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.

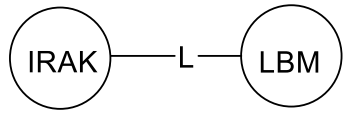
[0005] Aberrations in the process have recently been implicated in the pathogenesis of several diseases, both inherited and acquired. These diseases fall into two major groups: (a) those that result from loss of function with the resultant stabilization of certain proteins, and (b) those that result 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 ~~OF THE INVENTION~~

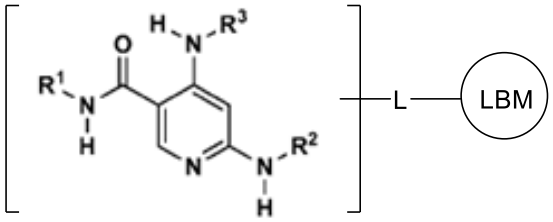
[0007a] In an aspect of the present disclosure, there is provided a compound of formula **I**:



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), —$(CH_2)_2CH(CH_3)NHC(O)(C_{1-6}$alkyl), —$(CH_2)_2CH(CH_3)NHC(O)(CH_2)_{0-1}NH(C_{1-6}$ alkyl), or —$(CH_2)_2CH(CH_3)NHC(O)(CH_2)_{0-1}N(C_{1-4}$ 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

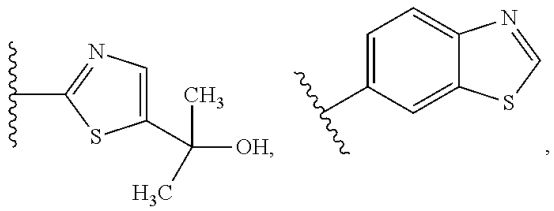
R^3 is:

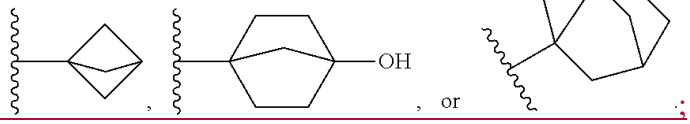
(a) C_{1-6} alkyl substituted with zero to 4 substituents independently selected from F, —OH, —CH_3, —CF_3, and C_{3-6}cycloalkyl;

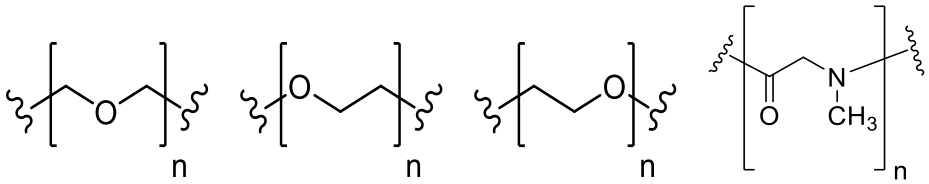
(b) C_{3-6} cycloalkyl substituted with zero to 2 substituents independently selected from F, —OH, C_{1-3} hydroxyalkyl, —CH_3, —CF_2H, —NH_2, and —$C(O)OCH_2CH_3$;

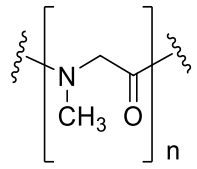
(c) oxetanyl, tetrahydropyranyl, or fluoro tetrahydropyranyl;

(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:

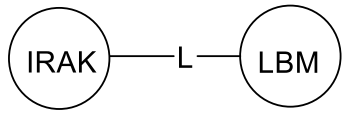
each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated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

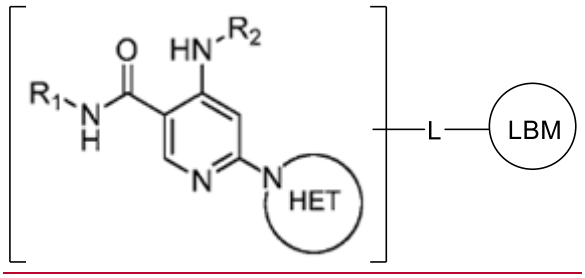
[0007b] In another aspect of the present disclosure, there is provided a compound of formula **I**:



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$_{1-}$

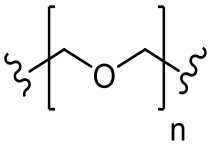
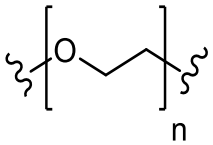
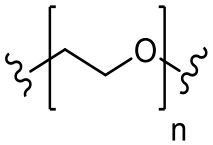
$_{6}$ alkylenyl)NHC(O)(C_{1-4}fluoroalkyl);

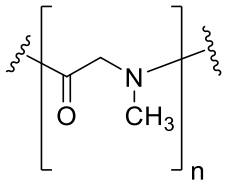
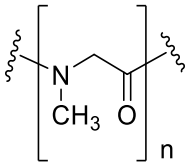
(ii) —(C_{1-4} alkylenyl)R_y wherein R_y is C_{3-6} cycloalkyl, azetidinyl, oxetanyl, oxazolyl, pyridinyl, tetrahydropyranyl, or morpholinyl, each substituted with zero to 2 substituents independently selected from F, —OH, and C_{1-3} alkyl;

(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.

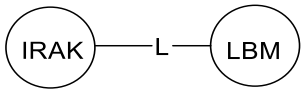
[0007c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

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

[0012] Compounds provided by ~~this invention~~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

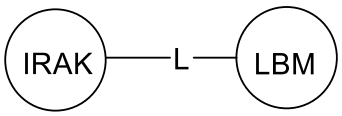
1. General Description of Certain Embodiments of the Invention:

[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:

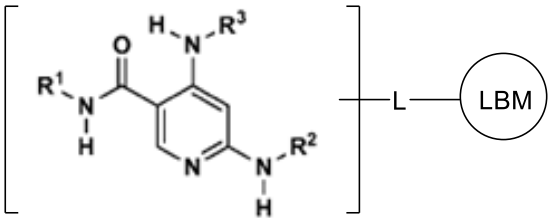
1. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

IRAK is an IRAK binding moiety capable of binding to ~~one or more of~~ IRAK ~~1, 2, 3, or~~ 4, 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

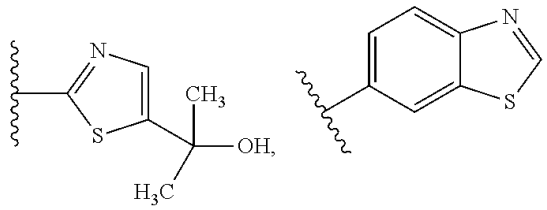
R^3 is:

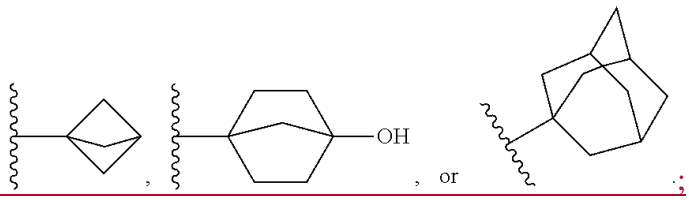
(a) C_{1-6} alkyl substituted with zero to 4 substituents independently selected from F, —OH, —CH_3, —CF_3, and C_{3-6}cycloalkyl;

(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;

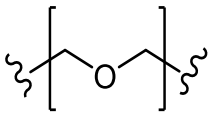
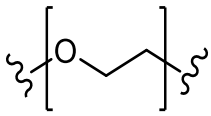
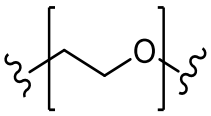
(d) phenyl substituted with zero to 2 substituents independently selected from —OH, —CN, —O(C_{1-3} alkyl), C_{1-3} hydroxyalkyl, —$C(O)NH_2$, —$S(O)_2NH_2$, —$NHS(O)_2$(C_{1-3} alkyl), pyrazolyl, imidazolyl, and methyl tetrazolyl; or

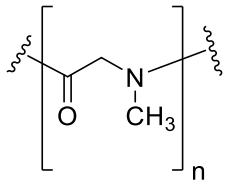
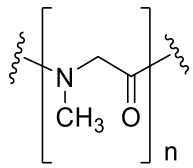


(e) 

;

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)-, -$S(O)_2$-, -$NRS(O)_2$-, -$S(O)_2NR$-, -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

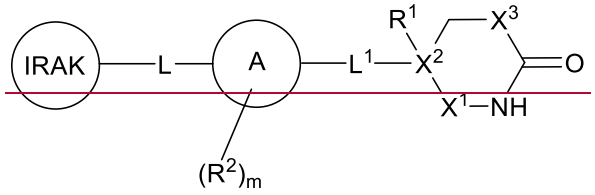
each of n is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

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~~moiety that connects IRAK to LBM~~; and

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

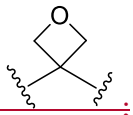
~~2. The compound of claim 1, wherein LBM is a cereblon binding moiety, a VHL binding moiety, an IAP E3 ligase binding moiety, or an MDM2 E3 ligase binding moiety..~~

3. The compound of claim 2, wherein LBM is a cereblon binding moiety and said compound is of formula I-I′:



I-I′

or a pharmaceutically acceptable salt thereof, wherein:

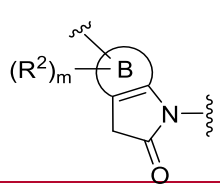
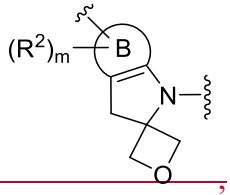
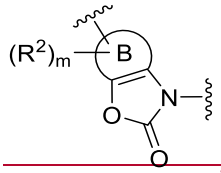
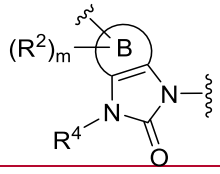
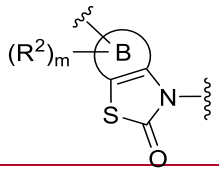
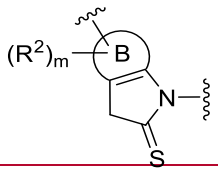
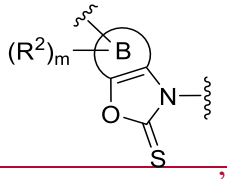
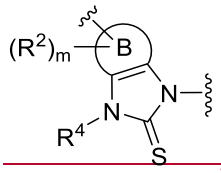
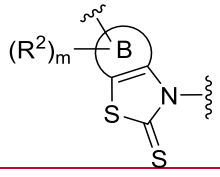
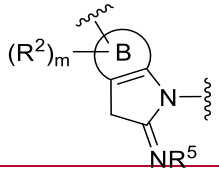
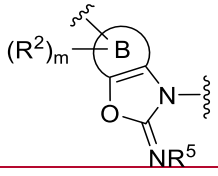
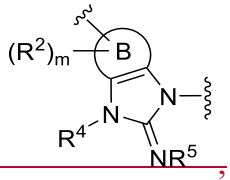
X^1 is a bivalent moiety selected from a covalent bond, CH_2, C(O), C(S), or  ;

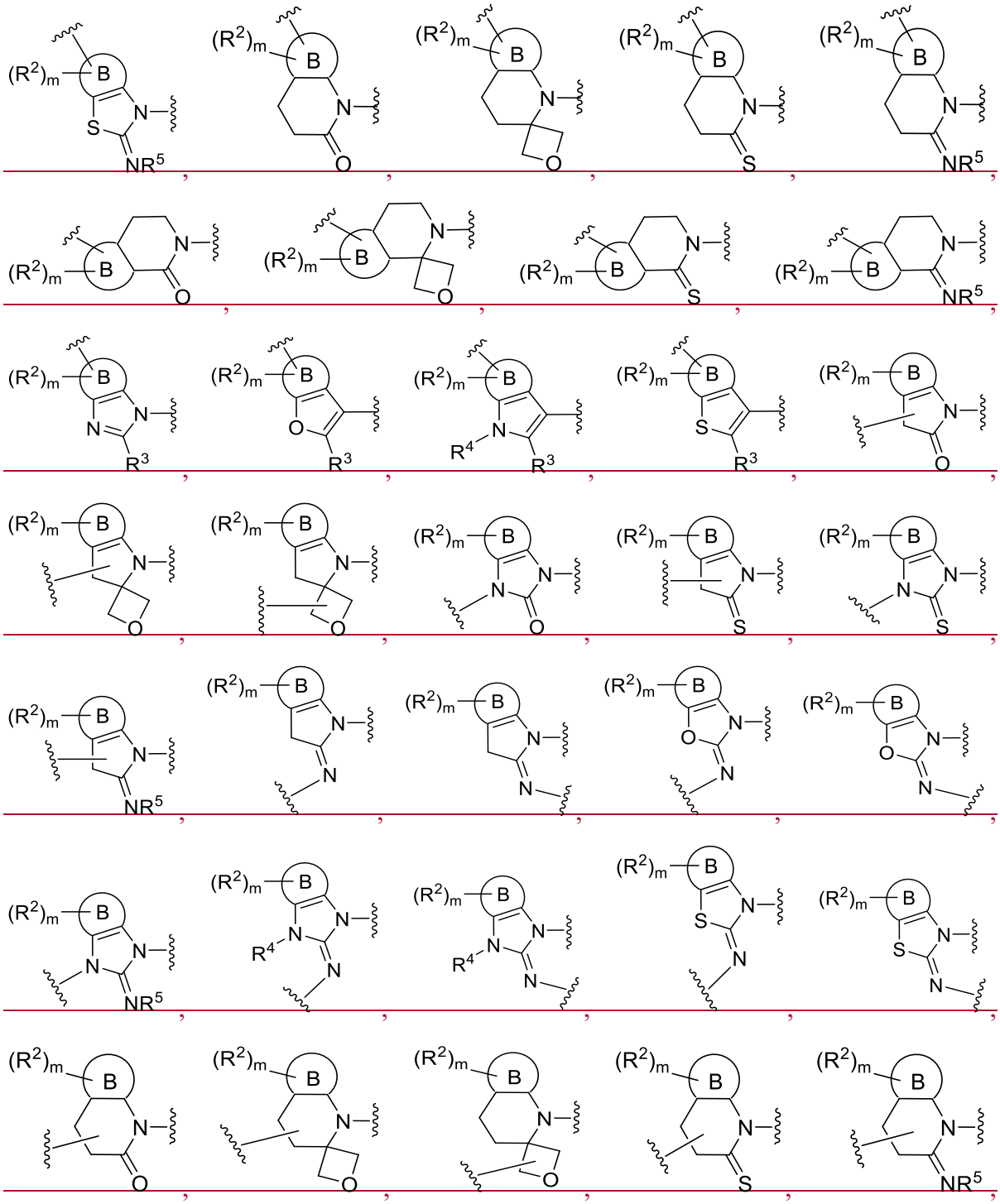
X^2 is a carbon atom or silicon atom;

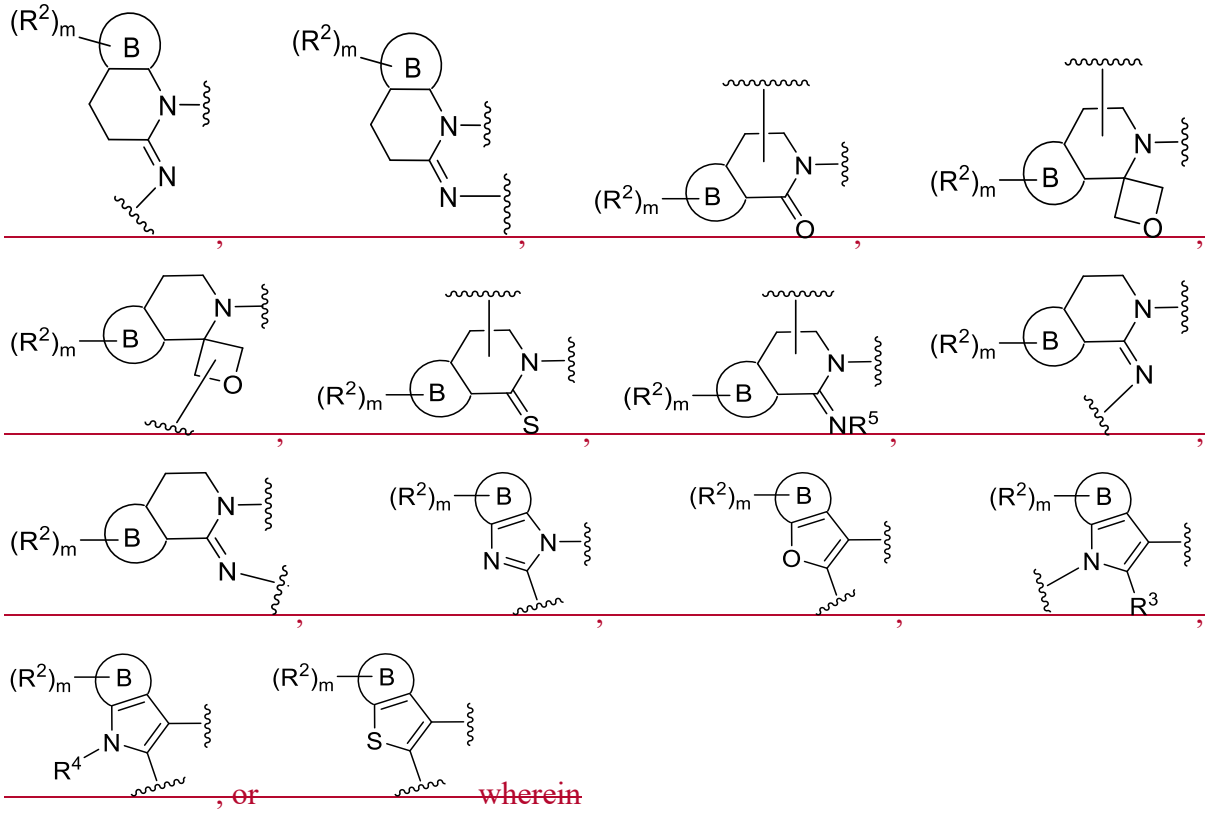
X^3 is a bivalent moiety selected from CH_2 or $Si(R_2)$;

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

each R^2 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 $N(R)S(O)_2R$;

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





, or wherein

Ring B 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;

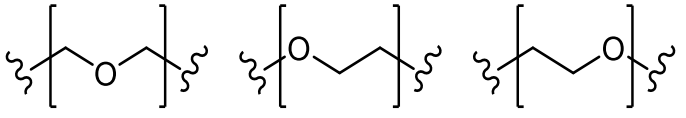
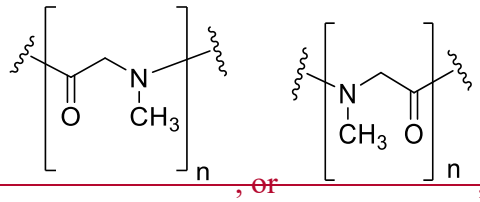
R^3 is selected from hydrogen, halogen, -OR, $-N(R)_2$, or -SR;

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

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

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

L^1 is a covalent bond or a 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;

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

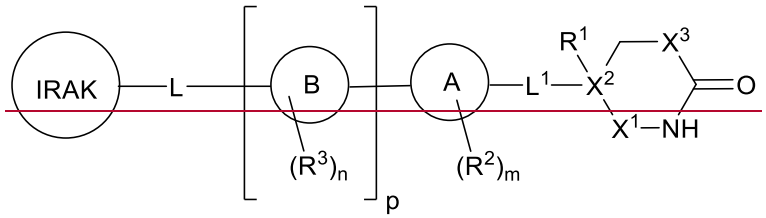
each of n is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

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

two R groups on the same nitrogen are optionally taken together with their intervening

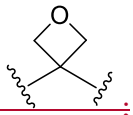
atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

4. The compound of claim 2, wherein LBM is a cereblon binding moiety and said compound is of formula **I-m′**:



I-m′

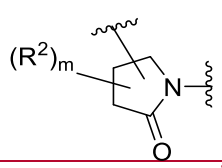
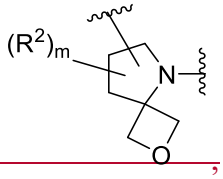
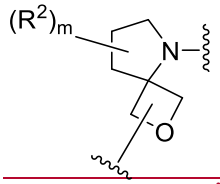
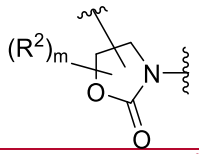
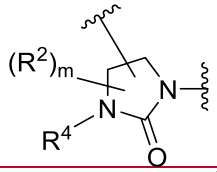
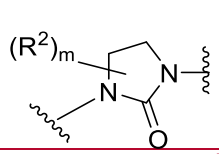
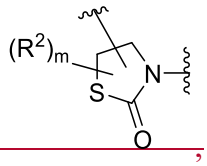
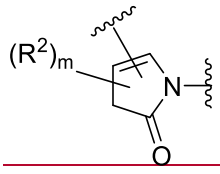
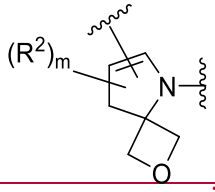
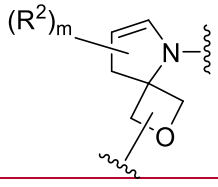
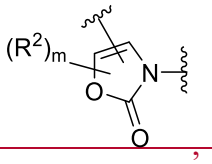
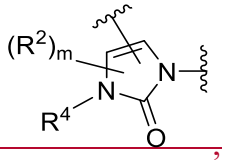
or a pharmaceutically acceptable salt thereof, wherein:

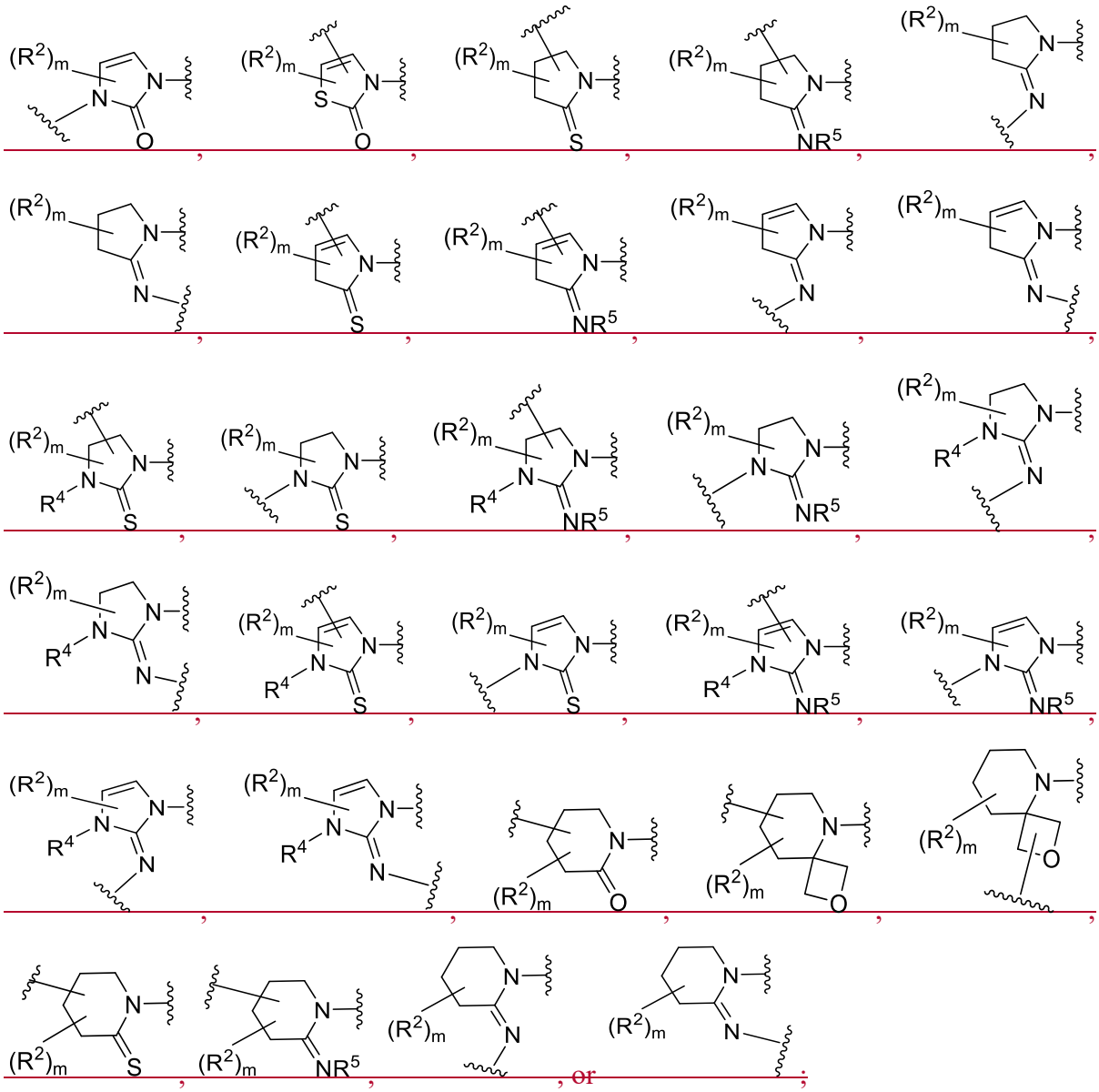
X^1 is a bivalent moiety selected from a covalent bond, CH_2, C(O), C(S), or  ;

X^2 is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from CH_2 or $Si(R_2)$;

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

Ring A is a mono- or bicyclic ring selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .



each R^2 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 $-N(R)S(O)_2R$;

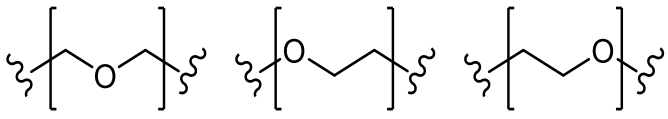
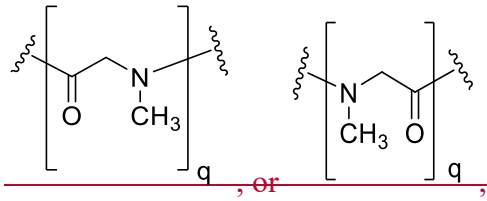
Ring B is selected from a 6-membered aryl containing 0-2 nitrogen atoms or a 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur;

each of R^3 and 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)$_2$R;~~

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

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

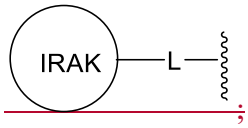
~~L^1 is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -S(O)$_2$-, -NRS(O)$_2$-, -S(O)$_2$NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-,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

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

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

p is 0 or 1, wherein when p is 0, the bond connecting Ring A and Ring B is connected to



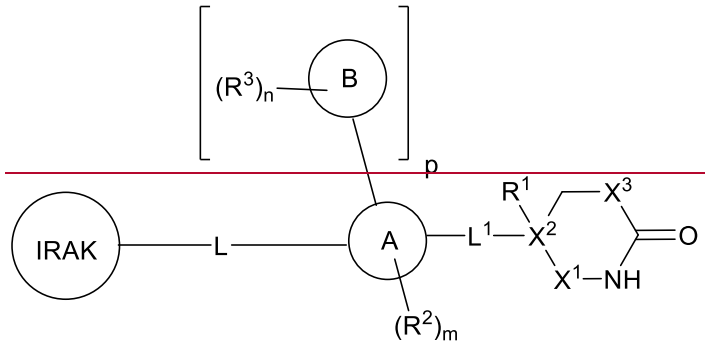
;

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

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

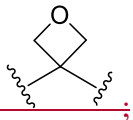
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

5. The compound of claim 2, wherein LBM is a cereblon binding moiety and said compound is selected formula **I-n′**:



I-n′

or a pharmaceutically acceptable salt thereof, wherein:

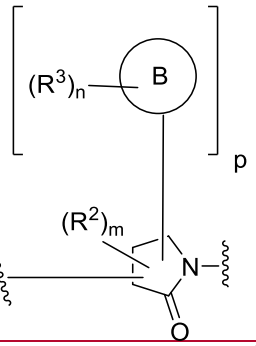
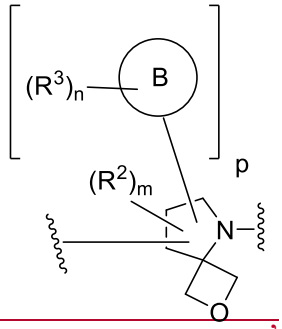
X^1 is a bivalent moiety selected from a covalent bond, CH_2, C(O), C(S), or 

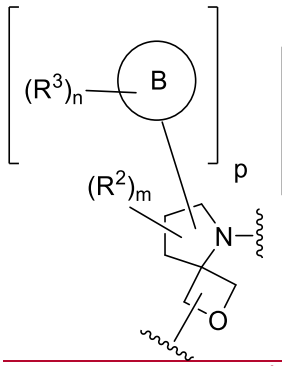
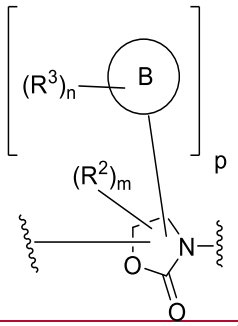
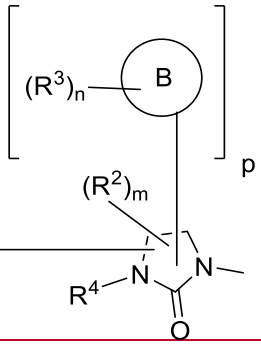
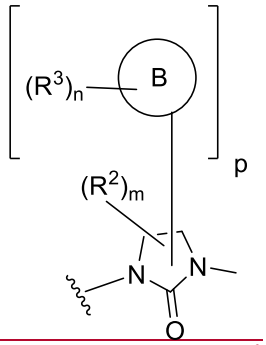
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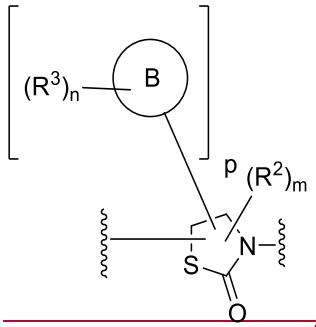
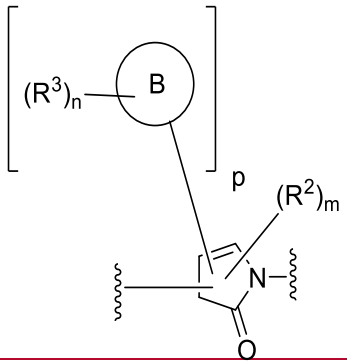
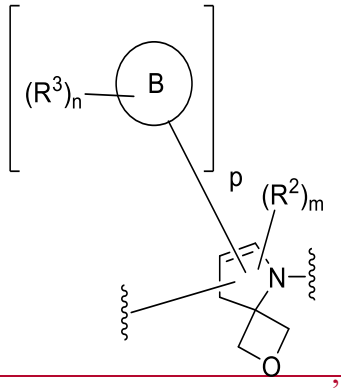
X^2 is a carbon atom or silicon atom;

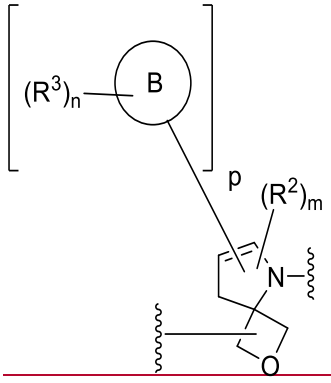
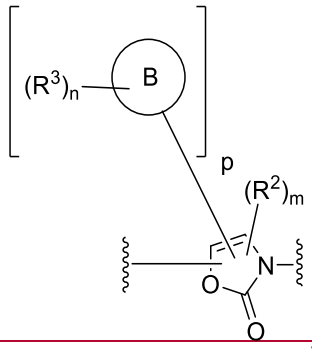
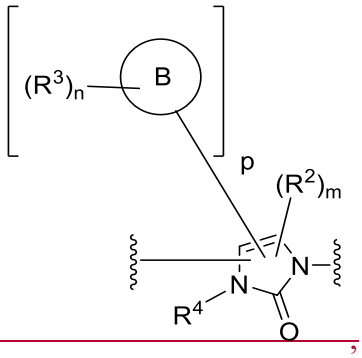
X^3 is a bivalent moiety selected from CH_2 or $Si(R_2)$;

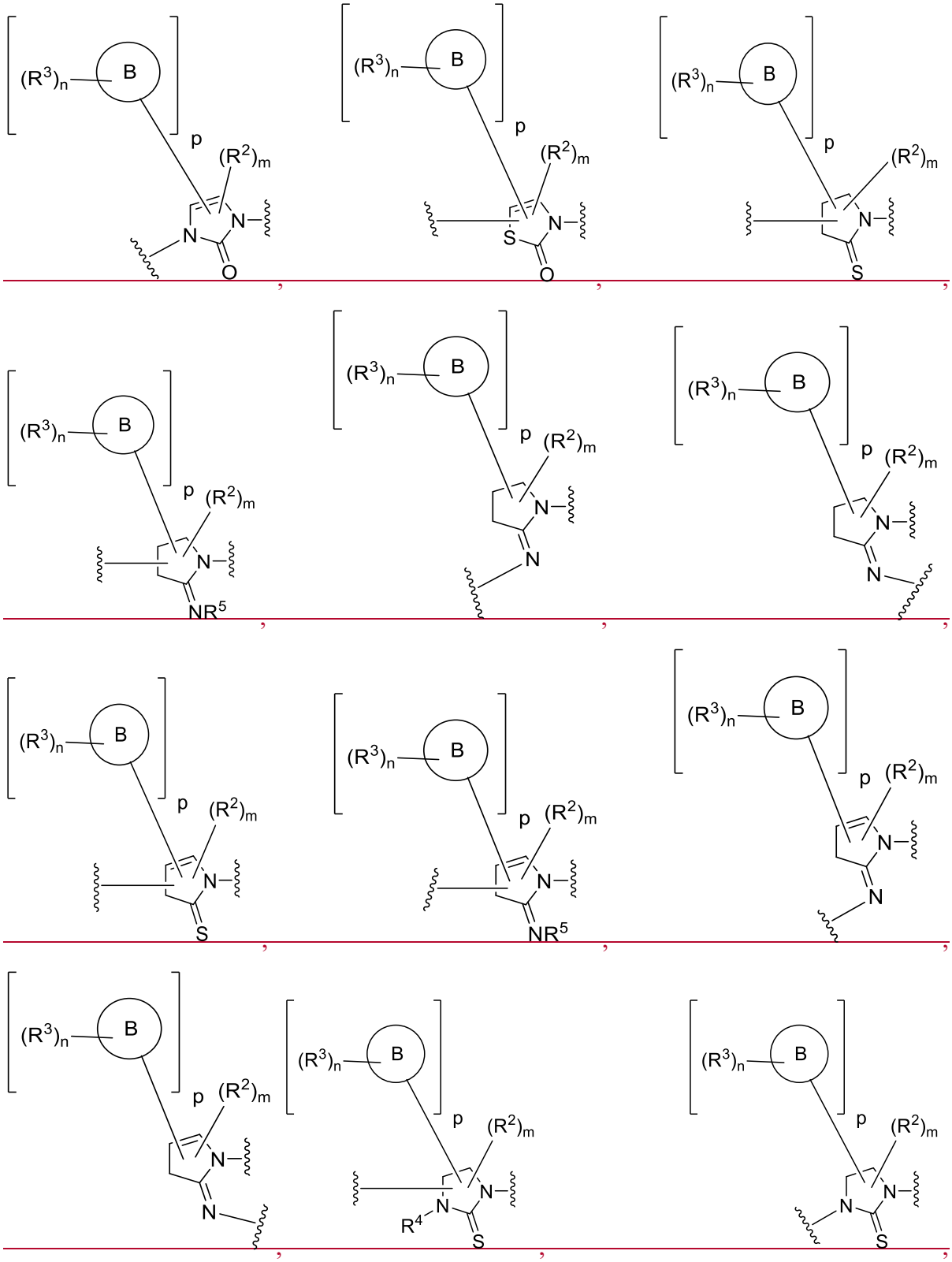
~~R^1 is hydrogen, deuterium, halogen, CN, OR, SR, S(O)R, $S(O)_2R$, $N(R)_2$, $Si(R)_3$, or an optionally substituted C_{1-4} aliphatic;~~

