and in the pathology of muscle wasting. Many diseases are associated with an abnormal UPP and negatively affect cell cycle and division, the cellular response to stress and to extracellular modulators, morphogenesis of neuronal networks, modulation of cell surface receptors, ion channels, the secretory pathway, DNA repair and biogenesis of organelles.

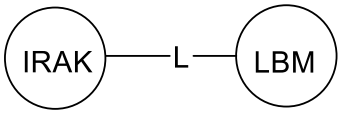
[0005] Aberrations in the process have recently been implicated in the pathogenesis of several diseases, both inherited and acquired. These diseases fall into two major groups: (a) those that result from loss of function with the resultant stabilization of certain proteins, and (b) those that result from gain of function, i.e. abnormal or accelerated degradation of the protein target.

[0006] The UPP is used to induce selective protein degradation, including use of fusion proteins to artificially ubiquitinate target proteins and synthetic small-molecule probes to induce proteasome-dependent degradation. Bifunctional compounds composed of a target protein-binding ligand and an E3 ubiquitin ligase ligand, induced proteasome-mediated degradation of selected proteins via their recruitment to E3 ubiquitin ligase and subsequent ubiquitination. These drug-like molecules offer the possibility of temporal control over protein expression. Such compounds are capable of inducing the inactivation of a protein of interest upon addition to cells or administration to an animal or human, and could be useful as biochemical reagents and lead to a new paradigm for the treatment of diseases by removing pathogenic or oncogenic proteins (Crews C, Chemistry & Biology, 2010, 17(6):551-555; Schnnekloth JS Jr., Chembiochem, 2005, 6(l):40-46).

[0007] An ongoing need exists in the art for effective treatments for disease, especially hyperplasias and cancers, such as multiple myeloma. However, non-specific effects, and the inability to target and modulate certain classes of proteins altogether, such as transcription factors, remain as obstacles to the development of effective anti-cancer agents. As such, small molecule therapeutic agents that leverage E3 ligase mediated protein degradation to target cancer-associated proteins such as interleukin-1 receptor-associated kinases ("IRAK") hold promise as therapeutic agents. Accordingly, there remains a need to find bifunctional compounds that are IRAK degraders useful as therapeutic agents.

SUMMARY

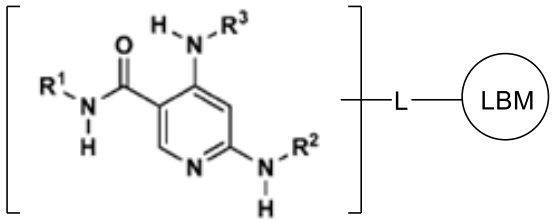
[0007a] In an aspect of the present disclosure, there is provided a compound of formula **I**:



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-vv-2:



I-vv-2,

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is:

(a) C_{2-3} hydroxyalkyl substituted with zero to 4 R^{1a} wherein R^{1a} is independently selected from F, Cl, —OH, —CHF_2, —CN, —CF_3, —OCH_3, and cyclopropyl;

(b) C_{1-3} alkyl substituted with —O(C_{1-3} alkyl) and zero to 4 R^{1a} wherein R^{1a} is independently selected from F, Cl, —OH, —CHF_2, —CN, —CF_3, and cyclopropyl;

(c) C_{4-8} alkyl substituted with zero to 7 R^{1a} wherein R^{1a} is independently selected from F, Cl, —OH, —CHF_2, —CF_3, —CN—OCH_3, cyclopropyl, and —$OP(O)(OH)_2$;

(d) —$(CH_2)_{2-4}$NHC(O)(C_{1-6} alkyl), —$(CH_2)_2$CH(CH_3)NHC(O)(C_{1-6}alkyl), —$(CH_2)_2$CH(CH_3)NHC(O)$(CH_2)_{0-1}$NH(C_{1-6} alkyl), or —$(CH_2)_2$CH(CH_3)NHC(O)$(CH_2)_{0-1}$N(C_{1-4} alkyl)$_2$;

(e) cyclohexyl substituted with zero to 2 substituents independently selected from —OH, —OCH_3, C_{1-6} alkyl, C_{1-6}hydroxyalkyl, —$C(O)NH_2$, —C(O)NH(C_{1-3} alkyl), —C(O)NH(C_{1-6}hydroxyalkyl), —C(O)NH(C_{3-6} cycloalkyl), —C(O)NH(C_{3-6} fluoro cycloalkyl), —NHC(O)(C_{1-3} alkyl), —NHC(O)O(C_{1-3} alkyl), —$NHS(O)_2CH_3$, —$S(O)_2NH_2$, —$S(O)_2$(C_{1-3} alkyl), —S(C_{1-3} alkyl), thiazolyl, methyl pyrazolyl, and C_{1-3} alkyl substituted with —OH and cyclopropyl;

(f) —$(CH_2)_2$(phenyl) wherein said phenyl is substituted with —$C(O)NH_2$, —C(O)NH(C_{1-3} alkyl), or —$S(O)_2NH_2$; or

(g) piperidinyl substituted with —C(O)(C_{1-3} alkyl);

R^2 is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazolyl, thiazolyl, or triazolyl, each substituted with zero to 2 substituents independently selected from F, Cl, —OH, —CN, C_{1-3} alkyl, —$CH_2C(O)OCH_3$, —O(C_{1-3}alkyl), —NH_2, —NH(C_{1-3} alkyl), —NH(cyclopropyl), —$C(O)NH_2$, —NHC(O)(C_{1-3} alkyl), —NH(tetrahydropyranyl), hydroxypyrrolidinyl, ═O, —O(piperidinyl), and pyridinyl; and

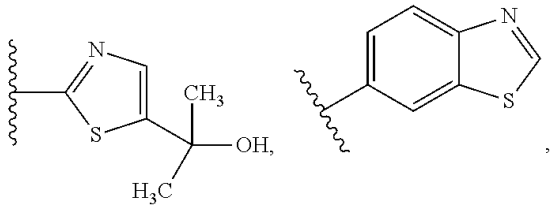
R^3 is:

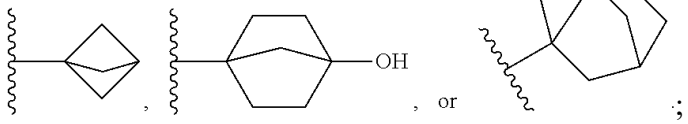
(a) C_{1-6} alkyl substituted with zero to 4 substituents independently selected from F, —OH, —CH_3, —CF_3, and C_{3-6}cycloalkyl;

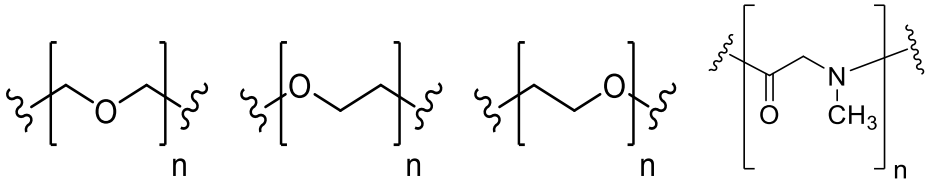
(b) C_{3-6} cycloalkyl substituted with zero to 2 substituents independently selected from F, —OH, C_{1-3} hydroxyalkyl, —CH_3, —CF_2H, —NH_2, and —$C(O)OCH_2CH_3$;

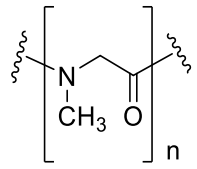
(c) oxetanyl, tetrahydropyranyl, or fluoro tetrahydropyranyl;

(d) phenyl substituted with zero to 2 substituents independently selected from —OH, —CN, —O(C_{1-3} alkyl), C_{1-3} hydroxyalkyl, —$C(O)NH_2$, —$S(O)_2NH_2$, —$NHS(O)_2$(C_{1-3} alkyl), pyrazolyl, imidazolyl, and methyl tetrazolyl; or



(e) ;

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-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -$NRS(O)_2$-, -$S(O)_2$NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, –NRC(O)O-, ,

or , wherein:

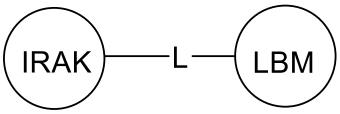
each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated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

each of n is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

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; and

LBM is a ligase binding moiety selected from a cereblon E3 ubiquitin ligase binding moiety and a VHL E3 ubiquitin ligase binding moiety.

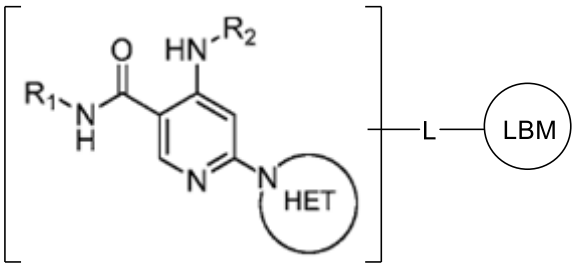
[0007b] In another aspect of the present disclosure, there is provided a compound of formula **I**:



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-hhh-1**:



I-hhh-1,

or a pharmaceutically acceptable salt thereof, wherein:

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

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

R_b is H or —NH_2;

R_1 is:

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

(ii) —(C_{1-3} alkylenyl)R_x, —(C_{1-3} fluoroalkylenyl)R_x, —(C_{1-3}alkylenyl)C(O)R_x, —(C_{1-}

$_{3}$ alkylenyl)C(O)NHR$_x$, —(C$_{1-3}$fluoroalkylenyl)C(O)R$_x$, or —CH$_2$CF=(tetrahydropyranyl), wherein R$_x$ is a cyclic group selected from C$_{3-6}$ cycloalkyl, tetrazolyl, 1,1-dioxidotetrahydrothiophenyl, 1,1-dioxidothiomorpholinyl, oxadiazolyl, piperidinyl, piperazinyl, pyrrolidinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyridinyl, imidazolyl, morpholinyl, phenyl, and triazinyl, wherein each cyclic group is substituted with zero to 3 substituents independently selected from F, —OH, —CH$_3$, —C(CH$_2$)$_2$OH, —OCH$_3$, —C(O)CH$_2$CN, —S(O)$_2$CH$_3$, —S(O)$_2$NH$_2$, —NHC(O)CH$_3$, —N(S(O)$_2$CH$_3$)$_2$, —CH$_2$CH$_2$(acetamidophenyl), —CH$_2$CH$_2$(methoxyphenyl), —CH$_2$CH$_2$(sulfamoylphenyl), oxetanyl, benzyl, and morpholinyl;

(iii) C$_{3-6}$ cycloalkyl or C$_{4-6}$ cycloalkenyl, each substituted with zero to 3 substituents independently selected from F, —OH, —CN, C$_{1-3}$alkyl, C$_{1-3}$ alkoxy, —S(C$_{1-3}$ alkyl), —NO$_2$, —S(O)$_2$(C$_{1-3}$ alkyl), C$_{1-4}$hydroxyalkyl, —C(C$_{1-3}$ alkyl)(OH)(C$_{3-6}$ cycloalkyl), —CH$_2$C(O)NH(C$_{1-3}$ alkyl), —NHC(O)(C$_{1-3}$ alkyl), —NHC(O)(C$_{1-4}$hydroxyalkyl), —C(O)NH(C$_{1-3}$ alkyl), —C(O)NH(C$_{1-3}$ deuteroalkyl), —C(O)NH(C$_{3-6}$ cycloalkyl), —NHC(O)O(C$_{1-3}$ alkyl), —NHS(O)$_2$(C$_{1-3}$alkyl), pyridinyl, imidazolyl, pyrazolyl, methylimidazolyl, methylpyrazolyl, and thiazolyl;

(iv) tetrahydropyranyl, piperidinyl, pyrazolyl, phenyl, pyridinyl, or pyrimidinyl, each substituted with zero to 1 substituent selected from —OH, C$_{1-3}$ alkyl, C$_{1-3}$ fluoroalkyl, C$_{1-4}$ hydroxyalkyl, C$_{1-3}$alkoxy, —C(O)(C$_{1-4}$ alkyl), —S(O)$_2$(C$_{1-4}$ alkyl), —S(O)$_2$NH(C$_{1-4}$ alkyl), —NH(C$_{1-3}$ alkyl), —N(C$_{1-3}$ alkyl)$_2$, —O(C$_{1-3}$ alkylenyl)N(C$_{1-3}$ alkyl)$_2$, —CH$_2$(morpholinyl), azetidinyl, oxetanyl, tetrahydropyranyl, morpholinyl, piperazinyl, piperidinyl, methylpiperazinyl, methoxypiperidinyl, pyridinyl, pyrimidinyl, methylsulfonyl azetidinyl, and —C(O)(methylsulfonyl azetidinyl); or

(v) pyrrolo[2,3-c]pyridinyl, bicyclo[2.2.1]heptan-1-ol, tetrahydrobenzo[d]thiazol-2-amine, or 1,3-diazaspiro[4.5]decane-2,4-dione; and

R$_2$ is:

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

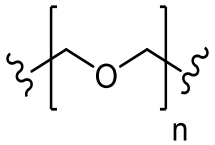
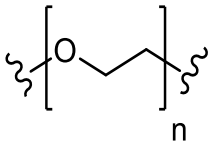
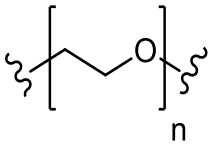
$_{6}$ alkylenyl)NHC(O)(C_{1-4}fluoroalkyl);

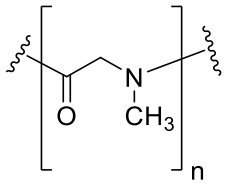
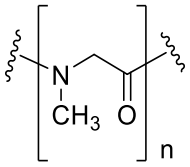
(ii) —(C_{1-4} alkylenyl)R_y wherein R_y is C_{3-6} cycloalkyl, azetidinyl, oxetanyl, oxazolyl, pyridinyl, tetrahydropyranyl, or morpholinyl, each substituted with zero to 2 substituents independently selected from F, —OH, and C_{1-3} alkyl;

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

(iv) adamantanyl, hydroxyadamantanyl, benzo[d]imidazolyl, benzo[d]oxazolyl, benzo[d]triazolyl, benzothiazolyl, bicyclo[1.1.1]pentanyl, or hydroxy-bicyclo[2.2.1]heptanyl; or

(v) phenyl, pyrazolyl, thiazolyl, thiadiazolyl, or indazolyl, each substituted with 0 to 2 substituents independently selected from F, Cl, —OH, —CN, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} fluoroalkyl, C_{1-4}cyanoalkyl, C_{1-3} alkoxy, C_{3-6} cycloalkyl, —(C_{1-3} alkylenyl)O(C_{1-3}alkyl), —(C_{1-3} alkylenyl)O(C_{1-3} fluoroalkyl), —C(O)NH_2, —C(O)NH(C_{1-3} alkyl), —NHC(O)(C_{1-3} alkyl), —NHC(O)$S(O)_2$(C_{1-3}alkyl), —$S(O)_2NH_2$, —$S(O)_2$(C_{1-3} alkyl), pyrazolyl, methyl pyrazolyl, imidazolyl, triazolyl, methyl tetrazolyl, ethyl tetrazolyl, phenyl, pyrimidinyl, fluoropyrimidinyl, and tetrahydropyranyl;

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-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -NRS$(O)_2$-, -$S(O)_2$NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, –NRC(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 4-7 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 4-7 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each of n is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

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;

LBM is a ligase binding moiety selected from a cereblon E3 ubiquitin ligase binding moiety and a VHL E3 ubiquitin ligase binding moiety.

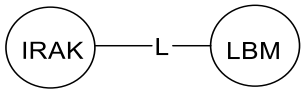
[0007c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0008] The present application relates novel bifunctional compounds, which function to recruit IRAK kinases to E3 Ubiquitin Ligase for degradation, and methods of preparation and uses

thereof. In particular, the present disclosure provides bifunctional compounds, which find utility as modulators of targeted ubiquitination of IRAK kinases, which are then degraded and/or otherwise inhibited by the bifunctional compounds as described herein. An advantage of the compounds provided herein is that a broad range of pharmacological activities is possible, consistent with the degradation/inhibition of IRAK kinases. In addition, the description provides methods of using an effective amount of the compounds as described herein for the treatment or amelioration of a disease condition, such as cancer, e.g., multiple myeloma.

[0009] The present application further relates to targeted degradation of IRAK kinases through the use of bifunctional molecules, including bifunctional molecules that link a cereblon-binding moiety to a ligand that binds IRAK kinasses.

[0010] It has now been found that compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are effective as degraders of IRAK kinases. Such compounds have the general formula **I**:



I

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

[0011] Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of signaling pathways implicating IRAK kinases. Such diseases, disorders, or conditions include those described herein.

[0012] Compounds provided by the 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

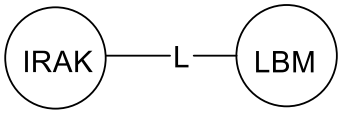
1. General Description of Certain Embodiments of the Invention:

[0013] 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

CLAIMS

We claim:

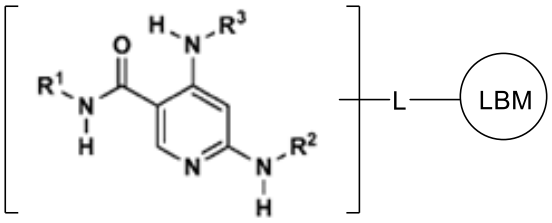
1. A compound of formula **I**:



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-vv-2:



I-vv-2,

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is:

(a) C_{2-3} hydroxyalkyl substituted with zero to 4 R^{1a} wherein R^{1a} is independently selected from F, Cl, —OH, —CHF_2, —CN, —CF_3, —OCH_3, and cyclopropyl;

(b) C_{1-3} alkyl substituted with —O(C_{1-3} alkyl) and zero to 4 R^{1a} wherein R^{1a} is independently selected from F, Cl, —OH, —CHF_2, —CN, —CF_3, and cyclopropyl;

(c) C_{4-8} alkyl substituted with zero to 7 R^{1a} wherein R^{1a} is independently selected from F, Cl, —OH, —CHF_2, —CF_3, —CN—OCH_3, cyclopropyl, and —$OP(O)(OH)_2$;

(d) —$(CH_2)_{2-4}$NHC(O)(C_{1-6} alkyl), —$(CH_2)_2$CH(CH_3)NHC(O)(C_{1-6}alkyl), —$(CH_2)_2$CH(CH_3)NHC(O)$(CH_2)_{0-1}$NH(C_{1-6} alkyl), or —$(CH_2)_2$CH(CH_3)NHC(O)$(CH_2)_{0-1}$N(C_{1-4} alkyl)$_2$;

(e) cyclohexyl substituted with zero to 2 substituents independently selected from —OH, —OCH_3, C_{1-6} alkyl, C_{1-6}hydroxyalkyl, —$C(O)NH_2$, —C(O)NH(C_{1-3} alkyl), —C(O)NH(C_{1-6}hydroxyalkyl), —C(O)NH(C_{3-6} cycloalkyl), —C(O)NH(C_{3-}

$_6$ fluoro cycloalkyl), —NHC(O)(C_{1-3} alkyl), —NHC(O)O(C_{1-3} alkyl), —$NHS(O)_2CH_3$, —$S(O)_2NH_2$, —$S(O)_2$(C_{1-3} alkyl), —S(C_{1-3} alkyl), thiazolyl, methyl pyrazolyl, and C_{1-3} alkyl substituted with —OH and cyclopropyl;

(f) —$(CH_2)_2$(phenyl) wherein said phenyl is substituted with —$C(O)NH_2$, —C(O)NH(C_{1-3} alkyl), or —$S(O)_2NH_2$; or

(g) piperidinyl substituted with —C(O)(C_{1-3} alkyl);

R^2 is phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazolyl, thiazolyl, or triazolyl, each substituted with zero to 2 substituents independently selected from F, Cl, —OH, —CN, C_{1-3} alkyl, —$CH_2C(O)OCH_3$, —O(C_{1-3}alkyl), —NH_2, —NH(C_{1-3} alkyl), —NH(cyclopropyl), —$C(O)NH_2$, —NHC(O)(C_{1-3} alkyl), —NH(tetrahydropyranyl), hydroxypyrrolidinyl, ═O, —O(piperidinyl), and pyridinyl; and

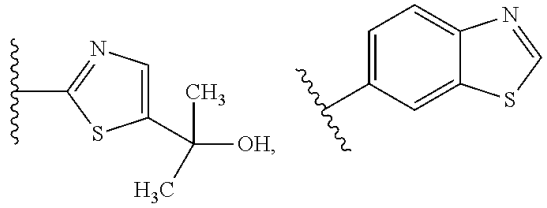
R^3 is:

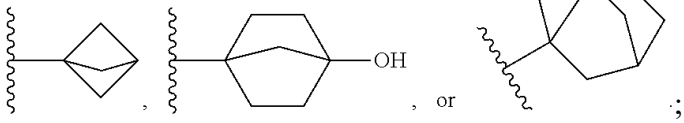
(a) C_{1-6} alkyl substituted with zero to 4 substituents independently selected from F, —OH, —CH_3, —CF_3, and C_{3-6}cycloalkyl;

(b) C_{3-6} cycloalkyl substituted with zero to 2 substituents independently selected from F, —OH, C_{1-3} hydroxyalkyl, —CH_3, —CF_2H, —NH_2, and —$C(O)OCH_2CH_3$;

(c) oxetanyl, tetrahydropyranyl, or fluoro tetrahydropyranyl;

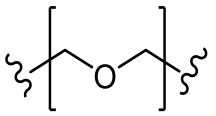
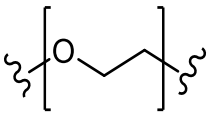
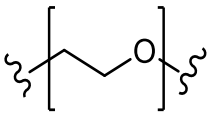
(d) phenyl substituted with zero to 2 substituents independently selected from —OH, —CN, —O(C_{1-3} alkyl), C_{1-3} hydroxyalkyl, —$C(O)NH_2$, —$S(O)_2NH_2$, —$NHS(O)_2$(C_{1-3} alkyl), pyrazolyl, imidazolyl, and methyl tetrazolyl; or

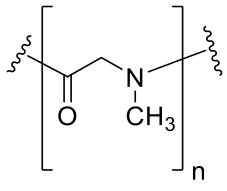
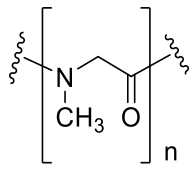


(e) 

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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-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -$NRS(O)_2$-, -$S(O)_2NR$-, -NRC(O)-, -

C(O)NR-, -OC(O)NR-, –NRC(O)O-, , , ,

, or , wherein:

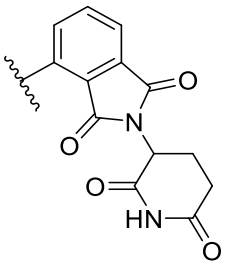
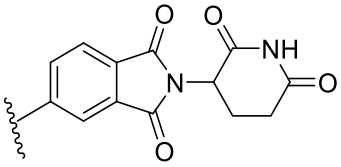
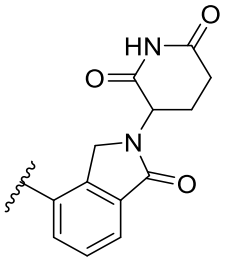
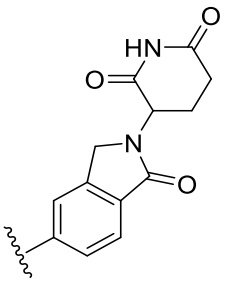
each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated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

each of n is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

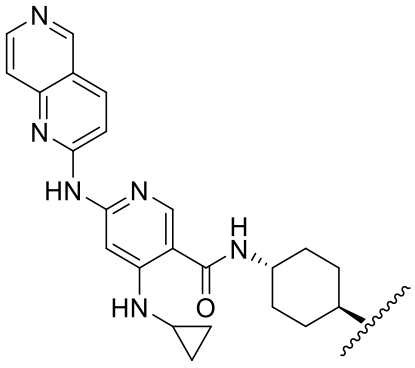
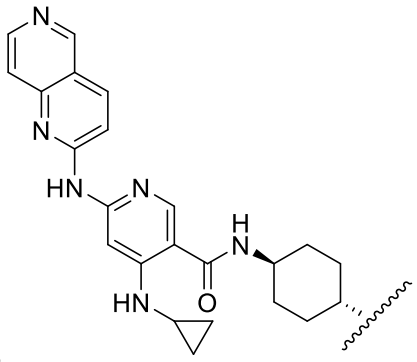
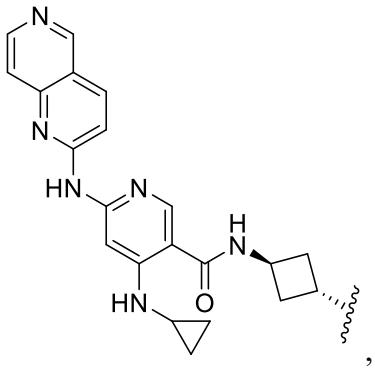
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

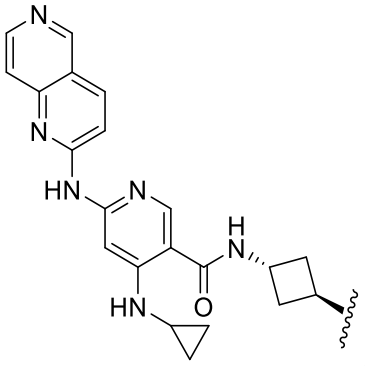
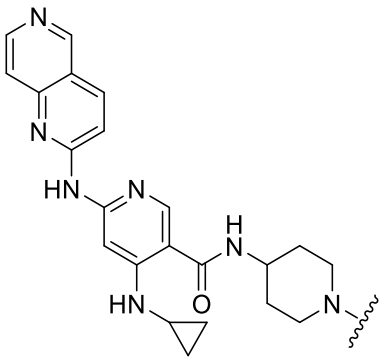
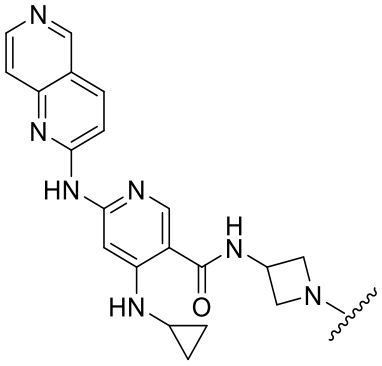
LBM is a ligase binding moiety selected from a cereblon E3 ubiquitin ligase binding moiety and a VHL E3 ubiquitin ligase binding moiety.

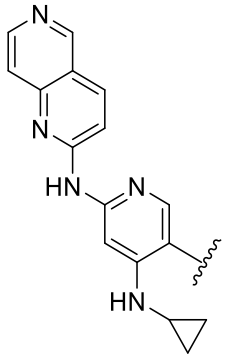
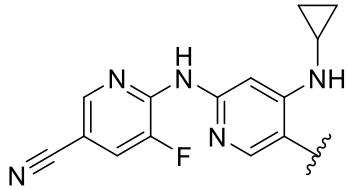
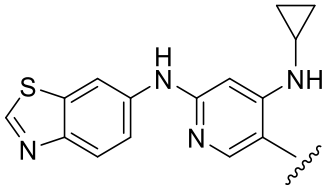
2. The compound according to claim 1, wherein the cereblon E3 ubiquitin ligase binding

moiety is selected from , , , and .

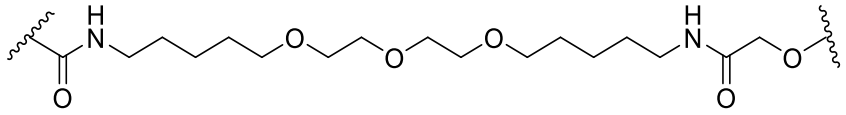
3. The compound according to claim 1, wherein the IRAK4 binding moiety is selected from:

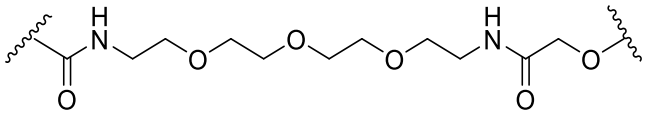
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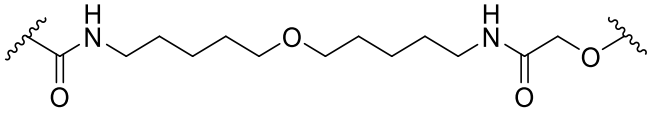
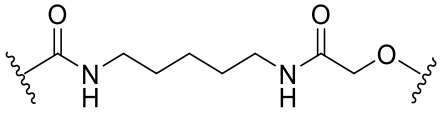
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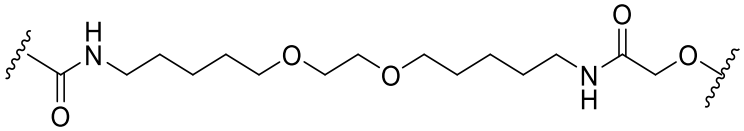
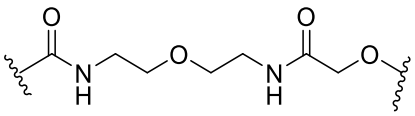

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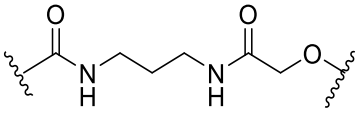
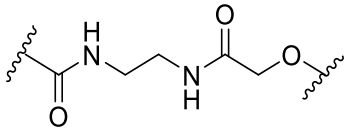
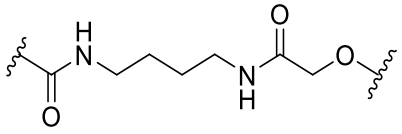
4. The compound of claim 1, wherein L is selected from:

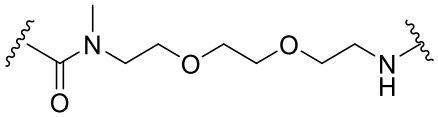
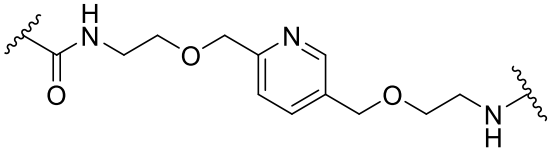

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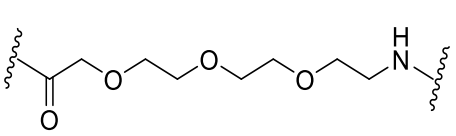
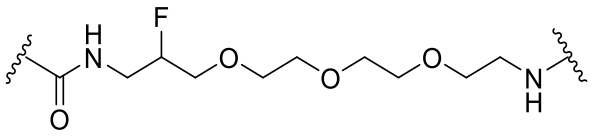

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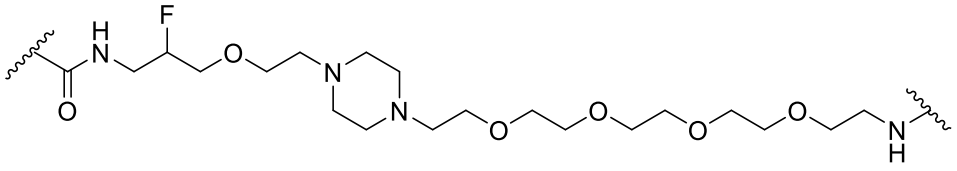

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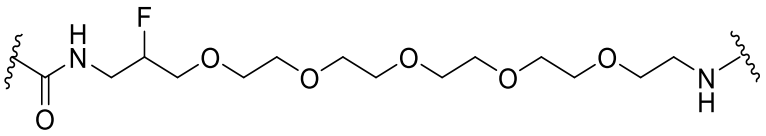

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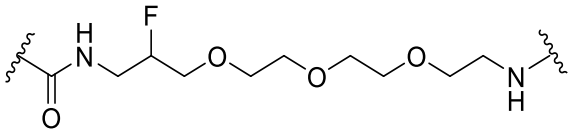

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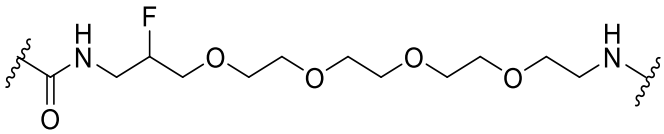

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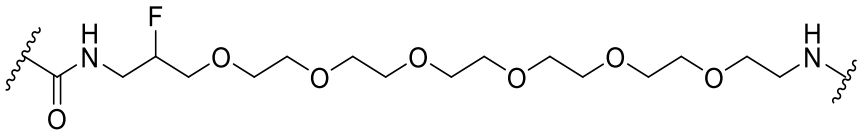

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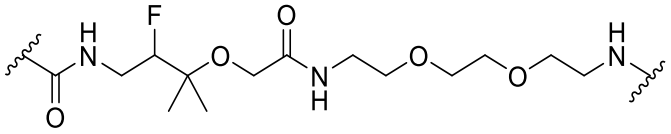

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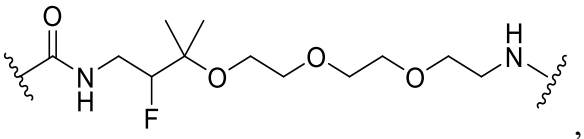

