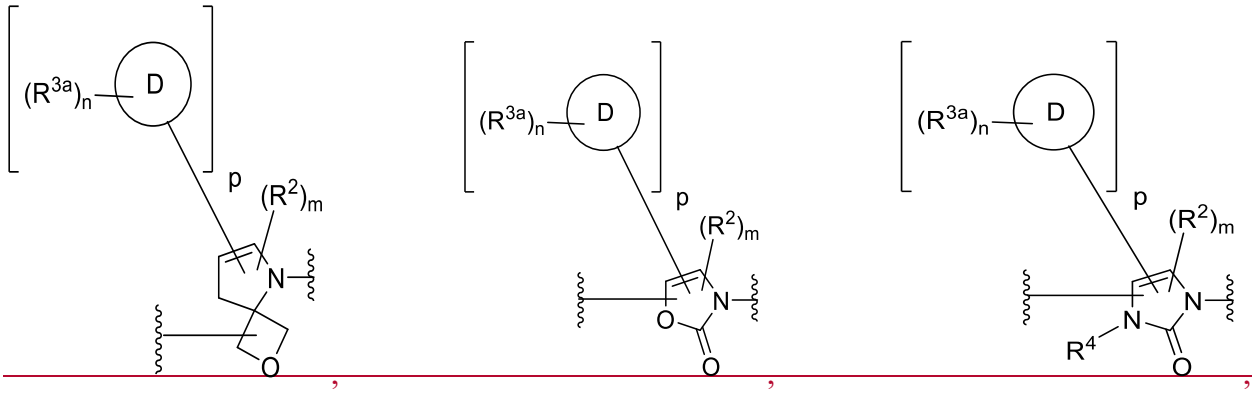
~~X^3 is a bivalent moiety selected from CR_2, NR, O, S, or $Si(R_2)$;~~

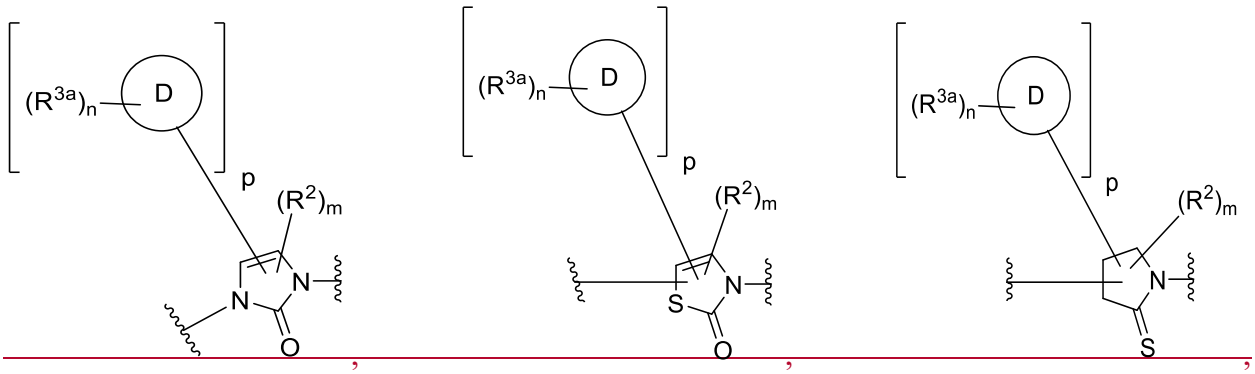
~~R^1 is hydrogen, deuterium, halogen, CN, OR, SR, S(O)R, $S(O)_2R$, NR_2, $P(O)(OR)_2$, $P(O)(NR_2)OR$, $P(O)(NR_2)_2$, $Si(OH)_2R$, $Si(OH)(R)_2$, $Si(R)_3$, or an optionally substituted C_{1-4} aliphatic;~~

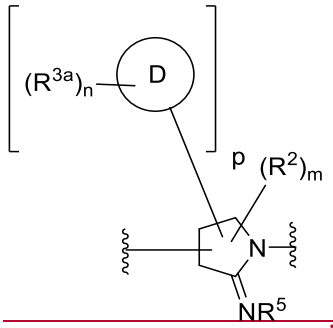
~~Ring C is a mono- or bicyclic ring selected from~~  ~~,~~







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D
p
(R2)m
N
NR5

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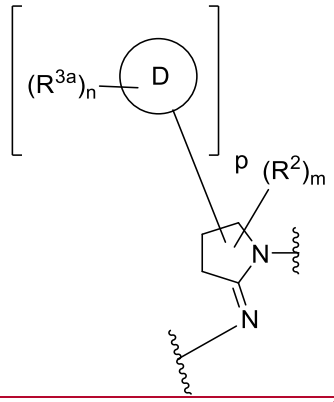
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D
p
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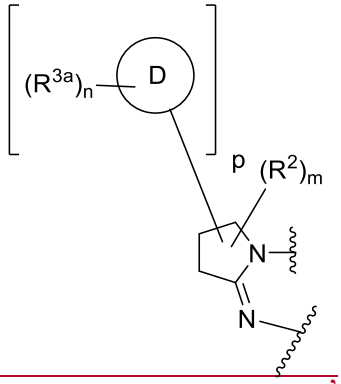
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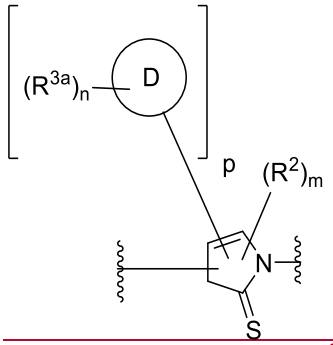
D
p
(R2)m
N
N

,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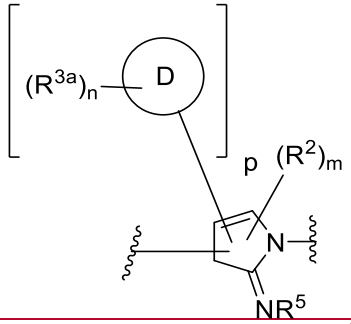
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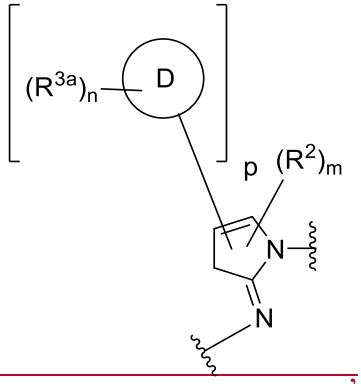
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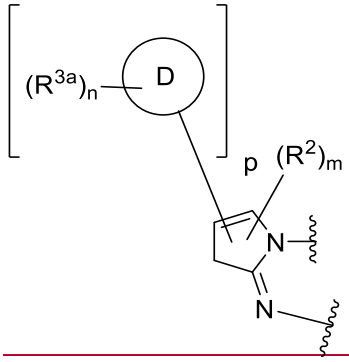
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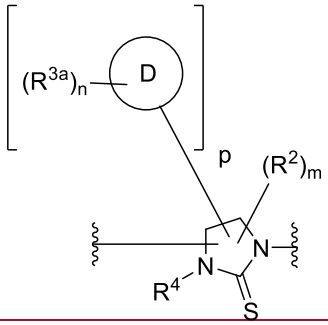
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D
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(R2)m
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S

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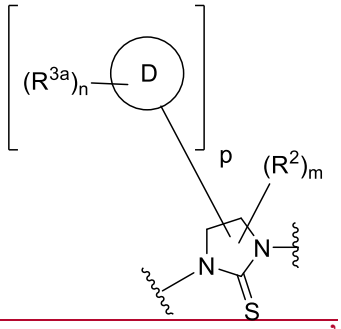
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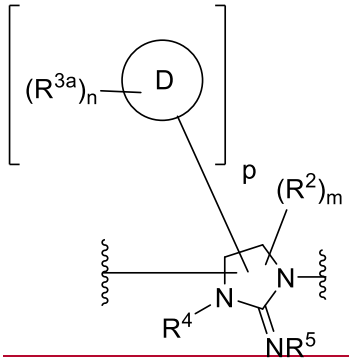
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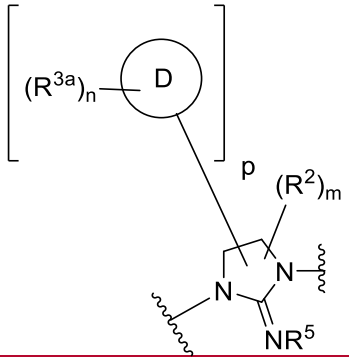
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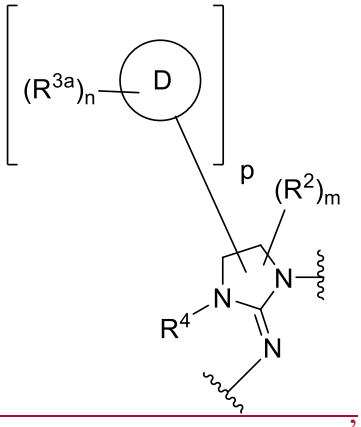
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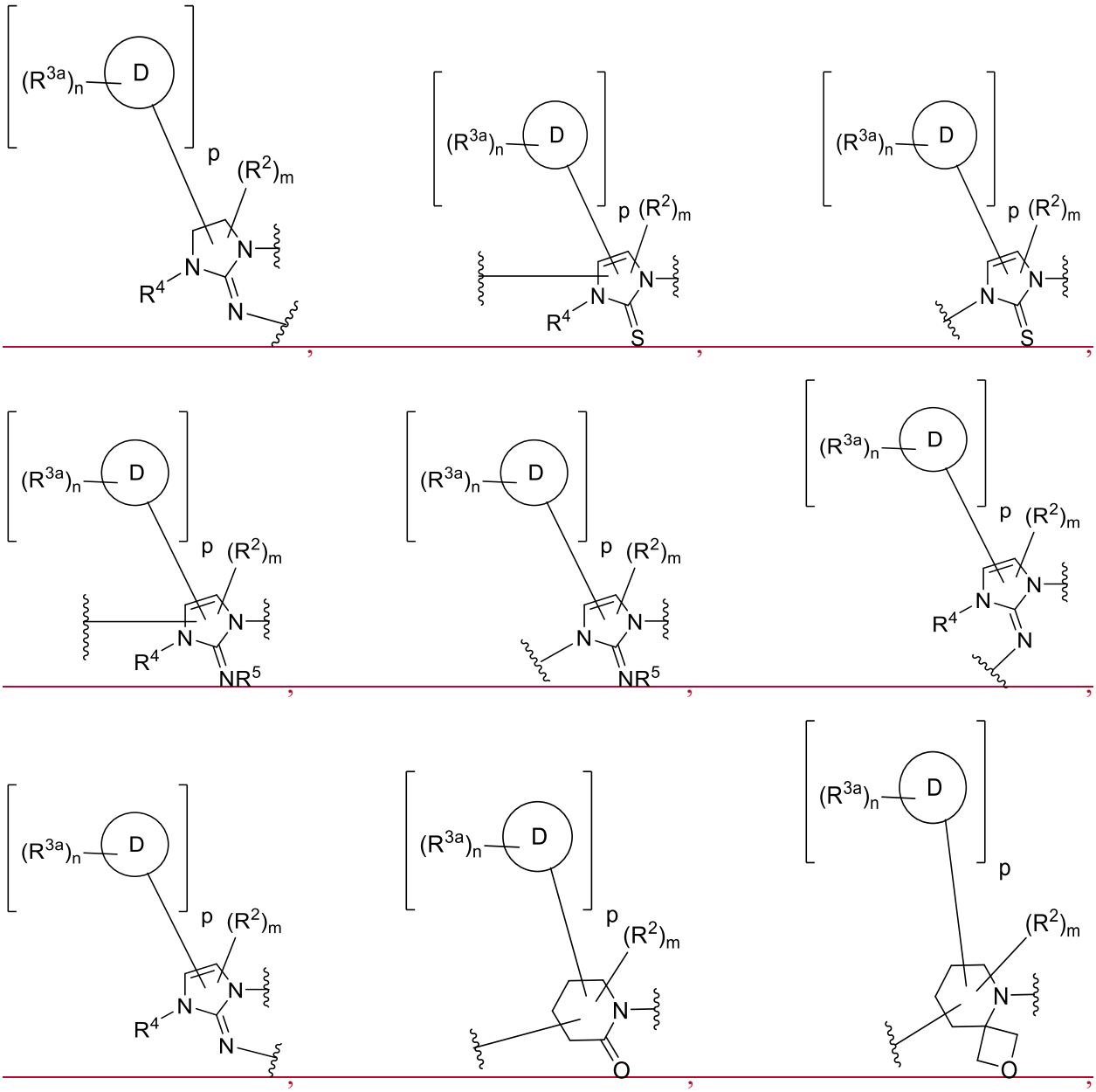

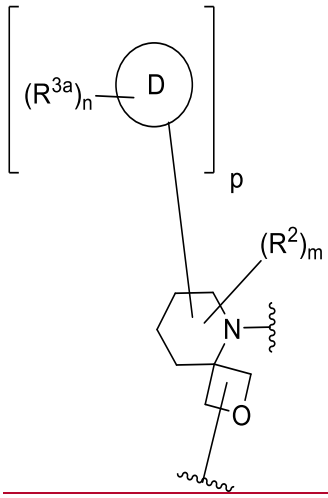
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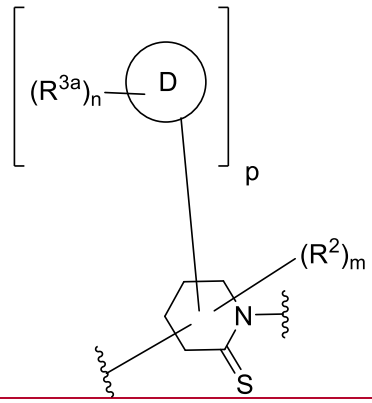
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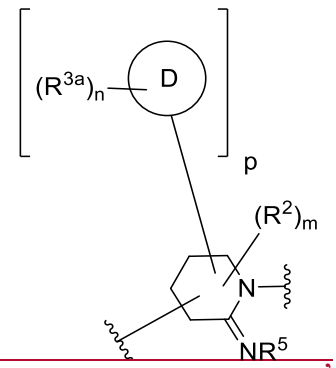
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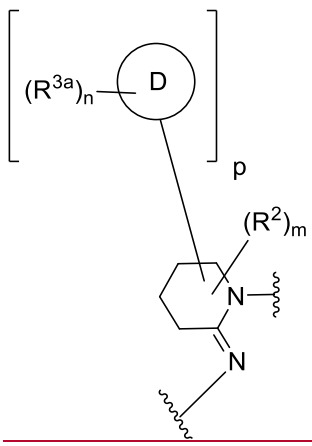
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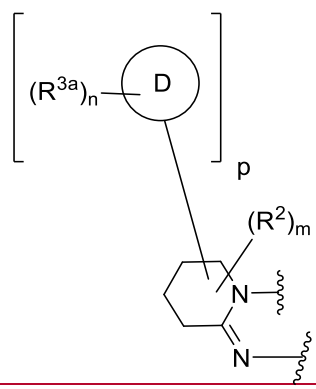
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each or R^2 and R^{3a} is independently hydrogen, deuterium, R^6, halogen, CN, NO_2, OR, -SR, $-N(R)_2$, $-Si(R)_3$, $-S(O)_2R$, $-S(O)_2N(R)_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)N(R)_2$, -C(O)N(R)OR, $-C(R)_2N(R)C(O)R$, $-C(R)_2N(R)C(O)N(R)_2$, -OC(O)R, $-OC(O)N(R)_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)(NR_2)$, $-OP(O)(NR_2)_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)N(R)_2$, $N(R)S(O)_2R$, $-NP(O)R_2$, $-N(R)P(O)(OR)_2$, $-N(R)P(O)(OR)(NR_2)$, $-N(R)P(O)(NR_2)_2$, or $N(R)S(O)_2R$;

Ring D is selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

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

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

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

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

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

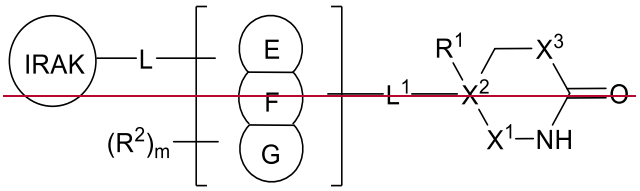
n is 0, 1, 2, 3 or 4;

p is 0 or 1; and

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

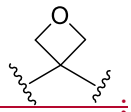
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

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



I-hh

or a pharmaceutically acceptable salt thereof, wherein:

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

X^2 is a carbon atom or silicon atom;

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

R^1 is hydrogen, deuterium, halogen, CN, OR, SR, S(O)R, $S(O)_2R$, $N(R)_2$, $P(O)(OR)_2$, $P(O)(NR_2)OR$, $P(O)(NR_2)_2$, $Si(OH)_2R$, $Si(OH)(R)_2$, $Si(R)_3$, or an optionally substituted C_{1-4} aliphatic;

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

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

each R^2 is independently hydrogen, deuterium, R^6, halogen, CN, NO_2, OR, SR, $N(R)_2$, $Si(R)_3$, $S(O)_2R$, $S(O)_2N(R)_2$, S(O)R, C(O)R, C(O)OR, $C(O)N(R)_2$, C(O)N(R)OR, $C(R)_2N(R)C(O)R$, $C(R)_2N(R)C(O)N(R)_2$, OC(O)R, $OC(O)N(R)_2$, $OP(O)R_2$, $OP(O)(OR)_2$, $OP(O)(OR)(NR_2)$, $OP(O)(NR_2)_2$, N(R)C(O)OR, N(R)C(O)R, $N(R)C(O)N(R)_2$, $N(R)S(O)_2R$, $NP(O)R_2$, N(R)P(O)(OR)2, N(R)P(O)(OR)(NR2), $N(R)P(O)(NR_2)_2$, or $N(R)S(O)_2R$;

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

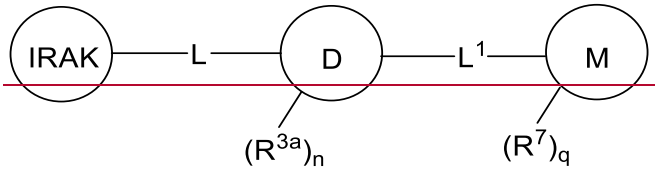
independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each of Ring E, Ring F, and Ring G is independently a fused ring selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 5- to 7-membered saturated or partially unsaturated carbocyclyl, 5- to 7-membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

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

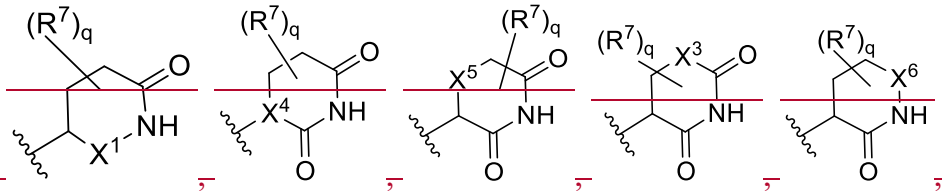
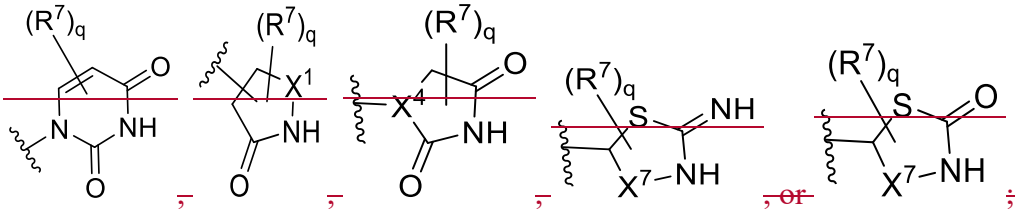
m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16.

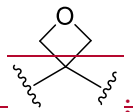
8. The compound of claim 3, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety and said compound is of formula **I-nn**:



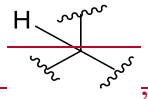
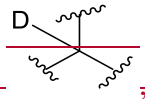
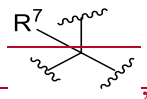
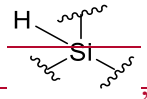
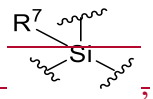
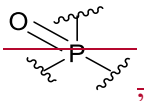
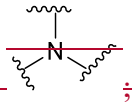
I-nn

or a pharmaceutically acceptable salt thereof, wherein:

Ring E is selected from  ,  , or ;

each of X^1, X^6, and X^7 is independently a bivalent moiety selected from a covalent bond, CH_2, $CHCF_3$, SO_2, S(O), P(O)R, P(O)OR, $P(O)NR_2$, C(O), C(S), or  ;

each of X^3 and X^5 is independently a bivalent moiety selected from a covalent bond, CR_2, NR, O, S, or SiR_2;

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

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

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

each R^{3a} is independently hydrogen, deuterium, R^6, halogen, CN, NO_2, OR, SR, NR_2, SiR_3, $S(O)_2R$, $S(O)_2NR_2$, S(O)R, C(O)R, C(O)OR, $C(O)NR_2$, C(O)N(R)OR, $C(R)_2N(R)C(O)R$, $C(R)_2N(R)C(O)N(R)_2$, OC(O)R, $OC(O)N(R)_2$, $OP(O)R_2$, $OP(O)(OR)_2$, $OP(O)(OR)NR_2$, $OP(O)(NR_2)_2$, N(R)C(O)OR, N(R)C(O)R, $N(R)C(O)NR_2$, $N(R)S(O)_2R$, $NP(O)R_2$, $N(R)P(O)(OR)_2$, $N(R)P(O)(OR)NR_2$, $N(R)P(O)(NR_2)_2$, or $N(R)S(O)_2R$;

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

each R^7 is independently hydrogen, deuterium, halogen, CN, OR, SR, S(O)R, $S(O)_2R$, NR_2, $P(O)(OR)_2$, $P(O)(NR_2)OR$, $P(O)(NR_2)_2$, $Si(OH)R_2$, $Si(OH)_2R$, SiR_3, or an optionally substituted C_{1-4} aliphatic; or

R^7 and X^1 or X^3 are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, carbocyclic ring or heterocyclic ring having 1-3 heteroatoms, independently selected from boron, nitrogen, oxygen, silicon, or sulfur;

two R^7 groups on the same carbon are optionally taken together with their intervening atoms to form a 3-6 membered spiro fused ring or a 4-7 membered heterocyclic ring having 1-2 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur;

two R^7 groups on adjacent carbon atoms are optionally taken together with their intervening atoms to form a 3-7 membered saturated, partially unsaturated, carbocyclic ring or heterocyclic ring having 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or a 7-13 membered saturated, partially unsaturated, bridged heterocyclic ring, or a spiro heterocyclic ring having 1-3 heteroatoms, independently selected from boron, nitrogen, oxygen, silicon, or sulfur;

Ring D is selected from 6-membered aryl, 6-membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, or sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

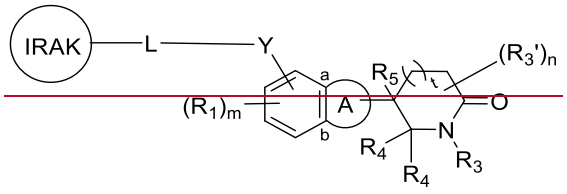
L^1 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with –O–, –C(O)–, –C(S)–, $-C(R)_2-$, –CH(R)–, $-C(F)_2-$, –N(R)–, –S–, $-S(O)_2-$ or –(C)=CH–;

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

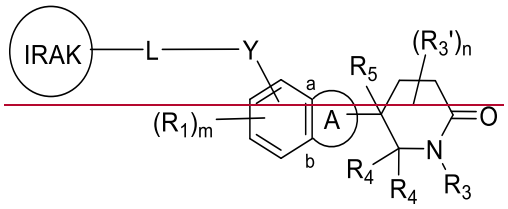
q is 0, 1, 2, 3, or 4.

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

(*i*)



~~I-oo-1~~



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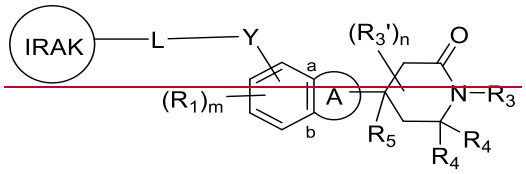
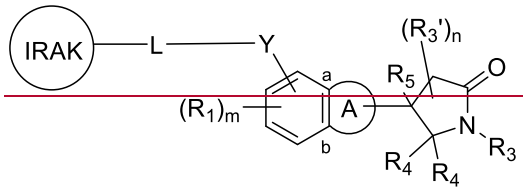


~~I-oo-3~~



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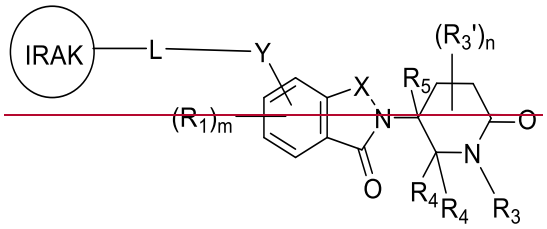

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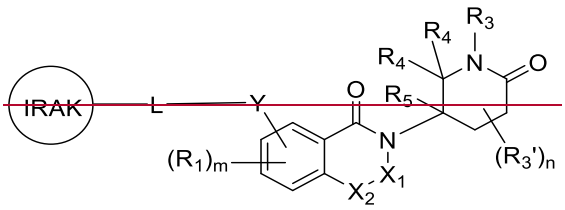

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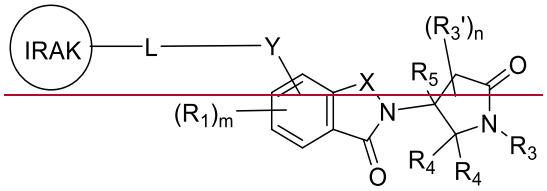

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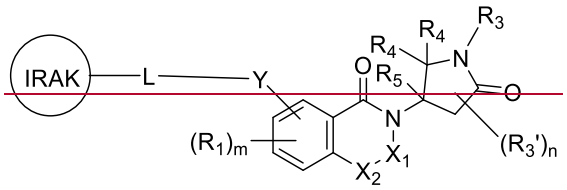
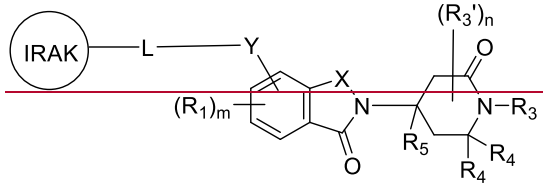
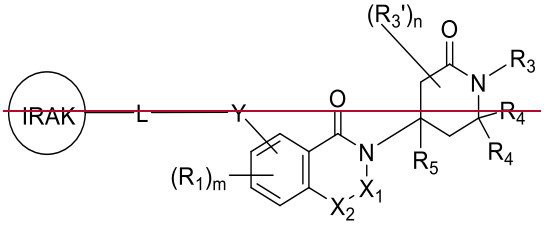


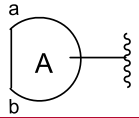
~~I-oo-8~~



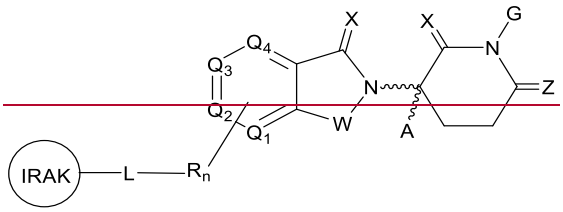
~~I-oo-9~~



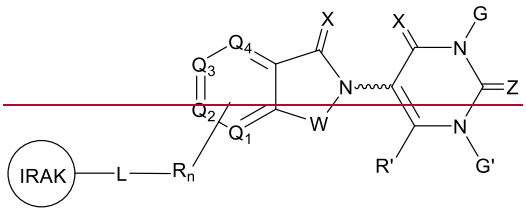
~~I-oo-10~~

~~or a pharmaceutically acceptable salt thereof, and wherein each of the variables~~  ~~, X, X_1, X_2, Y, R_1, R_3, R_3', R_4, R_5, t, m and n is as defined and described in WO 2017/007612 and US 2018/0134684;~~

~~*(ii)*~~



~~I-pp-1~~



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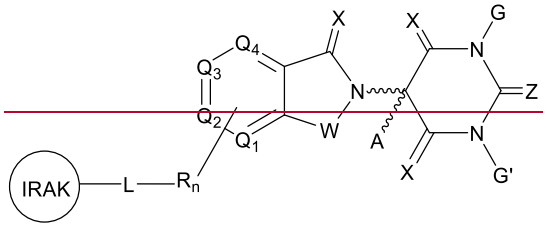

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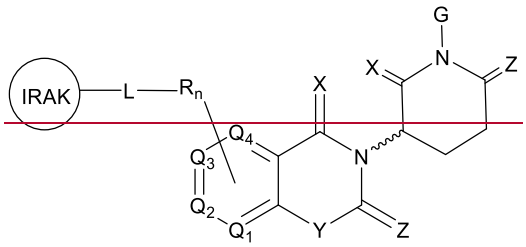

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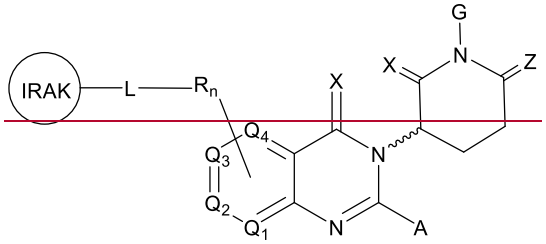

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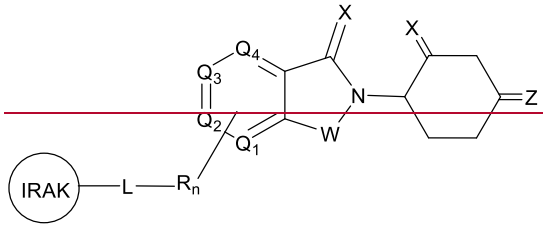
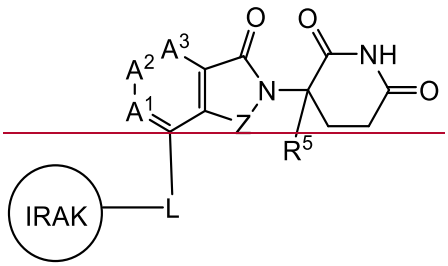


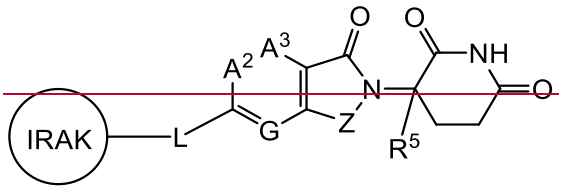
~~I-pp-6~~

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

~~*(iii)*~~



~~I-zz-1~~



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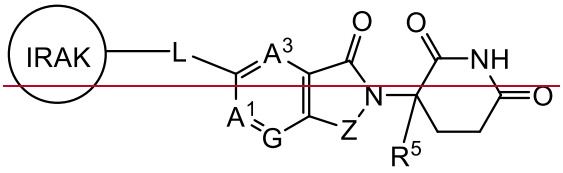

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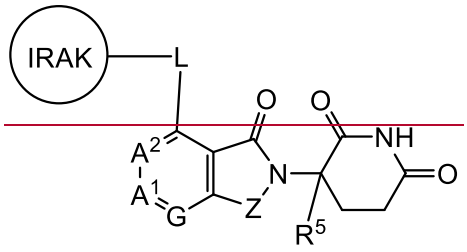
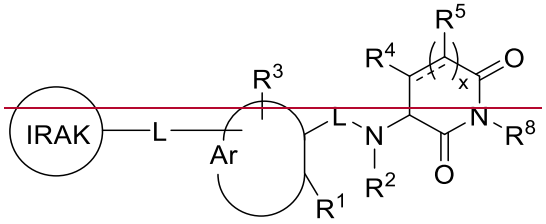


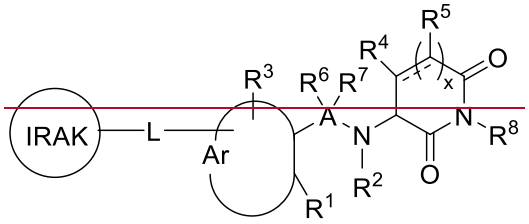
~~I-zz-4~~

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

~~(*iv*)~~



~~I-tt-1~~



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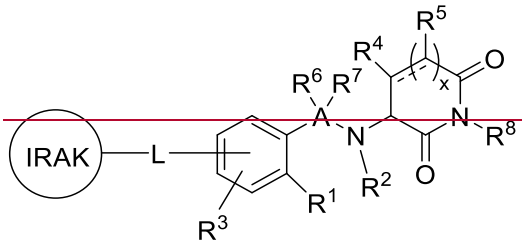

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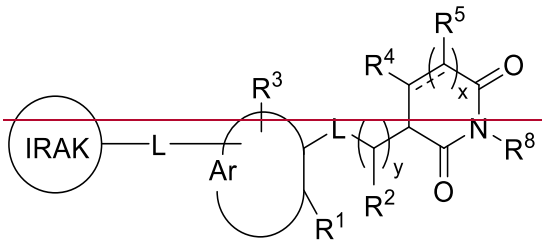
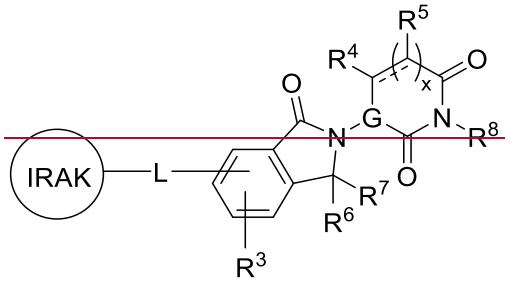
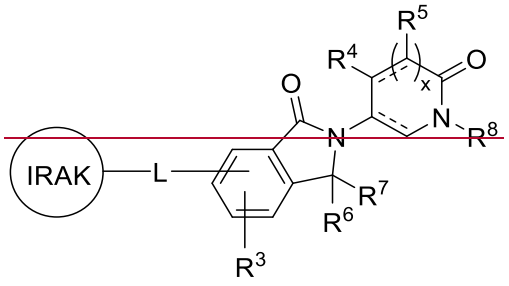


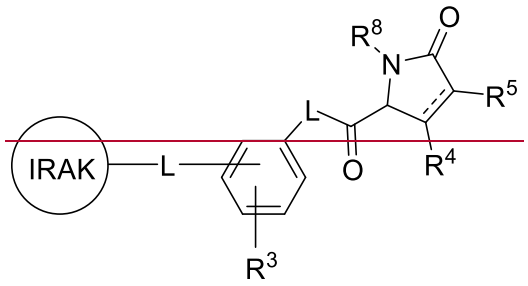
~~I-tt-4~~



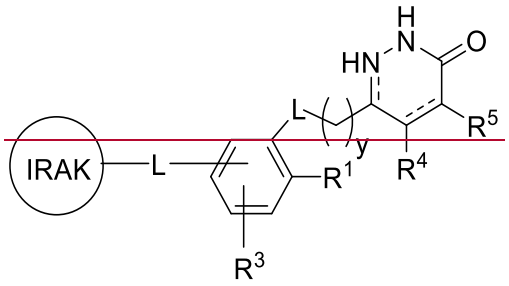
~~I-tt-5~~



~~I-tt-6~~



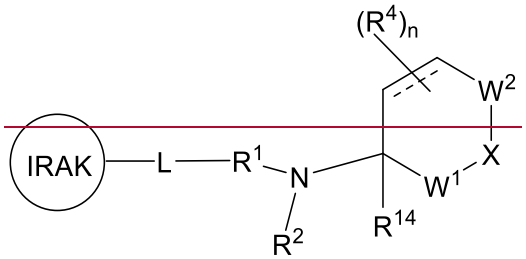
~~I-tt-7~~



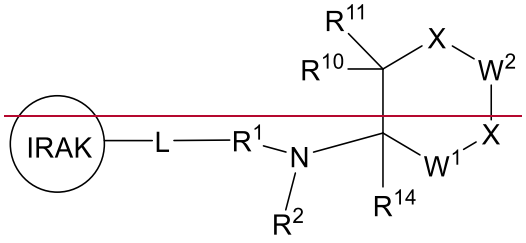
~~I-tt-8~~

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

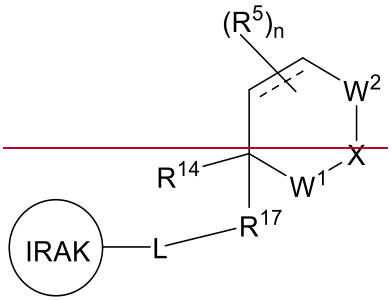
~~(v)~~



~~I-qq-1~~

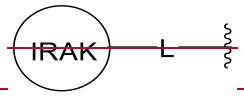


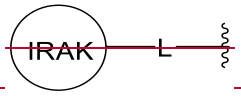
~~I-qq-2~~



~~I-qq-3~~

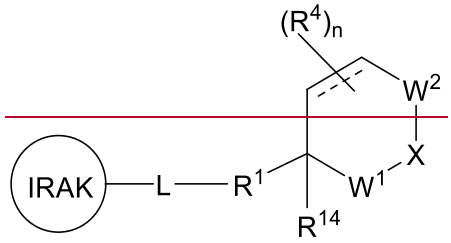
~~or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described herein, and wherein each of the variables R^1, R^2, R^4, R^5, R^{10}, R^{11}, R^{14}, R^{17}, W^1, W^2, X, ---, and n is as defined in WO 2017/197051 which is herein incorporated by reference in its entirety~~

~~and wherein~~ 

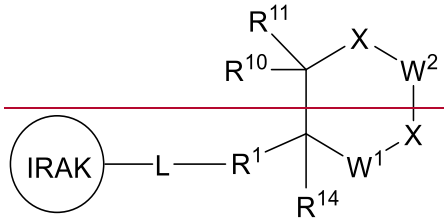
~~is attached to R^1, the ring formed by combining R^1 and R^2, or R^{17} at the site of attachment of R^{12} as defined in WO 2017/197051 such that~~ 

~~takes the place of the R^{12} substituent; or~~

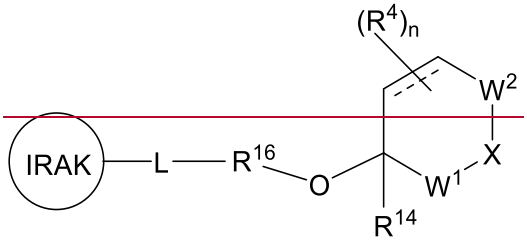
~~(*vi*)~~



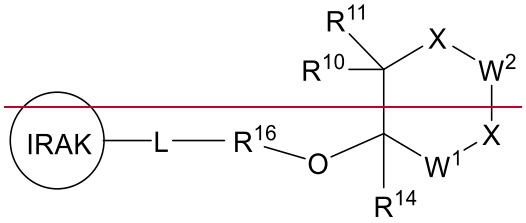
~~I-rr-1~~



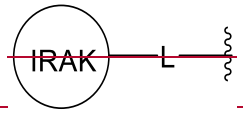
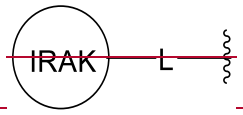
~~I-rr-2~~



~~I-rr-3~~



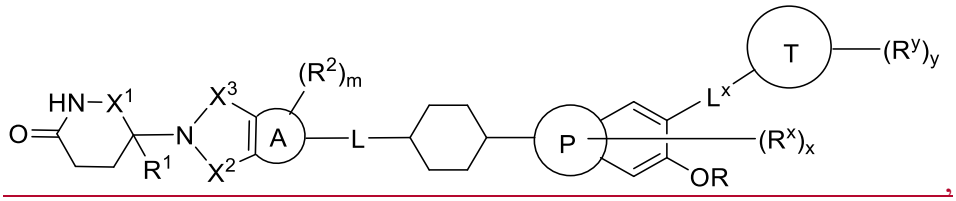
~~I-rr-4~~

~~or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described herein, and wherein each of the variables R^1, R^4, R^{10}, R^{11}, R^{14}, R^{16}, W^1, W^2, X, ---, and n is as defined in WO 2018/237026, the entirety of each of which is herein incorporated by reference, and wherein~~  ~~is attached to R^1 or R^{16} at the site of attachment of R^{12} as defined in WO 2018/237026, such that~~  ~~takes the place of the R^{12} substituent.~~

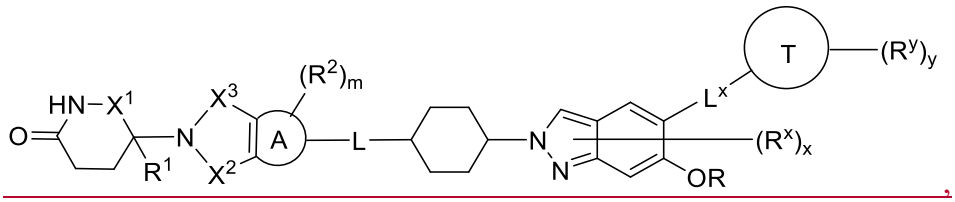
2. The compound of claim 1, wherein X is a 4-6 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

3. The compound of either claim 1 or claim 2, wherein Ring Q is benzo or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

4. The compound of any one of claims 1-3, wherein said compound is any one of formulae:



I-k-13



I-k-15

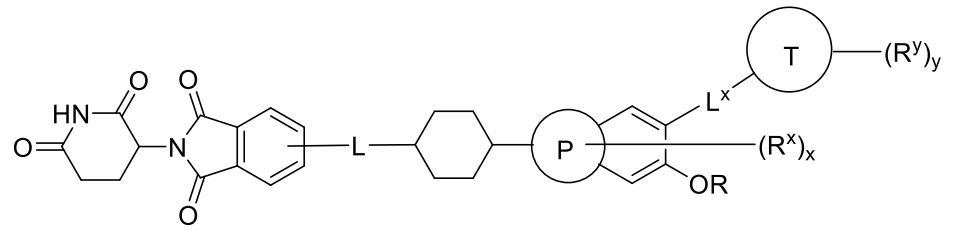
or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1-4, wherein Ring A^a is a 6-membered aryl.