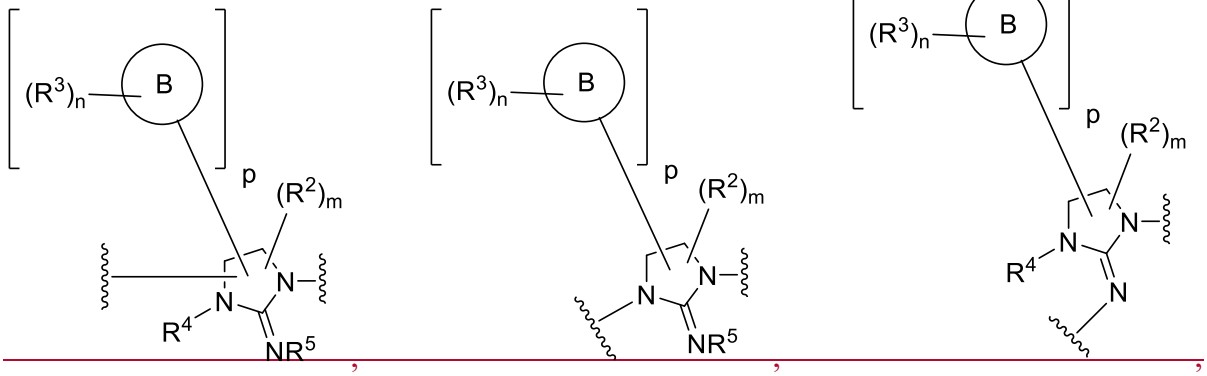
~~Ring A is a mono- or bicyclic ring selected from~~  ,  ,

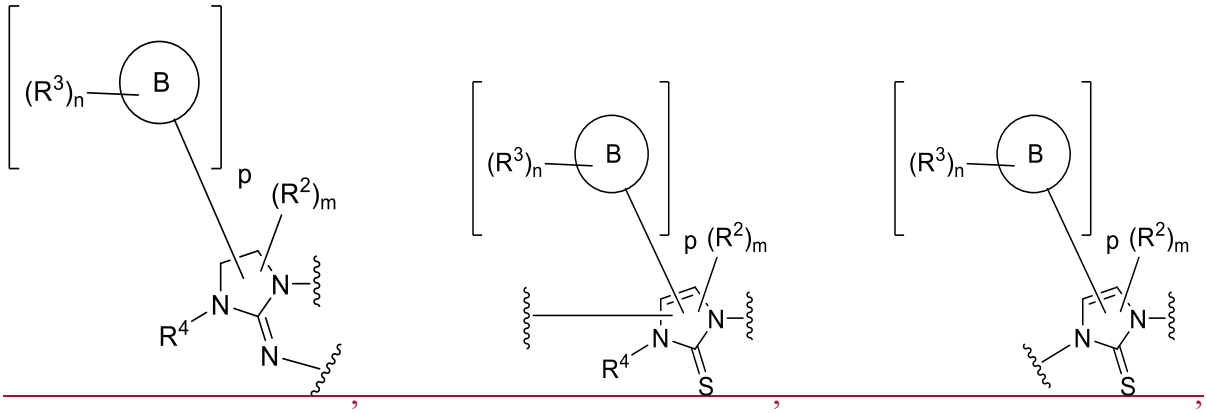
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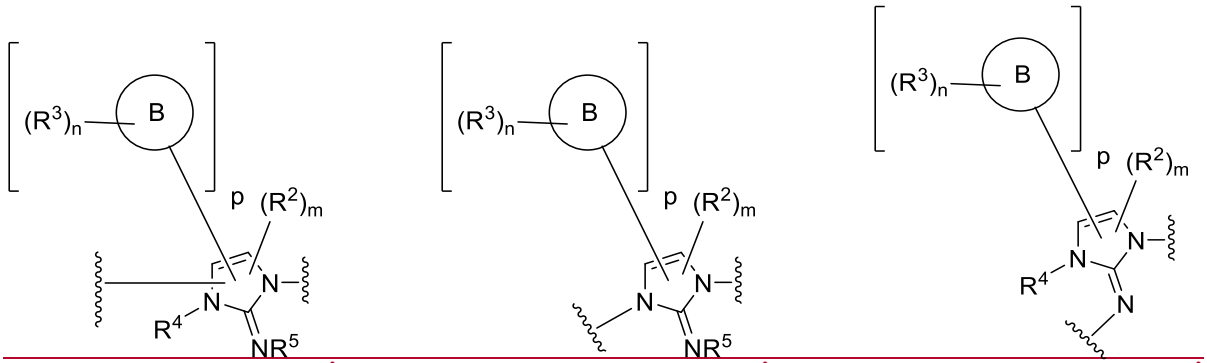
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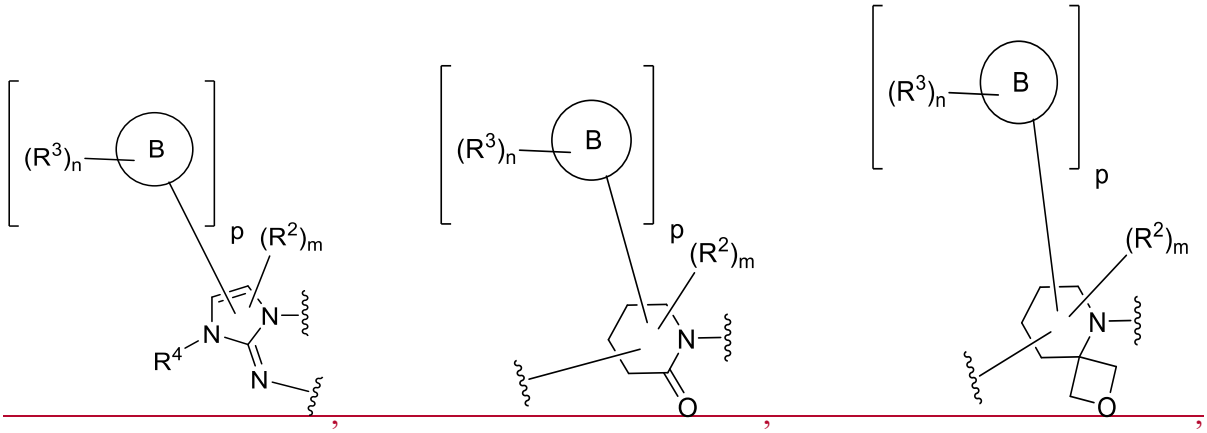
 ,  ,  ,

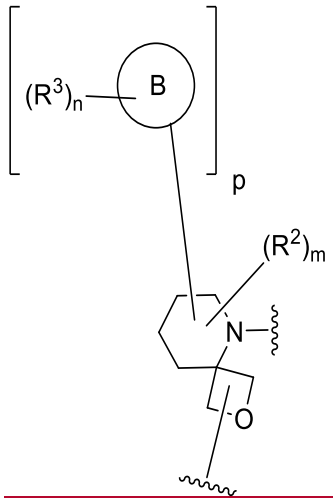


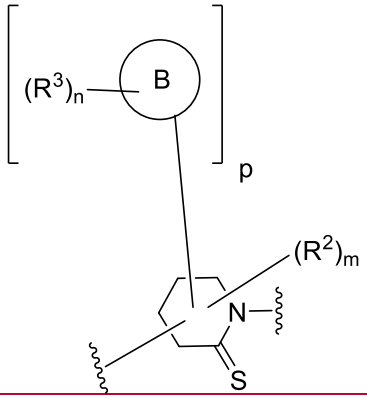


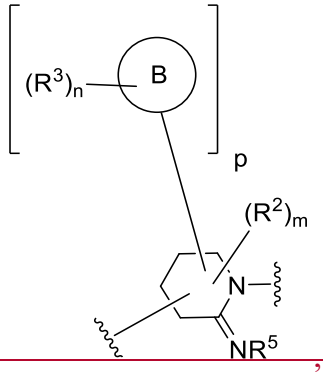


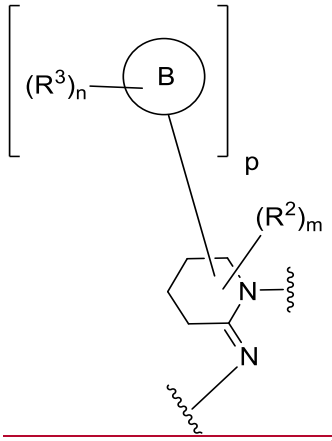


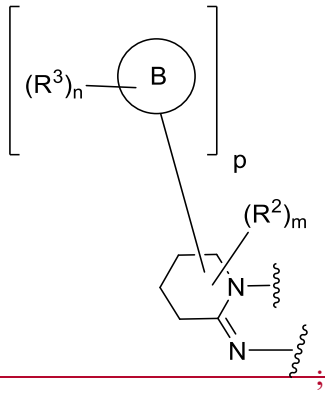




, 

, 

, 

, or 

;

each R^2 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 $-N(R)S(O)_2R$;

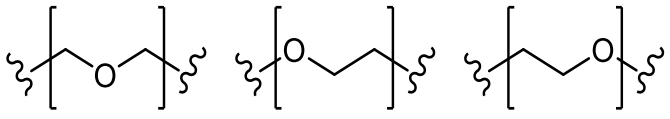
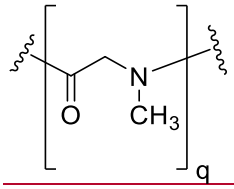
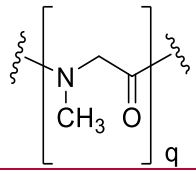
Ring B is selected from a 6-membered aryl containing 0-2 nitrogen atoms or a 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur;

each of R^3 and R^4 is independently hydrogen, R^6, halogen, CN, NO_2, OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

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

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

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

~~L^1 is a covalent bond or a 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;~~

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

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

~~p is 0 or 1;~~

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

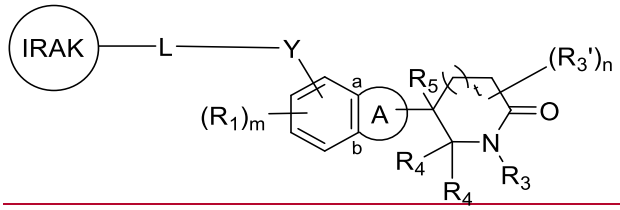
~~each R is independently hydrogen, or an optionally substituted group selected from C_{1-6}~~

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

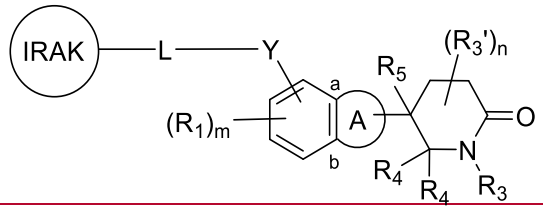
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur.

6. The compound of claim 1, wherein LBM is a cereblon binding moiety and said compound is selected from any of the following formulae:

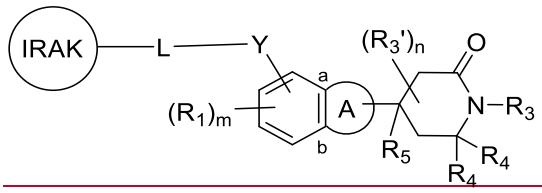
(*i*)



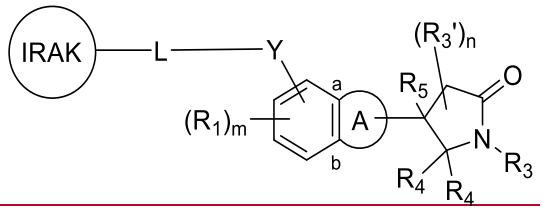
I-a-1



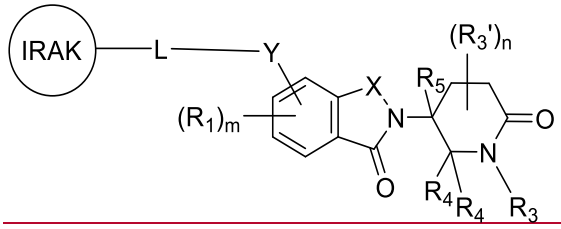
I-a-2



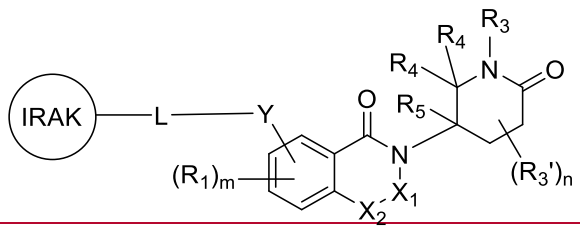
I-a-3



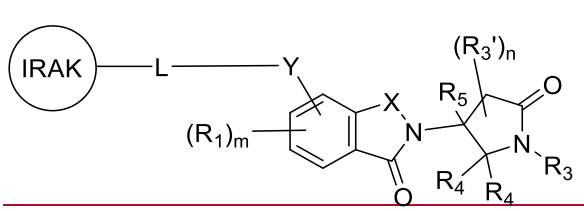
I-a-4

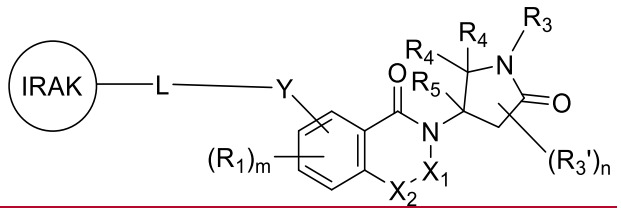


I-a-5

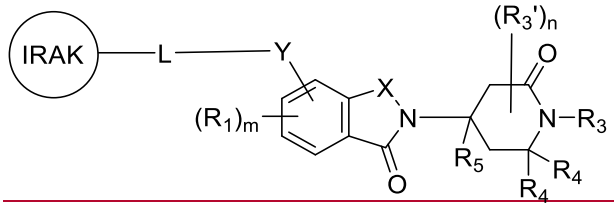


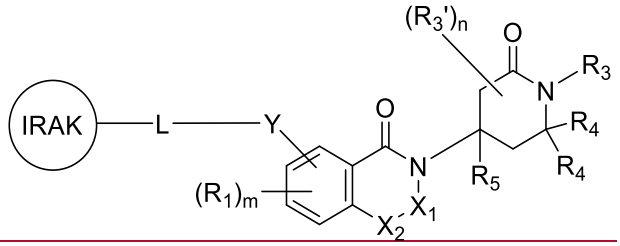
I-a-6



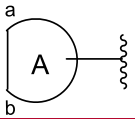


~~I-a-7~~ ~~I-a-8~~



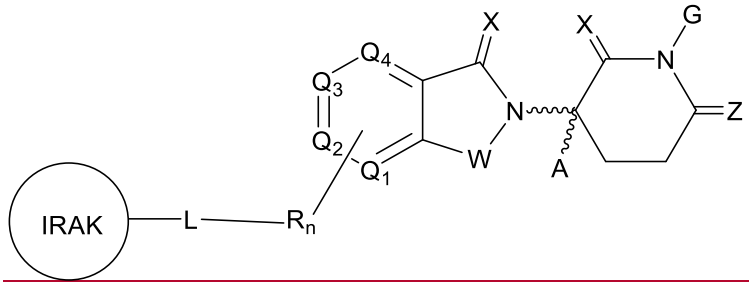


~~I-a-9~~ ~~I-a-10~~

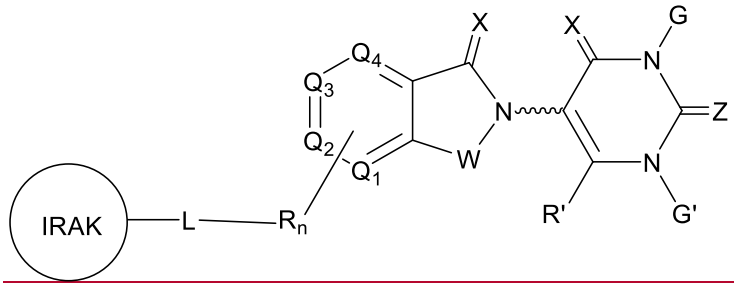
~~or a pharmaceutically acceptable salt thereof, and wherein each of the variables~~ 

~~, X, X_1, X_2, Y, R_1, R_3, R_3', R_4, R_5, t, m and n is as defined and described in US 2018/0134684, the entirety of which is herein incorporated by reference;~~

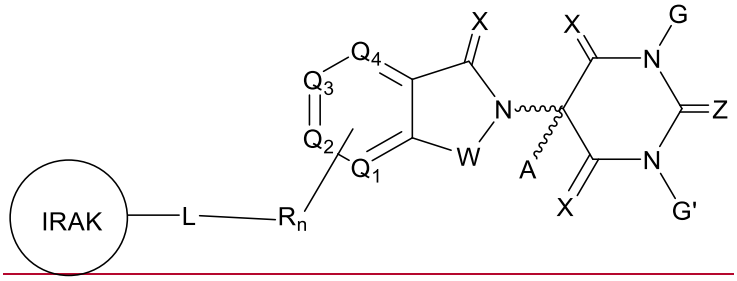
~~(*ii*)~~



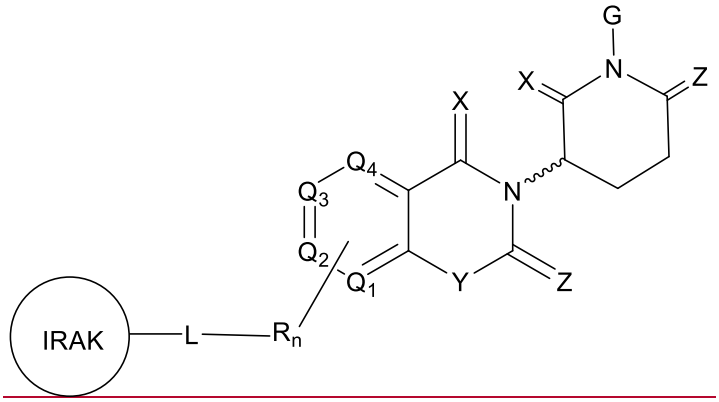
~~I-h-1~~



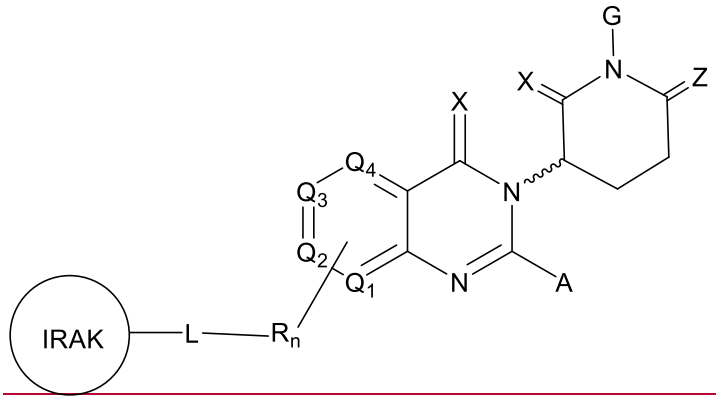
~~I-h-2~~



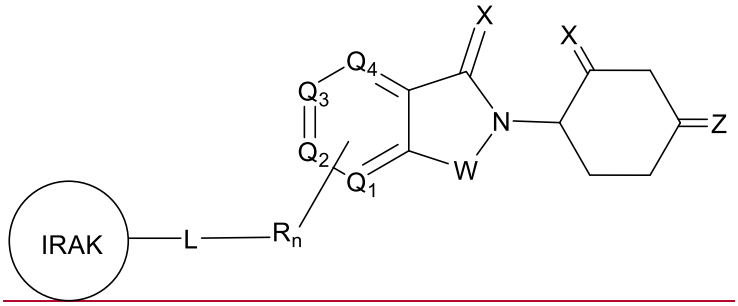
~~I h-3~~



~~I h-4~~



~~I h-5~~



~~I h-6~~

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

~~W is independently selected from the group CH_2, CHR, C=O, SO_2, NH, and N-alkyl;~~

~~X is independently selected from the group O, S and H_2,~~

~~Y is independently selected from the group NH, N-alkyl, N-aryl, N-hetaryl, N-cycloalkyl, N-heterocyclyl, O, and S;~~

~~Z is independently selected from the group O, and S or H_2except that both X and Z cannot be H_2;~~

~~G and G′ are independently selected from the group H, alkyl, OH, CH_2-heterocyclyl optionally substituted with R′, and benzyl optionally substituted with R′;~~

~~Q1-Q4 represent a carbon C substituted with a group independently selected from R′, N or N-oxide;~~

~~A is independently selected from the group H, alkyl, cycloalkyl, Cl and F;~~

~~R comprises, but is not limited to: CONR′R″, OR′, NR′R″, SR′, SO_2R′, SO_2NR′R″, CR′R″ , CR′NR′R″ , -aryl, hetaryl, -alkyl, cycloalkyl, -heterocyclyl, P(O)(OR′)R″, P(O)R′R″, OP(O)(OR′)R″, OP(O)R′R″, Cl, F, Br, I, CF_3, CN, NR′SO_2NR′R″, NR′CONR′R″, CONR′COR″, NR′C(=N-CN)NR′R″, C(=N-CN)NR′R″, NR′C(=N-CN)R″, NR′C(=C-NO_2)NR′R″, SO_2NR′COR″, NO_2, CO_2R′, C(C=N-OR′)R″, CR′=CR′R″, CCR′, S(C=O)(C=N-R′)R″, SF_5 and OCF_3;~~

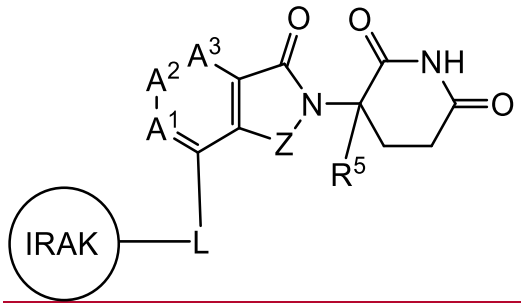
~~R′ and R″ are independently selected from a bond, H, alkyl, cycloalkyl, aryl, hetaryl, heterocyclyl;~~

~~n is an integer from 1-4;~~

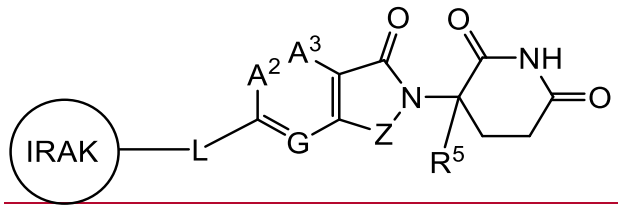
~~〰 represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific; and~~

~~R_n comprises 1-4 independent functional groups or atoms; or~~

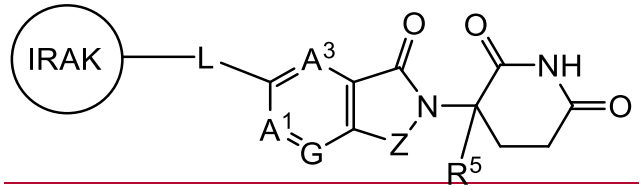
~~(*iii*)~~



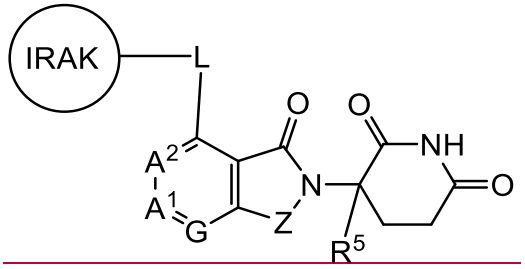
~~I-j-1~~



~~I-j-2~~



~~I-j-3~~



~~I-j-4~~

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

~~A^1 is selected from the group consisting of -C(R^{16a})= and -N=;~~

~~A^2 is selected from the group consisting of -C(R^{16b})= and -N=;~~

~~A^3 is selected from the group consisting of -C(R^{16c})= and -N=;~~

~~G is selected from the group consisting of -C(R^{16d})= and -N=;~~

~~Z is selected from the group consisting of -CH_2- and -C(=O)-;~~

~~R^5 is selected from the group consisting of hydrogen, methyl, and fluoro;~~

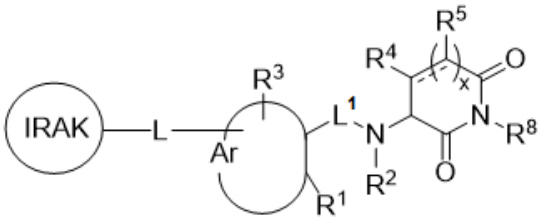
~~R^{16a} is selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl;~~

~~R^{16b} is selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl;~~

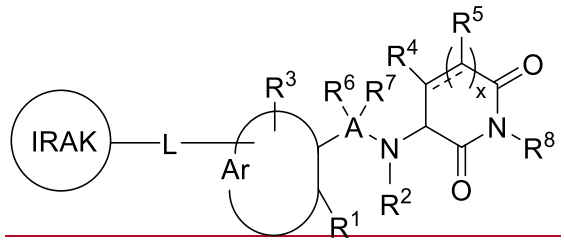
~~R^{16c} is selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; and~~

~~R^{16d} is selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl; or~~

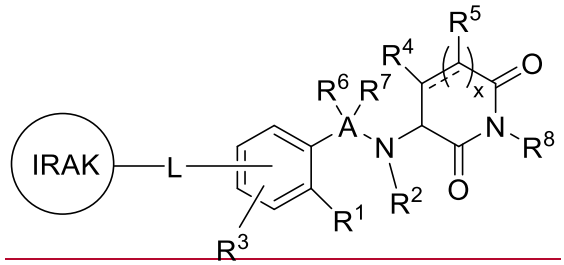
~~(*iv*)~~


IRAK
L
Ar
R3
L1
N
R2
R1
R4
R5
x
O
N
R8
O

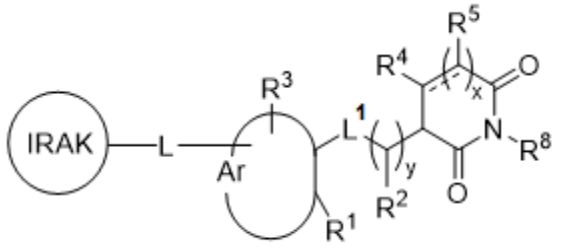
~~I-o~~


IRAK
L
Ar
R3
R6
R7
A
N
R2
R1
R4
R5
x
O
N
R8
O

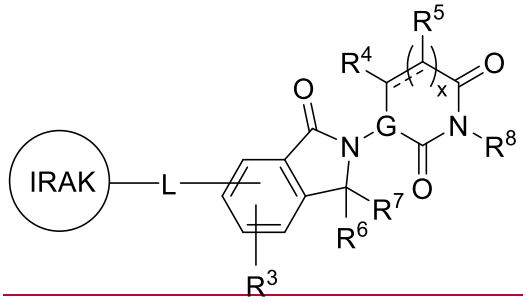
~~I-p~~


IRAK
L
R3
R6
R7
A
N
R2
R1
R4
R5
x
O
N
R8
O

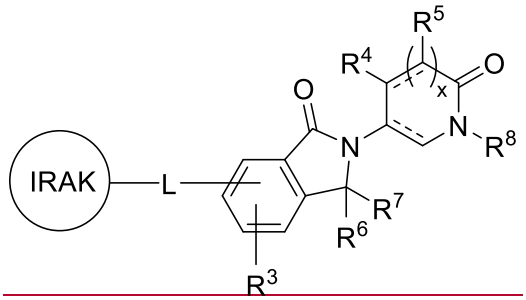
~~I-q~~


IRAK
L
Ar
R3
L1
y
R2
R1
R4
R5
x
O
N
R8
O

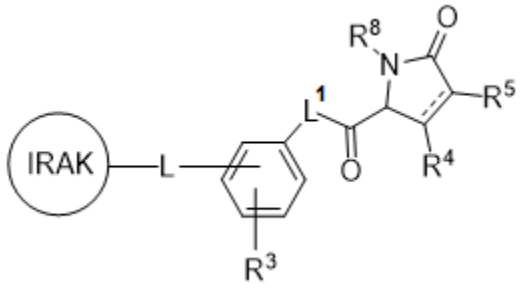
~~I-r~~


IRAK
L
R3
O
N
G
R6
R7
R4
R5
x
O
N
R8
O

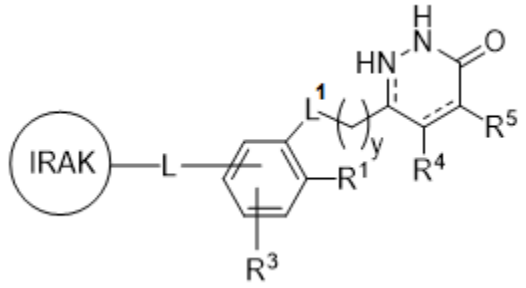
~~I-s~~



~~I-t~~



~~I-u~~



~~I-v~~

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

~~Ar is aryl, heteroaryl, cycloalkyl, or heterocyclyl;~~

~~L^1 is absent or a linker selected from the group consisting of $-SO_2-$, $-SO_2R'-$; $-SO_2R'R''-$, $-SO_2NR'R''-$; $-SO_2NR'R''C(=O)-$, $-NR'SO_2R''-$, $-R'SO_2NR'R'''-$, $-C(=O)-$, $-C(=O)R'-$, $-OC(=O)R'-$, $-C(=O)NR'R''-$, $-NR'C(=O)R''-$, $-NR'C(=O)R''C(=O)-$, $-OR'-$, $-NR'R''-$, $-SR'-$, $-N_3-$, $-C(=O)OR'-$, $-O(CR'R'')_rC(=O)R'-$, $-O(CR'R'')_rNR''C(=O)R'-$, $-O(CR'R'')_rNR''SO_2R'-$, $-OC(=O)NR'R''-$, $-NR'C(=O)OR''-$; and substituted or unsubstituted C_1-C_6 aliphatic alkyl;~~

~~wherein R', R'', and R''' are individually selected from hydrogen; substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted ether; substituted or unsubstituted cycloalkyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted~~

heteroaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylheteroaryl, or substituted or unsubstituted amine; and r is an integer from 1 to 6;

A is C, S; substituted of unsubstituted C_1-C_8 alkyl, or combinations thereof;

G comprises C, S, N, substituted of unsubstituted C1-C8 alkyl, or combinations thereof; R^3 is selected from the group consisting of hydrogen, halogen, hydroxyl, azide, alkoxyl, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, cyano, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, substituted or unsubstituted amine, substituted or unsubstituted amide, nitro, ester, morpholino, dioxolane, substituted or unsubstituted alkyl, substituted or unsubstituted alkylhalide, substituted or unsubstituted aralkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylheteroaryl, and combinations thereof;

R^1, R^2, and R^3 are individually selected from the group consisting of hydrogen, halogen, hydroxyl, azide, alkoxyl, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, cyano, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, substituted or unsubstituted amine, substituted or unsubstituted amide, nitro, ester, morpholino, dioxolane, substituted or unsubstituted alkyl, substituted or unsubstituted alkylhalide, substituted or unsubstituted aralkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted alkylheteroaryl, and combinations thereof; or

wherein R^1 and R^2 combine to form a 5-7 membered heterocyclic ring; and wherein when R^1 and R^2 combine to form a 5-7 membered heterocyclic ring, Ar is optionally not fused to the 5-7 membered heterocyclic ring but is a substituent of the 5-7 membered heterocyclic ring;

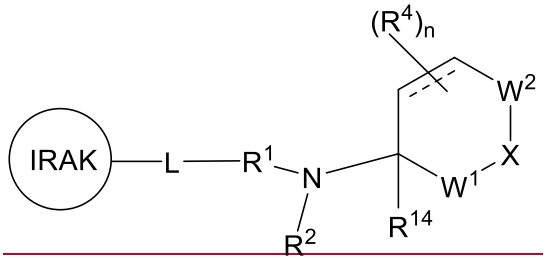
R^4 and R^5 are individually selected from the group consisting of hydrogen, halogen, hydroxyl, azide, ether, alkoxyl, sulfhydryl, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, substituted or unsubstituted alkyl, substituted or unsubstituted alkylhalide, substituted or unsubstituted aralkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, heterocyclyl, and combinations thereof;