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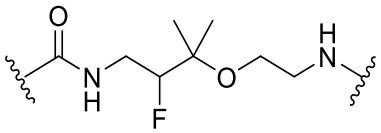

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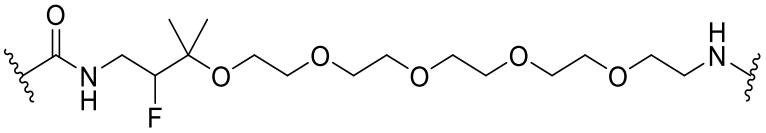

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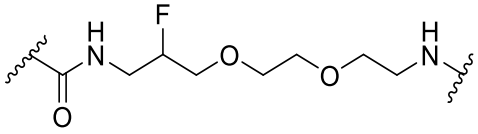

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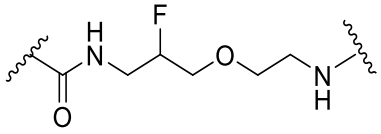

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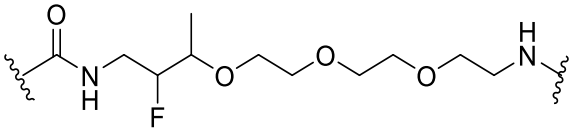

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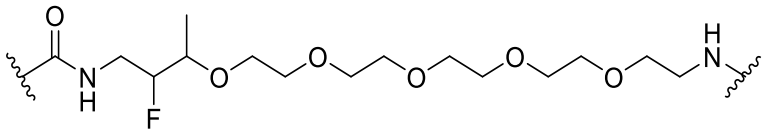
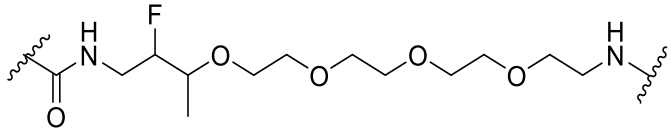
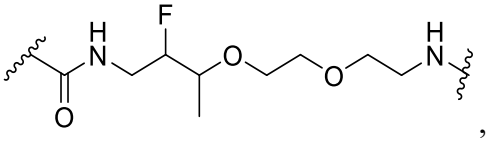
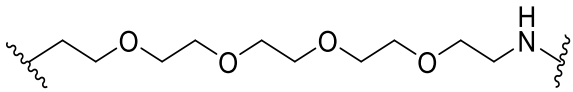
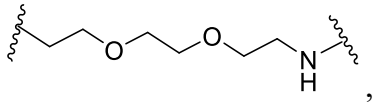
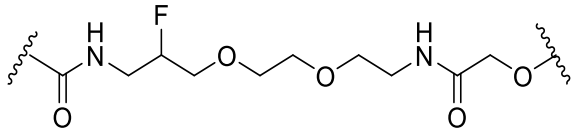
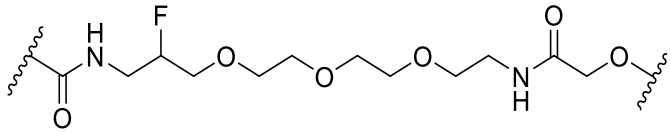
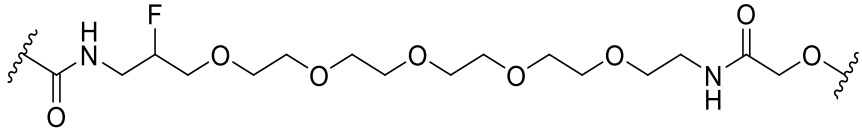
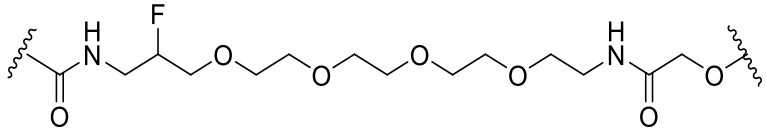
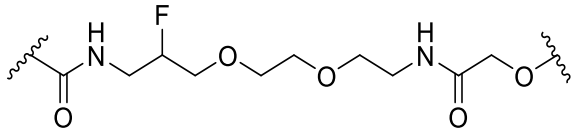
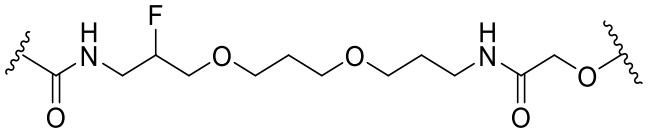
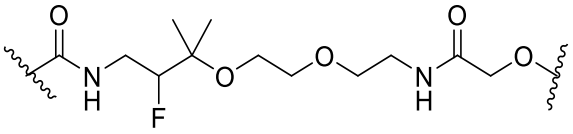
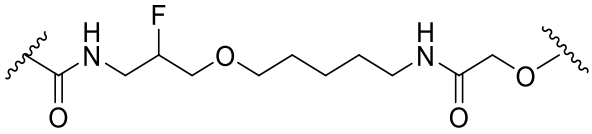
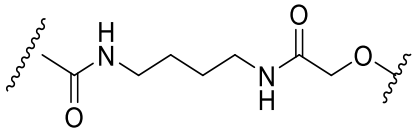
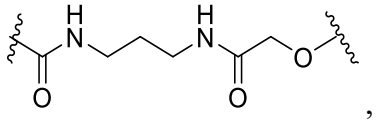

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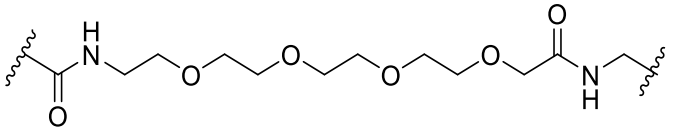
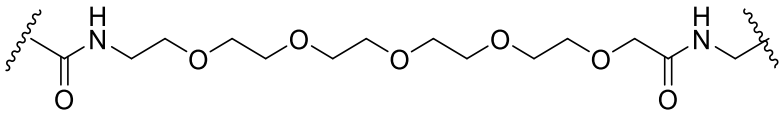
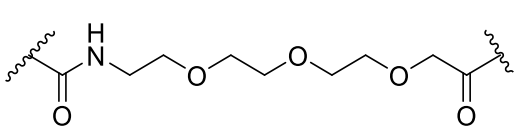
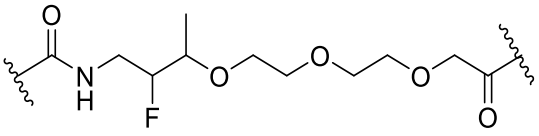
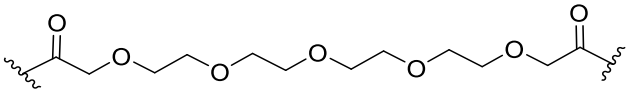
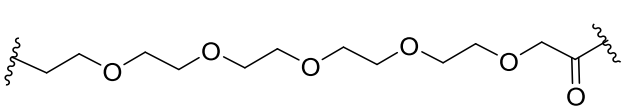
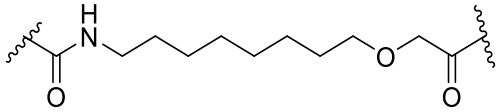
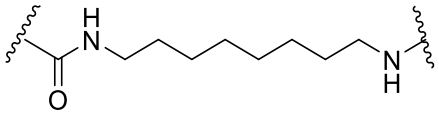
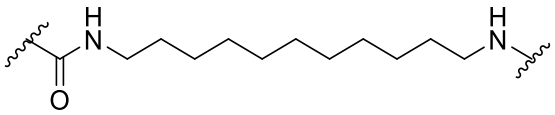
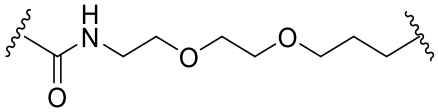
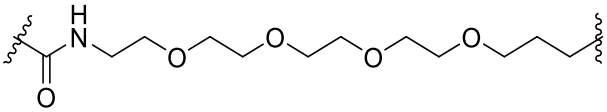
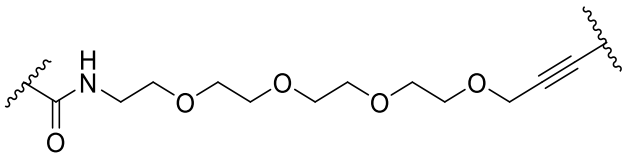
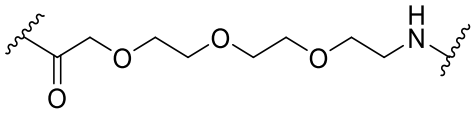
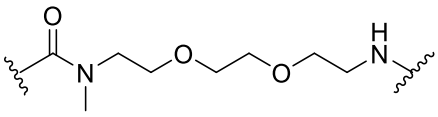
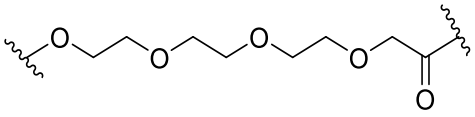
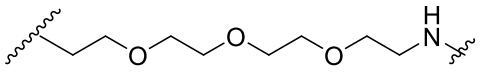
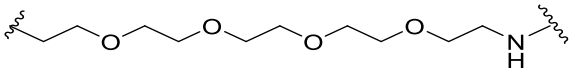
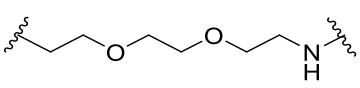
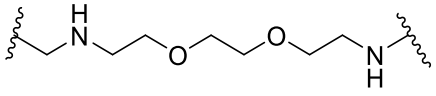

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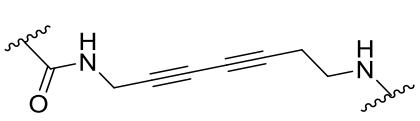
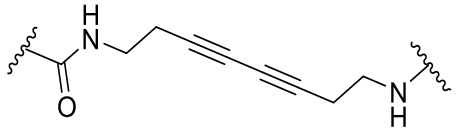
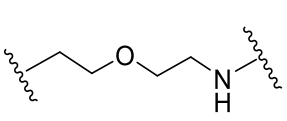

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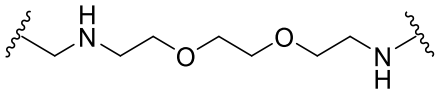
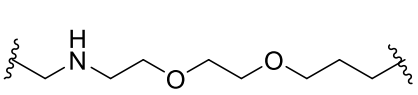
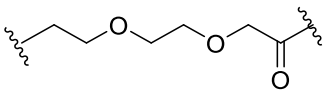
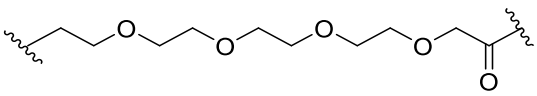
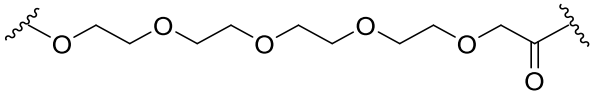
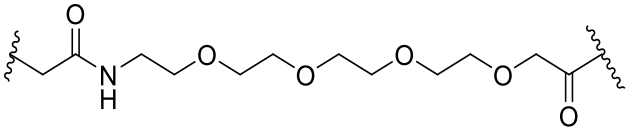
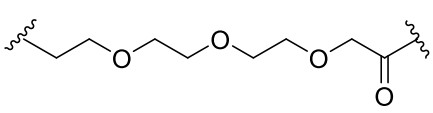
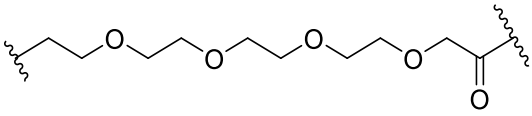
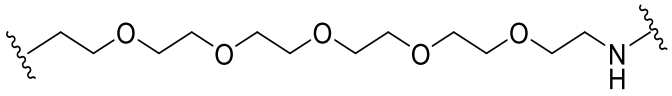
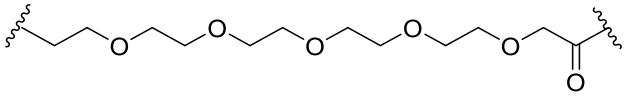
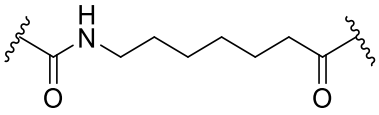
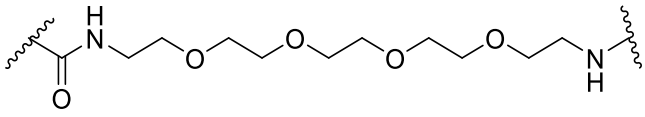
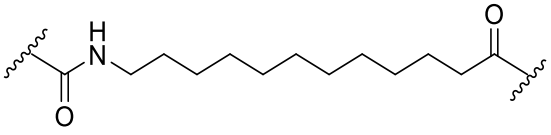
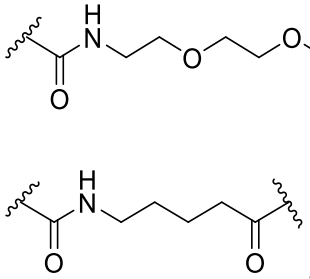
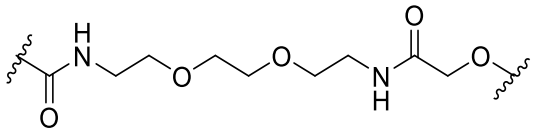
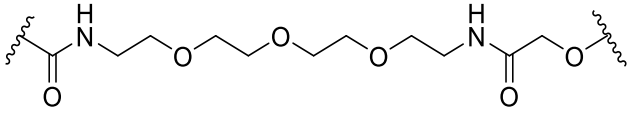
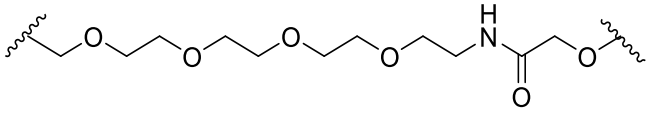
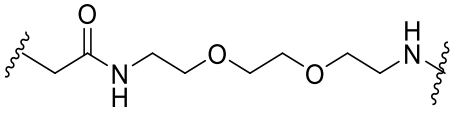
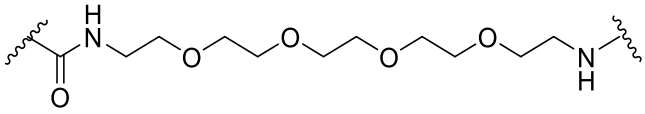

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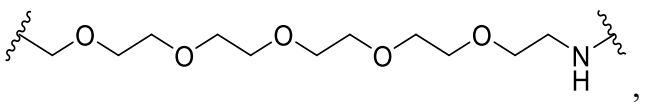
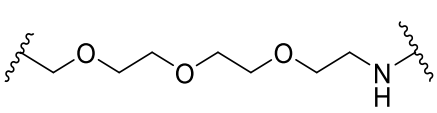

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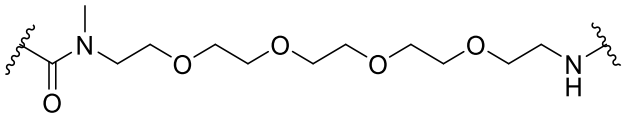
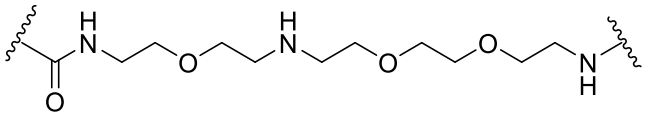
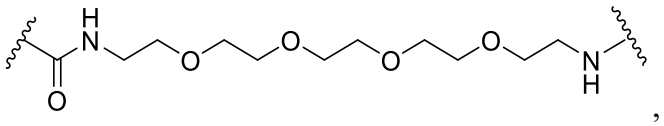
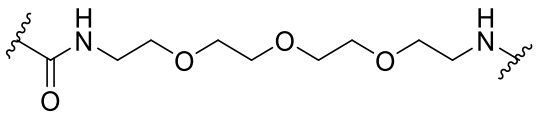
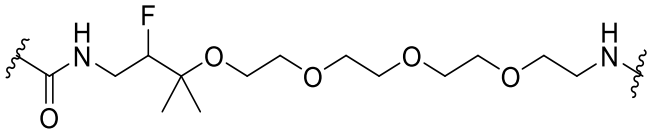
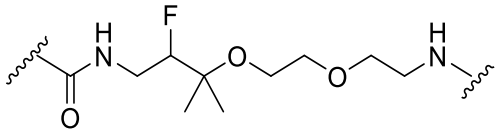
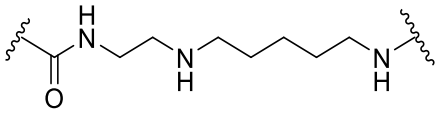
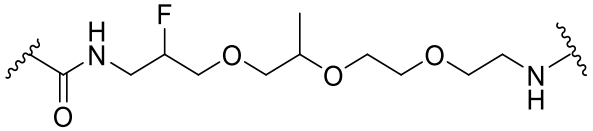
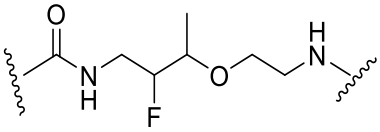
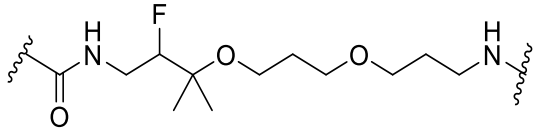
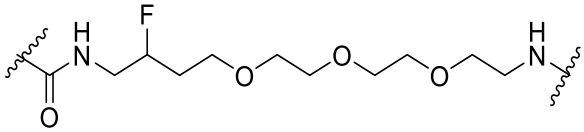
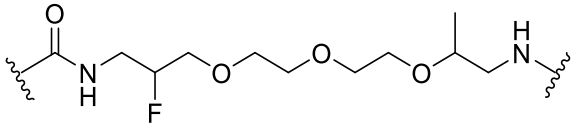
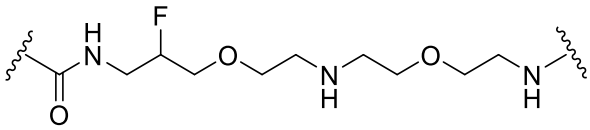
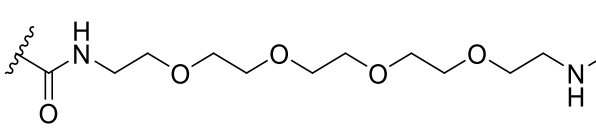
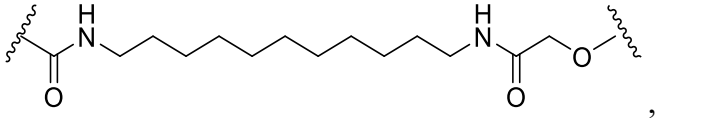
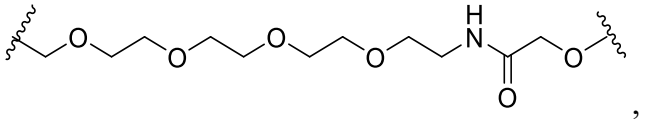
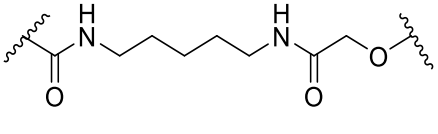

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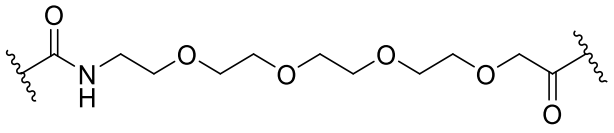
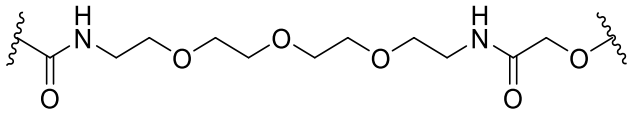
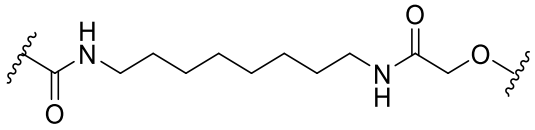
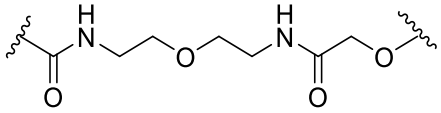
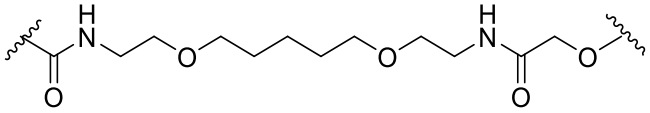
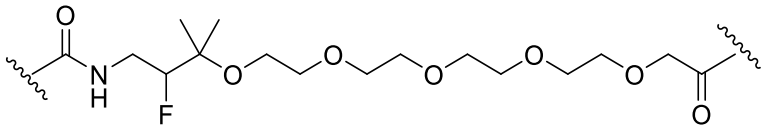
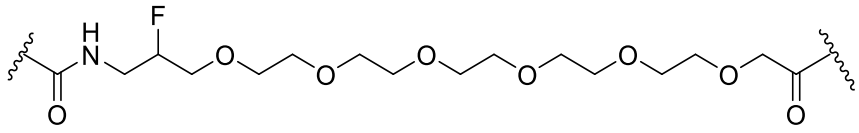
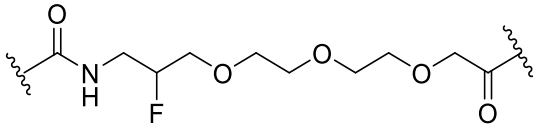
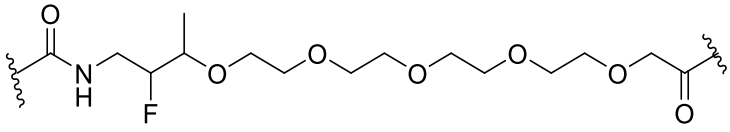
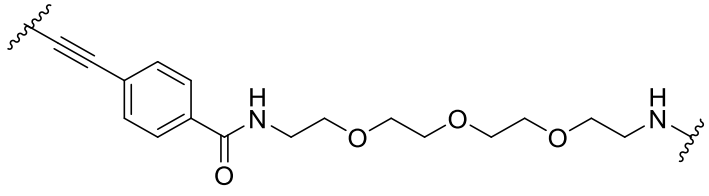
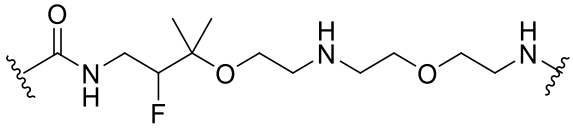
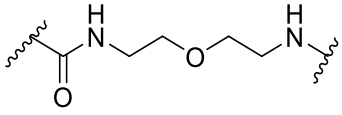
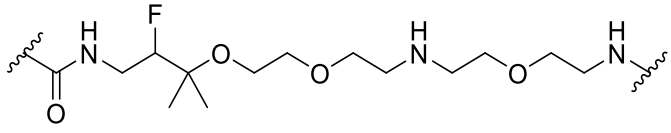
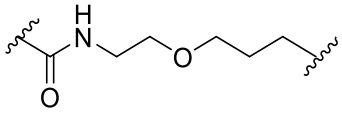
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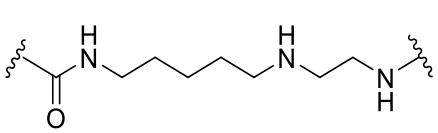
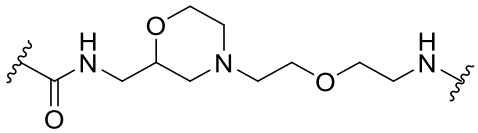
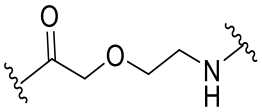
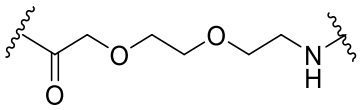
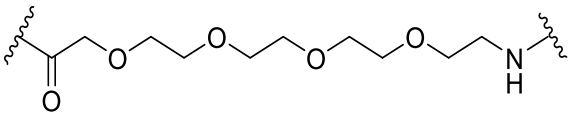
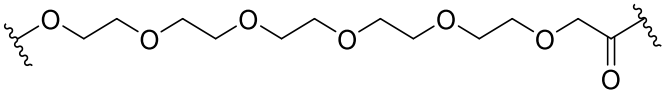
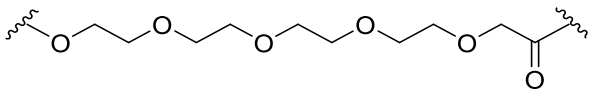
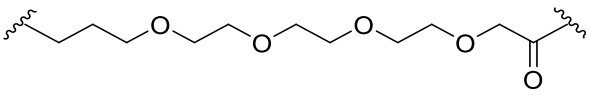
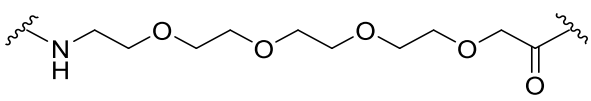
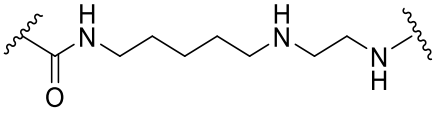
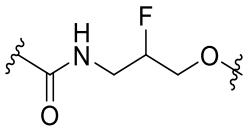
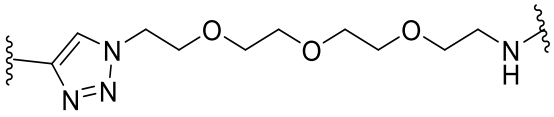
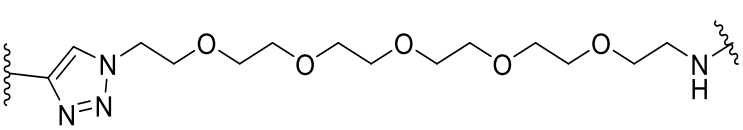
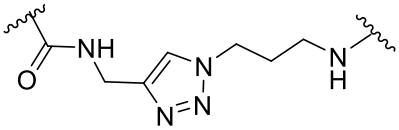
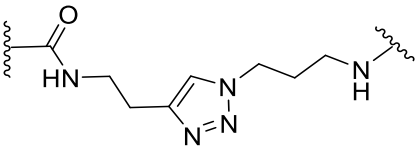
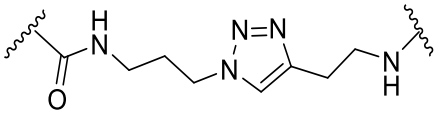
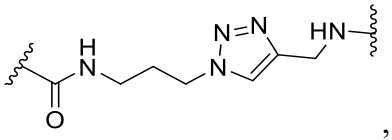
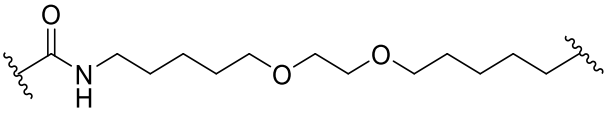
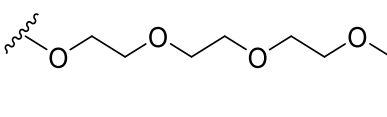
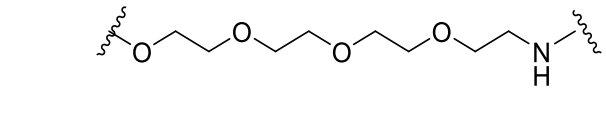

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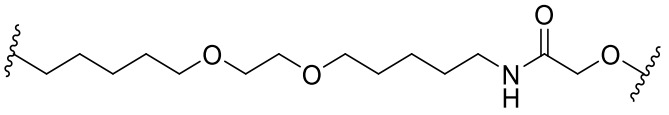
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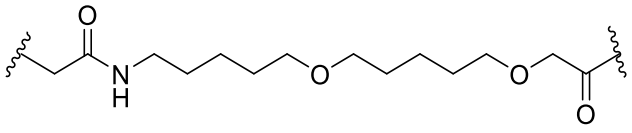

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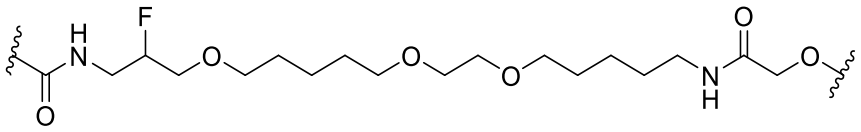

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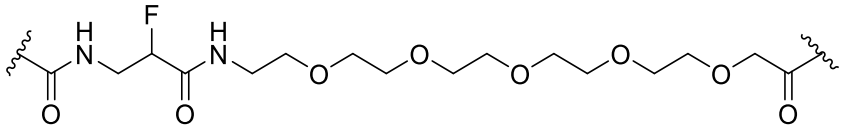

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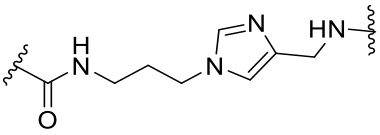
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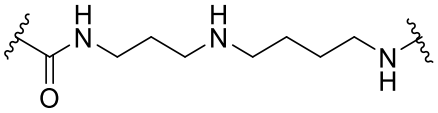
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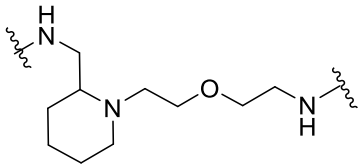