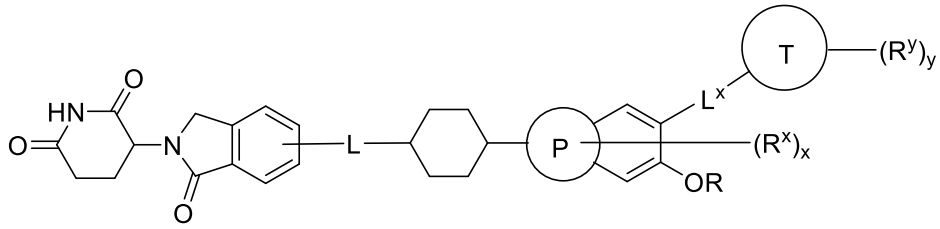
6. The compound of any one of claims 1-5, wherein Ring T is a 5-9 membered mono- or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

7. The compound of any one of claims 1-6, wherein L^x is a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with $-Cy^x-$, -O-, -S-, -C(O)-, -C(S)-, $-CR_2-$, -CRF-, $-CF_2-$, -NR-, -N=CR-, -CR=CR-, or $-S(O)_2-$.

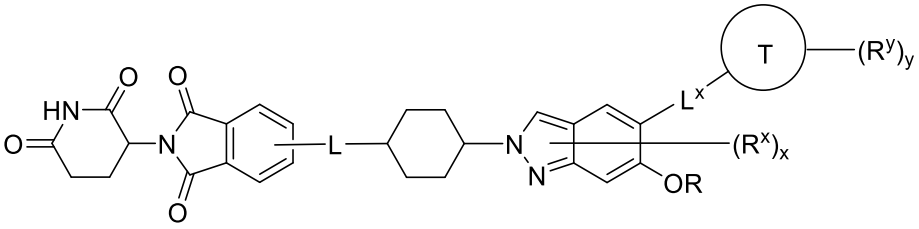
8. The compound of any one of claims 1-7, wherein said compound is any one of the following formulae:



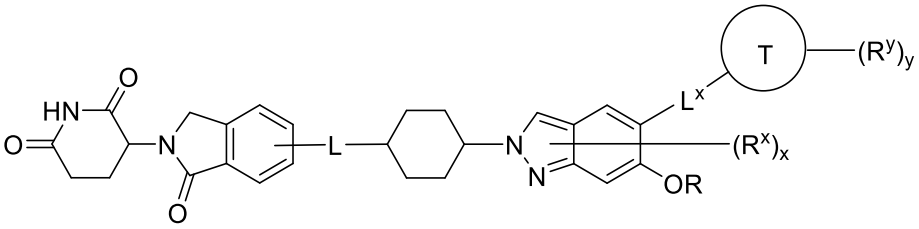
I-k-2



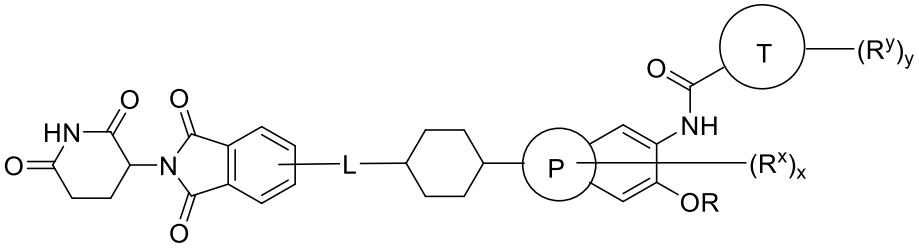
I-k-3



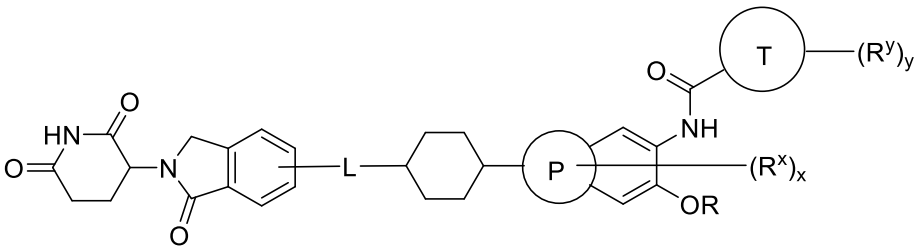
I-k-4



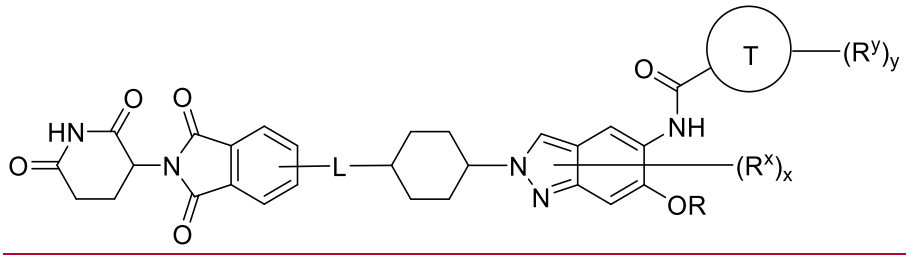
I-k-5



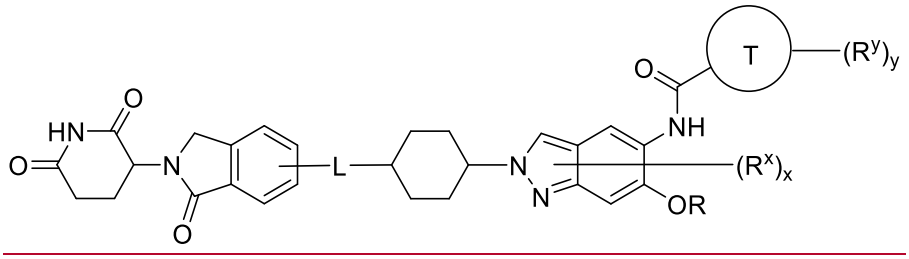
I-k-6



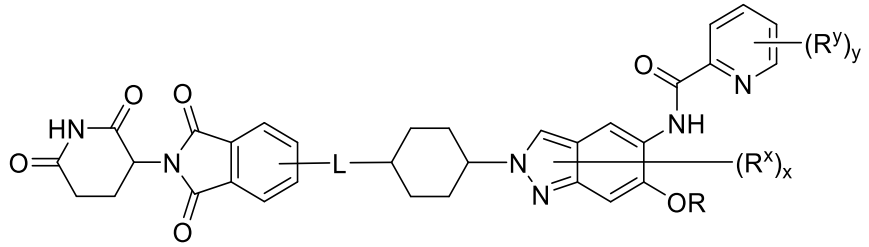
I-k-7



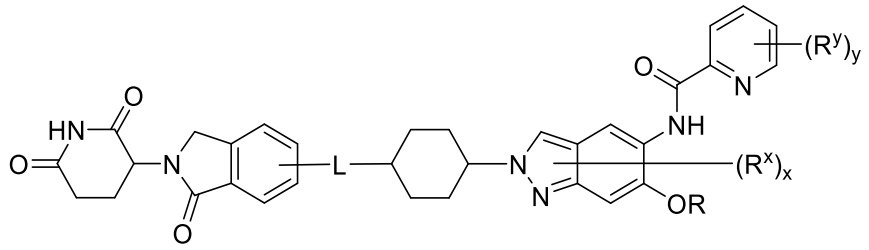
I-k-8



I-k-9



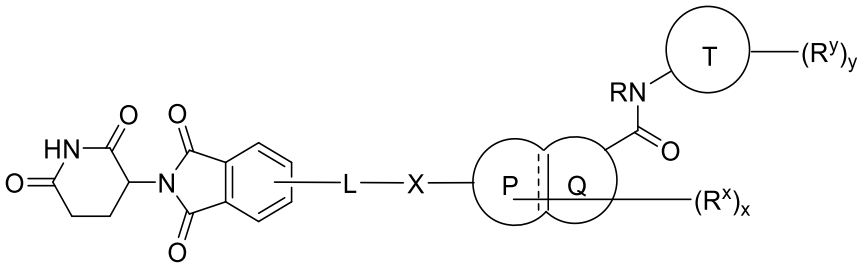
I-k-10



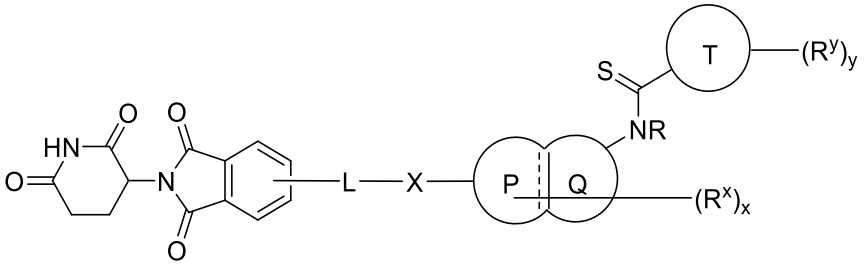
I-k-11

or a pharmaceutically acceptable salt thereof.

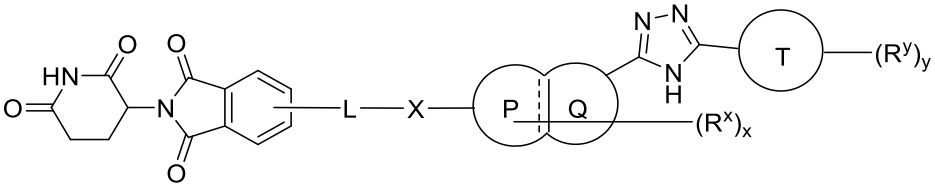
~~10~~9. The compound of claim ~~9~~1, wherein said compound is any one of formulae **I-i-1**, **I-i-2**, **I-i-3**, **I-i-4**, **I-i-5**, **I-i-6**, **I-i-7**, **I-j-1**, **I-j-2**, **I-j-3**, **I-j-4**, **I-k-1**, **I-l-1**, **I-l-2**, **I-l-3**, **I-m-1**, **I-n-1**, or **I-n-2**:



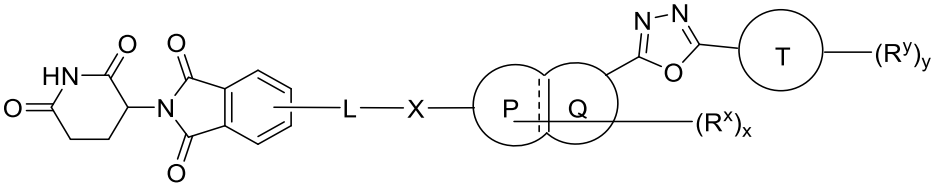
I-i-1



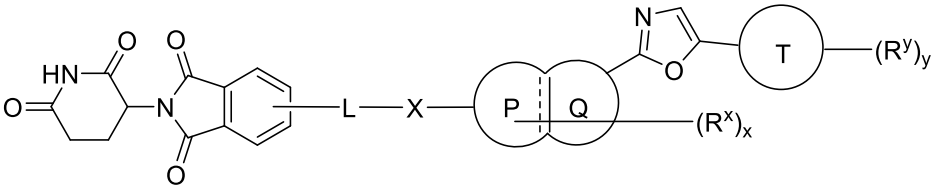
I-i-2



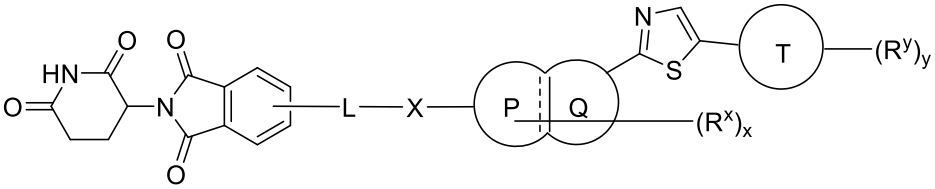
I-i-3



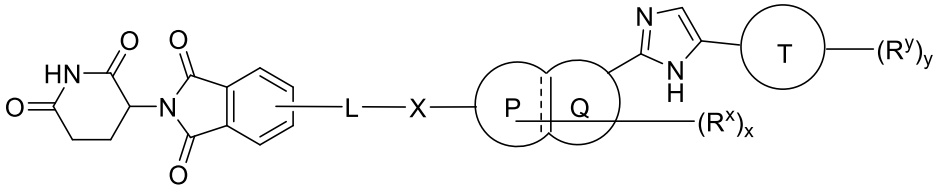
I-i-4



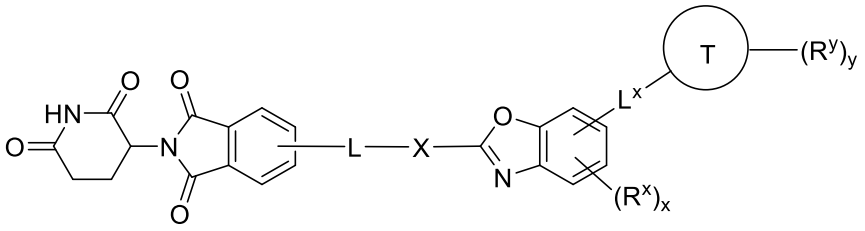
I-i-5



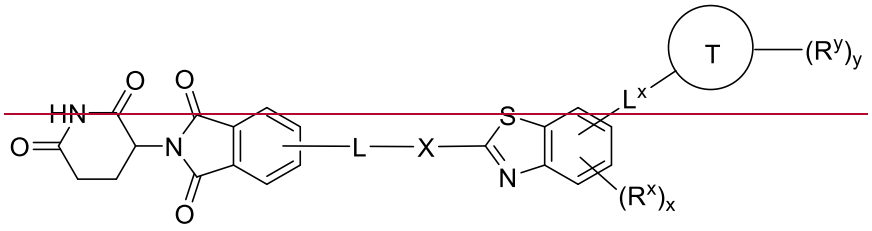
I-i-6



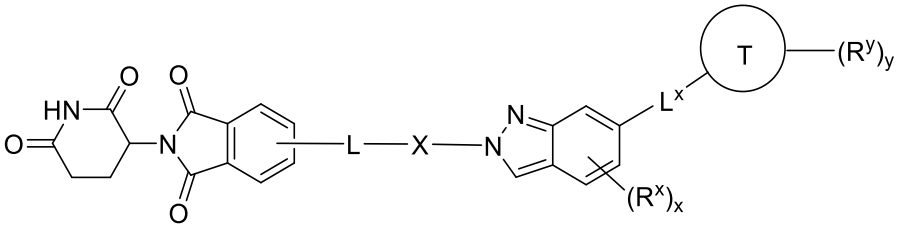
I-i-7



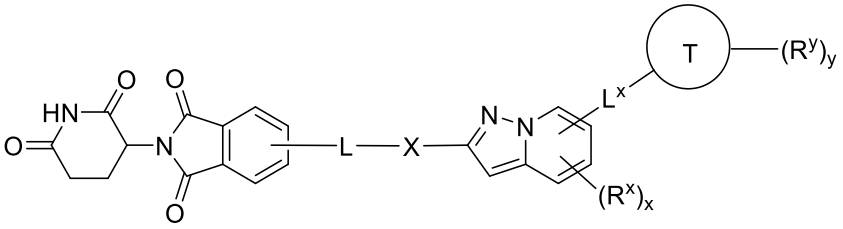
I-j-1



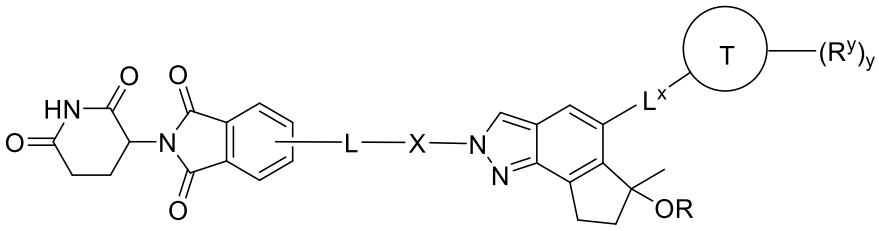
~~**I-j-2**~~



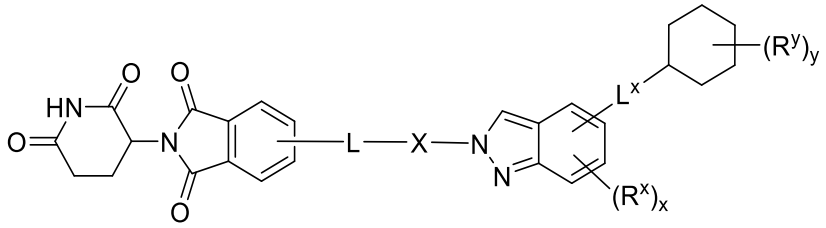
I-j-3



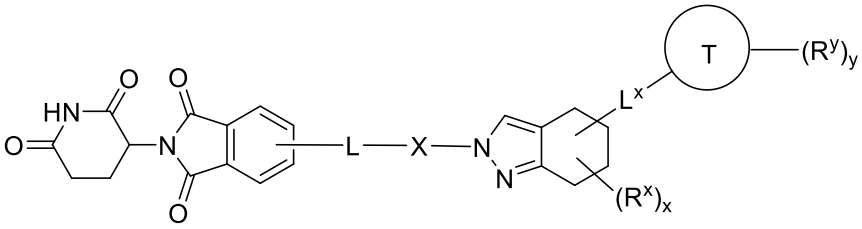
I-j-4



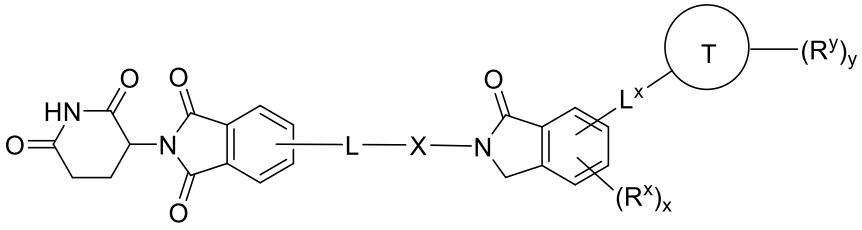
I-k-1



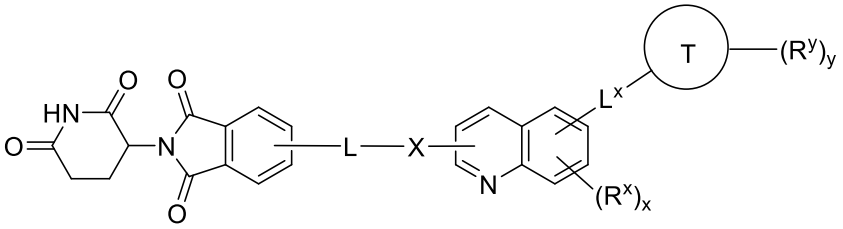
I-l-1



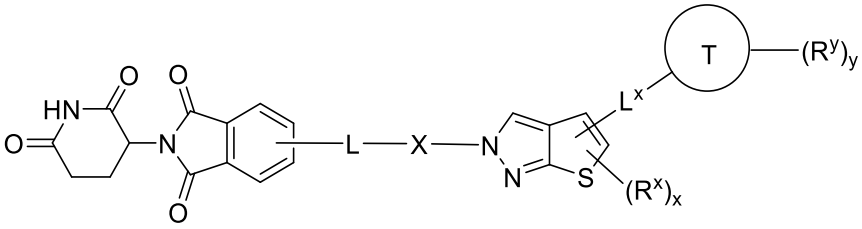
I-l-2



I-l-3



I-m-1



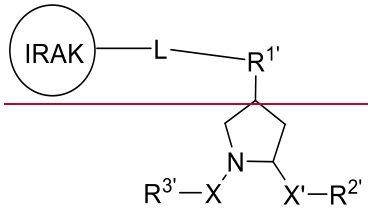
I-m-2

or a pharmaceutically acceptable salt thereof.

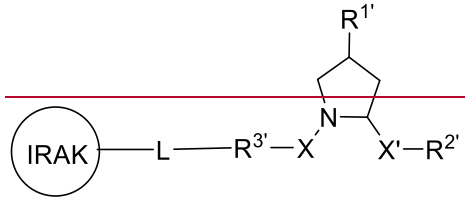
~~11. The compound of claim 3, wherein LBM is a VHL E3 ubiquitin ligase binding moiety and~~

~~said compound is selected from any of the following formulae:~~

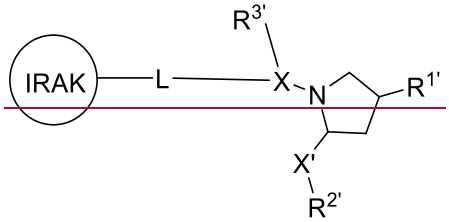
~~(*i*)~~



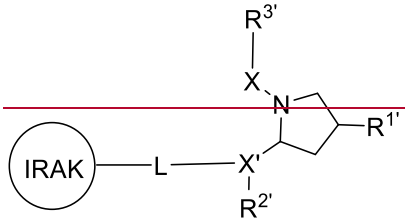
~~I-ww-1~~



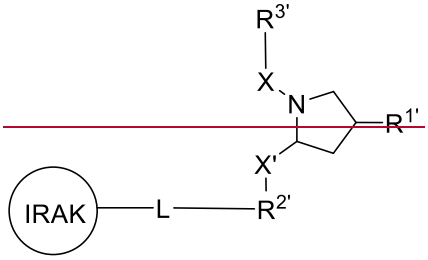
~~I-ww-2~~



~~I-ww-3~~



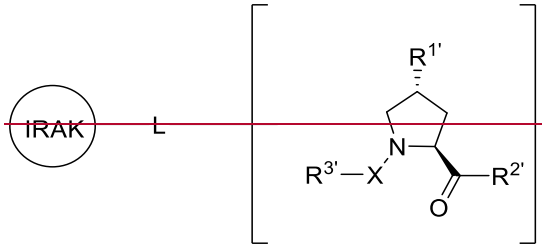
~~I-ww-4~~



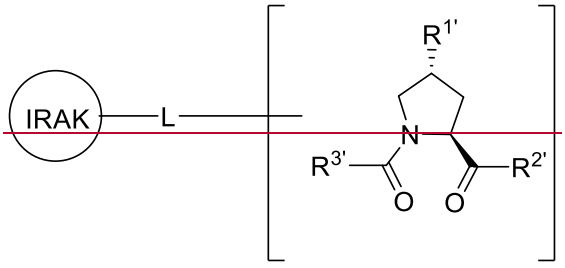
~~I-ww-5~~

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

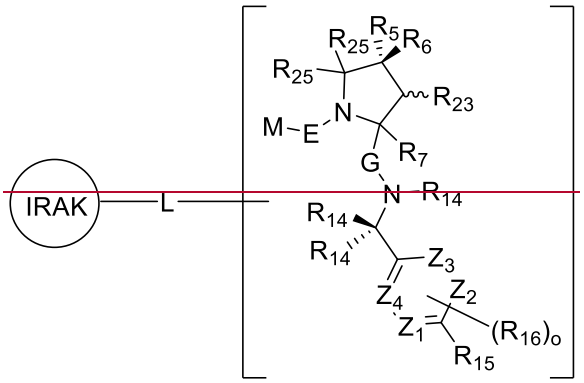
~~(*ii*)~~



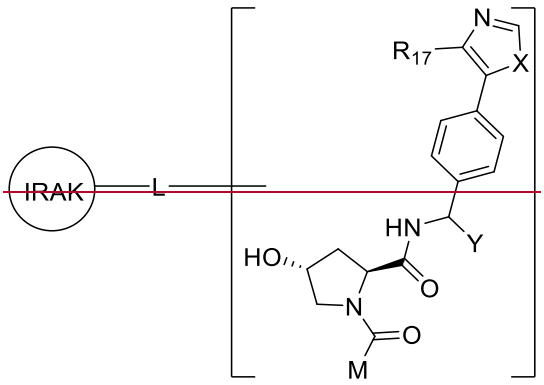
~~I-xx-1~~



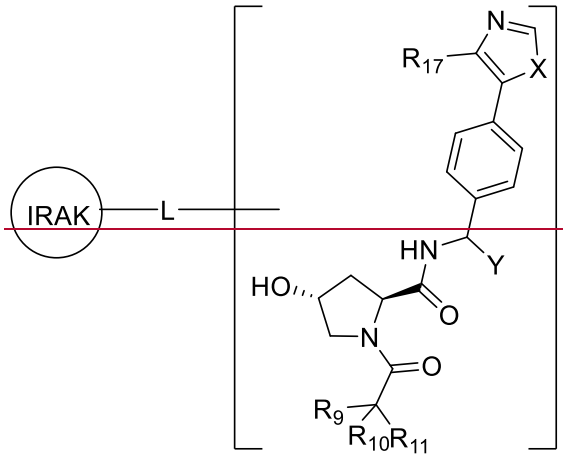
~~I-xx-2~~



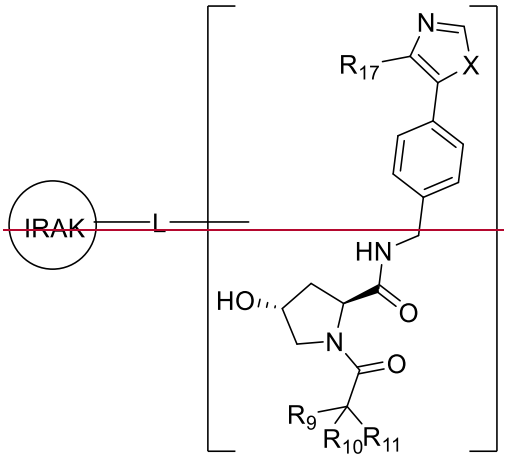
~~I-xx-3~~



~~I-xx-4~~



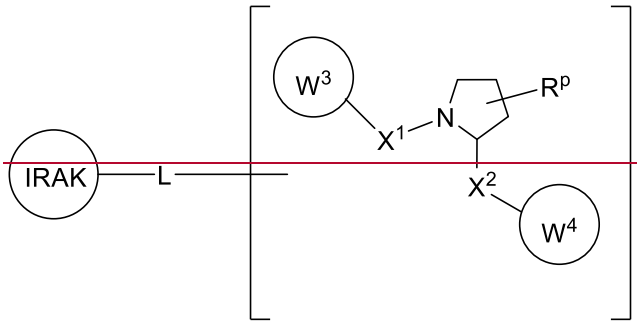
~~I-xx-5~~



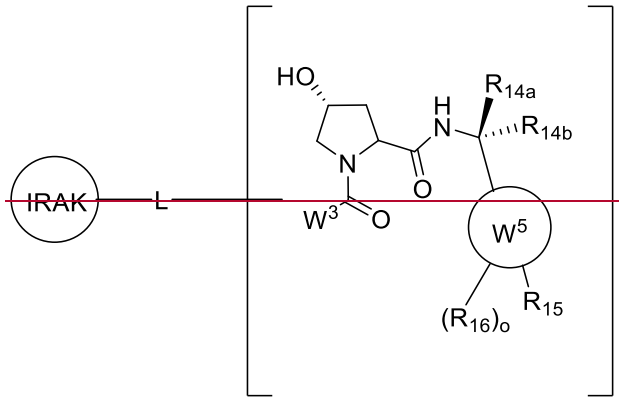
~~I-xx-6~~

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

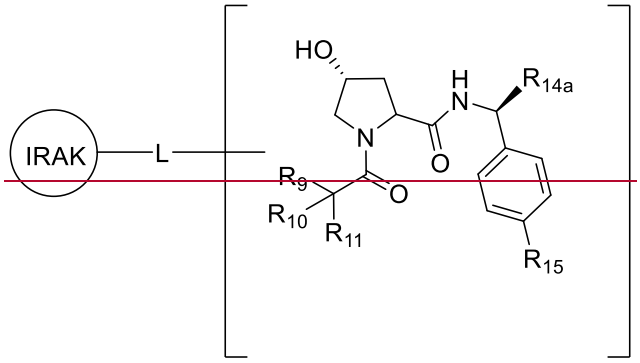
~~*(iii)*~~



~~I-yy-1~~



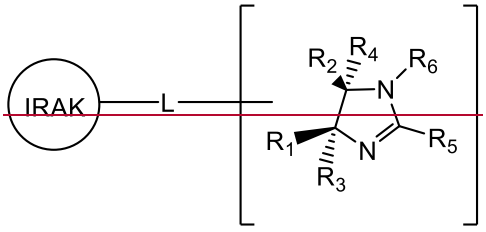
I-yy-2



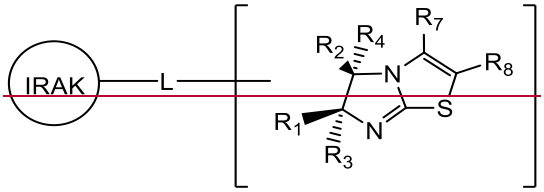
I-yy-3

or a pharmaceutically acceptable salt thereof, and wherein each of the variables R^9, R_9, R_{10}, R_{11}, R_{14a}, R_{14b}, R_{15}, R_{16}, W^3, W^4, W^5, X^1, X^2, and o is as defined and described in WO 2016/118666 and US 2016/0214972.

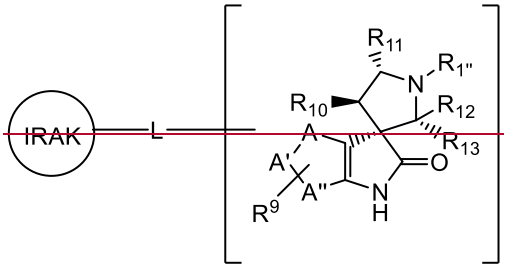
12. The compound of claim 3, wherein LBM is a MDM2 E3 ubiquitin ligase binding moiety and said compound is selected from any of the following formulae:



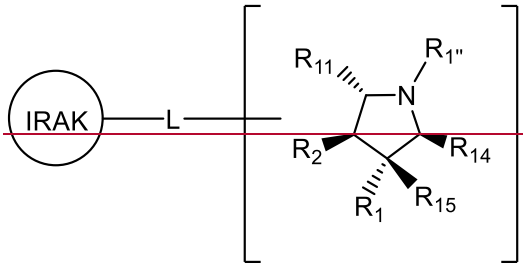
I-aaa-1



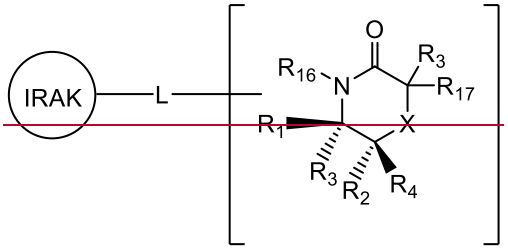
I-aaa-2



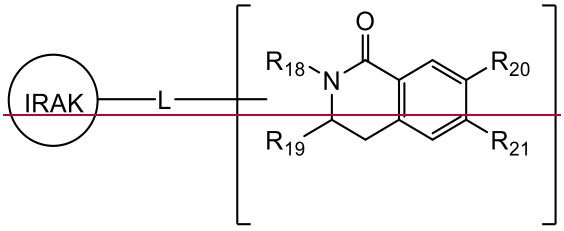
~~I-aaa-3~~



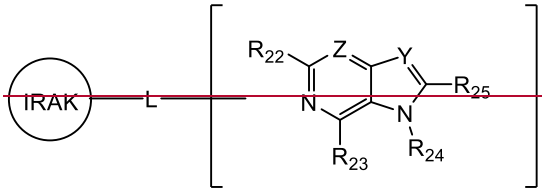
~~I-aaa-4~~



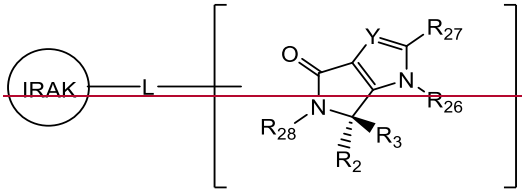
~~I-aaa-5~~



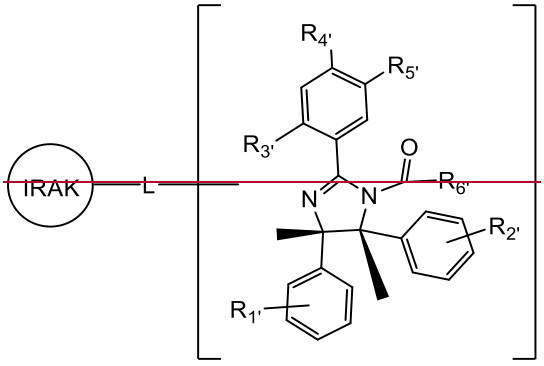
~~I-aaa-6~~



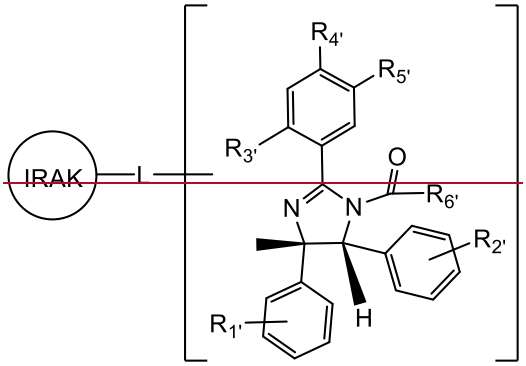
~~I-aaa-7~~



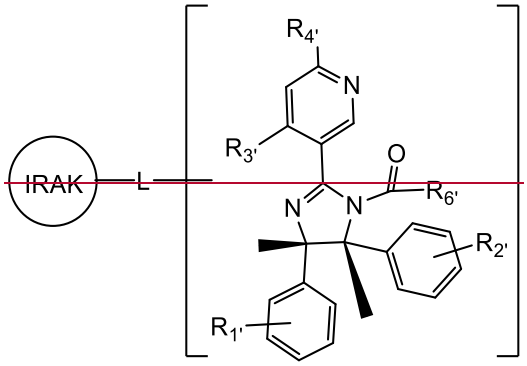
~~I-aaa-8~~



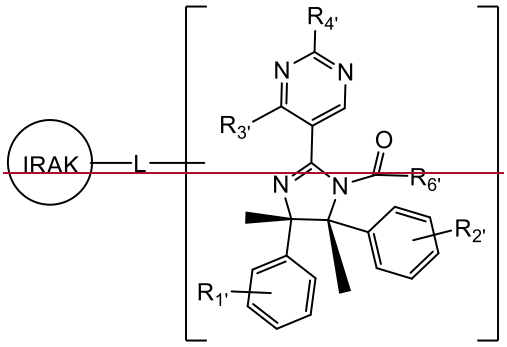
~~I-aaa-9~~



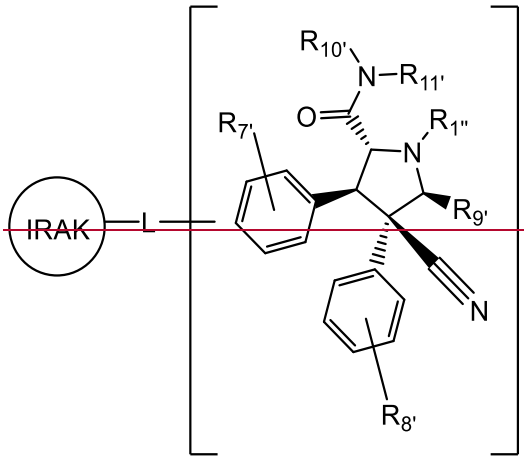
~~I-aaa-10~~



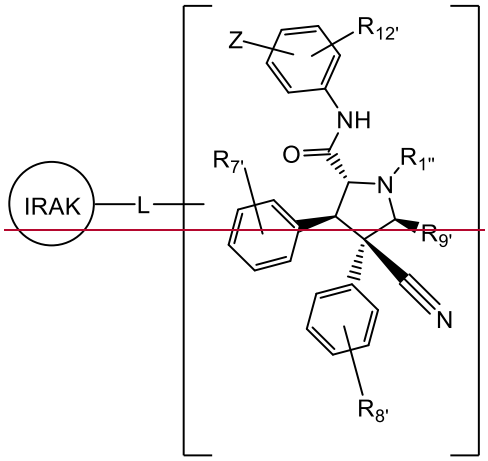
~~I-aaa-11~~



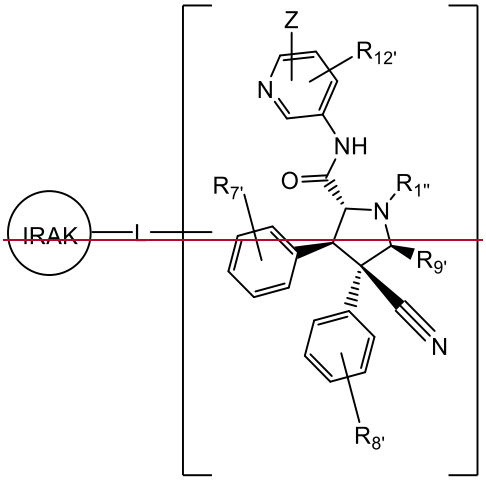
~~I-aaa-12~~



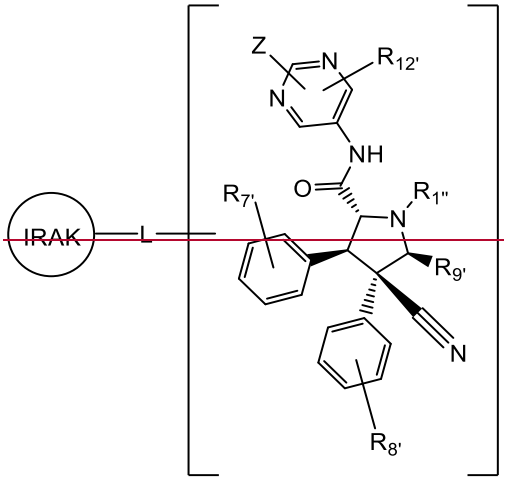
~~I-aaa-13~~



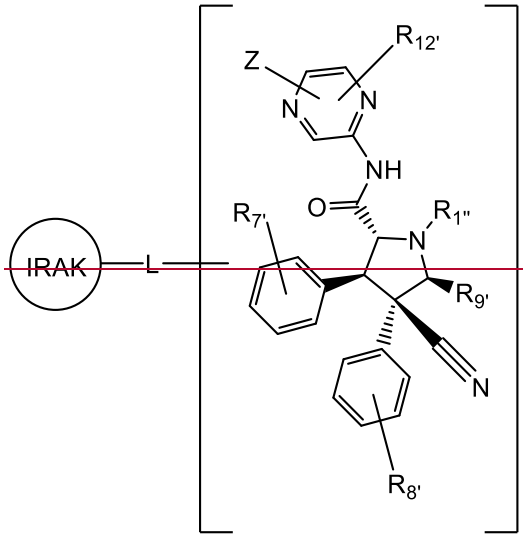
~~I-aaa-14~~



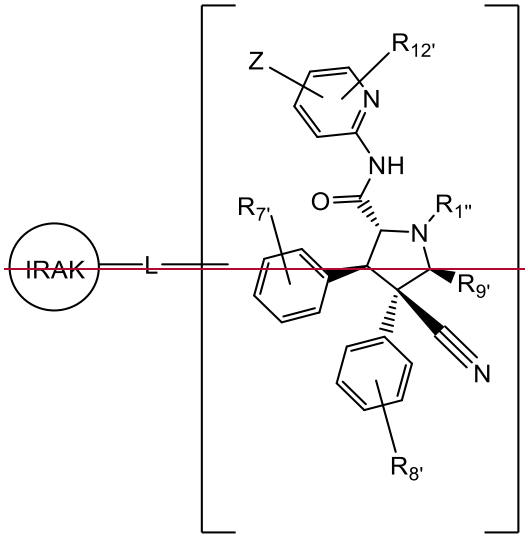
~~I-aaa-15~~



~~I-aaa-16~~



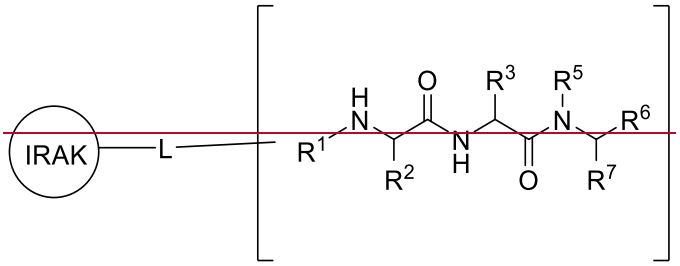
I-aaa-17



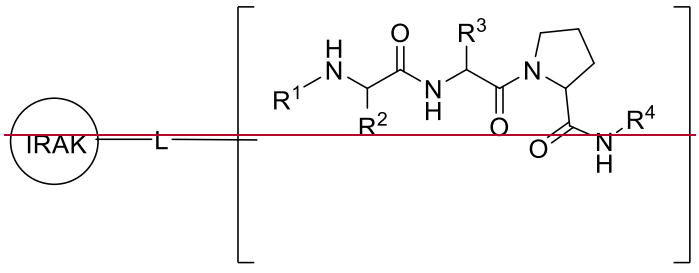
I-aaa-18

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

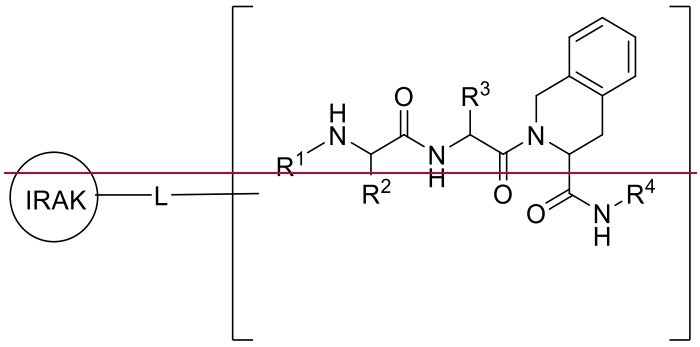
13. The compound of claim 3, wherein LBM is a IAP E3 ubiquitin ligase binding moiety and said compound is selected from any of the following formulae:



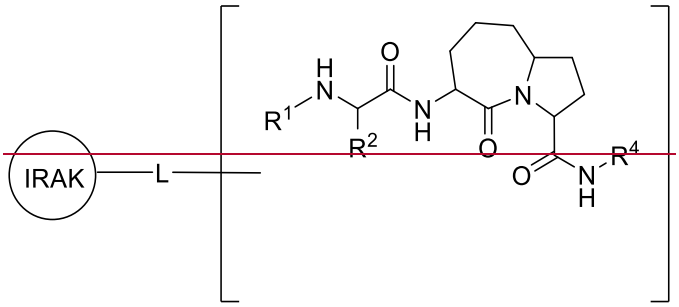
I-bbb-1



I-bbb-2



~~I-bbb-3~~

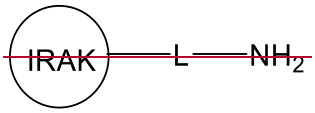


~~I-bbb-4~~

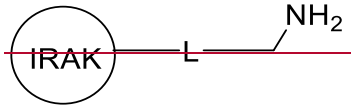
~~or a pharmaceutically acceptable salt thereof, and wherein each of the variables R^1, R^2, R^3, R^4, R^5, R^6, and R^7, is as defined and described in WO 2017/011590 and US 2017/0037004.~~

~~14. The compound of claim 3, wherein DIM is a lysine mimetic and said compound is selected from any one of the following formulae:~~

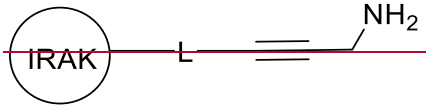
~~(*i*)~~



~~I-kkk-1~~



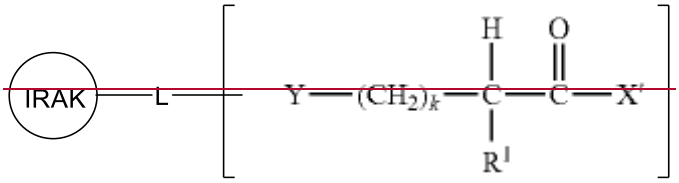
~~I-kkk-2~~



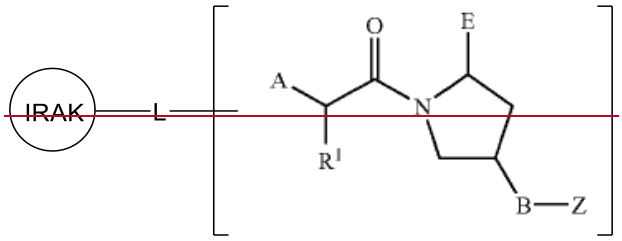
~~I-kkk-3~~

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

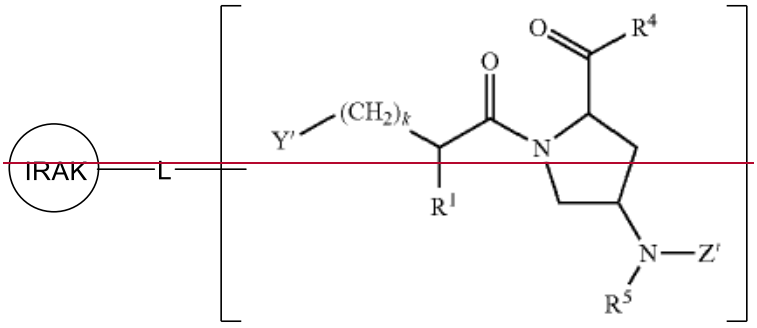
~~(*ii*)~~



~~I-III-1~~



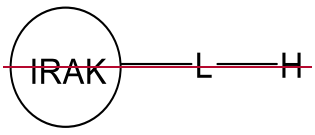
~~I-III-2~~



~~I-III-3~~

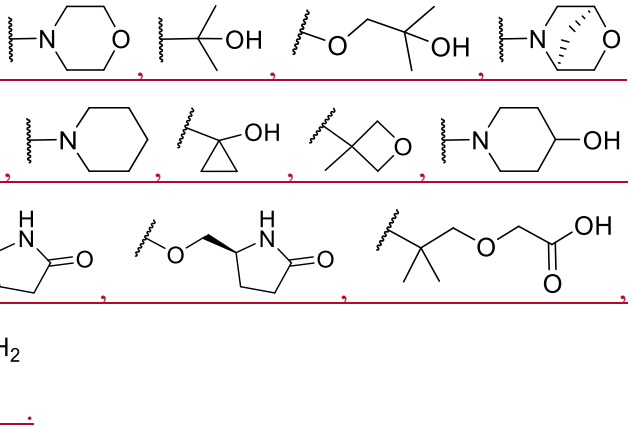
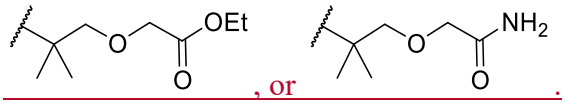
~~or a pharmaceutically acceptable salt thereof, wherein each of the variables R^1, R^4, R^5, A, B, E, Y, Y′, Z, Z′, and k are as defined and described in U.S. Pat. No. 7,622,496.~~

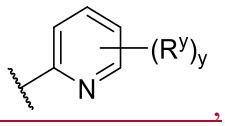
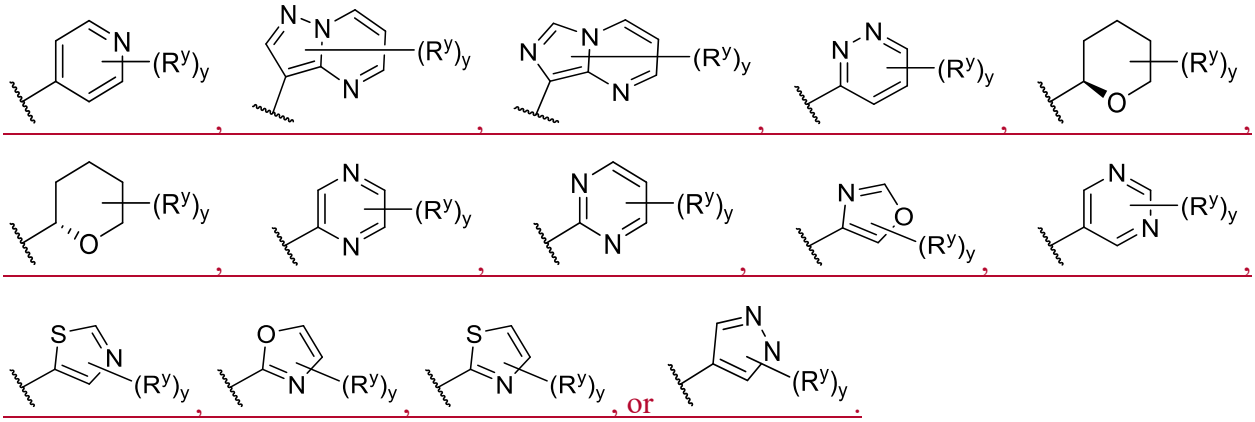
~~15. The compound of claim 3, wherein DIM is a hydrogen atom and said compound is formula **I-mmm**:~~



~~**I-mmm**~~

~~or a pharmaceutically acceptable salt thereof.~~

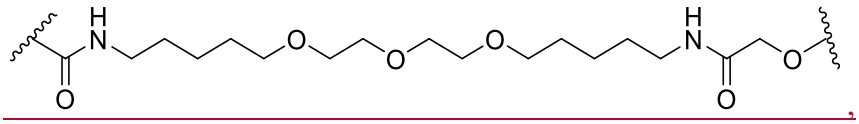
10. The compound of any one of claim 1-9, wherein R^x is fluoro, -Me, -CF_2H, -OMe, -OEt, -OiPr, -OCF_2H, -OCF_3, -SMe, -$S(O)_2Me$,  , or  .

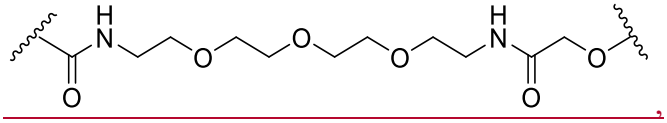
11. The compound of any one of claims 1-10, wherein Ring T is phenyl,  ,  , or .

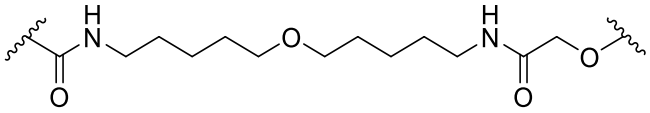
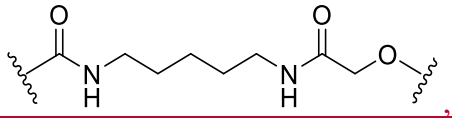
~~16~~12. The compound ~~according to~~ of any one of claims 1-~~15~~11, wherein L is a bivalent, saturated or unsaturated, straight or branched C_{1-30} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by ~~–C(D)(H)–, –C(D)$_2$–,~~ –Cy-, -O-, -N(R)-, –$Si(R)_2$–, –$Si(OH)(R)$–, –$Si(OH)_2$–, –P(O)(OR)–, –P(O)(R)–, –$P(O)(NR_2)$–, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -$N(R)S(O)_2$-, -$S(O)_2N(R)$-, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, or –N(R)C(O)O-~~, wherein: each Cy is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or~~

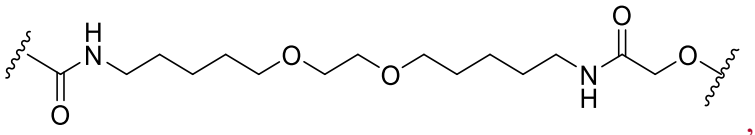
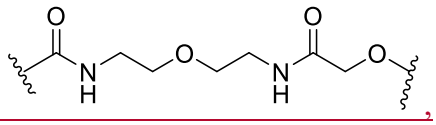
~~partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered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

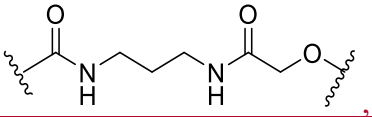
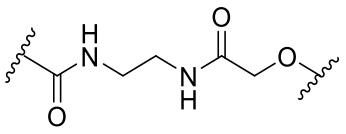
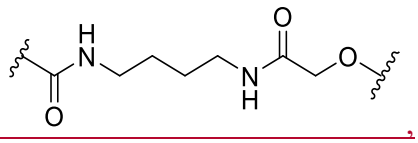
13. The compound of any one of claims 1-12, wherein L is

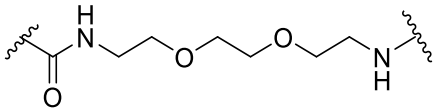
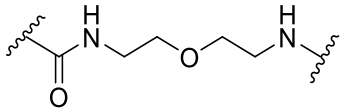
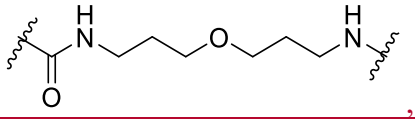
 ,

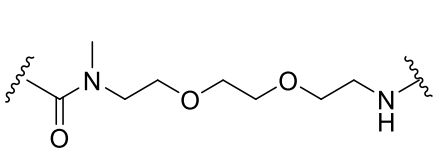
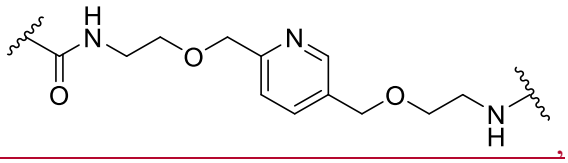
 ,