R^6 and R^7 are individually =O, hydrogen, C_1-C_8 alkyl, or R^6 and R^7 combine to form =O;

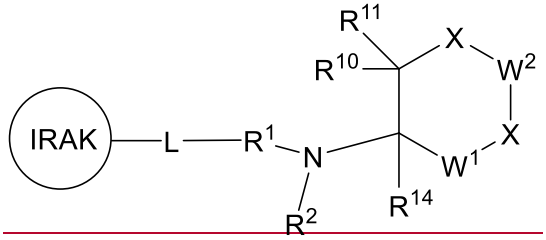
R^8 is selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkylhalide, substituted or unsubstituted aralkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted alkylaryl, and combinations thereof; and

x is 0, 1, or 2; or

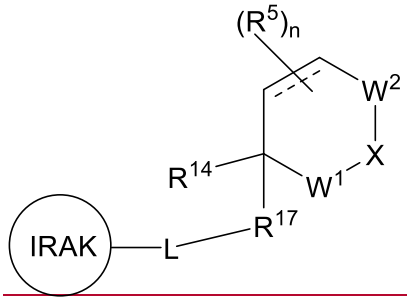
(v)



I z 1



I z 2



~~I z 3~~

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

~~W^1 is CR^6R^7, C=O, C=S, $C=CH_2$, SO_2, S(O), P(O)Oalkyl, P(O)NHalkyl, $P(O)N(alkyl)_2$, P(O)alkyl, P(O)OH, $P(O)NH_2$;~~

~~W^2 is CR^8R^9, C=O, C=S, $C=CH_2$, SO_2, S(O), P(O)Oalkyl, P(O)NHalkyl, $P(O)N(alkyl)_2$, P(O)alkyl, P(O)OH, $P(O)NH_2$;~~

~~X is independently selected from NH, NR^3, CH_2, CHR^3, $C(R^3)_2$, O, and S;~~

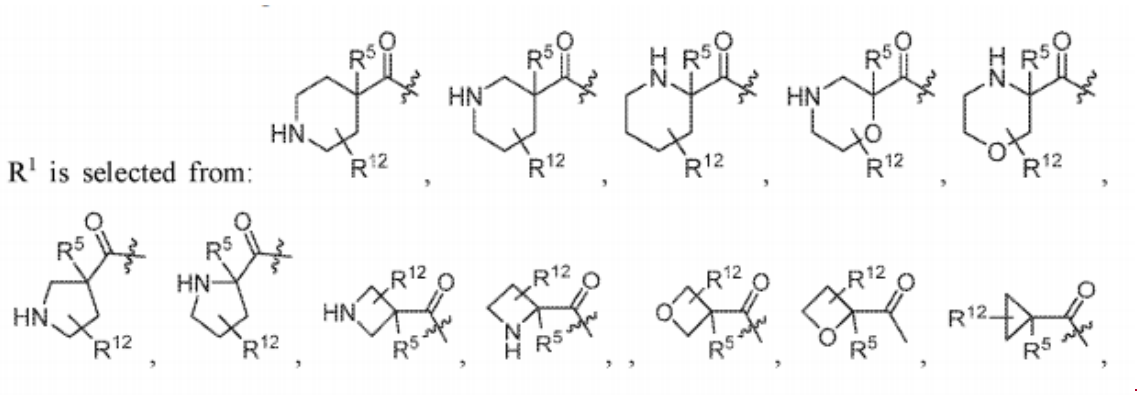
~~n is 0, 1, 2, or 3;~~

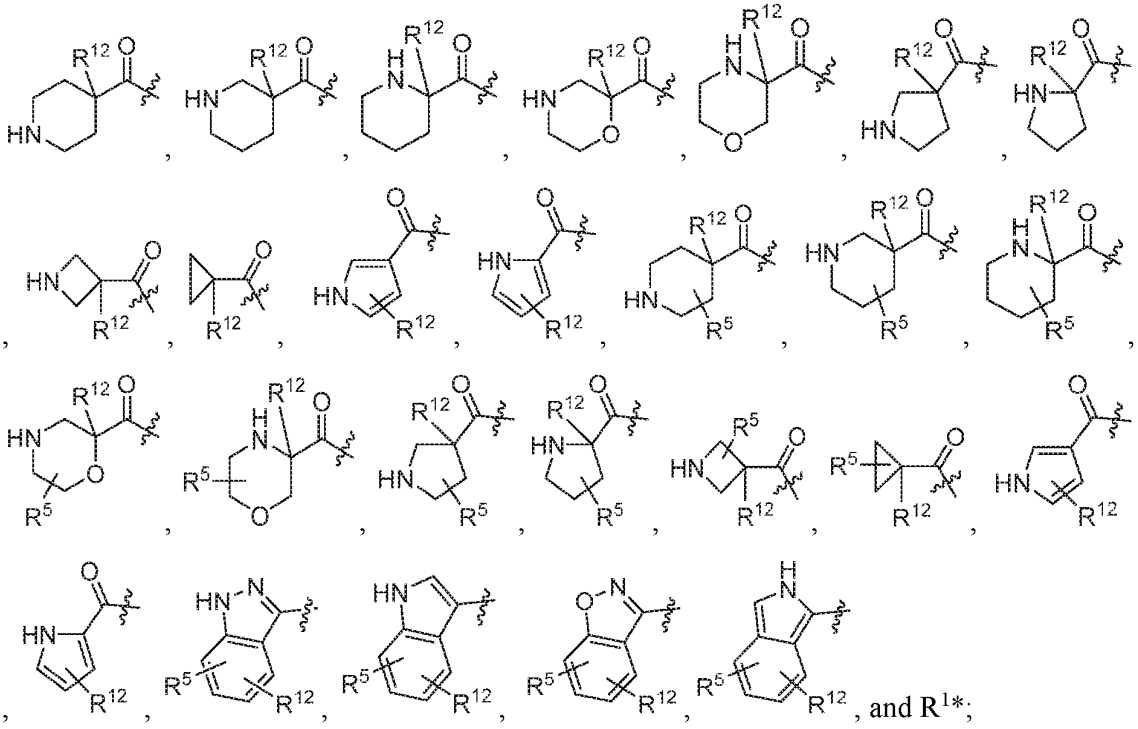
~~=== is a single or double bond;~~

~~wherein when === represents a single bond, n is 0, 1, 2, or 3;~~

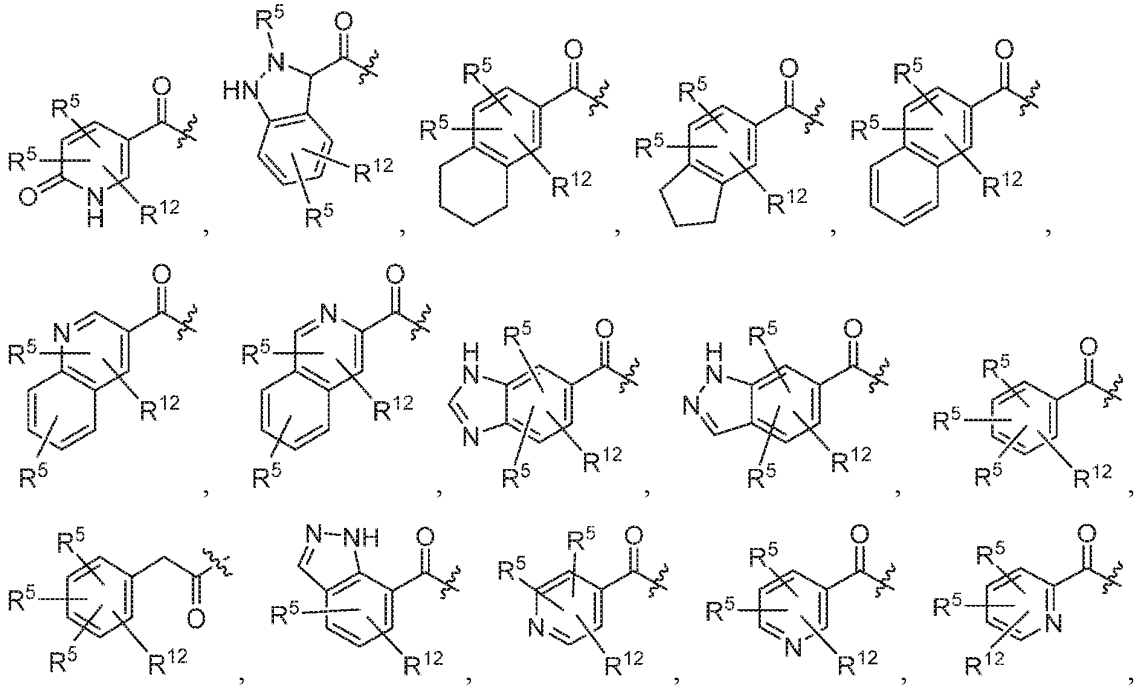
~~wherein when === represents a double bond, n is 0, 1, or 2;~~

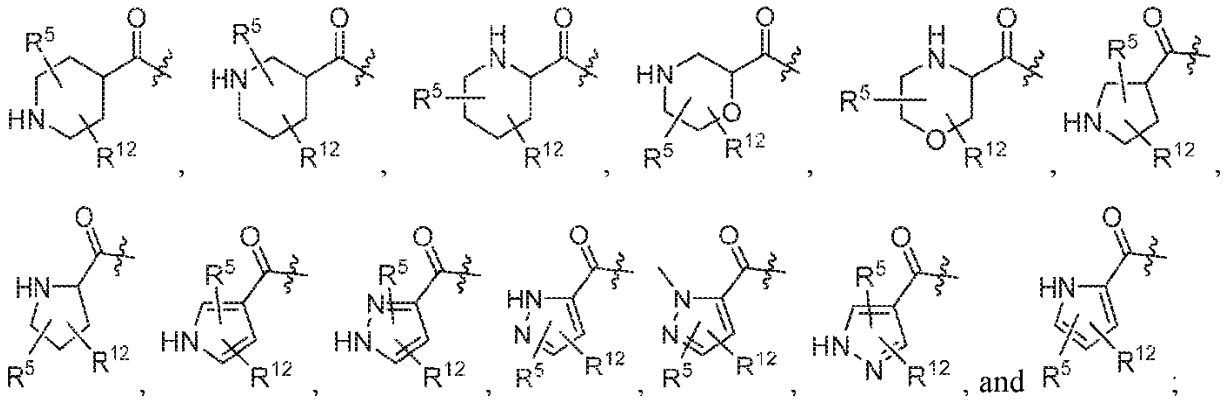
R^1 is selected from:




, and R^{1*};

or R^1 is selected from:

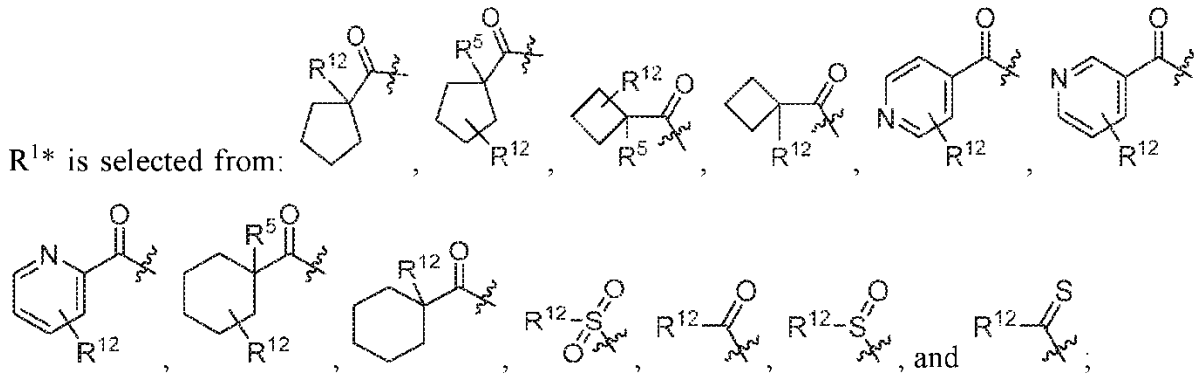




R^2 is alkyl, hydrogen, aliphatic, heteroaliphatic, aryl, heteroaryl or heterocyclic;

or R^1 and R^2 are combined to form a 4, 5, 6, 7, 8, 9, or 10 membered heterocyclo or heteroaryl species, wherein the heterocyclo or heteroaryl species is substituted with R^{12} at any desired position, wherein the heterocyclo or heteroaryl species is optionally further substituted with one or more substituents selected from R^5;

R^{1*} is selected from:



R^3 is selected at each instance from: alkyl, -C(O)H, -C(O)OH, -C(O)alkyl, -C(O)Oalkyl, alkene, and alkyne, aliphatic, heteroaliphatic, aryl, heteroaryl and heteroalkyl;

R^4 is selected at each instance from: alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, cyano, -NH(aliphatic), -N(aliphatic)$_2$, -$NHSO_2$(aliphatic), -N(aliphatic)SO_2alkyl, -$NHSO_2$(aryl, heteroaryl or heterocyclic), -N(alkyl)SO_2(aryl, heteroaryl or heterocyclic) -$NHSO_2$alkenyl, -N(alkyl)SO_2alkenyl, -$NHSO_2$alkynyl, -N(alkyl)SO_2alkynyl, and haloalkyl; aliphatic, heteroaliphatic, aryl, heteroaryl, heteroalkyl and carbocyclic;

or two R^4 substituents together with the carbon atom(s) to which they are bound can form a 3, 4, 5 or 6 membered ring; R^5 and R^{14} are selected at each instance from: hydrogen, alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, cyano, -NH(aliphatic), -N(aliphatic)$_2$, -$NHSO_2$(aliphatic), -N(aliphatic)SO_2alkyl, -$NHSO_2$(aryl, heteroaryl or

heterocyclic), -N(alkyl)SO_2(aryl, heteroaryl or heterocyclic) -$NHSO_2$alkenyl, -N(alkyl)SO_2alkenyl, -NHSO2alkynyl, -N(alkyl)SO_2alkynyl, and haloalkyl; aliphatic, heteroaliphatic, aryl, heteroaryl, heteroalkyl and carbocyclic;

or R^5 is independently selected from C(O)R^4, cyano, aryl, aryloxy, heterocyclo, heteroaryl, arylalkyl, alkoxy, hydroxyl, O-arylalkyl, or cycloalkyl;

R^6, R^7, R^8, R^9, R^{10}, and R^{11}, are independently selected from hydrogen, alkyl, aliphatic, heteroaliphatic, hydroxyl, alkoxy, amine, -NH(aliphatic), and -N(aliphatic)$_2$;

or R^6 and R^7 together with the carbon to which they are bound form a 3-, 4-, 5-, or 6- membered spirocarbocycle, or a 4-, 5-, or 6-membered spiroheterocycle comprising 1 or 2 heteroatoms selected from N and O;

or R^8 and R^9 together with the carbon to which they are bound form a 3-, 4-, 5-, or 6- membered spirocarbocycle, or a 4-, 5-, or 6-membered spiroheterocycle comprising 1 or 2 heteroatoms selected from N and O;

or R^{10} and R^{11} together with the carbon to which they are bound form a 3-, 4-, 5-, or 6-membered spirocarbocycle, or a 4-, 5-, or 6-membered spiroheterocycle comprising 1 or 2 heteroatoms selected from N and O;

or R^6 and R^8 form a 1 or 2 carbon bridged ring;

or R^6 and R^{10} form a 1 or 2 carbon bridged ring;

or R^8 and R^{10} form a 1 or 2 carbon bridged ring;

or R^{14} and R^6 form a 3, 4, 5, or 6 carbon fused ring;

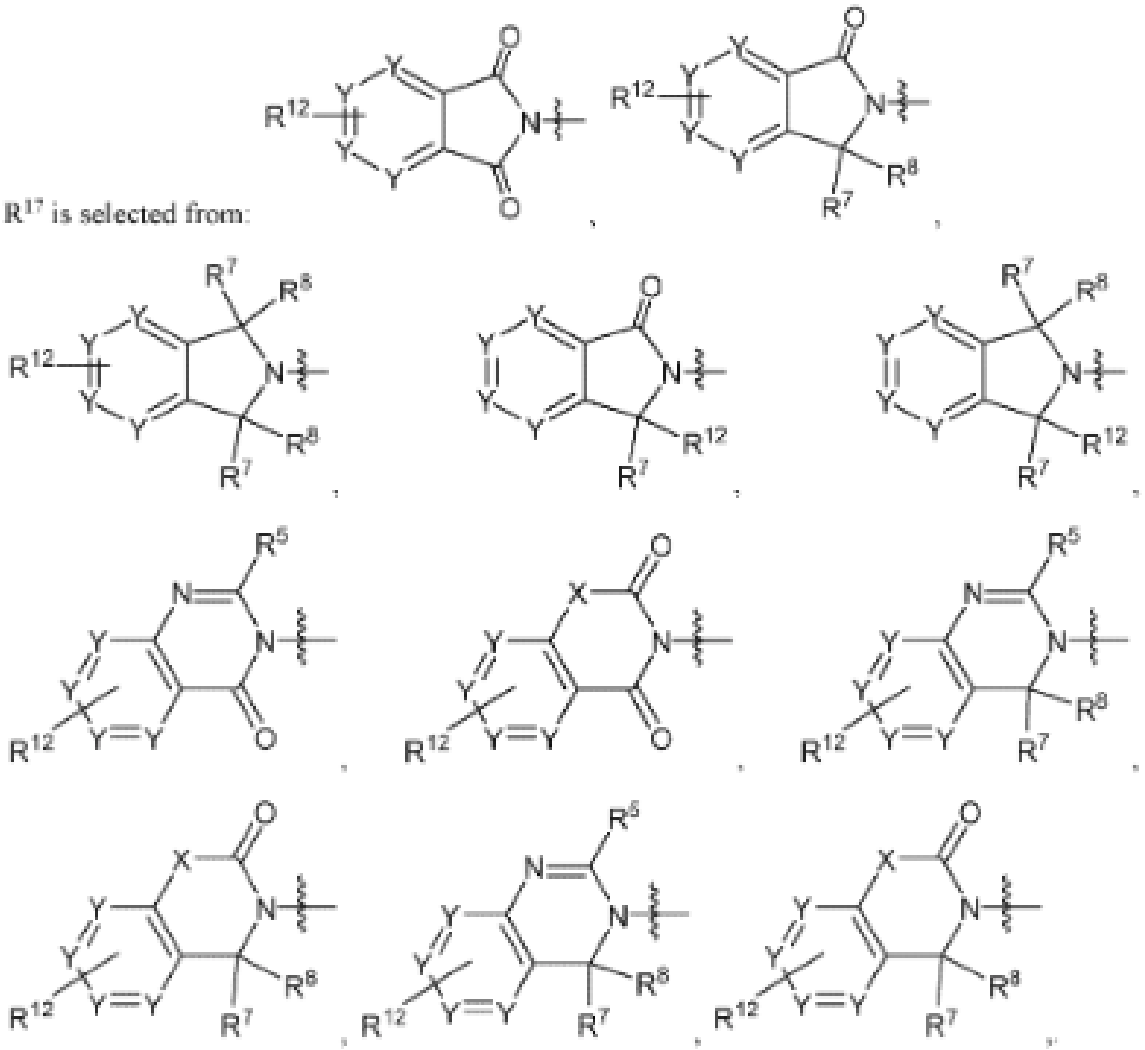
or R^{14} and R^{10} form a 3, 4, 5, or 6 carbon fused ring;

or R^{14} and R^8 form a 1 or 2 carbon bridged ring;

or R^{14} and R^4 form a 3, 4, 5, or 6 carbon fused ring wherein R^5 is on the carbon alpha to R^{14} or a 1, 2, 3, or 4 carbon bridged ring wherein R^5 is not on the carbon alpha to R^{14};

R^{12} is L;

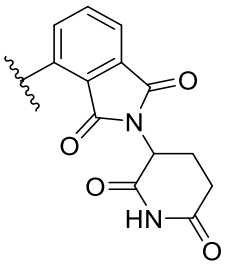
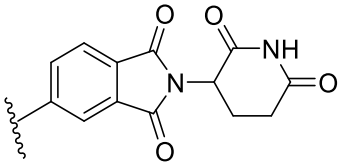
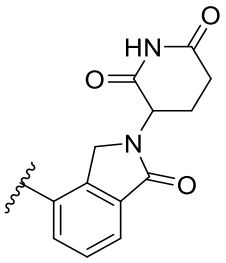
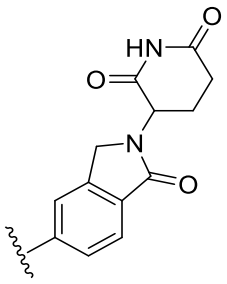
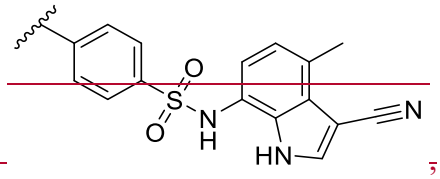
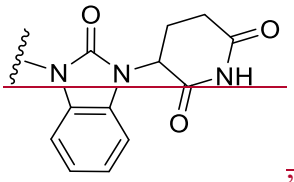
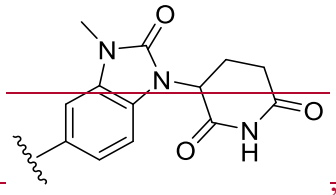
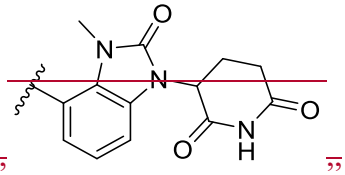
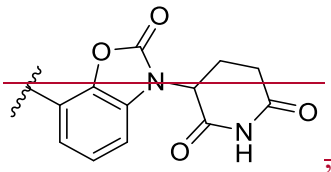
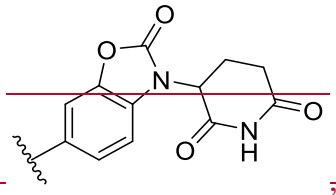
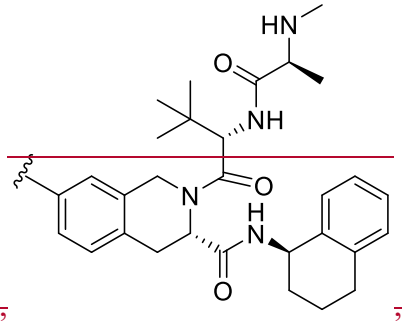
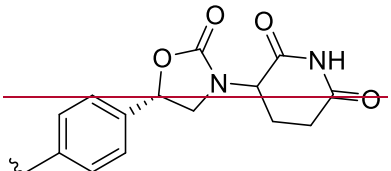
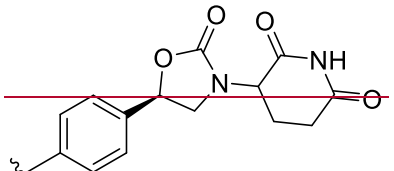
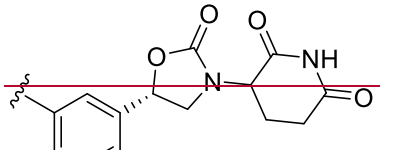
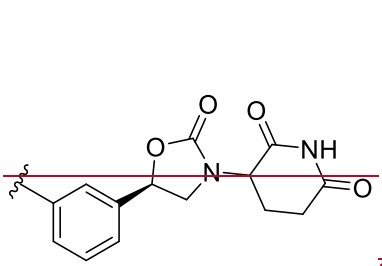
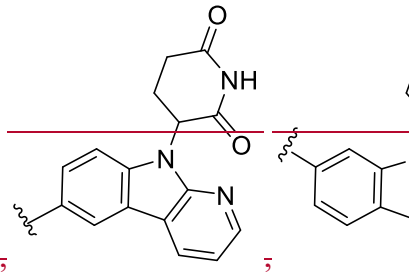
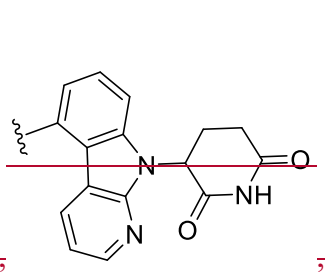
R^{17} is selected from:

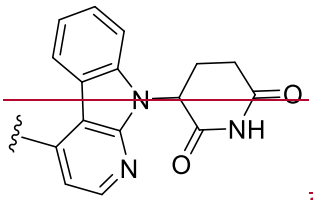
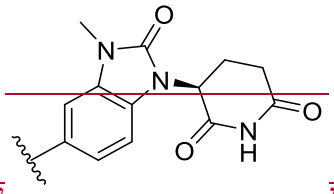
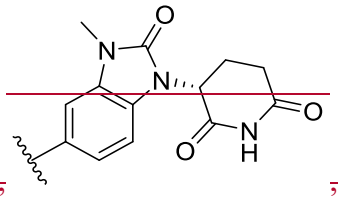
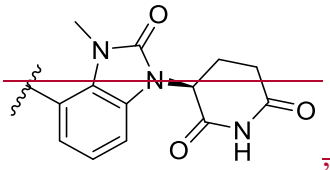
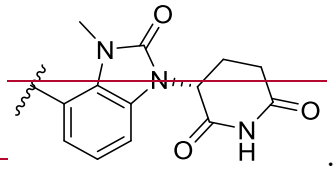


~~Y is independently selected from N, CH, or CR^{101}, wherein 0, 1, 2, or 3 instances of Y are selected to be N;~~

~~R^{101} is independently selected at each occurrence from hydrogen, alkyl, alkene, alkyne, haloalkyl, alkoxy, hydroxyl, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocycloalkyl, aryloxy, heteroaryloxy, CN, COOalkyl, COOH, NO_2, F, Cl, Br, I, CF_3, NH_2, NHalkyl, $N(alkyl)_2$, aliphatic, and heteroaliphatic.~~

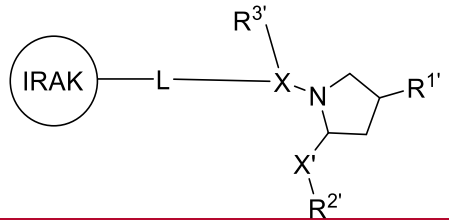
~~7~~2. The compound according to claim ~~2~~1, wherein the cereblon E3 ubiquitin ligase binding

moiety is selected from ~~the group consisting of:~~  ,  ,  , and  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , 

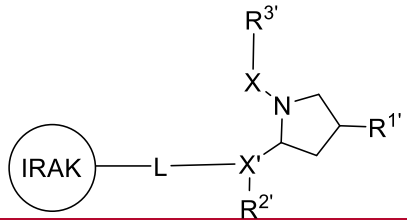






8. The compound of claim 2, wherein LBM is a VHL E3 ubiquitin ligase binding moiety and said compound is selected from any of the folling formulae:

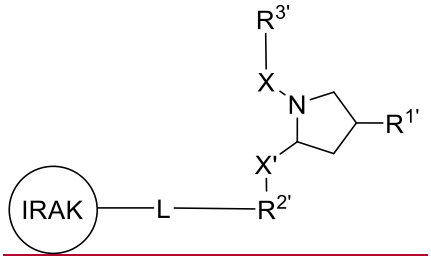
(1)



I-b-3



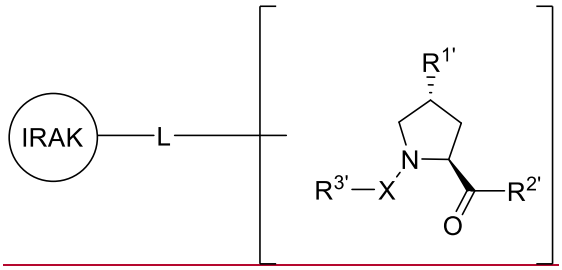
I-b-4



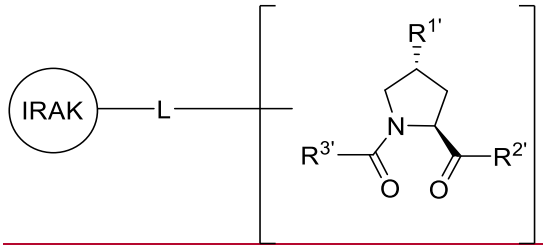
I-b-5

or a pharmaceutically acceptable salt thereof, wherein each of the variables $R^{1'}$, $R^{2'}$, $R^{3'}$, X, and X' is as defined and described in US 2014/0356322, the entirety of which is herein incorporated by reference; or

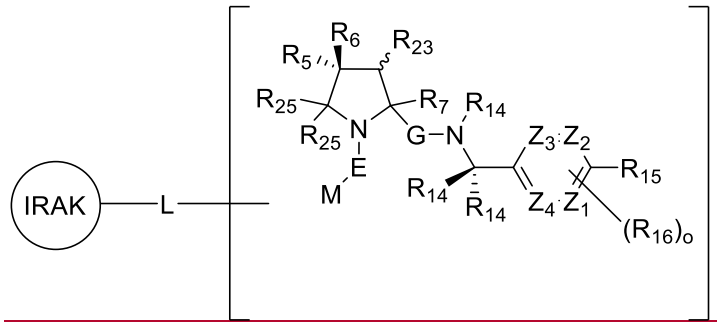
(2)



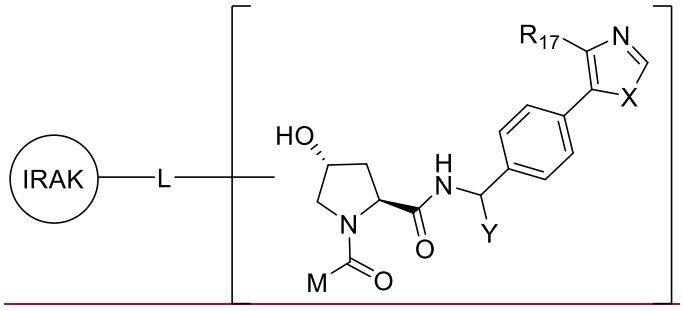
~~I-f-1~~



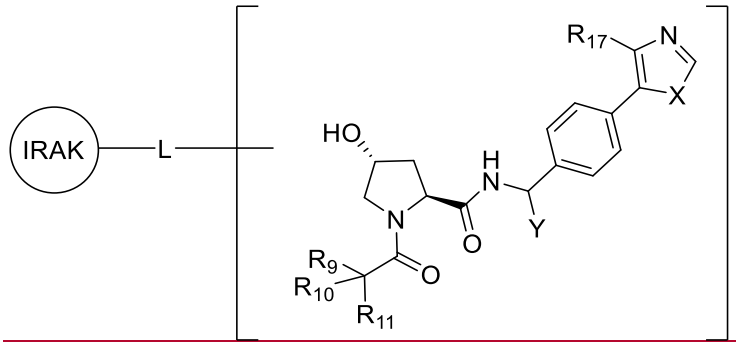
~~I-f-2~~



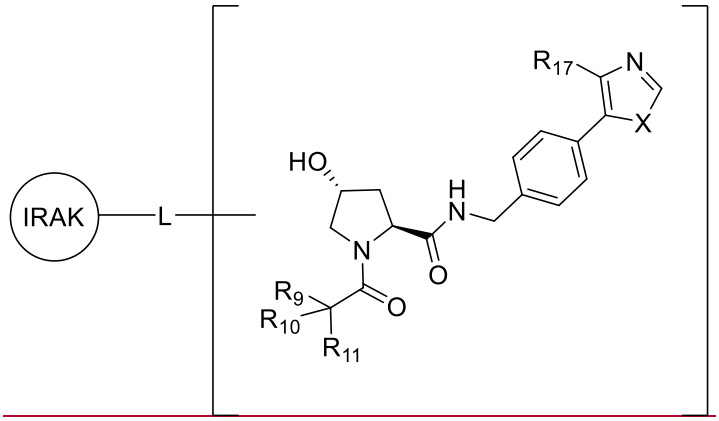
~~I-f-3~~



~~I-f-4~~

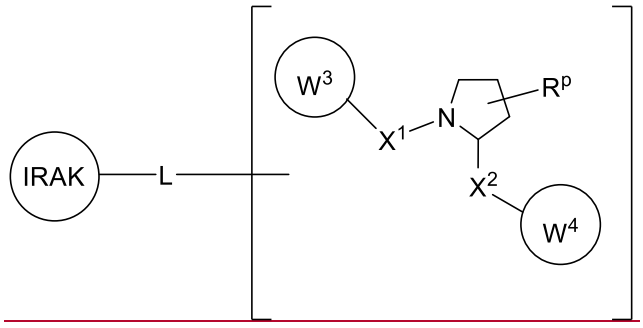


~~I-f-5~~

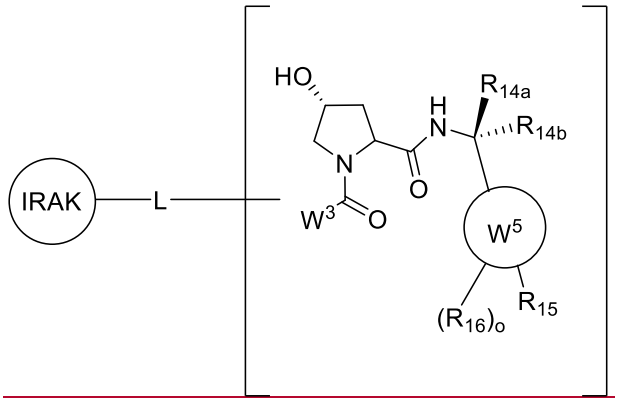


~~I-f-6~~

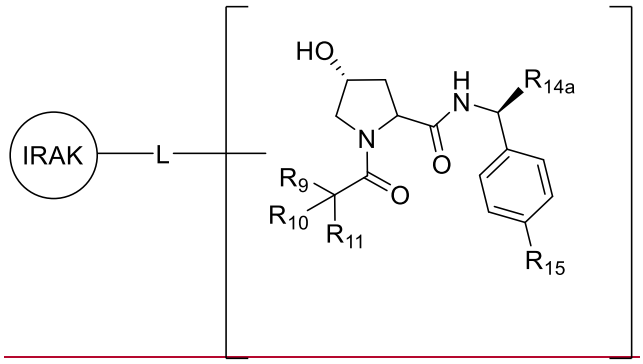
~~or a pharmaceutically acceptable salt thereof, wherein each of the variables $R^{1'}$, $R^{2'}$, $R^{3'}$, R_5, R_6, R_7, R_9, R_{10}, R_{11}, R_{14}, R_{15}, R_{16}, R_{17}, R_{23}, R_{25}, E, G, M, X, X', Y, Z_1, Z_2, Z_3, Z_4, and o is as defined and described in US 2016/0272639, the entirety of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