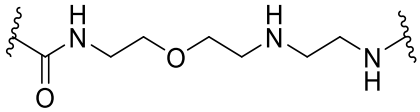


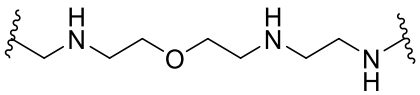


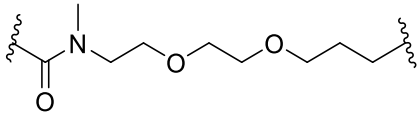


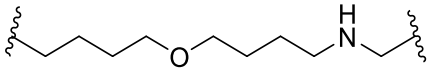


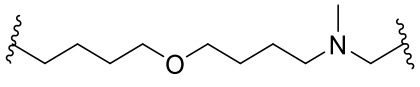


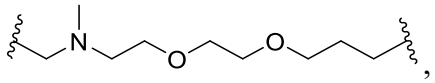


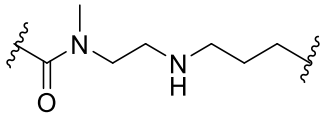


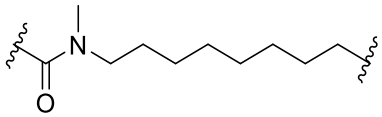


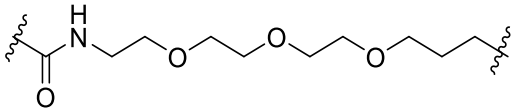


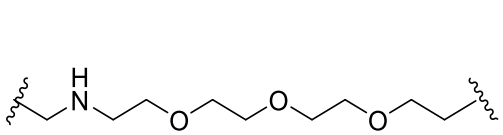


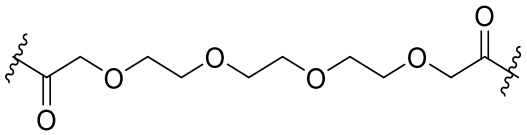


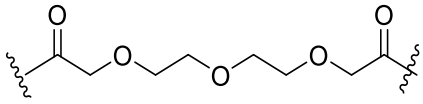


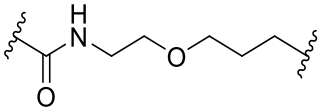


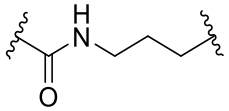


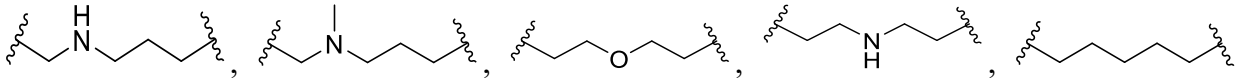


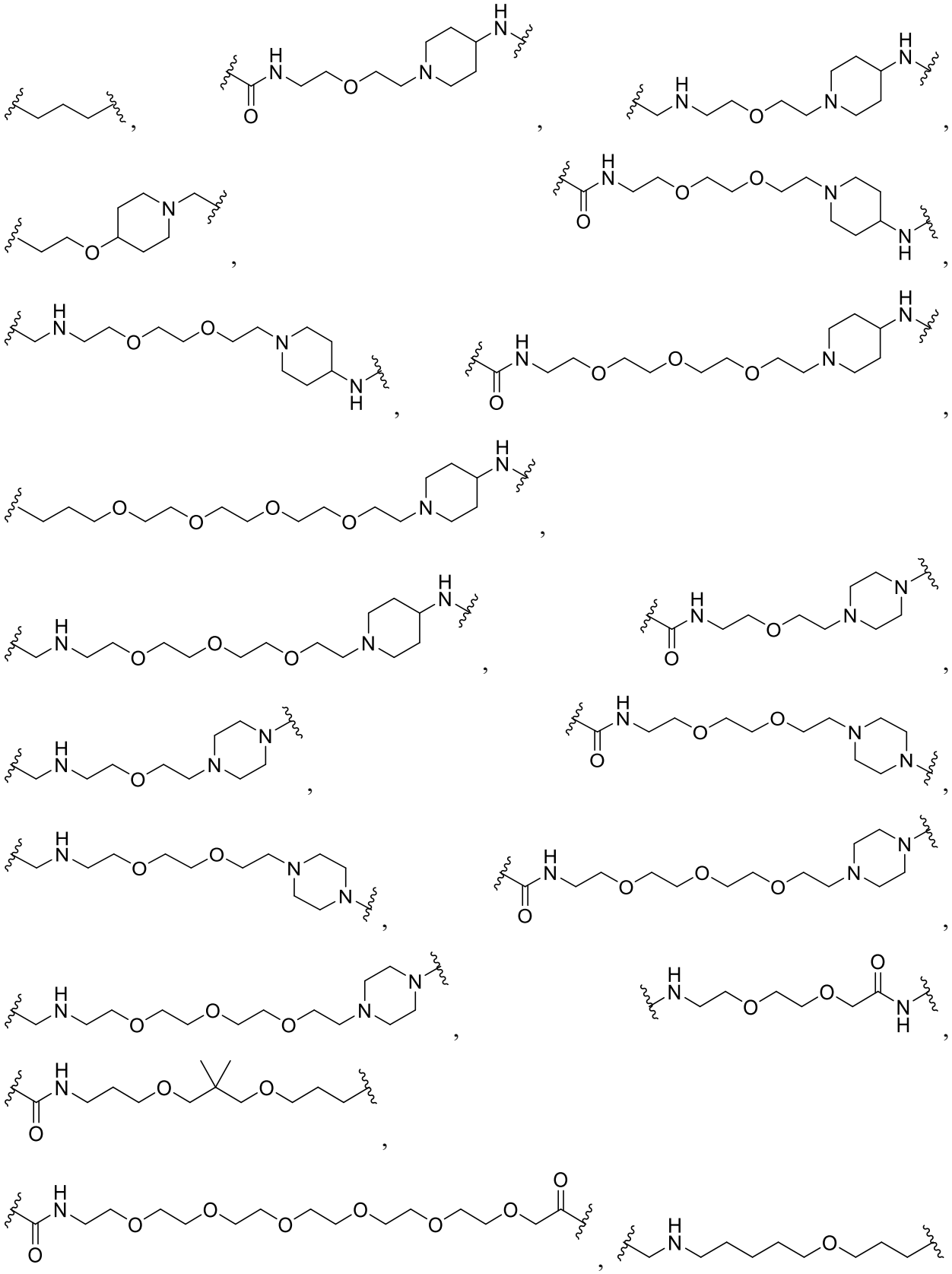


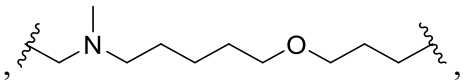
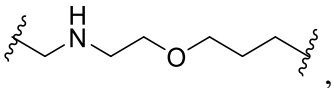
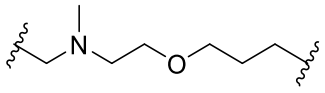
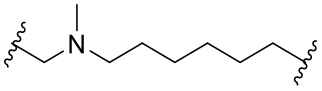
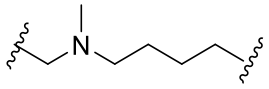
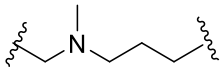
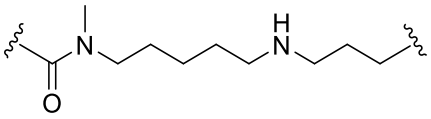
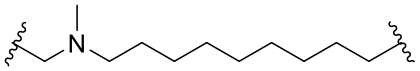
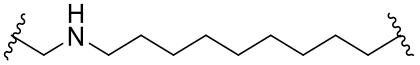
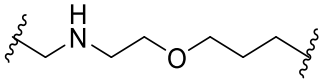
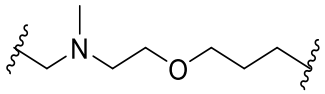
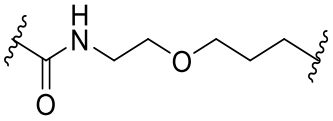
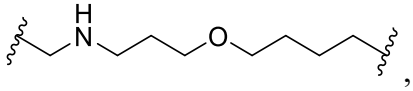
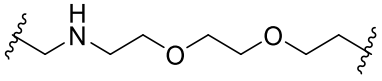
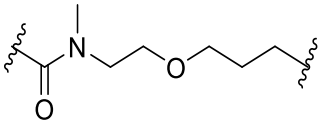
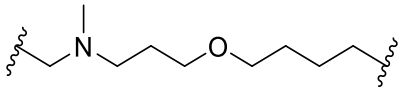
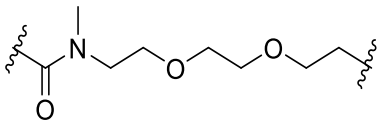
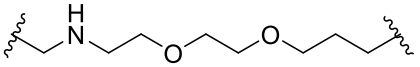
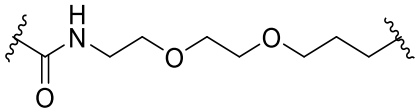
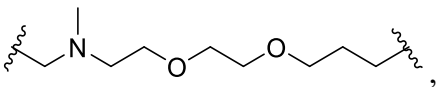
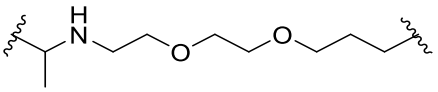
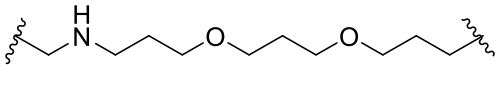
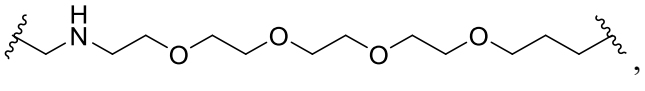
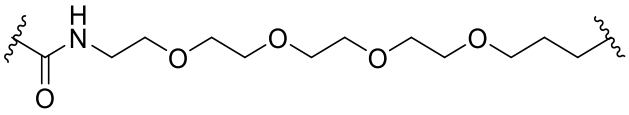
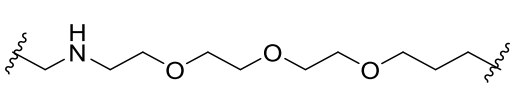
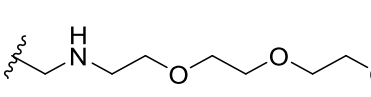
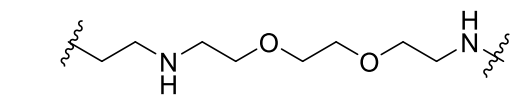
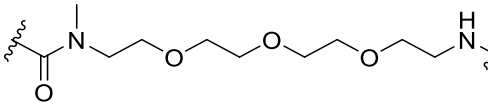
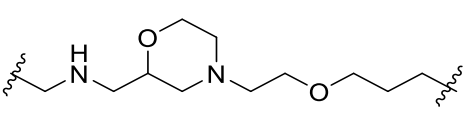
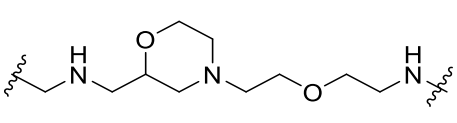


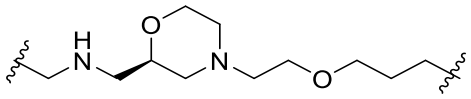
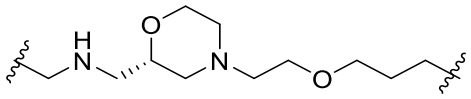
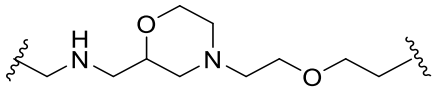
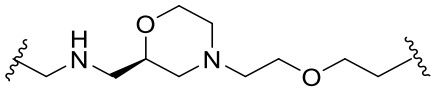
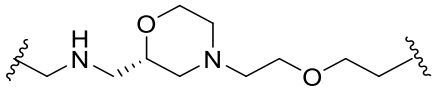
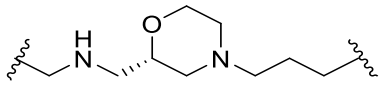
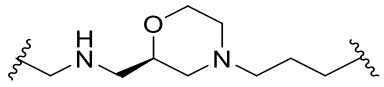
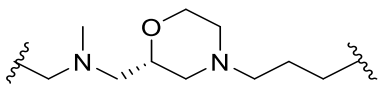
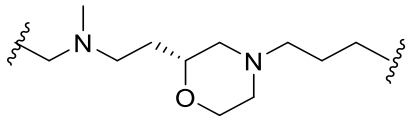
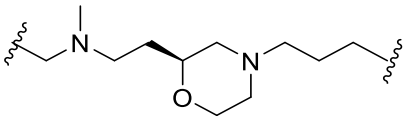
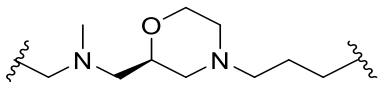
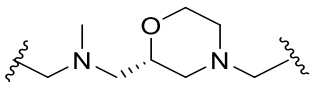
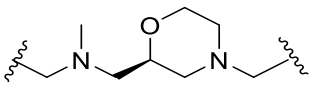
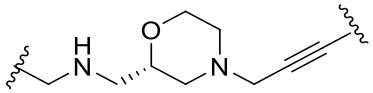
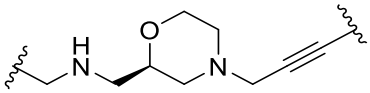
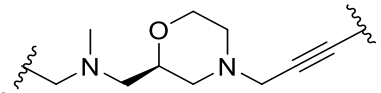
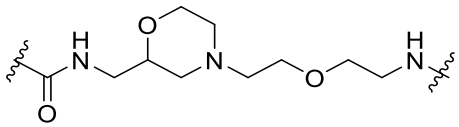
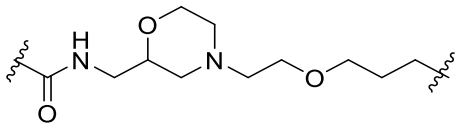
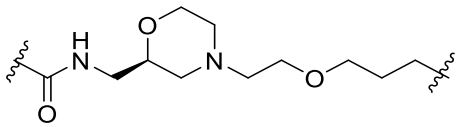
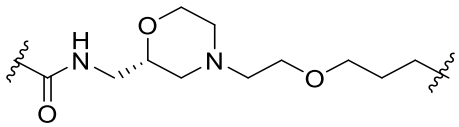
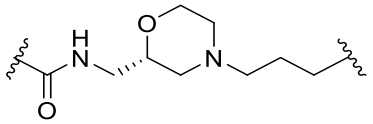
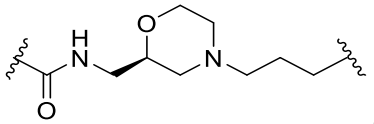
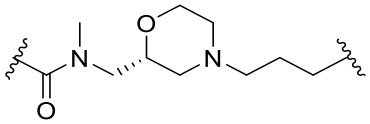
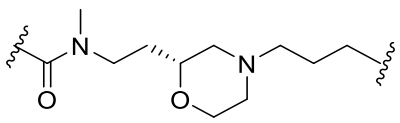
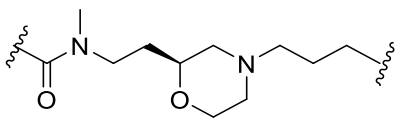
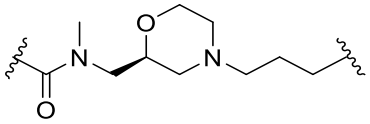
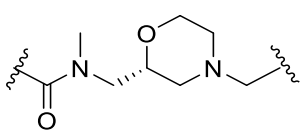
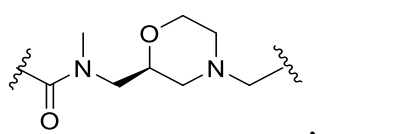
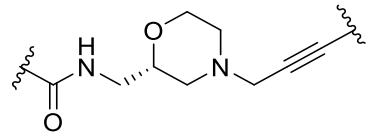
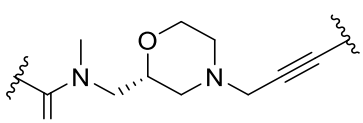
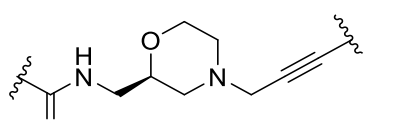
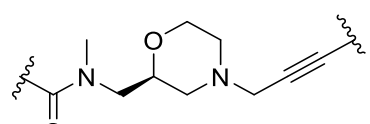








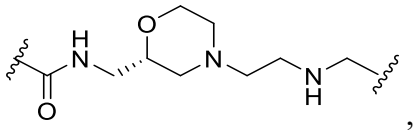
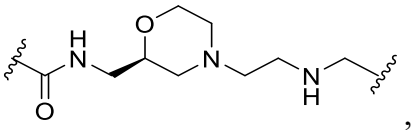
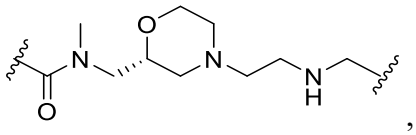
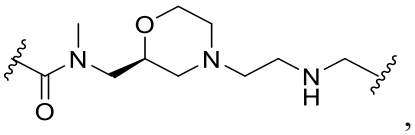
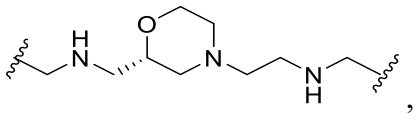
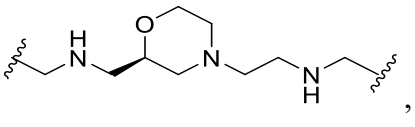
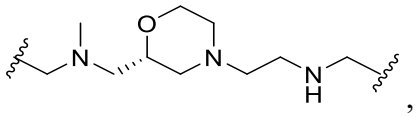
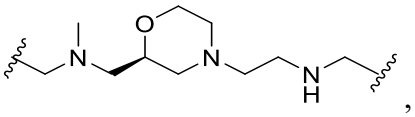
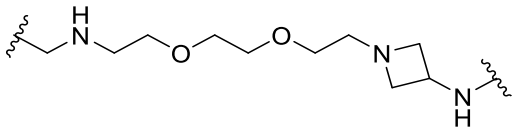
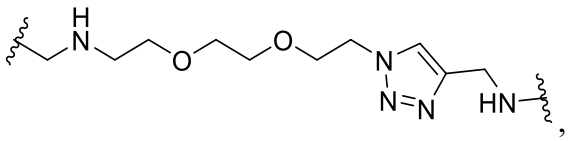
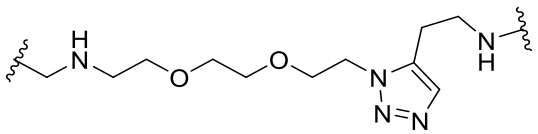
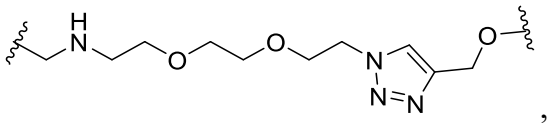
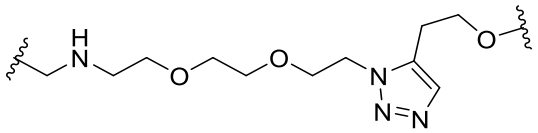
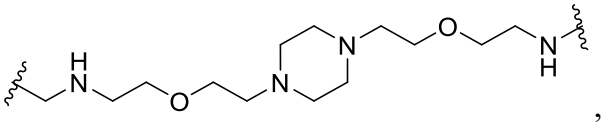
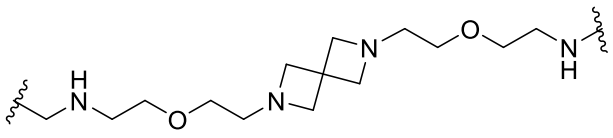
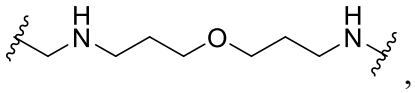
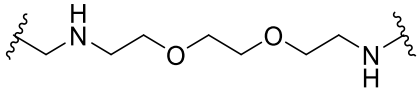
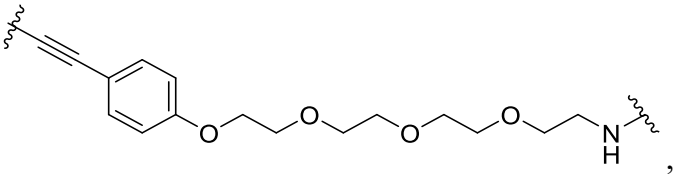
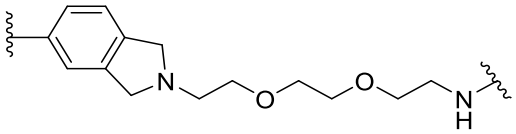
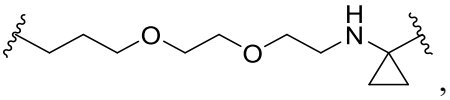
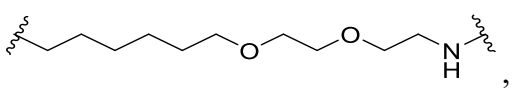
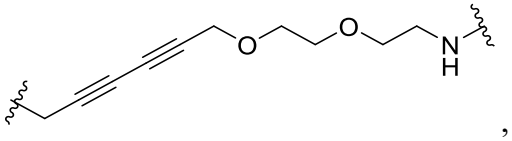































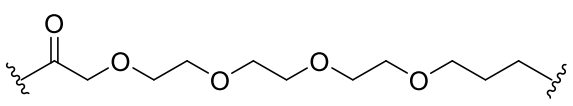
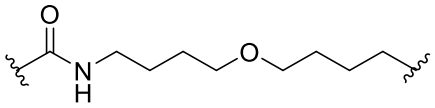
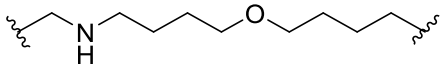
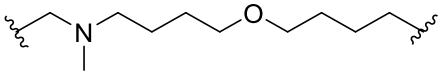
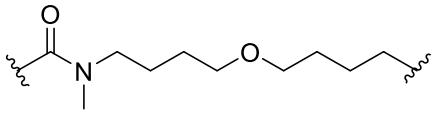
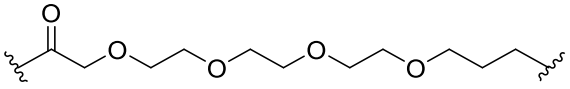
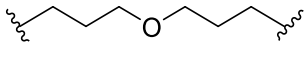
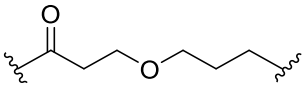
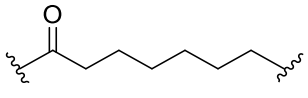
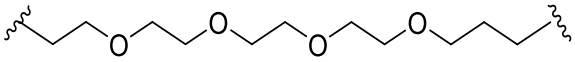
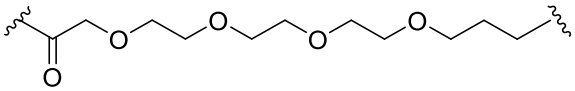
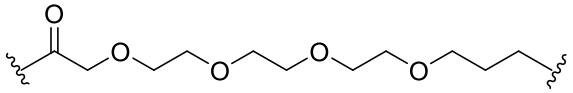
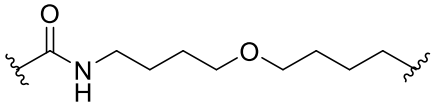
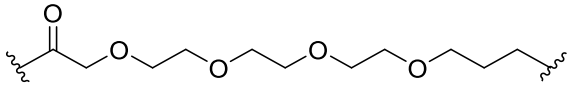
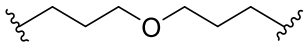
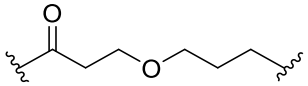
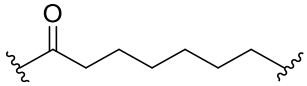
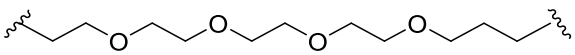
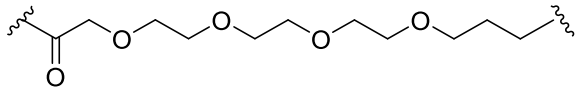
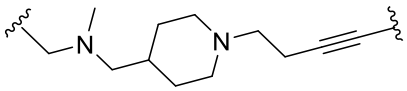
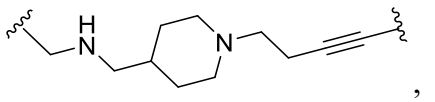
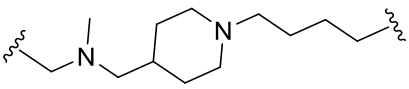
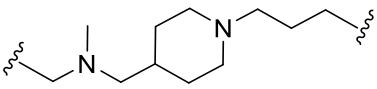
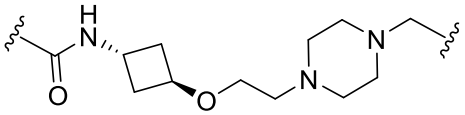
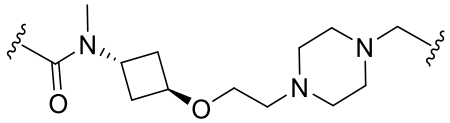