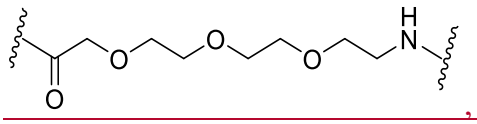
 ,  ,

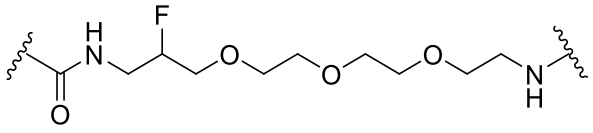
 ,  ,

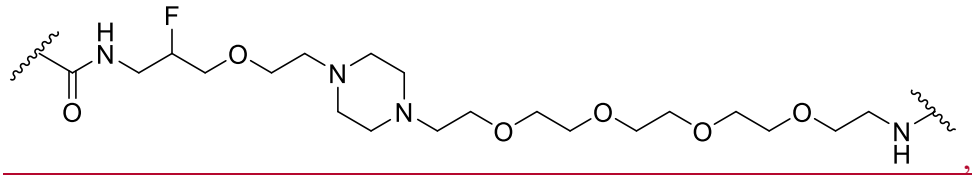
 ,  ,  ,

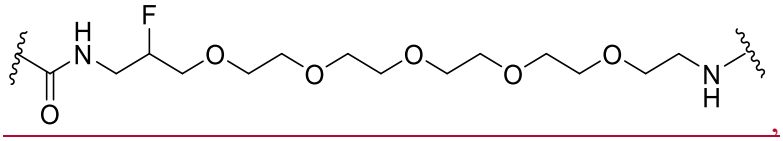
 ,  ,  ,

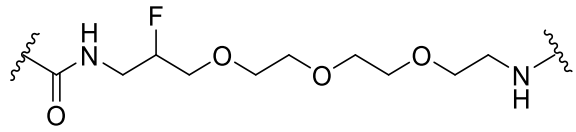
 ,  ,

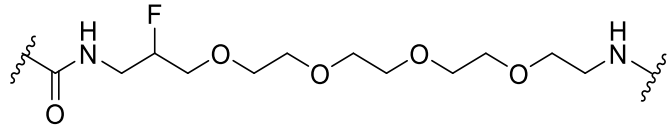


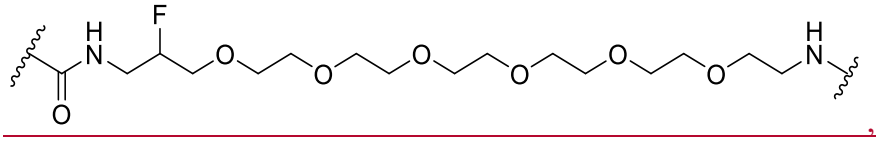


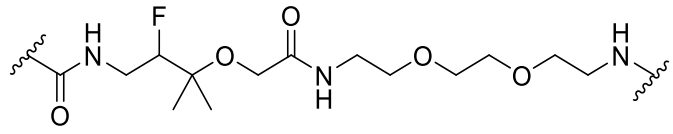


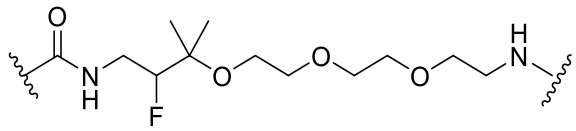


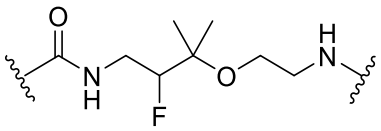


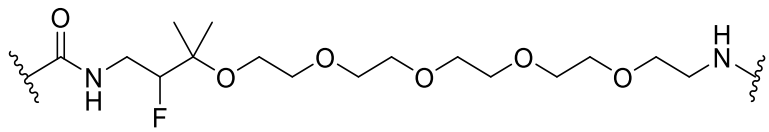


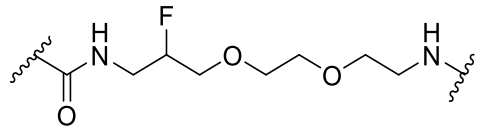


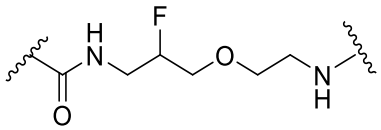


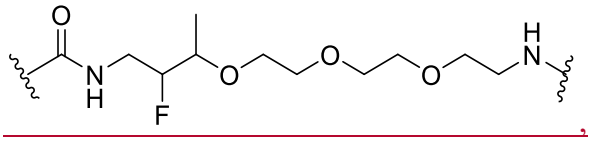


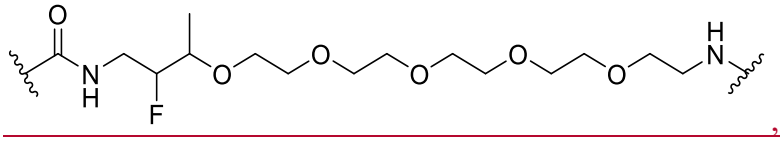


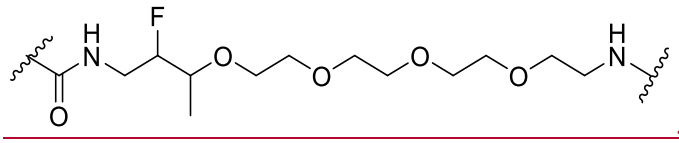


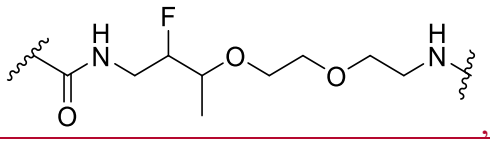


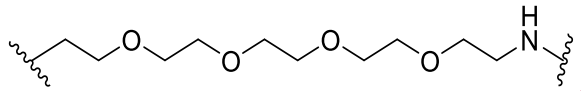


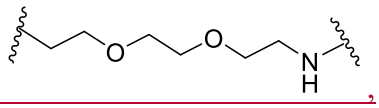


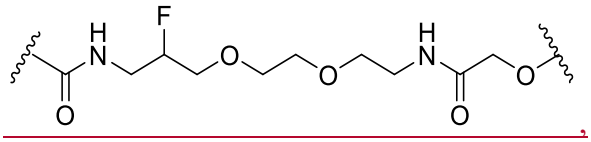


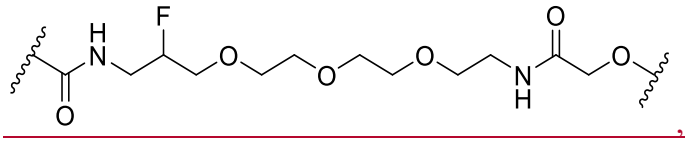


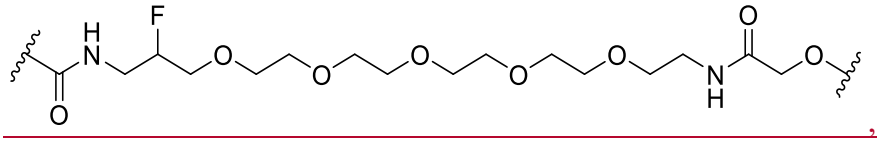


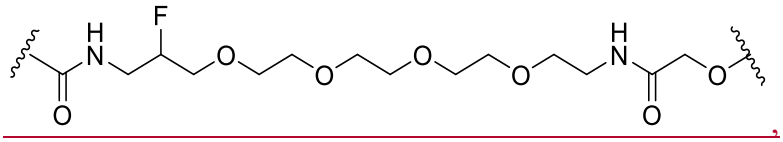


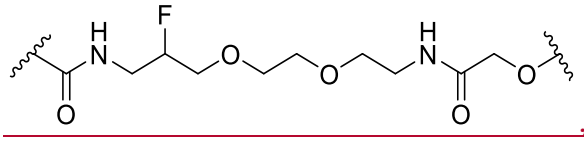


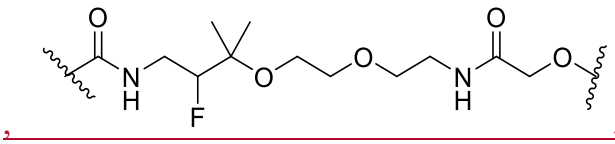


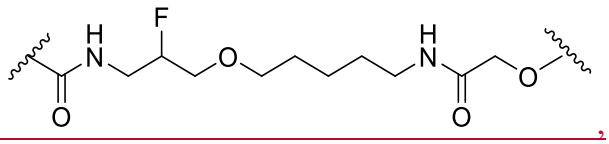


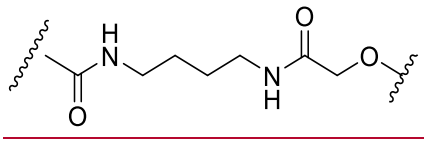


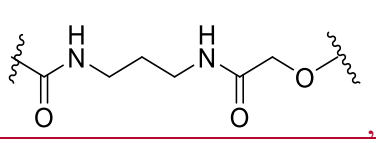


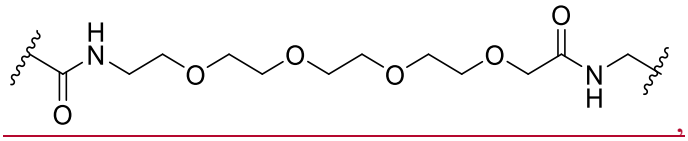


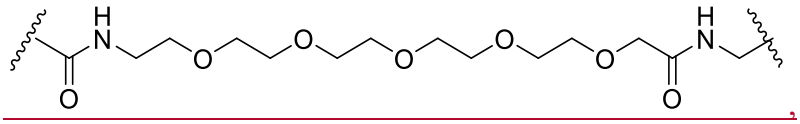


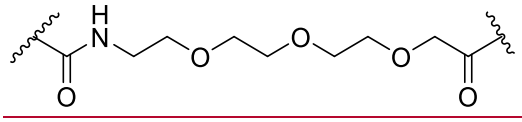


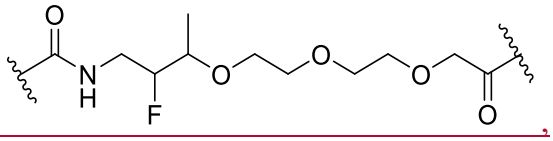


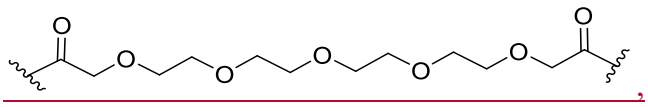


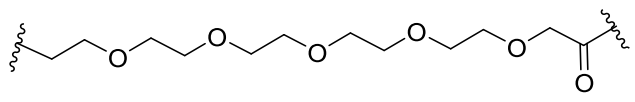


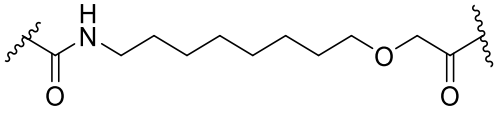


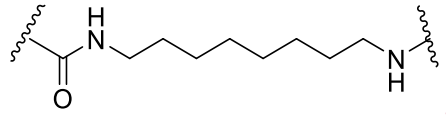


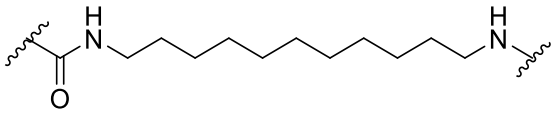


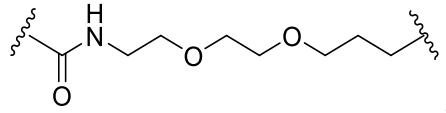


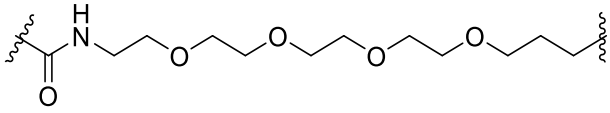


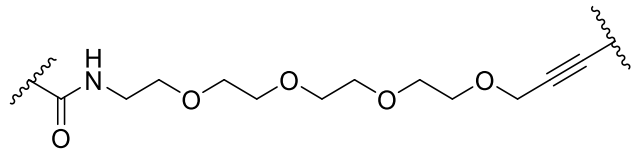


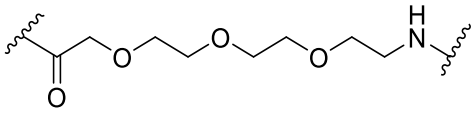


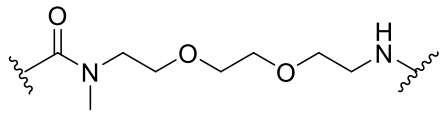


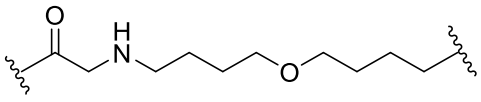


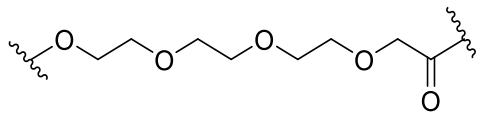


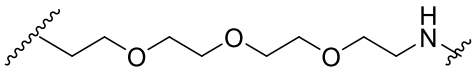


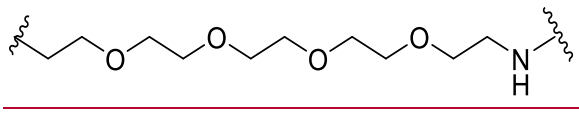


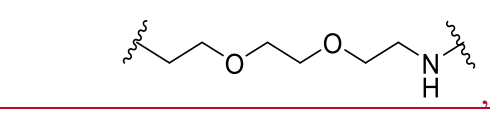


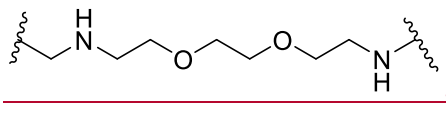




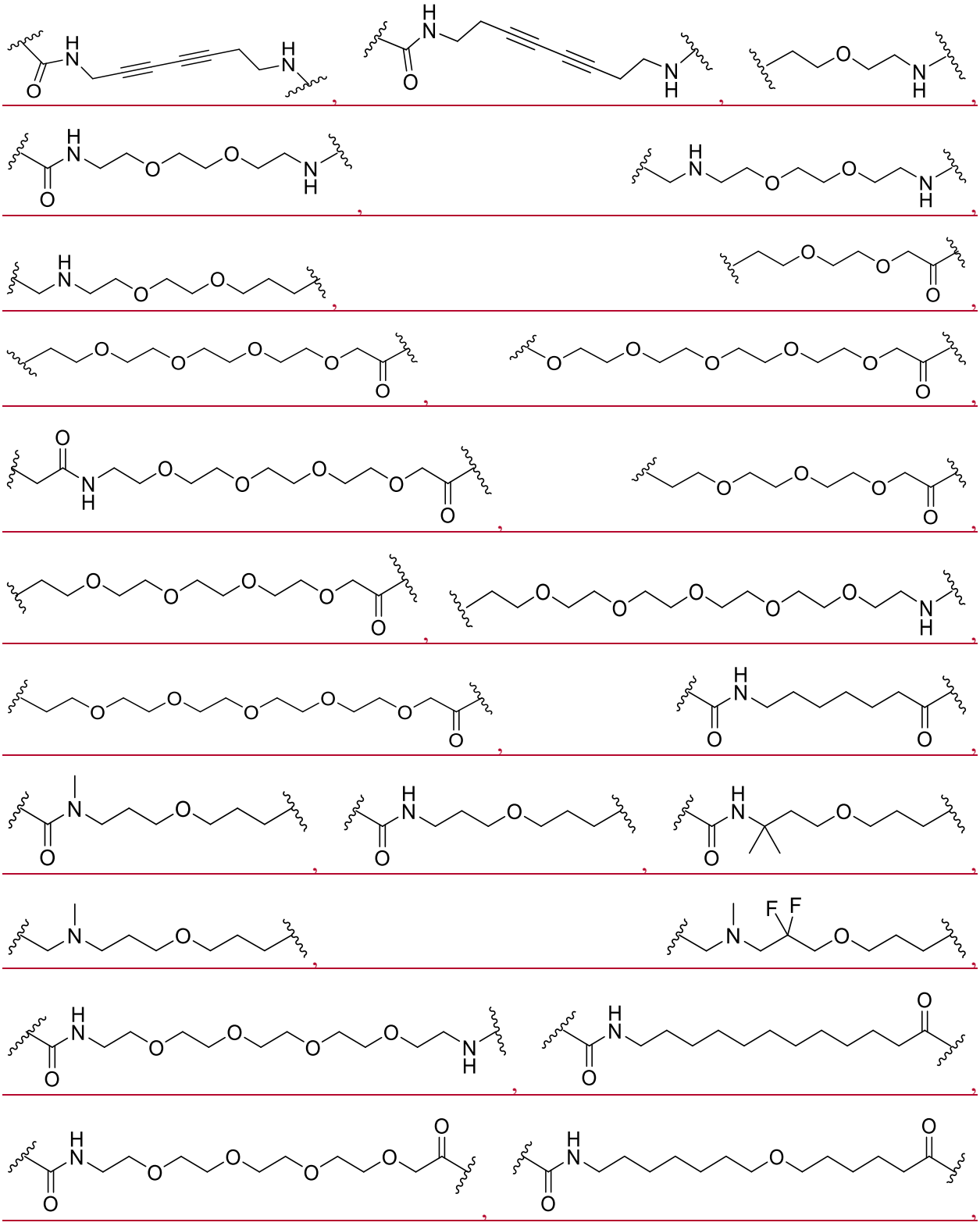


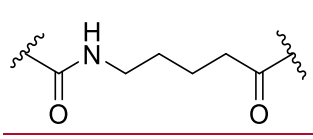


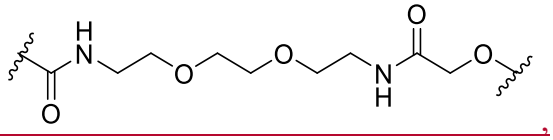


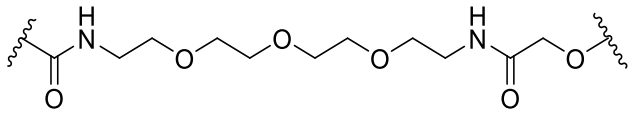


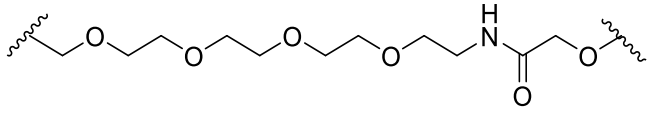


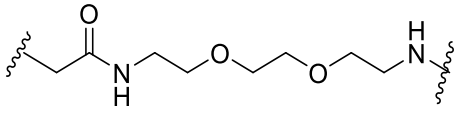


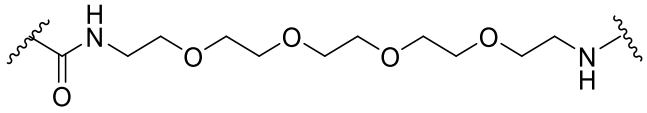


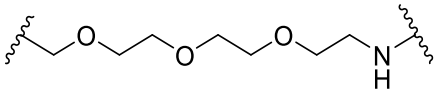


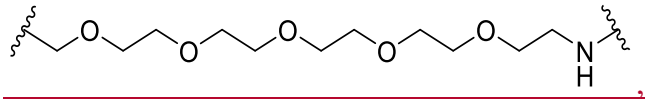


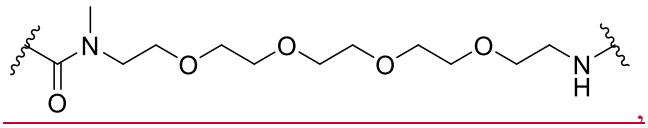


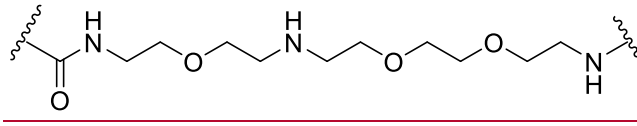


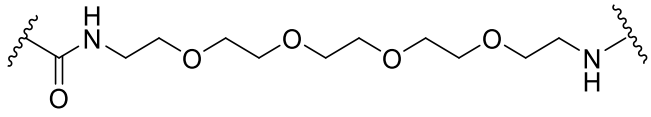


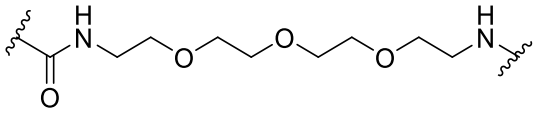


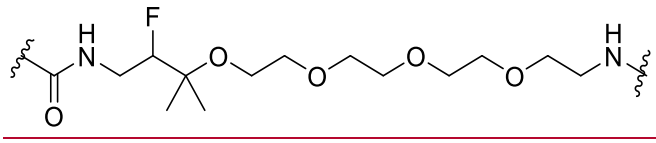


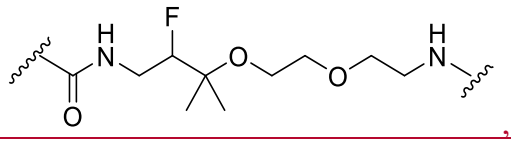


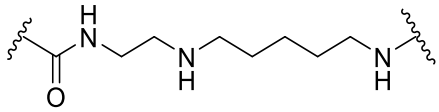


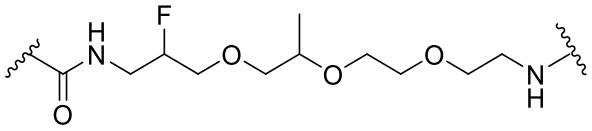


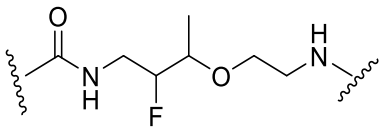


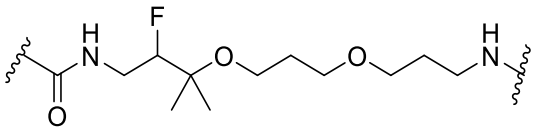


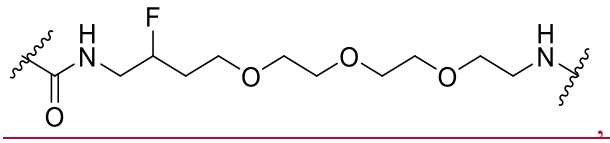


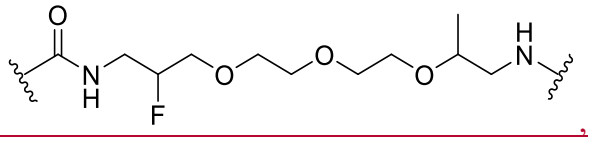


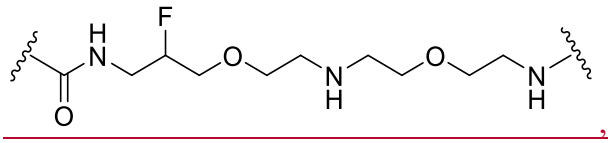


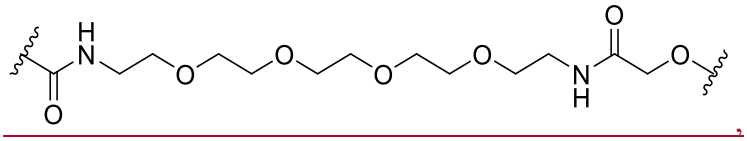


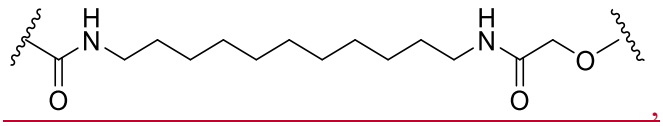


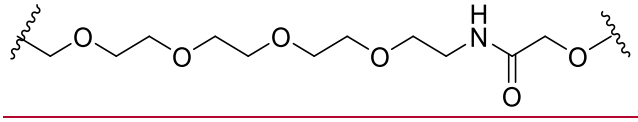


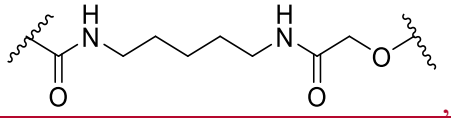


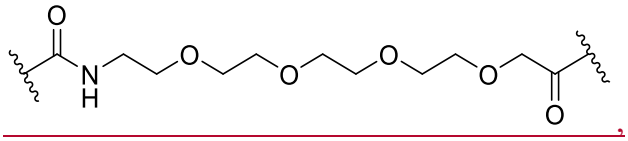


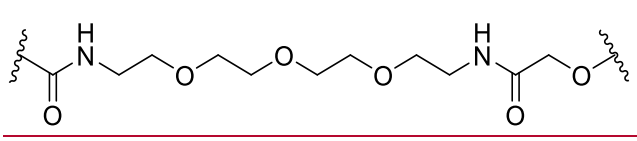


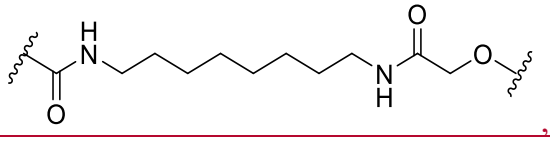


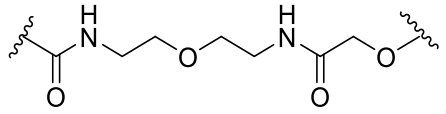


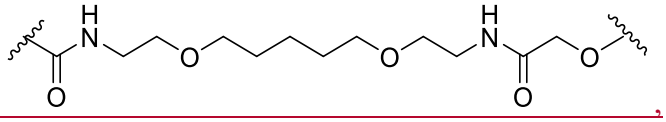


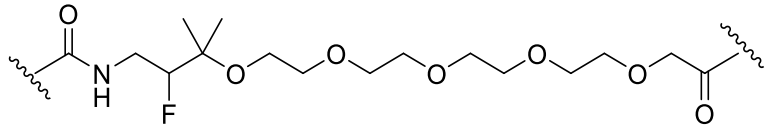


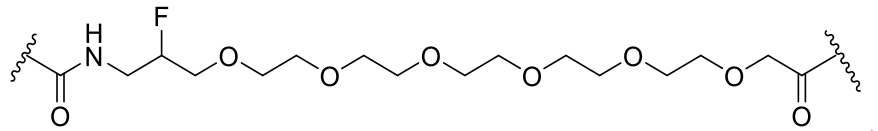


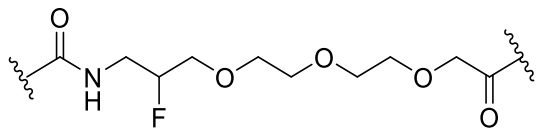


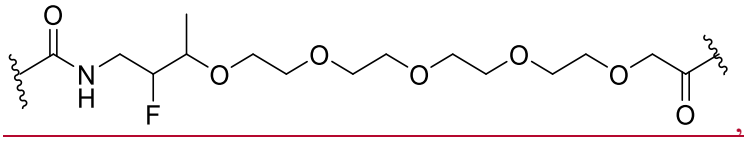


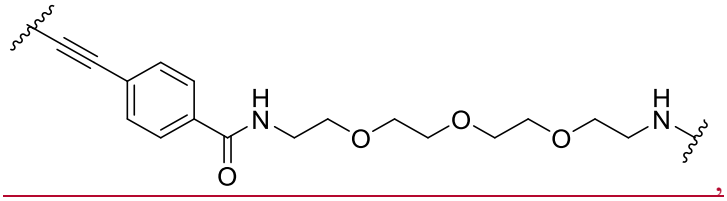


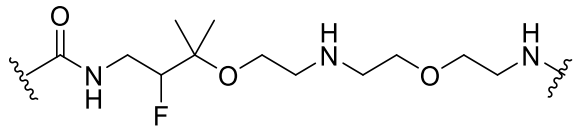


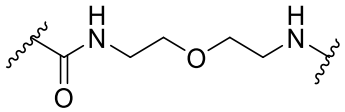


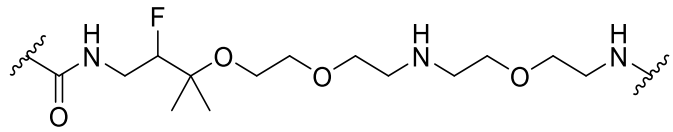


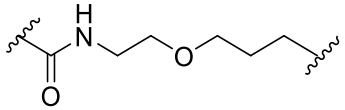


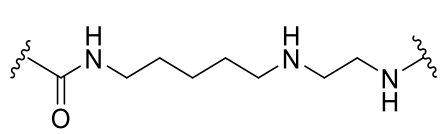


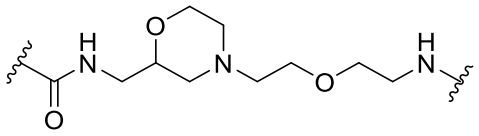


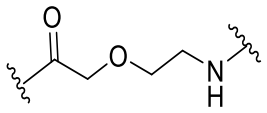


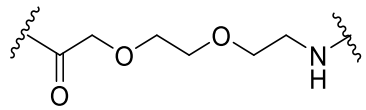


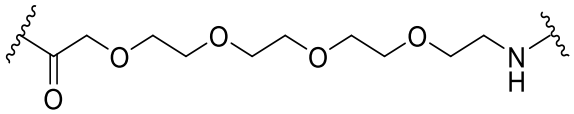


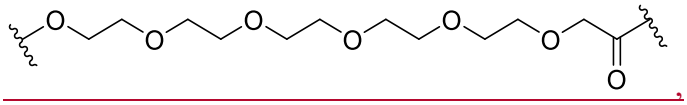


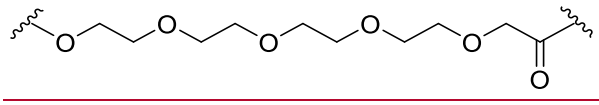


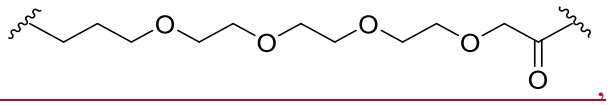


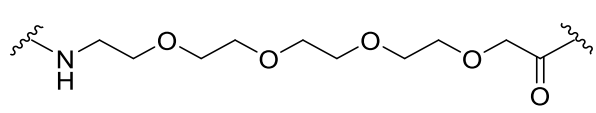


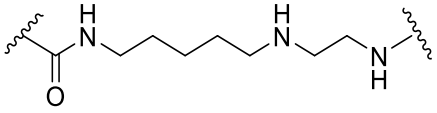


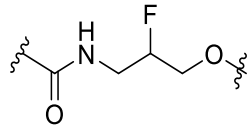


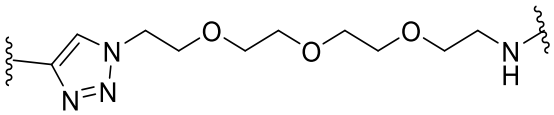


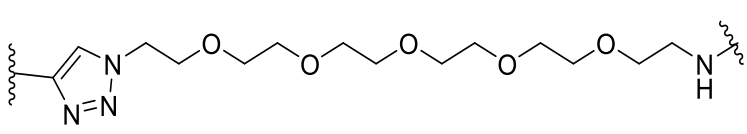


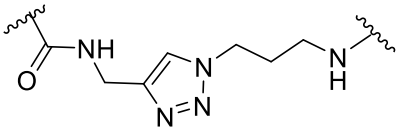


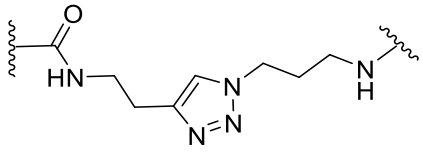


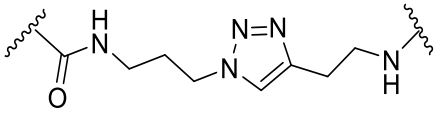


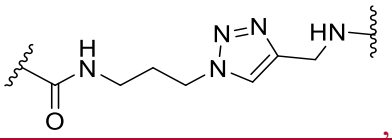


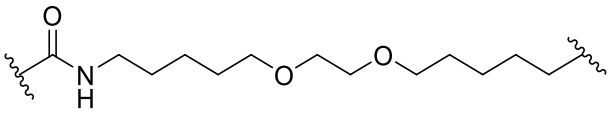


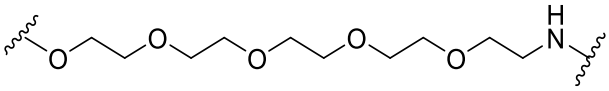


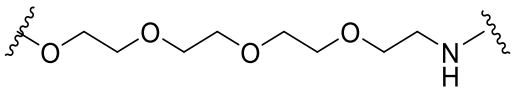


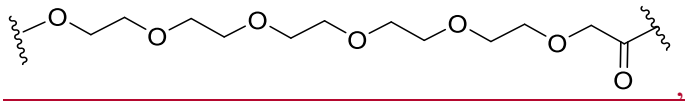


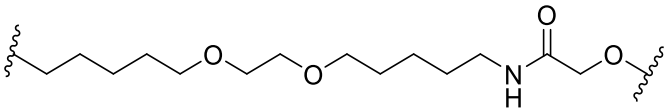


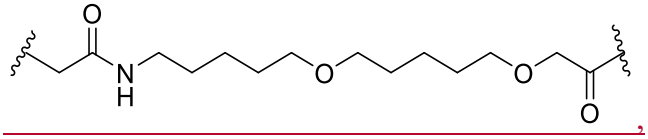


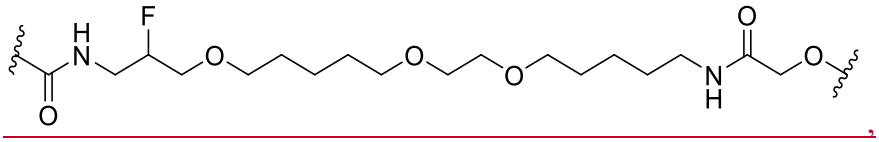


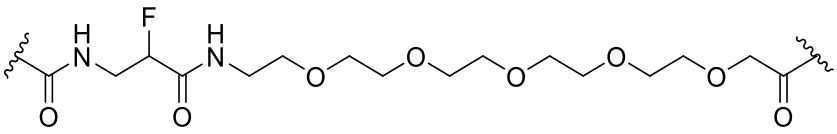


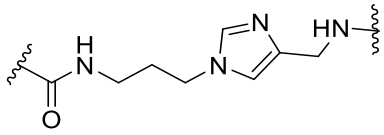


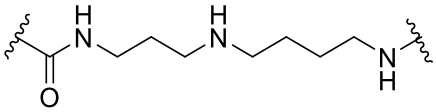


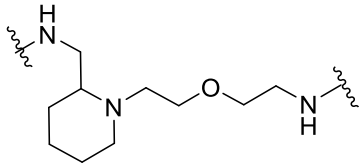


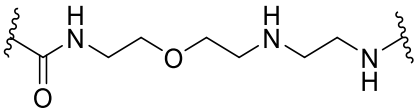


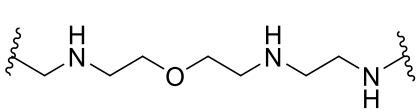


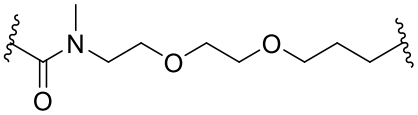


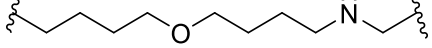




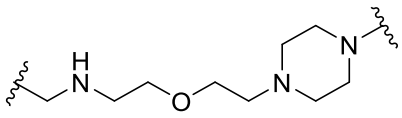
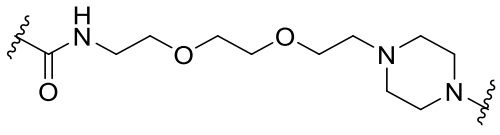
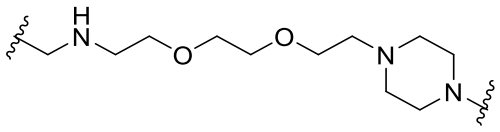
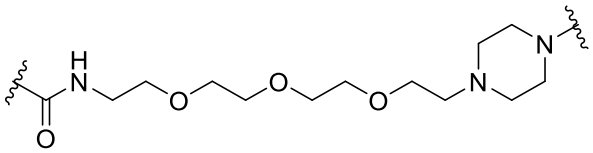
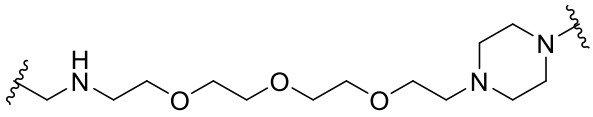
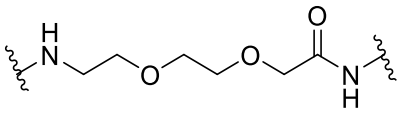
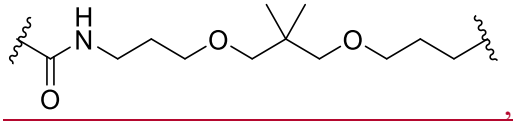
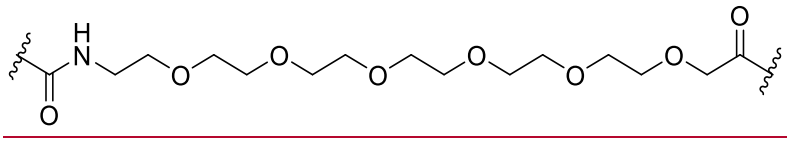
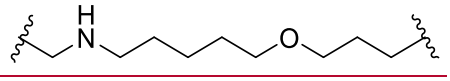
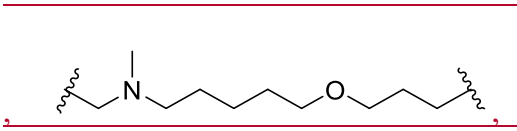
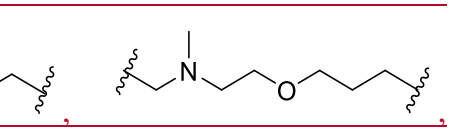


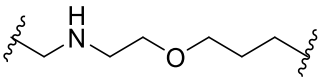


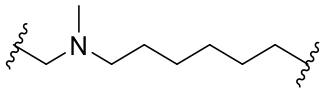
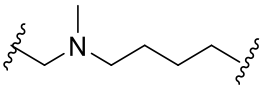
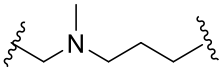
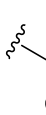


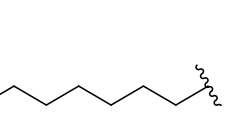
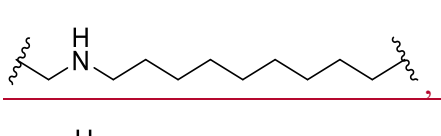
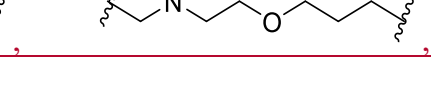


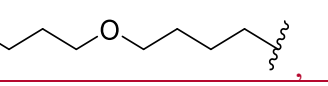
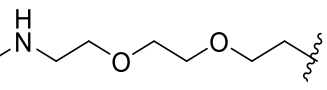
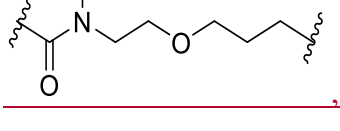
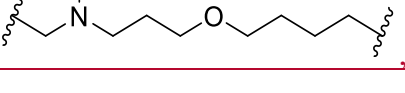
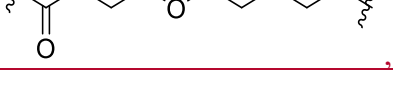
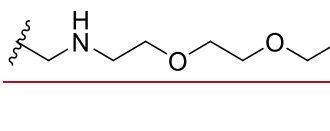


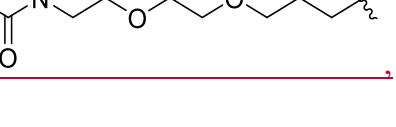












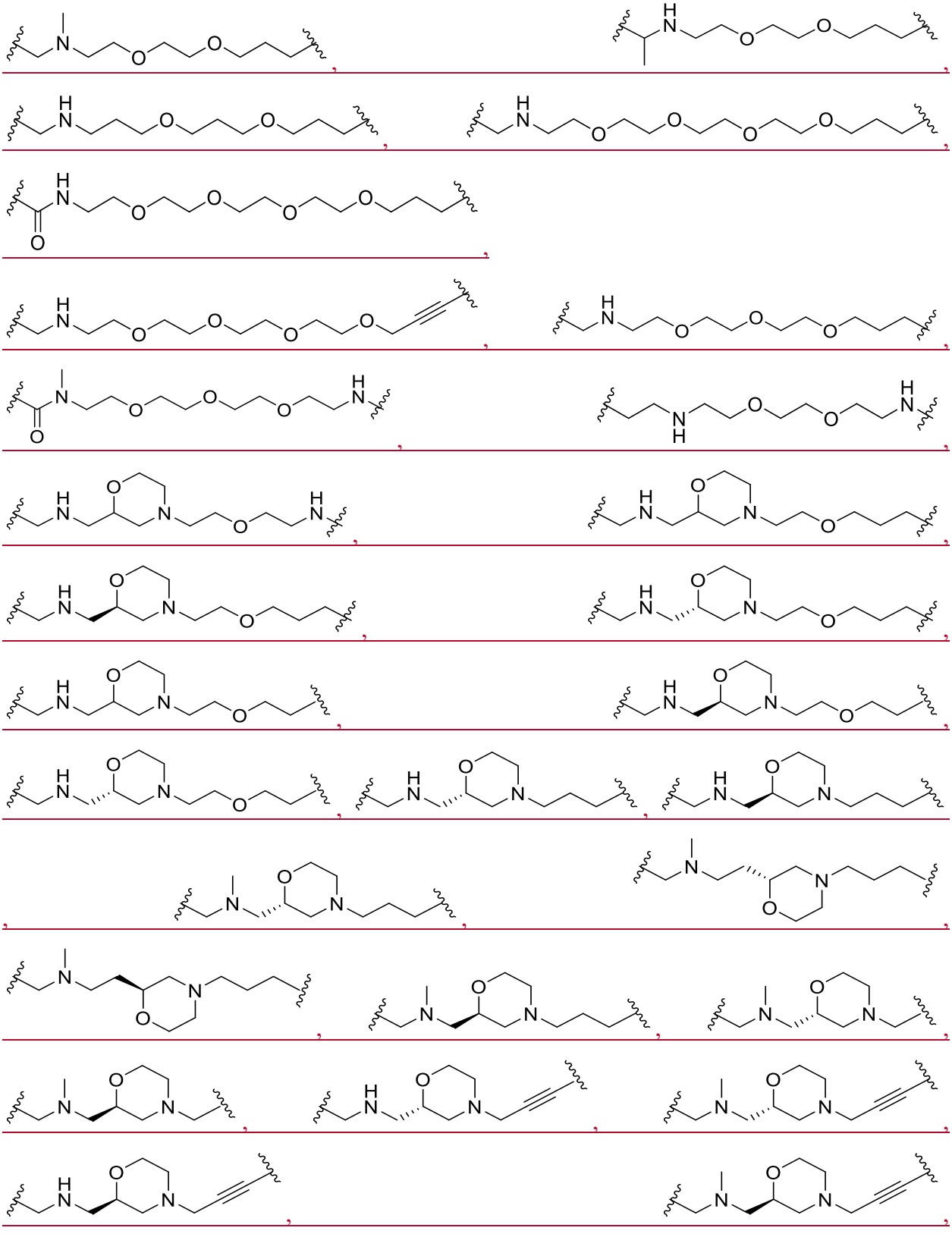


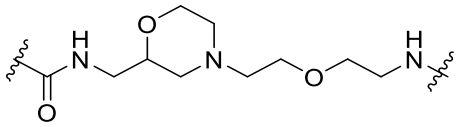
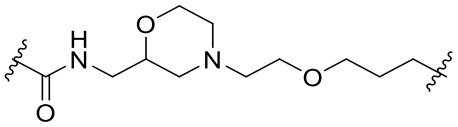
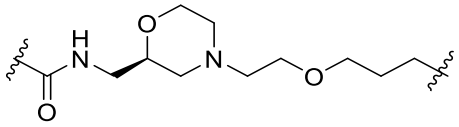
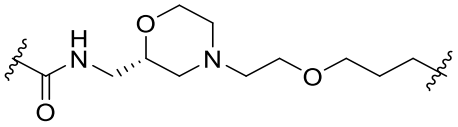
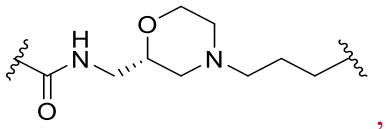
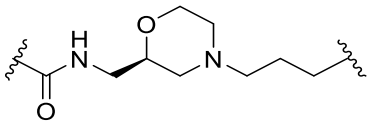
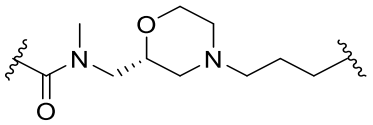
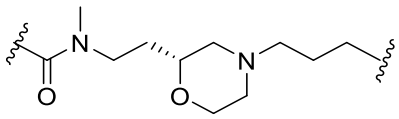
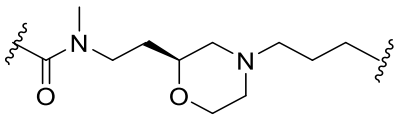
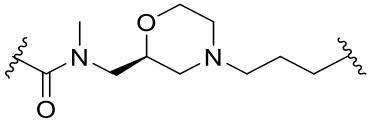
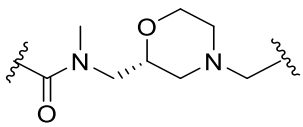
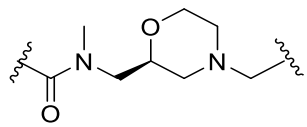
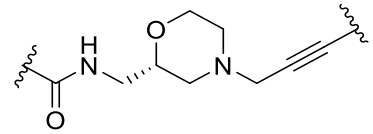





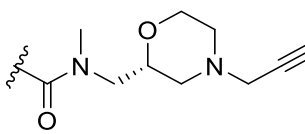
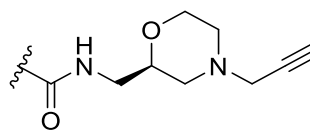




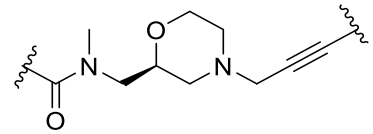
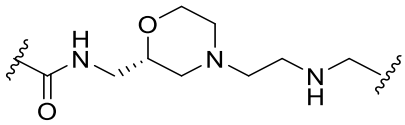
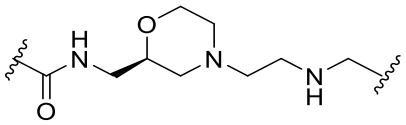
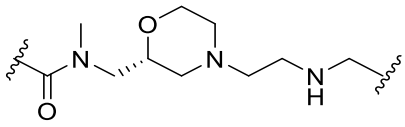
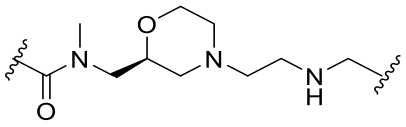
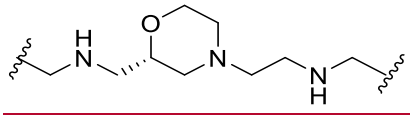
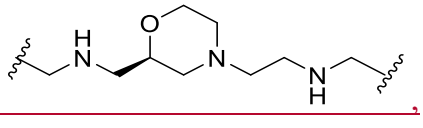
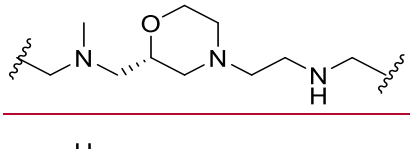
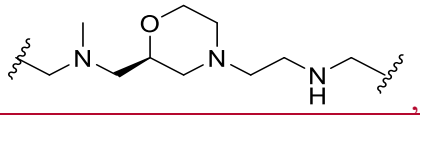
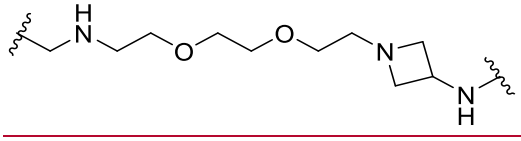
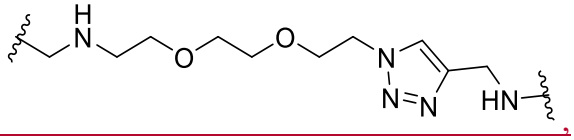







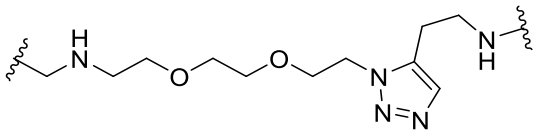


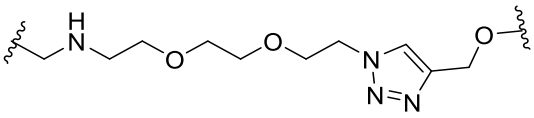


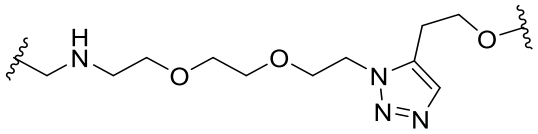














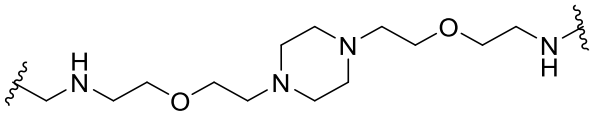



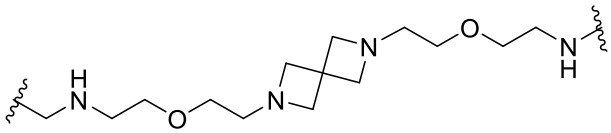












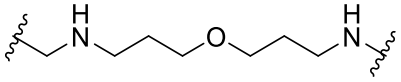


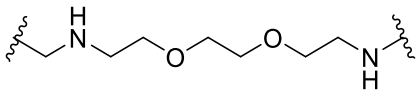


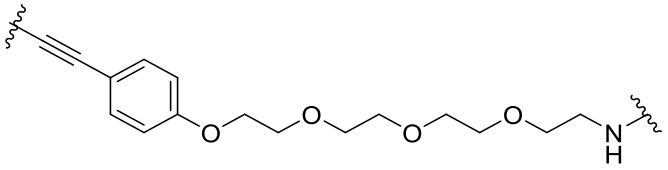


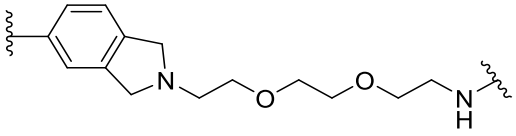


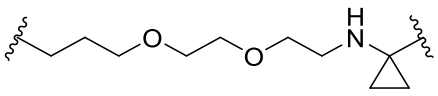


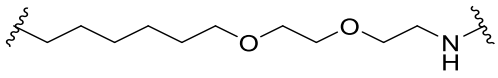


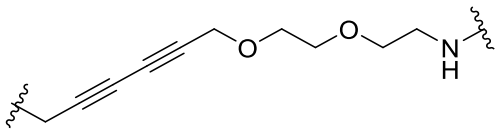


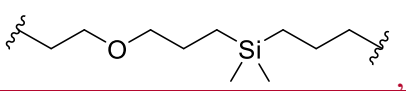


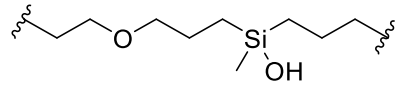


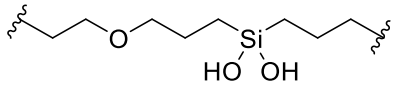


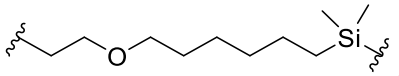


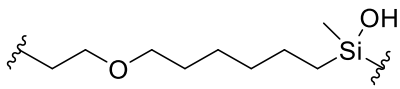


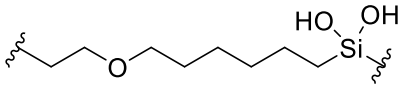


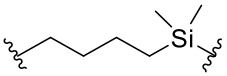


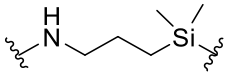


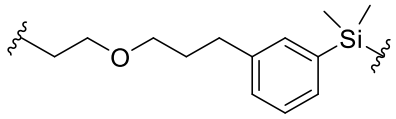


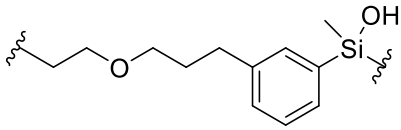


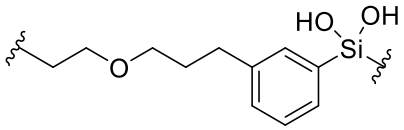


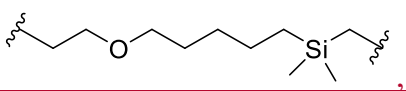


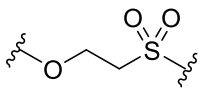


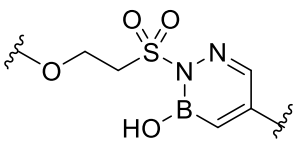


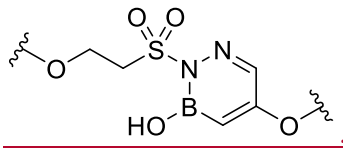
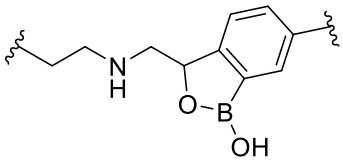
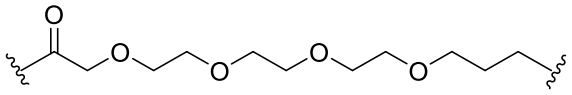
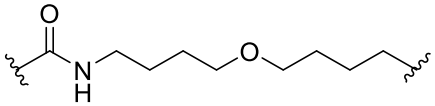
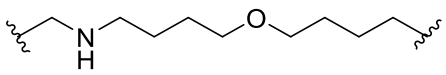
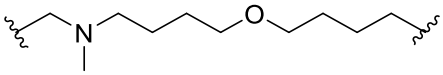
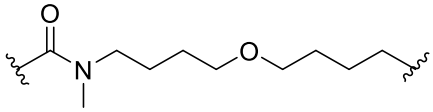
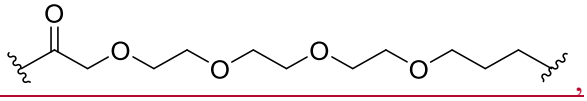
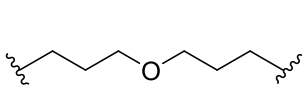
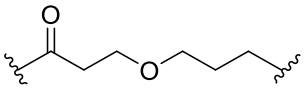
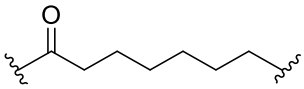
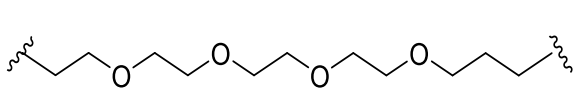
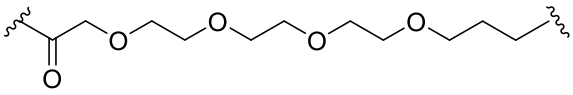
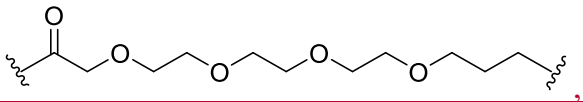
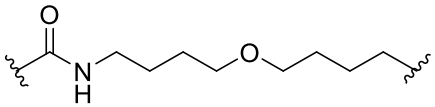
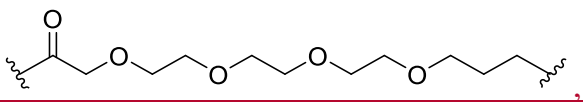
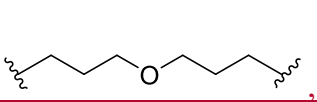
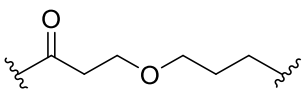
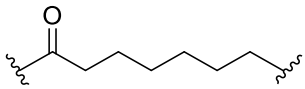
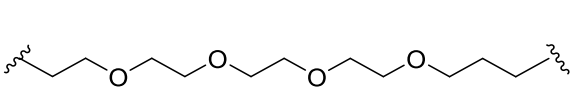
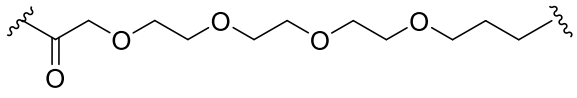
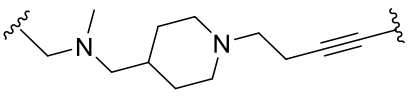
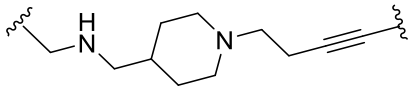
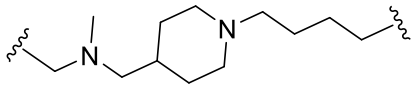
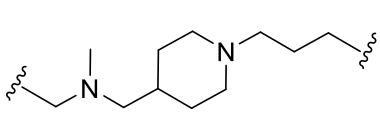
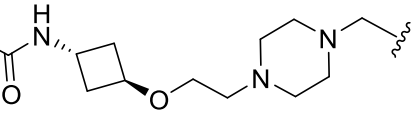


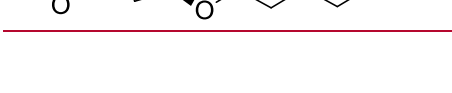
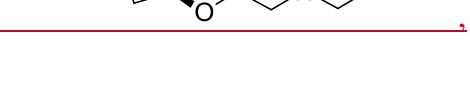


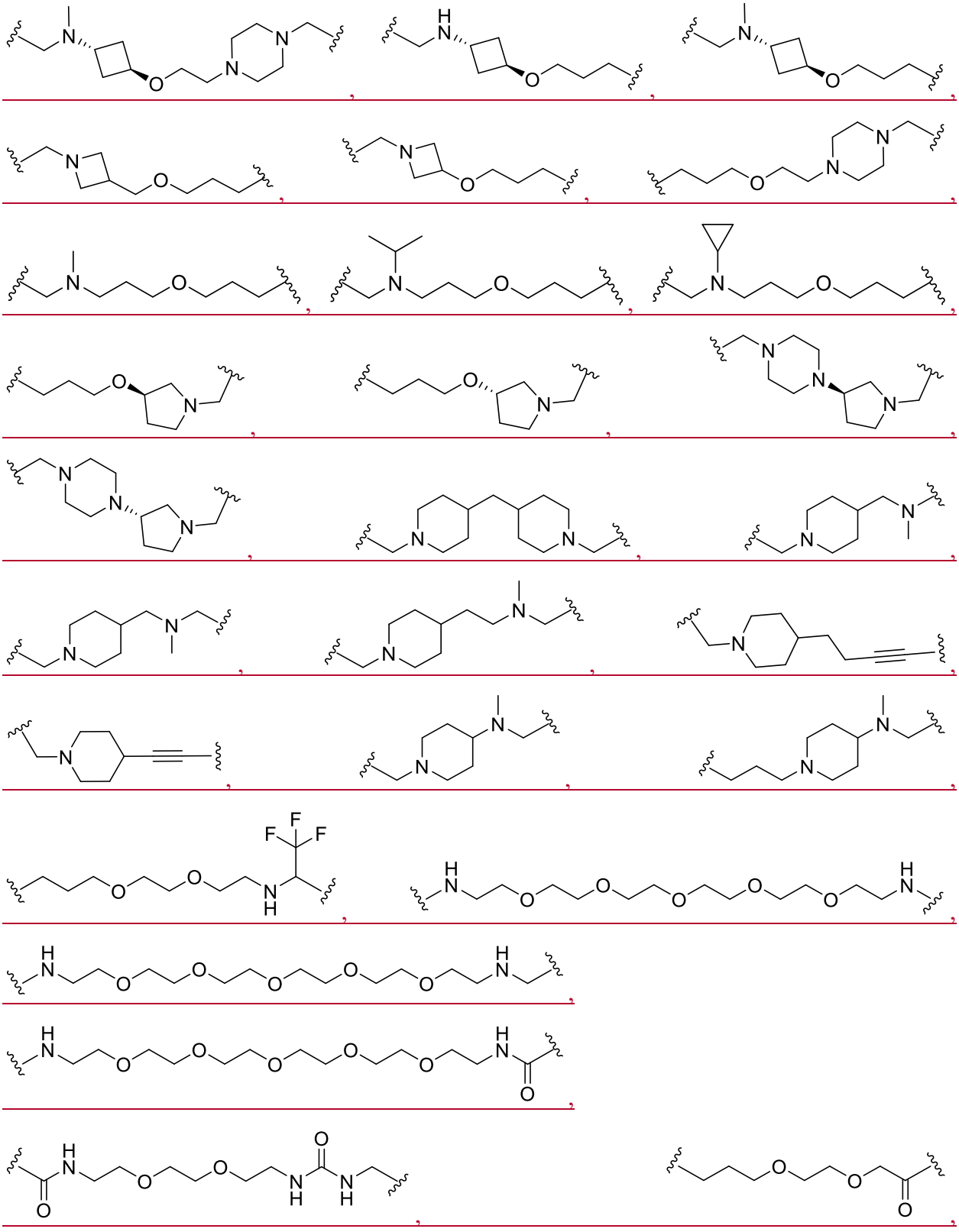


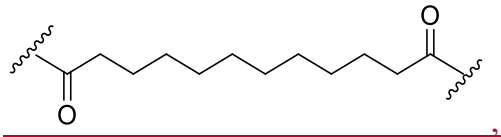
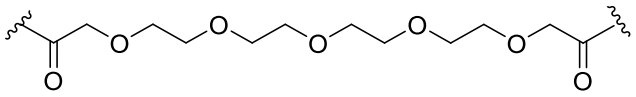
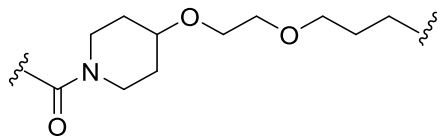
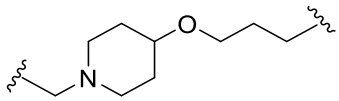
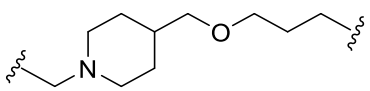
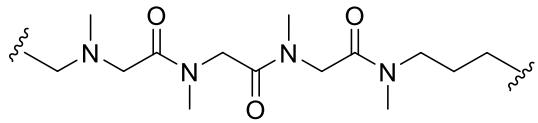
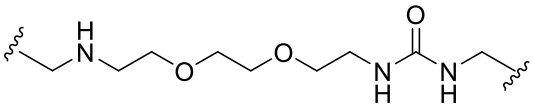
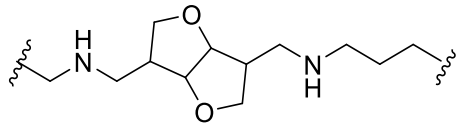
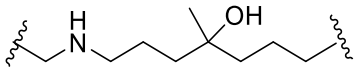
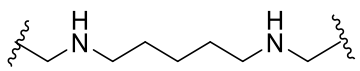
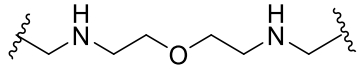
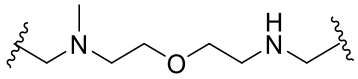
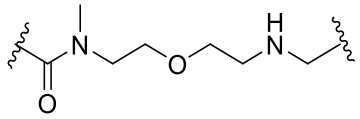
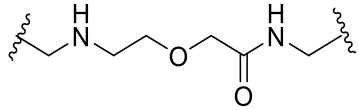
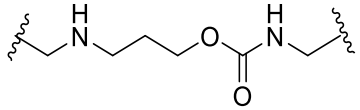
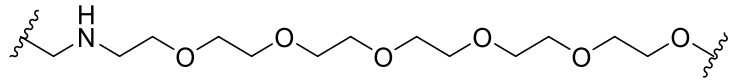
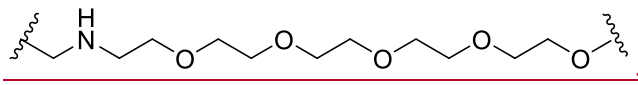
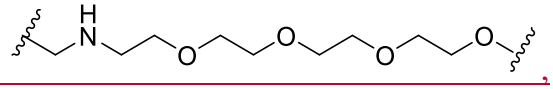
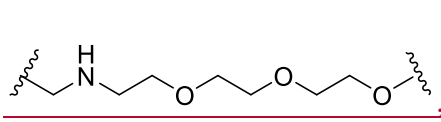
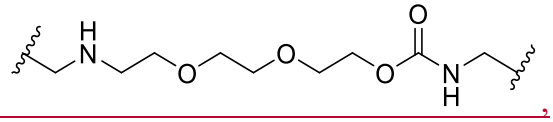
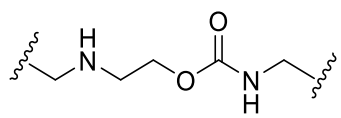
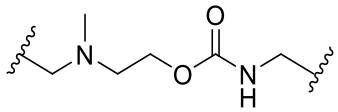
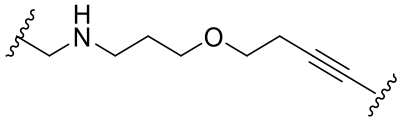
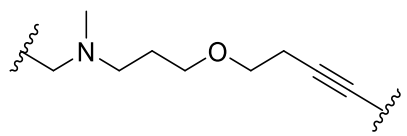
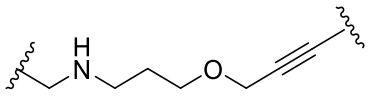
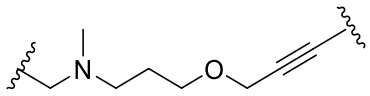


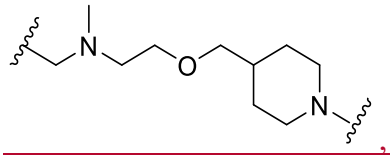
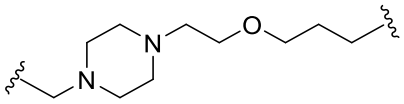
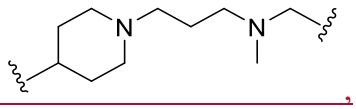
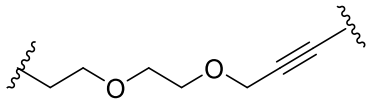
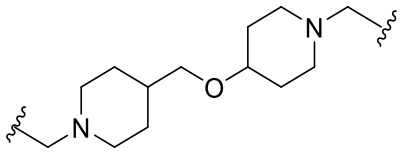
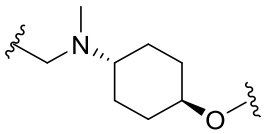
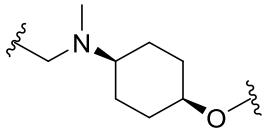
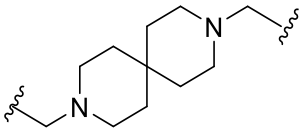
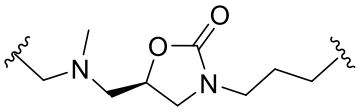
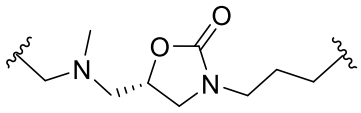
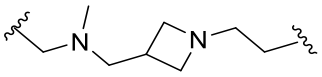
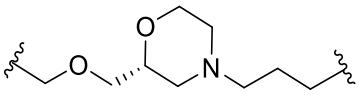
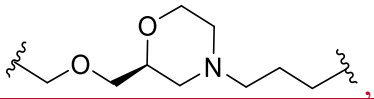
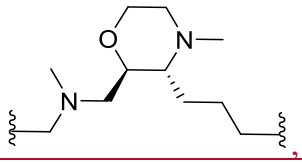
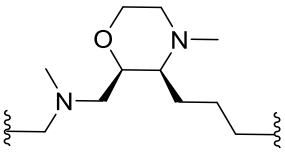
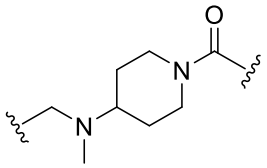
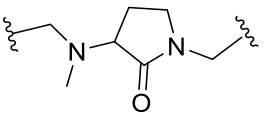
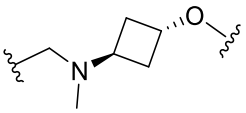
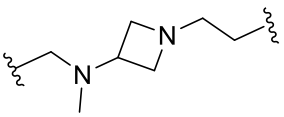
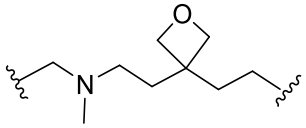
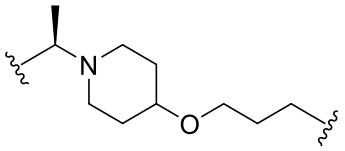
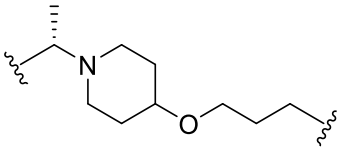
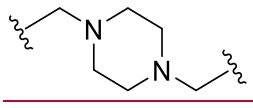
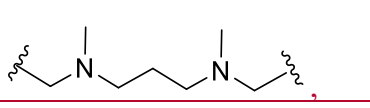
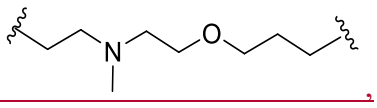
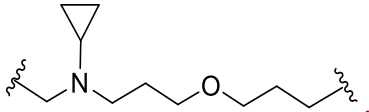
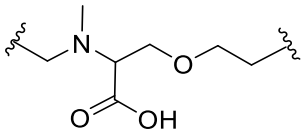
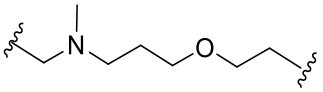
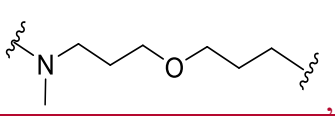
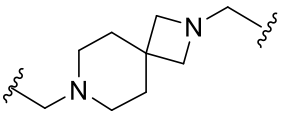
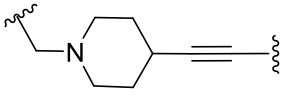