~~I-g-1~~



~~I g 2~~



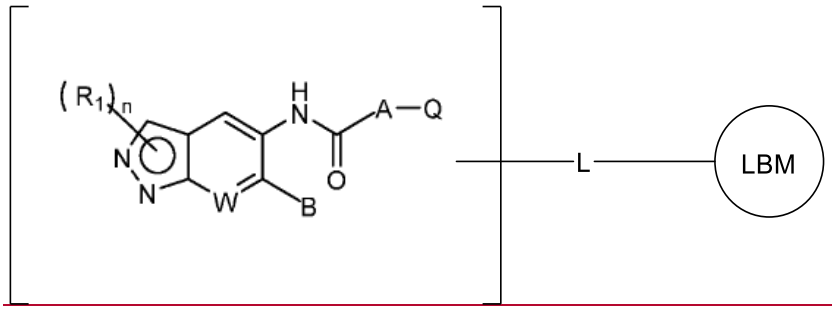
~~I g 3~~

~~or a pharmaceutically acceptable salt thereof, wherein each of the variables R^p, R_9, R_{10}, R_{11}, R_{14a}, R_{14b}, R_{15}, R_{16}, W^3, W^4, W^5, X^1, X^2, and o is as defined and described in US 2016/0214972, the entirety of which is herein incorporated by reference.~~

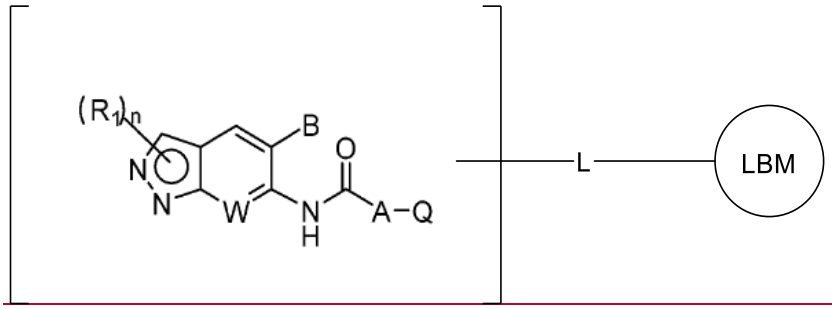
~~9. The compound of claim 2, wherein IRAK is an IRAK binding moiety capable of binding to IRAK4.~~

~~10. The compound of claim 9, wherein said compound is selected from any one of the following formulae:~~

~~(a)~~



~~I-dd-1~~



~~I-dd-2~~

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

~~A is optionally substituted heteroaryl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, optionally substituted (heterocycloalkyl)alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkyl-NR_x—, optionally substituted heterocycloalkyl-NR_x—, optionally substituted aryl-NR_x—, optionally substituted heteroaryl-NR_x—, optionally substituted cycloalkyl-O—, optionally substituted heterocycloalkyl-O—, optionally substituted aryl-O— or optionally substituted heteroaryl-O—; e.g., wherein each optional substituent independently represents an occurrence of R_z;~~

~~B is hydrogen, halogen, cyano, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkoxy, NR_aR_b, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, optionally substituted (cycloalkyl)alkyl, optionally substituted (heterocycloalkyl)alkyl, optionally substituted aralkyl, optionally substituted heteroaralkyl, optionally substituted cycloalkyl-NR_x—, optionally substituted heterocycloalkyl-NR_x—, optionally substituted aryl-NR_x—, optionally substituted heteroaryl-NR_x—, optionally substituted cycloalkyl-~~

O–, optionally substituted heterocycloalkyl-O–, optionally substituted aryl-O–, optionally substituted heteroaryl-O–; e.g., wherein each optional substituent independently represents an occurrence of R_y;

Q is absent or optionally substituted heterocycloalkyl, optionally substituted heteroaryl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted (heterocycloalkyl)alkyl, optionally substituted (heteroaryl)alkyl, optionally substituted aralkyl, optionally substituted (cycloalkyl)alkyl, NR_3R_4, $O-R_3$ or S–R; e.g., wherein each optional substituent independently represents an occurrence of R_z;

W is N or CH;

R_1 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, optionally substituted (heterocycloalkyl)alkyl, optionally substituted heterocycloalkyl, optionally substituted aralkyl, optionally substituted (heteroaryl)alkyl-, optionally substituted alkoxyalkyl, optionally substituted aminoalkyl, or $(CH_2)_m-R_2$; e.g., wherein each optional substituent independently represents halo, hydroxy, alkoxy, amino, nitro, cycloalkyl, aryl, heterocycloalkyl or heteroaryl;

R_2 is hydrogen, NR_aR_b, alkoxy, hydroxy, optionally substituted heteroaryl or optionally substituted heterocycloalkyl; e.g., wherein each optional substituent independently represents an occurrence of R_y;

each R_3 and R_4 is independently selected from optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted aralkyl, optionally substituted (cycloalkyl)alkyl, optionally substituted (heteroaryl)alkyl and optionally substituted (heterocycloalkyl)alkyl; e.g., wherein each optional substituent is independently selected from alkyl, halo, haloalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, amino, nitro, cycloalkyl, (cycloalkyl)alkyl, aryl, aralkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, heteroaryl and (heteroaryl)alkyl;

each R_a and R_b is independently selected from hydrogen, alkyl, aminoalkyl, acyl and heterocyclyl; or R_a and R_b are taken together with the nitrogen to which they are attached to form an optionally substituted ring;

R_x is hydrogen, alkyl, hydroxy, hydroxyalkyl, acyl or cycloalkyl;

each R_y and R_x is independently selected from hydroxy, hydroxyalkyl, halo, alkyl, oxo, haloalkyl, alkoxy, alkenyloxy, amino, nitro, cyano, SH, S(alkyl), glycinate, ester, thioester,

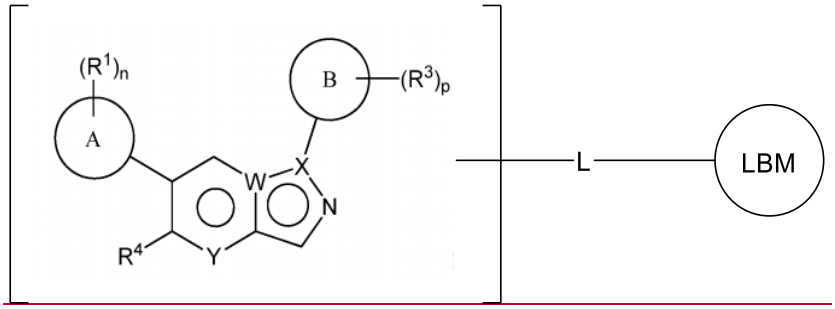
~~cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, aralkyl, and (heteroaryl)alkyl; optionally wherein the hydroxy, hydroxyalkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are further substituted by one or more substituents selected from alkyl, halo, alkenyl, amino, nitro, cycloalkyl and (cycloalkyl)alkyl; or~~

~~R_y and R_z taken together with the atoms to which they are attached form an alkyl chain having 1-10 carbon atoms; optionally wherein 1-3 carbon atoms are replaced by O, NH or S;~~

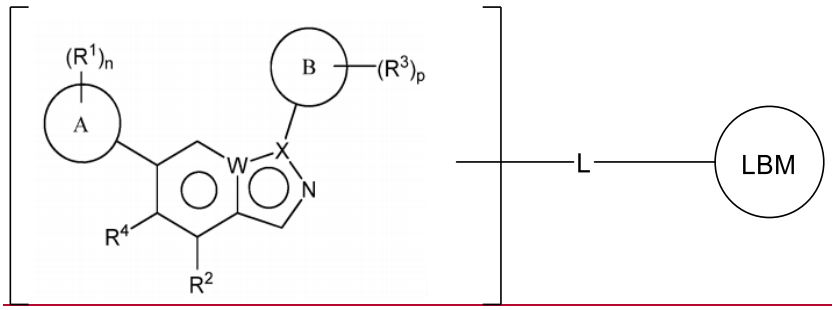
~~m is 1, 2, or 3; and~~

~~n is 1 or 2; or~~

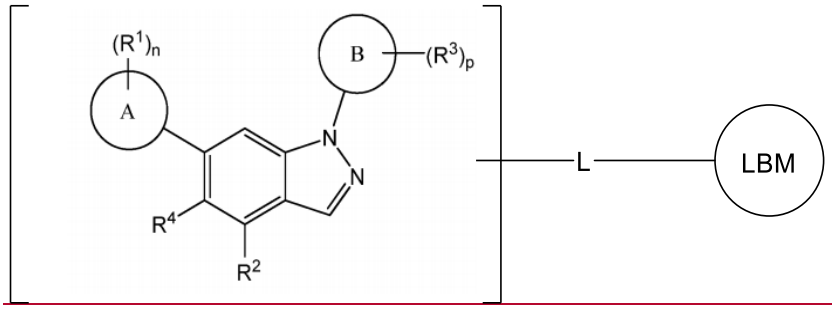
~~(b)~~



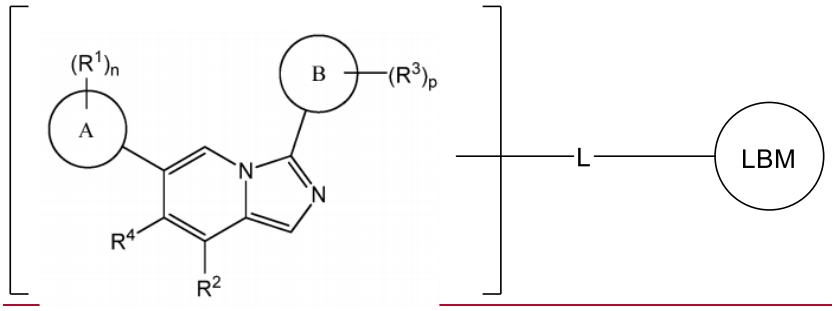
~~I-ee-1~~



~~I-ee-2~~



~~I-ee-3~~



I-ee-4

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from phenyl and 5- or 6-membered heteroaryl;

Ring B is selected from phenyl and 5- or 6-membered heteroaryl;

n is 0, 1, or 2;

p is 0, 1, or 2;

one of W and X is N, and the other of W and X is C;

Y is N or C—R^2;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 6-membered saturated heterocyclyl, halo, CN, $C(R^{1a})$=$NR(OR^{1a})$, $C(R^{1a})$=$N(R^{1a})$, $C(O)R^{1a}$, $C(O)_2R^{1a}$, $C(O)N(R^{1a})_2$, NO_2, $N(R^{1a})_2$, $N(R^{1a})C(O)R^{1a}$, $N(R^{1a})C(O)_2R^{1a}$, $N(R^{1a})C(O)N(R^{1a})_2$, $N(R^{1a})S(O)_2R^{1a}$, OR^{1a}, $OC(O)R^{1a}$, $OC(O)N(R^{1a})_2$, SR^{1a}, $S(O)R^{1a}$, $S(O)_2R^{1a}$, $S(O)N(R^{1a})_2$, and $S(O)_2N(R^{1a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, and 3- to 6-membered saturated heterocyclyl are optionally substituted with one or more R^{10}; or two R^1 substituents, together with their intervening atoms, form a C_{5-7}cycloalkyl or a saturated 5- to 7-membered heterocyclic ring, wherein said C_{5-7}cycloalkyl or a saturated 5- to 7-membered heterocyclic ring are optionally substituted with one or more R^{15};

R^{1a} in each occurrence is independently selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 6-membered monocyclic carbocyclyl, and 3- to 6-membered monocyclic heterocyclyl wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 6-membered monocyclic carbocyclyl, and 3- to 6-membered monocyclic heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{10};

R^{10} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 6-membered carbocyclyl, 3- to 6-membered heterocyclyl, halo, CN,

$C(R^{10a})=NR(OR^{10a})$, $C(R^{10a})=N(R^{10a})$, $C(O)R^{10a}$, $C(O)_2R^{10a}$, $C(O)N(R^{10a})_2$, NO_2, $N(R^{10a})_2$, $N(R^{10a})C(O)R^{10a}$, $N(R^{10a})C(O)_2R_{10a}$, $N(R^{10a})C(O)N(R^{10a})_2$, $N(R^{10a})S(O)_2R^{10a}$, OR^{10a}, $OC(O)R^{10a}$, $OC(O)N(R^{10a})_2$, SR^{10a}, $S(O)R^{10a}$, $S(O)_2R^{10a}$, $S(O)N(R^{10a})_2$, and $S(O)_2N(R^{10a})_2$;

R^{10a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more halo;

R^{15} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 6-membered carbocyclyl, 3- to 6-membered heterocyclyl, halo, CN, $C(R^{15a})=NR(OR^{15a})$, $C(R^{15a})=N(R^{15a})$, $C(O)R^{15a}$, $C(O)_2R^{15a}$, $C(O)N(R^{15a})_2$, NO_2, $N(R^{15a})_2$, $N(R^{15a})C(O)R^{15a}$, $N(R^{15a})C(O)_2R^{15a}$, $N(R^{15a})C(O)N(R^{15a})_2$, $N(R^{15a})S(O)_2R^{15a}$, OR^{15a}, $OC(O)R^{15a}$, $OC(O)N(R^{15a})_2$, SR^{15a}, $S(O)R^{15a}$, $S(O)_2R^{15a}$, $S(O)N(R^{15a})_2$, and $S(O)_2N(R^{15a})_2$;

R^{15a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more halo;

R^{2} is selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 7-membered carbocyclyl, 3- to 7-membered heterocyclyl, halo, CN, $C(R^{2a})=NR(OR^{2a})$, $C(R^{2a})=N(R^{2})$, $C(O)R^{2a}$, $C(O)_2R^{2a}$, $C(O)N(R^{2a})_2$, NO_2, $N(R^{2a})_2$, $N(R^{2a})C(O)R^{2a}$, $N(R^{2a})C(O)_2R^{2a}$, $N(R^{2a})C(O)N(R^{2a})_2$, $N(R^{2a})S(O)_2R^{2a}$, OR^{2a}, $OC(O)R^{2a}$, $OC(O)N(R^{2a})_2$, SR^{2a}, $S(O)R^{2a}$, $S(O)_2R^{2a}$, $S(O)N(R^{2a})_2$, and $S(O)_2N(R^{2a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 7-membered carbocyclyl, and 3-7 membered heterocyclyl are optionally substituted with one or more R^{20};

R^{2a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in each occurrence is optionally and independently substituted with one or more R^{20};

R^{20} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, 3- to 7-membered saturated heterocyclyl, halo, CN, $C(R^{20a})=NR(OR^{20a})$, $C(R^{20a})=N(R^{20a})$, $C(O)R^{20a}$, $C(O)_2R^{20a}$, $C(O)N(R^{20a})_2$, NO_2, $N(R^{20a})_2$, $N(R^{20a})C(O)R^{20a}$, $N(R^{20a})C(O)_2R^{20a}$, $N(R^{20a})C(O)N(R^{20a})_2$, $N(R^{20a})S(O)_2R^{20a}$, OR^{20a}, $OC(O)R^{20a}$, $OC(O)N(R^{20a})_2$, SR^{20a}, $S(O)R^{20a}$, $S(O)_2R^{20a}$, $S(O)N(R^{20a})_2$, and $S(O)_2N(R^{20a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, and 3-7 membered saturated heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{25};

R^{20a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with R^{25};

R^{25} is selected from halo and $-OR^{25a}$;

R^{25a} is selected from H and C_{1-6}alkyl;

R^{3} is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 6-membered saturated heterocyclyl, halo, $-CN$, $-C(R^{3a})=NR(OR^{3a})$, $-C(R^{3a})=N(R^{3a})$, $-C(O)R^{3a}$, $-C(O)_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-NO_2$, $-N(R^{3a})_2$, $-N(R^{3a})C(O)R^{3a}$, $-N(R^{3a})C(O)_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})_2$, $-N(R^{3a})S(O)_2R^{3a}$, $-OR^{3a}$, $-OC(O)R^{3a}$, $-OC(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O)_2R^{3a}$, $-S(O)N(R^{3a})_2$, and $-S(O)_2N(R^{3a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, and 3- to 6-membered saturated heterocyclyl are optionally substituted with one or more R^{30};

R^{3a} in each occurrence is independently selected from H, C_{1-6}alkyl, 3- to 6-membered carbocyclyl, and 3- to 6-membered heterocyclyl, wherein said C_{1-6}alkyl, 3- to 6-membered carbocyclyl, and 3- to 6-membered heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{30};

R^{30} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 6-membered carbocyclyl, 3- to 6-membered heterocyclyl, halo, $-CN$, $-C(R^{30a})=NR(OR^{30a})$, $-C(R^{30a})=N(R^{30a})$, $-C(O)R^{30a}$, $-C(O)_2R^{30a}$, $-C(O)N(R^{30a})_2$, $-NO_2$, $-N(R^{30a})_2$, $-N(R^{30a})C(O)R^{30a}$, $-N(R^{30a})C(O)_2R^{30a}$, $-N(R^{30a})C(O)N(R^{30a})_2$, $-N(R^{30a})S(O)_2R^{30a}$, $-OR^{30a}$, $-OC(O)R^{30a}$, $-OC(O)N(R^{30a})_2$, $-SR^{30a}$, $-S(O)R^{30a}$ $-S(O)_2R^{30a}$, $-S(O)N(R^{30a})_2$, and $-S(O)_2N(R^{30a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-6-membered carboyclyl, 3- to 6-membered heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{35};

R^{30a} in each occurrence is independently selected from H and C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with one or more R^{35};

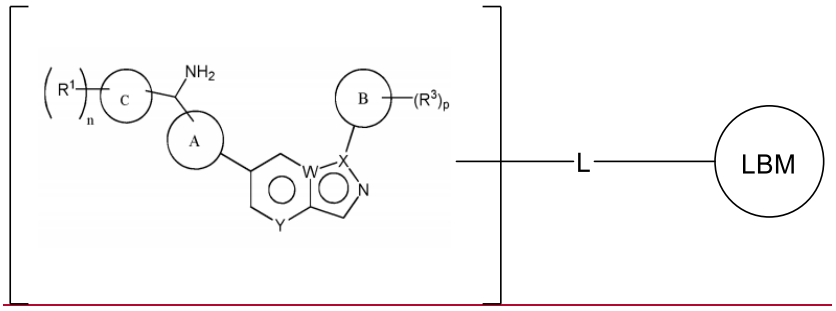
R^{35} in each occurrence is independently selected from halo and $-OR^{35a}$;

R^{35a} in each occurrence is independently selected from H and C_{1-6}alkyl;

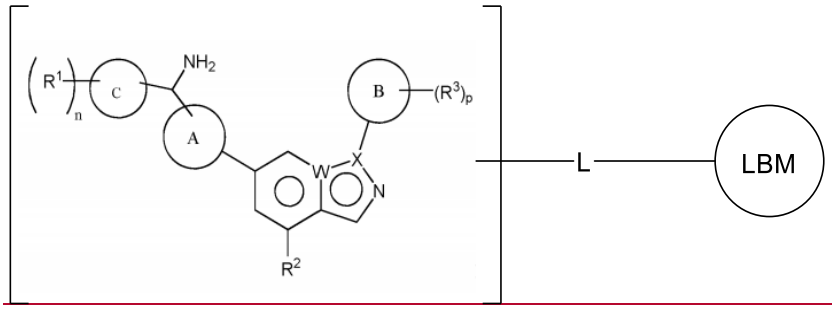
R^{4} is selected from H, halo, C_{1-6}alkyl, $N(R^{4a})_2$, and $-OR^{4a}$; and

R^{4a} in each occurrence is independently selected from H and C_{1-6}alkyl; or

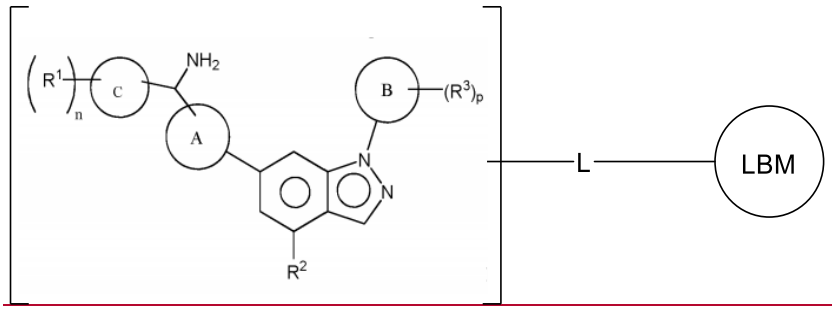
(c)



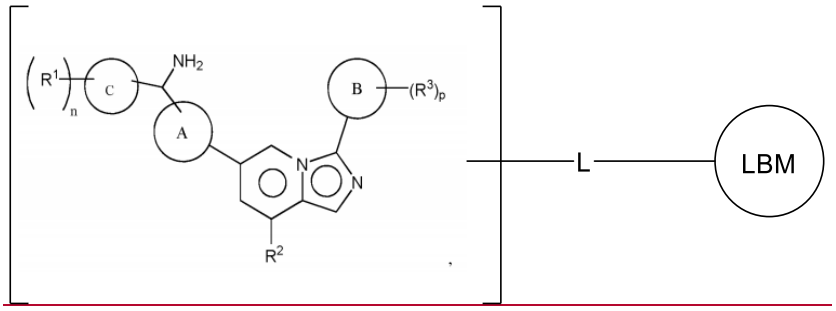
~~I-ff-1~~



~~I-ff-2~~



~~I-ff-3~~



~~I-ff-4~~

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

~~Ring A is selected from phenyl and 5- or 6-membered heteroaryl;~~

~~Ring B is selected from phenyl and 5- or 6-membered heteroaryl;~~

~~Ring C is a 3- to 6-membered carbocyclyl,~~

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

~~p is 0, 1, or 2;~~

~~one of W and X is N, and the other of W and X is C;~~

~~Y is N or C-R^2;~~

~~R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, -CN, -$C(R^{1a})$=$NR(OR^{1a})$, -$C(R^{1a})$=$N(R^{1a})$, -C(O)R^{1a}, -$C(O)_2R^{1a}$, -$C(O)N(R^{1a})_2$, -NO_2, -$N(R^{1a})_2$, -$N(R^{1a})C(O)R^{1a}$, -$N(R^{1a})C(O)_2R^{1a}$, -$N(R^{1a})C(O)N(R^{1a})_2$, -$N(R^{1a})S(O)_2R^{1a}$, -OR^{1a}, -$OC(O)R^{1a}$, -$OC(O)N(R^{1a})_2$, -SR^{1a}, -$S(O)R^{1a}$, -$S(O)_2R^{1a}$, -$S(O)N(R^{1a})_2$, and -$S(O)_2N(R^{1a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, and C_{2-6}alkynyl are optionally substituted with one or more R^{10};~~

~~R^{1a} in each occurrence is independently selected from H or C_{1-6}alkyl wherein said C_{1-6}alkyl in each occurrence are optionally and independently substituted with one or more R^{10};~~

~~R^{10} in each occurrence is independently selected from halo, -CN, -$C(R^{10a})$=$NR(OR)^{10a}$, -$C(R^{10a})$=$N(R^{10a})$, -C(O)R^{10a}, -$C(O)_2R^{10a}$, -$C(O)N(R^{10a})_2$, -NO_2, -$N(R^{10a})_2$, -$N(R^{10a})C(O)R^{10a}$, -$N(R^{10a})C(O)_2R^{10a}$, -$N(R^{10a})C(O)N(R^{10a})_2$, -$N(R^{10a})S(O)_2R^{10a}$, -$OR^{10a}$, -$OC(O)R^{10a}$, -$OC(O)N(R^{10a})_2$, -$SR^{10a}$, -$S(O)R^{10a}$, -$S(O)_2R^{10a}$, -$S(O)N(R^{10a})_2$, and -$S(O)_2N(R^{10a})_2$;~~

~~R^{10a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with one or more halo;~~

~~R is selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 7-membered carbocyclyl, 3-to 7-membered heterocyclyl, halo, -CN, -$C(R^{2a})$=$NR(OR^{2a})$, -$C(R^{2a})$=$N(R^{2a})$, -C(O)R^{2a}, -$C(O)_2R^{2a}$, -$C(O)N(R^{2a})_2$, -NO_2, -$N(R^{2a})_2$, -$N(R^{2a})C(O)R^{2a}$, -$N(R^{2a})C(O)_2R^{2a}$, -$N(R^{2a})C(O)N(R^{2a})_2$, -$N(R^{2a})S(O)_2R^{2a}$, -OR^{2a}, -$OC(O)R^{2a}$, -$OC(O)N(R^{2a})_2$, -SR^{2a}, -$S(O)R^{2a}$, -$S(O)_2R^{2a}$, -$S(O)N(R^{2a})_2$, and -$S(O)_2N(R^{2a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-to 7-membered carbocyclyl, and 3-7 membered heterocyclyl are optionally substituted with one or more R^{20};~~

~~R^{2a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl in each occurrence is optionally and independently substituted with one or more R 20 ;~~

~~R^{20} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, 3-to 7-membered saturated heterocyclyl, halo, -CN, -$C(R^{20a})$=$NR(OR^{20a})$, -$C(R^{20a})$=$N(R^{20a})$, -C(O)R^{20a}, -$C(O)_2R^{20a}$, -$C(O)N(R^{20a})_2$, -$N0_2$, -$N(R^{20a})_2$, -~~

~~$N(R^{20a})C(O)R^{20a}$, $-N(R^{20a})C(O)_2R^{20a}$, $-N(R^{20a})C(O)N(R^{20a})_2$, $-N(R^{20a})S(O)_2R^{20a}$, $-OR^{20a}$, $-OC(O)R^{20a}$, $-OC(O)N(R^{20a})_2$, $-SR^{20a}$, $-S(O)R^{20a}$, $-S(O)_2R^{20a}$, $-S(O)N(R^{20a})_2$, and $-S(O)_2N(R^{20a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, and 3-7 membered saturated heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{25};~~

~~R^{20a} in each occurrence is independently selected from H and C_{1-6}alkyl, wherein said C_{1-6}alkyl is optionally substituted with R^{25};~~

~~R^{25} is selected from halo and $-OR^{25a}$;~~

~~R^{25a} is selected from H and C_{1-6}alkyl;~~

~~R is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3-to 6-membered saturated heterocyclyl, halo, $-CN$, $-C(R^{3a})=NR(OR^{3a})$, $-C(R^{3a})=N(R^{3a})$, $-C(O)R^{3a}$, $-C(O)_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-NO_2$, $-N(R^{3a})_2$, $-N(R^{3a})C(O)R^{3a}$, $-N(R^{3a})C(O)_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})_2$, $-N(R^{3a})S(O)_2R^{3a}$, $-OR^{3a}$, $-OC(O)R^{3a}$, $-OC(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O)_2R^{3a}$, $-S(O)N(R^{3a})_2$, and $-S(O)_2N(R^{3a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, and 3-to 6-membered saturated heterocyclyl are optionally substituted with one or more R^{30};~~

~~R^{3a} in each occurrence is independently selected from H, C_{1-6}alkyl, 3- to 6-membered carbocyclyl, and 3- to 6-membered heterocyclyl, wherein said C_{1-6}alkyl, 3- to 6-membered carbocyclyl, and 3- to 6-membered heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{30};~~

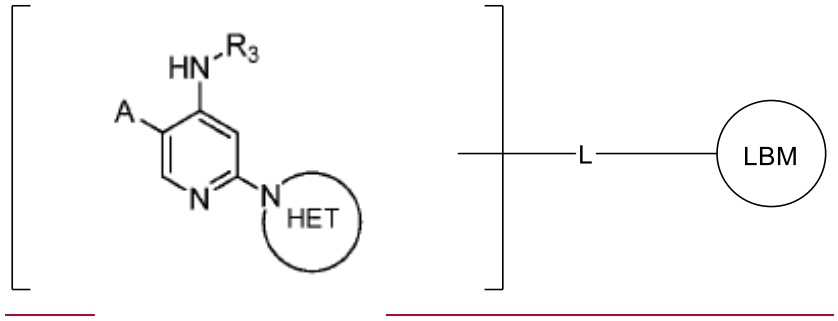
~~R^{30} in each occurrence is independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3- to 6-membered carbocyclyl, 3-to 6-membered heterocyclyl, halo, $-CN$, $-C(R^{30a})=NR(OR^{30a})$, $-C(R^{30a})=N(R^{30a})$, $-C(O)R^{30a}$, $-C(O)_2R^{30a}$, $-C(O)N(R^{30a})_2$, $-NO_2$, $-N(R^{30a})_2$, $-N(R^{30a})C(O)R^{30a}$, $-N(R^{30a})C(O)_2R^{30a}$, $-N(R^{30a})C(O)N(R^{30a})_2$, $-N(R^{30a})S(O)_2R^{30a}$, $-OR^{30a}$, $-OC(O)R^{30a}$, $-OC(O)N(R^{30a})_2$, $-SR^{30a}$, $-S(O)R^{30a}$, $-S(O)_2R^{30a}$, $-S(O)N(R^{30a})_2$, and $-S(O)_2N(R^{30a})_2$, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, 3-6 membered carbocyclyl, 3- to 6-membered heterocyclyl in each occurrence are optionally and independently substituted with one or more R^{35};~~

~~R^{30a} in each occurrence is independently selected from H and C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with one or more R^{35};~~

~~R^{35} in each occurrence is independently selected from halo and $-OR^{35a}$; and~~

R^{35a} in each occurrence is independently selected from H and C_{1-6}alkyl; or

(d)



I-gg-1

or a pharmaceutically acceptable salt thereof, wherein:

HET is a heteroaryl selected from pyrrolo[2,3-b]pyridinyl, pyrrolo[2,3-d]pyrimidinyl, pyrazolo[3,4-b]pyridinyl, pyrazolo[3,4-d]pyrimidinyl, imidazolo[4,5-b]pyridinyl, and imidazolo[4,5-d]pyrimidinyl, wherein said heteroaryl is attached to the pyridinyl group in the compound of Formula (I) by a nitrogen ring atom in said heteroaryl and wherein said heteroaryl is substituted with zero to 2 R_b;

A is pyrazolyl, imidazolyl, triazolyl, isoxazolyl, oxadiazolyl or dihydroisoxazolyl, each substituted with R_a;

R_3 is C_{2-3}alkyl, C_{2-3}fluoroalkyl, C_{3-4}hydroxyalkyl, or a cyclic group selected from C_{3-6}cycloalkyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, and pyrazolyl, wherein said cyclic group is substituted with zero to 2 substituents independently selected from F, OH, C_{1-2}alkyl, and CH_2CHF_2;

R_a is:

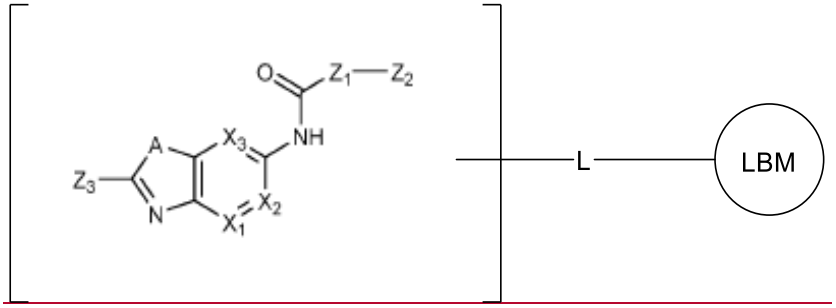
(i) H, F, C_1, OH, CN, C_{1-6}alkyl, C_{1-6}fluoroalkyl, C_{1-4}cyanoalkyl, C_{1-6}hydroxyalkyl, C_{1-5}hydroxy-fluoroalkyl, C_{2-4}alkenyl, C_{1-6}aminoalkyl, $(CH_2)_{1-3}NHR_y$, $(CH_2)_{1-3}NR_yR_y$, $CH_2CH(OH)$(phenyl), $CH(CH_2OH)$(phenyl), $CH_2CH(OH)CH_2$(phenyl), $CH_2CH(OH)CH_2O$(methoxyphenyl), $CH_2CH(NH_2)CH_2$(phenyl), $(CH_2CH_2O)_4H$, $(CH_2)_{1-3}O(C_{1-3}$alkyl), $CH_2CH(OH)CH_2O(C_{1-3}$alkyl), $CH_2C(O)(C_{1-3}$alkyl), $CH_2C(O)NR_yR_y$, $(CH_2)_{1-3}NR_yC(O)(C_{1-3}$alkyl), $CH_2C(O)O(C_{1-3}$alkyl), $C(O)NH_2$, $CH_2NR_yC(O)NH_2$, $(CH_2)_{1-2}NR_yC(O)O(C_{1-2}$alkyl), $(CR_yR_y)_{1-5}OC(O)CH_2NR_yR_y$, $CH_2CH_2S(O)_2CH_3$, $CH_2S(O)_2(C_{1-3}$alkyl), $CH_2S(O)_2$(phenyl), or NH(aminocyclohexyl); or

(ii) $(CH_2)_{0-3}R_z$ or $(CH_2)_{0-1}C(O)R_z$, wherein R_z is C_{3-6} cycloalkyl, azetidinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperazinyl, pyrrolyl, pyrrolidinonyl, morpholinyl, pyrrolidinyl, phenyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, dioxopyrimidinyl, benzo[d]imidazolyl, benzo[d]thiazolyl, 1,3-dioxolanyl, or 8-azabicyclo[3.2.1]octanyl, each substituted with zero to 4 substituents independently from F, CN, OH, NR_yR_y, C_{1-3} alkyl, C_{1-3} fluoroalkyl, C_{1-3} hydroxyalkyl, $CH(phenyl)_2$, $O(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ deuteroalkyl), $C(O)(C_{1-5}$ hydroxyalkyl), $C(O)(C_{1-3}$ fluoroalkyl), $C(O)(C_{3-6}$cycloalkyl), $C(O)O(C_{1-3}$ alkyl), $C(O)NR_yR_y$, C(O)(phenyl), C(O)(pyridinyl), $C(O)CH_2(C_{3-6}$ cycloalkyl), $C(O)O(C_{1-4}$ alkyl), $NH(C_{1-4}$ alkyl), $NH(C_{1-3}$ fluoroalkyl), $NHC(O)CH_3$, $NHC(O)O(C_{1-3}$ alkyl), $NHC(O)OC(CH_3)_3$, $S(O)_2(C_{1-3}$ alkyl), $OS(O)_2(C_{1-3}$ alkyl), methyl oxadiazolyl, and pyrimidinyl;