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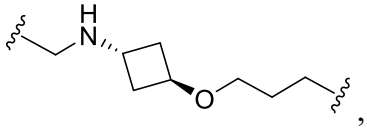
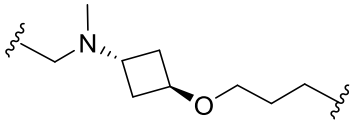
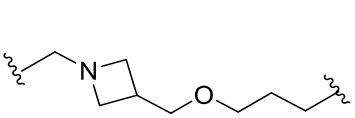
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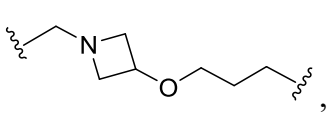
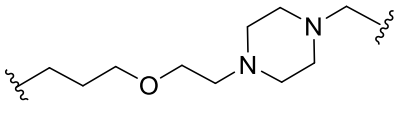
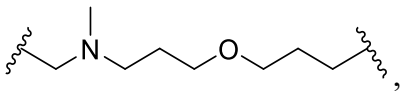
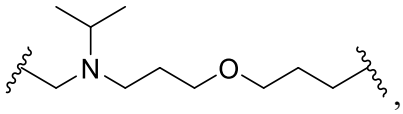
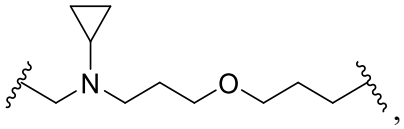
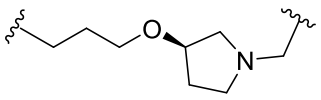
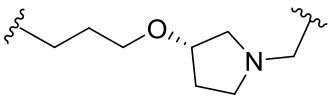
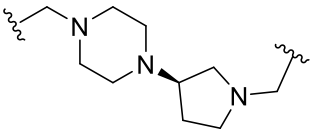
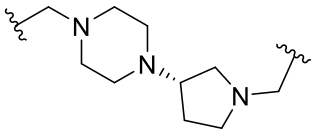
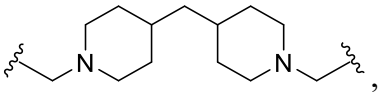
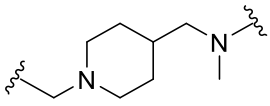
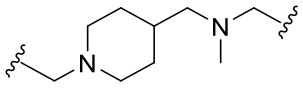
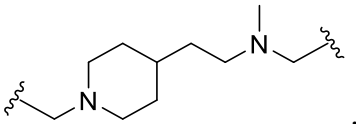
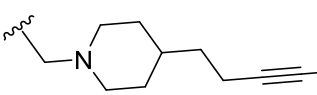
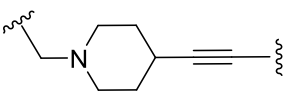
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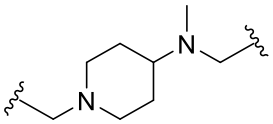
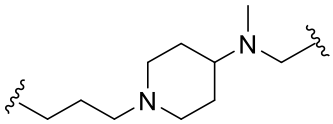
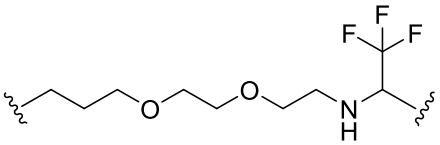
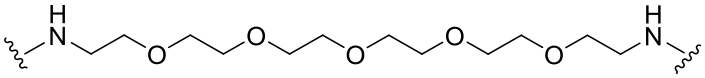
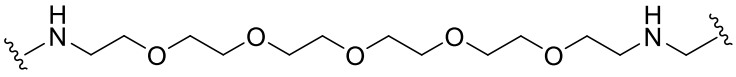
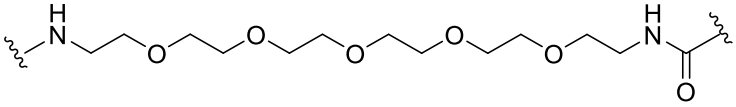
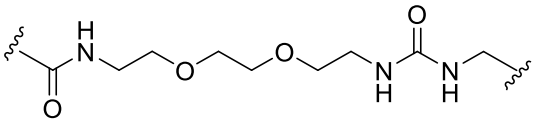
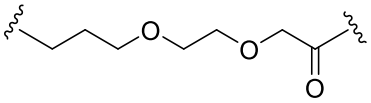
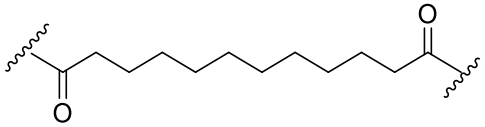
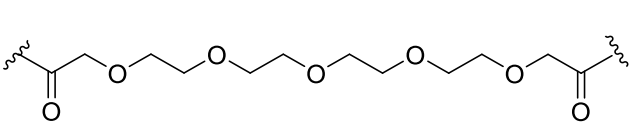
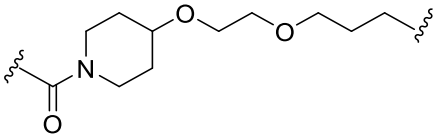
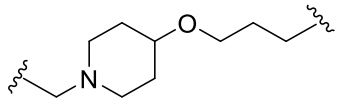
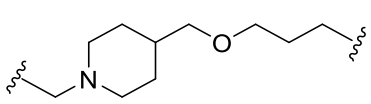
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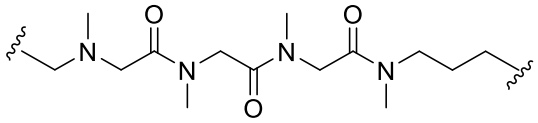
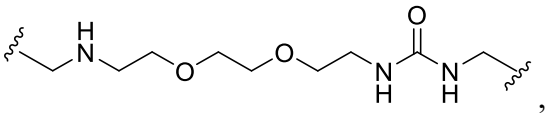
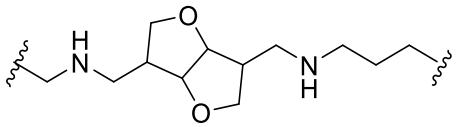
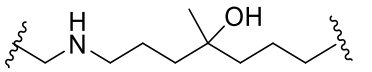
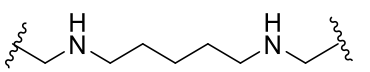
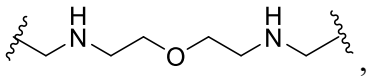
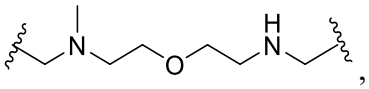
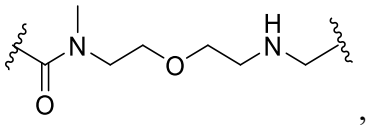
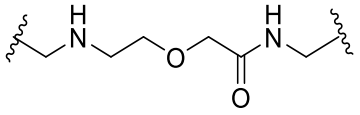
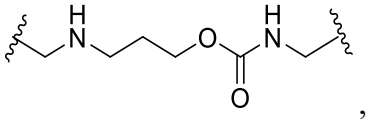
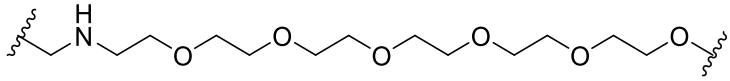
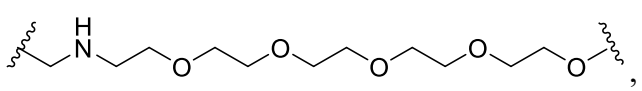
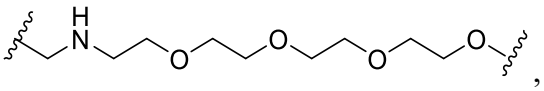
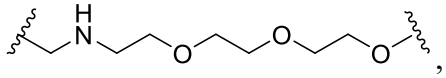
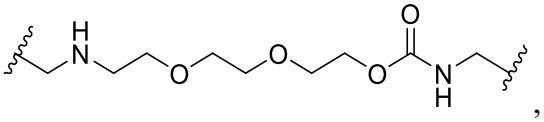
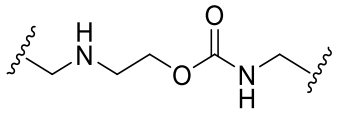
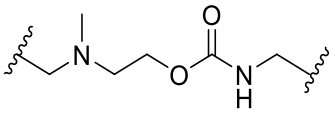
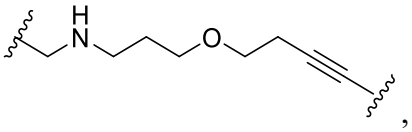
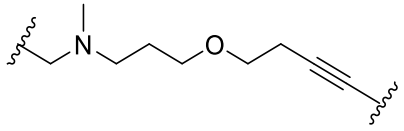
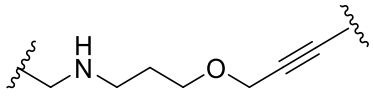
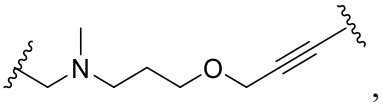
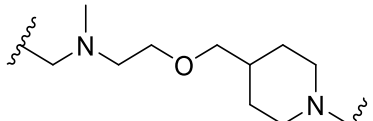
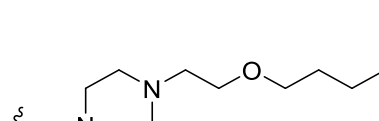
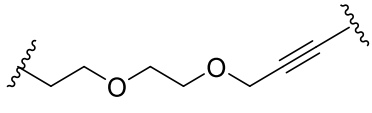
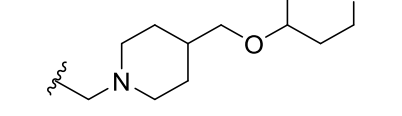
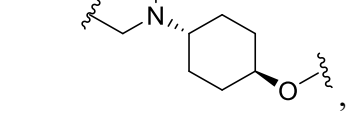
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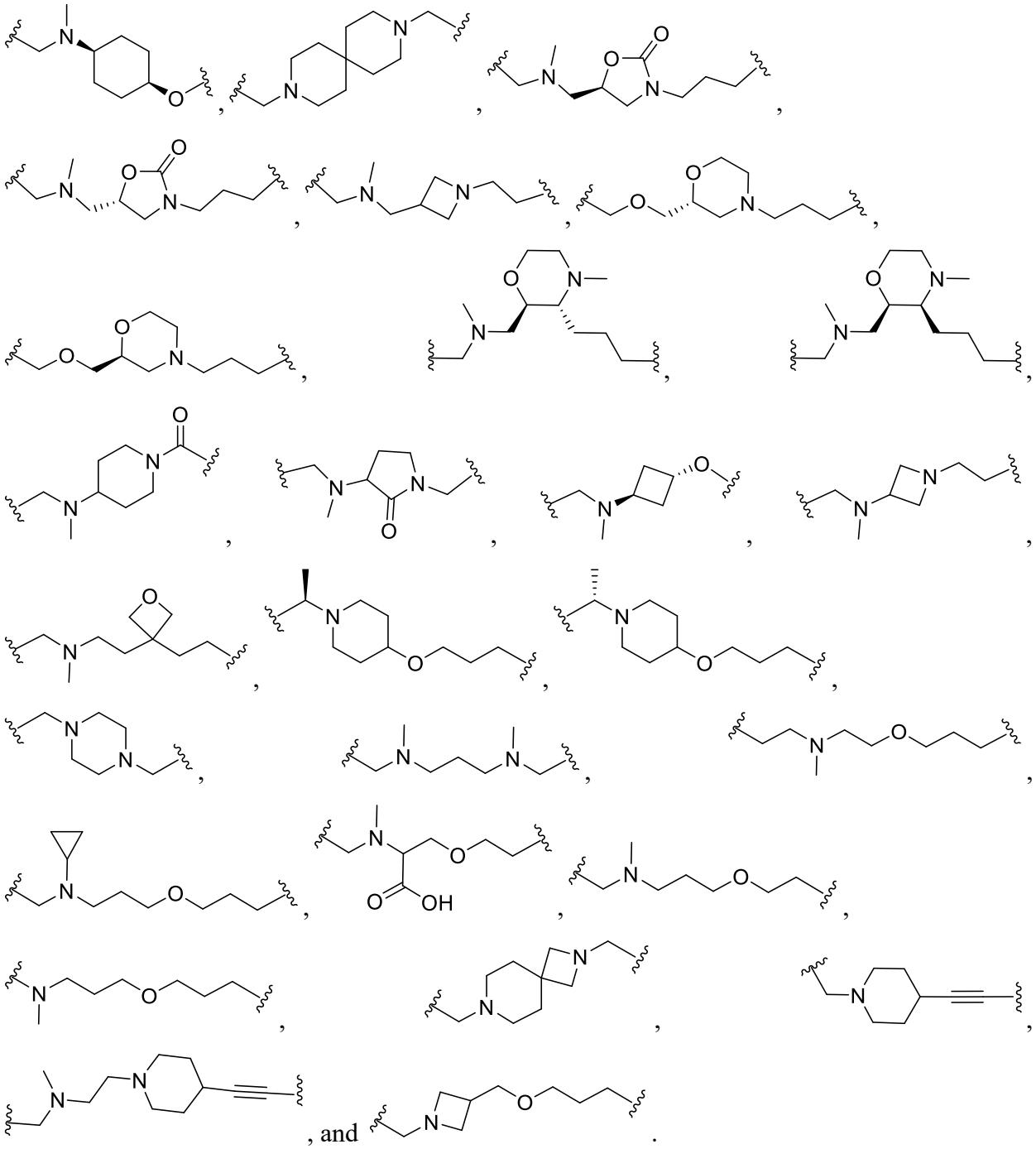
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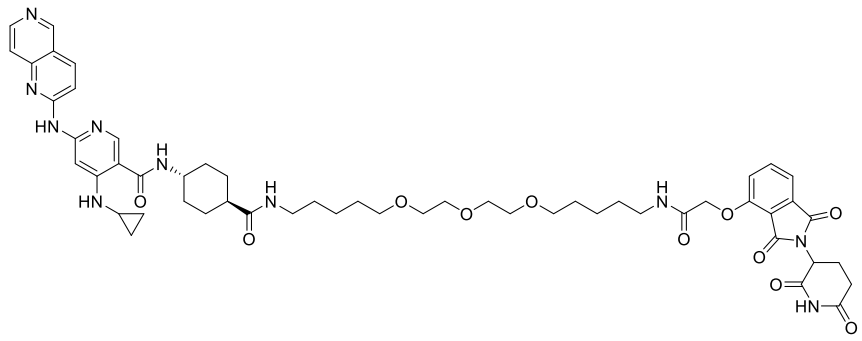
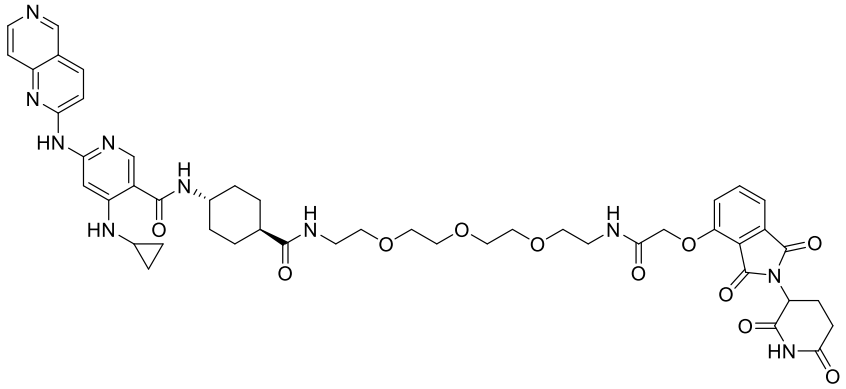
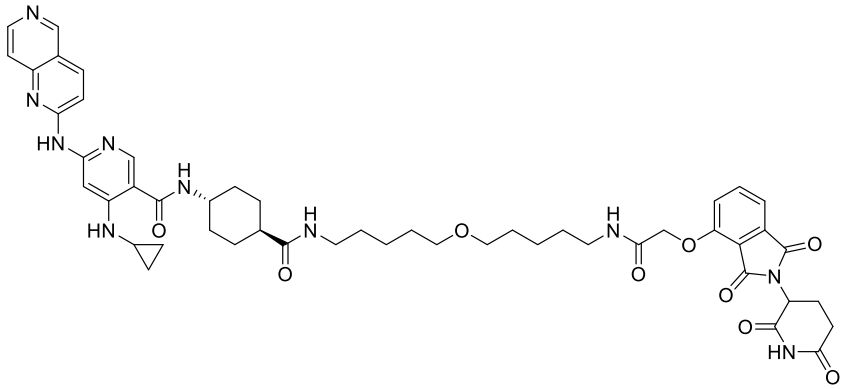
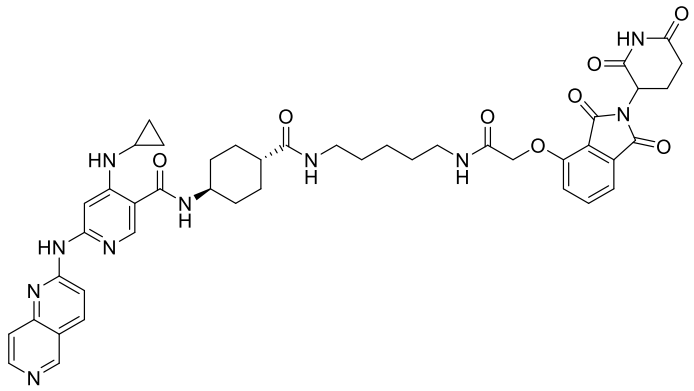
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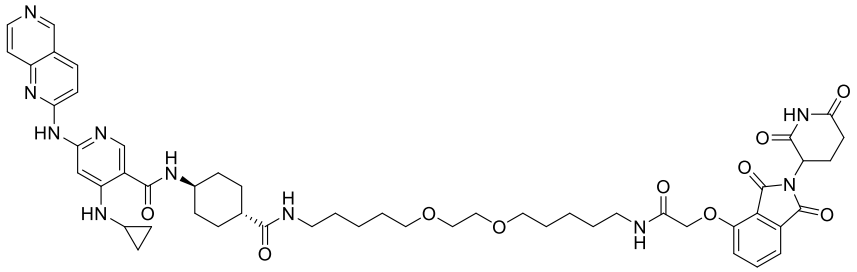
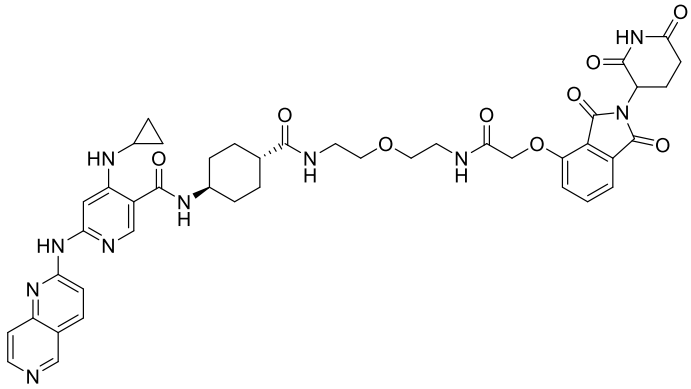
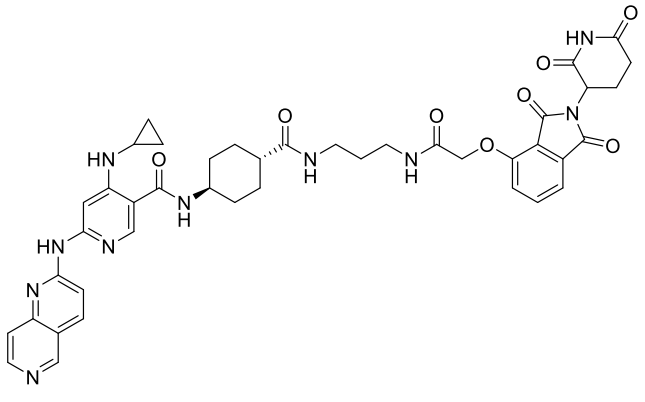
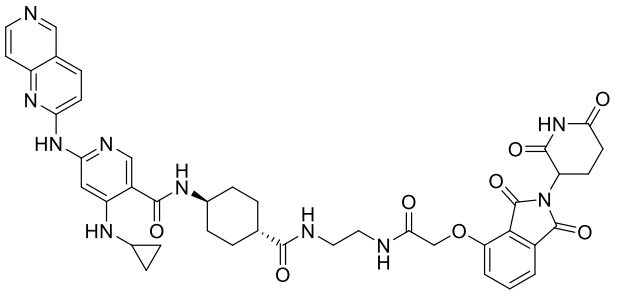
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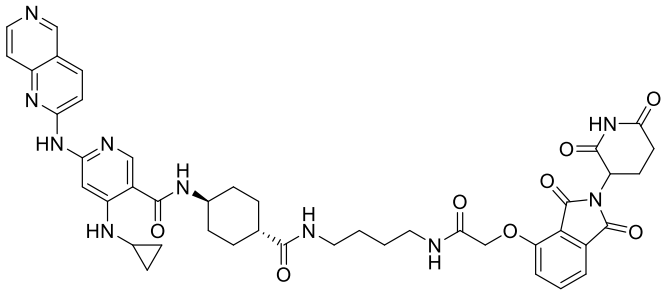
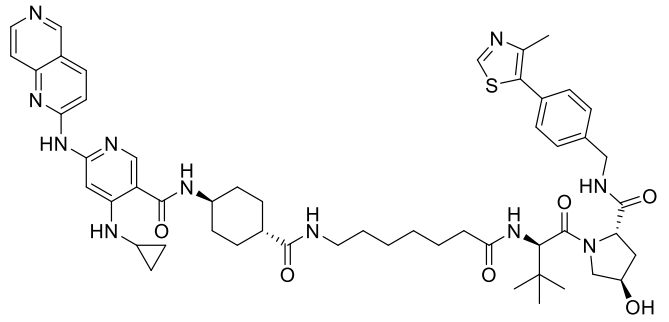
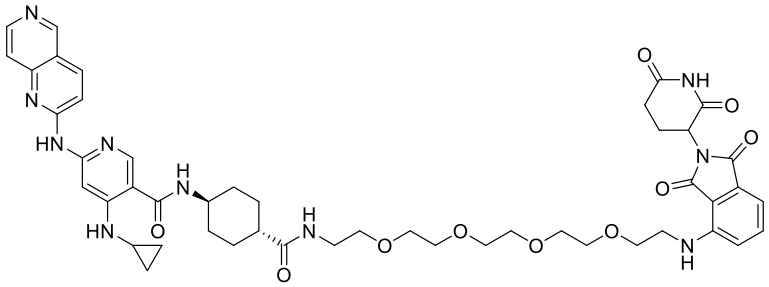
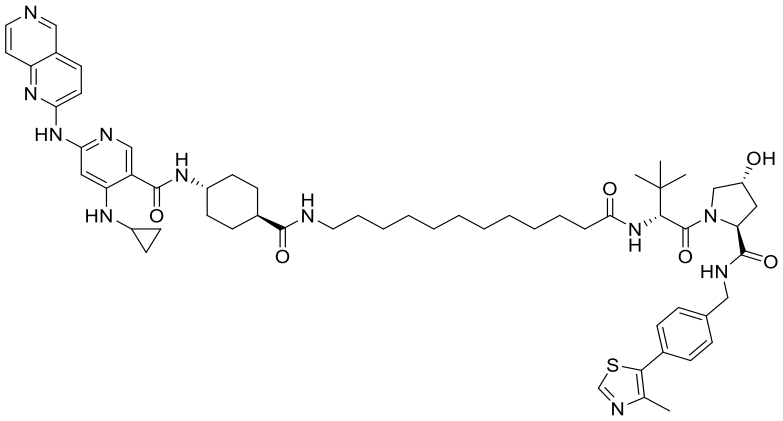


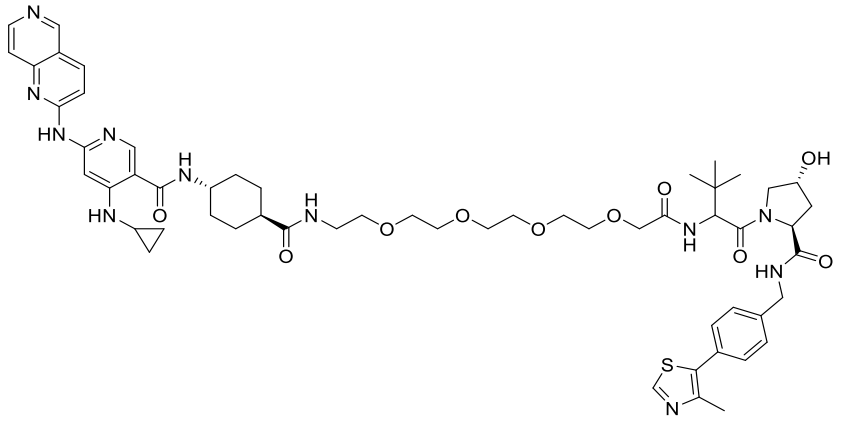
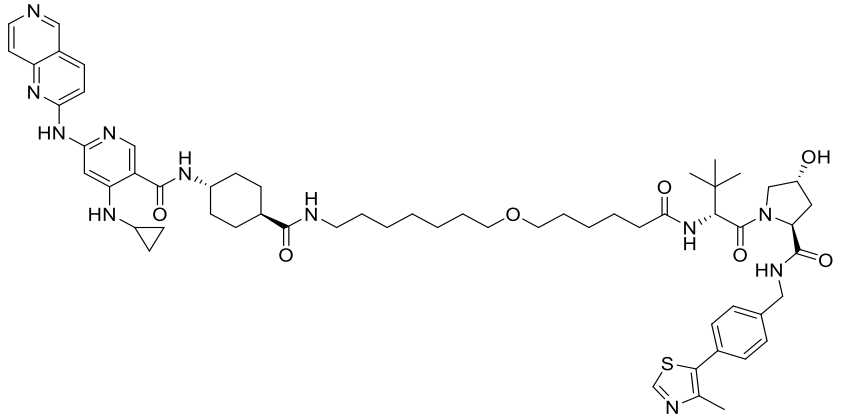
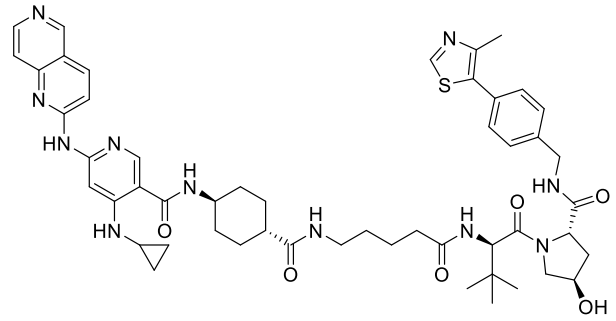
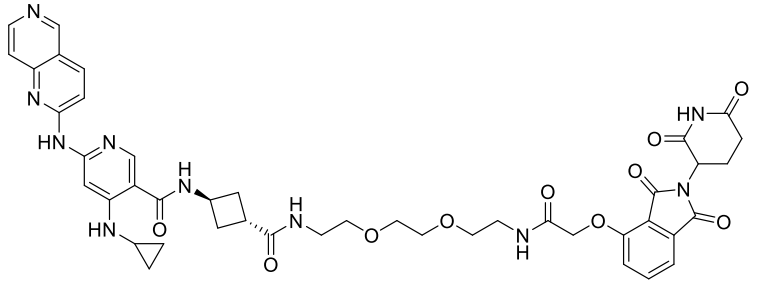
5. The compound of claim 1, wherein said compound is selected from any one of the following compounds, or a pharmaceutically acceptable salt thereof.

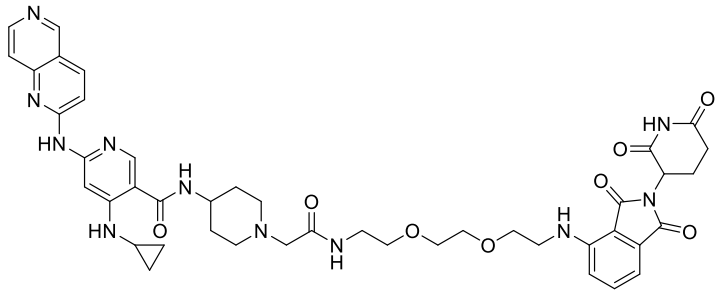
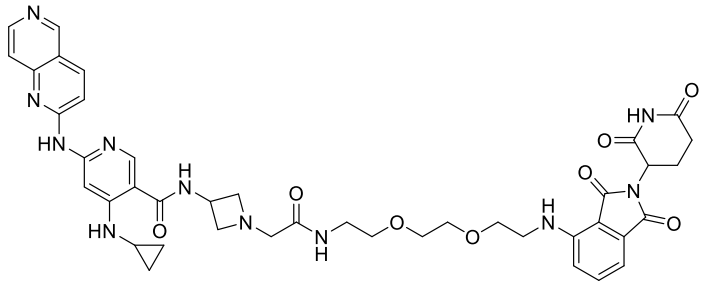
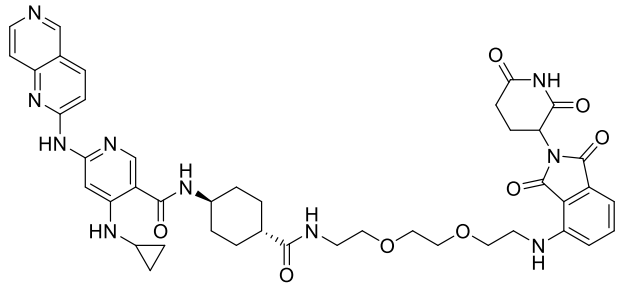
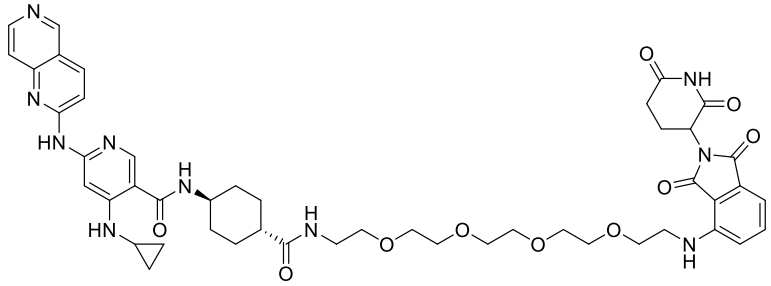
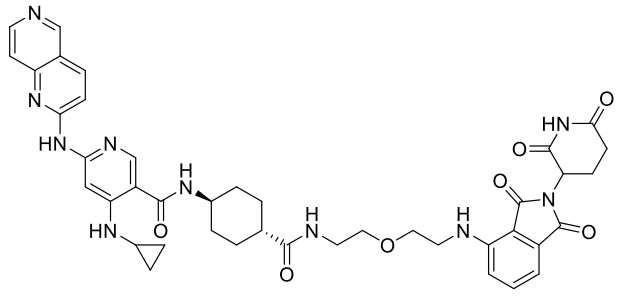
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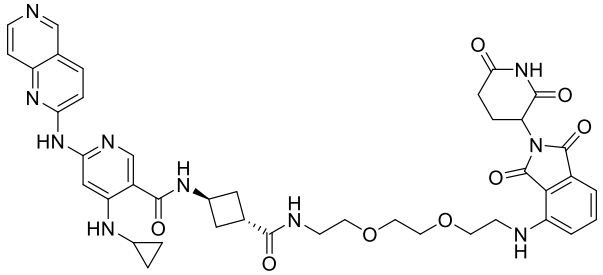
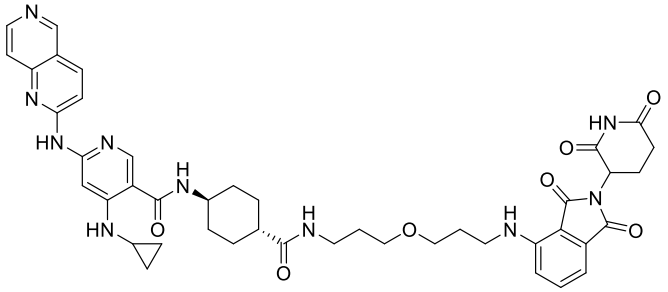
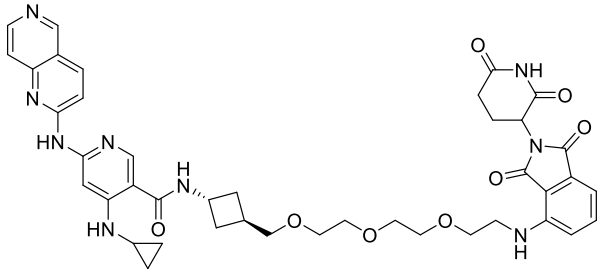
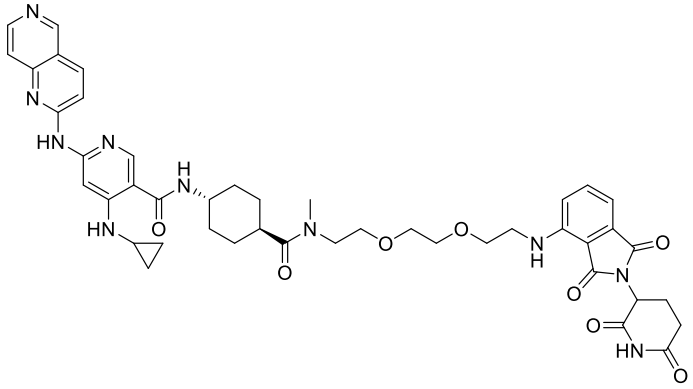
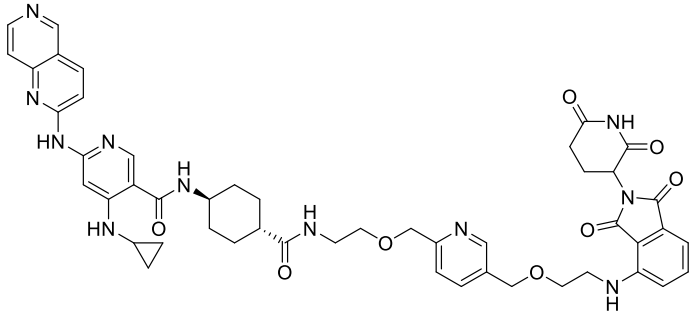
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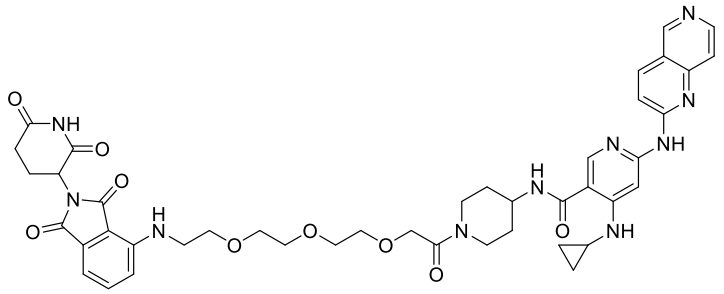
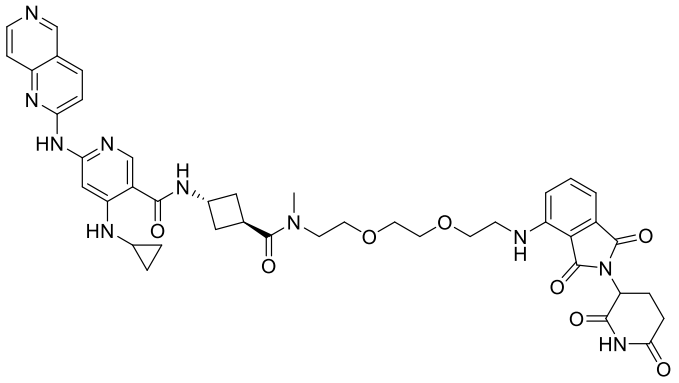
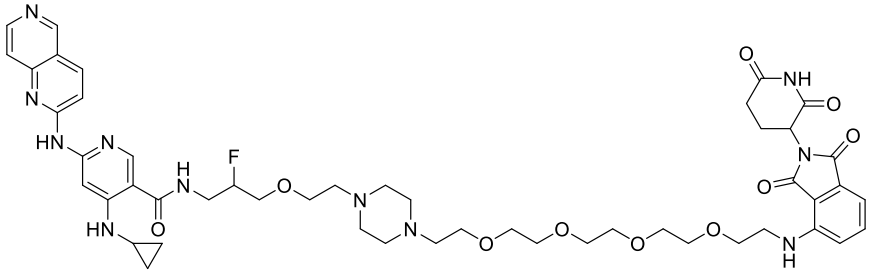
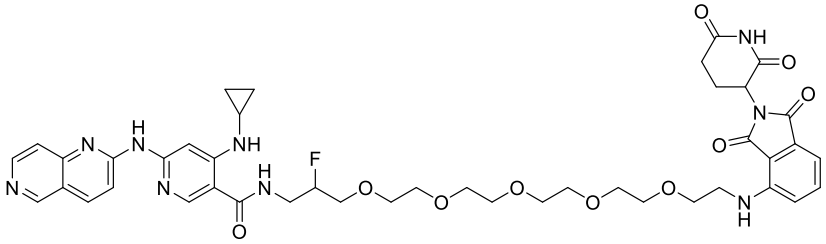
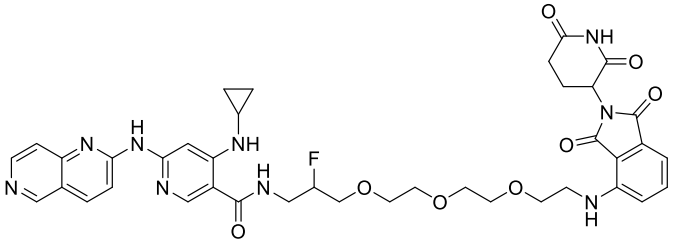
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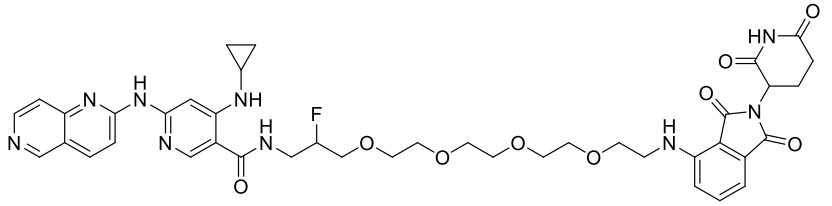
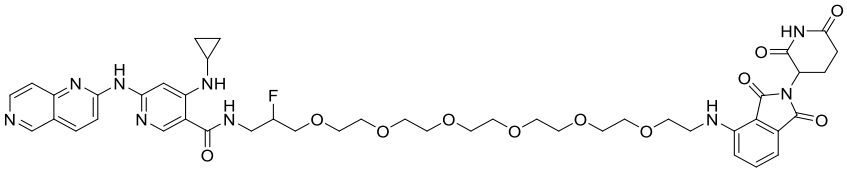
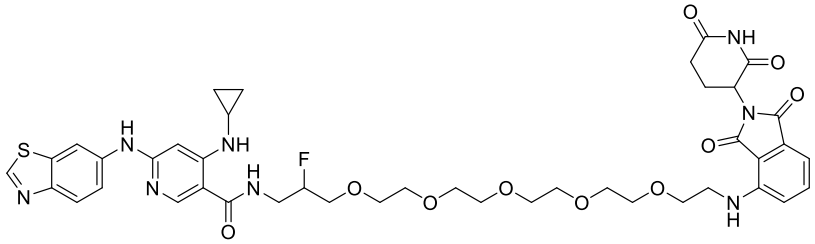
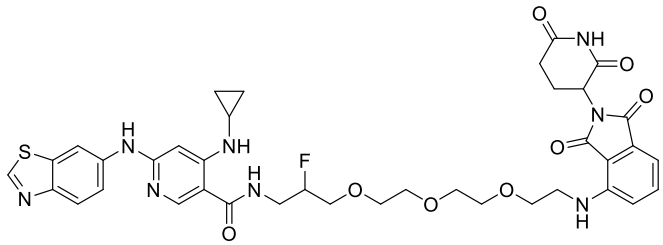
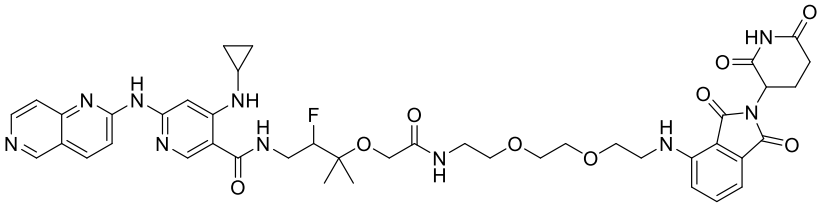
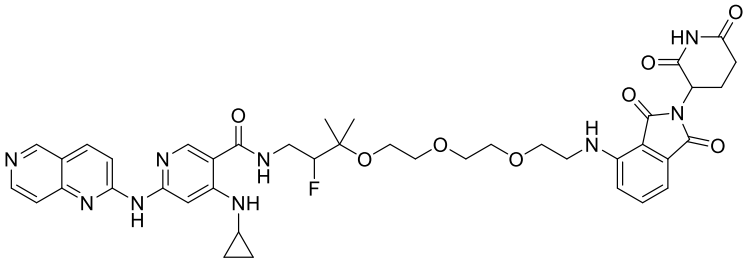
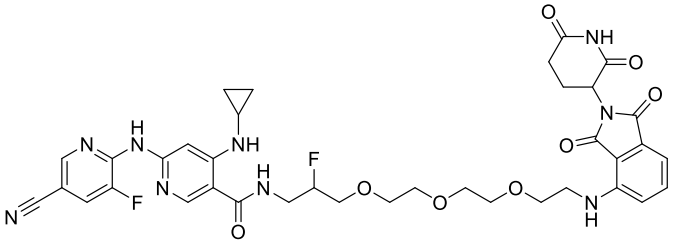
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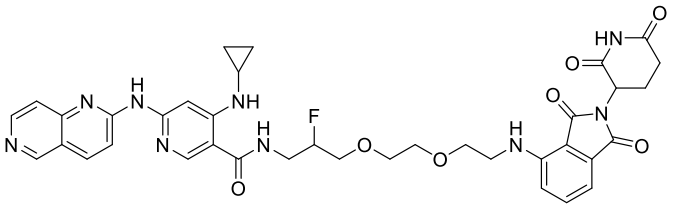
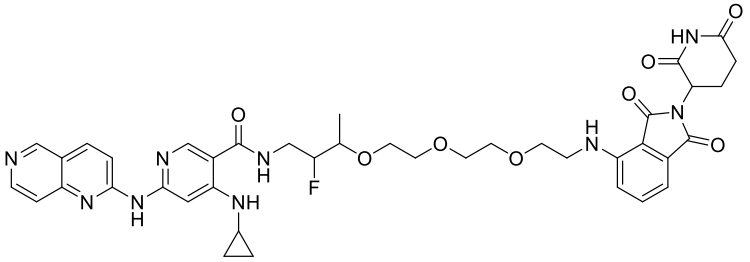
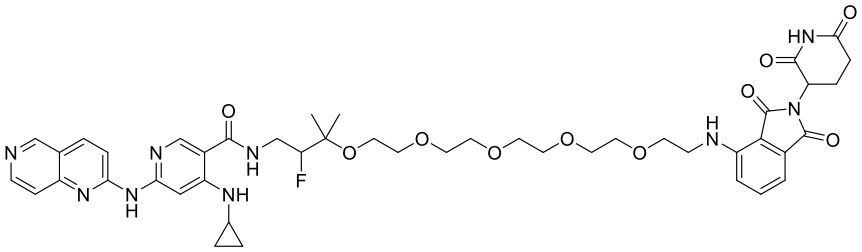
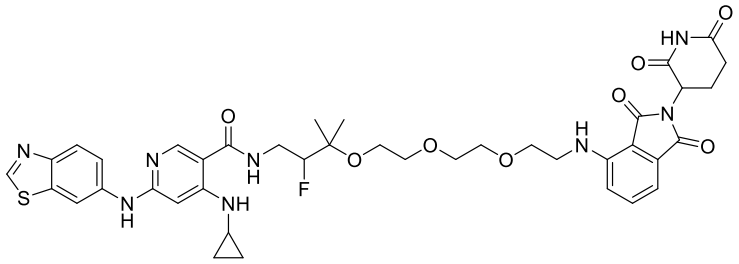
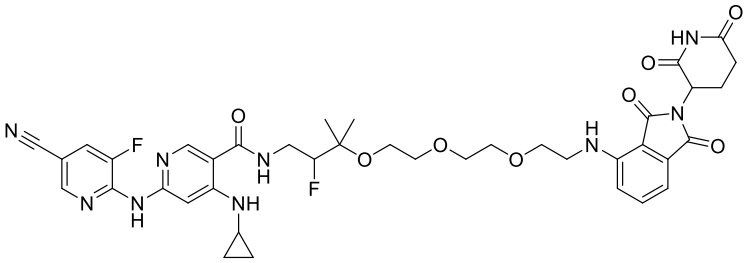
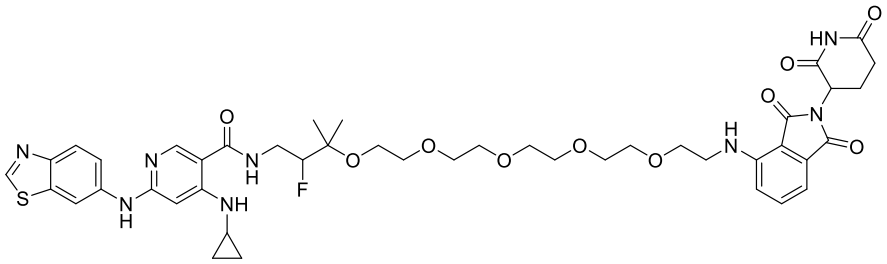
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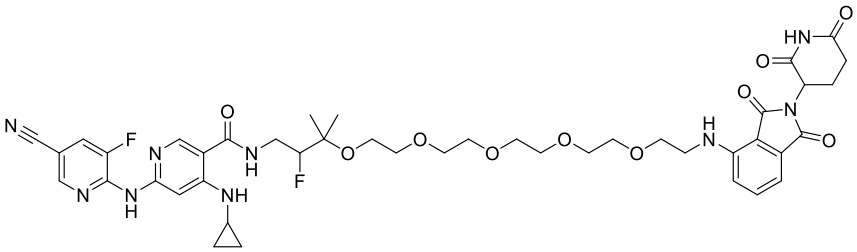
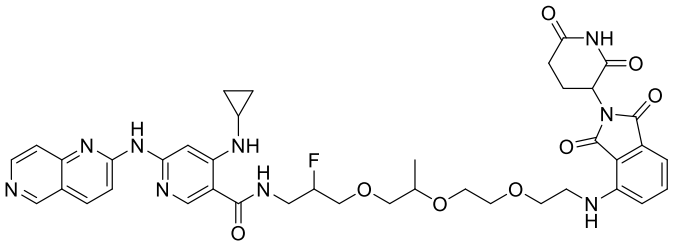
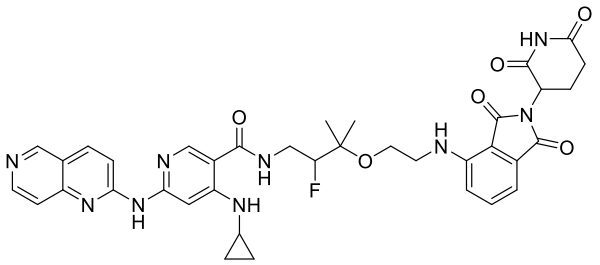
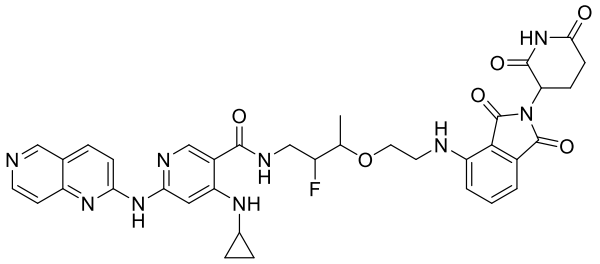
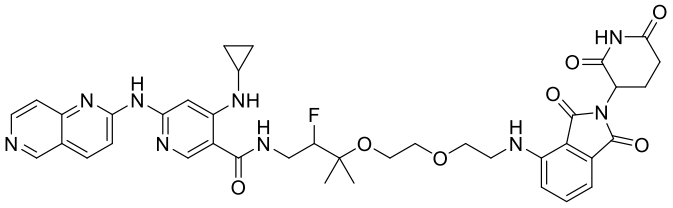
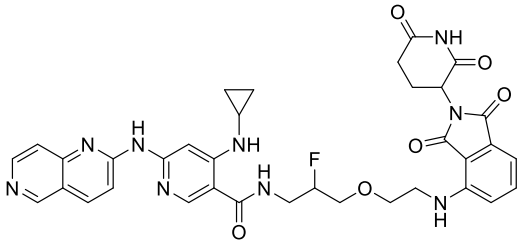
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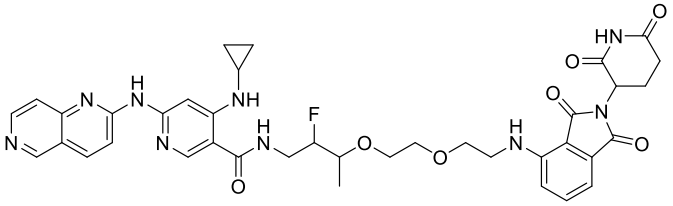
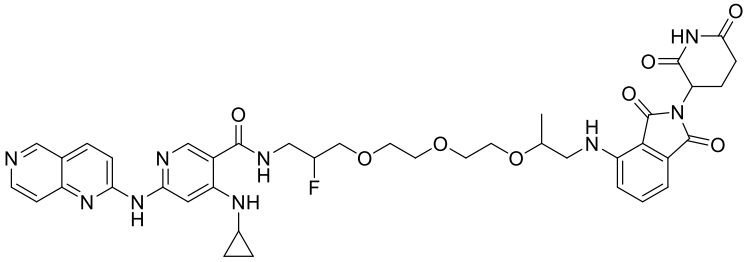
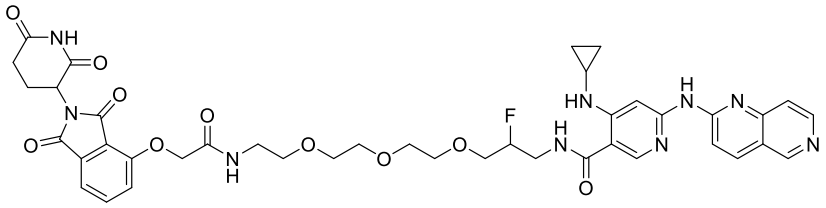
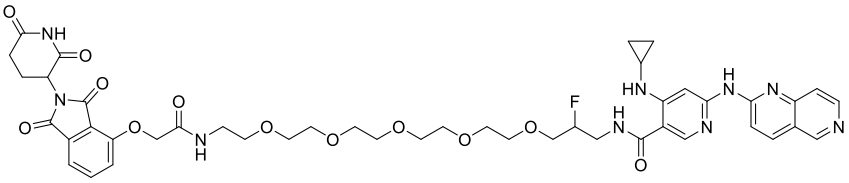
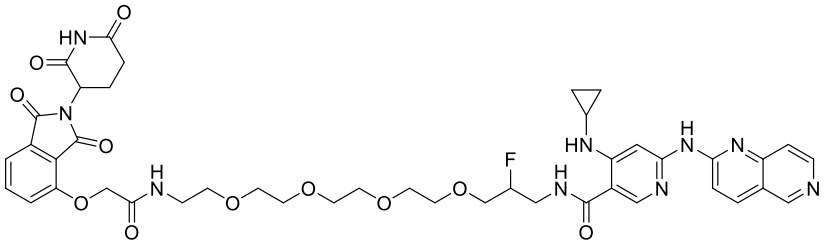
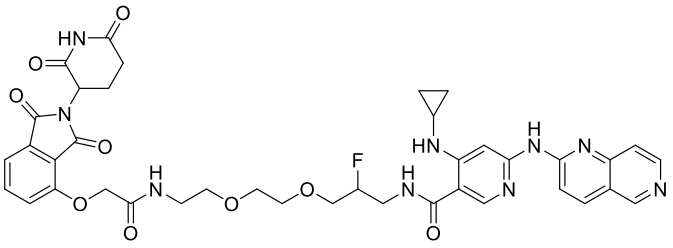
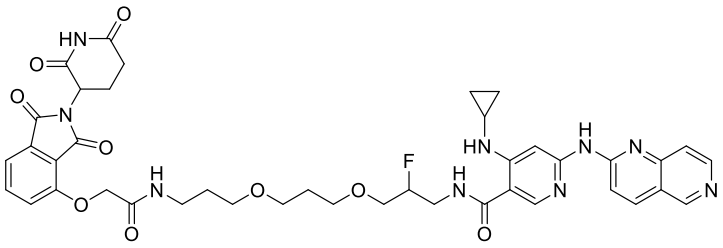
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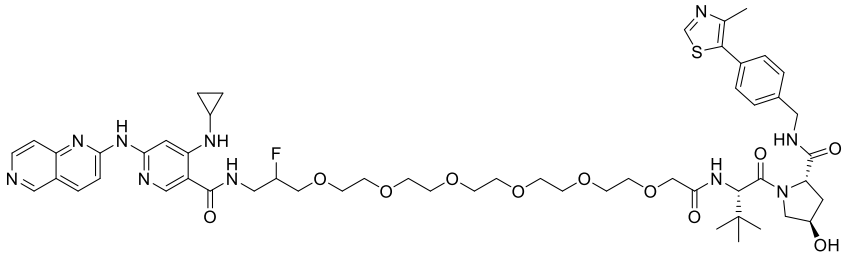
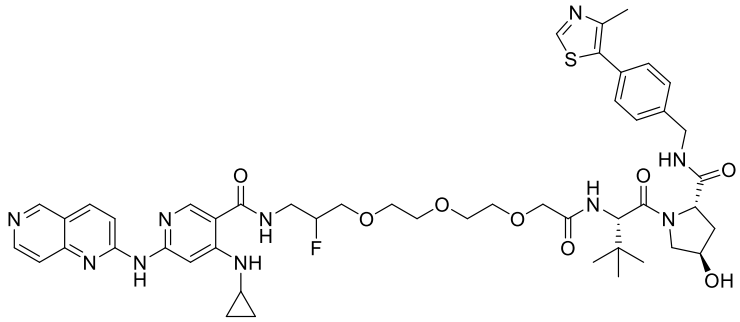
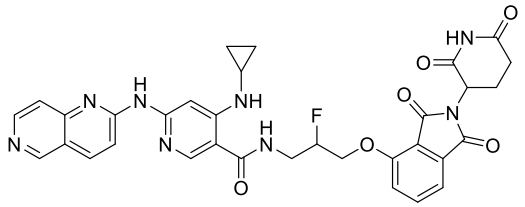
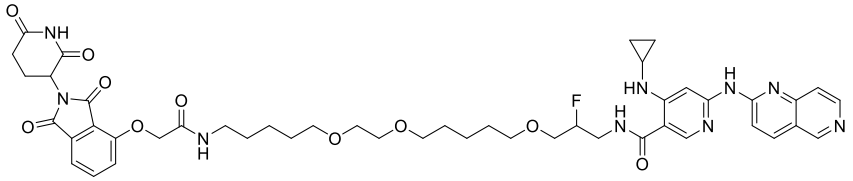
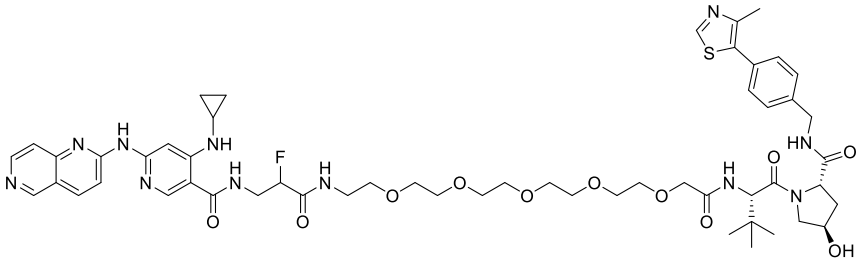
I-#	Structure
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I-44	
I-47	
I-48	
I-49	