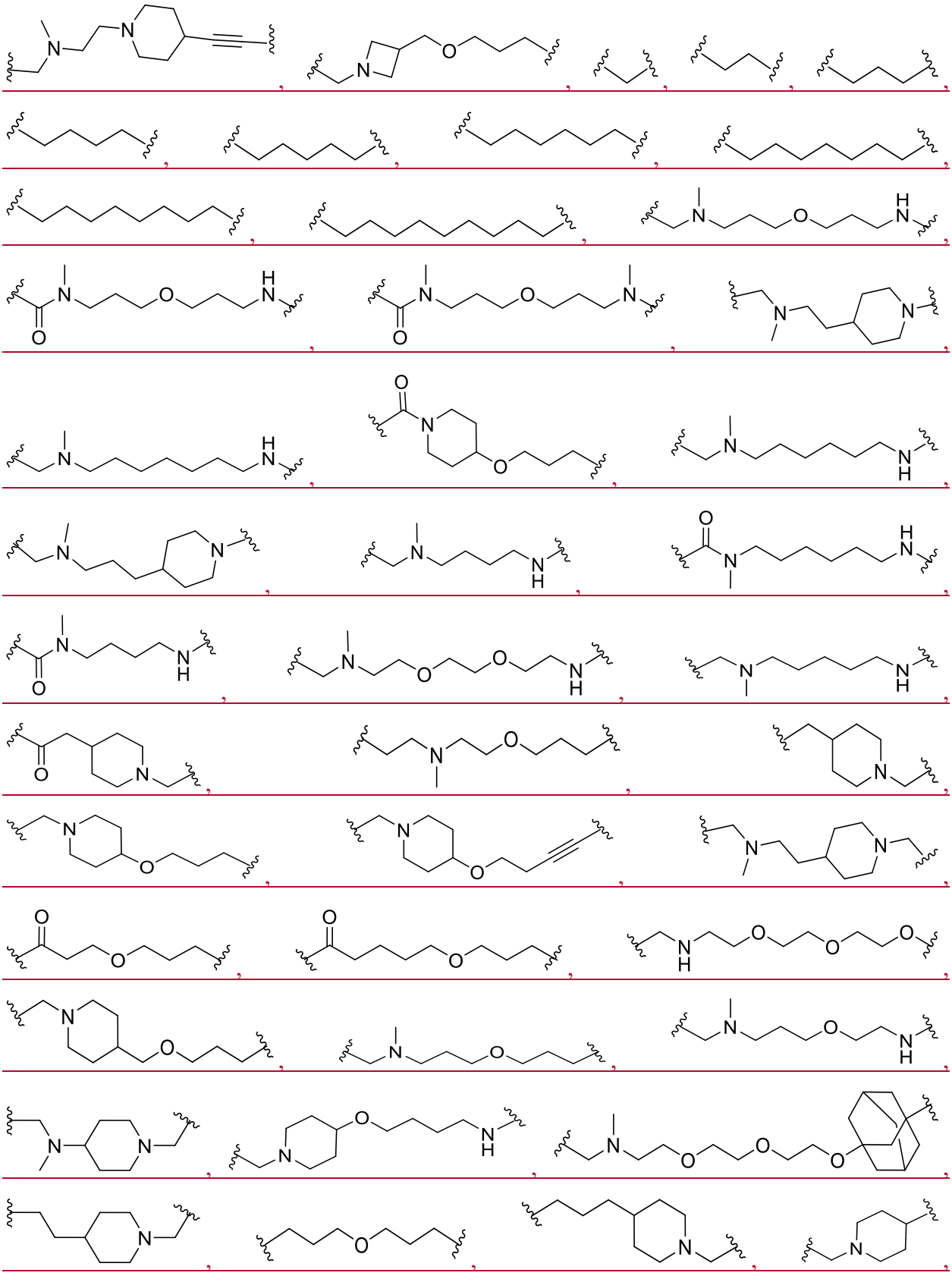



























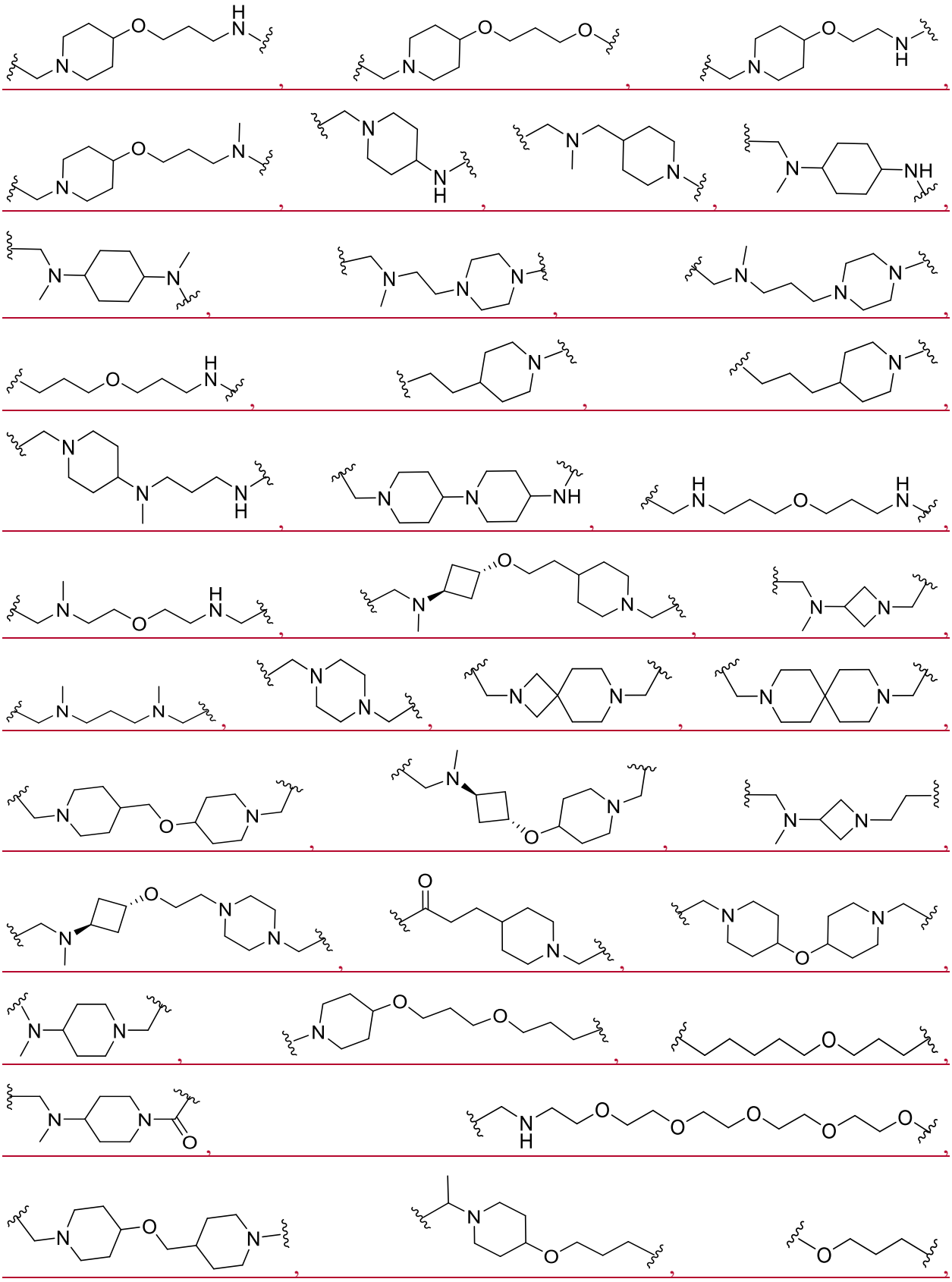




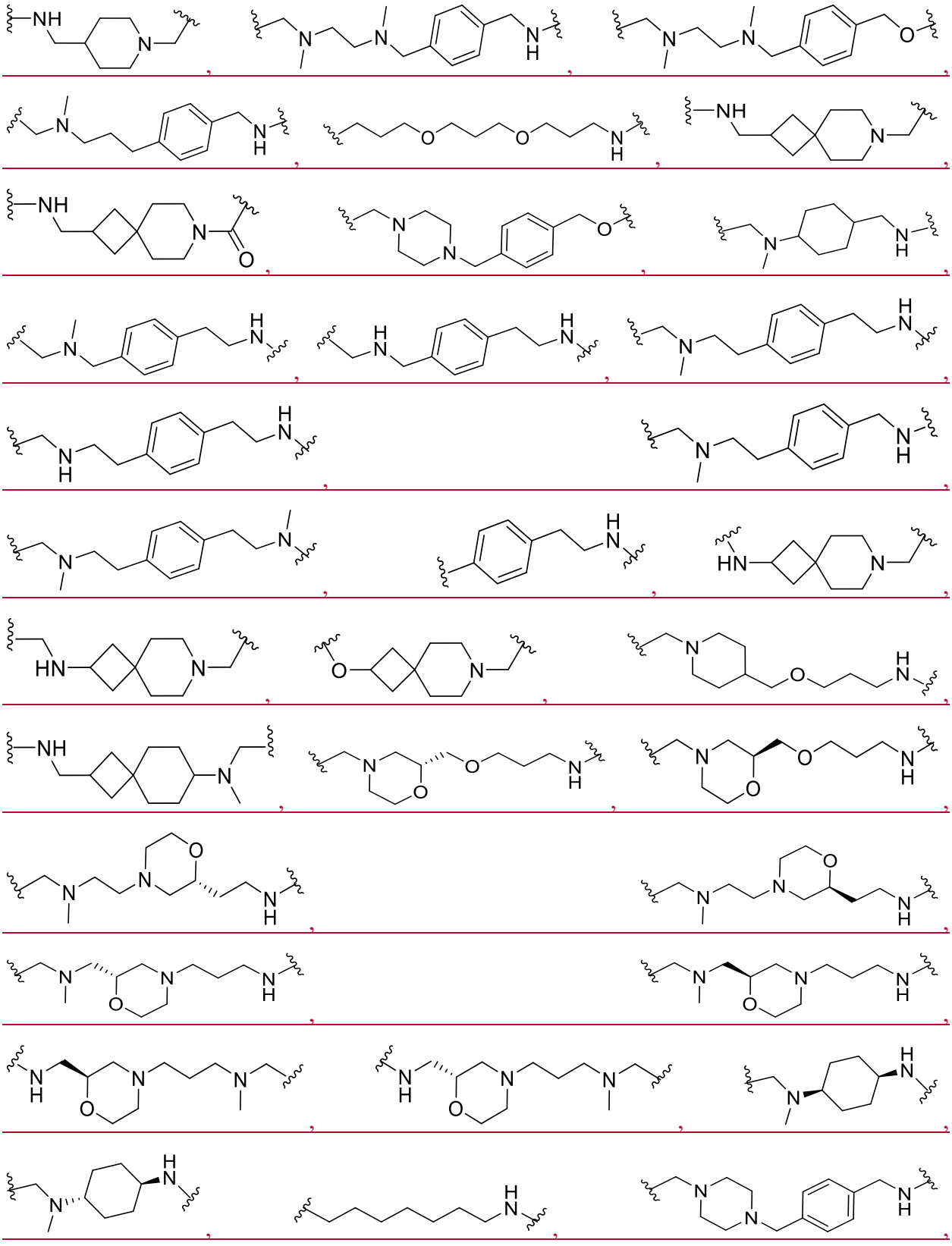


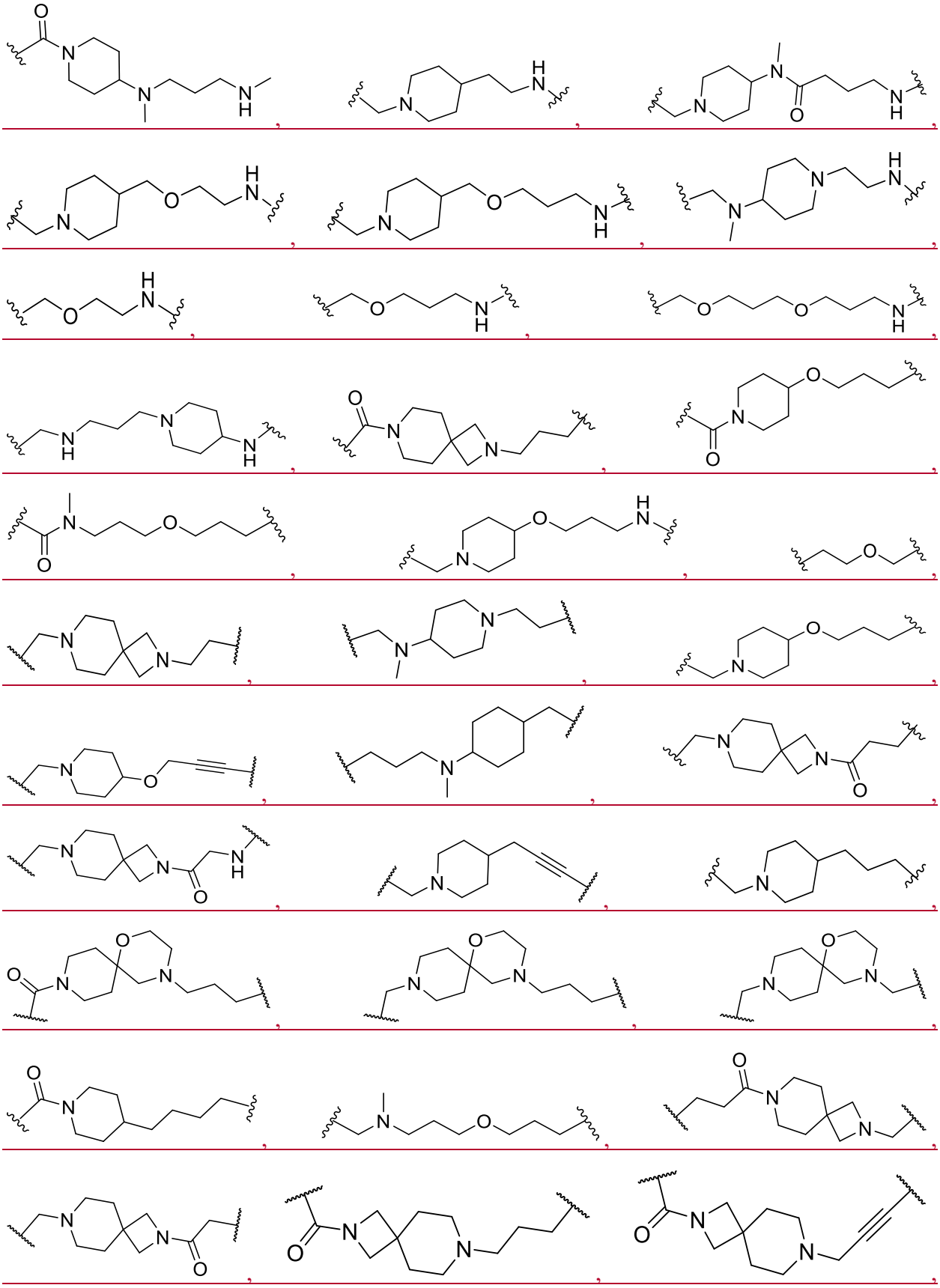



























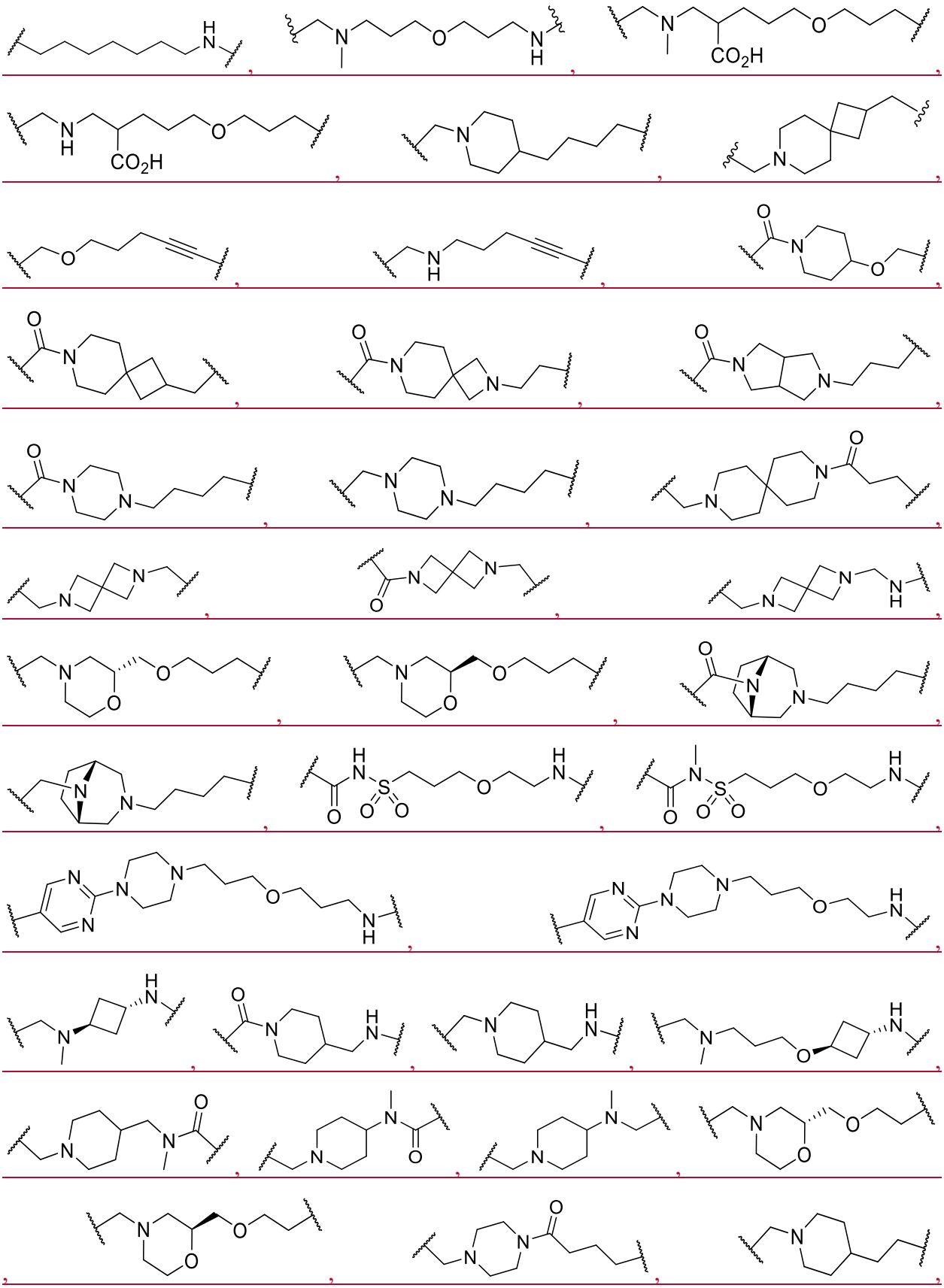
































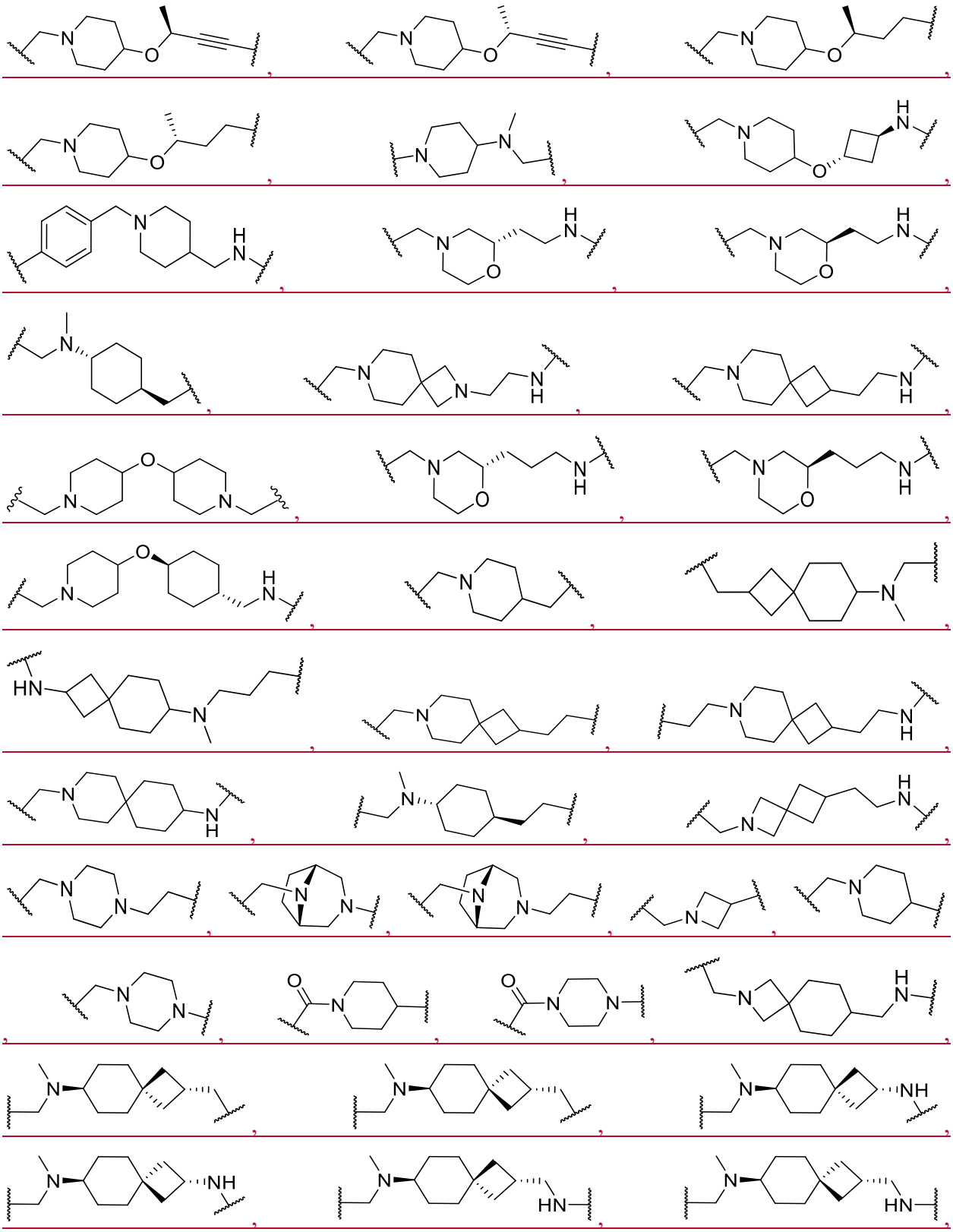


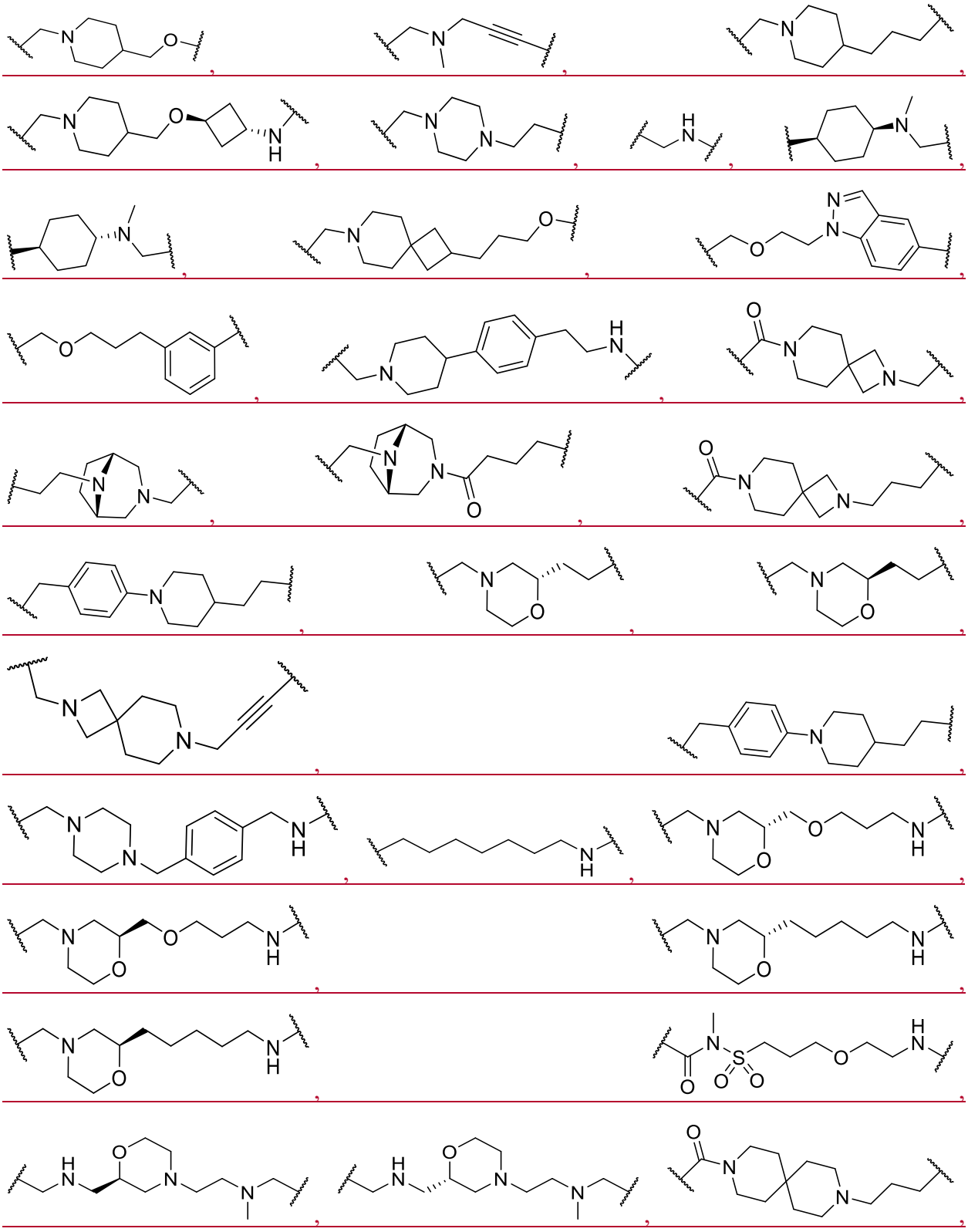


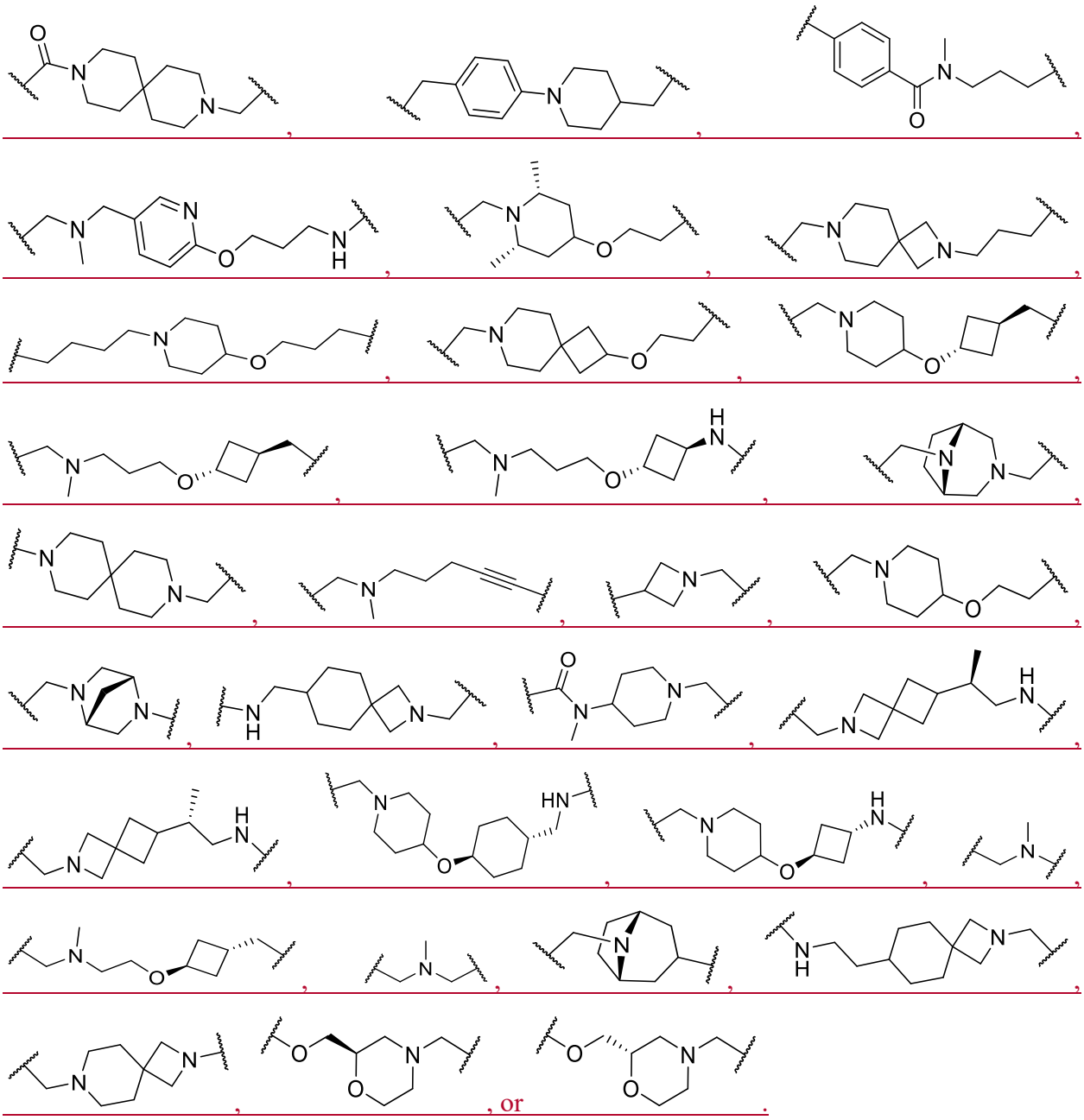




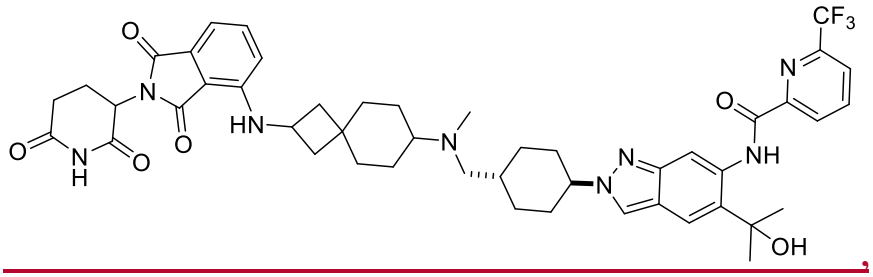


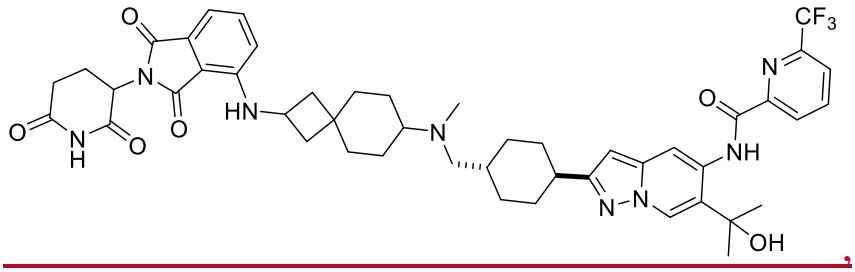


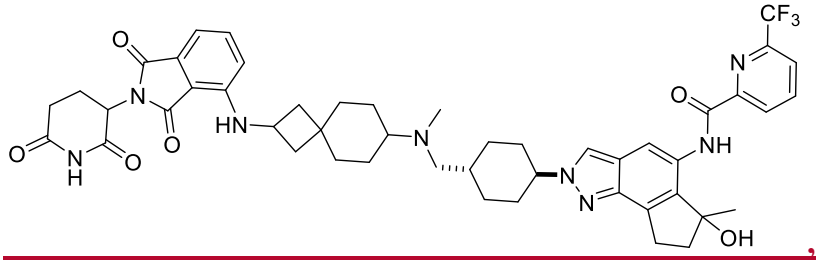


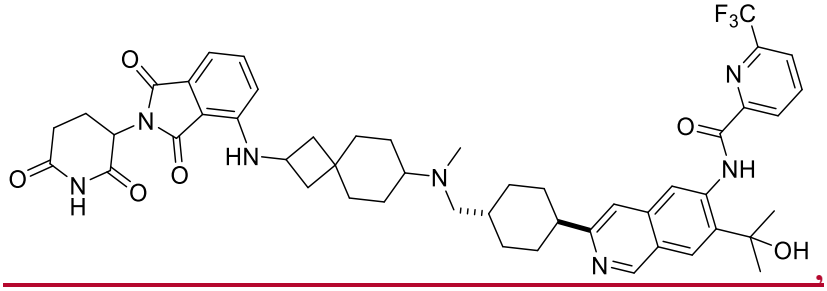


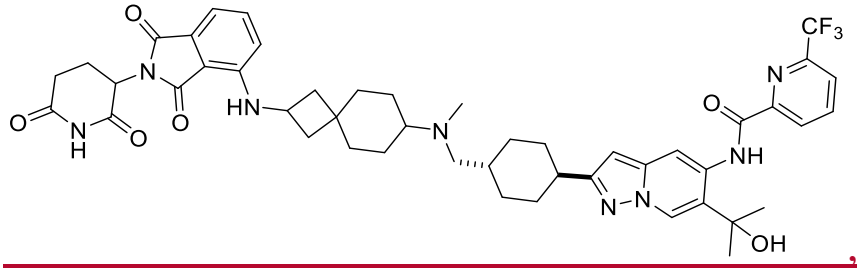
~~17~~14. The compound of any of one of claims 1-~~16~~13, wherein said compound is selected from any one of the following compounds:

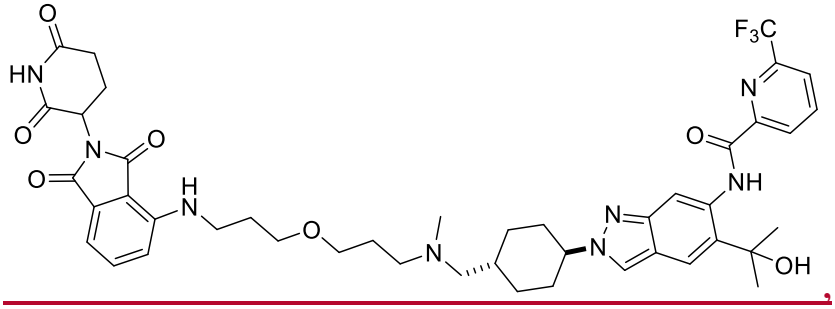
I-2  ,

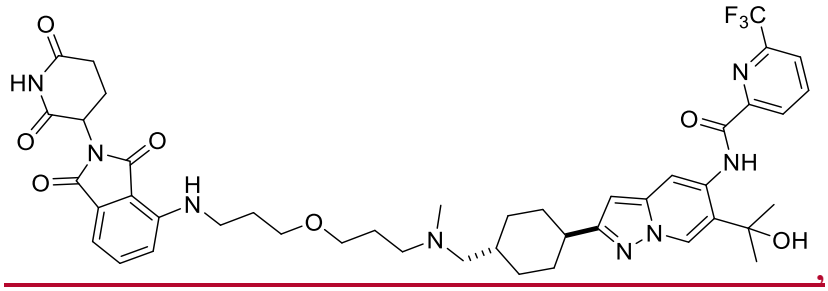
I-3  ,

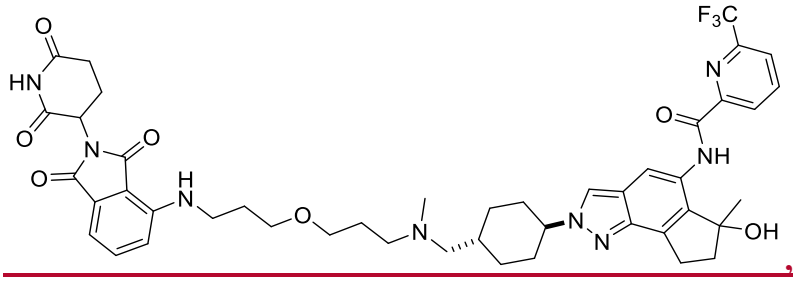
I-4  ,

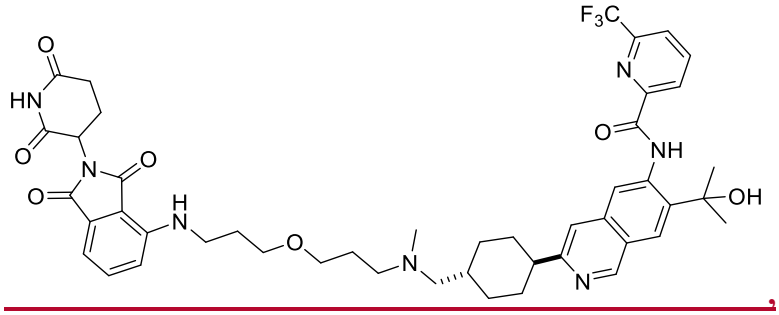
I-5  ,

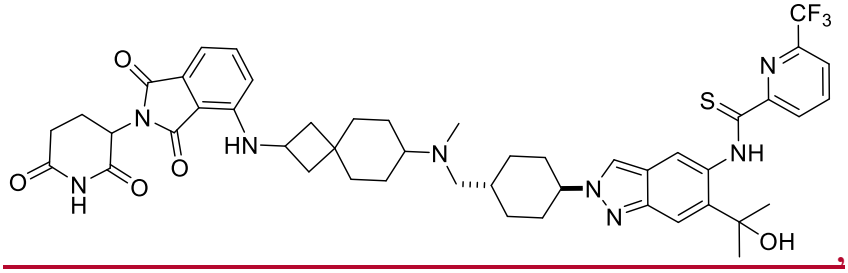
I-6  ,

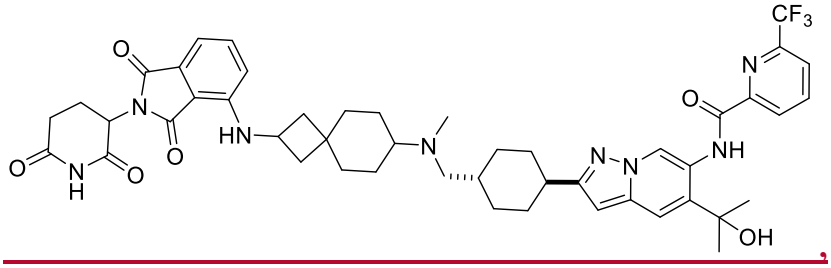
I-7  ,

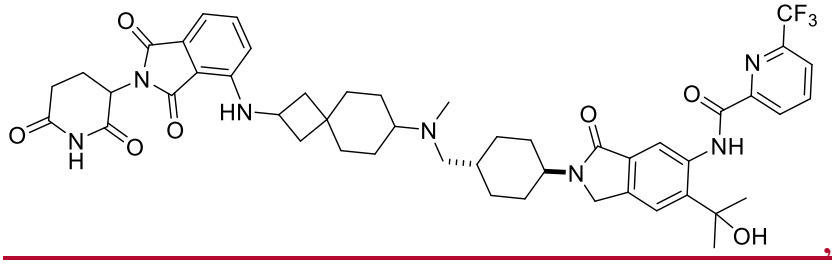
I-8 

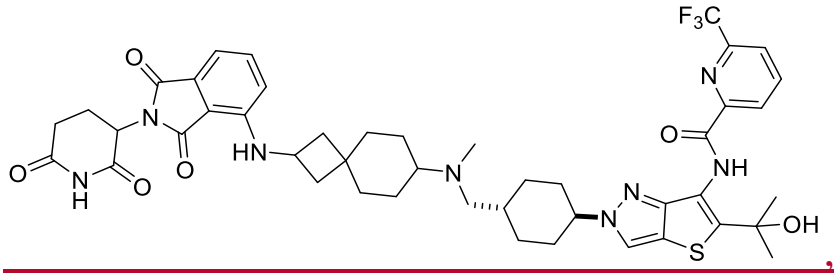
I-9 

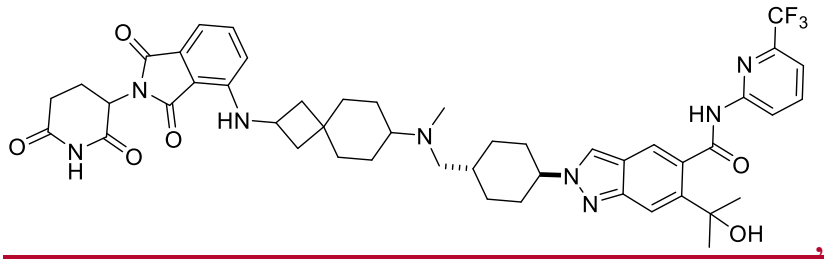
I-10 

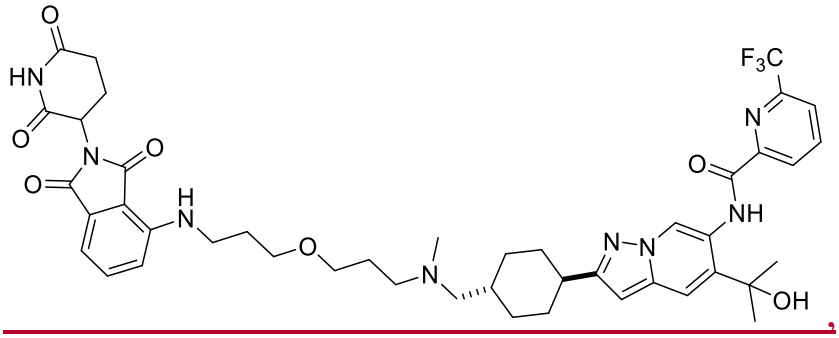
I-11 

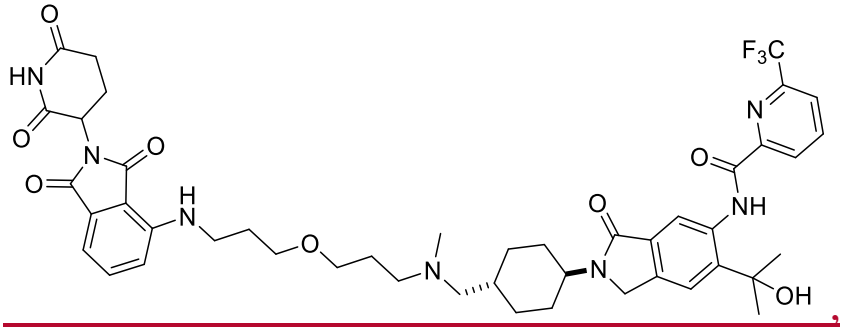
I-12 

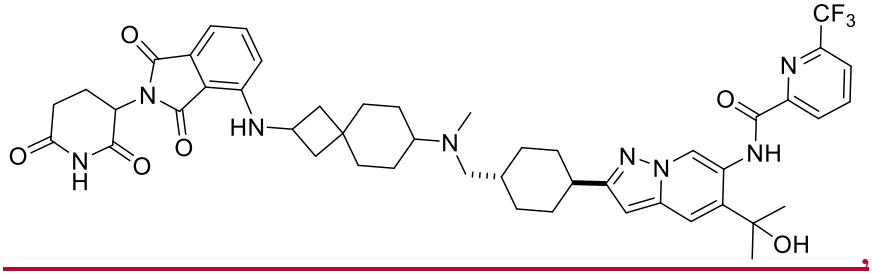
I-14 

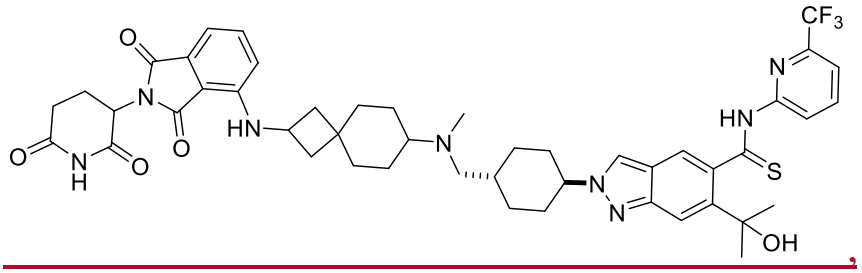
I-15 

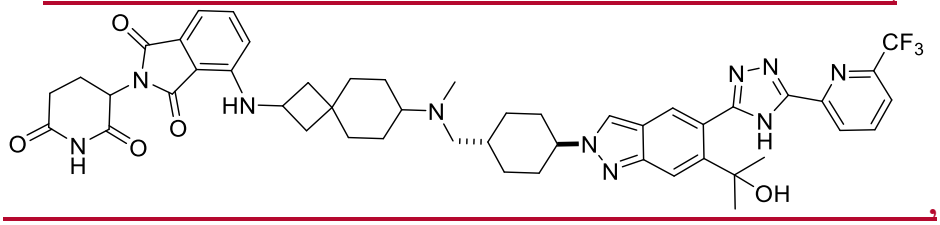
I-16 

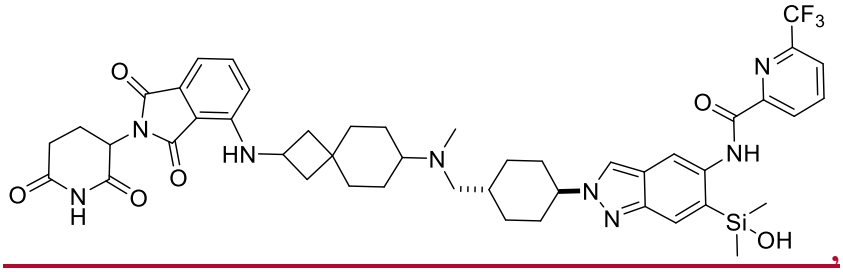
I-17 

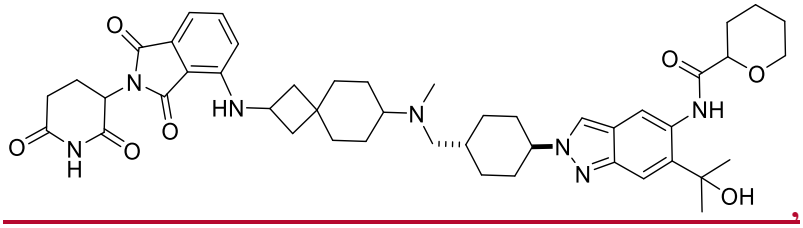
I-19 

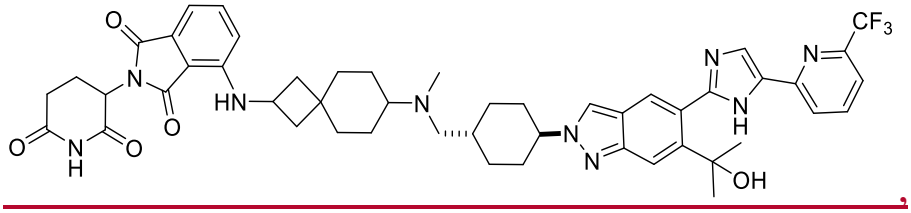
I-20 

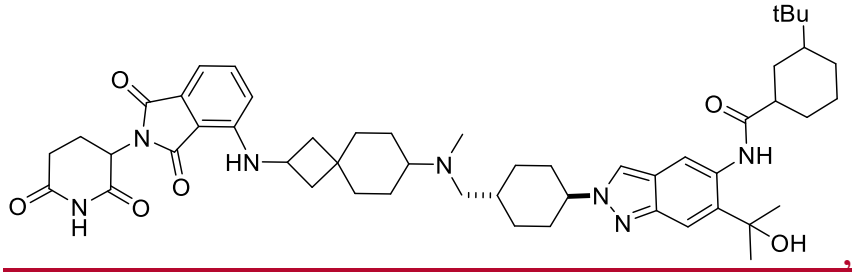
I-21 

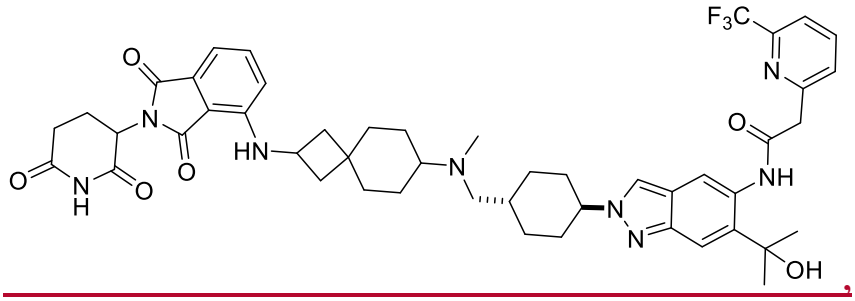
I-22 

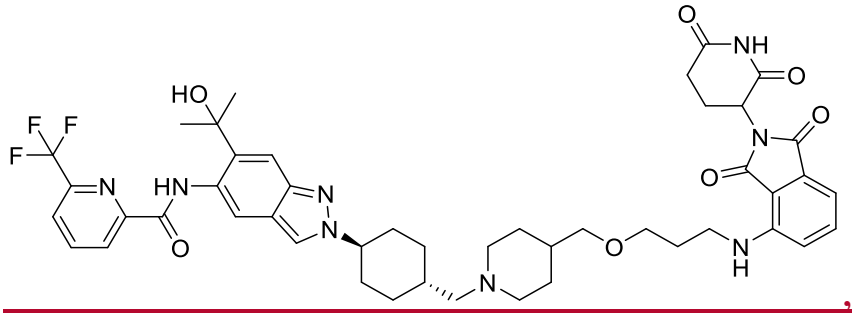
I-23 

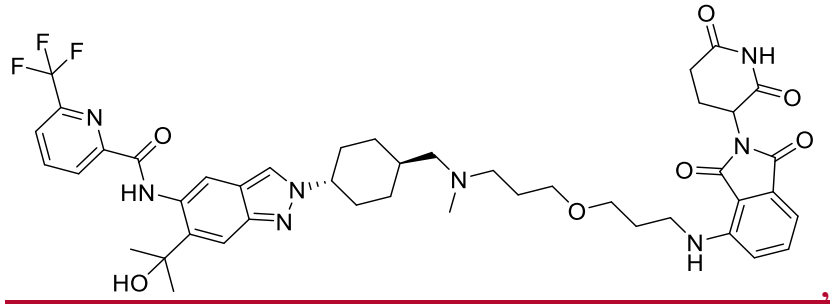
I-24 

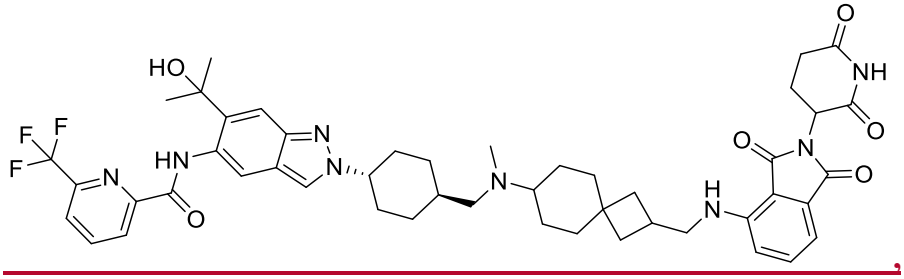
I-26 

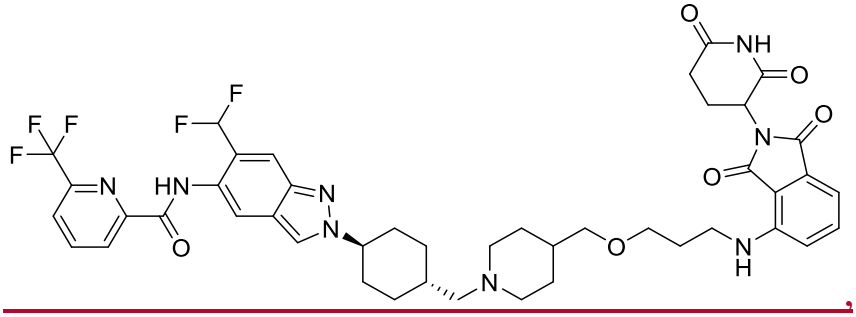
I-27 

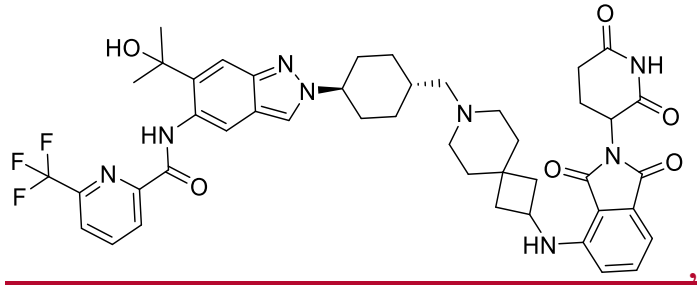
I-28 

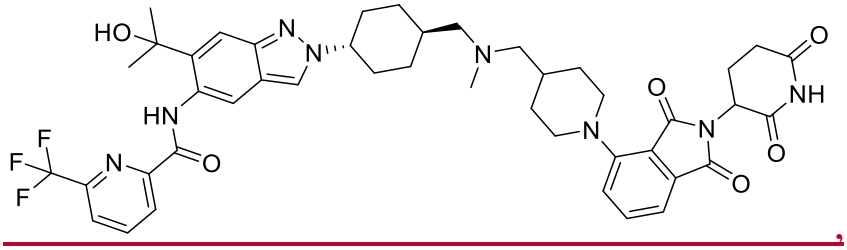
I-29 

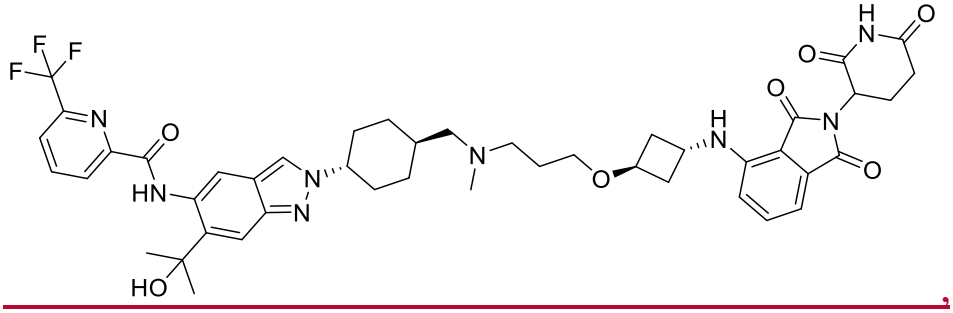
I-31 

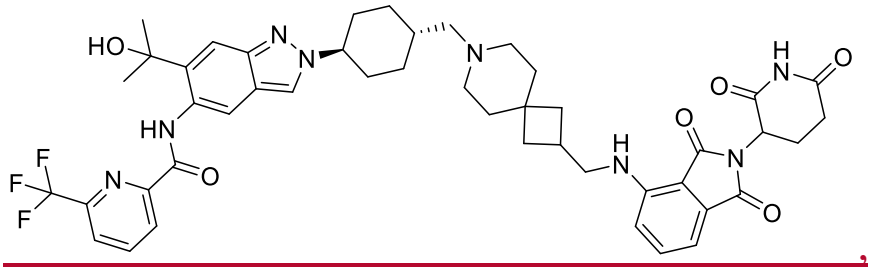
I-32 

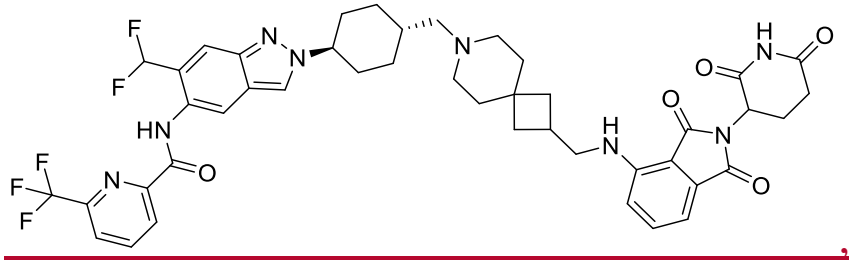
I-33 

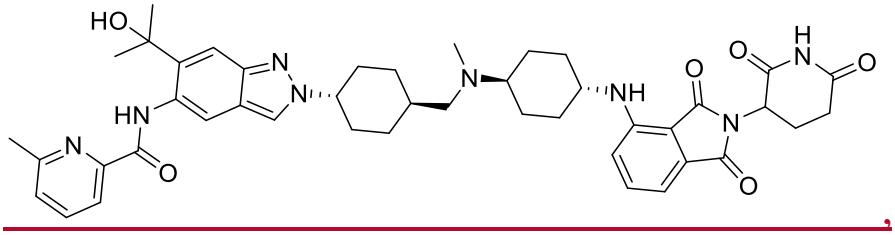
I-35  ,

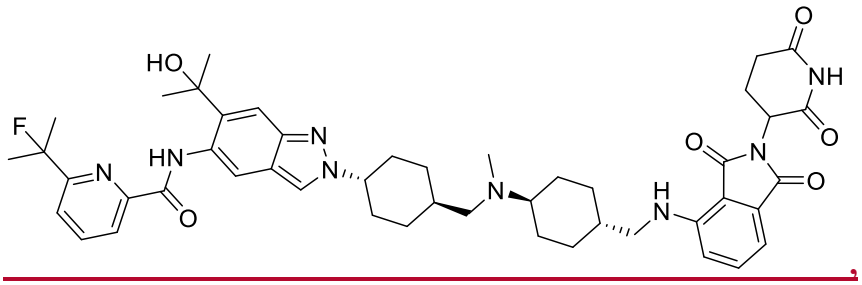
I-40  ,

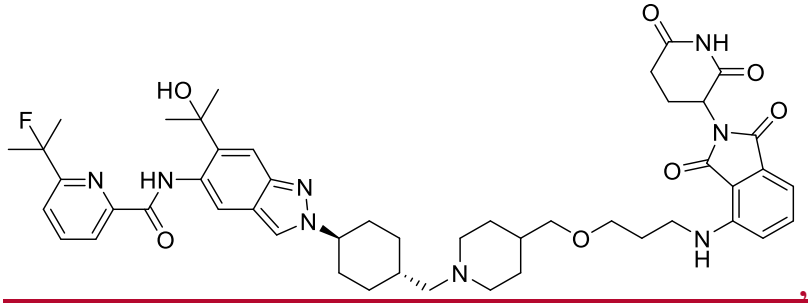
I-41  ,

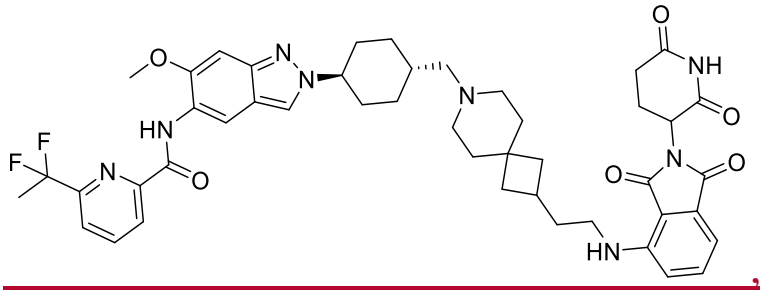
I-42  ,

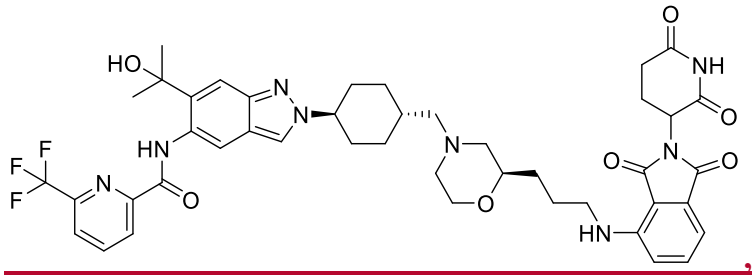
I-46  ,

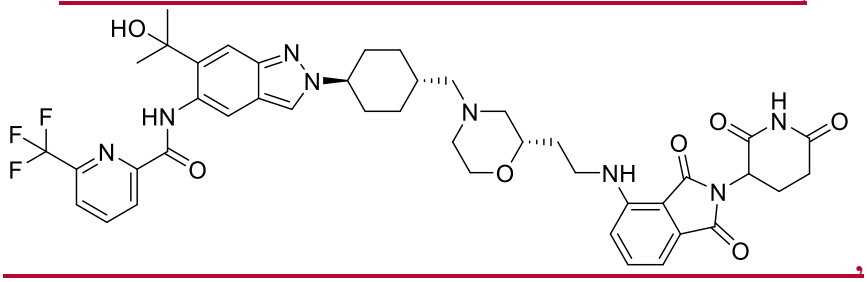
I-47  ,

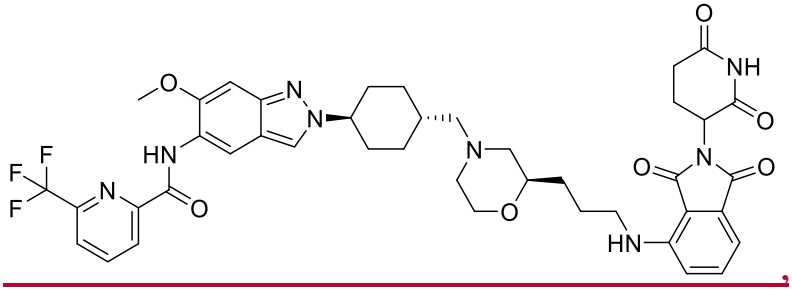
I-58 

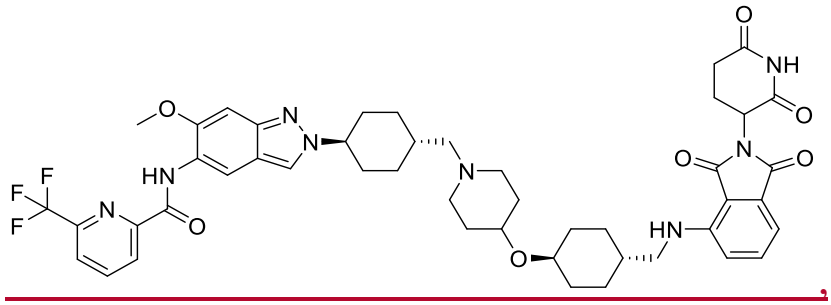
I-59 

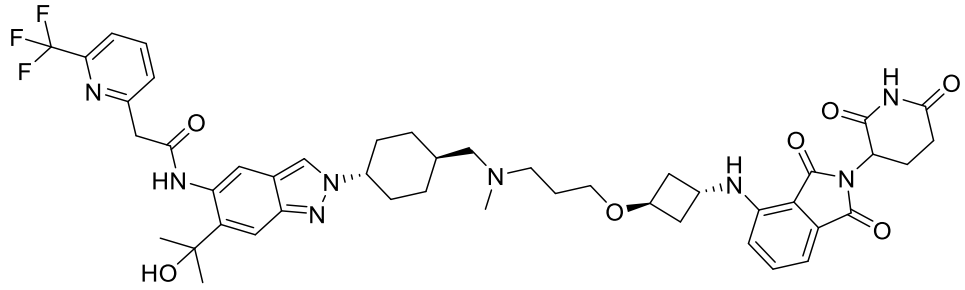
I-63 

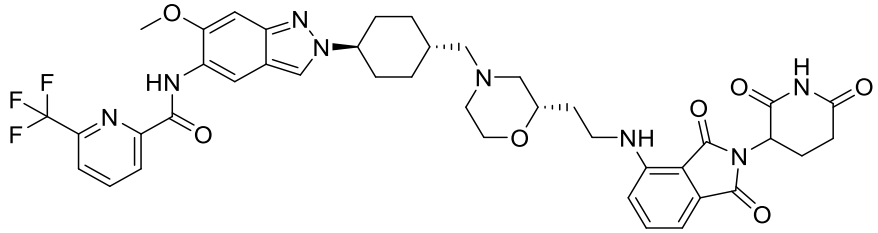
I-64 

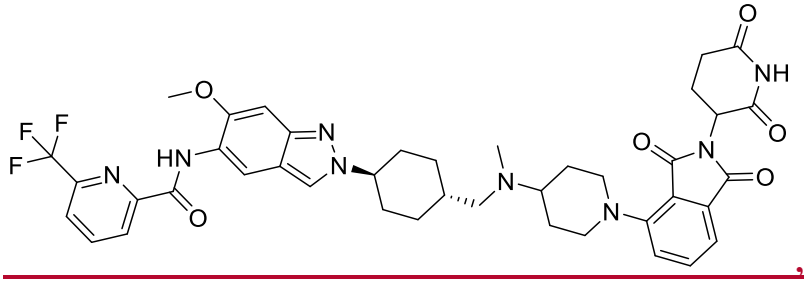
I-65 

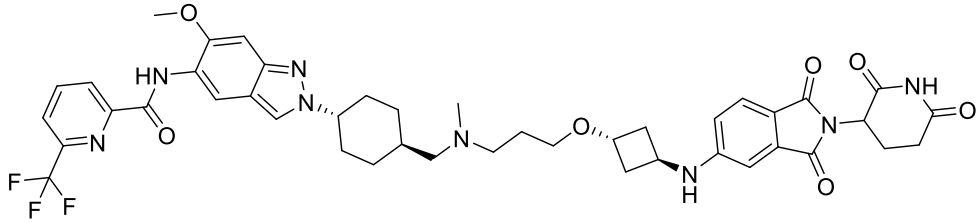
I-68 

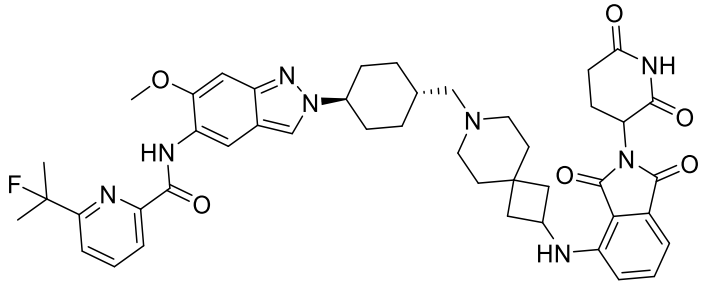
I-69 

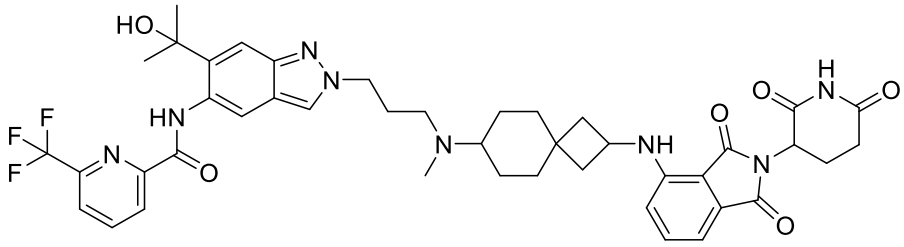
I-70 

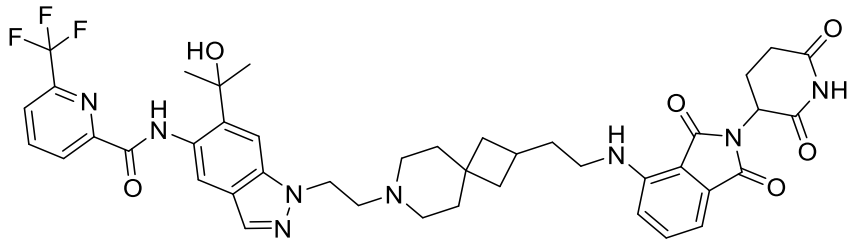
I-71 

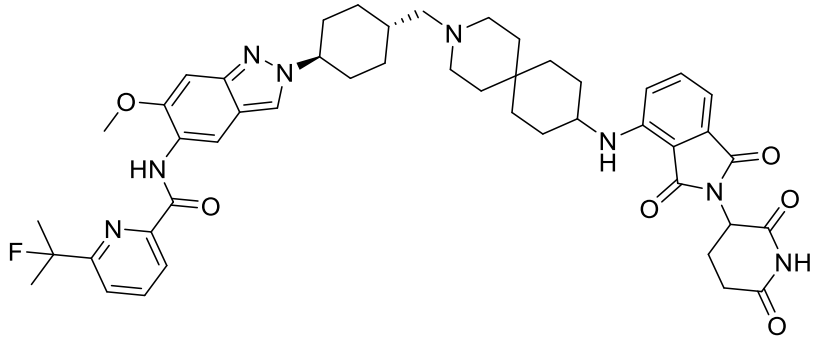
I-76 

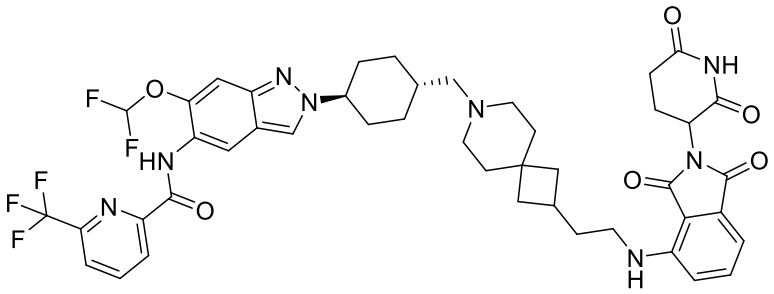
I-77 

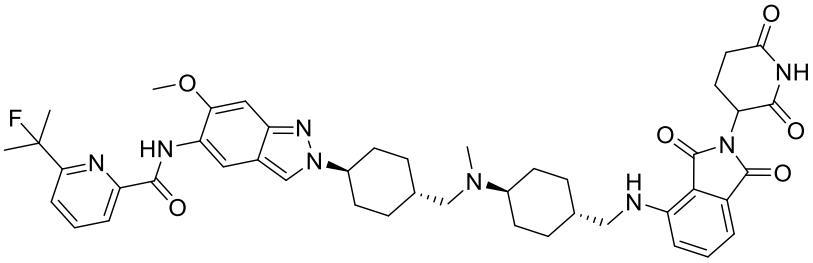
I-78 

I-79 

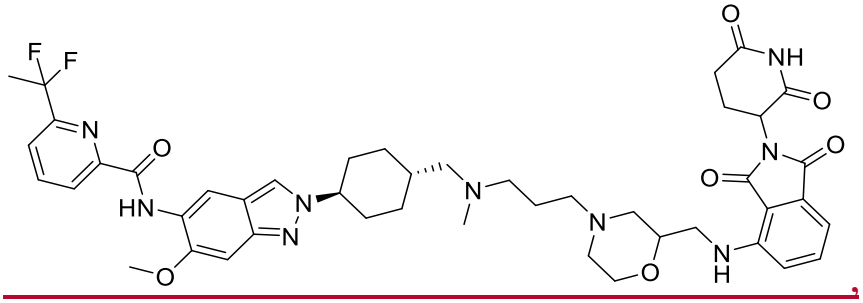
I-87 

I-88 

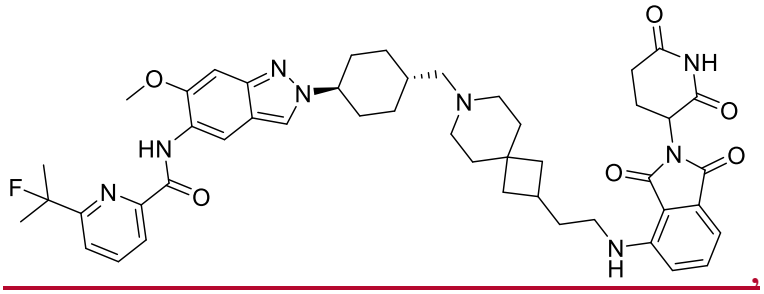
I-89 

I-90 

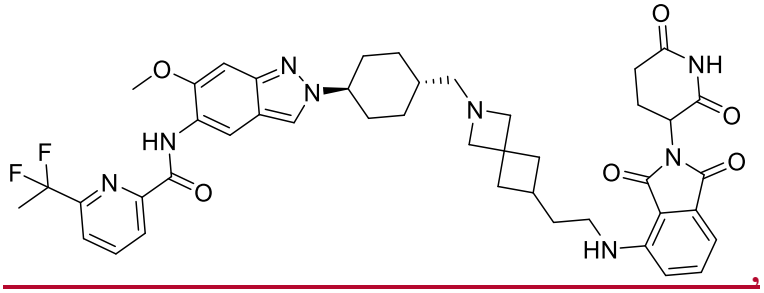
I-91



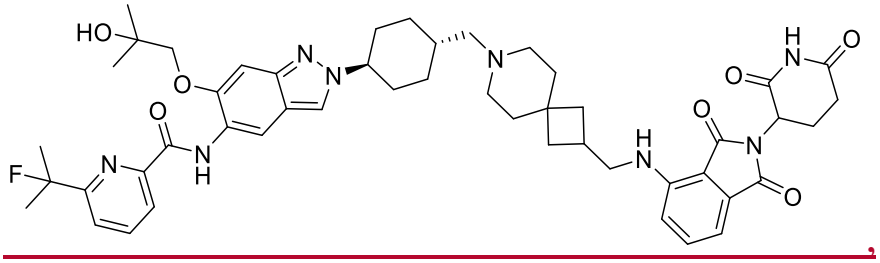
I-92



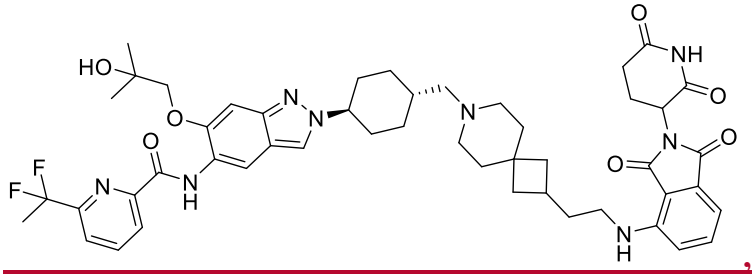
I-93



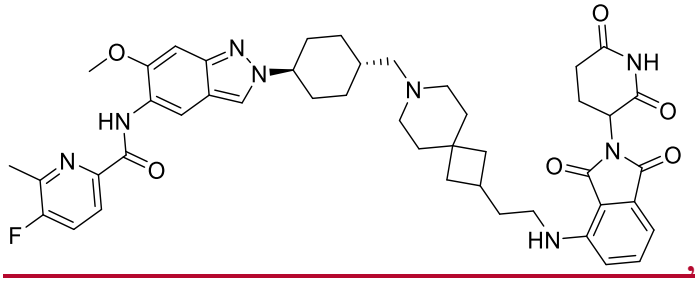
I-118

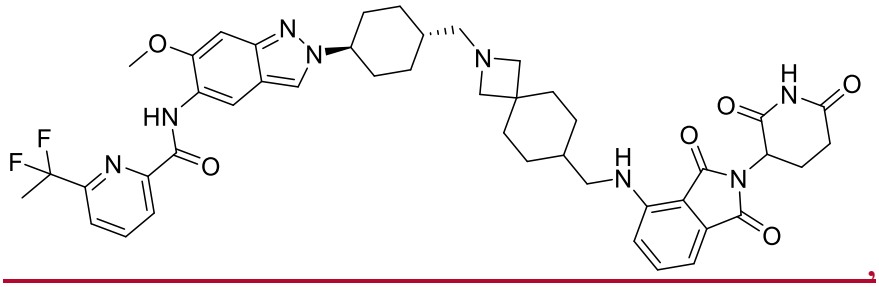


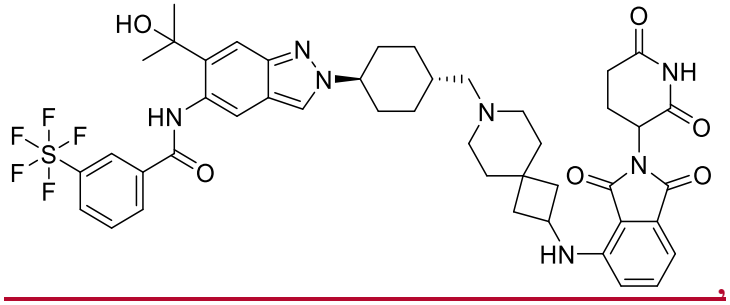
I-119

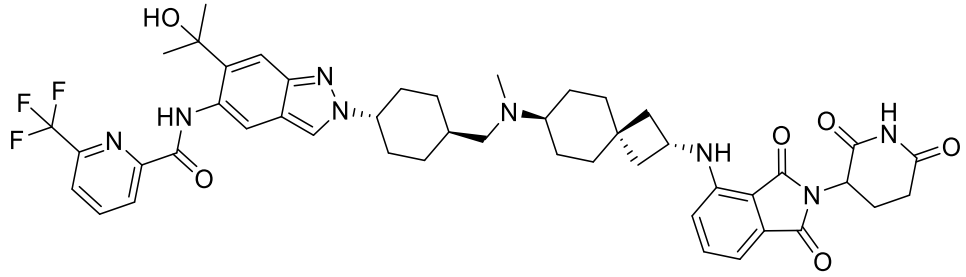


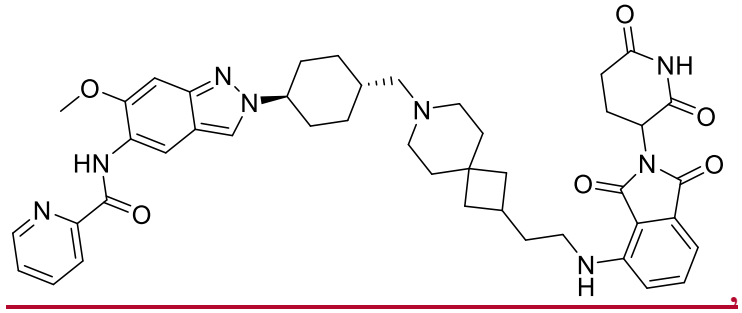
I-121

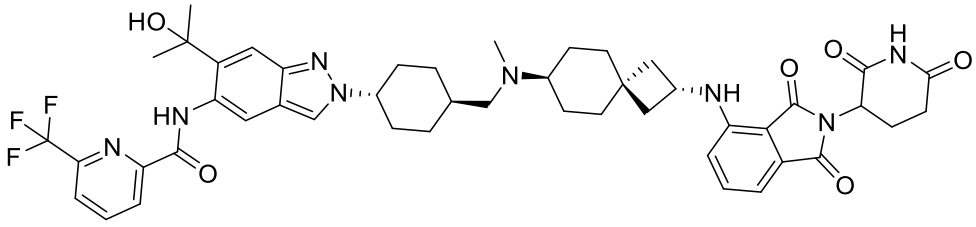


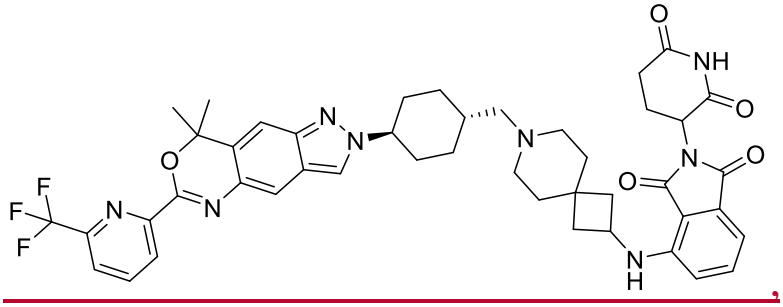
I-122  ,

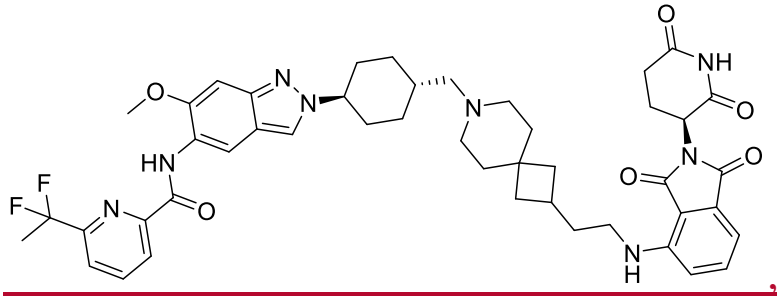
I-123  ,

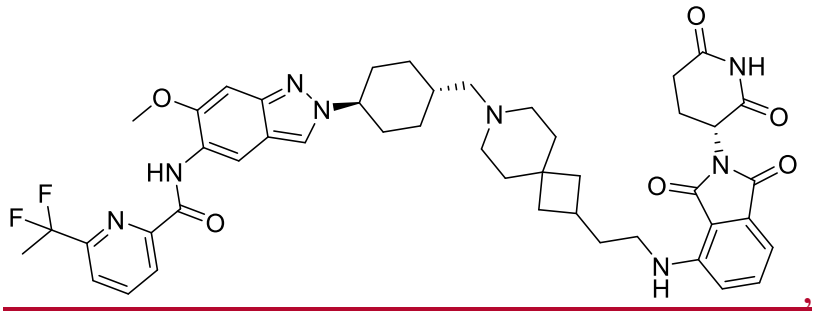
I-124  ,

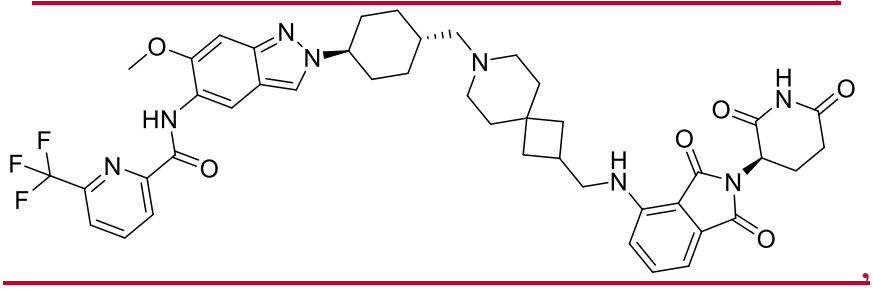
I-125  ,

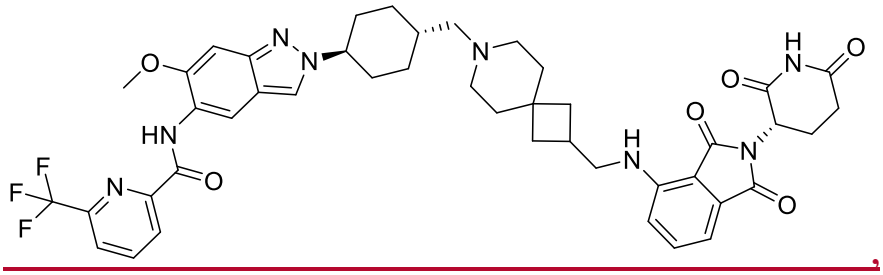
I-126  ,

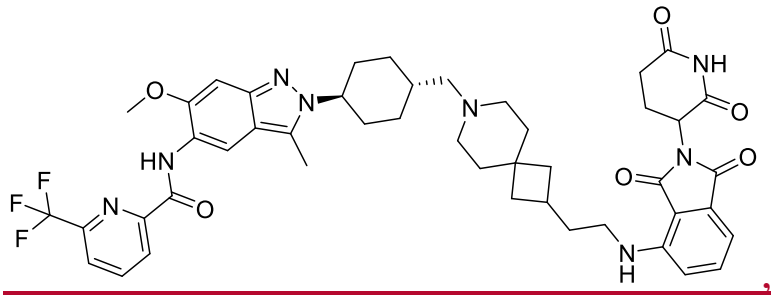
I-127  ,

I-128  ,

I-129  ,

I-130  ,

I-131  ,

I-136  ,

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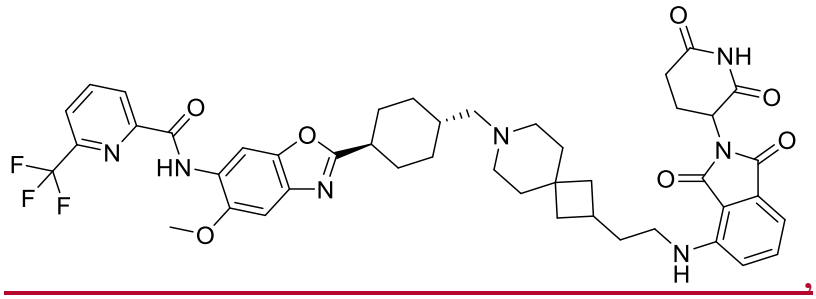