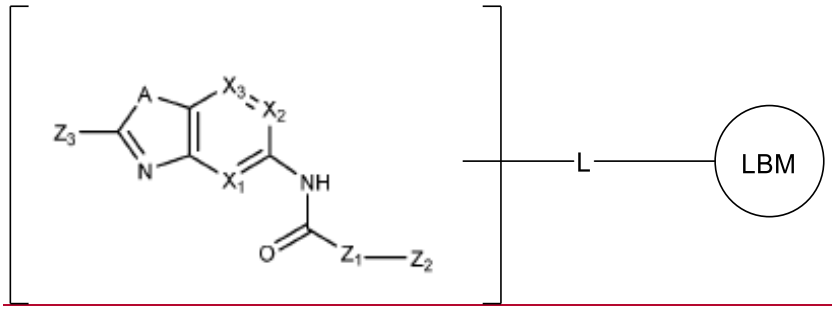
each R_b is independently selected from H, Cl, CN, NH_2, and $C(O)NH_2$, wherein said heteroaryl is attached to the pyridinyl group by a nitrogen atom in said heteroaryl; and

each R_y is independently H or C_{1-2} alkyl; or

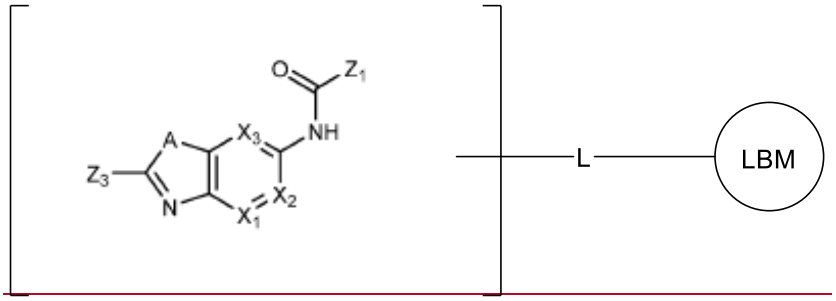
(e)



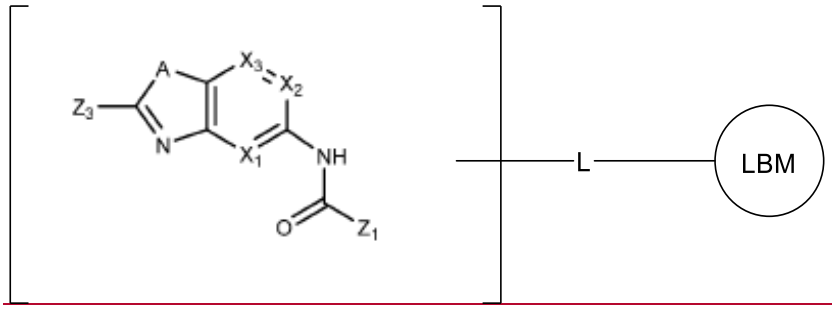
I-hh-1



I-hh-2



I-hh-3



I-hh-4

or a pharmaceutically acceptable salt thereof, wherein:

each X_1, X_2 and X_3 are independently CR^2 or N;

A is O, S, S(O) or $S(O)_2$;

Z_1 is optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted (heterocycloalkyl)alkyl-, optionally substituted aralkyl-, optionally substituted heteroaralkyl-, optionally substituted (cycloalkyl)alkyl-, optionally substituted aryloxy-, optionally substituted heteroaryloxy-, optionally substituted heterocycloalkyloxy-, optionally substituted cycloalkyloxy-, optionally substituted aryl-NR′-, optionally substituted heteroaryl-NR′-, optionally substituted heterocycloalkyl-NR′-, optionally substituted cycloalkyl-NR′-, optionally substituted aryl-S-, optionally substituted heteroaryl-S-, optionally substituted heterocycloalkyl-S-, optionally substituted cycloalkyl-S-, optionally substituted (cycloalkyl)alkyl-NR′-, optionally substituted aralkyl-NR′-, optionally substituted (heterocycloalkyl)alkyl-NR′-, optionally substituted heteroaralkyl-NR′-, optionally substituted (cycloalkyl)alkyl-S-, optionally substituted aralkyl-S-, optionally substituted (heterocycloalkyl)alkyl-S-, optionally substituted heteroaralkyl-S-, optionally substituted (cycloalkyl)alkyl-O-, optionally

substituted aralkyl-O- , optionally substituted (heterocycloalkyl)alkyl-O- , optionally substituted heteroaralkyl-O- ; e.g., wherein each optional substituent independently represents an occurance of R_x;

Z_2 is absent or optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, optionally substituted aryloxy-, optionally substituted heteroaryloxy-, optionally substituted cycloalkyloxy-, optionally substituted heterocycloalkyloxy-, optionally substituted (cycloalkyl)alkyl-, optionally substituted aralkyl-, optionally substituted (heterocycloalkyl)alkyl-, optionally substituted heteroaralkyl-, optionally substituted (cycloalkyl)alkyl-NR″- , optionally substituted aralkyl-NR″- , optionally substituted (heterocycloalkyl)alkyl-NR″- , optionally substituted heteroaralkyl-NR″- , optionally substituted (cycloalkyl)alkyl-O- , optionally substituted aralkyl-O- , optionally substituted (heterocycloalkyl)alkyl-O- , optionally substituted heteroaralkyl-O- , optionally substituted (cycloalkyl)alkyl-S- , optionally substituted aralkyl-S- , optionally substituted (heterocycloalkyl)alkyl-S- or optionally substituted heteroaralkyl-S- ; e.g., wherein each optional substituent independently represents an occurance of R_y;

Z_3 is optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, optionally substituted aryloxy-, optionally substituted heteroaryloxy-, optionally substituted cycloalkyloxy-, optionally substituted heterocycloalkyloxy-, optionally substituted (cycloalkyl)alkyl-, optionally substituted aralkyl-, optionally substituted (heterocycloalkyl)alkyl-, optionally substituted heteroaralkyl-, optionally substituted (cycloalkyl)-NR‴- , optionally substituted aryl-NR‴- , optionally substituted heteroaryl-NR‴- , optionally substituted heterocycloalkyl-NR‴- , optionally substituted aryl-S- , optionally substituted heteroaryl-S- , optionally substituted cycloalkyl-S- , optionally substituted heterocycloalkyl-S- , optionally substituted (cycloalkyl)alkyl-NR‴- , optionally substituted aralkyl-NR‴- , optionally substituted (heterocycloalkyl)alkyl-NR‴- , optionally substituted heteroaralkyl-NR‴- , optionally substituted (cycloalkyl)alkyl-O- , optionally substituted aralkyl-O- , optionally substituted (heterocycloalkyl)alkyl-O- , optionally substituted heteroaralkyl-O- , optionally substituted (cycloalkyl)alkyl-S- , optionally substituted aralkyl-S- , optionally substituted (heterocycloalkyl)alkyl-S- or

optionally substituted heteroaralkyl-S-; e.g., wherein each optional substituent independently represents an occurance of R_z;

each R^2 is independently selected from hydrogen, alkyl, haloalkyl, halo, cyano, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl-, optionally substituted cycloalkyloxy-, optionally substituted aryl, optionally substituted aralkyl-, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, optionally substituted (heterocycloalkyl)alkyl-, optionally substituted heteroaralkyl-, NR_aR_b, O R_3 and S R_3; e.g., wherein each optional substituent independently represents alkyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, SH, S(alkyl), cyano, amido, amino, carboxylate, glycinate, alaninate, oxo, aryl, cycloalkyl, heterocycloalkyl or heteroaryl;

each R′, R″ and R‴ is independently selected from hydrogen, alkyl, hydroxy, hydroxyalkyl, acyl and cycloalkyl;

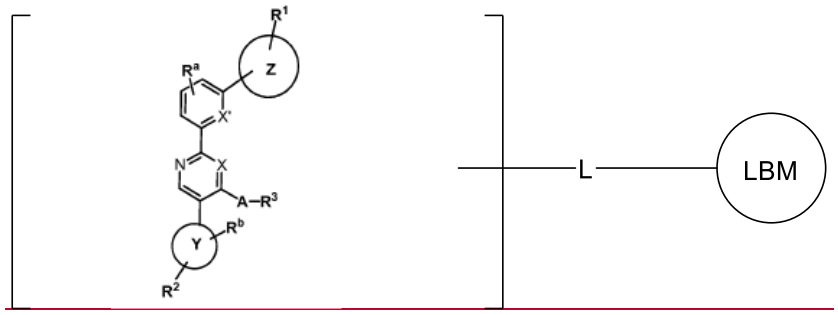
each R_x, R_y and R_z is independently selected from alkyl, alkenyl, alkynyl, halo, hydroxy, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, SH, S(alkyl), cyano, amido, carboxylic acid, carboxylate, ester, thioester, alkoxycarbonyl, C(O)NH(alkyl), oxo, cycloalkyl, cycloalkyloxy, (cycloalkyl)alkyl-, aryl, aralkyl-, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl-, heteroaralkyl-, NR_aR_b, O R_4 or S R_4; optionally wherein the cycloalkyl, aryl, heterocycloalkyl, and heteroaryl are further substituted by one or more substituents selected from halo, haloalkyl, amino, hydroxy, alkyl, cyano, nitro, alkenyl, aminoalkyl, hydroxyalkyl and haloalkoxy;

each R_a and R_b is independently selected from hydrogen, alkyl, aminoalkyl, acyl, aminoacyl, halo, haloalkyl, hydroxy, haloalkoxy, hydroxyalkyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (cycloalkyl)alkyl-, (heterocycloalkyl)alkyl-, aralkyl-, and (heteroaryl)alkyl-; optionally wherein the cycloalkyl, heterocycloalkyl, aryl and heteroaryl are further substituted by one or more substituents selected from alkyl, halo, alkenyl, cyano, hydroxy, hydroxyalkyl, alkoxy, amino and nitro; or

R_a and R_b are taken together along with the atoms which they are attached to form a 3 to 8 membered optionally substituted ring; and

each R_3 and R_4 is independently selected from hydrogen, alkyl, aminoacyl, phosphate, phosphonate, alkylphosphate, alkoxycarbonyl, cycloalkyl, (cycloalkyl)alkyl-, aryl, heteroaryl, heterocycloalkyl, aralkyl-, heteroaralkyl and (heterocycloalkyl)alkyl-; or

(f)



I-ii-1

or a pharmaceutically acceptable salt thereof, wherein:

X is CR or N;

A is O, S, SO_2, SO, NRC(O), $NRSO_2$, or N(R); or A is absent;

R^3 is R, halogen, -haloalkyl, OR, SR, CN, NO_2, SO_2R, SOR, C(O)R, CO_2R, $C(O)N(R)_2$, NRC(O)R, $NRC(O)N(R)_2$, $NRSO_2R$, or $N(R)_2$; or

when A is NRC(O), $NRSO_2$, or N(R); then R and R^3, together with the atoms to which each is attached, may form a 3-7 membered heterocylic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted;

X′ is CR or N;

Ring Z is a 3-7 membered heterocylic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted;

R^1 is R, halogen, -haloalkyl, OR, SR, CN, NO_2, SO_2R, SOR, C(O)R, CO_2R, $C(O)N(R)_2$, NRC(O)R, $NRC(O)N(R)_2$, $NRSO_2R$, or $N(R)_2$;

R^a is absent, R, halogen, -haloalkyl, OR, SR, CN, NO_2, SO_2R, SOR, C(O)R, CO_2R, $C(O)N(R)_2$, NRC(O)R, $NRC(O)N(R)_2$, $NRSO_2R$, or $N(R)_2$;

Ring Y is an optionally substituted 5-6 membered monocyclic heteroaryl ring having 2-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

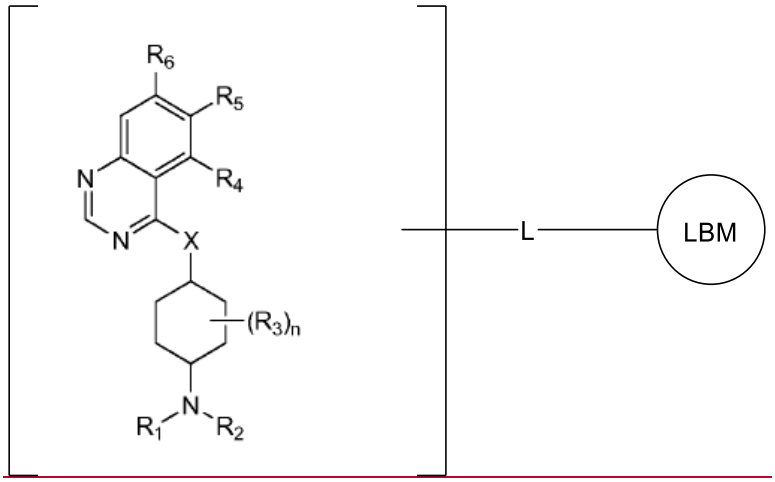
R^2 is R, halogen, -haloalkyl, OR, SR, CN, NO_2, SO_2R, SOR, C(O)R, CO_2R, $C(O)N(R)_2$, NRC(O)R, $NRC(O)N(R)_2$, $NRSO_2R$, or $N(R)_2$;

R^b is absent, R, halogen, -haloalkyl, OR, SR, CN, NO_2, SO_2R, SOR, C(O)R, CO_2R, $C(O)N(R)_2$, NRC(O)R, $NRC(O)N(R)_2$, $NRSO_2R$, or $N(R)_2$;

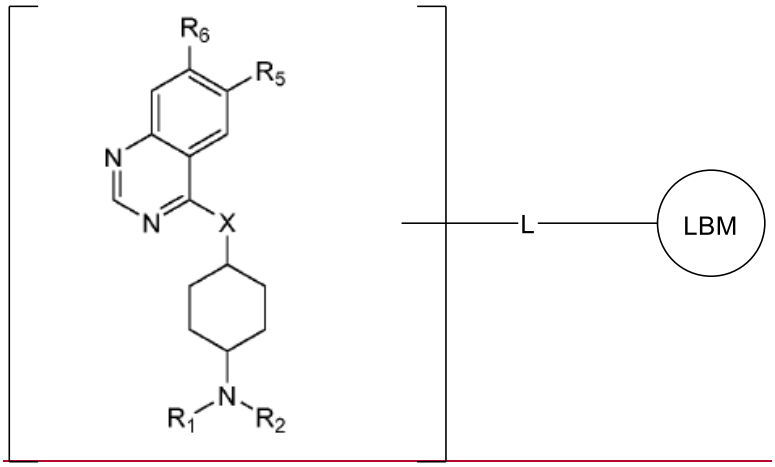
each R is independently hydrogen, C_{1-6} aliphatic, C_{3-10} aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocylic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted; or

two R groups on the same atom are taken together with the atom to which they are attached to form a C_{3-10} aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocylic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted; or

(g)



I-jj-1



~~I-jj-2~~

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

~~X is NH or O;~~

~~b is 0 or 1;~~

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

~~R_1 and R_2 are independently H, (C_1-C_4)alkyl and heterocyclyl, or $R_1$and R_2 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic (fused, bridged or spirocyclic) heterocycle containing 3-8 carbon atoms optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said alkyl and heterocycle are optionally substituted with one or more substituents selected from R_a;~~

~~R_3 is (C_1-C_4)alkyl wherein two adjacent alkyl groups can join together and form a bridged moiety of 3-6 carbon atoms;~~

~~R_4 is absent, halo or O_b(C_1-C_4)alkyl;~~

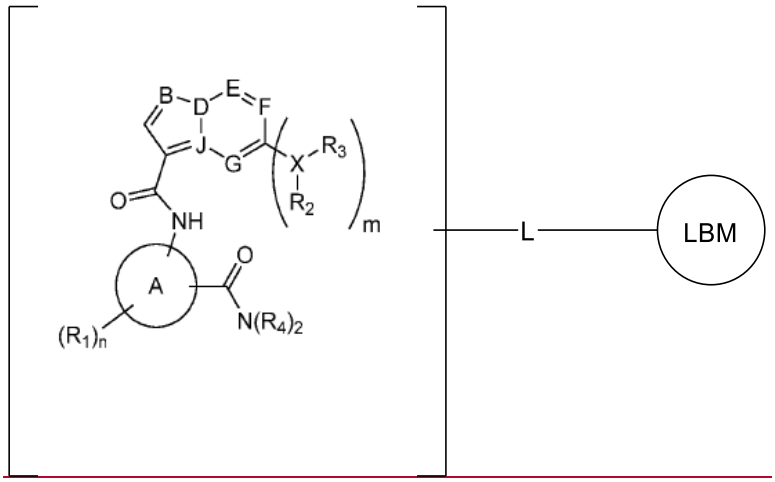
~~R_5 is selected from C_1-C_4 alkyl and C_2-C_4 alkenyl which are optionally substituted with one or more substituents selected from R_b;~~

~~R_6 is absent, halo, or O(C_1-C_4)alkyl;~~

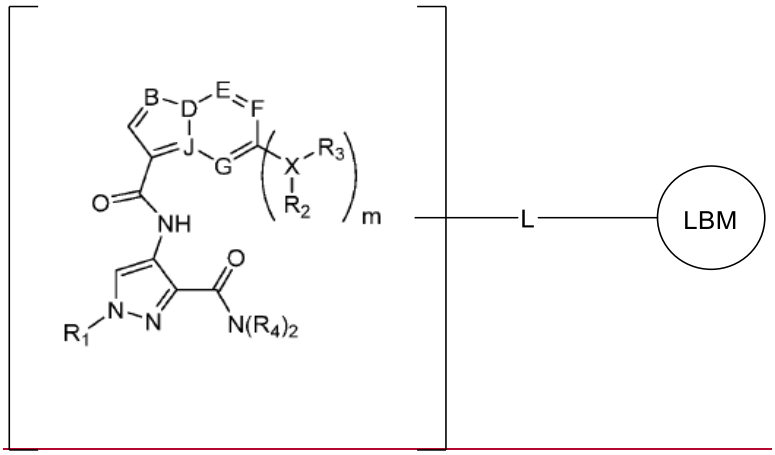
~~R_a is halo, oxo, OH, O_b(C_1-C_4)alkyl, CF_3, SO_2(C_1-C_4)alkyl, or heterocyclyl, said heterocyclyl optionally substituted with one or more substituents independently selected from F, and (C_1-C_4)alkyl; and~~

~~R_b is independently selected from OH, halo, O_b(C_1-C_4)alkyl, and CN; or~~

~~(h)~~



I-kk-1



I-kk-2

or a pharmaceutically acceptable salt thereof, wherein:

B is CH, N or S; D is CH or N; E is CH or N; F is CH or N; G is CH or N; and J is C or N, wherein when B is S then D is CH, E is N, F is CH, G is N and J is C;

X is O, S, CH_2 or N;

m is 0 or 1; n is 0, 1 or 2;

Ring A is pyridinyl, pyrazolyl, thiophenyl, furanyl or phenyl;

R_1 is independently selected from $(C_1\text{-}C_4)$alkyl, pyrimidine, piperidine and phenyl, each optionally substituted with $(C_1\text{-}C_4)$alkyl, OH, halo, $O(C_1\text{-}C_4)$alkyl, methylpiperidine, $S(O)_2R_c$, $C(O)N(R_b)_2$, or $C(O)O(C_1\text{-}C_4)$alkyl;

R_2 is absent or H and R_3 is independently selected from: $(C_1\text{-}C_4)$alkyl, pyranyl, cyclopentyl, cyclohexyl, cycloheptyl, thiopyranyl, pyrazolyl, piperidinyl, morpholinyl, piperazinyl

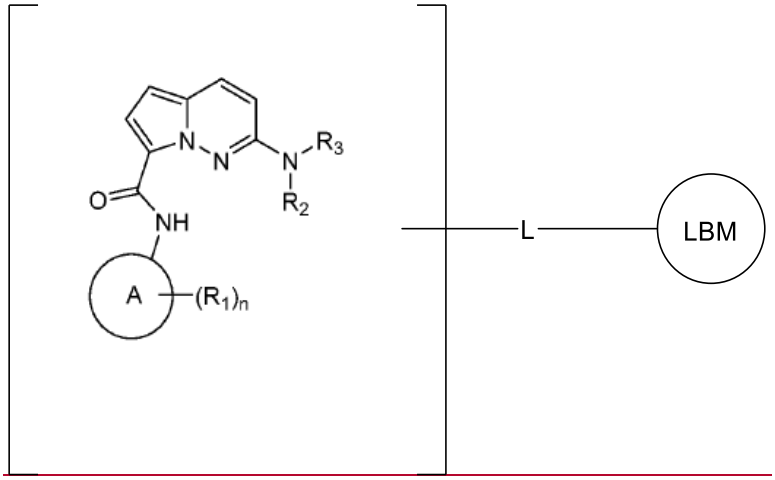
each optionally substituted with one or more substituents independently selected from halo, OH, oxo, $N(R_b)_2$, oxopyrrolidinyl, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form piperazine or morpholine, each optionally substituted with oxo;

R_4 is independently H or methyl;

R_b is independently selected from H and $(C_1\text{-}C_4)$alkyl; and

R_c is methyl; or

(i)



I-II-1

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is aryl or heterocyclyl;

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

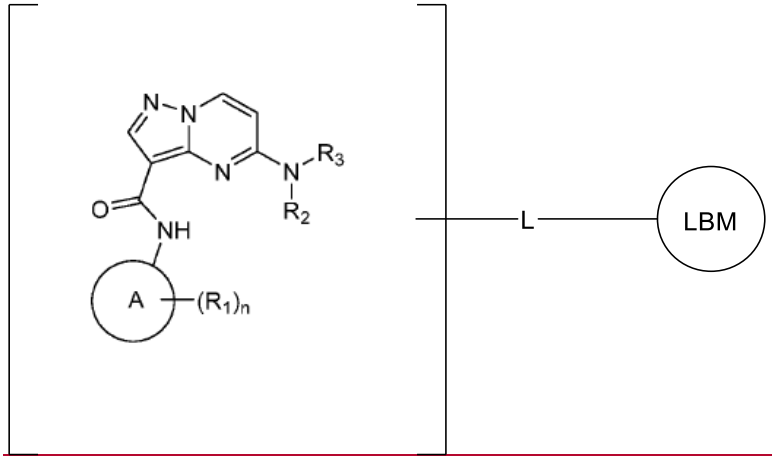
R_1 is independently selected from: $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, heterocyclyl, CF_3, CHF_2, CN, halo, said alkyl, cycloalkyl and heterocyclyl optionally substituted with halo, OH, CH_3, and OCH_3;

R_2 is H and R_3 is independently selected from: $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, and heterocyclyl each optionally substituted with one or more halo, OH, $N(R_b)_2$, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a heterocyclyl, said heterocyclyl optionally substituted with one or more substituents selected from R_a;

R_a is independently selected from $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, CF_3, CHF_2, OH, halo and NH_2, said alkyl optionally substituted with $(C_3\text{-}C_6)$cycloalkyl and CF_3; and

R_b is independently selected from H and (C_1-C_4)alkyl; or

(j)



I-mm-1

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is aryl or heterocyclyl;

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

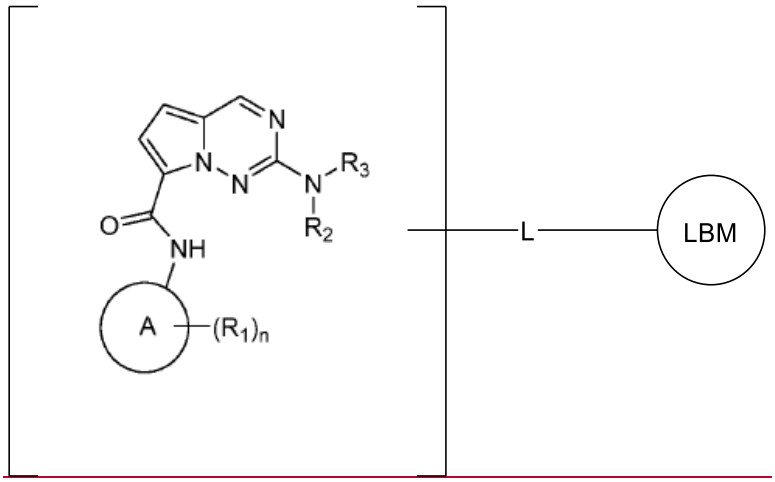
R_1 is independently selected from: (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, heterocyclyl, CF_3, CHF_2, CN and halo, said alkyl, cycloalkyl and heterocyclyl optionally substituted with halo, OH, CH_3, and OCH_3;

R_2 is H and R_3 is independently selected from: (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, and heterocyclyl each optionally substituted with one or more halo, OH, $N(R_b)_2$, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a heterocyclyl, said heterocyclyl optionally substituted with one or more substituents selected from R_a;

R_a is independently selected from (C_1-C_4)alkyl, (C_3-C_6)cycloalkyl, CF_3, CHF_2, OH, halo and NH_2, said alkyl optionally substituted with (C_3-C_6)cycloalkyl or CF_3; and

R_b is independently selected from H and (C_1-C_4)alkyl; or

(k)



I-nn-1

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is aryl or heterocyclyl;

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

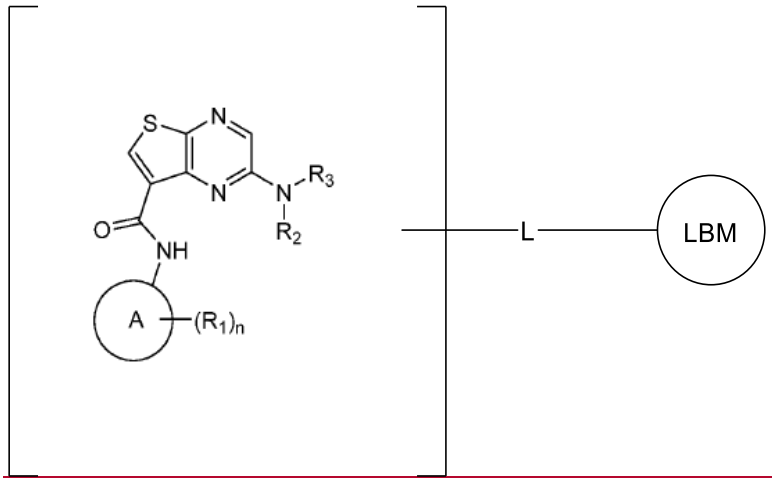
R_1 is independently selected from: $(C_1$-$C_4)$alkyl, $(C_3$-$C_6)$cycloalkyl, heterocyclyl, CF_3, CHF_2, CN, halo, said alkyl, cycloalkyl and heterocyclyl optionally substituted with halo, OH, CH_3, and OCH_3;

R_2 is H and R_3 is independently selected from: $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, and heterocyclyl each optionally substituted with one or more halo, OH, $N(R_b)_2$, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a heterocyclyl, said heterocyclyl optionally substituted with one or more substituents selected from R_a;

R_a is independently selected from $(C_1$-$C_4)$alkyl, $(C_3$-$C_6)$cycloalkyl, CF_3, CHF_2, OH, halo and NH_2, said alkyl optionally substituted with $(C_3$-$C_6)$cycloalkyl and CF_3; and

R_b is independently selected from H and $(C_1$-$C_4)$alkyl; or

(l)



~~I-oo-1~~

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

~~Ring A is aryl or heterocyclyl;~~

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

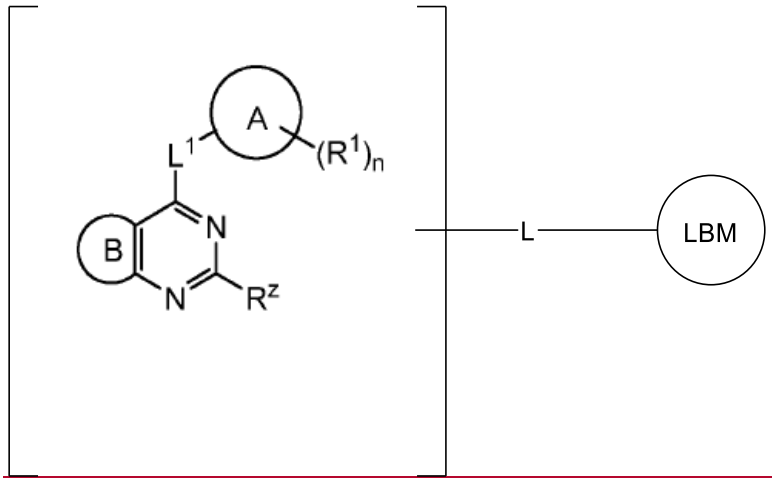
~~R_1 is independently selected from: $(C_1$-$C_4)$alkyl, $(C_3$-$C_6)$cycloalkyl, heterocyclyl, CF_3, CHF_2, CN, halo, said alkyl, cycloalkyl and heterocyclyl optionally substituted with halo, OH, CH_3, and OCH_3;~~

~~R_2 is H and R_3 is independently selected from: $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl and heterocyclyl each optionally substituted with one or more halo, OH, $N(R_b)_2$, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a heterocyclyl, said heterocyclyl optionally substituted with one or more substituents selected from R_a;~~

~~R_a is independently selected from $(C_1$-$C_4)$alkyl, $(C_3$-$C_6)$cycloalkyl, CF_3, CHF_2, OH, halo and NH_2, said alkyl optionally substituted with $(C_3$-$C_6)$cycloalkyl and CF_3; and~~

~~R_b is independently selected from H and $(C_1$-$C_4)$alkyl; or~~

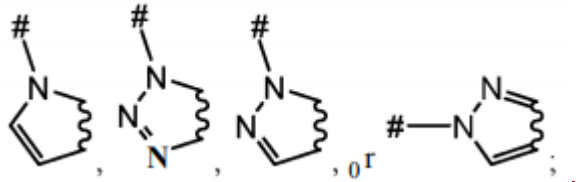
~~(m)~~



I-pp-1

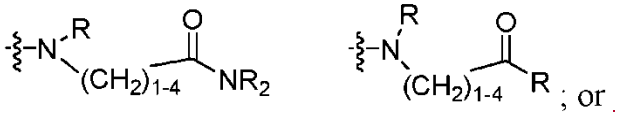
or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is 

wherein ~~~ represents the portion of the ring fused to the pyrimidine ring and # is $-L^2(R^4)_p-R^X$;

each R^1 and $R^{1'}$ is independently $-R^2$, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-N(R)_2$, $-S(O)_2R$, $-S(O)_2N(R)_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, $-C(O)N(R)OR$, $-N(R)C(O)OR$, $-N(R)C(O)N(R)_2$, Cy, or $-N(R)S(O)_2R$; or R^1 is selected from one of the following formulae:



; or

two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Cy is independently an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-10 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from

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

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

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

each R^4 is independently halogen, -CN, $-NO_2$, -OR, -SR, $-N(R)_2$, $-S(O)_2R$, $-S(O)_2N(R)_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)N(R)_2$, $-N(R)C(O)R$, $-N(R)C(O)N(R)_2$, $-C(O)N(R)OR$, $-N(R)C(O)OR$, $-N(R)S(O)_2N(R)_2$, $-N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^x is hydrogen, $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, -C(O)OR, -C(O)R, $-N(R)_2$, -NH[Ar], -OR, or $-S(O)_2N(R)_2$;

R^z is hydrogen, $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, -C(O)OR, -C(O)R, $-N(R)_2$, -NH[Ar], -OR, or $-S(O)_2N(R)_2$;

[Ar] is phenyl or a 5-6 membered heteroaromatic ring having 1-4 heteroatoms indepently selected from nitrogen, oxygen, and sulfur, wherein [Ar] is substituted by m instances of R^1;

L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -N(R)-, -N(R)C(O)-, -C(O)N(R)-, -N(R)S(O)2-, $-S(O)_2N(R)$-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- or $-S(O)_2$-;

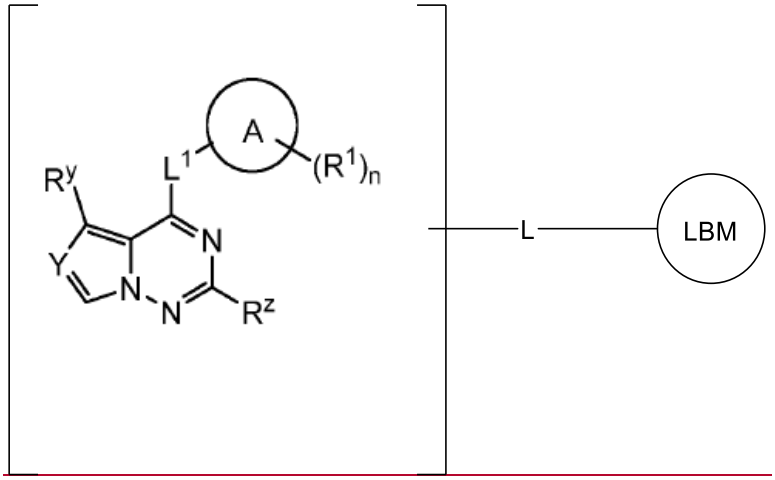
~~L^2 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $-N(R)-$, $-N(R)C(O)-$, $-C(O)N(R)-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$ or $-S(O)_2-$;~~

~~m is 0-4;~~

~~n is 0-4; and~~

~~p is 0-2; or~~

~~(n)~~



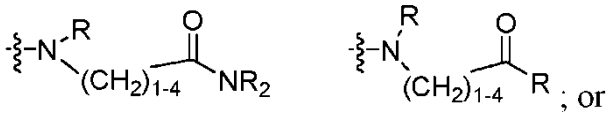
~~I-qq-1~~

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

~~Y is N or C-R^x;~~

~~Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;~~

~~each R^1 and R^x is independently $-R^2$, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-N(R)_2$, $-S(O)_2R$, $-S(O)_2N(R)_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, $-C(O)N(R)OR$, $-N(R)C(O)OR$, $-N(R)C(O)N(R)_2$, Cy, or $-N(R)S(O)_2R$; or R^1 is selected from one of the following formulas:~~