I-#	Structure
I-50	
I-51	
I-52	
I-54	
I-55	
I-56	
I-58	

I-#	Structure
I-61	
I-62	
I-64	
I-65	
I-67	
I-68	

I-#	Structure
I-69	
I-70	
I-74	
I-77	
I-80	
I-81	

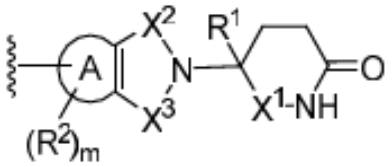
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I-93	
I-96	
I-97	
I-98	
I-99	
I-100	

I-#	Structure
I-119	
I-120	
I-174	
I-206	
I-207	

6. A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

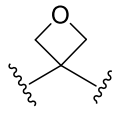
7. The pharmaceutical composition according to claim 6, further comprising an additional therapeutic agent.

8. The compound according to claim 1, wherein the cereblon E3 ubiquitin ligase binding moiety is



,

wherein:

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

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

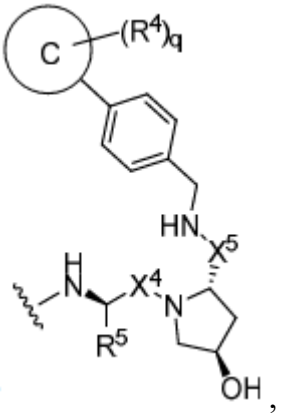
each R^2 is hydrogen, $–R^6$, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

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

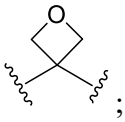
Ring A is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5 to 7-membered partially saturated carbocyclyl, 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 5-membered heteroaryl with 1-3 heteroatoms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

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

9. The compound according to claim 1, wherein the VHL E3 ubiquitin ligase binding

moiety is ,

wherein:

each of X^4 and X^5 is independently a bivalent moiety selected from $–CH_2–$, –C(O)–, –C(S)–, or ;

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 $-N(R)S(O)_2R$;

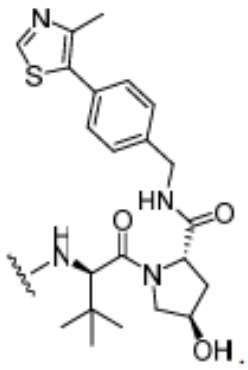
R^5 is hydrogen or C_{1-6} aliphatic;

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;

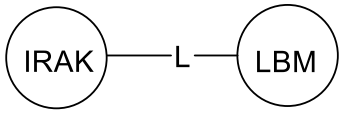
Ring C is a selected from 6-membered aryl containing 0-2 nitrogen atoms or a 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur; and

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

10. The compound according to claim 1, wherein the VHL E3 ubiquitin ligase binding

moiety is .

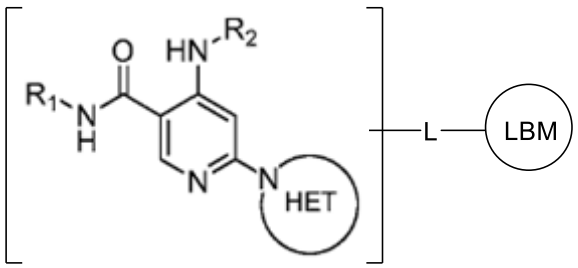
11. A compound of formula **I**:



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-hhh-1**:



I-hhh-1,

or a pharmaceutically acceptable salt thereof, wherein:

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

R_a is H, F, Cl, Br, —CN, —OH, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-4}hydroxyalkyl, C_{1-4} alkoxy, —NH_2, —NH(C_{1-4} alkyl), —N(C_{1-4} alkyl)$_2$, —NH(C_{1-4} hydroxyalkyl), —NH(C_{1-4} fluoroalkyl), —NH(C_{1-6} hydroxy-fluoroalkyl), —C(O)NH_2, —CH_2NHC(O)(C_{1-6} alkyl), —CH_2NHC(O)(C_{1-6}hydroxyalkyl), —CH_2NHC(O)NH(C_{1-6} alkyl), —

$CH_2NHC(O)NHCH_2$(phenyl), —$CH_2NHC(O)N(C_{1-4}$ alkyl$)_2$, —$CH_2NHC(O)O(C_{1-4}$ alkyl), —$CH_2NHC(O)(C_{3-6}$ cycloalkyl), —$CH_2NHC(O)$(tetrahydrofuranyl), —$CH_2NHC(O)CH_2(C_{3-6}$ cycloalkyl), —$CH_2NHC(O)CH_2$(tetrahydropyranyl), —$CH_2NHC(O)CH_2$(phenyl), —$NHC(O)(C_{1-4}$ alkyl), pyrrolidinyl, hydroxypyrrolidinyl, or pyridazinyl;

R_b is H or —NH_2;

R_1 is:

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

(ii) —(C_{1-3} alkylenyl)R_x, —(C_{1-3} fluoroalkylenyl)R_x, —(C_{1-3}alkylenyl)C(O)R_x, —(C_{1-3} alkylenyl)C(O)NHR_x, —(C_{1-3}fluoroalkylenyl)C(O)R_x, or —CH_2CF=(tetrahydropyranyl), wherein R_x is a cyclic group selected from C_{3-6} cycloalkyl, tetrazolyl, 1,1-dioxidotetrahydrothiophenyl, 1,1-dioxidothiomorpholinyl, oxadiazolyl, piperidinyl, piperazinyl, pyrrolidinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyridinyl, imidazolyl, morpholinyl, phenyl, and triazinyl, wherein each cyclic group is substituted with zero to 3 substituents independently selected from F, —OH, —CH_3, —$C(CH_2)_2OH$, —OCH_3, —$C(O)CH_2CN$, —$S(O)_2CH_3$, —$S(O)_2NH_2$, —$NHC(O)CH_3$, —$N(S(O)_2CH_3)_2$, —CH_2CH_2(acetamidophenyl), —CH_2CH_2(methoxyphenyl), —CH_2CH_2(sulfamoylphenyl), oxetanyl, benzyl, and morpholinyl;

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

$_{6}$ cycloalkyl), —$CH_2C(O)NH(C_{1-3}$ alkyl), —$NHC(O)(C_{1-3}$ alkyl), —$NHC(O)(C_{1-4}$hydroxyalkyl), —$C(O)NH(C_{1-3}$ alkyl), —$C(O)NH(C_{1-3}$ deuteroalkyl), —$C(O)NH(C_{3-6}$ cycloalkyl), —$NHC(O)O(C_{1-3}$ alkyl), —$NHS(O)_2(C_{1-3}$alkyl), pyridinyl, imidazolyl, pyrazolyl, methylimidazolyl, methylpyrazolyl, and thiazolyl;

(iv) tetrahydropyranyl, piperidinyl, pyrazolyl, phenyl, pyridinyl, or pyrimidinyl, each substituted with zero to 1 substituent selected from —OH, C_{1-3} alkyl, C_{1-3} fluoroalkyl, C_{1-4} hydroxyalkyl, C_{1-3}alkoxy, —$C(O)(C_{1-4}$ alkyl), —$S(O)_2(C_{1-4}$ alkyl), —$S(O)_2NH(C_{1-4}$ alkyl), —$NH(C_{1-3}$ alkyl), —$N(C_{1-3}$ alkyl)$_2$, —$O(C_{1-3}$ alkylenyl)$N(C_{1-3}$ alkyl)$_2$, —CH_2(morpholinyl), azetidinyl, oxetanyl, tetrahydropyranyl, morpholinyl, piperazinyl, piperidinyl, methylpiperazinyl, methoxypiperidinyl, pyridinyl, pyrimidinyl, methylsulfonyl azetidinyl, and —C(O)(methylsulfonyl azetidinyl); or

(v) pyrrolo[2,3-c]pyridinyl, bicyclo[2.2.1]heptan-1-ol, tetrahydrobenzo[d]thiazol-2-amine, or 1,3-diazaspiro[4.5]decane-2,4-dione; and

R_2 is:

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

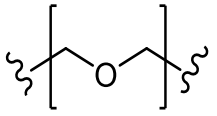
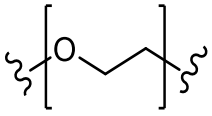
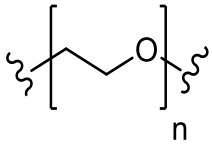
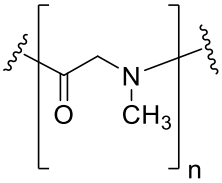
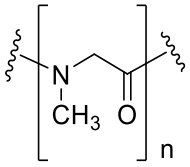
(ii) —(C_{1-4} alkylenyl)R_y wherein R_y is C_{3-6} cycloalkyl, azetidinyl, oxetanyl, oxazolyl, pyridinyl, tetrahydropyranyl, or morpholinyl, each substituted with zero to 2 substituents independently selected from F, —OH, and C_{1-3} alkyl;

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

—$S(O)_2(C_{1\text{-}3}$ alkyl), imidazolyl, phenyl, pyrimidinyl, fluoropyrimidinyl, chloropyrimidinyl, and methoxypyrimidinyl;

(iv) adamantanyl, hydroxyadamantanyl, benzo[d]imidazolyl, benzo[d]oxazolyl, benzo[d]triazolyl, benzothiazolyl, bicyclo[1.1.1]pentanyl, or hydroxy-bicyclo[2.2.1]heptanyl; or

(v) phenyl, pyrazolyl, thiazolyl, thiadiazolyl, or indazolyl, each substituted with 0 to 2 substituents independently selected from F, Cl, —OH, —CN, $C_{1\text{-}4}$ alkyl, $C_{1\text{-}4}$ hydroxyalkyl, $C_{1\text{-}4}$ fluoroalkyl, $C_{1\text{-}4}$cyanoalkyl, $C_{1\text{-}3}$ alkoxy, $C_{3\text{-}6}$ cycloalkyl, —($C_{1\text{-}3}$ alkylenyl)O($C_{1\text{-}3}$alkyl), —($C_{1\text{-}3}$ alkylenyl)O($C_{1\text{-}3}$ fluoroalkyl), —$C(O)NH_2$, —C(O)NH($C_{1\text{-}3}$ alkyl), —NHC(O)($C_{1\text{-}3}$ alkyl), —NHC(O)$S(O)_2$($C_{1\text{-}3}$alkyl), —$S(O)_2NH_2$, —$S(O)_2$($C_{1\text{-}3}$ alkyl), pyrazolyl, methyl pyrazolyl, imidazolyl, triazolyl, methyl tetrazolyl, ethyl tetrazolyl, phenyl, pyrimidinyl, fluoropyrimidinyl, and tetrahydropyranyl;

L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched $C_{1\text{-}50}$ hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -NR$S(O)_2$-, -$S(O)_2$NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, –NRC(O)O-, , , , , or , wherein:

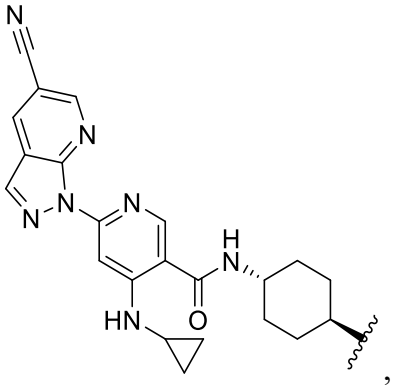
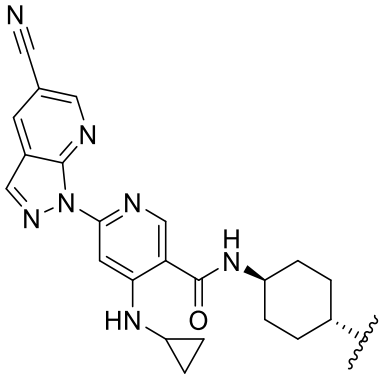
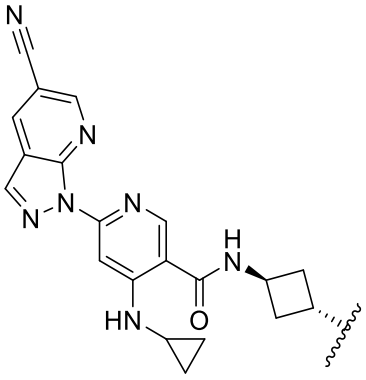
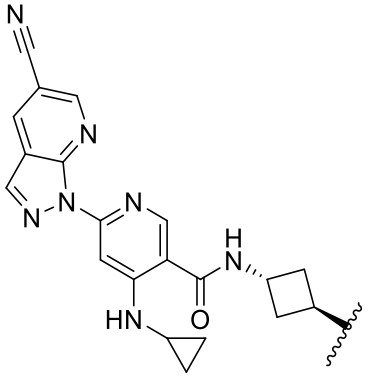
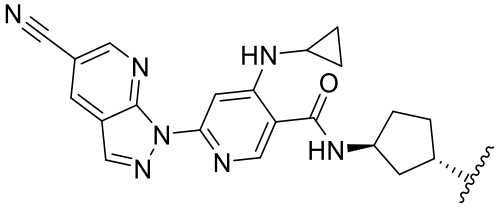
each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated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

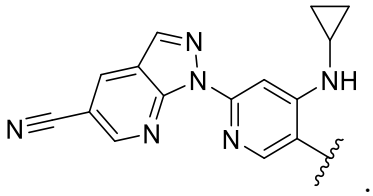
partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently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

each of n is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

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;

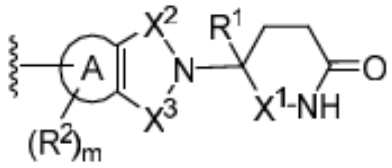
LBM is a ligase binding moiety selected from a cereblon E3 ubiquitin ligase binding moiety and a VHL E3 ubiquitin ligase binding moiety.

12. The compound according to claim 11, wherein the IRAK4 binding moiety is selected from: , , , , , and



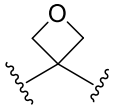
.

13. The compound according to claim 11, wherein the cereblon E3 ubiquitin ligase binding moiety is



,

wherein:

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

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

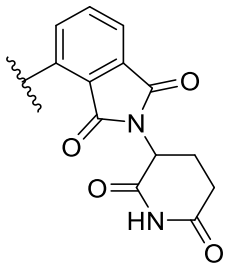
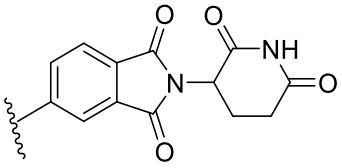
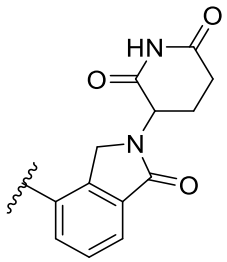
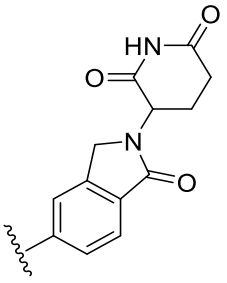
each R^2 is hydrogen, $–R^6$, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

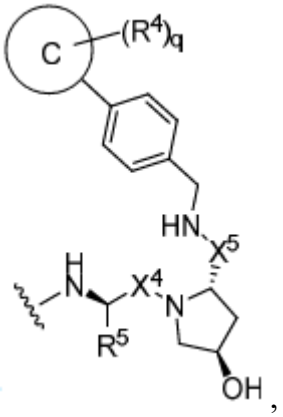
each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

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

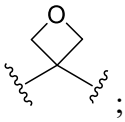
m is 0, 1, 2, 3 or 4.

14. The compound according to claim 11, wherein the cereblon E3 ubiquitin ligase binding moiety is selected from:

, , , and .

15. The compound according to claim 11, wherein the VHL E3 ubiquitin ligase binding moiety is ,

wherein:

each of X^4 and X^5 is independently a bivalent moiety selected from $–CH_2–$, –C(O)–, –C(S)–, or ;

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 $-N(R)S(O)_2R$;

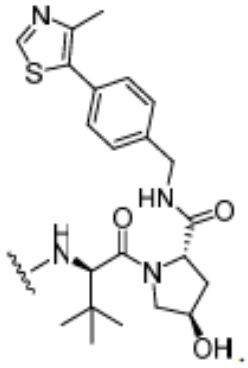
R^5 is hydrogen or C_{1-6} aliphatic;

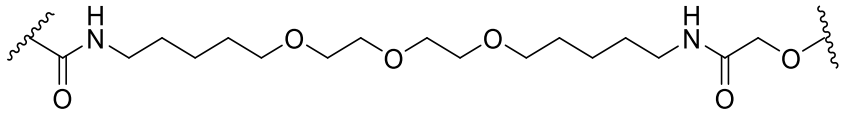
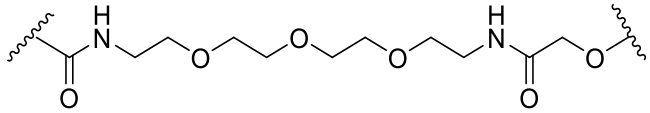
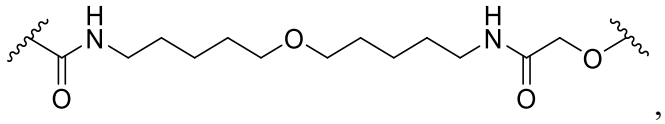
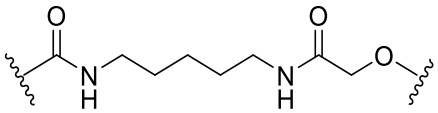
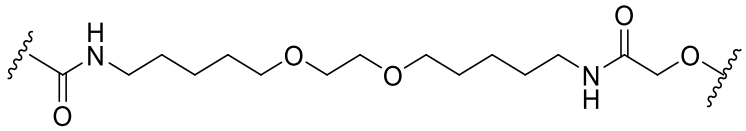
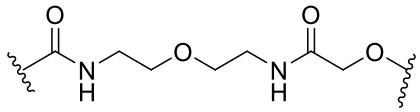
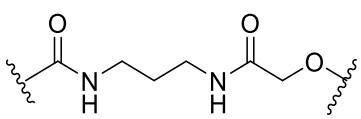
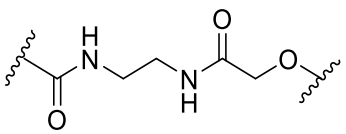
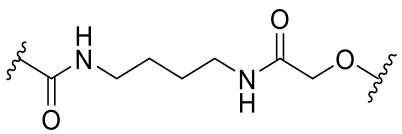
each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl

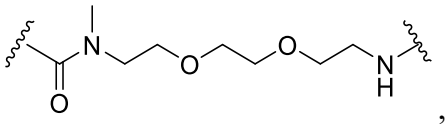
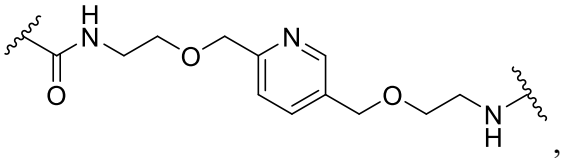
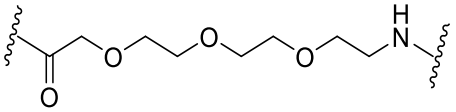
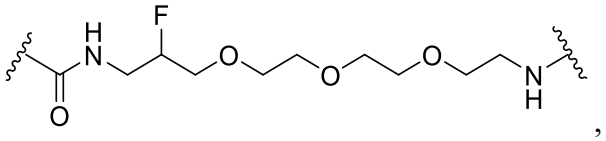
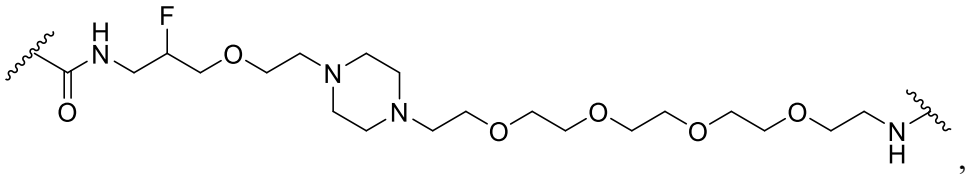
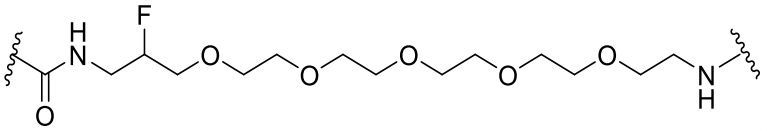
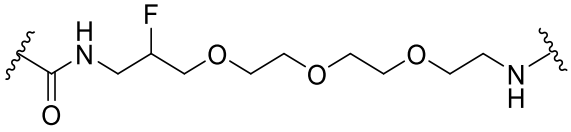
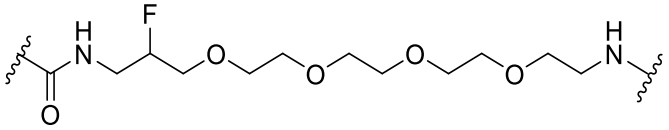
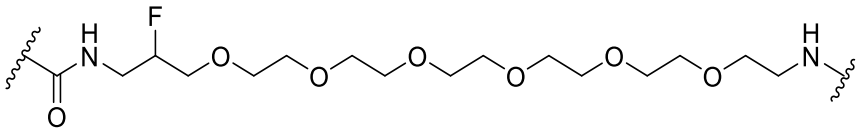
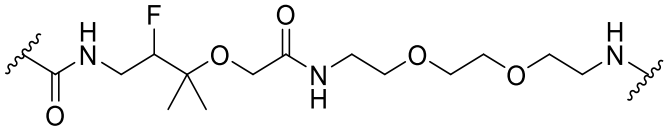
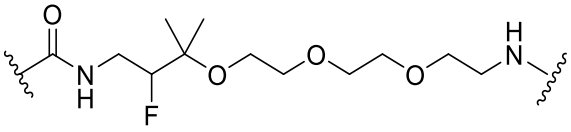
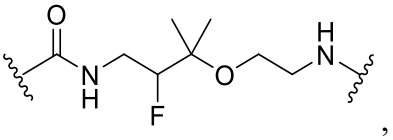
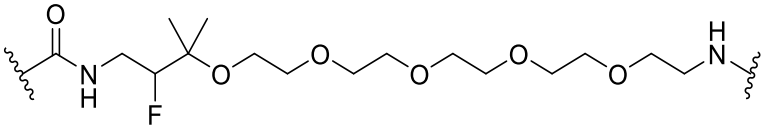
ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