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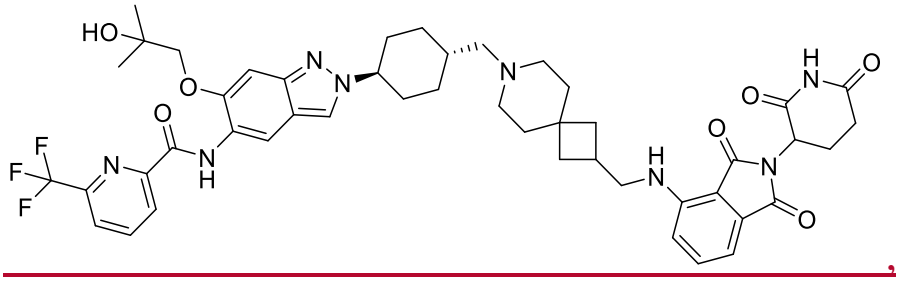

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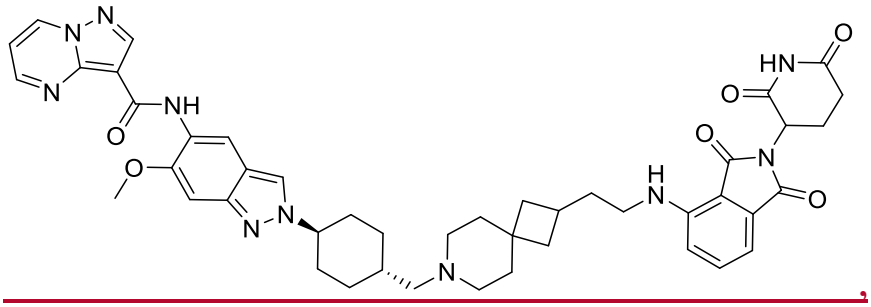

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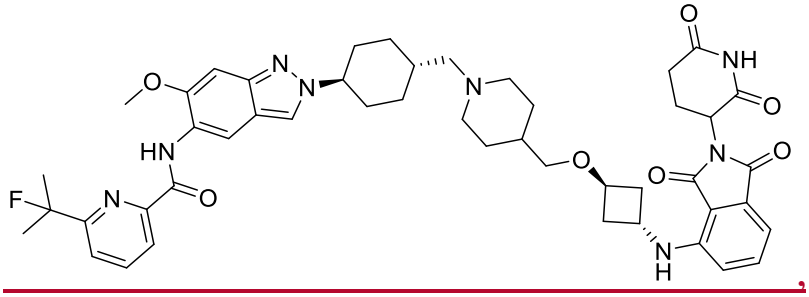

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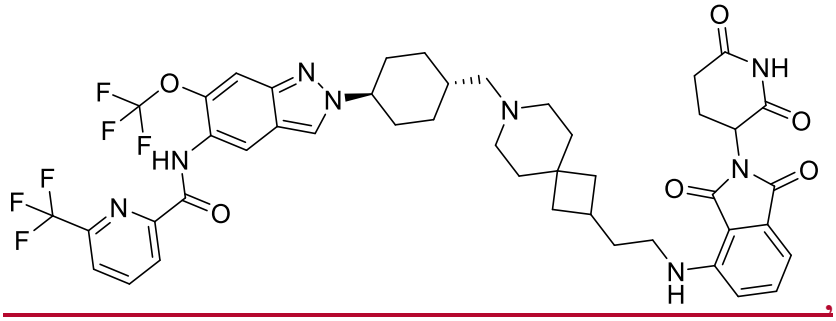

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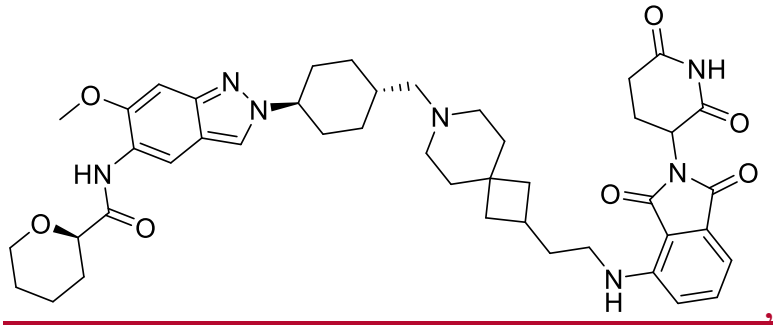

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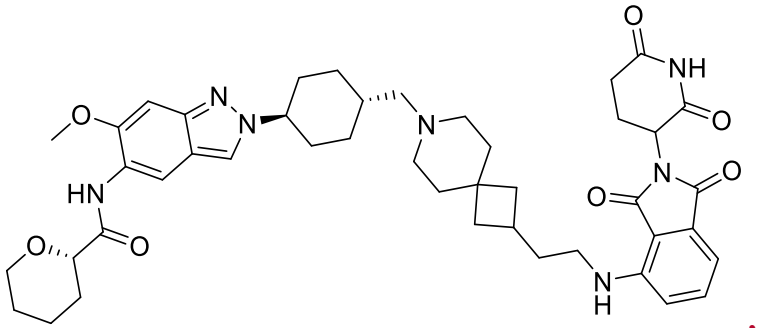

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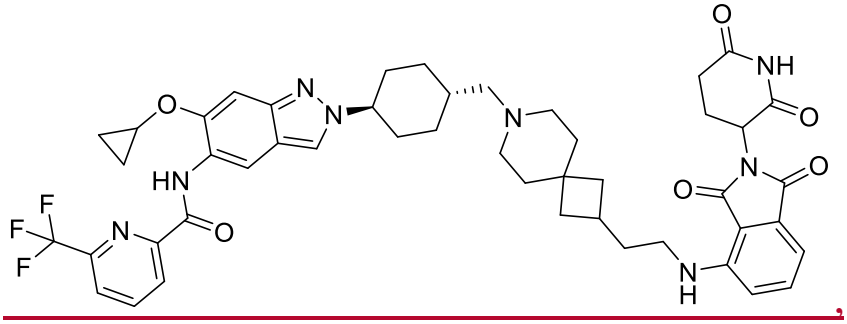

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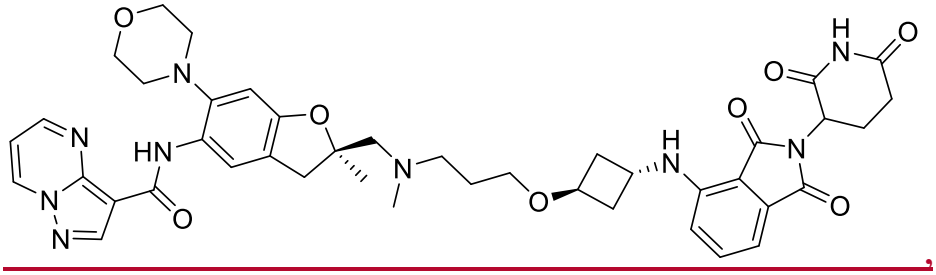

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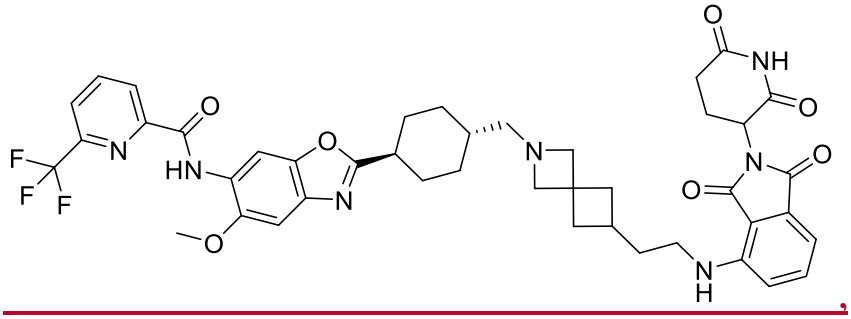
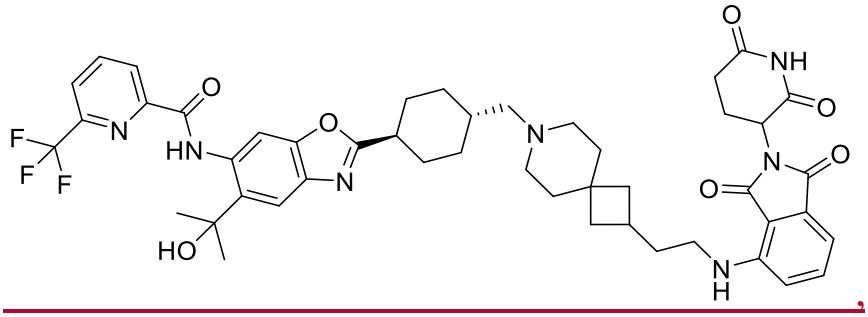
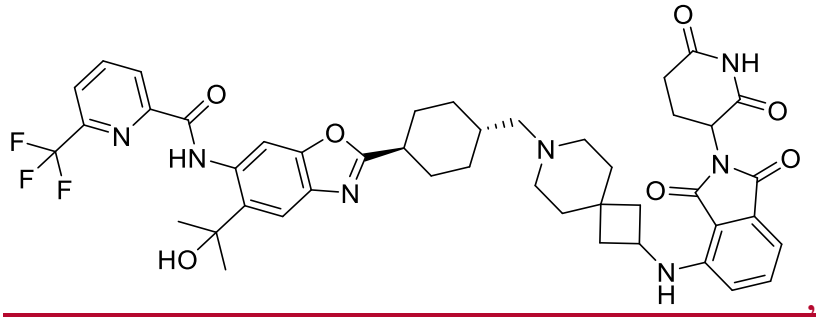
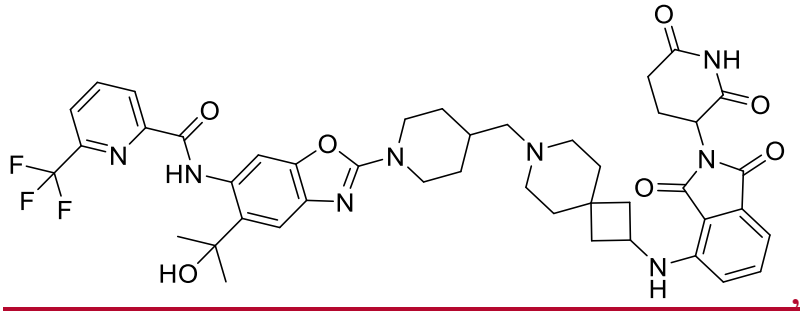
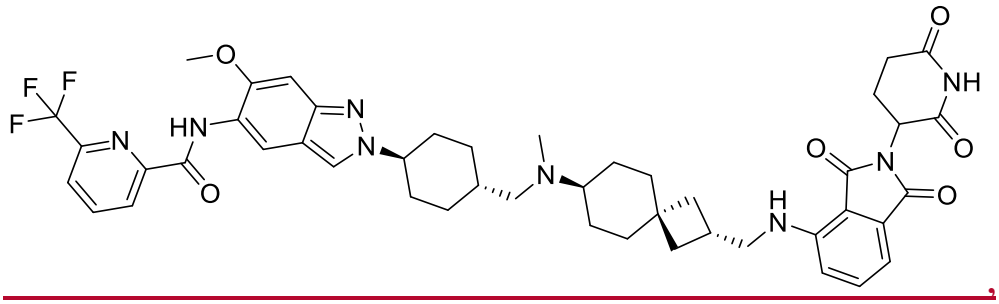
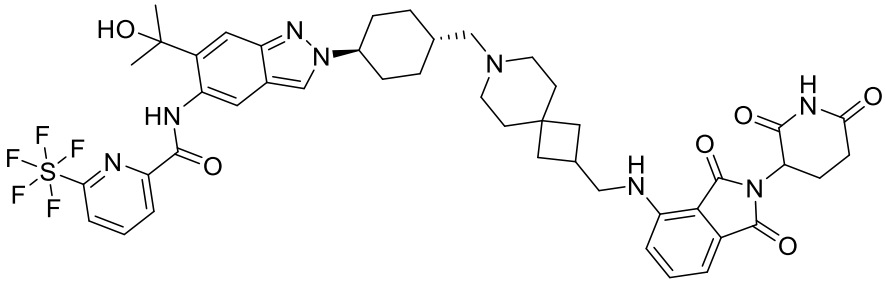


I-182 

I-183 

I-184 

I-185 

I-187 

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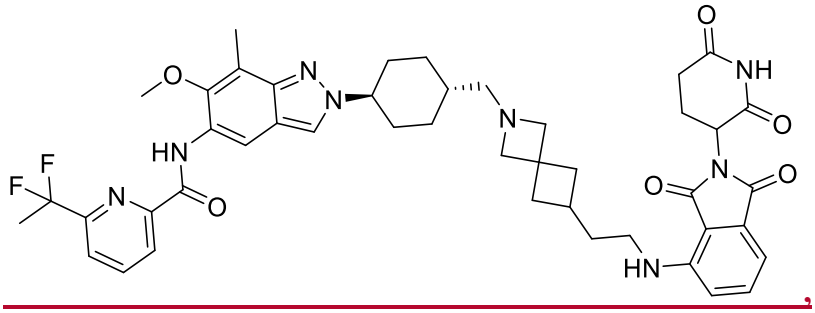

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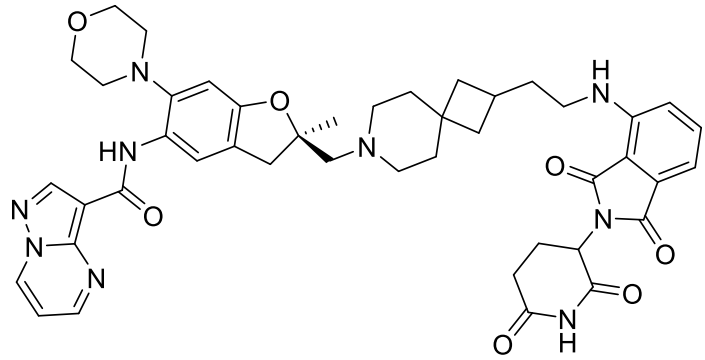

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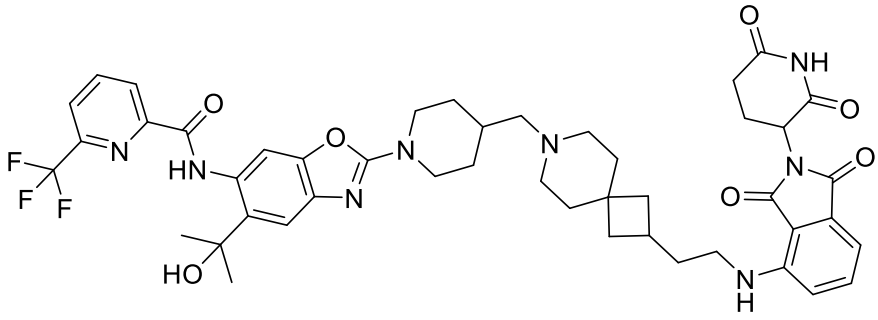

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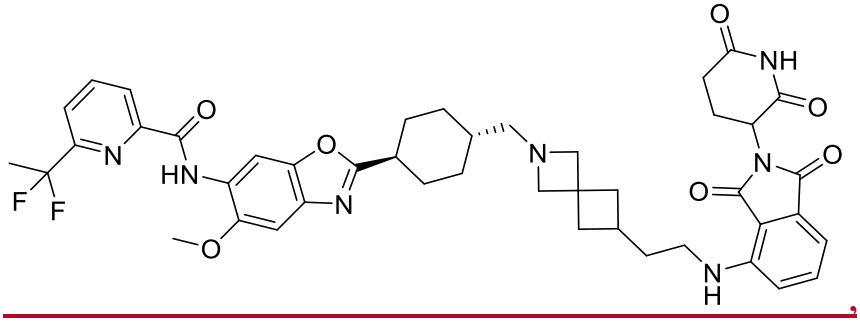

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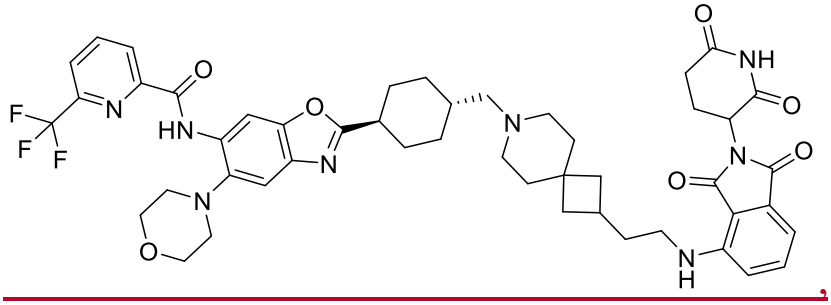

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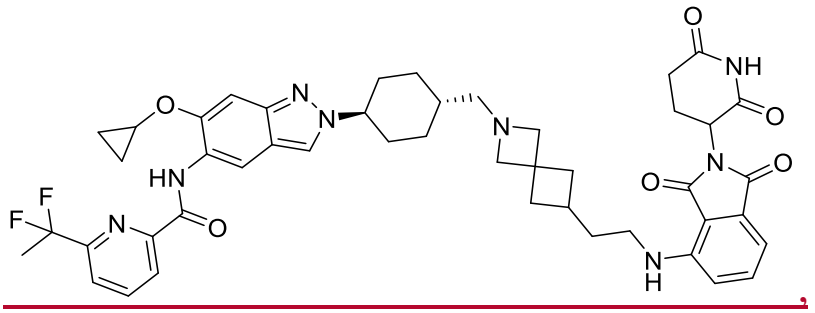

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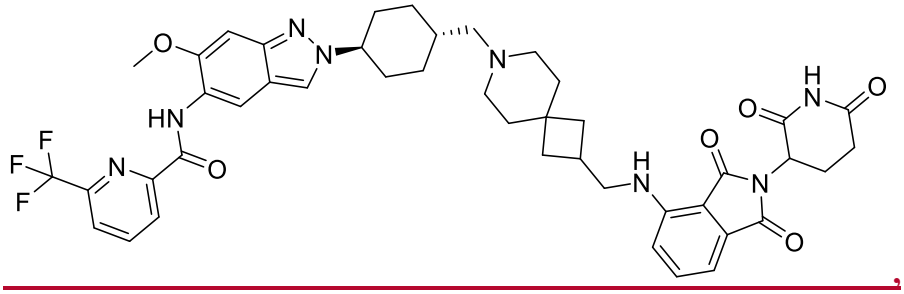

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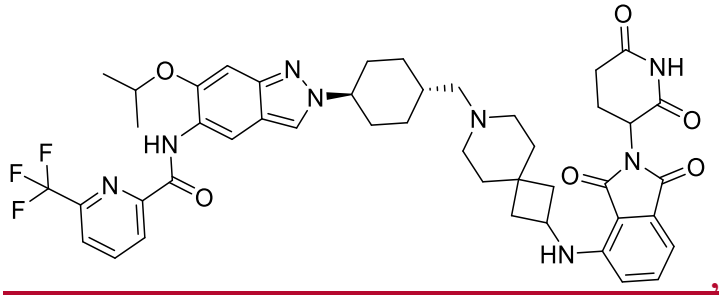

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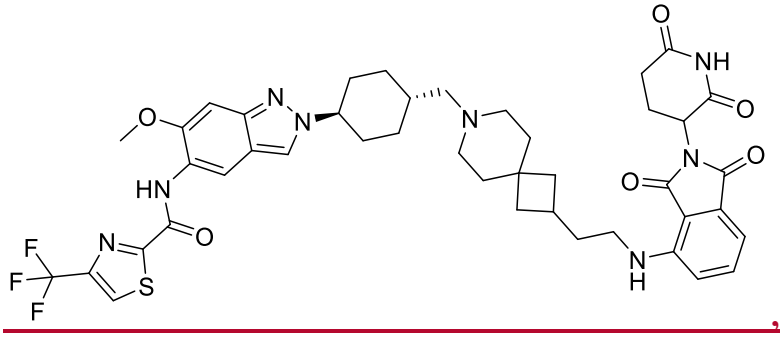

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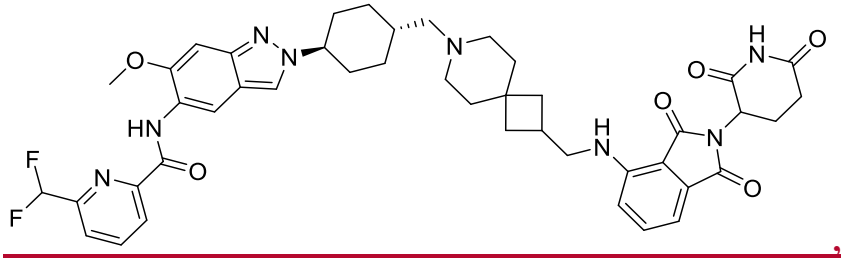
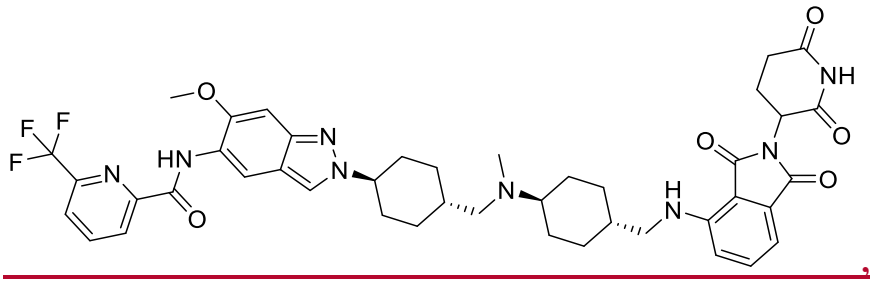
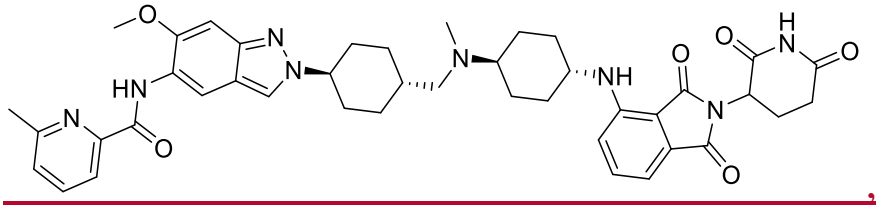
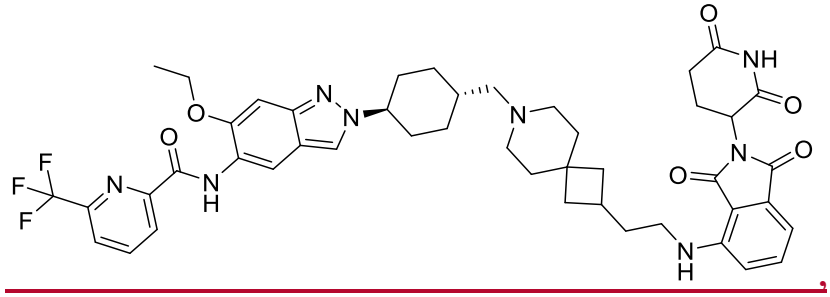
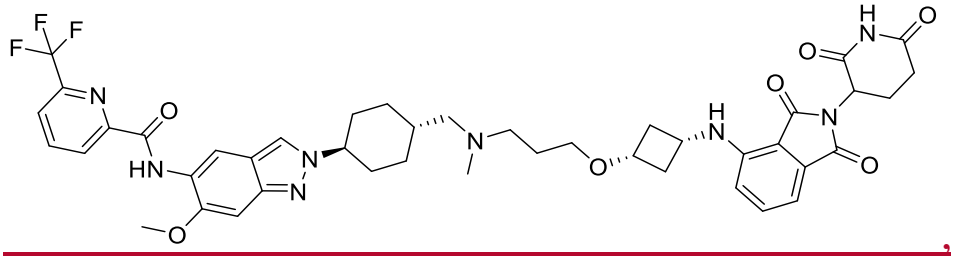
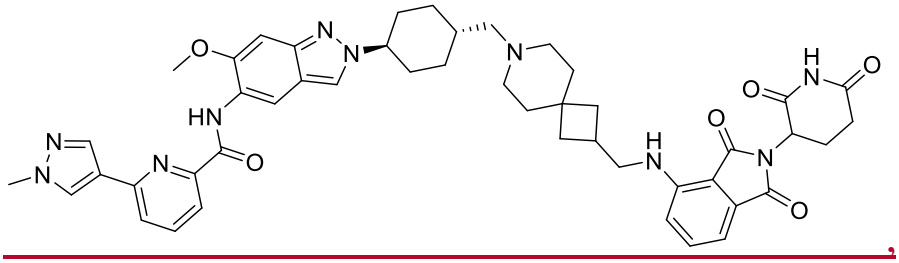