; or

two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Cy is independently an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-10 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen, or an optionally substituted group selected from Ci-6 aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or: two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;

each R^2 is independently an optionally substituted group selected from Ci-$_6$aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each of R^x and R^y is independently hydrogen, $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, $-C(O)OR$, $-C(O)R$, $-N(R)_2$, $-H[Ar]$, $-OR$, or $-S(O)_2N(R)_2$; or

R^x and R^y are taken together together with their intervening atoms to form a 4-7 membered partially unsaturated carbocyclic ring or a partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^z is hydrogen, $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, $-C(O)OR$, $-C(O)R$, $-N(R)_2$, $-NH[Ar]$, $-OR$, or $-S(O)_2N(R)_2$;

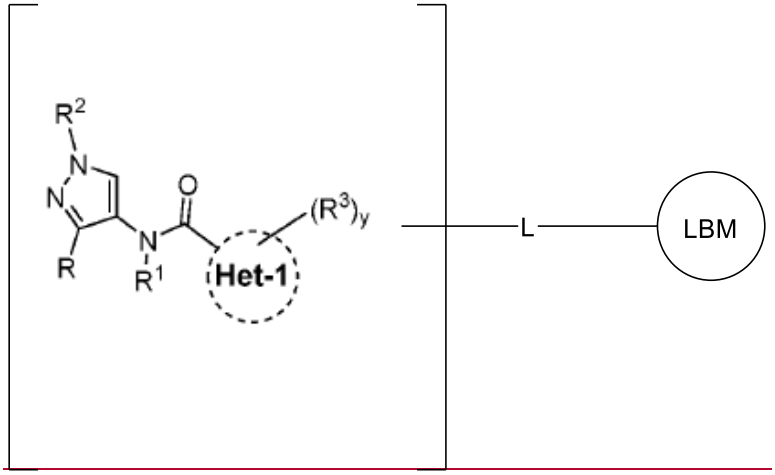
[Ar] is phenyl or a 5-6 membered heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said [Ar] is substituted by m instances of R^r;

~~L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -N(R)-, -N(R)C(O)-, -C(O)N(R)-, -N(R)S(O)$_2$-, -S(O)$_2$N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- or -S(O)$_2$-;~~

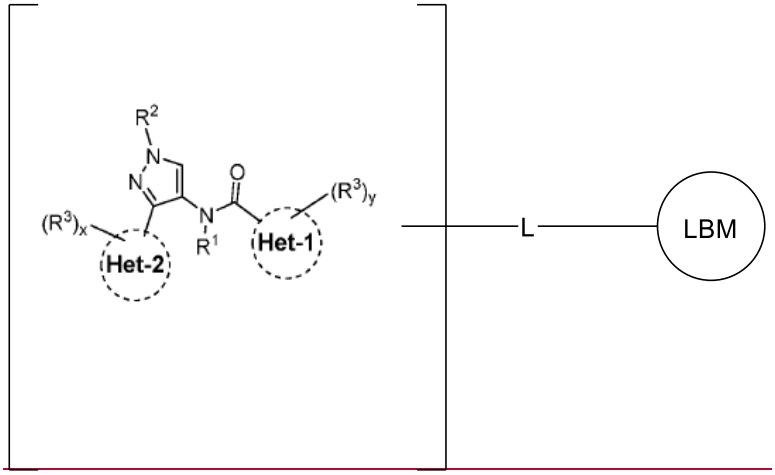
~~m is 0-4; and~~

~~n is 0-4; or~~

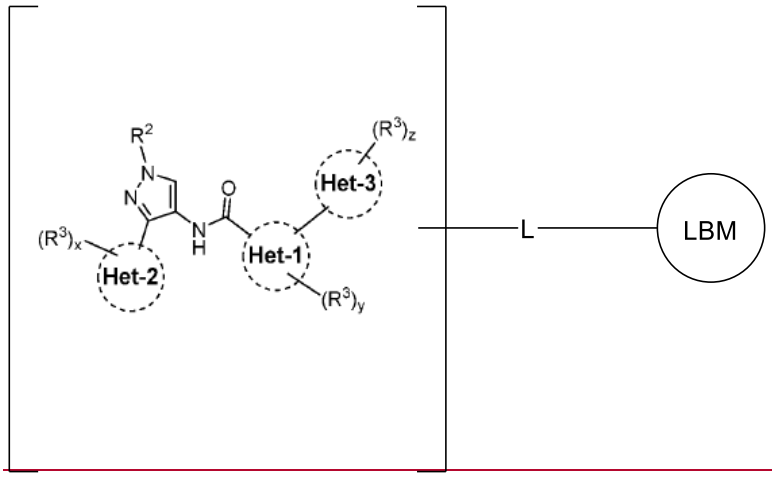
~~(o)~~



~~I-rr-1~~



~~I-rr-2~~



I-rr-3

or a pharmaceutically acceptable salt thereof, wherein:

R is aliphatic, heteroaliphatic, heteroaryl, aryl, halo, amide or CN;

R^1 is H, aliphatic or heteroaliphatic;

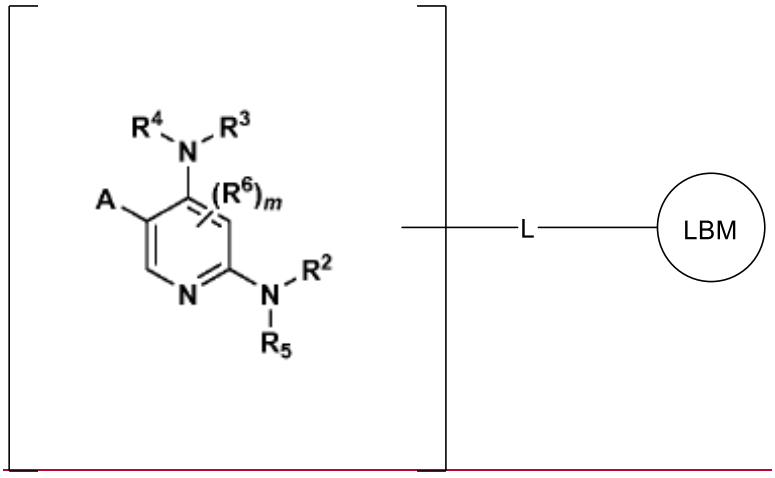
or R and R^1, together with the atoms to which they are attached, form a heterocyclyl ring;

R^2 is H, aliphatic, heteroaliphatic, heterocycloaliphatic, aryl, amide, heterocyclyl or araliphatic;

each R^3 independently is H, aliphatic, halogen, heteroaliphatic, O-aliphatic, heterocyclyl, aryl, araliphatic, O-heterocyclyl, hydroxyl, nitro, cyano, carboxyl, carboxyl ester, acyl, amide, amino, sulfonyl, sulfonamide, sulfanyl, sulfinyl, haloalkyl, alkylphosphate, or alkylphosphonate;

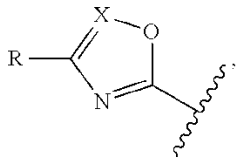
y is from 1 to 6; or

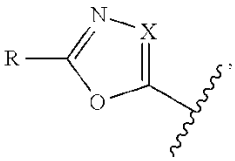
(p)



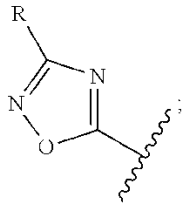
I-ss-1

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





or



~~A is~~

~~X is N or C—R^{7};~~

~~R is hydrogen, R^{1}, halogen, cyano, nitro, OR^{1}, C(=O)R^{1}, C(=O)OR^{1}, C(=O)NR^{11}R^{1}, S(=O)$_2$R^{1}, NR^{11}C(=O)R^{1}, NR^{11}C(=O)NR^{11}R^{11}, NR^{11}C(=O)OR^{1}, NR^{11}S(=O)$_2$R^{1} or NR^{11}R^{11};~~

~~R^{1} is C$_{1-6}$ alkyl substituted with 0-4 R^{1a}, C$_{1-6}$ haloalkyl, C$_{2-6}$ alkenyl substituted with 0-3 R^{1a}, C$_{2-6}$ alkynyl substituted with 0-3 R^{1a}, C$_{3-10}$ cycloalkyl substituted with 0-3 R^{1a}, C$_{6-10}$ aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a};~~

~~R^{1a} is hydrogen, =O, F, Cl, Br, OCF$_3$, CN, NO$_2$, (CH$_2$)$_r$OR^{b}, (CH$_2$)$_r$SR^{b}, (CH$_2$)$_r$C(O)R^{b}, (CH$_2$)$_r$C(O)OR^{b}, (CH$_2$)$_r$OC(O)R^{b}, (CH$_2$)$_r$NR^{11}R^{11}, (CH$_2$)$_r$C(O)NR^{11}R^{11}, (CH$_2$)$_r$NR^{b}C(O)R^{c}, (CH$_2$)$_r$NR^{b}C(O)OR^{c}, NR^{b}C(O)NR^{11}R^{11}, S(O)$_p$NR^{11}R^{11}, NR^{b}S(O)$_p$R^{c}, S(O)R^{c}, S(O)$_2$R^{c}, C$_{1-6}$ alkyl substituted with 0-2 R^{a}, C$_{1-6}$ haloalkyl, (CH$_2$)$_r$-3-14 membered carbocycle substituted with 0-3 R^{a}, or (CH$_2$)$_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and S(O)$_p$ substituted with 0-3 R^{a};~~

~~R^{2} is C$_{6-10}$ aryl substituted with 0-4 R^{2a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted with 1-4 R^{2a}, or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-4 R^{2a};~~

~~R^{2a} at each occurrence is independently selected from hydrogen, =O, halo, OCF$_3$, CN, NO$_2$, (CH$_2$)$_r$OR^{b}, (CH$_2$)$_r$SR^{b}, (CH$_2$)$_r$C(O)R^{b}, (CH$_2$)$_r$C(O)OR^{b}, (CH$_2$)$_r$OC(O)R^{b}, (CH$_2$)$_r$NR^{11}R^{11}, (CH$_2$)$_r$C(O)NR^{11}R^{11}, (CH$_2$)$_r$NR^{b}C(O)R^{c}, (CH$_2$)$_r$NR^{b}C(O)OR^{c}, NR^{b}C(O)NR^{11}R^{11}, S(O)$_p$NR^{11}R^{11}, NR^{b}S(O)$_p$R^{c}, S(O)R^{c}, S(O)$_2$R^{c}, C$_{1-6}$ alkyl~~

substituted with 0-2 R^a, C_{1-6} haloalkyl, $(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-2 R^a;

R^3 is C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{3a}, C_{2-6} alkynyl substituted with 0-3 R^{3a}, C_{3-10} cycloalkyl substituted with 0-3 R^{3a}, C_{6-10} aryl substituted with 0-3 R^{3a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3a} or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3a};

R^{3a} is hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, $(CH_2)_rOR^b$, $(CH_2)_rSR^b$, $(CH_2)_rC(O)R^b$, $(CH_2)_rC(O)OR^b$, $(CH_2)_rOC(O)R^b$, $(CH_2)_rNR^{11}R^{11}$, $(CH_2)_rC(O)NR^{11}R^{11}$, $(CH_2)_rNR^bC(O)R^e$, $(CH_2)_rNR^bC(O)OR^e$, $NR^bC(O)NR^{11}R^{11}$, $S(O)_pNR^{11}R^{11}$, $NR^bS(O)_pR^e$, $S(O)R^e$, $S(O)_2R^e$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-1 R^a;

R^4 and R^5 are independently selected from hydrogen, C_{1-4} alkyl substituted with 0-1 R^f, (CH_2)-phenyl substituted with 0-3 R^d, and a (CH_2)-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$;

R^6 and R^7 are independently at each occurrence is selected from hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, $(CH_2)_rOR^b$, $(CH_2)_rSR^b$, $(CH_2)_rC(O)R^b$, $(CH_2)_rC(O)OR^b$, $(CH_2)_rOC(O)R^b$, $(CH_2)_rNR^{11}R^{11}$, $(CH_2)_rC(O)NR^{11}R^{11}$, $(CH_2)_rNR^bC(O)R^e$, $(CH_2)_rNR^bC(O)OR^e$, $NR^bC(O)NR^{11}R^{11}$, $S(O)_pNR^{11}R^{11}$, $NR^bS(O)_pR^e$, $S(O)_2R^e$, $S(O)_2R^e$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $(CH_2)_r$-3-14 membered carbocycle substituted with 0-3 R^a, or $(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a, provided R^6 and R^7 are not both hydrogen;

R^{11} at each occurrence is independently hydrogen, R^e, C_{1-4} alkyl substituted with 0-1 R^f, CH_2-phenyl substituted with 0-3 R^d, or (CH_2)-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^d; or

R^{11} and along with another R^{11}, R^1, or R^2 on the same nitrogen atom may join to form an optionally substituted heterocycle;

R^a is hydrogen, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $(CH_2)_rOR^b$, $(CH_2)_rSR^b$, $(CH_2)_rC(O)R^b$, $(CH_2)_rC(O)OR^b$, $(CH_2)_rOC(O)R^b$, $(CH_2)_rNR^{11}R^{11}$, $(CH_2)_rC(O)NR^{11}R^{11}$, $(CH_2)_rNR^bC(O)R^c$, $(CH_2)_rNR^bC(O)OR^c$, $NR^bC(O)NR^{11}R^{11}$, $(O)_pNR^{11}R^{11}$, $NR^bS(O)_pR^c$, $S(O)R^c$, $S(O)_2R^c$, C_{1-6} alkyl substituted with 0-1 R^f, C_{1-6} haloalkyl, $(CH_2)_r$-3-14 membered carbocycle, or $(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; or two R^a on adjacent or the same carbon atom form a cyclic acetal of the formula $-O-(CH_2)_n-O-$, or $-O-CF_2-O-$, wherein n is selected from 1 or 2;

R^b is hydrogen, R^e, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6}haloalkyl, C_{3-6} cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-3 R^d;

R^c is C_{1-6} alkyl substituted with 0-1 R^f, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl substituted with 0-3 R^f;

R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO_2, OR^e, $(CH_2)_rC(O)R^c$, NR^eR^e, $NR^eC(O)OR^c$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl substituted with 0-3 R^f;

R^e is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $(CH_2)_r$-phenyl substituted with 0-3 R^f;

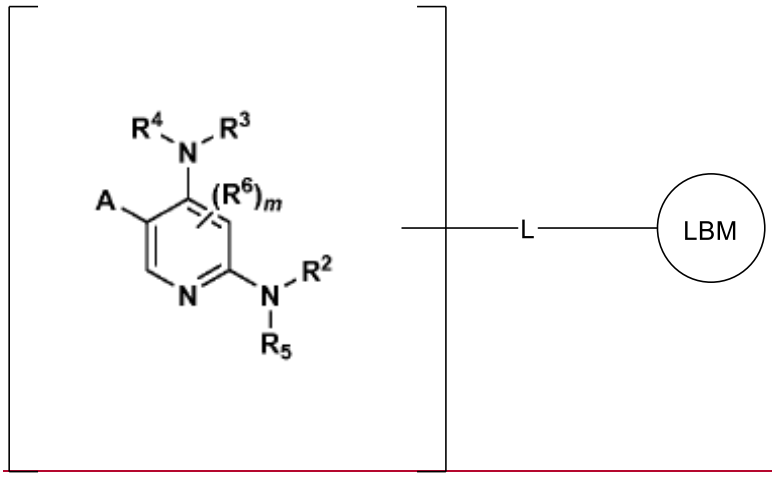
R^f is hydrogen, halo, NH_2, OH, or $O(C_{1-6}$alkyl);

p is 0, 1, or 2;

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

m is 0, 1, or 2; or

(q)



I-tt-1

or a pharmaceutically acceptable salt thereof, wherein:

A is a triazole optionally substituted by 0-2 R;

X is N or C—R^7;

R is hydrogen, R′, halogen, cyano, nitro, OR^1, $C(=O)R^1$, $C(=O)OR^1$, $C(=O)NR^{11}R^1$, $S(=O)_2R^1$, $NR^{11}C(=O)R'$, $NR^{11}C(=O)NR^{11}R^1$, $NR^{11}C(=O)OR'$, $NR^{11}S(=O)_2R^1$ or $NR^{11}R^1$;

R^1 is C_{1-6} alkyl substituted with 0-4 R^{1a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{1a}, C_{2-6} alkynyl substituted with 0-3 R^{1a}, C_{3-10}cycloalkyl substituted with 0-3 R^{1a}, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a};

R^{1a} is hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, $(CH_2)_rOR^b$, $(CH_2)_rSR^b$, $(CH_2)_rC(O)R^b$, $(CH_2)_rC(O)OR^b$, $(CH_2)_rOC(O)R^b$, $(CH_2)_rNR^{11}R^{11}$, $(CH_2)_rC(O)NR^{11}R^{11}$, $(CH_2)_rNR^bC(O)R^c$, $(CH_2)_rNR^bC(O)OR^c$, $NR^bC(O)NR^{11}R^{11}$, $S(O)_pNR^{11}R^{11}$, $NR^bS(O)_pR^c$, $S(C)R^c$, $S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $(CH_2)_r$-3-14 membered carbocycle substituted with 0-3 R^a, or $(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^2 is C_{6-10} aryl substituted with 0-4 R^{2a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted with 1-4 R^{2a}, or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-4 R^{2a};

R^{2a} at each occurrence is independently selected from hydrogen, =O, halo, OCF_3, CN, NO_2, $(CH_2)_rOR^b$, $(CH_2)_rSR^b$, $(CH_2)_rC(O)R^b$, $(CH_2)_rC(O)OR^b$, $(CH_2)_rOC(O)R^b$, $(CH_2)_rNR^{11}R^{11}$, $(CH_2)_rC(O)NR^{11}R^{11}$, $(CH_2)_rNR^bC(O)R^c$, $(CH_2)_rNR^bC(O)OR^c$, $NR^bC(O)NR^{11}R^{11}$, $S(O)_pNR^{11}R^{11}$, $NR^bS(O)_pR^c$, $S(O)R^c$, $S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, 0, and $S(O)_p$ substituted with 0-2 R^a;

R^3 is C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{3a}, C_{2-6} alkynyl substituted with 0-3 R^{3a}, C_{3-10}cycloalkyl substituted with 0-3 R^{3a}, C_{6-10} aryl substituted with 0-3 R^{3a}, a 5-10 membered heterocyclyl containing 1-4 heteroatoms

selected from N, O, and S, substituted with 0-3 $R^{3'}$ or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3a};

R^{3a} is hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, $(CH_2)_rOR^b$, $(CH_2)_rSR^b$, $(CH_2)_rC(O)R^b$, $(CH_2)_rC(O)OR^b$, $(CH_2)_rOC(O)R^b$, $(CH_2)_rNR^{11}R^{11}$, $(CH_2)_rC(O)NR^{11}R^{11}$, $(CH_2)_rNR^bC(O)R^c$, $(CH_2)_rNR^bC(O)OR^c$, $NR^bC(O)NR^{11}R^{11}$, $S(O)_pNR^{11}R^{11}$, $NR^bS(O)_pR^c$, $S(O)R^c$, $S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6}haloalkyl, $(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-1 R^a;

R^4 and R^5 are independently selected from hydrogen, C_{1-4} alkyl substituted with 0-1 R^f, (CH_2)-phenyl substituted with 0-3 R^d, and a (CH_2)-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$;

R^6 and R^7 are independently at each occurrence is selected from hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, $(CH_2)_rOR^b$, $(CH_2)_rSR^b$, $(CH_2)_rC(O)R^b$, $(CH_2)_rC(O)OR^b$, $(CH_2)_rOC(O)R^b$, $(CH_2)_rNR^{11}R^{11}$, $(CH_2)_rC(O)NR^{11}R^{11}$, $(CH_2)_rNR^bC(O)R^c$, $(CH_2)_rNR^bC(O)OR^c$, $NR^bC(O)NR^{11}R^{11}$, $S(O)_pNR^{11}R^{11}$, $NR^bS(O)_pR^c$, $S(O)R^c$, $S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6}haloalkyl, $(CH_2)_r$-3-14 membered carbocycle substituted with 0-3 R^a, or $(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a, provided R^6 and R^7 are not both hydrogen;

R^{11} at each occurrence is independently hydrogen, R^e, C_{1-4} alkyl substituted with 0-1 R^f, CH_2-phenyl substituted with 0-3 R^d, or (CH_2)-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^d; or

R^{11} and along with another R^{11}, R^1, or R^2 on the same nitrogen atom may join to form an optionally substituted heterocycle;

R^a is hydrogen, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $(CH_2)_rOR^b$, $(CH_2)_rSR^b$, $(CH_2)_rC(O)R^b$, $(CH_2)_rC(O)OR^b$, $(CH_2)_rOC(O)R^b$, $(CH_2)_rNR^{11}R^{11}$, $(CH_2)_rC(O)NR^{11}R^{11}$, $(CH_2)_rNR^bC(O)R^c$, $(CH_2)_rNR^bC(O)OR^c$, $NR^bC(O)NR^{11}R^{11}$, $S(O)_pNR^{11}R^{11}$, $NR^bS(O)_pR^c$, $S(O)R^c$, $S(O)_2R^c$, C_{1-6} alkyl substituted with 0-1 R^f, C_{1-6} haloalkyl, $(CH_2)_r$-3-14 membered carbocycle, or $(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected

from N, O, and $S(O)_p$; or two R^a on adjacent or the same carbon atom form a cyclic acetal of the formula —O—$(CH_2)_n$—O—, or —O—CF_2—O—, wherein n is selected from 1 or 2;

R^b is hydrogen, R^e, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-3 R^d;

R^c is C_{1-6} alkyl substituted with 0-1 R^f, C_{3-6} cycloalkyl, or $(CH_2)_r$-phenyl substituted with 0-3 R^f;

R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO_2, OR^e, $(CH_2)_rC(O)R^e$, NR^eR^e, $NR^eC(O)OR^e$, C_{1-6} alkyl, or $(CH_2)_r$-phenyl substituted with 0-3 R^f;

R^e is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $(CH_2)_r$-phenyl substituted with 0-3 R^f;

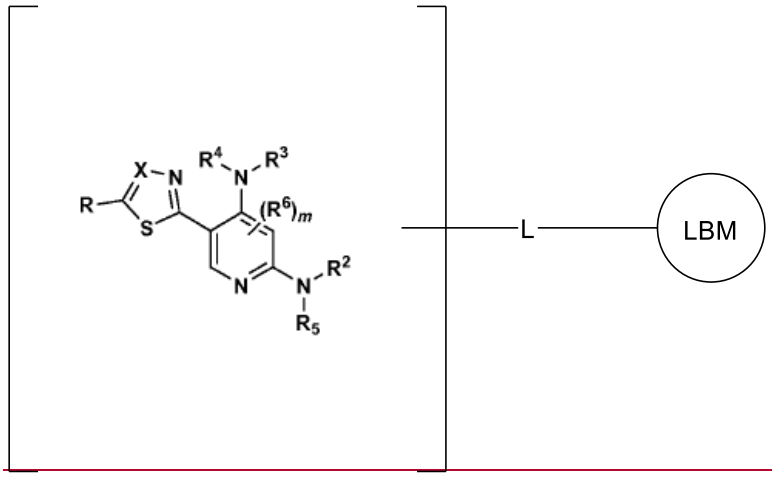
R^f is hydrogen, halo, NH_2, OH, or $O(C_{1-6}$alkyl);

p is 0, 1, or 2;

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

m is 0, 1, or 2; or

(r)



I-uu-1

or a pharmaceutically acceptable salt thereof, wherein:

X is N or C—R^7;

R is R^1, halogen, cyano, nitro, —O—R^1, —C(=O)—R^1, —C(=O)O—R^1, —C(=O)NR^{11}—R^1, —$S(=O)_2$—R^1, —$NR^{11}C(=O)$—R^1, —$NR^{11}C(=O)NR^{11}$—R^1, —$NR^{11}C(=O)O$—R^1, —$NR^{11}S(=O)_2$—R^1, or —NR^{11}—R^1;

R^1 is C_{1-6} alkyl substituted with 0-4 R^{1a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{1a}, C_{2-6} alkynyl substituted with 0-3 R^{1a}, C_{3-10}cycloalkyl substituted with 0-3 R^{1a}, C_{6-10} aryl substituted with 0-3 R^{1a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{1a};

R^{1a} is hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, $(CH_2)_rOR^b$, $(CH_2)_rSR^b$, $(CH_2)_rC(O)R^b$, $(CH_2)_rC(O)OR^b$, $(CH_2)_rOC(O)R^b$, $(CH_2)_rNR^{11}R^{11}$, $(CH_2)_rC(O)NR^{11}R^{11}$, $(CH_2)_rNR^bC(O)R^c$, $(CH_2)_rNR^bC(O)OR^c$, $NR^bC(O)NR^{11}R^{11}$, $S(O)_pNR^{11}R^{11}$, $NR^bS(O)_pR^c$, $S(O)R^c$, $S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $(CH_2)_r$-3-14 membered carbocycle substituted with 0-3 R^a, or $(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$substituted with 0-3 R^a;

R^2 is C_{6-10} aryl substituted with 0-4 R^{2a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-4 R^{2a}, a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-4 R^{2a};

R^{2a} at each occurrence is independently selected from hydrogen, =O, halo, OCF_3, CN, NO_2, $(CH_2)_rOR^b$, $(CH_2)_rSR^b$, $(CH_2)_rC(O)R^b$, $(CH_2)_rC(O)OR^b$, $(CH_2)_rOC(O)R^b$, $(CH_2)_rNR^{11}R^{11}$, $(CH_2)_rC(O)NR^{11}R^{11}$, $(CH_2)_rNR^bC(O)R^c$, $(CH_2)_rNR^bC(O)OR^c$, $NR^bC(O)NR^{11}R^{11}$, $S(O)_pNR^{11}R^{11}$, $NR^bS(O)_pR^c$, $S(O)R^c$, $S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-2 R^a;

R^3 is C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^{3a}, C_{2-6} alkynyl substituted with 0-3 R^{3a}, C_{3-10}cycloalkyl substituted with 0-3 R^{3a}, C_{6-10} aryl substituted with 0-3 R^{3a}, a 5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3a}, or a 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, substituted with 0-3 R^{3a};

R^{3a} is hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, $(CH_2)_rOR^b$, $(CH_2)_rSR^b$, $(CH_2)_rC(O)R^b$, $(CH_2)_rC(O)OR^b$, $(CH_2)_rOC(O)R^b$, $(CH_2)_rNR^{11}R^{11}$, $(CH_2)_rC(O)NR^{11}R^{11}$, $(CH_2)_rNR^bC(O)R^c$, $(CH_2)_rNR^bC(O)OR^c$, $NR^bC(O)NR^{11}R^{11}$, $S(O)_pNR^{11}R^{11}$, $NR^bS(O)_pR^c$, $S(O)R^c$, $S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl,

~~$(CH_2)_r$-3-14 membered carbocycle substituted with 0-1 R^a, or $(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-1 R^a;~~

~~R^4 and R^5 are independently selected from hydrogen, C_{1-4} alkyl substituted with 0-1 R^f, (CH_2)-phenyl substituted with 0-3 R^d, and a (CH_2)-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$;~~

~~R^6 and R^7 are independently at each occurrence is selected from hydrogen, =O, F, Cl, Br, OCF_3, CN, NO_2, $(CH_2)_rOR^b$, $(CH_2)_rSR^b$, $(CH_2)_rC(O)R^b$, $(CH_2)_rC(O)OR^b$, $(CH_2)_rOC(O)R^b$, $(CH_2)_rNR^{11}R^{11}$, $(CH_2)_rC(O)NR^{11}R^{11}$, $(CH_2)_rNR^bC(O)R^c$, $(CH_2)_rNR^bC(O)OR^c$, $NR^bC(O)NR^{11}R^{11}$, $S(O)_pNR^{11}R^{11}$, $NR^bS(O)_pR^c$, $S(O)R^c$, $S(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, $(CH_2)_r$-3-14 membered carbocycle substituted with 0-3 R^a, or $(CH_2)_r$-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a, provided R^6 and R^7 are not both hydrogen;~~

~~R^{11} at each occurrence is independently R^e, C_{1-4} alkyl substituted with 0-1 R^f, CH_2-phenyl substituted with 0-3 R^d, or (CH_2)-5-7 membered heterocycle or heteroaryl, each comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^d;~~

~~alternatively, R^{11} and along with another R^{11}, R^1, or R^2 on the same nitrogen atom may join to form an optionally substituted azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, or 4-(C_{1-6} alkyl)piperazinyl;~~

~~R^a is R^d, F, Cl, Br, OCF_3, CF_3, CHF_2, CN, NO_2, $(CH_2)_rOR^b$, $(CH_2)_rSR^b$, $(CH_2)_rC(O)R^b$, $(CH_2)_rC(O)OR^b$, $(CH_2)_rOC(O)R^b$, $(CH_2)_rNR^{11}R^{11}$, $(CH_2)_rC(O)NR^{11}R^{11}$, $(CH_2)_rNR^bC(O)R^c$, $(CH_2)_rNR^bC(O)OR^c$, $NR^bC(O)NR^{11}R^{11}$, $S(O)_pNR^{11}R^{11}$, $NR^bS(O)_pR^c$, $S(O)_2R^c$, $S(O)_2R^c$, C_{1-6} alkyl substituted with 0-1 R^f, C_{1-6} haloalkyl, $(CH_2)_r$-3-14 membered carbocycle, or $(CH_2)_r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$; alternatively two R^a on adjacent or the same carbon atom form a cyclic acetal of the formula $-O-(CH_2)_n-O-$, or $-O-CF_2-O-$, wherein n is selected from 1 or 2;~~

~~R^b is R^e, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C_{3-6}cycloalkyl substituted with 0-2 R^d, or $(CH_2)_r$-phenyl substituted with 0-3 R^d;~~

~~R^c is C_{1-6} alkyl substituted with 0-1 R^f, C_{3-6} cycloalkyl, or $(CH_2)_r$ phenyl substituted with 0-3 R^f;~~

~~R^d is hydrogen, F, Cl, Br, OCF_3, CF_3, CN, NO_2, OR^e, $(CH_2)_rC(O)R^e$, NR^eR^e, $NR^eC(O)OR^e$, C_{1-6} alkyl, or $(CH_2)_r$ phenyl substituted with 0-3 R^f;~~

~~R^e is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $(CH_2)_r$ phenyl substituted with 0-3 R^f;~~

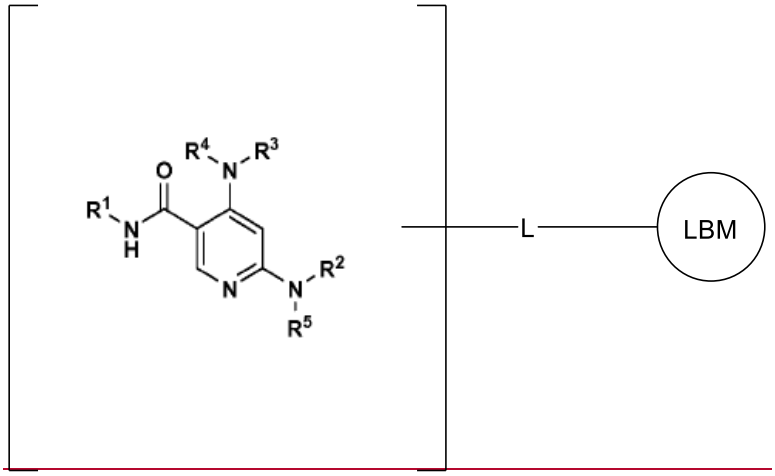
~~R^f is hydrogen, halo, NH_2, OH, or $O(C_{1-6}$alkyl);~~

~~p is 0, 1, or 2;~~

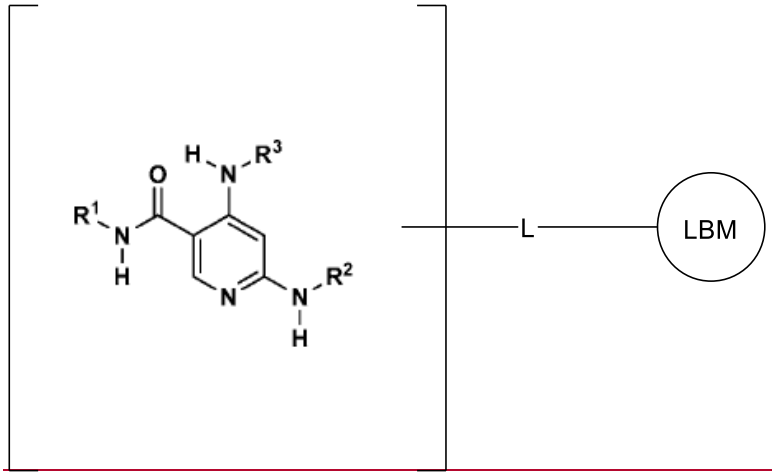
~~r is 0, 1, 2, 3, or 4; and~~

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

~~(s)~~



~~I-vv-1~~



~~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), $(CH_2)_2CH(CH_3)NHC(O)(C_{1-6}$alkyl), $(CH_2)_2CH(CH_3)NHC(O)(CH_2)_{0-1}NH(C_{1-6}$ alkyl), or $(CH_2)_2CH(CH_3)NHC(O)(CH_2)_{0-1}N(C_{1-4}$ 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

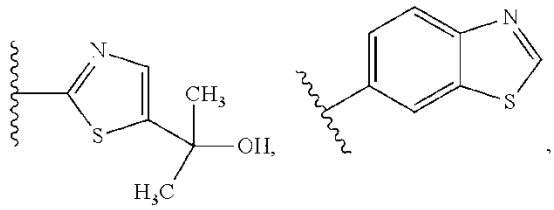
R^3 is:

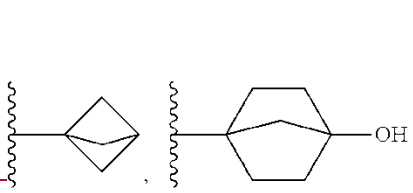
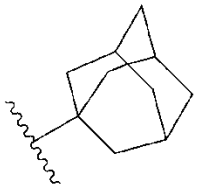
(a) C_{1-6} alkyl substituted with zero to 4 substituents independently selected from F, OH, CH_3, CF_3, and C_{3-6}cycloalkyl;