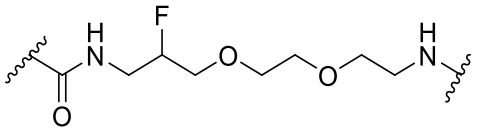
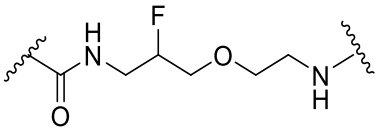
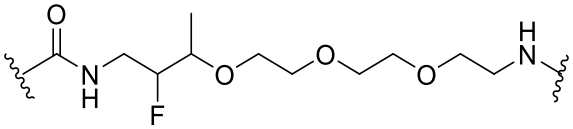
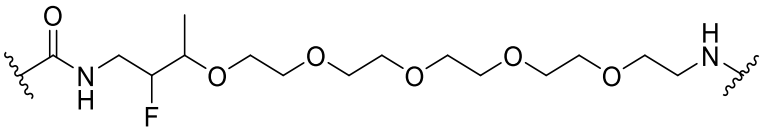
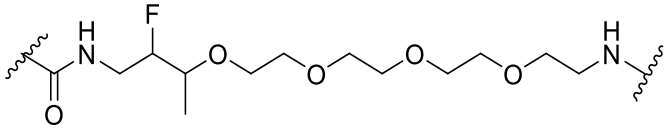
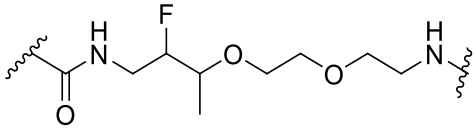
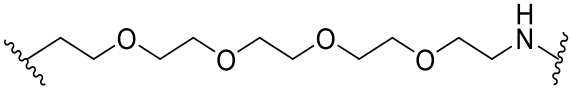
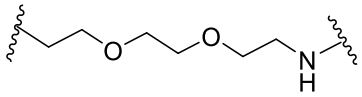
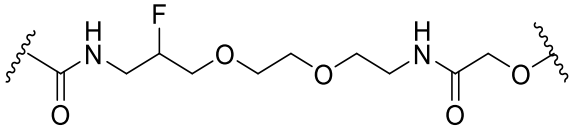
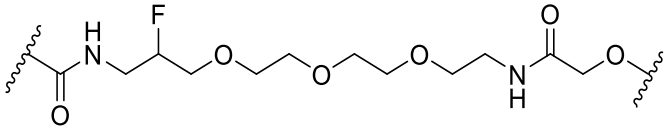
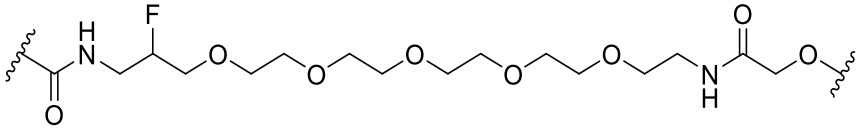
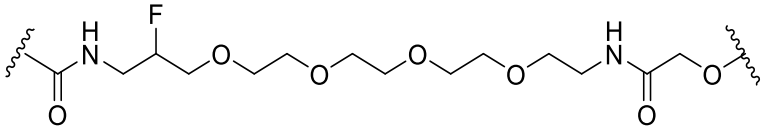
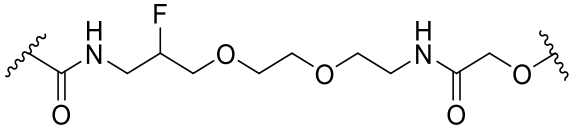
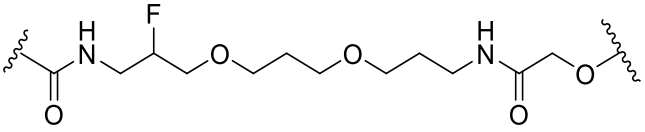
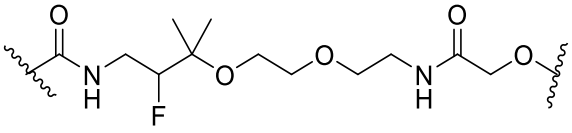
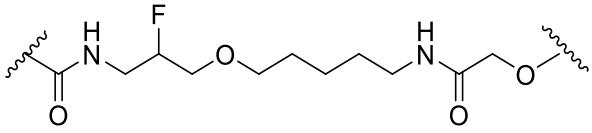
Ring C is a selected from 6-membered aryl containing 0-2 nitrogen atoms or a 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur; and

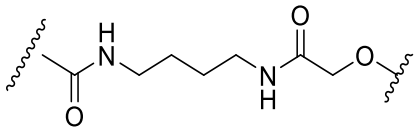
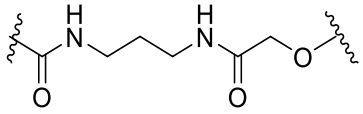
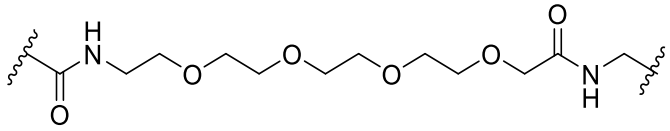
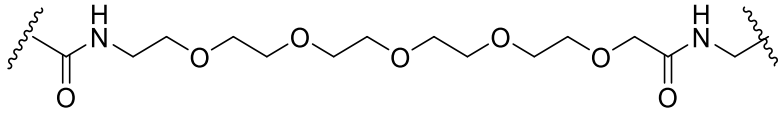
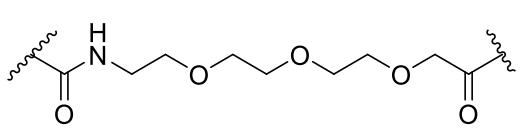
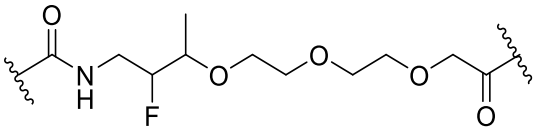
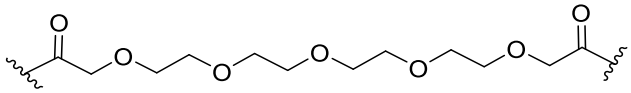
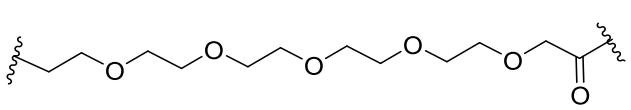
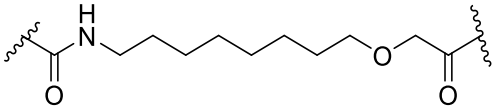
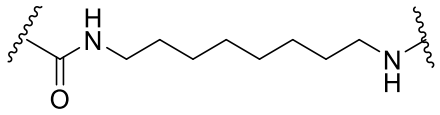
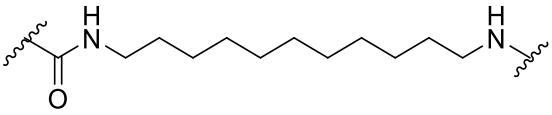
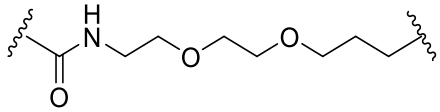
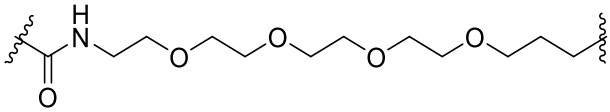
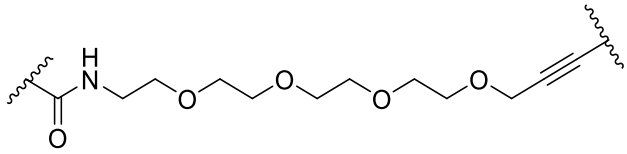
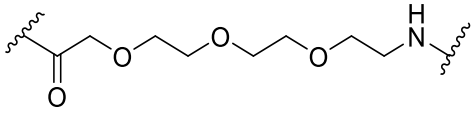
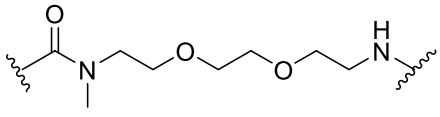
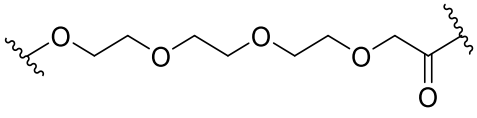
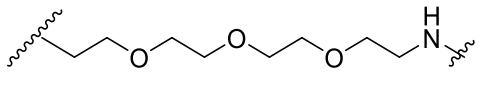
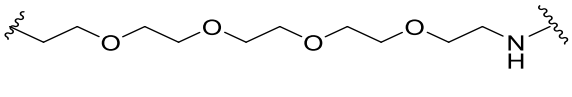
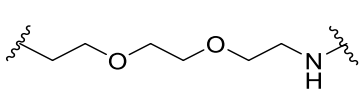
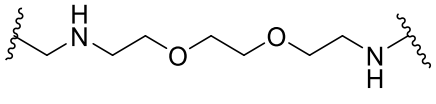
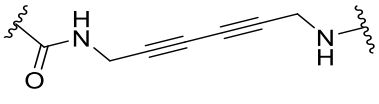
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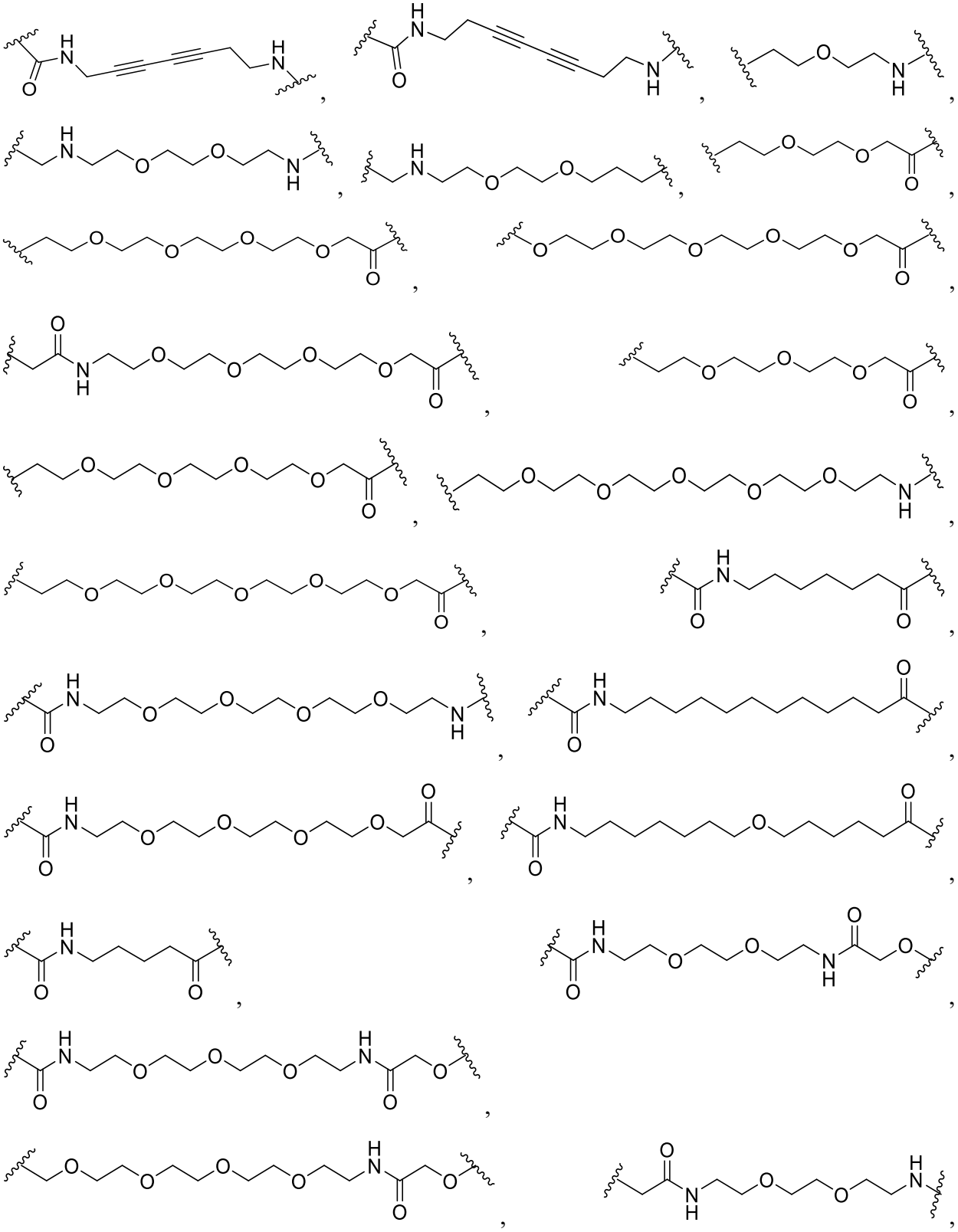
16. The compound according to claim 11, wherein the VHL E3 ubiquitin ligase binding moiety is .

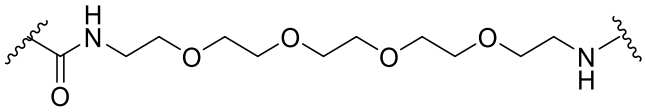
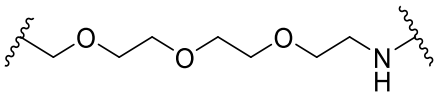
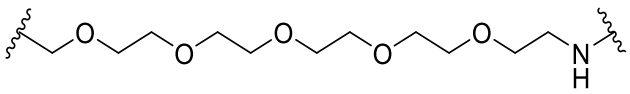
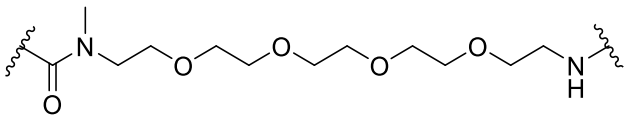
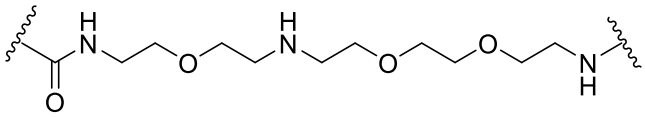
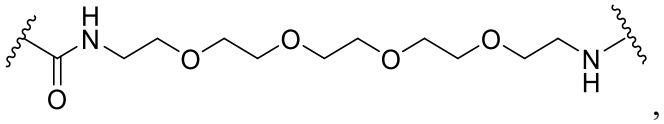
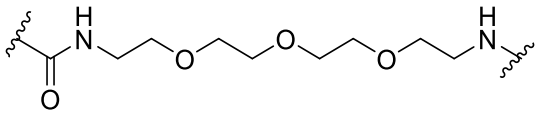
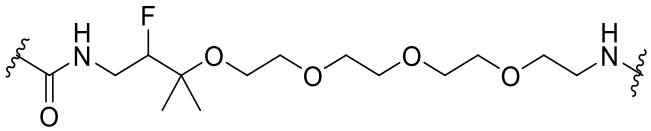
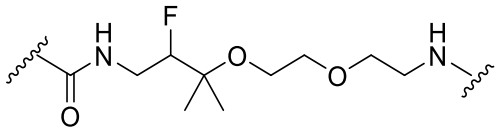
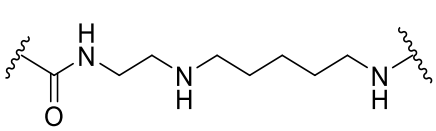
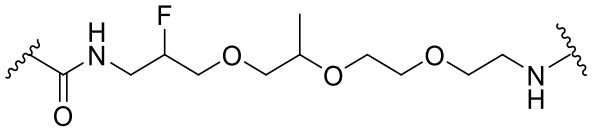
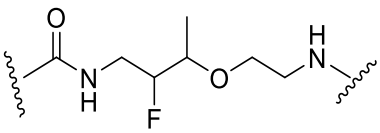
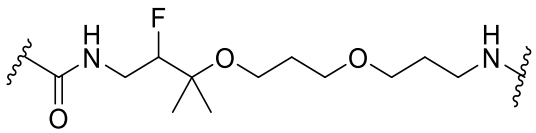
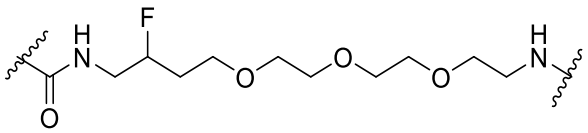
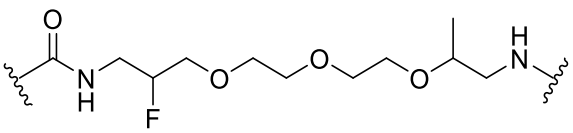
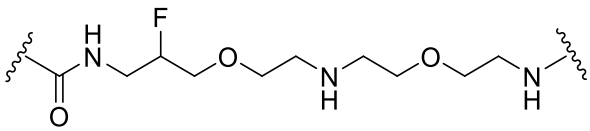
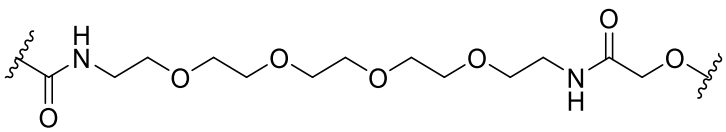
17. The compound according to claim 11, wherein L is selected from: , , , , , , , , .

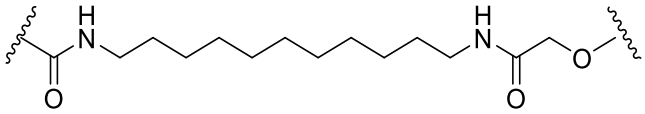
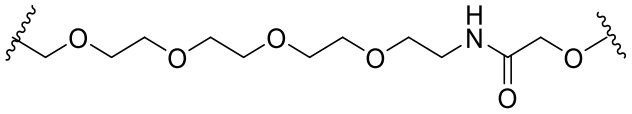
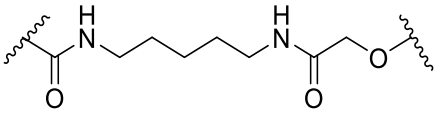
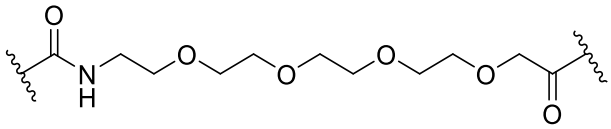
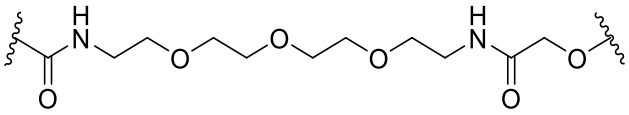
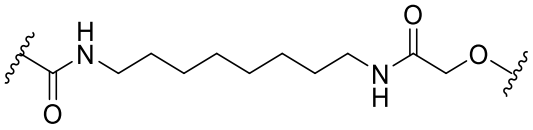
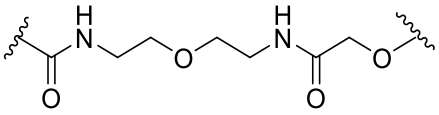
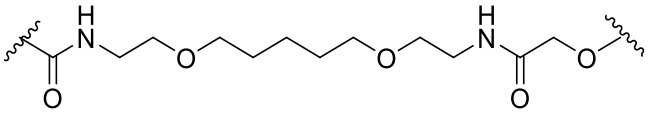
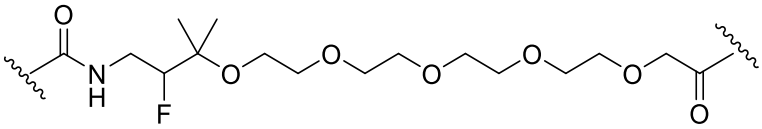
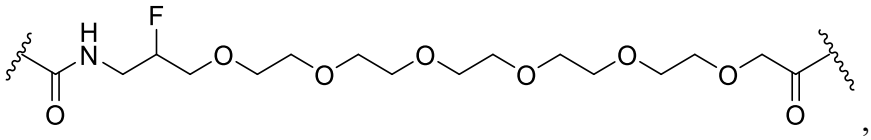
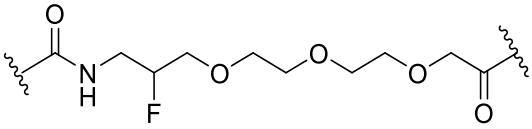
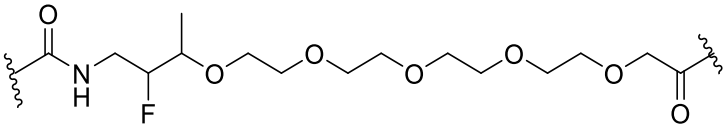
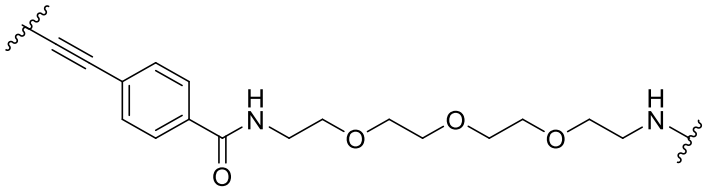

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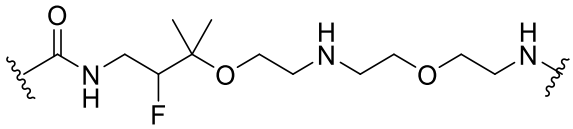
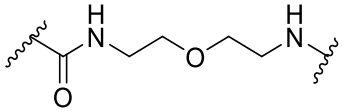
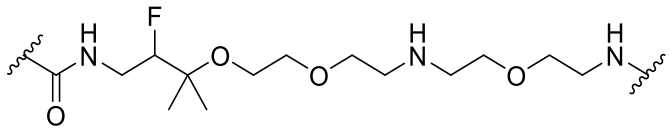
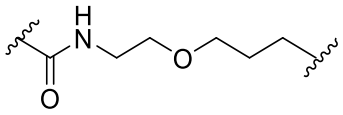
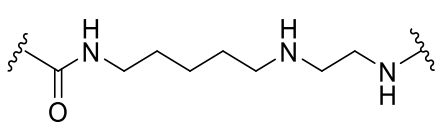
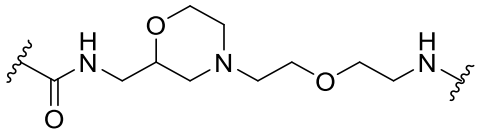
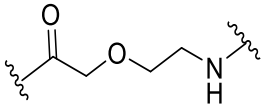
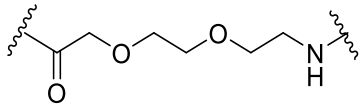
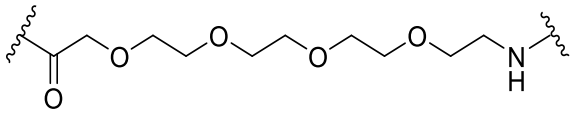
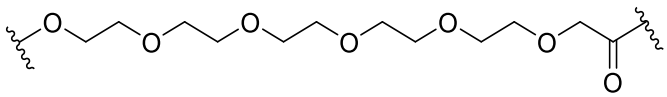
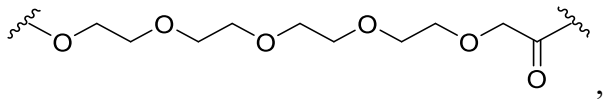
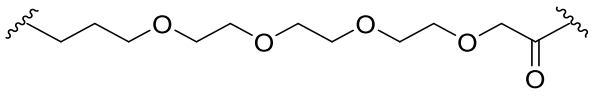
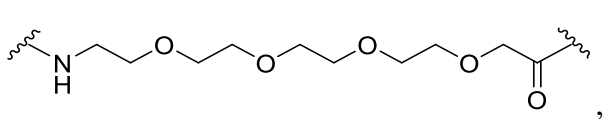
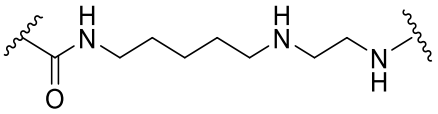
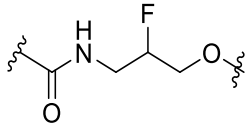
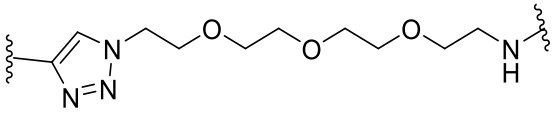
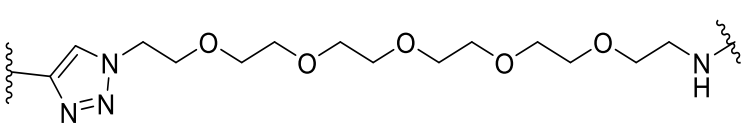
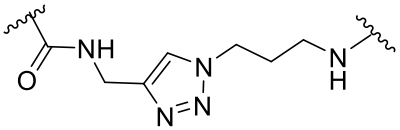
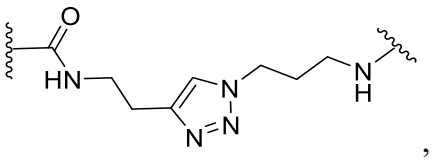
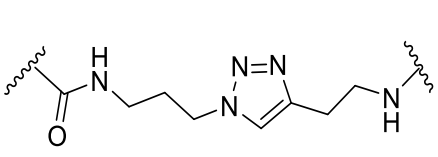
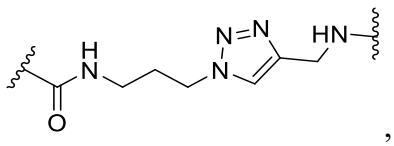
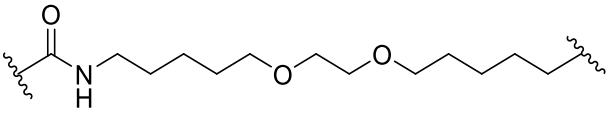

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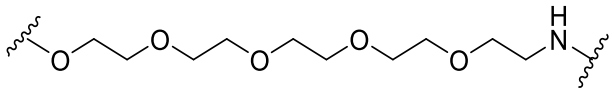
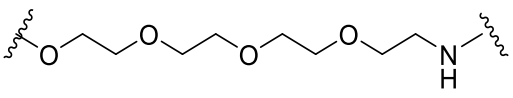
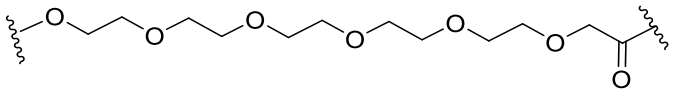
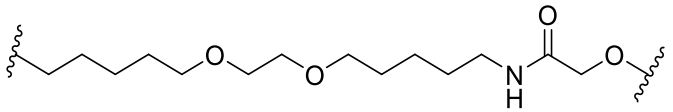
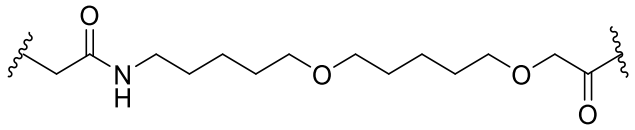
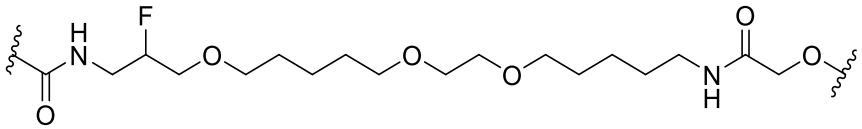
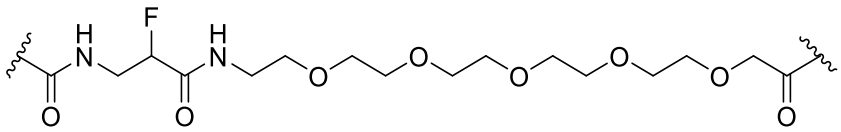
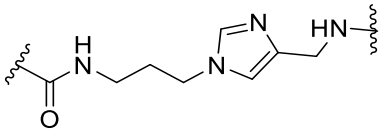
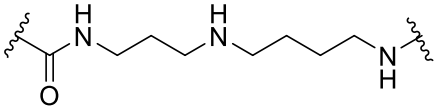
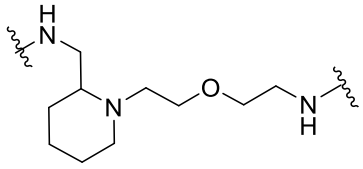
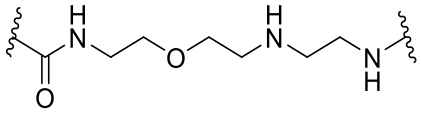
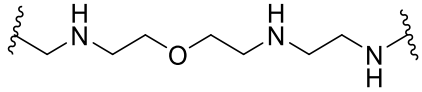
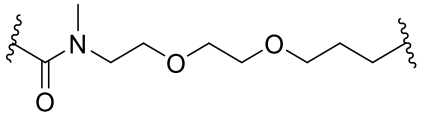
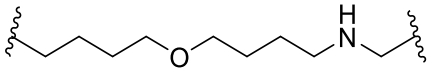
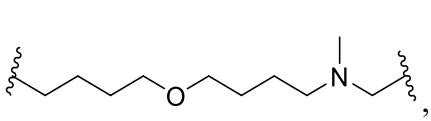
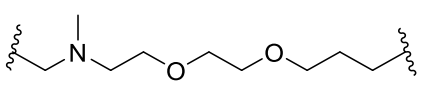
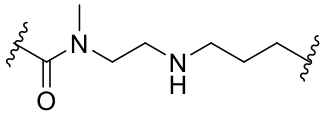
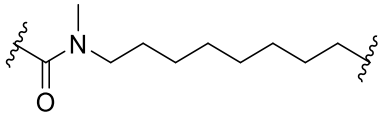
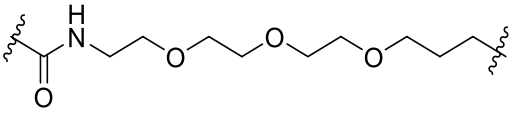

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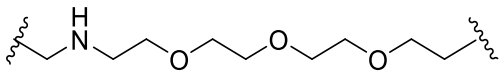
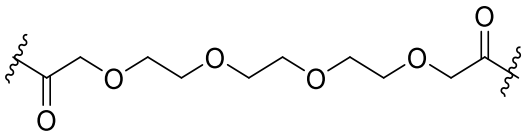
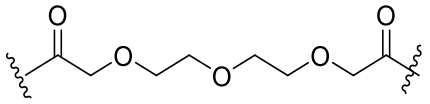
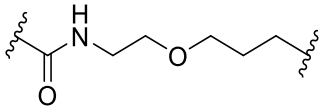
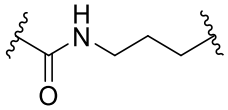
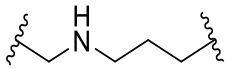
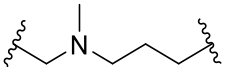
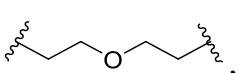
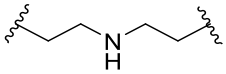
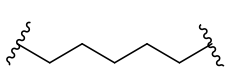
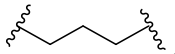
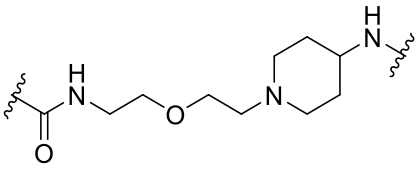
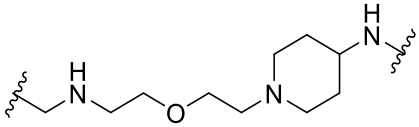
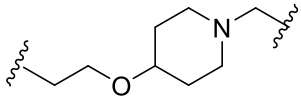
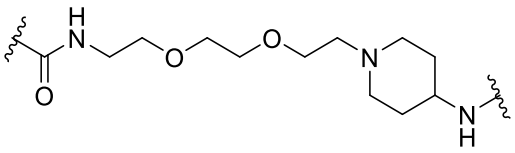
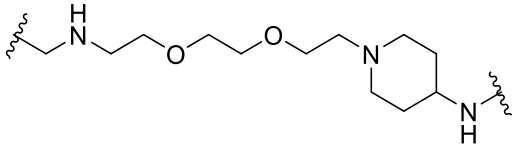
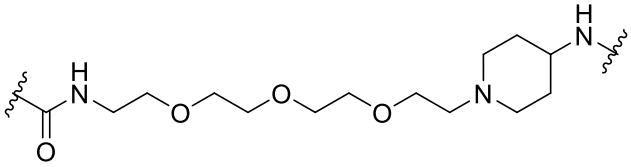
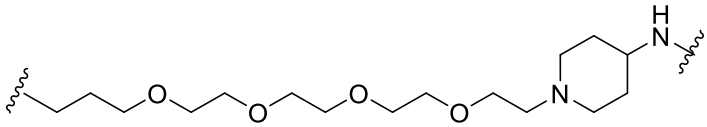