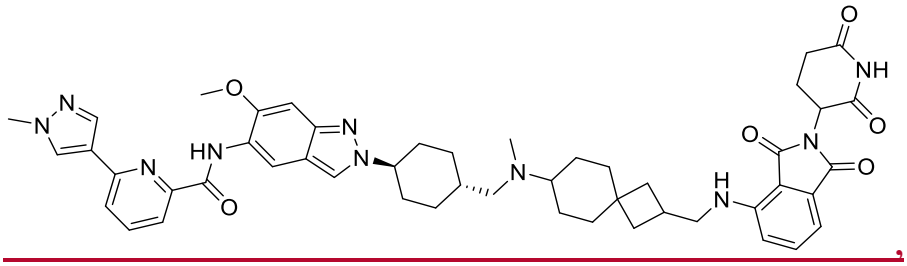
I-210 

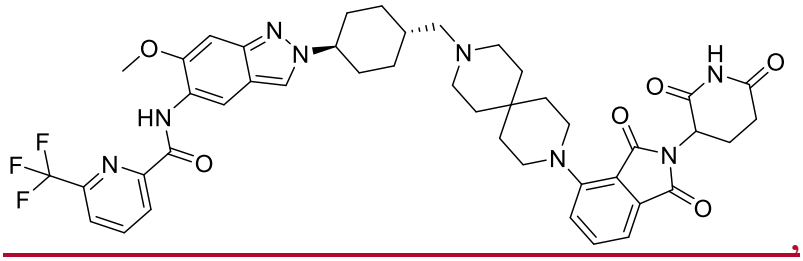
I-211 

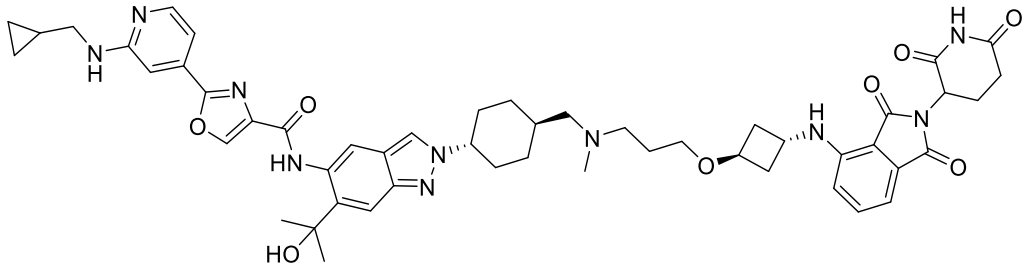
I-212 

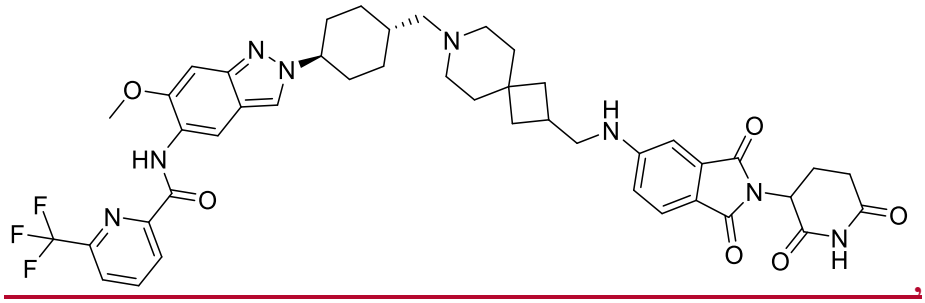
I-213 

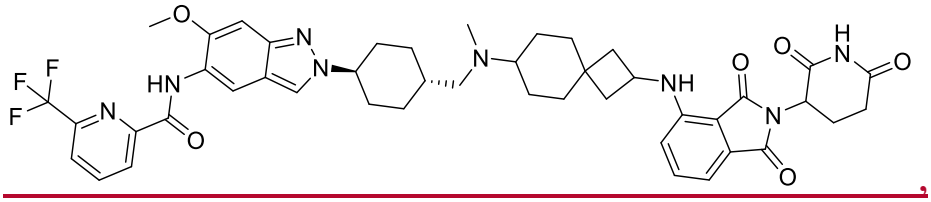
I-218 

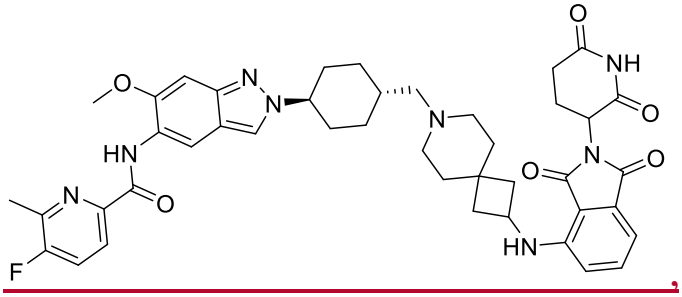
I-219 

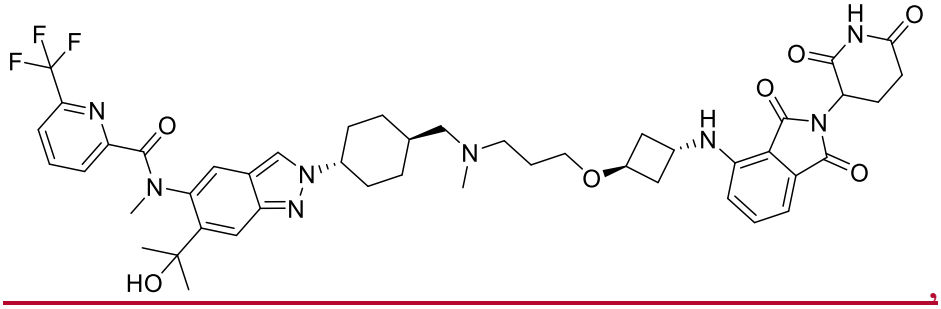
I-220  ,

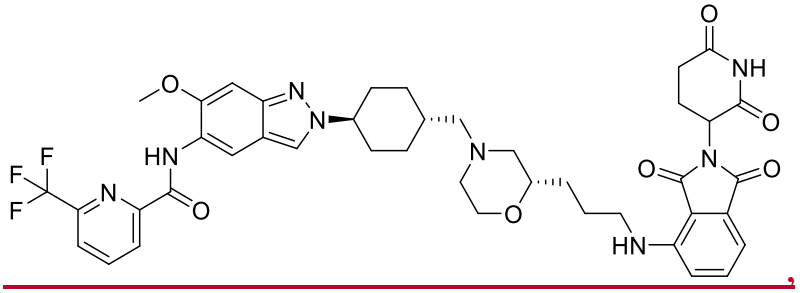
I-221  ,

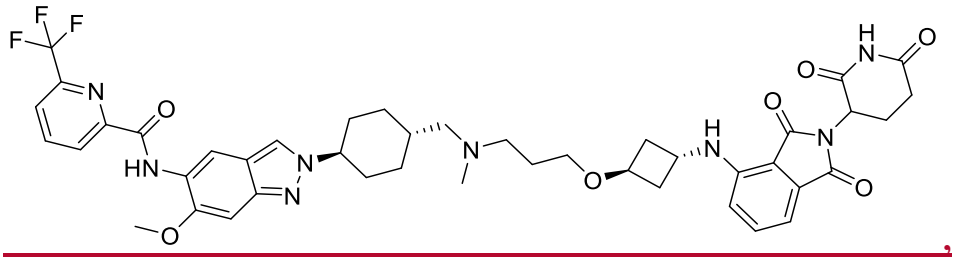
I-222  ,

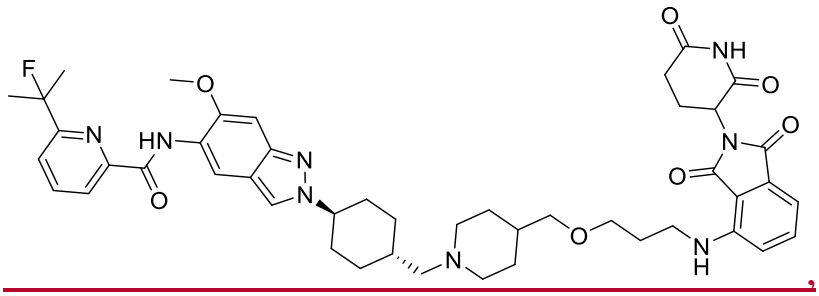
I-223  ,

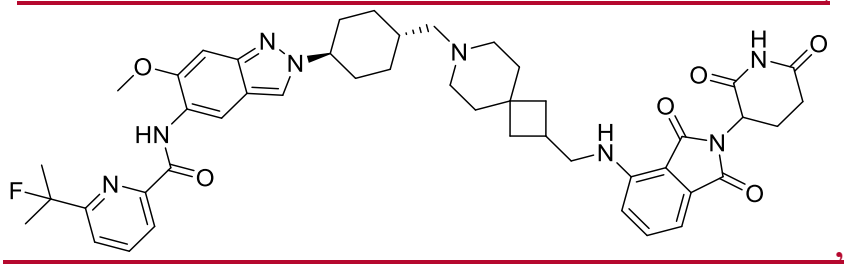
I-224  ,

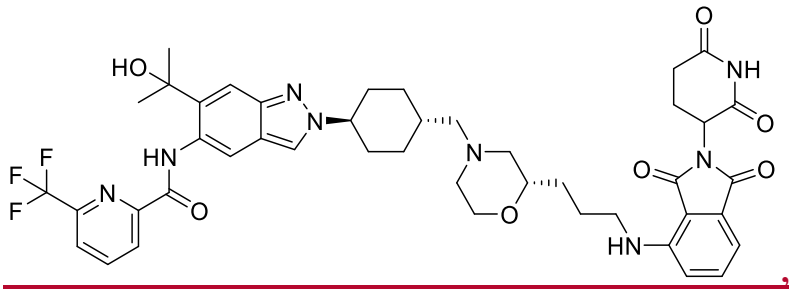
I-225  ,

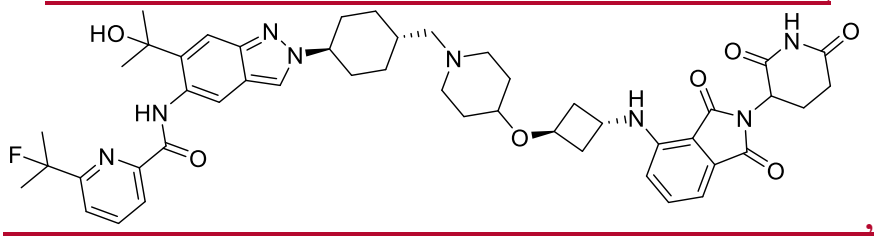
I-227 

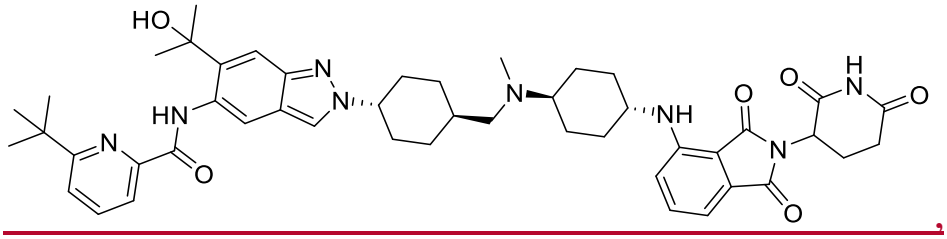
I-230 

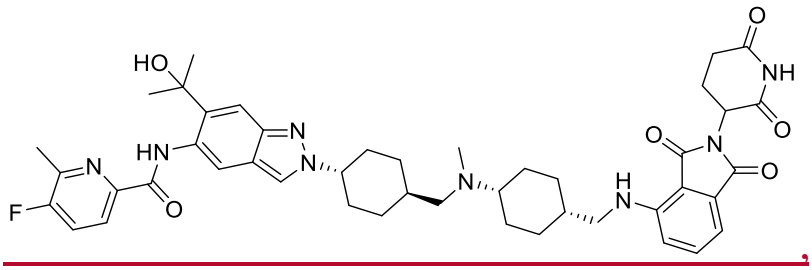
I-231 

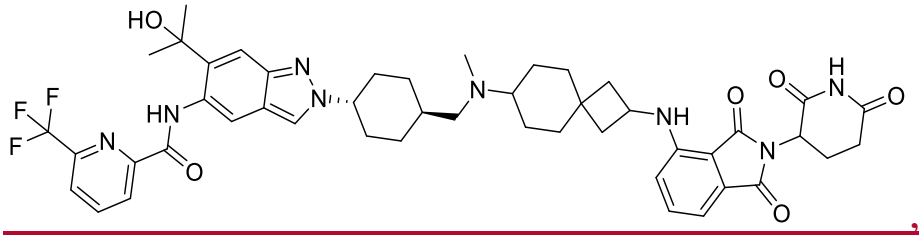
I-232 

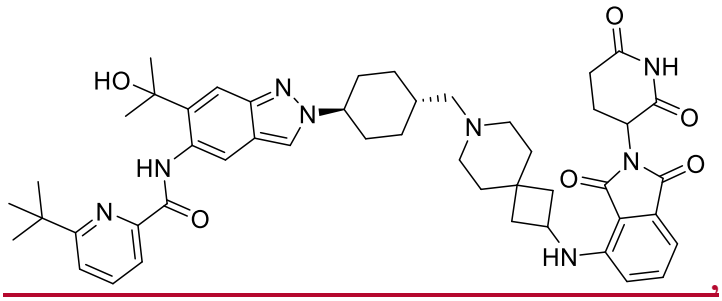
I-233 

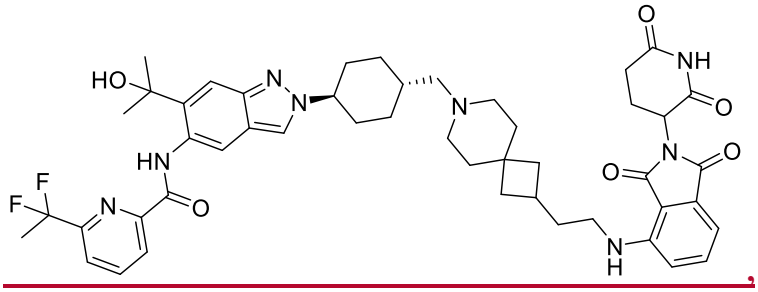
I-234 

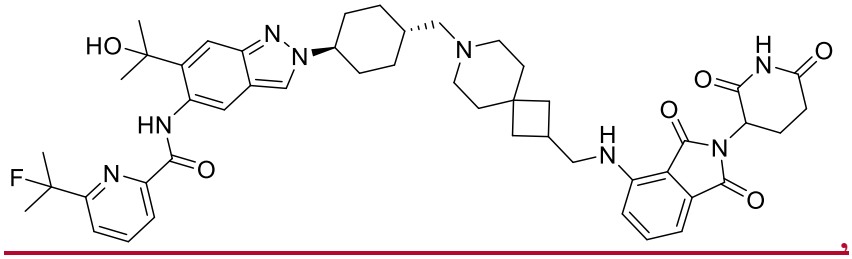
I-236 

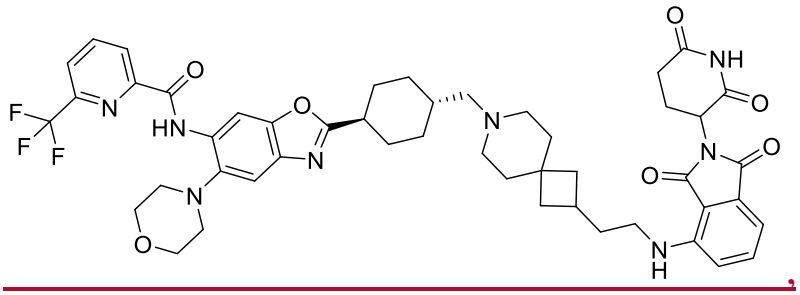
I-237 

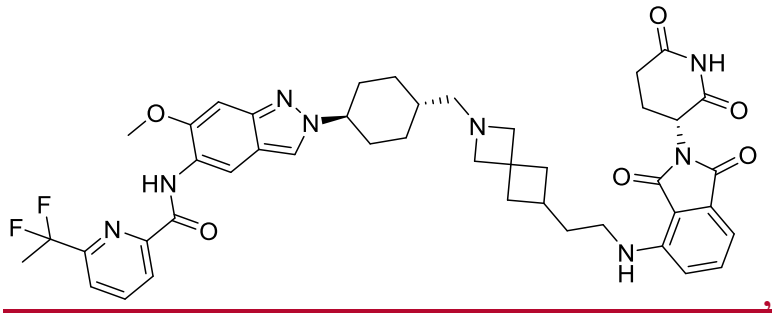
I-238 

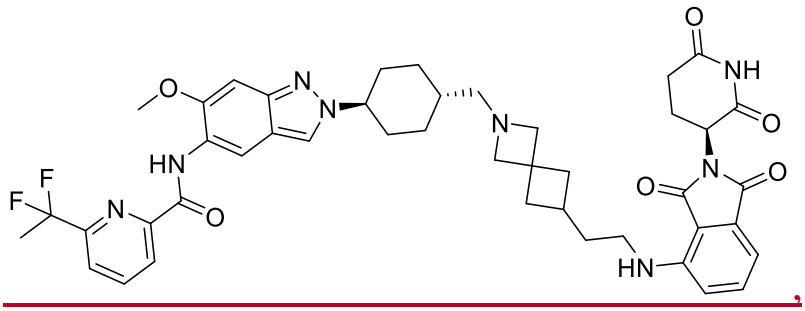
I-249 

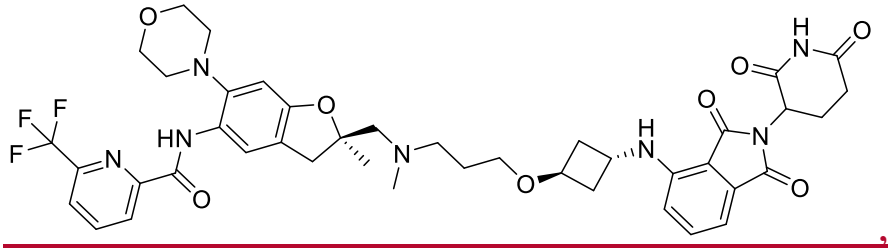
I-250 

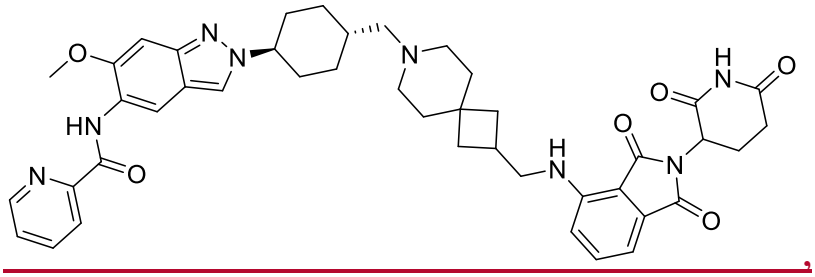
I-251 

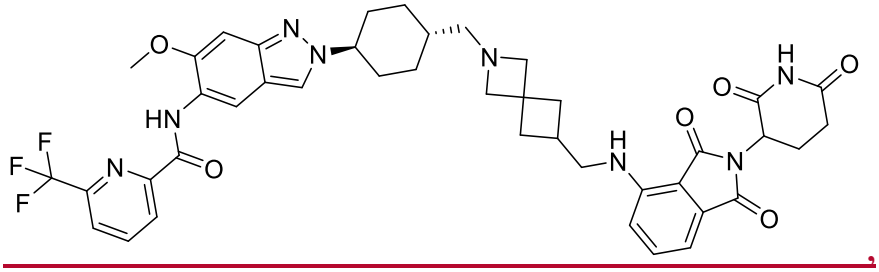
I-252 

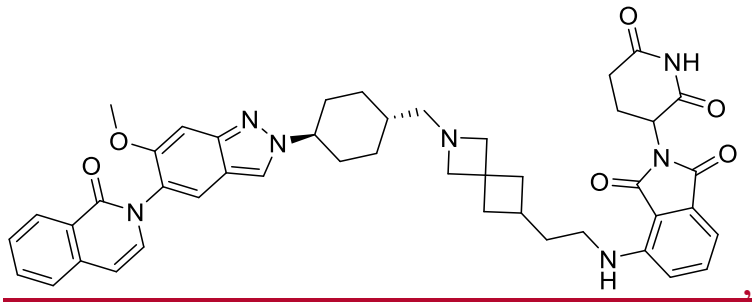
I-254 

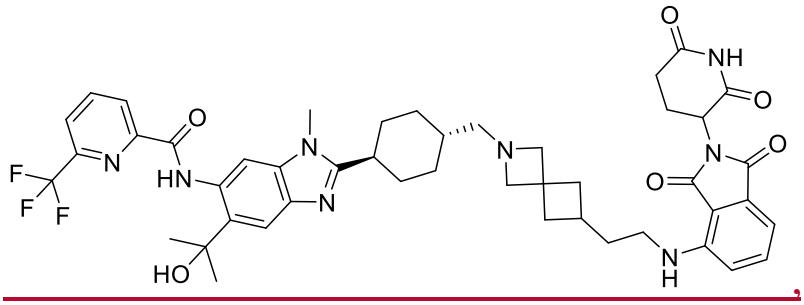
I-255 

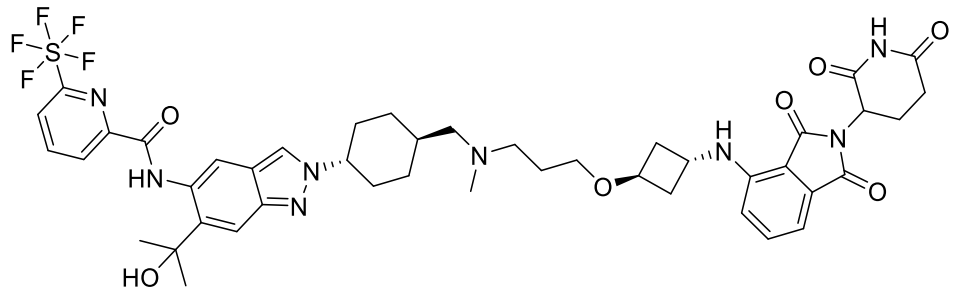
I-256 

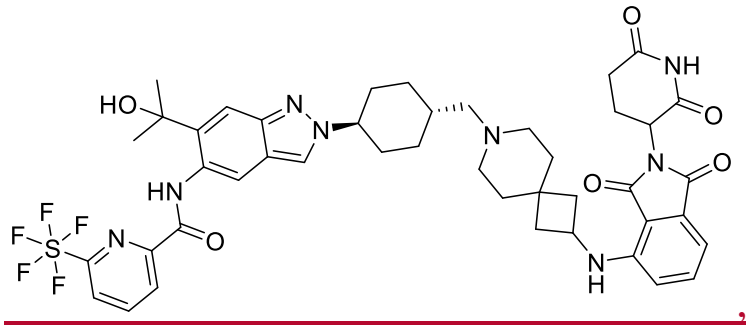
I-273 

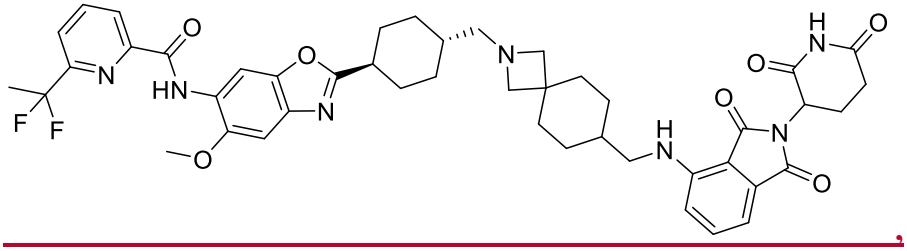
I-274 

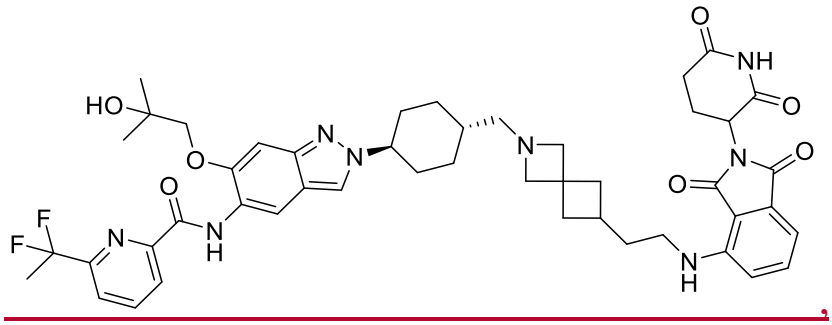
I-286  ,

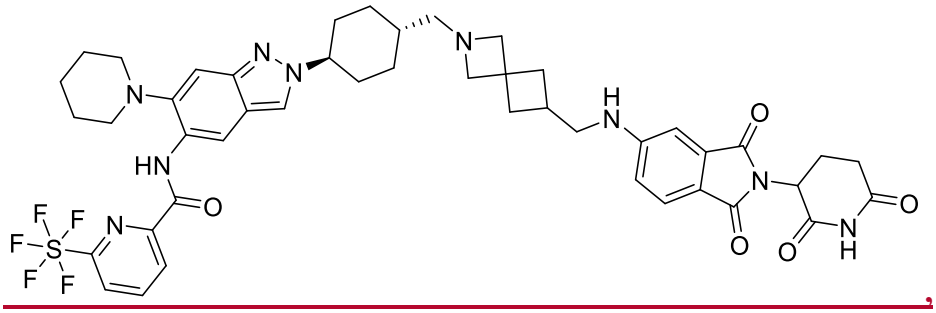
I-287  ,

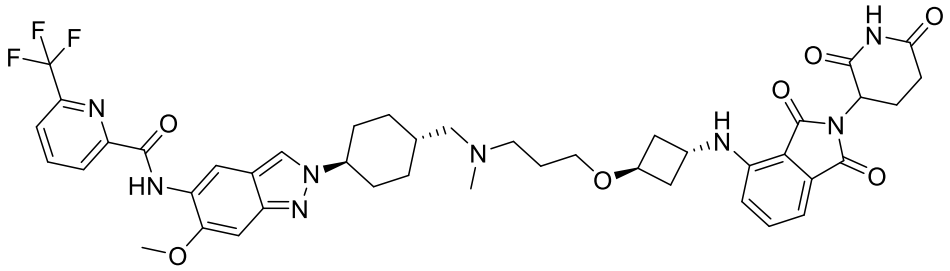
I-290  ,

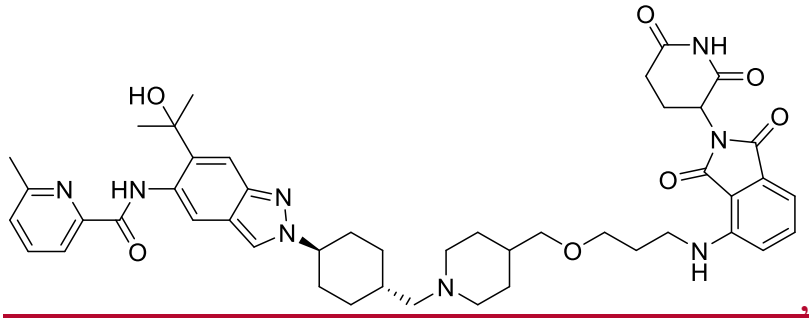
I-291  ,

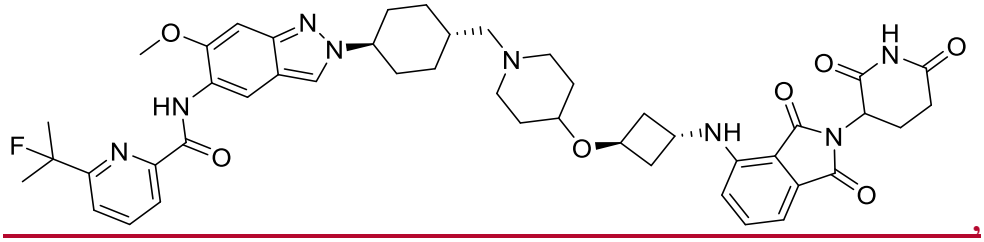
I-292  ,

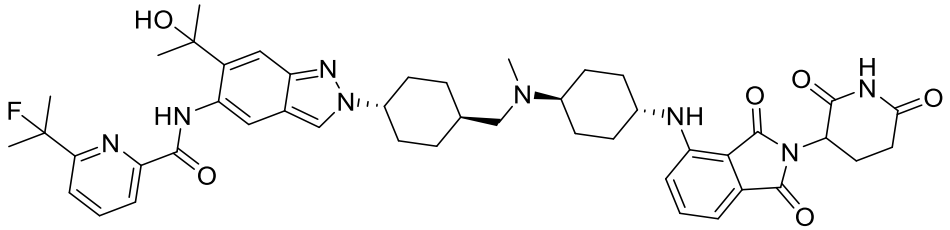
I-296 

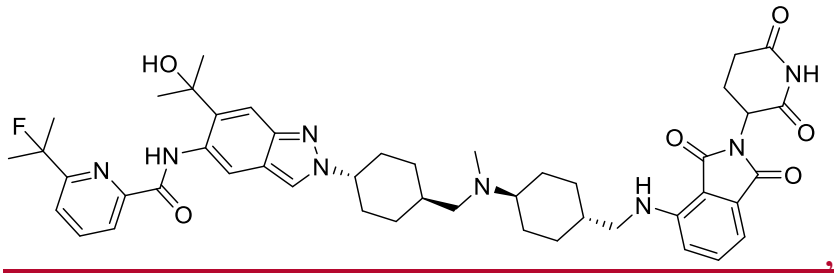
I-297 

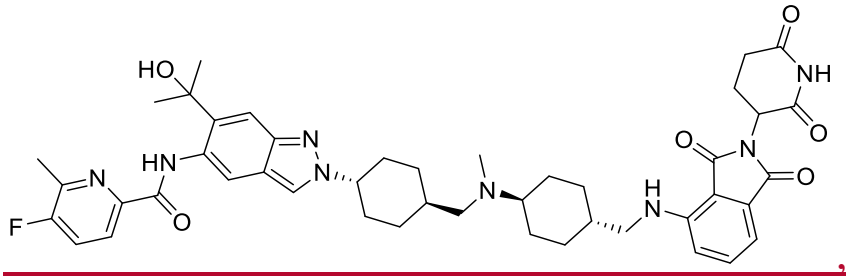
I-303 

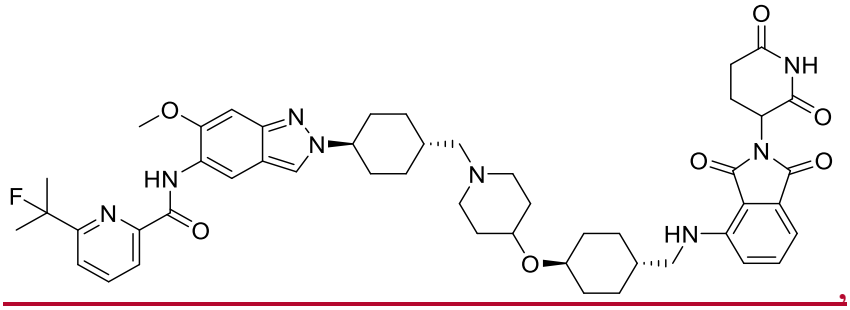
I-304 

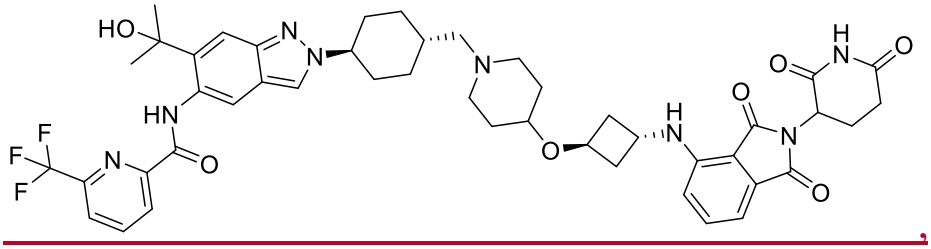
I-305 

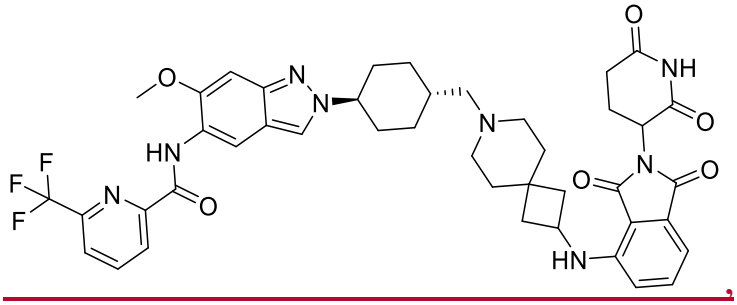
I-306 

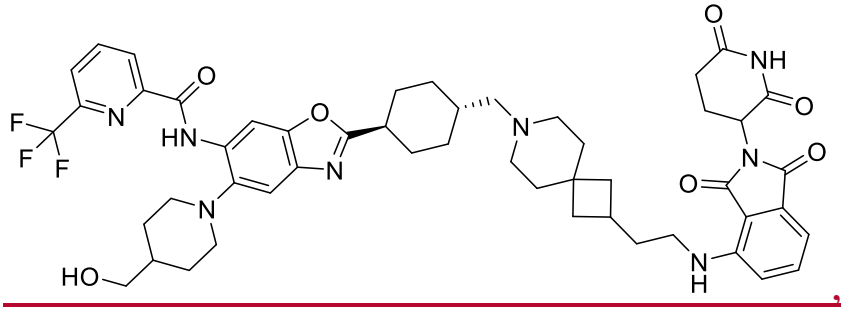
I-307 

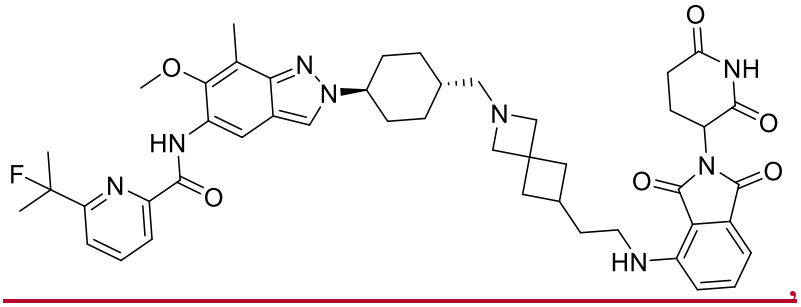
I-308 

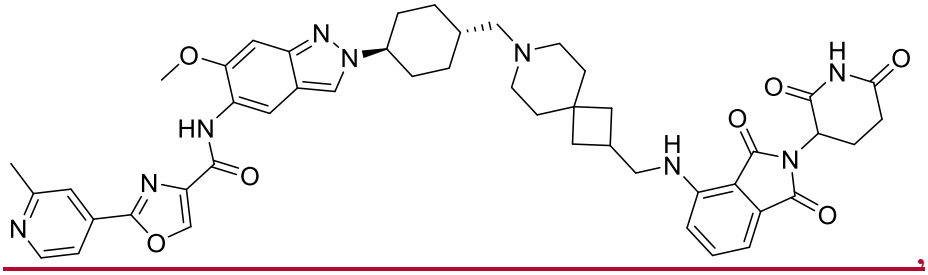
I-311 

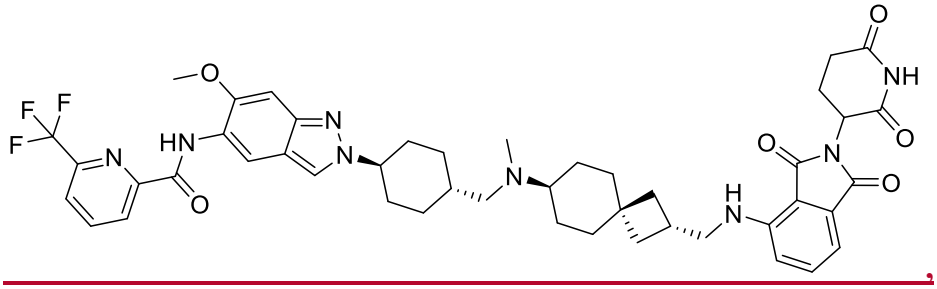
I-312 

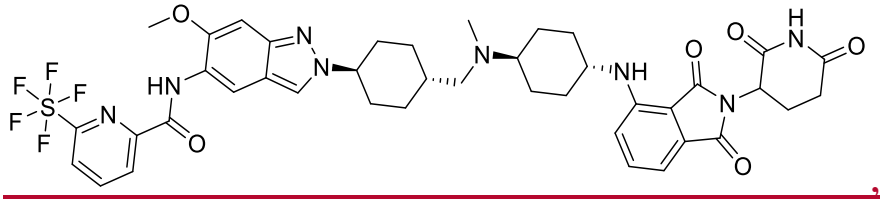
I-313 

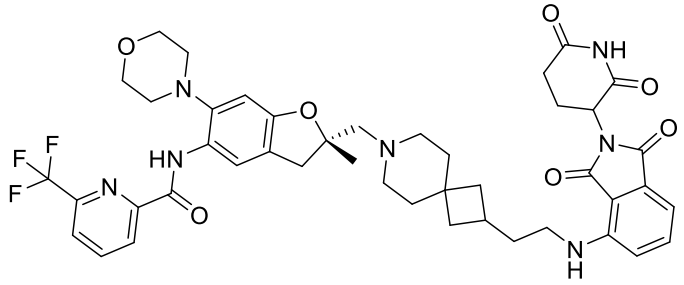
I-314 

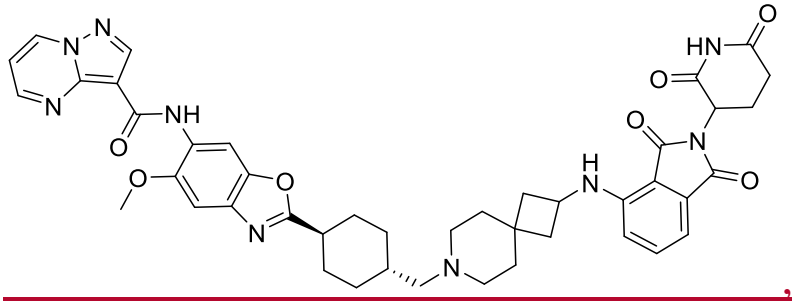
I-315 

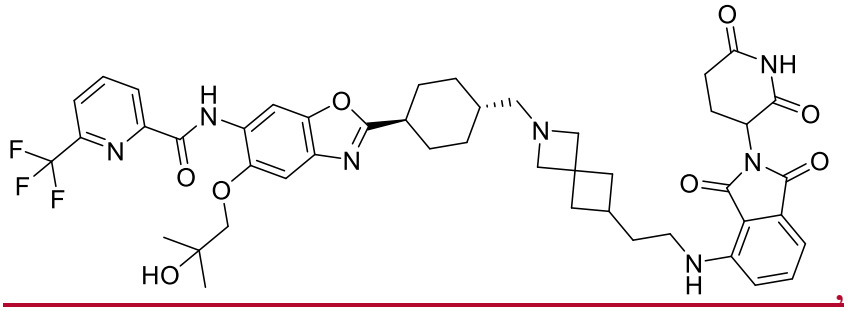
I-316 

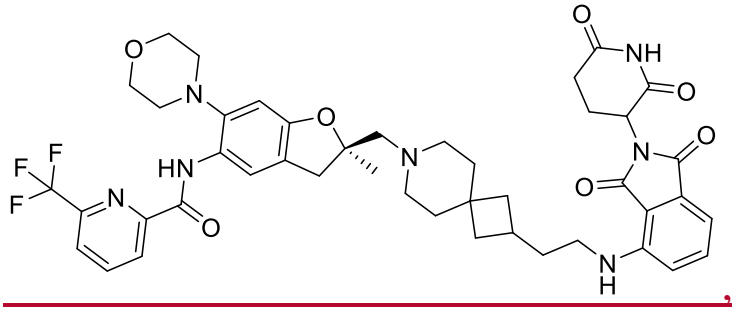
I-317 

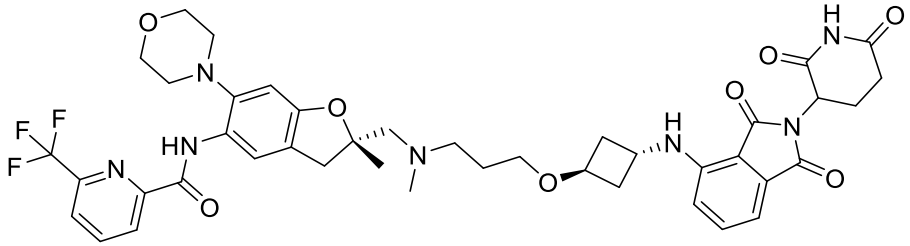
I-318 

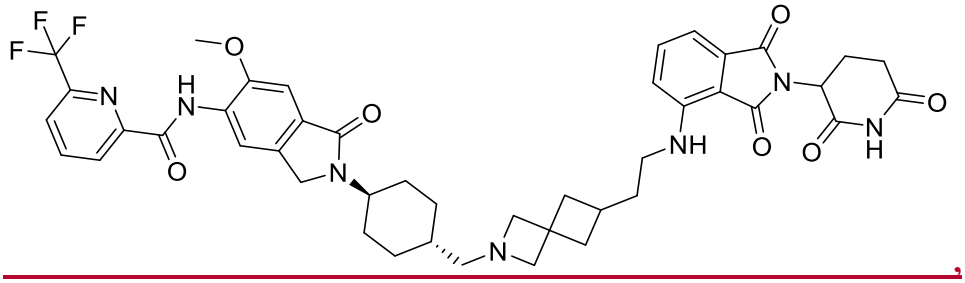
I-319 

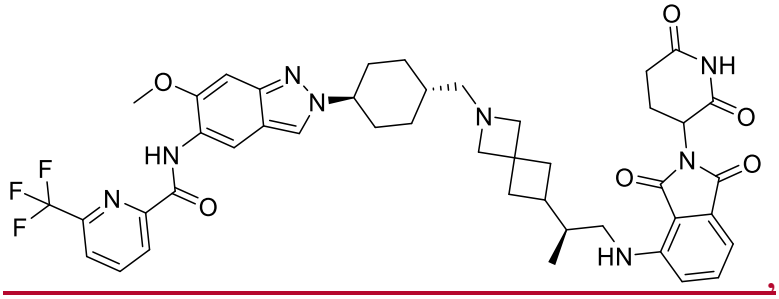
I-321 

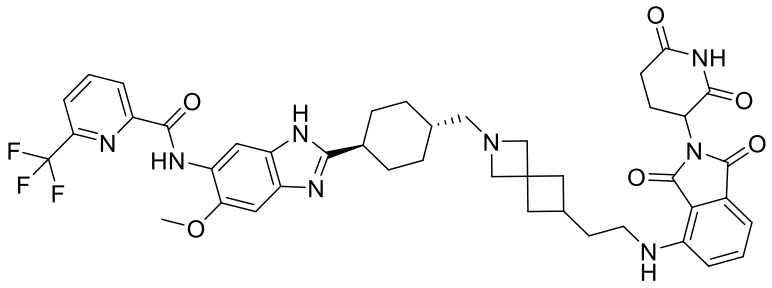
I-323  ,

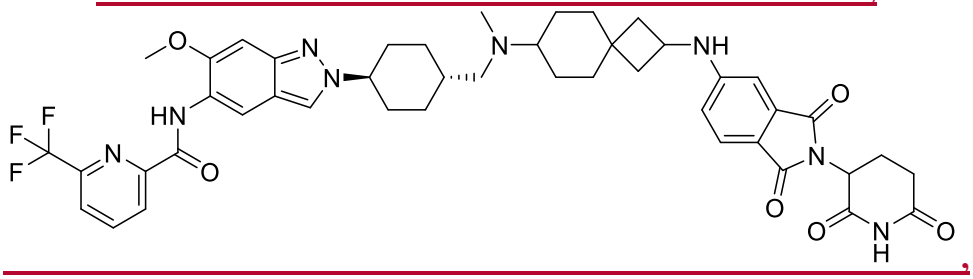
I-326  ,

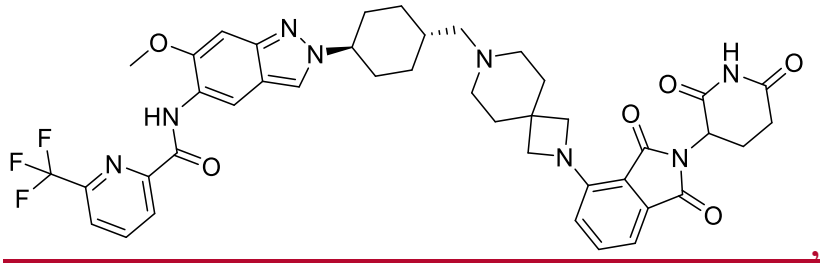
I-330  ,

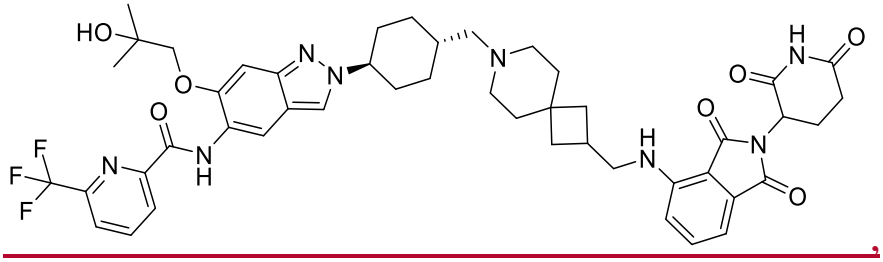
I-331  ,

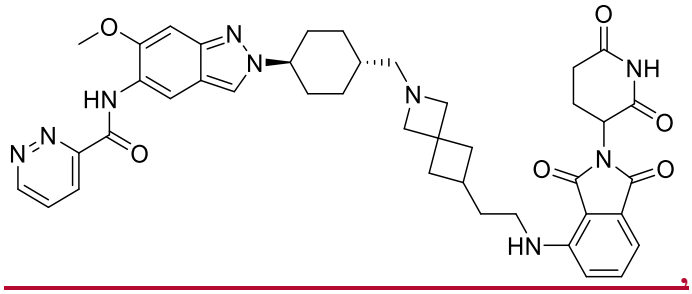
I-332  ,

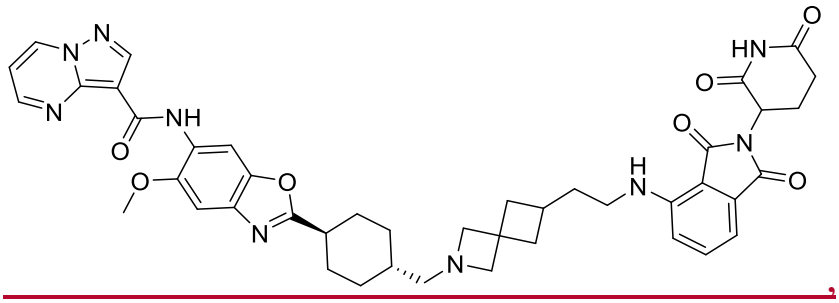
I-334  ,

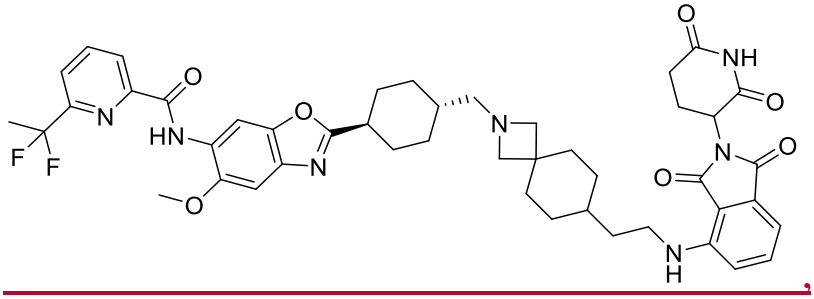
I-335  ,

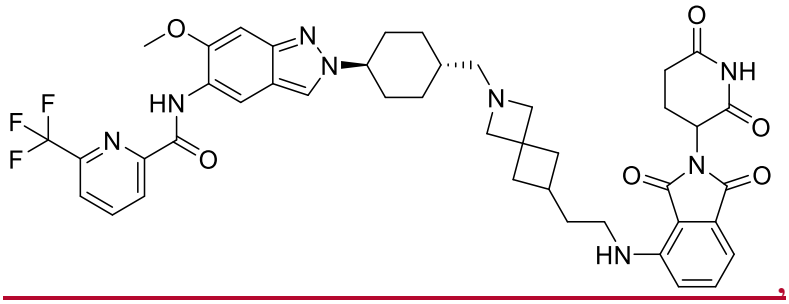
I-336  ,

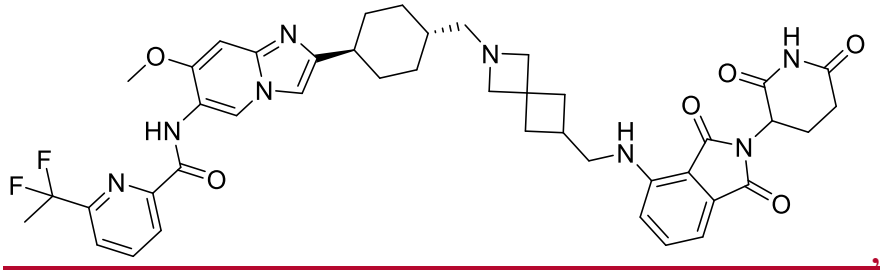
I-337  ,

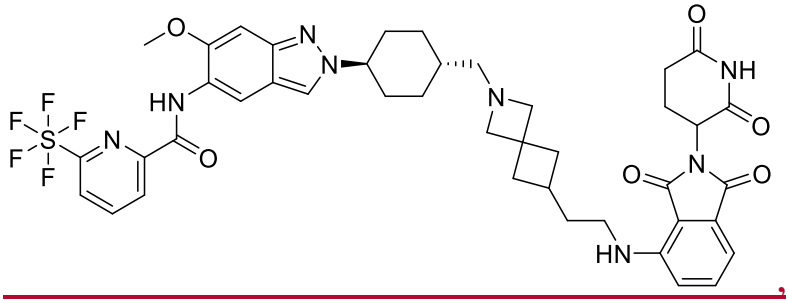
I-338  ,

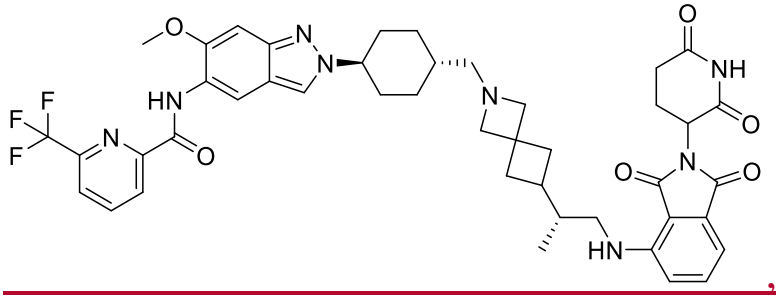
I-339  ,

I-340  ,

I-344  ,

I-345  ,

I-346  ,

I-347  ,

~~depicted in **Table 1,**~~ or a pharmaceutically acceptable salt thereof.

~~18~~15. A pharmaceutical composition comprising a compound ~~according any~~ of any one of claims 1-~~17~~14, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

16. A compound of any one of claims 1-14, or a pharmaceutical composition of claim 15, for use in therapy.

~~19~~17. Use of a compound of any one of claims 1-14, or a pharmaceutical composition of claim 15, in the manufacture of a medicament for ~~A method of~~ degrading and/or inhibiting an IRAK protein kinase in a patient or biological sample, ~~comprising administering~~wherein the compound or pharamaceutical composition is to be administered to said patient, or ~~contacting~~ said biological sample is contacted with ~~a~~ said compound ~~according to any one of claims 1-17,~~ or ~~a~~ pharmaceutical composition ~~thereof~~.

~~20~~18. ~~A method of treating an IRAK-mediated disorder, disease, or condition in a patient comprising administering to said patient~~ Use of a compound ~~according to any~~ of any one of claims 1-~~17~~14, or a pharmaceutical composition of claim 15 ~~thereof~~, in the manufacture of a medicament for treating an IRAK-mediated disorder, disease, or condition in a patient.

~~21~~19. The ~~method~~ use of claim ~~20~~18, 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.

~~22~~20. The ~~method~~ use of claim ~~21~~19, wherein the cancer or proliferative disorder is selected from the group consisting of a benign or malignant tumor, solid tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastoma, neuroblastoma, multiple myeloma, gastrointestinal cancer, colon carcinoma, colorectal adenoma, a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial

character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphoma, Hodgkin's or Non-Hodgkin's lymphoma, a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, an IL-1 driven disorder, a MyD88 driven disorder, smoldering or indolent multiple myeloma, and a hematological malignancy selected from leukemia, diffuse large B-cell lymphoma (DLBCL), ABC DLBCL, chronic lymphocytic leukemia (CLL), chronic lymphocytic lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, Waldenström's macroglobulinemia (WM), splenic marginal zone lymphoma, multiple myeloma, plasmacytoma, or intravascular large B-cell lymphoma.

~~23~~21. The ~~method~~ use of claim ~~22~~20, wherein the MyD88 driven disorder is selected from the group consisting of ABC DLBCL, Waldenström's macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma, and chronic lymphocytic leukemia.

~~24~~22. The ~~method~~ use of claim ~~22~~20, wherein the IL-1 driven disorder is smoldering or indolent multiple myeloma.

~~25~~23. The ~~method~~ use of claim ~~21~~19, 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.

~~26~~24. The ~~method~~ use of claim ~~21~~19, 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.