(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 $C(O)OCH_2CH_3$;

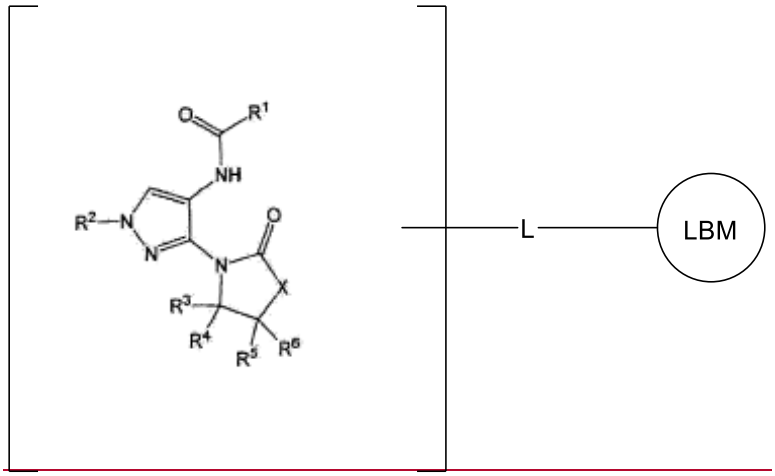
(c) oxetanyl, tetrahydropyranyl, or fluoro tetrahydropyranyl;

(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)  , or  ; or

(f)



I xx-1

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is an optionally substituted aromatic heterocyclic group or an optionally substituted C_{6-14} aryl group;

R^2 is a hydrogen atom or a substituent;

R^3 and R^4 are independently a hydrogen atom or a substituent, or R^3 and R^4 in combination optionally form an optionally substituted ring;

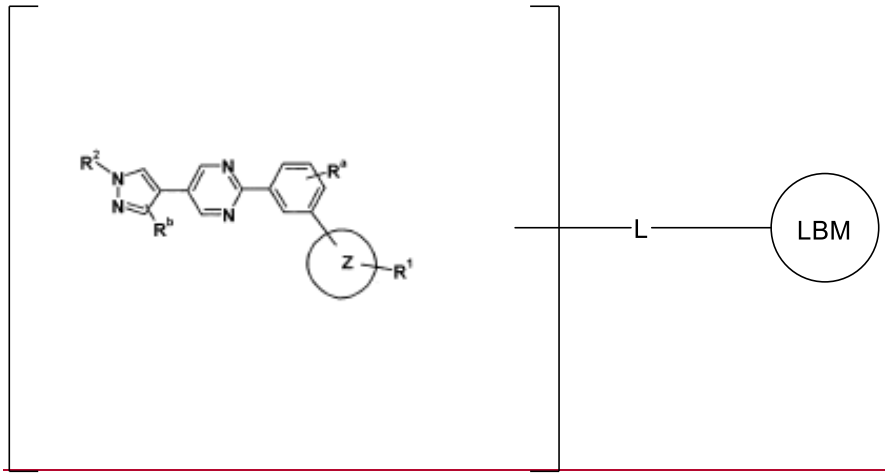
R^5 and R^6 are independently a hydrogen atom or a substituent, or R^5 and R^6 in combination optionally form an optionally substituted ring;

X is CR^7R^8, NR^9, O or S;

R^7 and R^8 are independently a hydrogen atom or a substituent, or R^7 and R^8 in combination optionally form an optionally substituted ring; and

R^9 is a hydrogen atom or a substituent; or

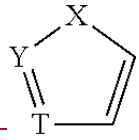
(u)



I-zz-1

or a pharmaceutically acceptable salt thereof, wherein:

R^1 denotes absent, A or Q-Het,

Z is 

wherein

X denotes O, S or N,

Y denotes C or N,

T denotes C or N, or

Z denotes a pyridine or a pyridazine group,

R^a is absent, OR^3, CF_3, Hal, or NO_2,

R^b is absent, A, or COHet,

R^2 denotes H, Het, Q-Het, Cyc, A or OA,

each Het is independently a 4-9 membered monocyclic ring or a fused, spiro or bridged bicyclic ring, which is saturated, unsaturated, or aromatic, which contains 1 to 3 heteroatoms independently selected from N, O, and S, and a group CO, SO or SO_2, and wherein 1 or 2 H atoms may be replaced by A, OA, COA, CN, Hal, NO_2, OR^3, SOA and/or SO_2A,

Cyc denotes a 4-8 saturated carbocyclic ring optionally containing a group SO, SO_2, or CO, and optionally substituted once or twice by a group selected from $CO(NR^3)_2$, COHet, OR^3, Het^1, A, CH_2Het^1, NH_2, NHCOA, OCH_2Cyc^1, SO_2A and =SA(=NH)(=O),

each Q is independently a linear or branched alkylene, having 1 to 6 carbon atoms wherein 1-5 H atoms may be replaced by a group independently selected from OR^3, Hal, and $N(R^3)_2$, and wherein 1 or 2 CH_2 groups may be replaced by a group independently selected from CO, SO, SO_2 and NR^3, or Q denotes a 4-8-membered bivalent heterocyclic ring, which is saturated, unsaturated or aromatic and which contains 1 to 3 heteroatoms independently selected from N, O and S,

each A is independently a linear or branched alkyl having 1 to 10 carbon atoms wherein 1 to 7 H atoms may be replaced by a group independently selected from =O, OR^3, Hal, $NHSO_2A$, SO_2A, SOA, and $N(R^3)_2$, and wherein 1, 2 or 3 non-adjacent CH_2 groups may be replaced by a group independently selected from CO, NR^3 and O,

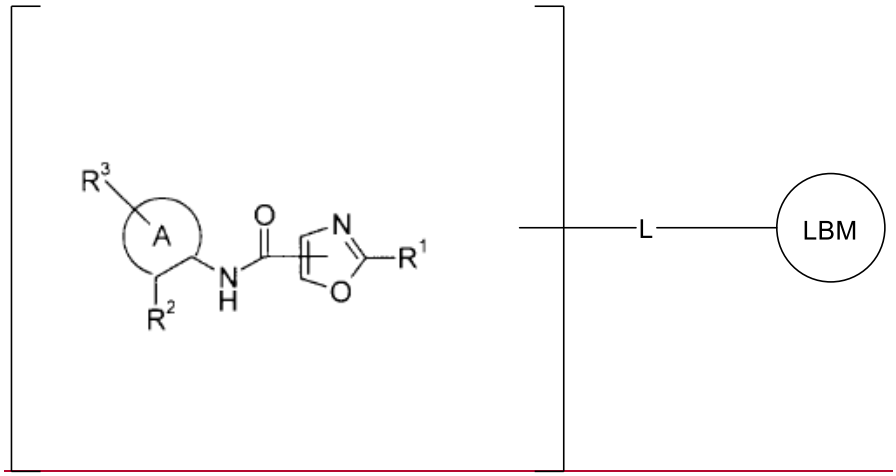
each Hal is independently F, Cl, Br or I,

each R^3 is independently H or C_1-C_6-alkyl wherein 1 H atom may be replaced by a group selected from OH, O C_1-C_6-alkyl, and Hal,

each Het^1 is independently a five- or six-membered saturated monocyclic heterocycle which contains 1-3 N- and/or O-atoms, which optionally is monosubstituted by A,

Cyc^1 denotes cycloalkyl with 3-7 atoms; or

(v)



I-aaa-1

or a pharmaceutically acceptable salt thereof, wherein:

~~Ring A is a monocyclic heteroaryl;~~

~~R^1 is one to three optionally substituted with R^{10} monocyclic or bicyclic heteroaryl;~~

~~R^2 is, $-C(O)NH_2$, $-C(O)NH-R^0$, $-C(O)NH-R^{00}-OH$, $-C(O)NH-R^{00}-OR^0$, $-C(O)N(R^0)_2$, $-C(O)NH$-cycloalkyl, $-C(O)NH$-heterocycloalkyl, $-C(O)NH$-(pyrazolyl optionally substituted with R^0), $-C(O)-R^0$, $-C(O)$-cycloalkyl, $-S(O)_2NH_2$, $-S(O)_2NH-R^0$, $-S(O)_2NH$-cycloalkyl, $-R^{00}-OH$, $-R^{00}-OR^0$, $-R^{00}$-(morpholin-4-yl)-phenyl, oxadiazolyl, or tetrazolyl optionally substituted with R^0, wherein oxadiazolyl in R^2 is, R^0, R^{00}-OH or may be substituted with R^0-OR^0;~~

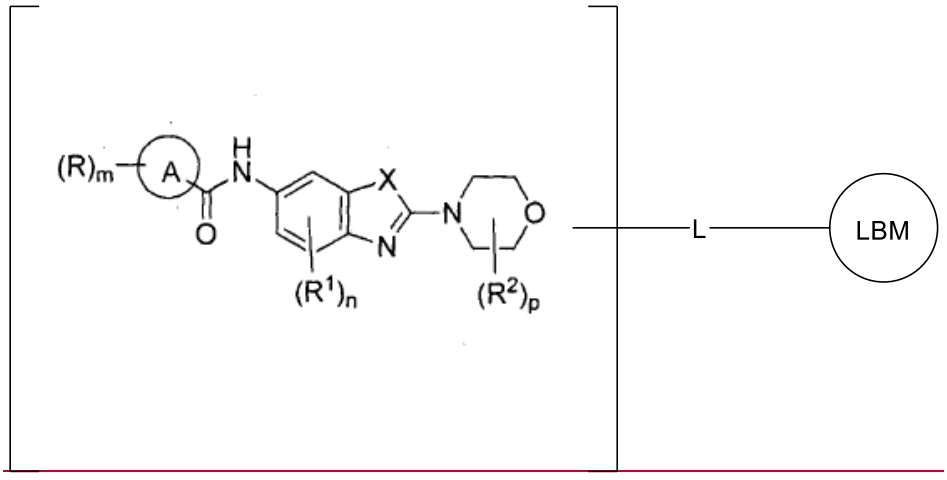
~~R^3 is, H, R^0, halogeno-lower alkyl, cycloalkyl, heterocycloalkyl, phenyl, pyridyl, pyrimidinyl, pyrazinyl, $-C(O)N(R^0)_2$, $-R^{00}$-cycloalkyl, $-R^{00}$-heterocycloalkyl, $-R^{00}$-phenyl, $-R^{00}$-OH or a $-R^{00}-OR^0$, wherein the cycloalkyl in R^3, heterocycloalkyl, phenyl and pyridyl, R^0, halogen, $-C(O)OR^0$, $-C(O)-R^0$, $-OH$, $-OR^0$, $-S(O)_2-R^0$, -O-halogeno-lower alkyl, $-OR^{00}$-(morpholin-4-yl), $-R^{00}$-OH, $-R^{00}-OR^0$, morpholin-4-yl or, $-R^{00}$-(morpholin-4-yl) may be substituted;~~

~~R^{10} may be the same or different from each other, R^0, halogen, halogeno-lower alkyl, cycloalkyl, $-OR^0$, optionally substituted amino, -O-halogeno-lower alkyl, $-R^{00}$-OH, $-R^{00}-OR^0$ or, $-R^{00}$- is optionally amino substituted,~~

~~R^0 is the same or different from each other, lower alkyl,~~

~~R^{00} are identical or different from each other, it is a lower alkylene; or~~

~~(w)~~



~~I-bbb-1~~

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

X is selected from O, S, and NH;

A is selected from aryl or heteroaryl;

R at each occurrence is independently selected from hydrogen, cyano, halo, hydroxy, $-NO_2$, $-NR^3R^4$, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyi, optionally substituted heterocycloalkyl or optionally substituted heteroaryl; wherein the optional substituent, in each occurrence, is independently selected from halo, alkyl, haloalkyl, cyano, $-NR^5R^6$ or $-COOR^7$;

R^1 at each occurence is independently selected from hydrogen, halogen, alkyl, aryl, heterocycloalkyl, heterocycloalkylalkyi, heteroaryl, Y-arylalkyl or -Y-cycloalkyl; wherein cycloalkyi, aryl, heterocycloalkyl, heterocycloalkylalkyi, heteroaryl and arylalkyl can be optionally substituted with hydroxy, alkyl, haloalkyl, cyano or halo;

Y is selected from direct bond, O, -C(O)- or NR^7;

R^2 at each occurence is independently selected from hydrogen, carboxy, cyano, hydroxy, hydroxyalkyl, alkyl, aryl, heteroaryl, $-SO^2R^5$ or oxo;

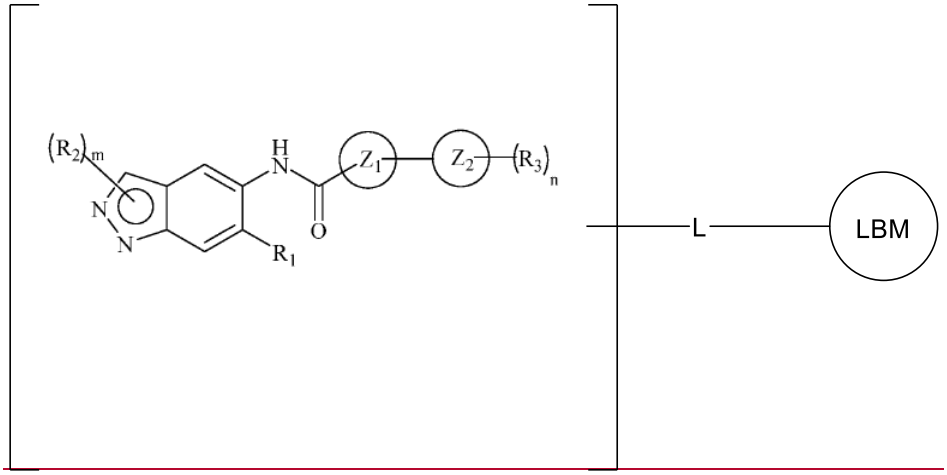
R^3 and R^4 are independently selected from hydrogen, hydroxyalkyl, aminoalkyl, optionally substituted alkyl, optionally substituted heterocyclyl, optionally substituted aryl; wherein the optional substituent, in each occurrence, is independently selected from halo, haloalkyl or $-COOR^7$;

R^5 and R^6 are independently selected from hydrogen, alkyl, COR^7 or $-COOR^7$;

R^7 at each occurrence is independently selected from hydrogen or alkyl; and

m, n and p are selected from 1, 2 or 3; or

(x)



I-ccc-1

or a pharmaceutically acceptable salt thereof, wherein:

Ring Z_1 is an optionally substituted heteroaryl;

Ring Z_2 is an optionally substituted heterocycloalkyl, optionally substituted heteroaryl or a direct bond;

R_1 is alkyl, cyano, $-NR_aR_b$ or optionally substituted groups selected from cycloalkyl, aryl or heterocyclyl; wherein the substituent, at each occurrence, independently is alkyl, alkoxy, halogen, hydroxyl, hydroxyalkyl, amino, aminoalkyl, nitro, cyano, haloalkyl, haloalkoxy, $-OCO-CH_2-O$-alkyl, $-OP(O)(O\text{-alkyl})_2$ or $-CH_2-OP(O)(O\text{-alkyl})_2$;

R_2, at each occurrence, independently is an optionally substituted group selected from alkyl or cycloalkyl; wherein the substituent, at each occurrence, is independently halogen, alkoxy, hydroxyl, hydroxyalkyl, haloalkyl or haloalkoxy;

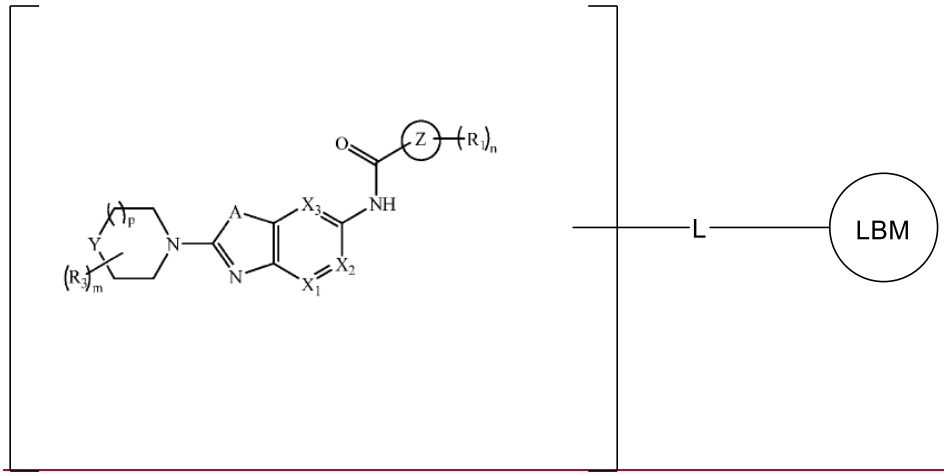
R_3, at each occurrence, independently is hydrogen, halogen, alkyl, haloalkyl, haloalkoxy, alkoxy, $-NR_aR_b$, hydroxyl or hydroxyalkyl;

R_a is hydrogen or alkyl;

R_b is hydrogen, alkyl, acyl, hydroxyalkyl, $-SO_2$-alkyl or optionally substituted cycloalkyl;

'm' and 'n' are independently 1 or 2; or

(y)



I-ddd-1

or a pharmaceutically acceptable salt thereof, wherein:

X_1 and X_3 independently are CH or N; X_2 is CR_2 or N; provided one and not more than one of X_1, X_2 or X_3 is N;

A is O or S;

Y is CH_2 or O;

Ring Z is aryl or heterocyclyl;

R_1, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or NR_aR_b;

R_2 is hydrogen, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or NR_aR_b; wherein the substituent is alkyl, amino, halo or hydroxyl;

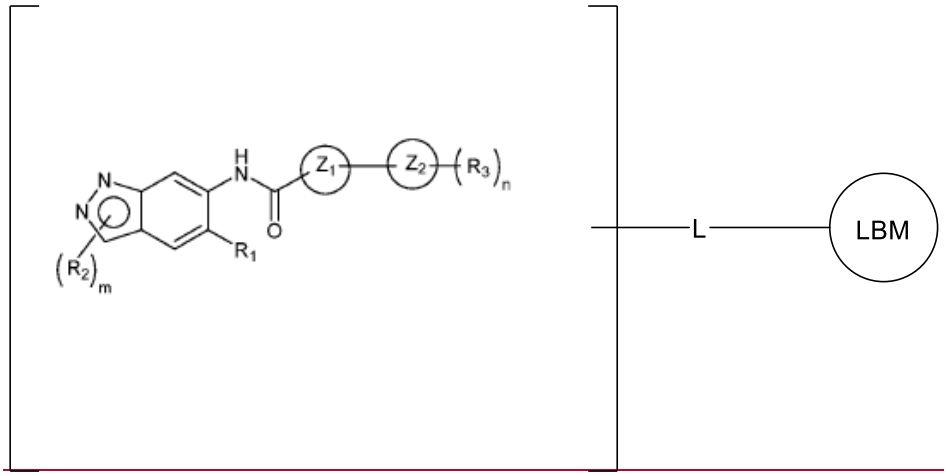
R_3, at each occurrence, is alkyl or hydroxyl;

R_a and R_b are independently hydrogen, alkyl, acyl or heterocyclyl;

m and n are independently 0, 1 or 2;

p is 0 or 1; or

(z)



I-ccc-1

or a pharmaceutically acceptable salt thereof, wherein:

Z_1 is optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or is absent;

Z_2 is optionally substituted cycloalkyl, aryl or heterocyclyl;

R_1 is hydrogen, optionally substituted alkyl, amino, halogen, cyano, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted arylalkyl or optionally substituted heterocyclylalkyl;

R_2 at each occurrence is hydrogen, halogen, amino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted arylalkyl or optionally substituted heterocyclylalkyl;

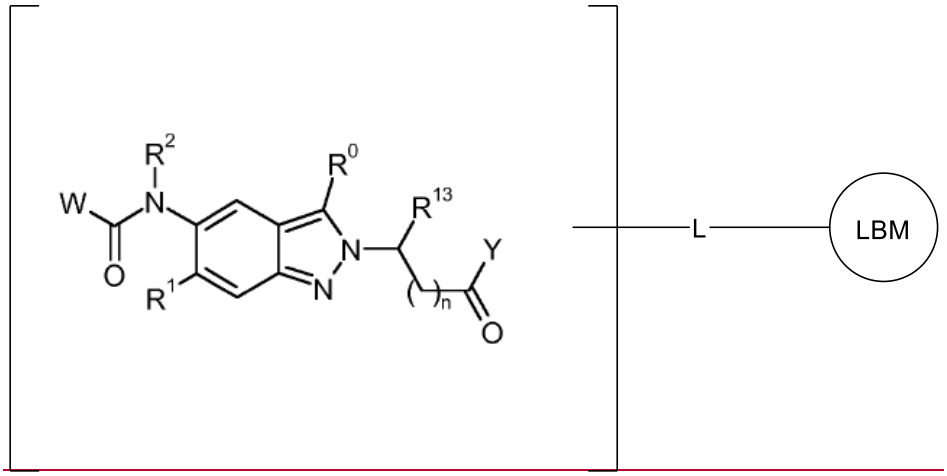
R_3 at each occurrence is hydroxy, halogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl or $-NR_aR_b$;

R_a and R_b, independently for each occurrence, are hydrogen, optionally substituted alkyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted arylalkyl or optionally substituted heterocyclylalkyl;

m at each occurrence, is 0, 1 or 2; and

n at each occurrence, is 0, 1, or 2; or

(aa)



I-fff-1

or a pharmaceutically acceptable salt thereof, wherein:

R^0 represents hydrogen or C_1-C_4-alkyl, where the C_1-C_4-alkyl radical may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy and halogen;

R^1 represents hydrogen, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $C(=O)NH_2$, $C(=O)N(H)R^a$, $C(=O)N(R^a)R^b$, $C(=O)R^d$, hydroxy or C_1-C_6-alkyl, where the C_1-C_6-alkyl radical is optionally mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$ C_1-C_6-alkyl, NH_2, NHR^a, $N(R^a)R^b$, C_1-C_6-alkoxy which is optionally mono- or polysubstituted by

identical or different radicals from the group consisting of halogen, C_3-C_8-cycloalkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, heterocycloalkyl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^e,

or represents C_1-C_6-alkoxy, where the C_1-C_6-alkoxy radical may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$-C_1-C_6-alkyl, NH_2, NHR^a, $N(R^a)R^b$, C_3-C_8-cycloalkyl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_1-C_6-alkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_3-C_8-cycloalkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, heterocycloalkyl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^e, aryl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^e, or 5- or 6-membered heteroaryl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^e,

or represents C_3-C_8-cycloalkoxy or heterocycloalkoxy which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1-C_6-alkyl,

or represents aryloxy or 5- or 6-membered heteroaryloxy in which aryloxy and 5- or 6-membered heteroaryloxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, C_1-C_6-alkyl and C_1-C_6-alkoxy,

or represents C_3-C_8-cycloalkyl or heterocycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1-C_6-alkyl,

or represents C_2-C_6-alkenyl or C_2-C_6-alkynyl,

or represents aryl, 5- to 10-membered heteroaryl, aryl-C_1-C_4-alkyl or 5- or 6-membered heteroaryl-C_1-C_4-alkyl, where aryl and heteroaryl may optionally be mono- or

polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C(=O)OH, C(=O)OR^a, C_1-C_6-alkyl, C_3-C_8-cycloalkyl and C_1-C_6-alkoxy;

R^a represents C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, heterocycloalkyl, aryl or heteroaryl, where alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C_1-C_3-alkyl, C_1-C_3-alkoxy, heterocycloalkyl, C(=O)O C_1-C_6-alkyl and S(=O)$_2$ C_1-C_6-alkyl;

R^b represents C_1-C_6-alkyl or C_3-C_{10}-cycloalkyl;

or R^a and R^b together with the nitrogen atom form a 5- or 6-membered heterocycle which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, and C_1-C_6-alkyl;

R^c represents hydroxy, halogen, cyano, C_1-C_3-alkyl or C_1-C_3-alkoxy;

R^d represents hydrogen, C_1-C_6-alkyl or C_3-C_{10}-cycloalkyl;

R^2 represents hydrogen, C_1-C_6-alkyl or C_3-C_6-cycloalkyl;

R^{13} represents hydrogen or C_1-C_6-alkyl;

W represents 5-membered heteroaryl which contains one to three heteroatoms selected from the group consisting of N, O and S and may optionally be monosubstituted by R^3 and optionally be mono- or polysubstituted by identical or different radicals R^4 or

W represents pyridyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl or 1,3,5-triazinyl which may optionally be monosubstituted by R^3 and optionally be mono- or polysubstituted by identical or different radicals R^4;

R^3 represents hydrogen, halogen, cyano, C(=O)R^a, NH_2, NHR^a, N(R^a)R^b, N(H)C(=O)R^a or C_1-C_6-alkyl,

where C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)R^a, C(=O)OH, C(=O)OR^a, S(=O)$_2$ C_1-C_6-alkyl, NH_2, NHR^a, N(R^a)R^b, C_1-C_6-alkoxy, C_3-C_8-cycloalkoxy,

where C_1-C_6-alkoxy and C_3-C_8-cycloalkoxy may optionally be mono- or polysubstituted by identical or different halogen radicals;

or C_1-C_6-alkyl is optionally mono- or polysubstituted by identical or radicals from the group consisting of C_3-C_6-cycloalkyl and heterocycloalkyl,

where C_3-C_6-cycloalkyl and heterocycloalkyl may optionally be mono-, di- or trisubstituted by identical or different radicals from the group consisting of halogen, cyano, C_1-C_3-alkyl and C_1-C_3-alkoxy,

or C_1-C_6-alkyl is optionally mono- or polysubstituted by identical or different radicals from the group consisting of aryl and 5- or 6-membered heteroaryl,

where aryl and 5- or 6-membered heteroaryl may optionally be mono-, di- or trisubstituted by identical or different radicals from the group consisting of halogen, cyano, C_1-C_3-alkyl and C_1-C_3-alkoxy,

or R^3 represents C_1-C_6-alkoxy,

where C_1-C_6-alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_3-C_8-cycloalkyl, C_1-C_4-alkoxy, C_3-C_8-cycloalkoxy,

or represents C_3-C_6-cycloalkyl, heterocycloalkyl or C_5-C_{11}-spirocycloalkyl, where cycloalkyl, heterocycloalkyl and spirocycloalkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)R^a$, $C(=O)OH$, $C(=O)OR^a$, C_1-C_6-alkyl and C_1-C_4-alkoxy;

or represents aryl or 5- to 10-membered heteroaryl,

where aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, NO_2, NH_2, NHR^a, $N(R^a)R^b$, $N(H)C(=O)R^a$, C_3-C_8-cycloalkyl, C_1-C_3-alkoxy and C_1-C_3-alkyl, where

C_1-C_3-alkyl may optionally be mono- or polysubstituted by identical or different halogen radicals;

R^4 represents halogen, hydroxy, cyano or C_1-C_6-alkyl, where C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_1-C_6-alkoxy, where C_1-C_6-alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{10}-cycloalkyl, 3- to 10-membered heterocycloalkyl and aryl, where aryl may optionally be mono- or polysubstituted by identical or different radicals R;

or R^4 represents aryl or heteroaryl which may optionally be mono- or polysubstituted by identical or different radicals R;

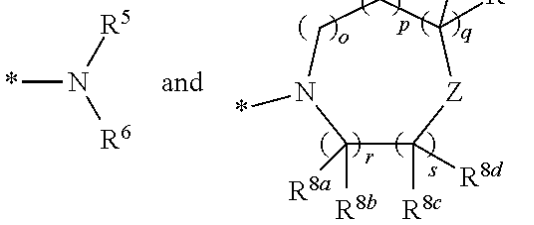
or R^4 represents $C(=O)R^a$, $C(=O)NH_2$, $C(=O)N(H)R^a$, $C(=O)N(R^a)R^b$, $C(=O)OR^a$, NH_2, NHR^a, $N(R^a)R^b$, $N(H)C(=O)R^a$, $N(R^a)C(=O)R^a$, $N(H)C(=O)NH_2$, $N(H)C(=O)NHR^a$, $N(H)C(=O)N(R^a)R^b$, $N(R^a)C(=O)NH_2$, $N(R^a)C(=O)NHR^a$, $N(R^a)C(=O)N(R^a)R^b$, $N(H)C(=O)OR^a$, $N(R^a)C(=O)OR^a$, NO_2, $N(H)S(=O)R^a$, $N(R^a)S(=O)R^a$, $N(H)S(=O)_2R^a$, $N(R^a)S(=O)_2R^a$, $N=S(=O)(R^a)R^b$, $OC(=O)R^a$, $OC(=O)NH_2$, $OC(=O)NHR^a$, $OC(=O)N(R^a)R^b$, SH, SR^a, $S(=O)R^a$, $S(=O)_2R^a$, $S(=O)_2NH_2$, $S(=O)_2NHR^a$, $S(=O)_2N(R^a)R^b$ or $S(=O)(=N-R^a)R^b$;

R represents halogen, cyano, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{10}-cycloalkyl, 3- to 10-membered heterocycloalkyl, aryl, heteroaryl, $C(=O)R^a$, $C(=O)NH_2$, $C(=O)N(H)R^a$, $C(=O)N(R^a)R^b$, $C(=O)OR^a$, NH_2, NHR^a, $N(R^a)R^b$, $N(H)C(=O)R^a$, $N(R^a)C(=O)R^a$, $N(H)C(=O)NH_2$, $N(H)C(=O)NHR^a$, $N(H)C(=O)N(R^a)R^b$, $N(R^a)C(=O)NH_2$, $N(R^a)C(=O)NHR^a$, $N(R^a)C(=O)N(R^a)R^b$, $N(H)C(=O)OR^a$, $N(R^a)C(=O)OR^a$, NO_2, $N(H)S(=O)R^a$, $N(R^a)S(=O)R^a$, $N(H)S(=O)_2R^a$, $N(R^a)S(=O)_2R^a$, $N=S(=O)(R^a)R^b$, OH, C_1-C_6-alkoxy, $OC(=O)R^a$, $OC(=O)NH_2$, $OC(=O)NHR^a$, $OC(=O)N(R^a)R^b$, SH, SR^a, $S(=O)R^a$, $S(=O)_2R^a$, $S(=O)_2NH_2$, $S(=O)_2NHR^a$, $S(=O)_2N(R^a)R^b$ or $S(=O)(=NR^a)R^b$;

n represents 0 or 1;

Y represents a group selected from:

(II)



where * represents the point of attachment of the group to the remainder of the molecule;

R^5 represents hydrogen, C_1-C_6-alkyl or C_3-C_{10}-cycloalkyl, where

C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$-C_1-C_6-alkyl, $N(R^a)R^b$, C_1-C_4-alkoxy and C_3-C_8-cycloalkyl;

R^6 represents hydrogen or C_1-C_6-alkyl, where

C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C_3-C_{10}-cycloalkyl, $C(=O)R^a$,

~~C(=O)OH, C(=O)OR^{a}, S(=O)$_2$—C$_1$-C$_6$-alkyl, N(R^{a})R^{b}, C$_1$-C$_4$-alkoxy and C$_3$-C$_8$-cycloalkoxy, or represents C$_3$-C$_{10}$-cycloalkyl, where~~

~~C$_3$-C$_{10}$-cycloalkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C$_1$-C$_6$-alkyl, where~~

~~C$_1$-C$_6$-alkyl may optionally be substituted by hydroxy, or represents heterocycloalkyl, where~~

~~heterocycloalkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, cyano, C$_1$-C$_3$-alkyl and C$_1$-C$_3$-alkoxy, or represents aryl or 5- or 6-membered heteroaryl, where~~

~~aryl and 5- or 6-membered heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, cyano, C$_1$-C$_3$-alkyl, C$_1$-C$_3$-alkoxy, S(=O)$_2$NH$_2$, S(=O)$_2$NHR^{a} and S(=O)$_2$N(R^{a})R^{b};~~

~~R^{7a} represents hydrogen, halogen, N(R^{a})R^{b}, C$_1$-C$_6$-alkyl or C$_3$-C$_{10}$-cycloalkyl, where C$_1$-C$_6$-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^{a}, S(=O)$_2$—C$_1$-C$_6$-alkyl, N(R^{a})R^{b}, C$_1$-C$_4$-alkoxy, C$_3$-C$_8$-cycloalkyl and heterocycloalkyl;~~

~~R^{7b} represents hydrogen, halogen or C$_1$-C$_6$-alkyl, where C$_1$-C$_6$-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^{a}, S(=O)$_2$—C$_1$-C$_6$-alkyl, N(R^{a})R^{b}, C$_1$-C$_4$-alkoxy, C$_3$-C$_8$-cycloalkyl and heterocycloalkyl;~~

~~or R^{7a} and R^{7b} together with the carbon atom form C$_3$-C$_6$-cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C$_1$-C$_6$-alkyl,~~

~~or R^{7a} and R^{7b} together represent an oxo group;~~

~~R^{7c} represents hydrogen, halogen, N(R^{a})R^{b}, C$_1$-C$_6$-alkyl or C$_3$-C$_{10}$-cycloalkyl, where~~

~~C$_1$-C$_6$-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^{a}, S(=O)$_2$—C$_1$-C$_6$-alkyl, N(R^{a})R^{b}, C$_1$-C$_4$-alkoxy, C$_3$-C$_8$-cycloalkyl and heterocycloalkyl;~~

~~R^{7d} represents hydrogen, halogen or C$_1$-C$_6$-alkyl, where~~

~~C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)$_2$-C_1-C_6-alkyl, N(R^a)R^b, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl and heterocycloalkyl;~~

~~or R^{7c} and R^{7d} together with the carbon atom form C_3-C_6-cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1-C_6-alkyl,~~

~~or R^{7c} and R^{7d} together represent an oxo group;~~

~~R^{8a} represents hydrogen, halogen, N(R^a)R^b, C_1-C_6-alkyl or C_3-C_{10}-cycloalkyl, where~~

~~C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)$_2$-C_1-C_6-alkyl, N(R^a)R^b, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl and heterocycloalkyl;~~