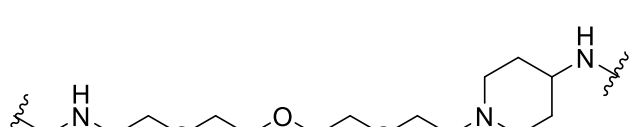
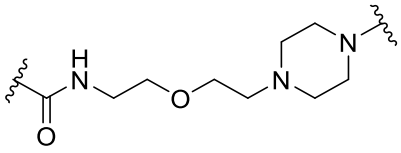
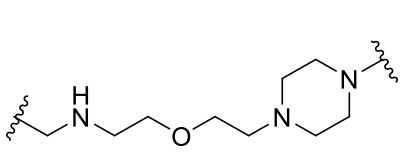
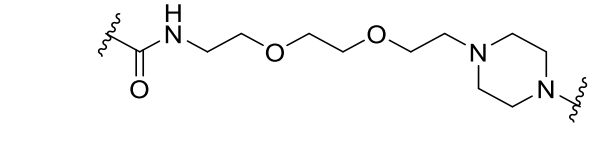
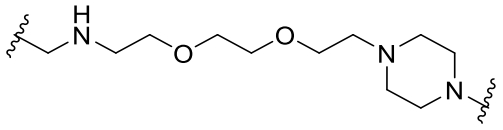
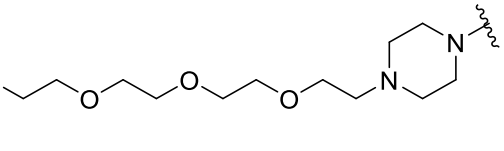

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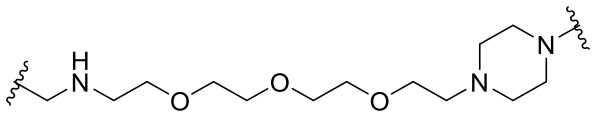
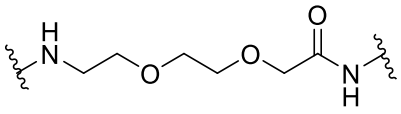
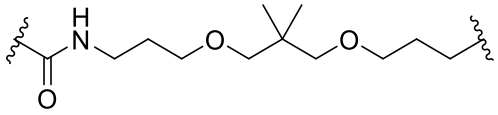
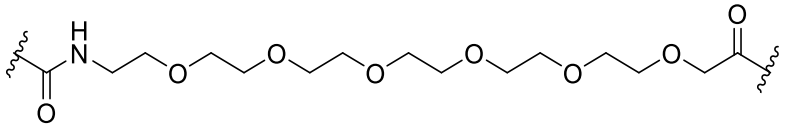
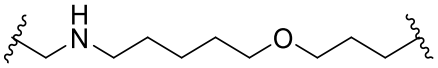
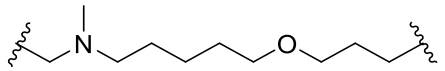
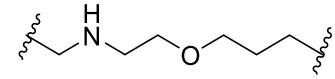
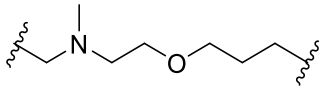
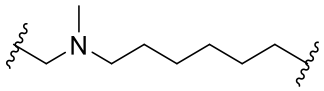
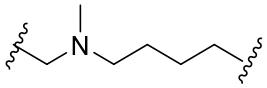
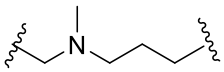
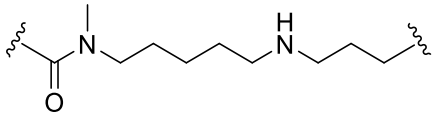
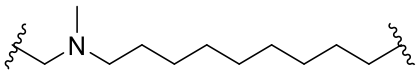
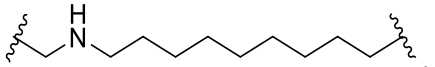
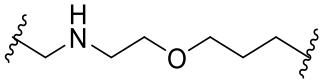
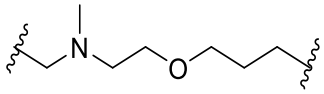
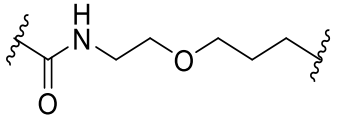
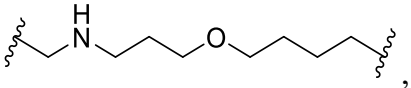
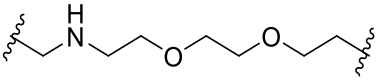
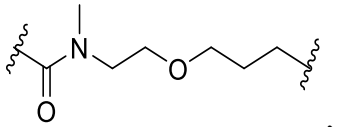
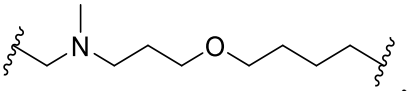
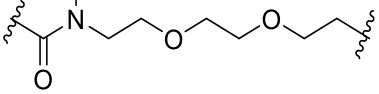
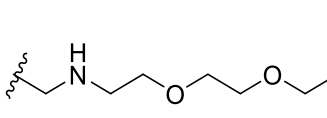

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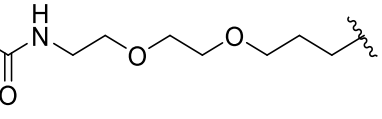
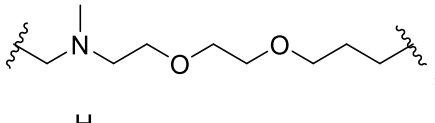
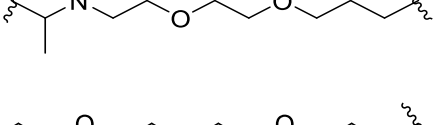
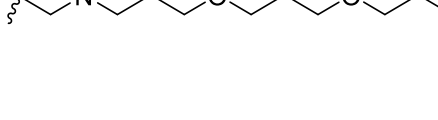

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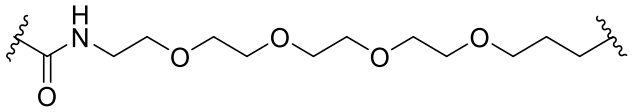
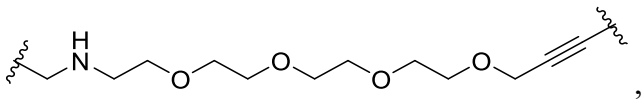
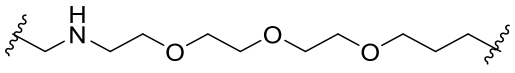
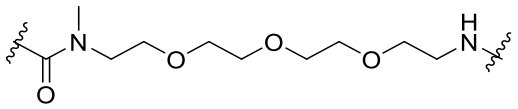
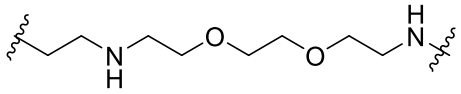
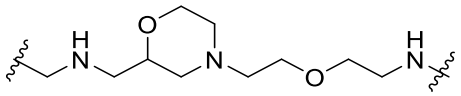
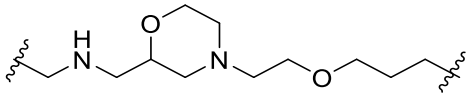
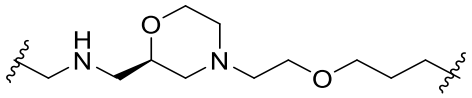
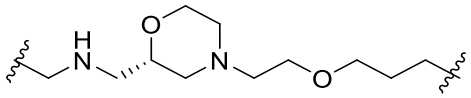
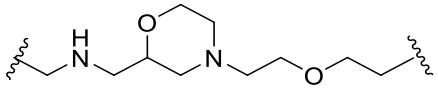
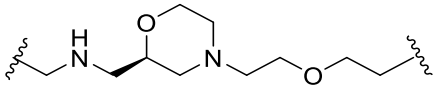
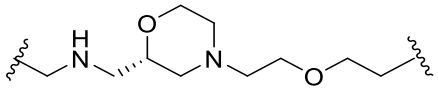
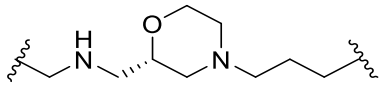
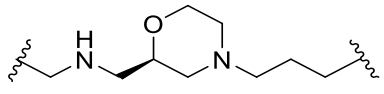
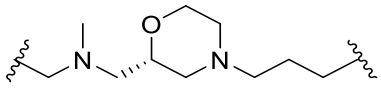
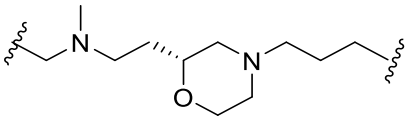
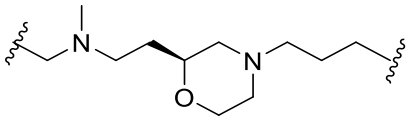
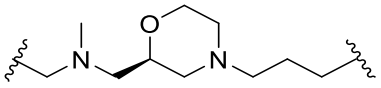
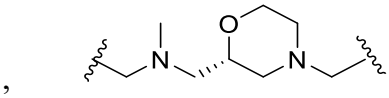
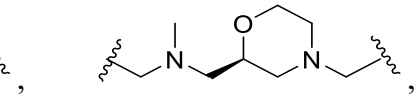
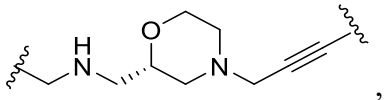
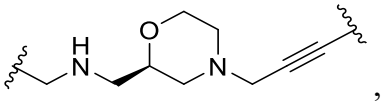
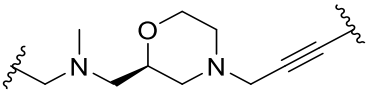
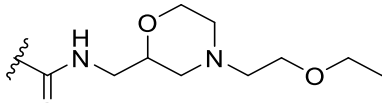

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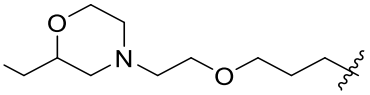
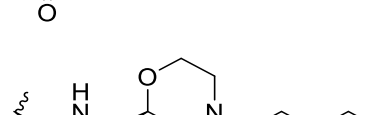
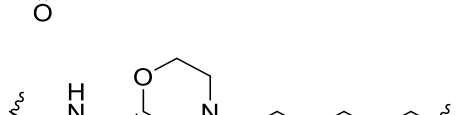
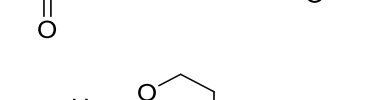
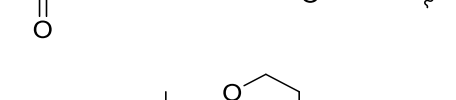
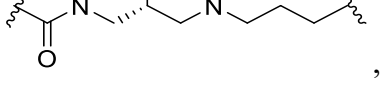
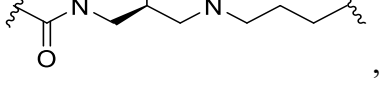
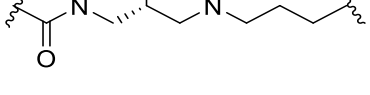
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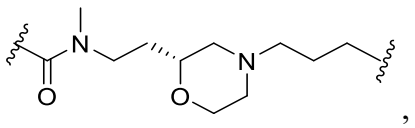
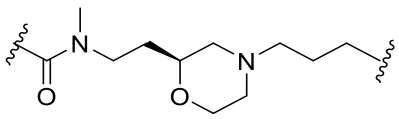
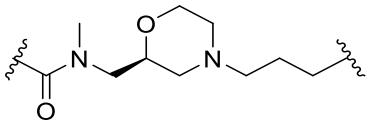
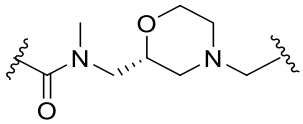
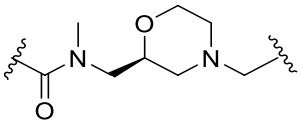
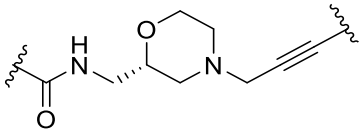
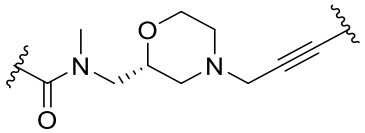
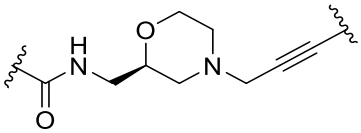
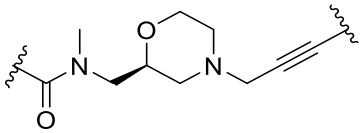
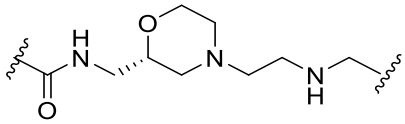
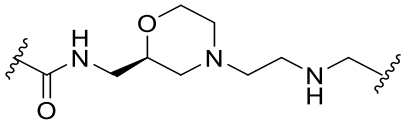
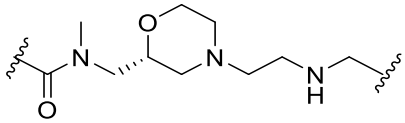
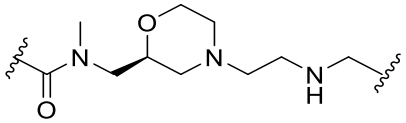
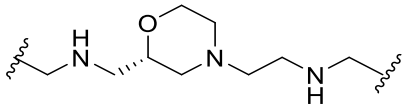
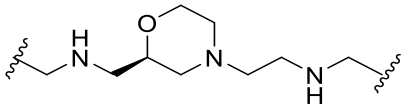
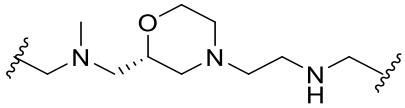
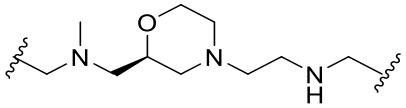
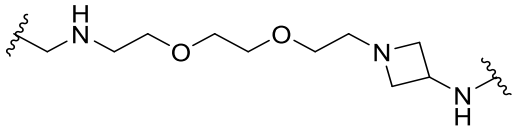
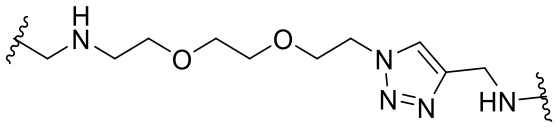
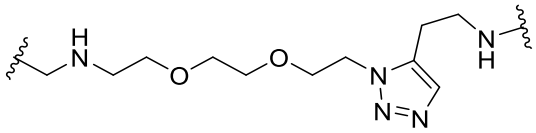
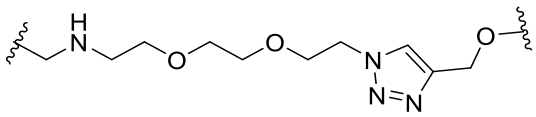
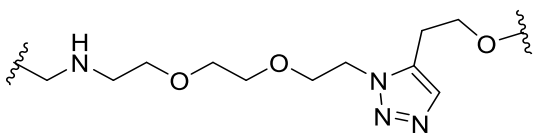
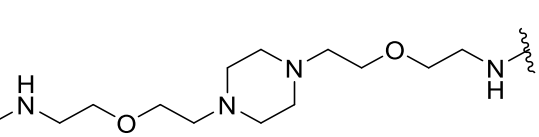
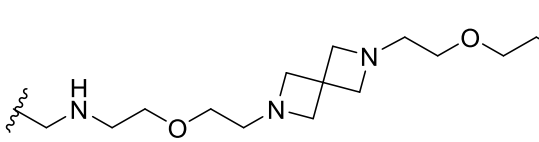
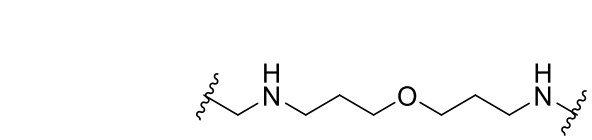
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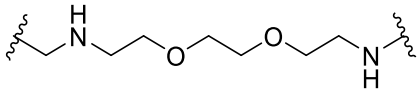
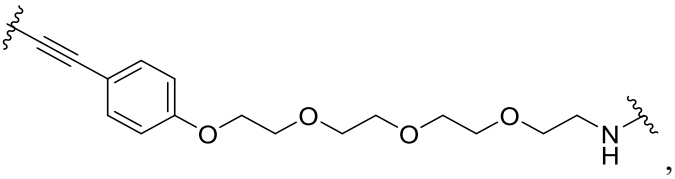
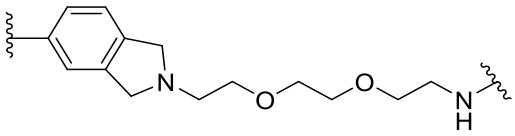
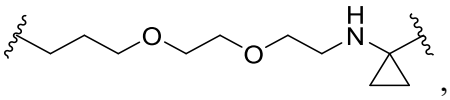
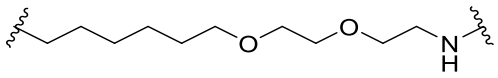
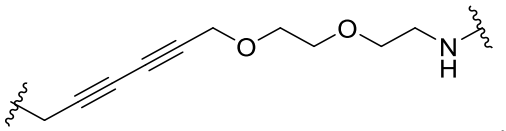
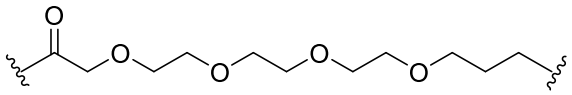
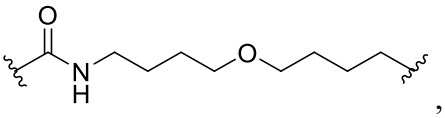
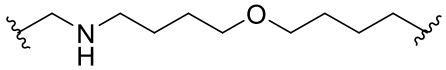
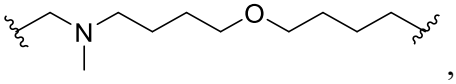
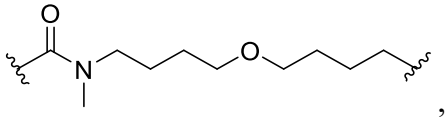
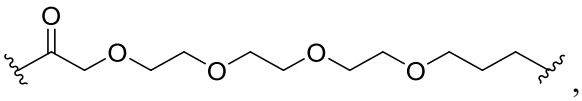
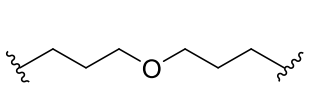
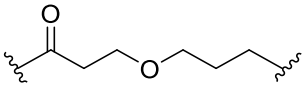
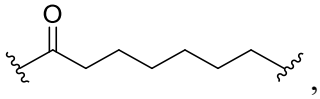
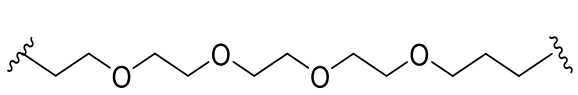
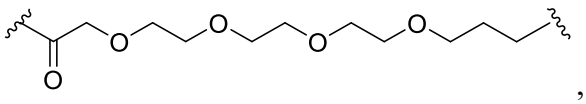
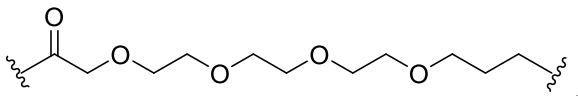
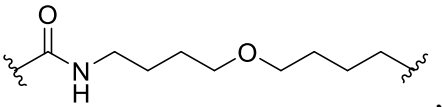
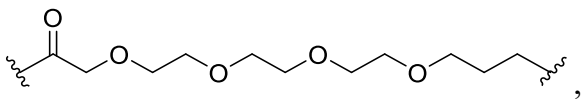
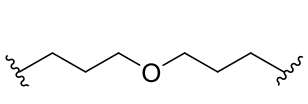
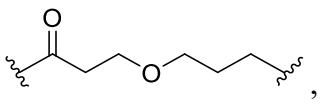
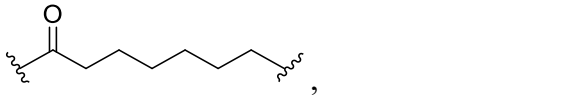
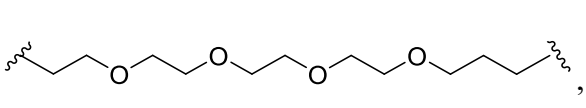
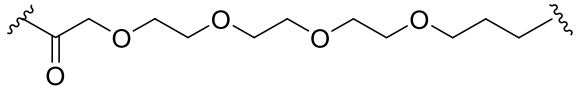
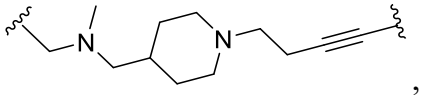

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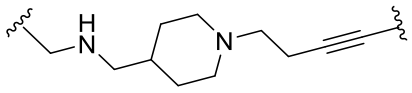
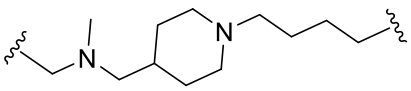
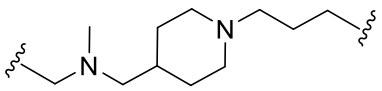
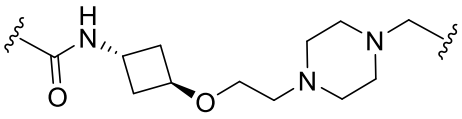
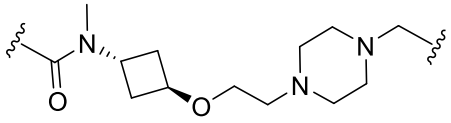
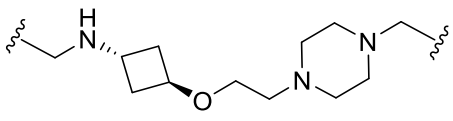
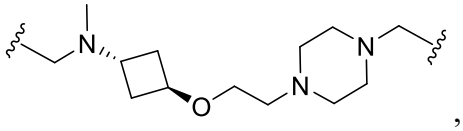
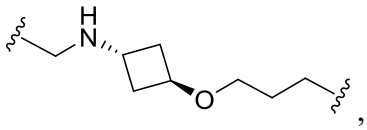
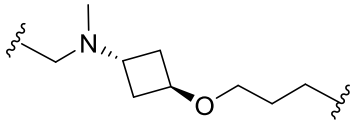
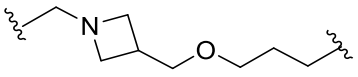
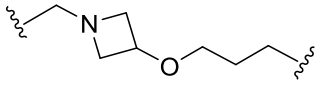
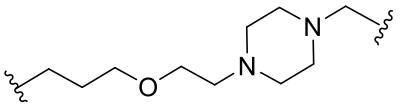
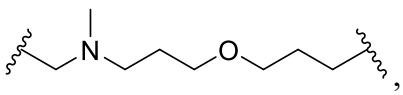
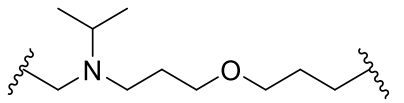
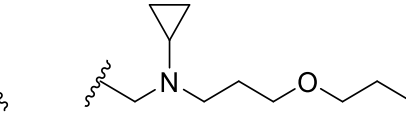
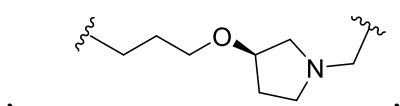
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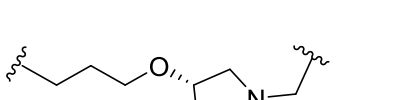
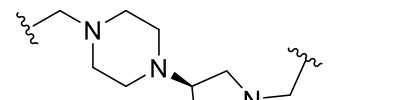
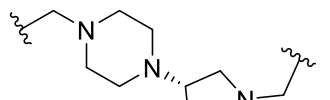
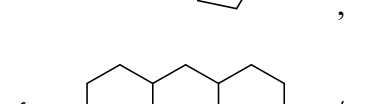
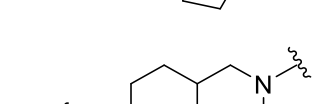
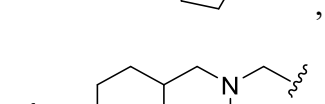
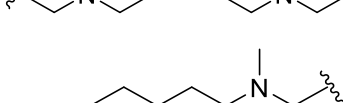
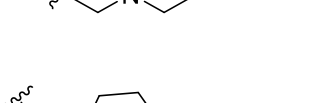
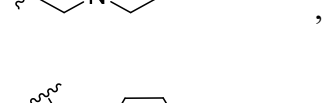
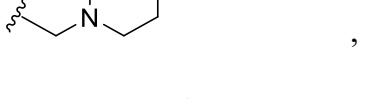
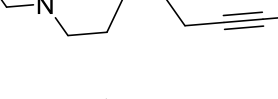
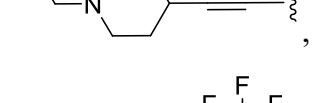
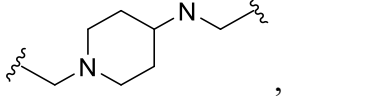
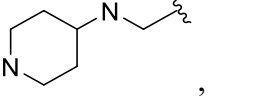
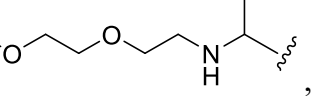
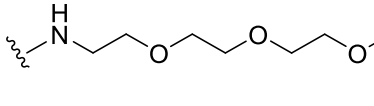
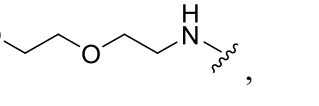
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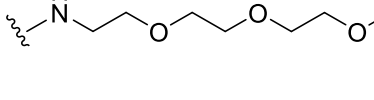
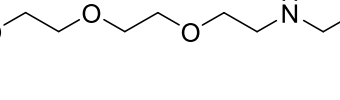

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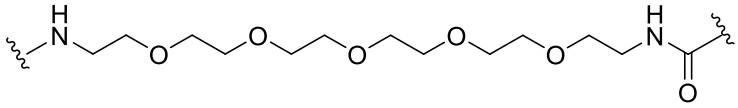
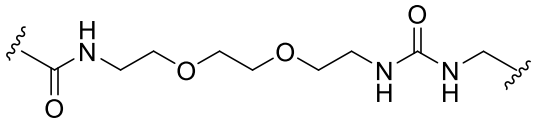
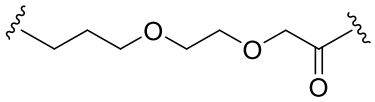
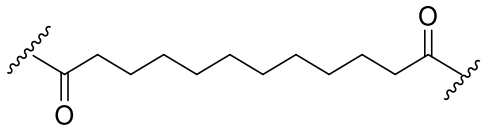
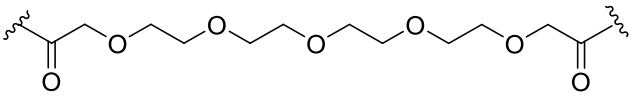
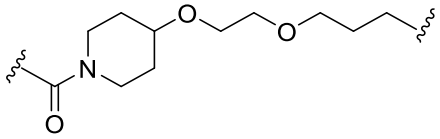
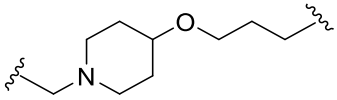
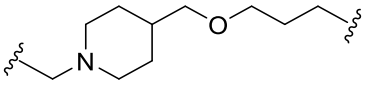
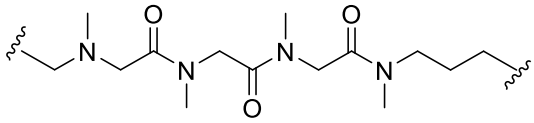
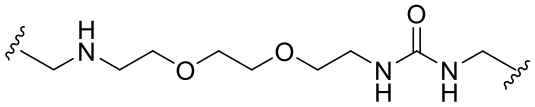
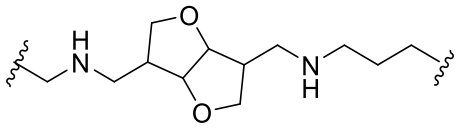
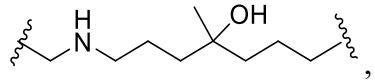
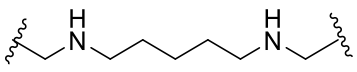
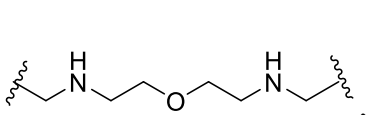
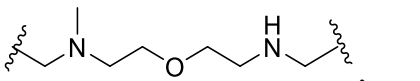
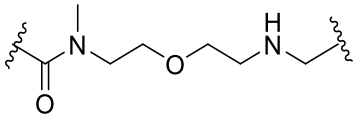
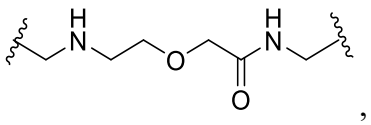
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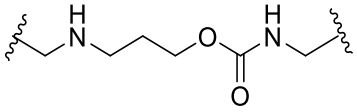
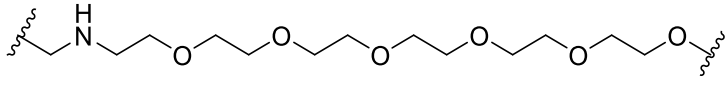
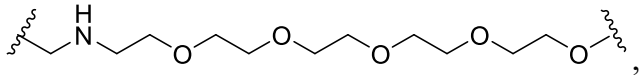
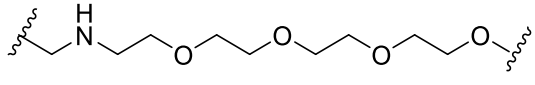
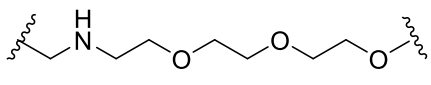
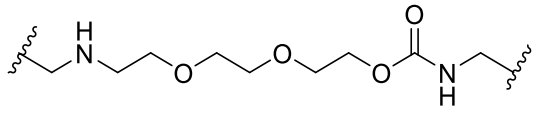
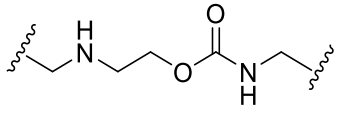
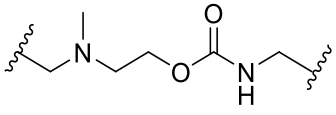
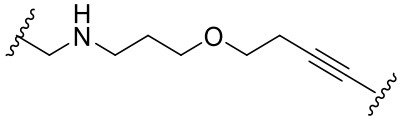
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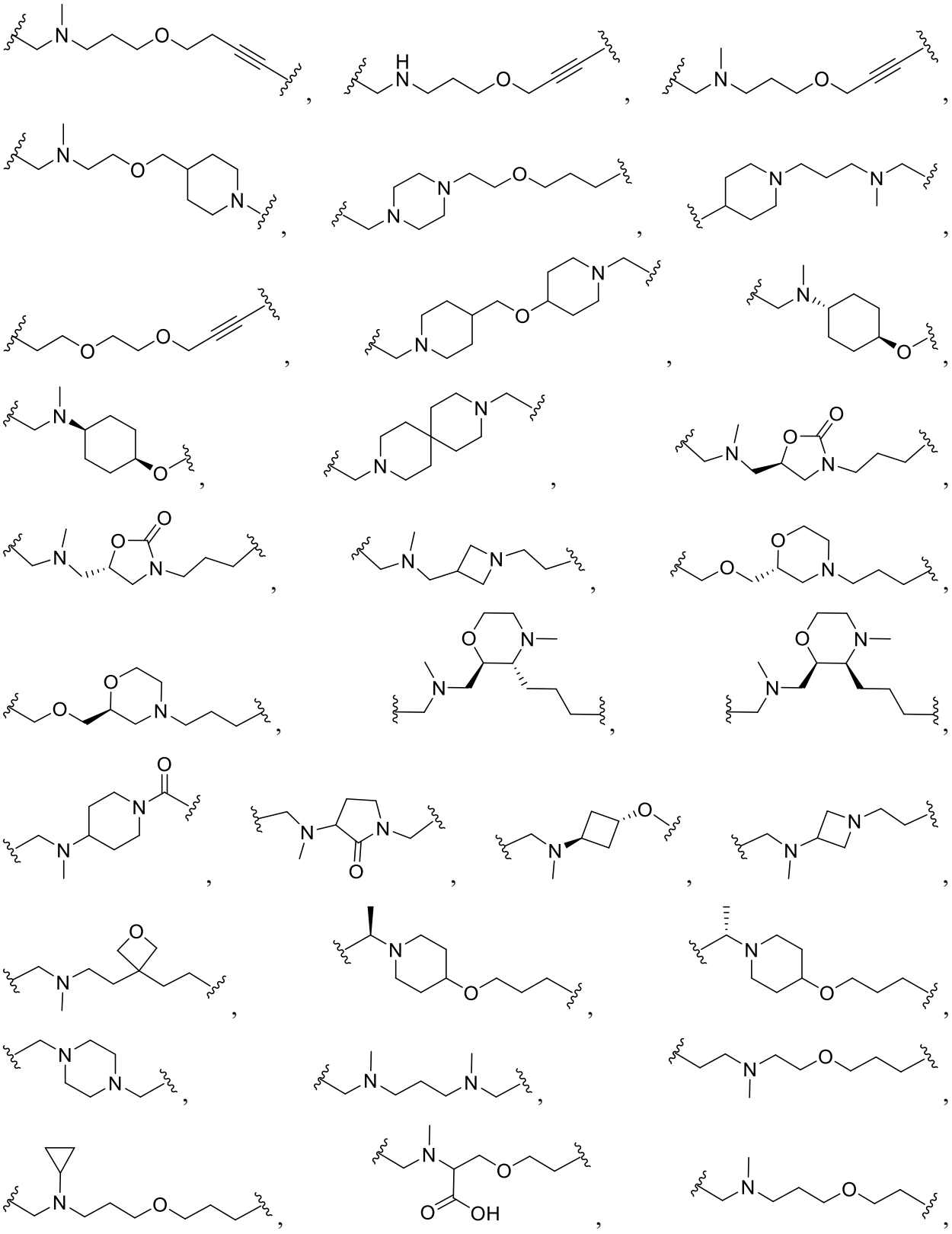
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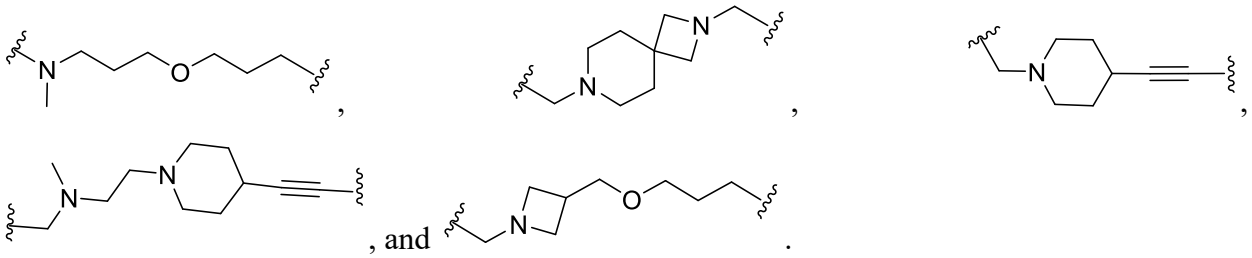

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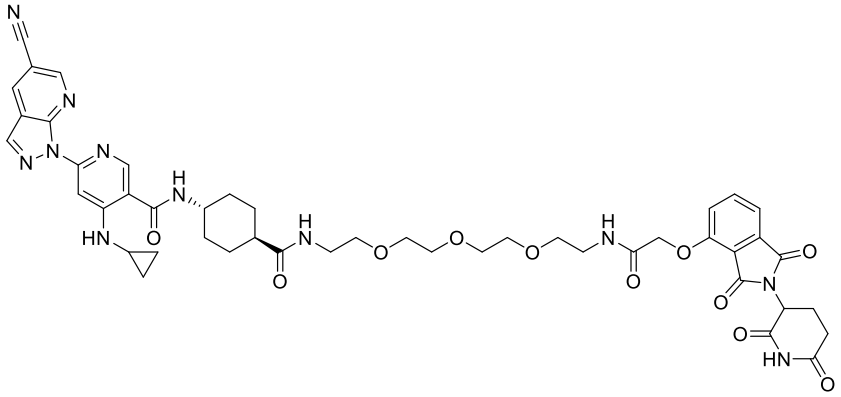
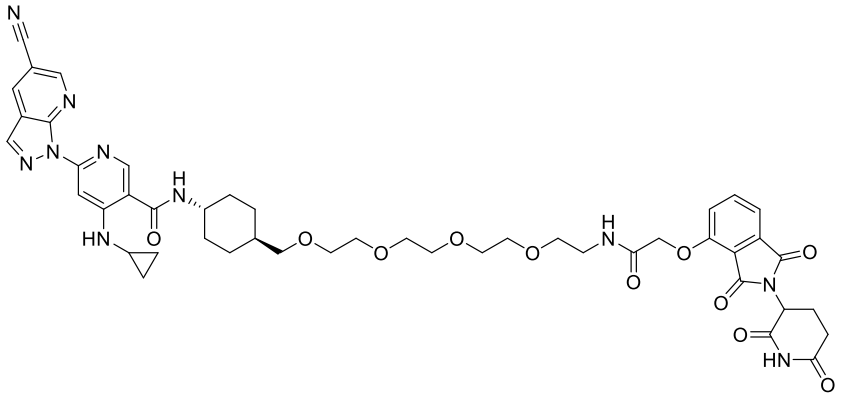
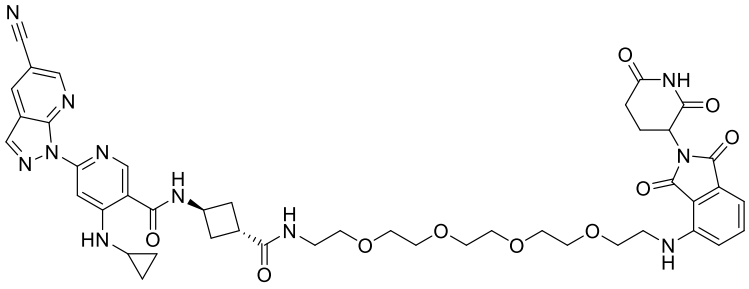
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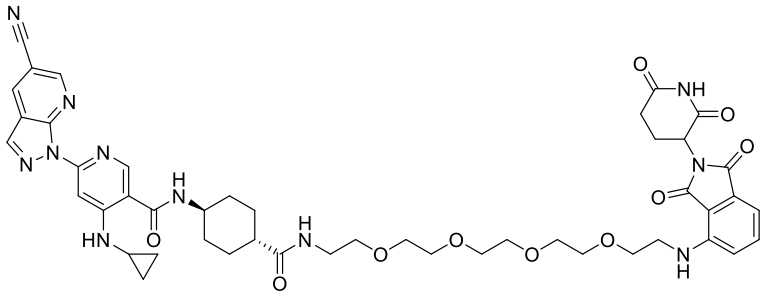
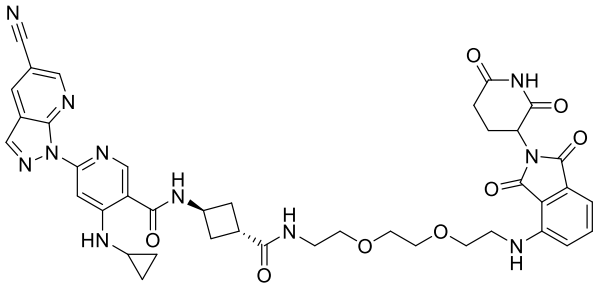
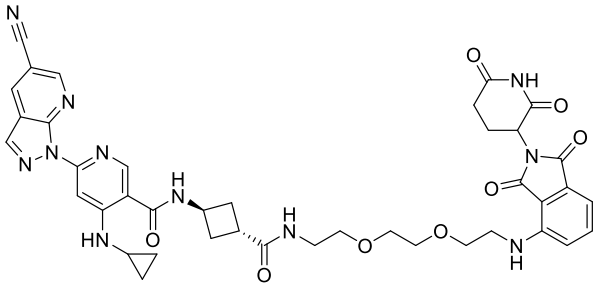
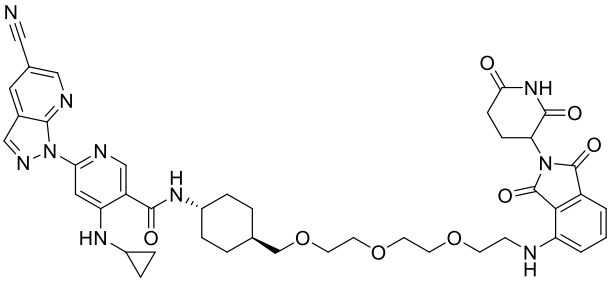
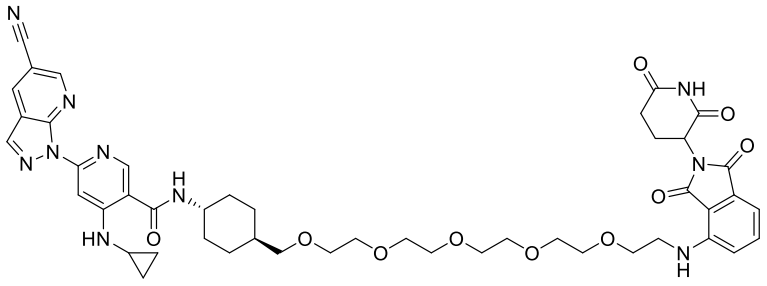
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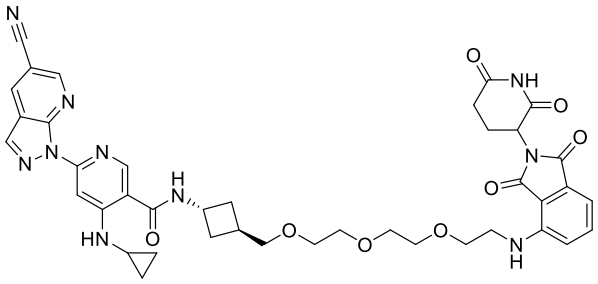
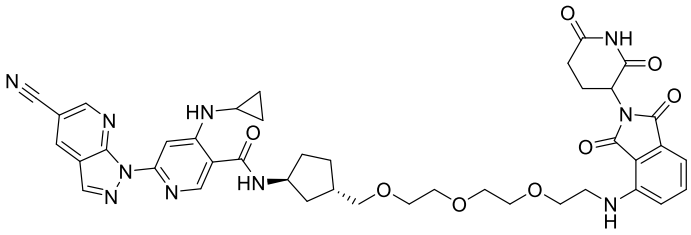
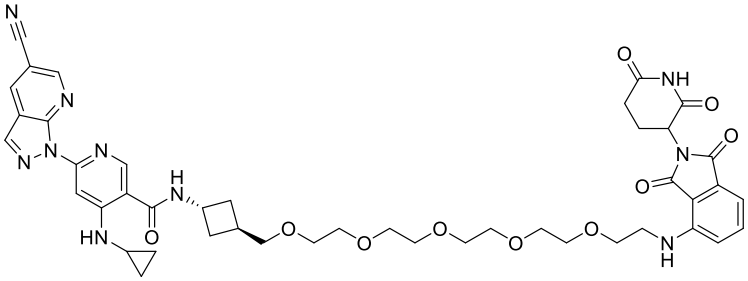
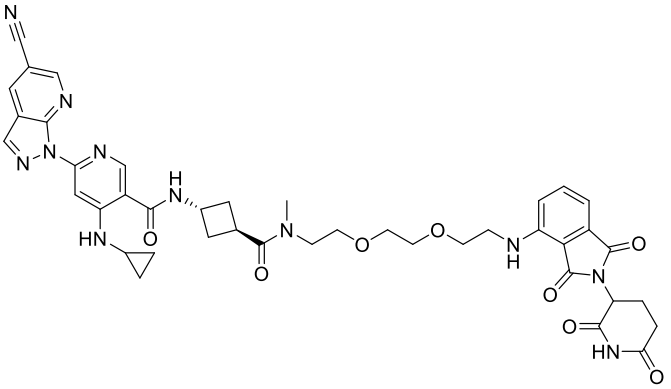
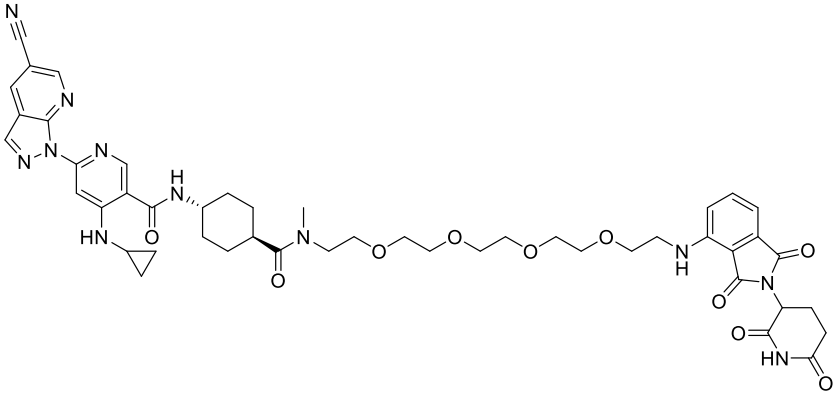


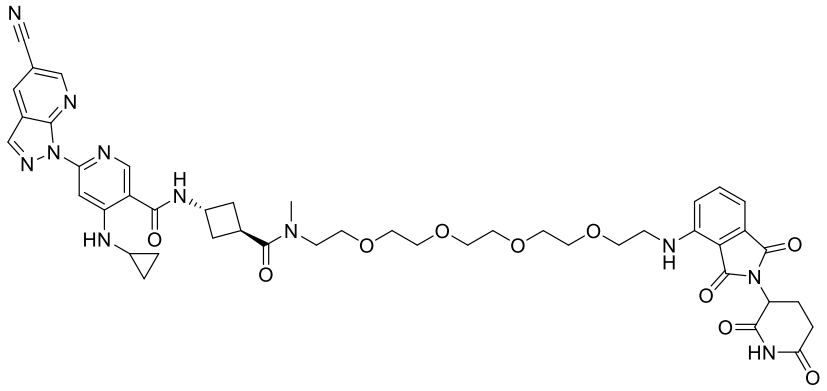
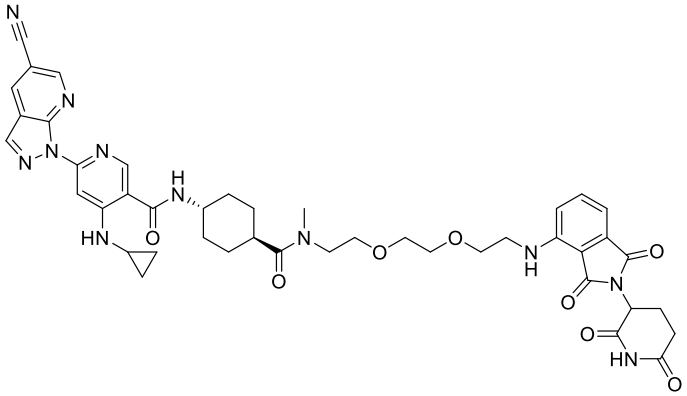
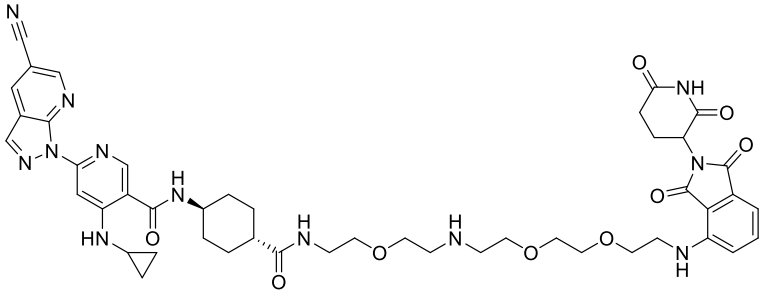
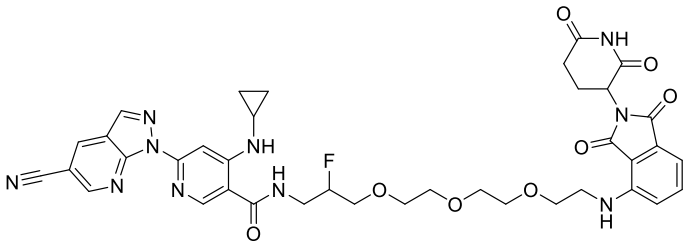
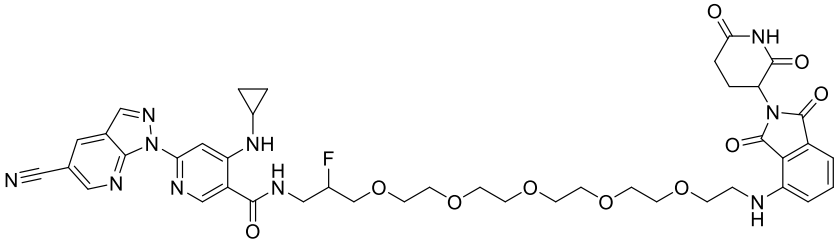


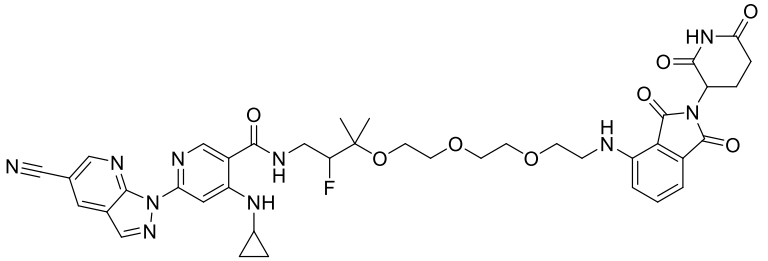
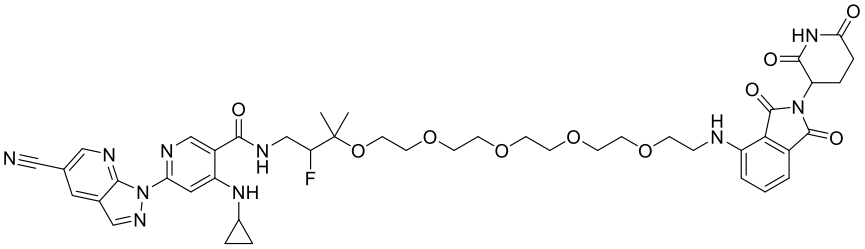
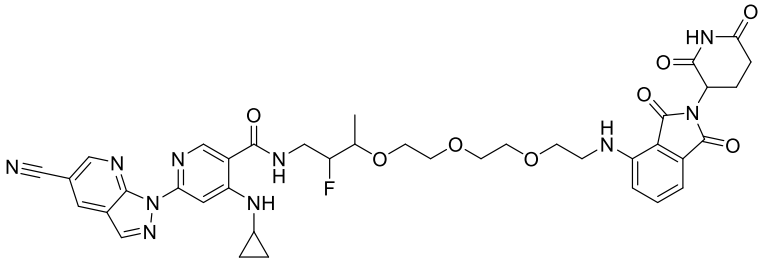
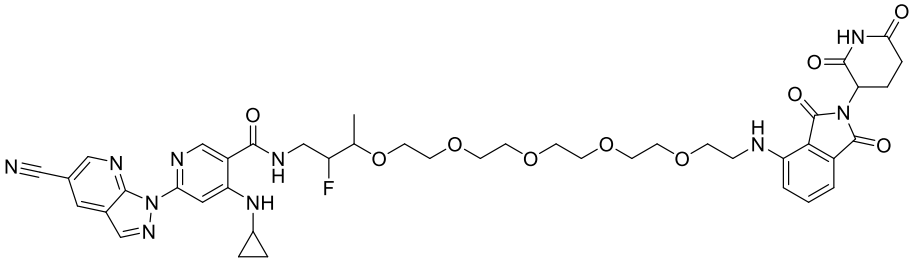
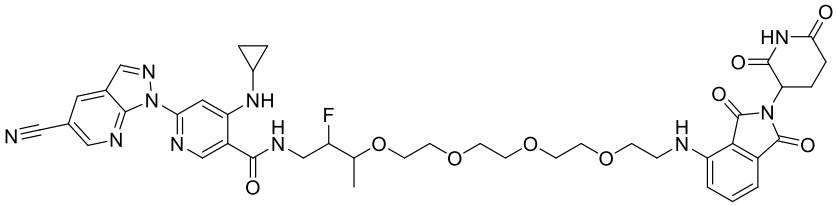
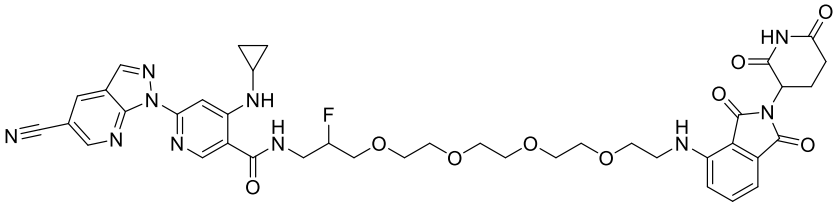
18. The compound according to claim 11, wherein said compound is selected from any one of the following compounds, or a pharmaceutically acceptable salt thereof.

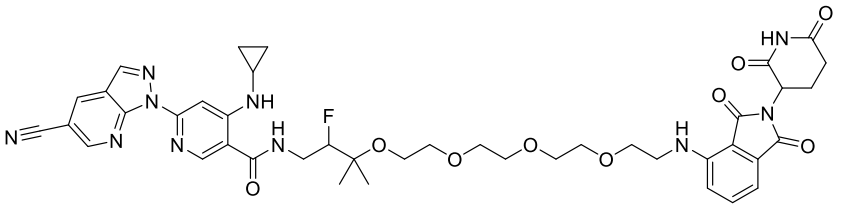
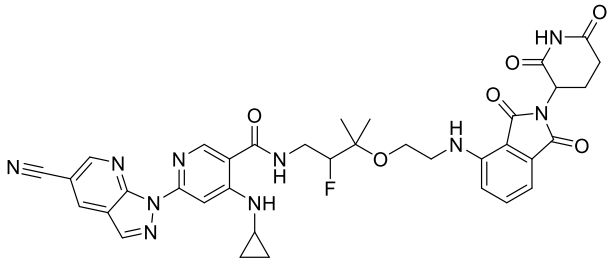
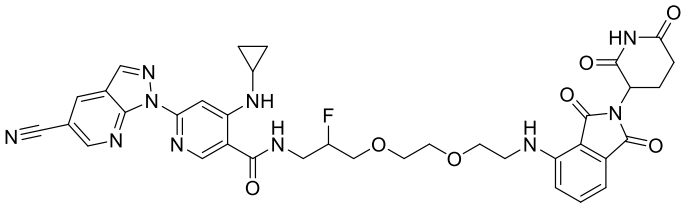
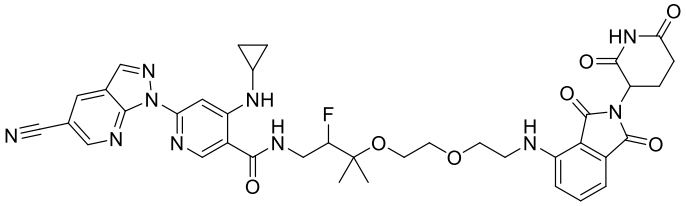
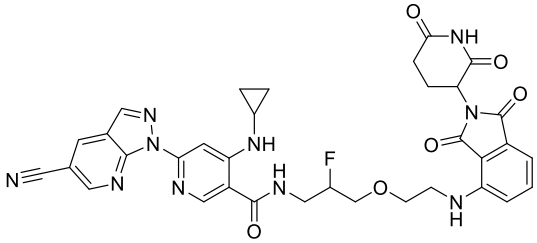
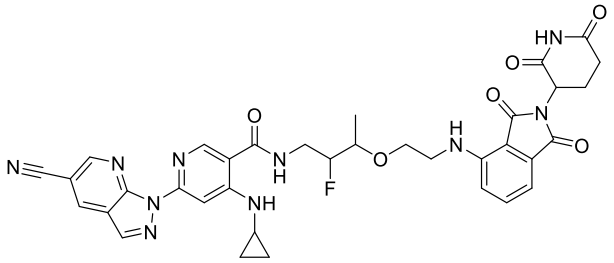
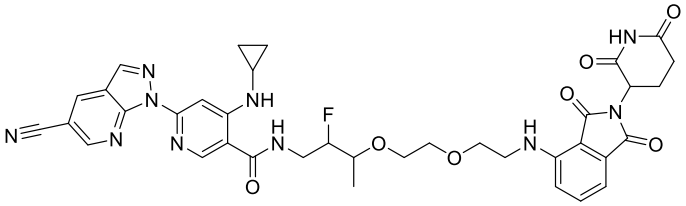
I-#	Structure
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I-18	
I-21	

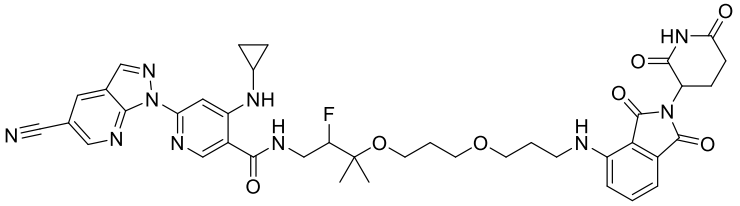
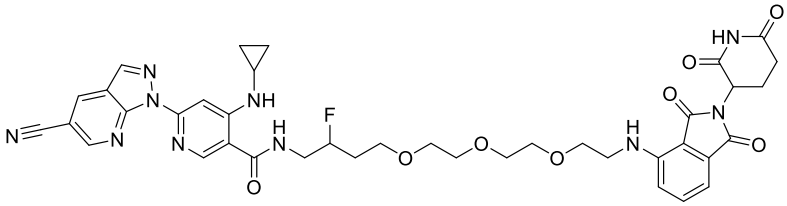
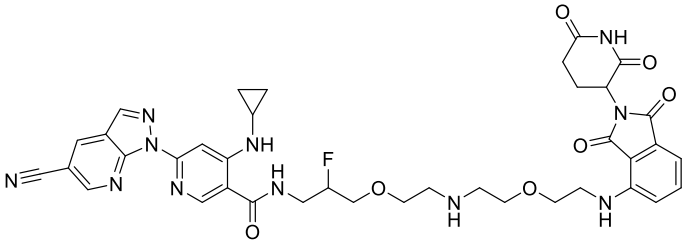
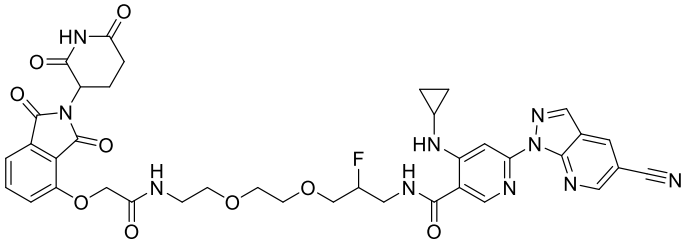
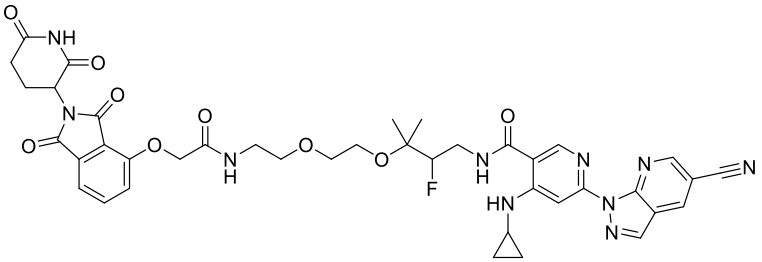
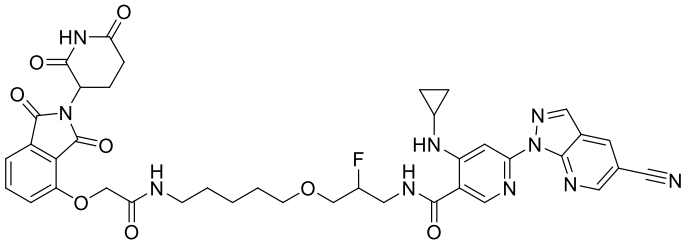
I-#	Structure
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I-29	
I-32	
I-33	

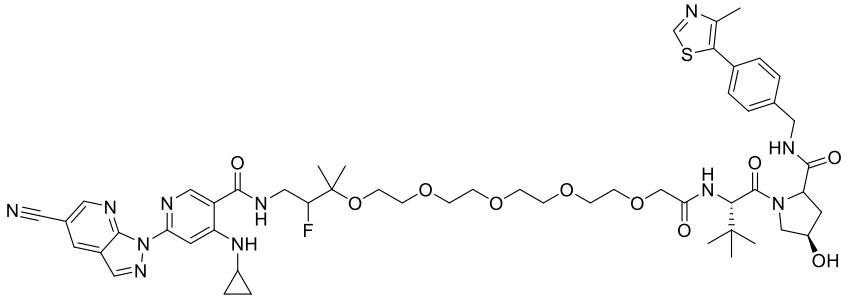
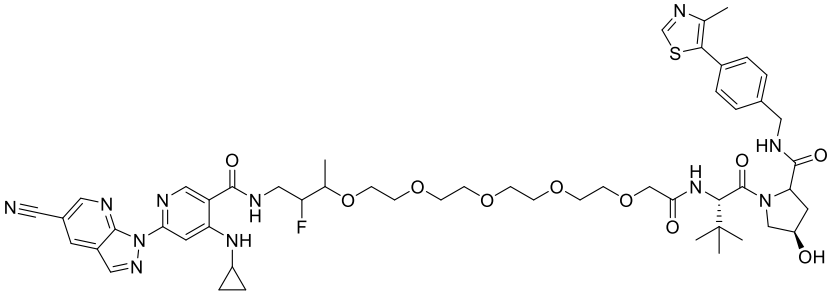
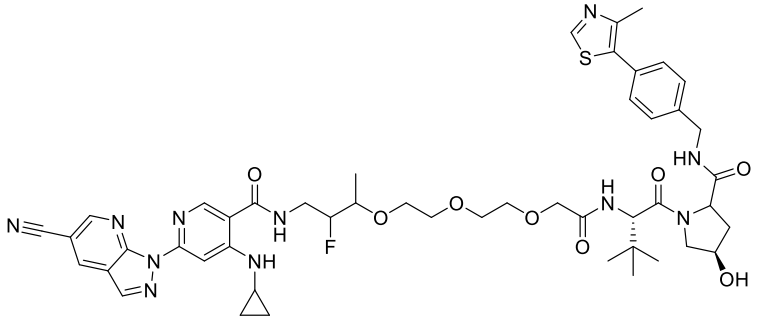
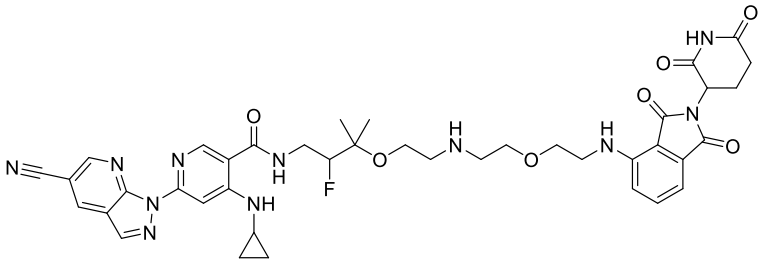
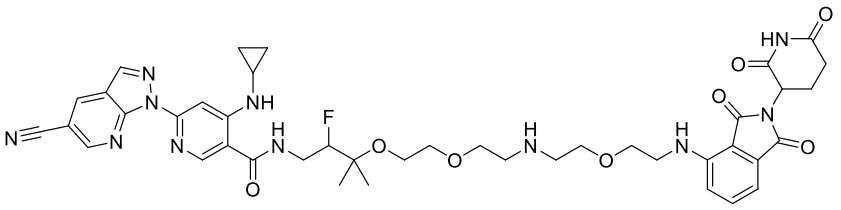
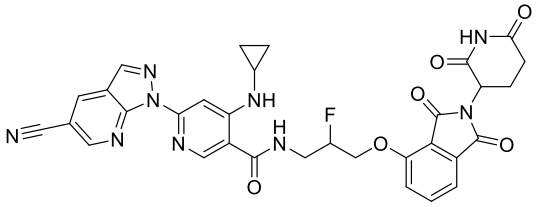
I-#	Structure
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I-35	
I-36	
I-37	
I-38	

I-#	Structure
I-39	
I-42	
I-45	
I-46	
I-57	

I-#	Structure
I-59	
I-60	
I-63	
I-66	
I-71	
I-72	

I-#	Structure
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I-75	
I-76	
I-79	
I-82	
I-83	
I-85	

I-#	Structure
I-86	
I-88	
I-94	
I-95	
I-101	
I-102	

I-#	Structure
I-118	
I-121	
I-122	
I-129	
I-131	
I-173	

19. A pharmaceutical composition comprising a compound according to claim 11, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

20. The pharmaceutical composition according to claim 19, further comprising an additional therapeutic agent.