~~R^{8b} represents hydrogen, halogen or C_1-C_6-alkyl, where~~

~~C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)$_2$-C_1-C_6-alkyl, N(R^a)R^b, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl and heterocycloalkyl;~~

~~or R^{8a} and R^{8b} together with the carbon atom form C_3-C_6-cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1-C_6-alkyl,~~

~~R^{8c} represents hydrogen, halogen, N(R^a)R^b, C_1-C_6-alkyl or C_3-C_{10}-cycloalkyl, where~~

~~C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)$_2$-C_1-C_6-alkyl, N(R^a)R^b, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl and heterocycloalkyl;~~

~~R^{8d} represents hydrogen, halogen or C_1-C_6-alkyl, where~~

~~C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)$_2$-C_1-C_6-alkyl, N(R^a)R^b, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl and heterocycloalkyl;~~

~~or R^{8c} and R^{8d} together with the carbon atom form C_3-C_6-cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1-C_6-alkyl,~~

~~or R^{8c} and R^{8d} together represent an oxo group;~~

~~o represents 0, 1 or 2,~~

p represents 0, 1 or 2,

q represents 0, 1 or 2,

r represents 0, 1 or 2,

s represents 0, 1 or 2,

where o, p, q, r and s do not simultaneously represent 0;

Z represents a group selected from C(=O), CR^9R^{10}, NR^{11}, O, S, S(=O) and $S(=O)_2$;

R^9 represents hydrogen or C_1-C_6-alkyl,

R^{10} represents hydrogen, halogen, cyano, $C(=O)R^a$, C(=O)OH, $C(=O)OR^a$, $C(=O)NH_2$, $C(=O)N(H)R^a$, $C(=O)N(R^a)R^b$, $N(H)C(=O)R^a$, $N(R^b)C(=O)R^a$, $S(=O)_2R^a$, hydroxy, $N(R^a)R^b$ and C_1-C_6-alkyl, where

C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)R^a$, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$, C_1-C_6-alkyl, $N(R^a)R^b$, C_1-C_4-alkoxy and C_3-C_8-cycloalkoxy, or represents C_1-C_6-alkoxy, where

C_1-C_6-alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$, C_1-C_6-alkyl, $N(R^a)R^b$, C_3-C_8-cycloalkyl, C_1-C_4-alkoxy, C_3-C_8-cycloalkoxy, heterocycloalkyl, aryl and 5- or 6-membered heteroaryl, where

aryl and 5- or 6-membered heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, cyano, C_1-C_3-alkyl and C_1-C_3-alkoxy, or represents aryloxy or 5- or 6-membered heteroaryloxy in which aryloxy and 5- or 6-membered heteroaryloxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, C_1-C_3-alkyl and C_1-C_3-alkoxy,

or represents C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_4-alkyl, heterocycloalkyl or heterocycloalkyl-C_1-C_4-alkyl, which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)R^a$, C(=O)OH, $C(=O)OR^a$, C_1-C_6-alkyl and C_1-C_6-alkoxy, where

C_1-C_6-alkoxy may optionally be mono- or polysubstituted by identical or different halogen radicals or an oxo group;

or represents C_2-C_6-alkenyl or C_2-C_6-alkynyl,

~~or represents aryl, 5- to 10-membered heteroaryl, aryl-C_1-C_4-alkyl or 5- or 6-membered heteroaryl-C_1-C_4-alkyl, where~~

~~aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C(=O)OH, C(=O)OR^a, NHR^a, $N(R^a)R^b$, C_1-C_3-alkyl, C_3-C_8-cycloalkyl and C_1-C_3-alkoxy;~~

~~or R^9 and R^{10} together with the carbon atom form C_3-C_8-cycloalkyl or a 4- to 6-membered heterocycle, where~~

~~the C_3-C_8-cycloalkyl radical or the 4- to 6-membered heterocycle may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C_1-C_6-alkyl, C(=O)R^a and an oxo group;~~

~~R^{11} represents hydrogen, C(=O)R^a, C(=O)OR^a, $C(=O)NH_2$, C(=O)N(H)R^a, C(=O)$N(R^a)R^b$, $S(=O)_2R^a$, $S(=O)_2N(R^a)R^b$ or C_1-C_6-alkyl, where~~

~~C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)R^a, C(=O)OR^a, $C(=O)NH_2$, C(=O)N(H)R^a, C(=O)$N(R^a)R^b$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_3-C_8-cycloalkyl, C_1-C_4-alkoxy and C_3-C_8-cycloalkoxy, where~~

~~C_3-C_8-cycloalkyl, C_1-C_4-alkoxy and C_3-C_8-cycloalkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy and halogen;~~

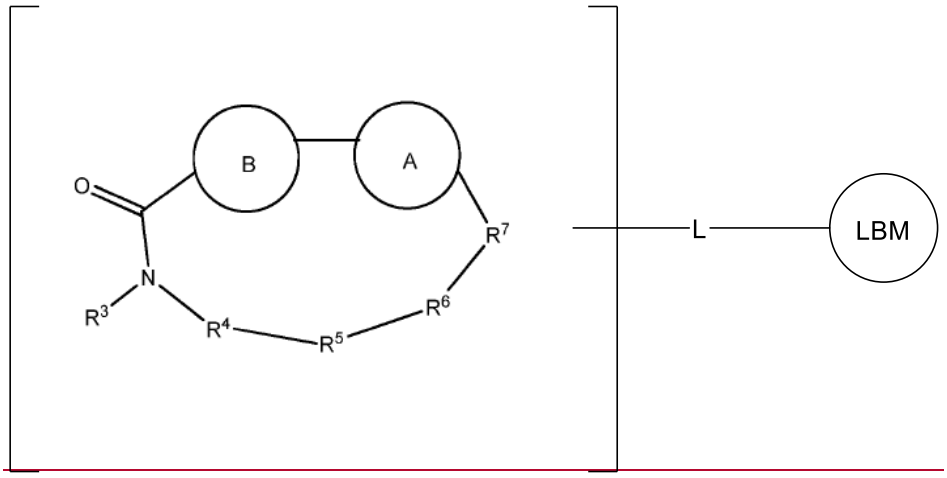
~~or represents C_3-C_8-cycloalkyl, heterocycloalkyl or heterocycloalkyl-C_1-C_4-alkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C_1-C_6-alkyl, C_1-C_6-alkoxy, where alkyl and alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen and an oxo group,~~

~~or represents C_2-C_6-alkenyl or C_2-C_6-alkynyl,~~

~~or represents aryl, 5- to 10-membered heteroaryl, aryl-C_1-C_4-alkyl or 5- or 6-membered heteroaryl-C_1-C_4-alkyl, where~~

~~aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C(=O)OH, C(=O)OR^a, C_1-C_3-alkyl, C_3-C_8-cycloalkyl and C_1-C_3-alkoxy; or~~

~~(bb)~~



~~I-ggg-1~~

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

~~Ring A is phenylene or 5- to 6-membered heteroarylene containing 1-3 heteroatoms chosen from O, S, and N, wherein ring A is optionally substituted with lower alkyl that is further optionally substituted,~~

~~Ring B is phenylene, 5- to 6-membered heterocycloalkylene containing 1-3 heteroatoms chosen from O, S, and N, or 5- to 6-membered heteroarylene containing 1-3 heteroatoms chosen from O, S, and N, wherein ring B is optionally substituted with lower alkyl that is further optionally substituted,~~

~~R^3 is chosen from hydrogen, lower alkyl optionally substituted with alkoxy, amino, N-(alkyl)amino, N,N-(dialkyl)amino, or phenyl, heterocycloalkyl, and heteroaryl,~~

~~wherein phenyl, heterocycloalkyl, and heteroaryl are optionally substituted with one or two groups independently chosen from lower alkyl and wherein alkoxy is optionally substituted with tri(alkyl)silyl,~~

~~R^4 is chosen from heteroarylene and arylene, each of which is optionally substituted, or R^4 and R^3 taken together with the nitrogen to which they are bound, form an optionally substituted 3- to 7-membered heterocycloalkyl ring, or R^4 is an alkylene chain having 1-3 carbon atoms that is optionally substituted with one or two groups independently chosen from lower alkyl and cycloalkyl, each of which groups is optionally substituted with hydroxyl or alkoxy, or R^4 is absent,~~

~~R^5 is chosen from C(O)NR^{51}, NR^{52}, and O or R^5 is absent, provided that if R^4 is absent, then R^5 is absent,~~

R^6 is an alkylene or alkenylene chain having one or two double bonds,

wherein the alkylene or alkenylene chain has 2 to 10 carbon atoms,

wherein the alkylene or alkenylene chain is optionally substituted with one or two groups independently chosen from lower alkyl and cycloalkyl, each of which groups is optionally substituted with hydroxyl or alkoxy, and

further wherein one or two of the carbon atoms in the alkylene chain is optionally replaced by an O, S, SO, SO_2, or NR^{61}, and

wherein two of the carbon atoms in the alkylene chain, are optionally connected by a two or three carbon atom alkylene chain to form a 5- to 7-membered ring.

R^7 is chosen from NR^{71} and O or R^7 is absent,

R^{51} is chosen from hydrogen and lower alkyl,

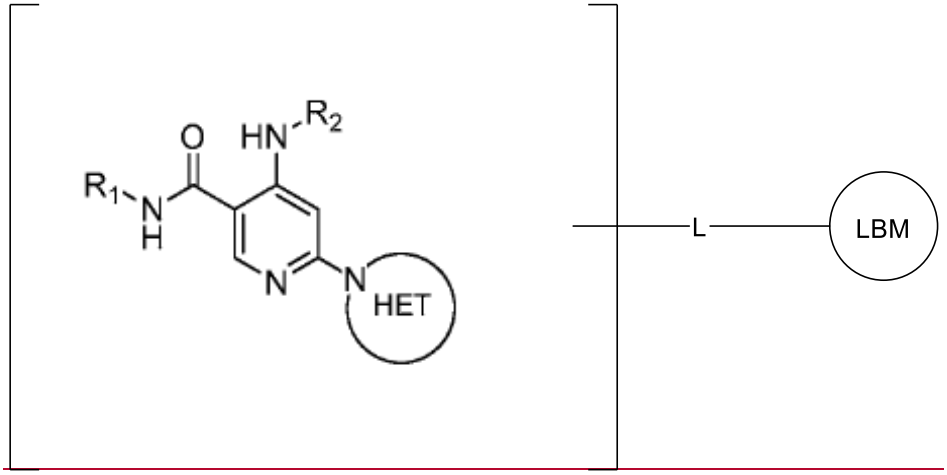
R^{52} is chosen from hydrogen, lower alkyl, and —C(O)OR^{81},

R^{61} is chosen from hydrogen, lower alkyl, and —C(O)OR^{81},

R^{71} is chosen from hydrogen, lower alkyl, and —C(O)OR^{81}, and

R^{81} is lower alkyl; or

(cc)



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), $S(O)_2$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;

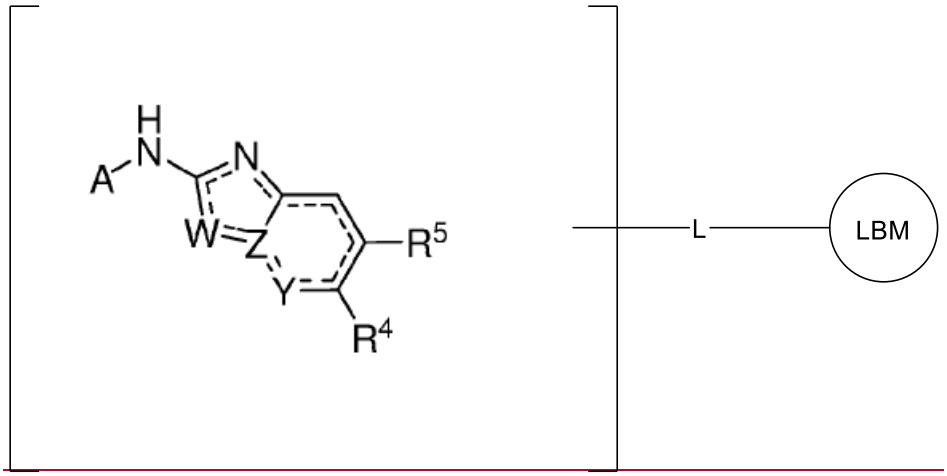
(iii) C_{3-6} cycloalkyl, azetidinyl, oxetanyl, furanyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, or tetrahydropyranyl, each substituted with zero to 3 substituents

~~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 hydroxybicyclo[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; or~~

~~(dd)~~



~~I-iii-1~~

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

~~--- is a single or double bond;~~

W is selected from CH, CH—CH, O, S, NR^6, and CO;

Y is N or CR^9;

Z is N or C, and Z is N if W is CH and Y is CR^9;

R^4 is selected from hydrogen, halogen, OR^6, CN, NR^7R^8, CH_2OR^6, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted non-aromatic ring, an optionally substituted carbocycle, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_1-C_6heteroalkyl, an optionally substituted C_1-C_6 alkenyl, an optionally substituted C_1-C_6 alkynyl, CO_2R^6, SO_3R^6, SO_2R^6 and $SO_2NR^7R^8$;

R^5 is selected from hydrogen, halogen, OR^6, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_1-C_6 heteroalkyl, an optionally substituted C_1-C_6haloheteroalkyl, an optionally substituted C_1-C_6 alkenyl, and an optionally substituted C_1-C_6 alkynyl;

or R^4 and R^5 are linked to form an optionally substituted non-aromatic ring;

each R^6 is independently selected from an optionally substituted aryl, an optionally substituted heteroaryl, and an optionally substituted non-aromatic ring, each optionally fused with a substituted aryl or a substituted heteroaryl, hydrogen, an optionally substituted C_1-C_{10}alkyl, an optionally substituted C_1-C_{10} haloalkyl, and an optionally substituted C_1-C_{10} heteroalkyl;

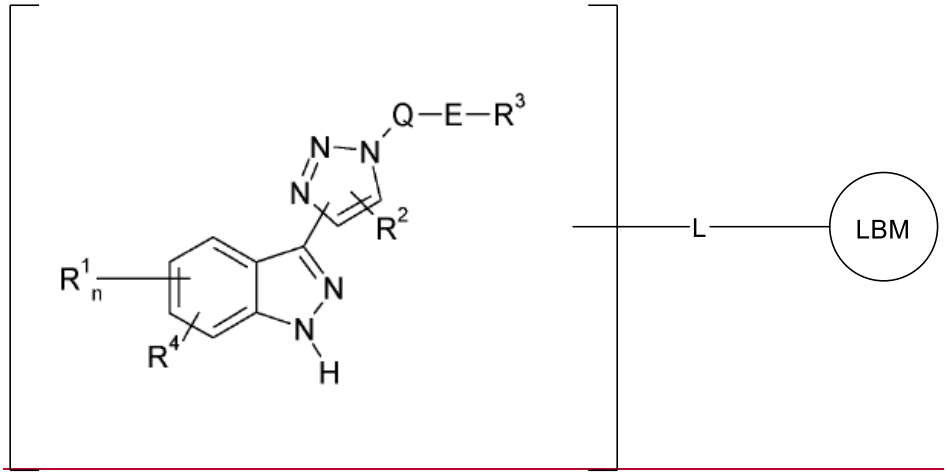
each R^7 and R^8 is independently selected from an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted non-aromatic ring, each optionally fused with a substituted aryl or a substituted heteroaryl, hydrogen, an optionally substituted C_1-C_{10} alkyl, an optionally substituted C_1-C_{10} haloalkyl, an optionally substituted C_1-C_{10} alkenyl, an optionally substituted C_1-C_{10} alkynyl, and an optionally substituted C_1-C_{10} heteroalkyl, or R^7 and R^8 are linked to form an optionally substituted non-aromatic ring;

R^9 is selected from hydrogen, halogen, OR^6, CN, NR^7R^8, CH_2OR^6, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted non-aromatic ring, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_1-C_6 heteroalkyl, an optionally substituted C_1-C_6 alkenyl, an optionally substituted C_1-C_6 alkynyl, CO_2R^6, SO_3R^6, and $SO_2NR^7R^8$;

A is an optionally substituted aryl or an optionally substituted heteroaryl group;

each optionally substituted group is either unsubstituted or substituted with one or more groups independently selected from alkyl, heteroalkyl, alkenyl, alkynyl, haloalkyl, heterohaloalkyl, aryl, arylalkyl, heteroaryl, non-aromatic ring, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, =O, =S, amino, and protected derivatives of amino groups; or

(ee)



I-jjj-1

or a pharmaceutically acceptable salt thereof, wherein:

Q denotes Ar or Het;

E denotes $(CH_2)_mCO$, $(CH_2)_mSO_2$, $(CH_2)_q$, $(CH_2)_mNHCO$, or a single bond;

R^1 denotes H, OH, NH$_2$, C_1-C_6-alkyl, OC_1-C_6-alkyl, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, Cyc, Hal, Het^1, O-Het^1, CO-Het^1, NH-Het^1, CO-Ar^1, O-Ar^1, Ar^1, NH-Ar^1, $(CH_2)_qHet^1$, CONH-$(CH_2)_qHet^1$, CONH-Het^1, $(CH_2)_qO$-Het^1, $(CH_2)_qO$-Ar^1, $(CH_2)_qAr^1$, CONH-$(CH_2)_qAr^1$, CONH-Ar^1, CONHC_3-C_6-cycloalkyl, $(CH_2)_qHal$, $(CH_2)_qCyc$, CF_3, $(CH_2)_sNH$-$(CH_2)_q$-Het^1, $(CH_2)_sNH$-$(CH_2)_q$-Ar^1, wherein NH$_2$, C_1-C_6-alkyl, OC_1-C_6-alkyl, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_6-cycloalkyl may be substituted by 1 to 3 groups independently selected from OC_1-C_3-alkyl, OH, CONH$_2$, NH$_2$;

R^2 denotes H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, Hal, CF_3, preferably H;

R^3 denotes Het^1, Ar^1, NR^aR^b, COOH, $(CH_2)_qHet^1$, $(CH_2)_qAr^1$, $(CH_2)_qNR^aR^b$, $(CH_2)_qCOOH$, or C_1-C_6-alkyl wherein 1 to 3 hydrogen atoms may be independently replaced by OH or CF_3;

R^4 denotes H, C_1-C_6-alkyl, C_2-C_6-alkenyl, Hal;

R^a denotes H, linear, branched or cyclic C_1-C_6-alkyl;

R^b denotes H, Het^b, Ar^b, CO-Het^b, CO-Ar^b, a C_3-C_8-cycloalkyl or a linear or branched alkyl having 1 to 6 carbon atoms, wherein 1 to 3 hydrogen atoms may be replaced by Het^b, Ar^b, NH_2, $N(C_1$-C_6-alkyl$)_2$, $NH(C_1$-C_6-alkyl), $N(C_1$-C_6-alkyl$)(C_3$-C_8-cycloalkyl), $NH(C_3$-C_8-cycloalkyl), $O(C_1$-C_6-alkyl), CN, OH, CF_3, Hal;

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

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

q is 1, 2, or 3;

s is 0, 1, 2 or 3;

Hal denotes Cl, Br, I, F, preferably Cl or F;

Ar denotes a divalent monocyclic or fused bicyclic arylen group having 6 to 14 carbon atoms, which may be further substituted with 1 to 4 substitutents selected from Hal, C_1-C_6-alkyl, $(CH_2)_mOC_1$-C_6-alkyl, CN, OH, NO_2, CF_3, $(CH_2)_mCOOH$, $(CH_2)_mCOOC_1$-C_6-alkyl;

Het denotes a divalent monocyclic or fused bicyclic unsaturated, saturated or aromatic heterocyclic group having 1 to 5 heteroatom independently selected from N, O, S and/or a group C=O, which may be further substituted with 1 to 4 substituent selected from Hal, C_1-C_6-alkyl, $(CH_2)_mOC_1$-C_6-alkyl, CN, OH, NO_2, CF_3, $(CH_2)_mCOOH$, $(CH_2)_mCOOC_1$-C_6-alkyl;

Ar^1 denotes a monocyclic or bicyclic, aromatic carbocyclic ring having 6 to 14 carbon atoms, which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, CF_3, OCF_3, NO_2, CN, perfluoroalkyl, Hal, CF_3, OCF_3, NO_2, CN, perfluoroalkyl, linear or branched C_1-C_6-alkyl, cycloalkyl, OH, OC_1-C_6-alkyl, COC_1-C_6-alkyl, NH_2, COH, COOH, $CONH_2$, a group R^b such as $CH_2O(C_1$-C_6-alkyl), $SO_2NR^aR^b$ or $SO_2(C_1$-C_6alkyl);

Het^1 denotes a monocyclic or bicyclic (fused, bridged or spiro) saturated, unsaturated or aromatic heterocyclic ring having 1 to 4 heteroatom independently selected from N, O, S and/or a

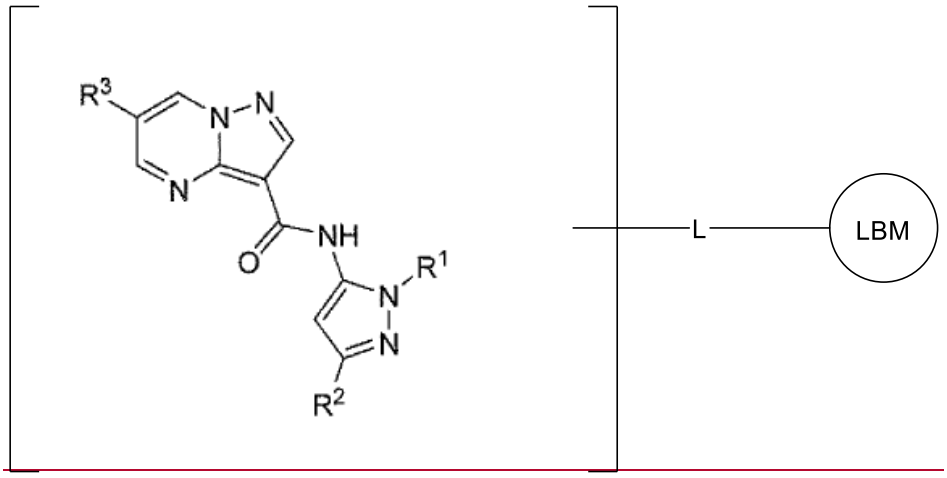
~~CO group, which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, CF_3, OCF_3, NO_2, CN, perfluoroalkyl, linear or branched C_1-C_6-alkyl, C_3-C_8-cycloalkyl, OH, OC_1-C_6-alkyl, NH_2, $N(C_1$-C_6-alkyl$)_2$, COH, COOH, $CONH_2$, COC_1-C_6-alkyl, $NHCO(C_3$-C_6cycloalkyl), a group R^b, $SO_2NR^aR^b$ or $SO_2(C_1$-C_6alkyl);~~

~~Het^b denotes a monocyclic or bicyclic (fused or spiro) saturated, unsaturated or aromatic heterocyclic ring having 1 to 4 heteroatom independently selected from N, O, S and/or a CO group, which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, CF_3, OCF_3, NO_2, CN, perfluoroalkyl, OH, OC_1-C_6-alkyl, NH_2, COH, COOH, $CONH_2$, or by a linear or branched C_1-C_6-alkyl wherein 1 to 3 hydrogen atoms may be replaced by NH_2, $N(C_1$-C_6-alkyl$)_2$, $NH(C_1$-C_6-alkyl), $N(C_1$-C_6-alkyl$)(C_3$-C_8-cycloalkyl), $NH(C_3$-C_8-cycloalkyl), $O(C_1$-C_6-alkyl), CN, OH, CF_3, Hal, C_3-C_8-cycloalkyl, or by a 4 to 8-membered heterocyclic ring containing an heteroatom selected from O, S and N;~~

~~Ar^b denotes a monocyclic or bicyclic, aromatic carbocyclic ring having 6 to 14 carbon atoms, which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, CF_3, OCF_3, NO_2, CN, perfluoroalkyl, Hal, CF_3, OCF_3, NO_2, CN, perfluoroalkyl, OH, OC_1-C_6-alkyl, NH_2, COH, COOH, $CONH_2$, or by a linear or branched C_1-C_6-alkyl wherein 1 to 3 hydrogen atoms may be replaced by NH_2, $N(C_1$-C_6-alkyl$)_2$, $NH(C_1$-C_6-alkyl), $N(C_1$-C_6-alkyl$)(C_3$-C_8-cycloalkyl), $NH(C_3$-C_8-cycloalkyl), $O(C_1$-C_6-alkyl), CN, OH, CF_3, Hal, C_3-C_8-cycloalkyl, or by a 4 to 8-membered heterocyclic ring containing an heteroatom selected from O, S and N;~~

~~Cyc denotes a saturated or unsaturated carbocyclic ring having 3 to 8 carbon atoms, preferrably 5 or 6 carbon atoms, wherein 1 to 5 H atoms are replaced by Hal, CF_3, OCF_3, NO_2, CN, perfluoroalkyl, Hal, CF_3, OCF_3, NO_2, CN, perfluoroalkyl, linear or branched C_1-C_6-alkyl, cycloalkyl, OH, OC_1-C_6-alkyl, COC_1-C_6-alkyl, NH_2, COH, COOH, $CONH_2$, a group R^b such as $CH_2O(C_1$-C_6-alkyl), $SO_2NR^aR^b$ or $SO_2(C_1$-C_6alkyl); or~~

~~(ff)~~



I-kkk-1

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is aryl, heteroaryl, heterocyclyl or (C_{1-6} alkyl)R^6, wherein said aryl, heteroaryl, and heterocyclyl groups are optionally substituted with one or two substituents selected from the group consisting of halo, cyano, R^4, C_{3-8} cycloalkyl, C_{1-3} aminoalkyl, C_{1-3}hydroxyalkyl, OR^4, NR^4R^5, NR^4COR^6, $NR^4SO_2R^6$, $SO_2NR^4R^5$, $CONR^4R^5$ and $CONR^4R^5$;

R^2 is aryl, heteroaryl, C_{3-8} cycloalkyl, heterocyclyl or (C_{1-6} alkyl)R^6, wherein said aryl, heteroaryl, cycloalkyl and heterocyclyl groups are optionally substituted with one or two substituents selected from the group consisting of halo, cyano, oxo, hydroxyl, imino, hydroxyimino, R^4, OR^4, $O(C_{3-8}$ cycloalkyl), $(C{=}O)OR^4$, SO_mR^6, SO_mR^4, NR^4R^5, $SO_2NR^4R^5$ and $NR^4SO_2R^6$;

R^3 is halo, cyano, oxo, hydroxyl, imino, hydroxyimino, R^4, OR^4, C_{3-8}cycloalkyl, SO_mR^6, $SO_mR^4NR^4R^5$ or $(C{=}O)NR^4R^5$, $NR^4(CO)R^6$, $SO_mNR^4R^5$ and $NR^4SO_2R^6$;

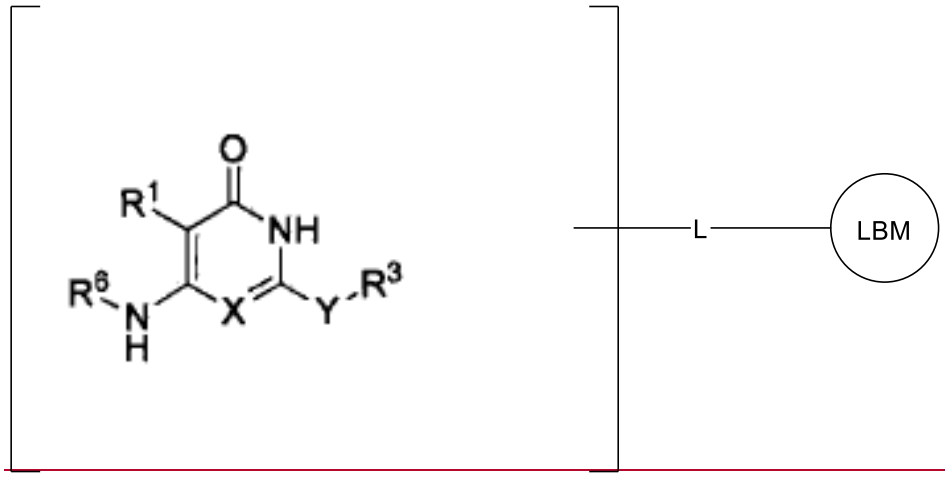
R^4 is hydrogen or C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to three halo or hydroxyl;

R^5 is hydrogen or C_{1-6} alkyl, wherein said alkyl is optionally substituted with halo or hydroxyl;

R^6 is aryl, heteroaryl, C_{3-8} cycloalkyl or heterocyclyl;

m is an integer from zero to two; or

(gg)



I-III-1

or a pharmaceutically acceptable salt thereof, wherein:

X is —N═ or —CH═;

Y is selected from the group consisting of —NR^2—, —CH_2—, —CHR— and —O—, such that when Y is —CHR—, R and R^3 together with the carbon to which they are attached optionally form a 4- to 6-membered cycloalkyl, cycloalkenyl or heterocyclic ring, wherein the 4- to 6-membered cycloalkyl, cycloalkenyl, or heterocyclic ring is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, CF_3, heterocyclyl, halogen, —$COOR^8$, —NHR^8, —SR^8, —OR^8, —SO_2R^8, —COR^8, —$NHCOR^8$, and —$CONHR^8$; or when Y is —NR^2—, R^2 and R^3 together with the nitrogen to which they are attached optionally form a 4- to 6-membered heterocyclic ring, wherein the 4- to 6-membered heterocyclic ring is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, CF_3, heterocyclyl, halogen, —$COOR^8$, —NHR^8, —SR^8, —OR^8, —SO_2R^8, —COR^8, —$NHCOR^8$, and —$CONHR^8$;

R^1 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{3-8} cycloalkyl, aryl, heterocyclyl, halogen, —$COOR^7$, —NHR^7, —SR^7, —OR^7, —SO_2R^7, —COR^7, —$NHCOR^7$, and —$CONHR^7$; wherein said alkyl, cycloalkyl, aryl and heterocyclyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, CN, phenyl, CF_3, heterocyclyl, halogen, —$COOR^8$, —NHR^8, —SR^8, —OR^8, —SO_2R^8, —COR^8, —$NHCOR^8$, and —$CONHR^S$,

wherein said NHR^8 is optionally substituted with $N(C_{1-4}alkyl)NH_2$ or $N(C_{3-6}cycloalkyl)NH_2$;

R^2 is selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{3-8} cycloalkyl;

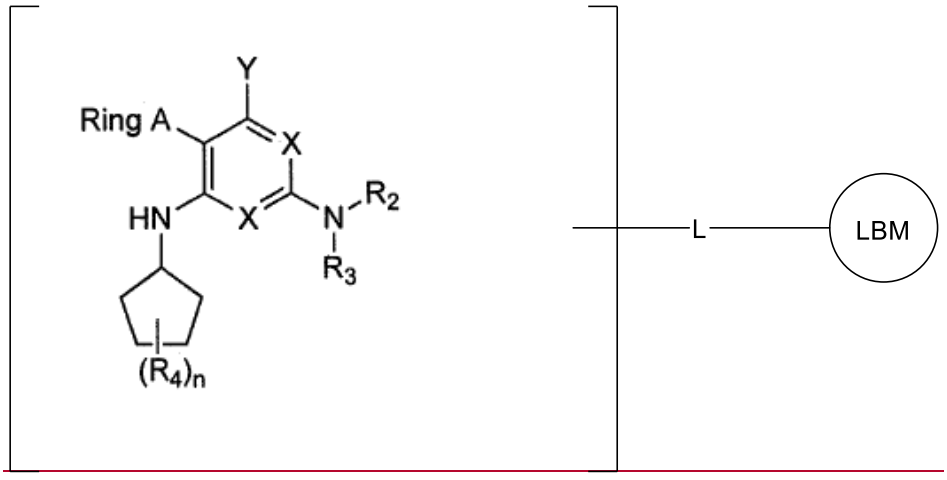
R^3 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{3-8}cycloalkyl, aryl, heterocyclyl, and $COOR^7$; wherein said alkyl, cycloalkyl, aryl and heterocyclyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, CF_3, heterocyclyl, halogen, $COOR^8$, NHR^8, SR^8, OR^8, SO_2R^8, COR^8, $NHCOR^8$, and $CONHR^8$;

R^6 is selected from the group consisting of C_{1-10} alkyl, C_{3-8} cycloalkyl, aryl, heterocyclyl, $COOR^7$, SO_2R^7, and COR^7; wherein said alkyl, cycloalkyl, aryl and heterocyclyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, CF_3, heterocyclyl, halogen, $COOR^8$, NHR^8, SR^8, OR^8, SO_2R^8, COR^8, $NHCOR^8$, and $CONHR^8$;

R^7 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{3-8}cycloalkyl, aryl, and heteroaryl; wherein said alkyl, cycloalkyl, aryl and heterocyclyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} alkyl, C_{3-6}cycloalkyl, phenyl, CF_3, heterocyclyl, halogen, $COOR^8$, NHR^8, SR^8, OR^8, SO_2R^8, COR^8, $NHCOR^8$, and $CONHR^8$; and

R^8 is selected from the group consisting of hydrogen, C_{1-6} alkyl and C_{3-6} cycloalkyl; or

(hh)



I-mmm-1

or a pharmaceutically acceptable salt thereof, wherein:

~~X is independently CH or N;~~

~~Y is H or methyl;~~

~~a is 0 or 1; b is 0 or 1; m is 0, 1 or 2; n is 0, 1, 2, 3 or 4;~~

~~Ring A is $(C_3$-$C_8)$cycloalkenyl, aryl or heterocycle optionally substituted with one to three substituents independently selected from R_1;~~

~~R_1 is selected from: H, oxo, $(C{=}O)_aO_b(C_1$-$C_{10})$alkyl, $(C{=}O)_aO_b$-aryl, $(C{=}O)_aO_b(C_2$-$C_{10})$alkenyl, $(C{=}O)_aO_b(C_2$-$C_{10})$alkynyl, CO_2H, halo, OH, $O_b(C_1$-$C_6)$fluoroalkyl, $(C{=}O)_aNR_5R_6$, CN, $(C{=}O)_aO_b(C_3$-$C_8)$cycloalkyl, $S(O)_mNR_5R_6$, SH, $S(O)_m$ $(C_1$-$C_{10})$alkyl and $(C{=}O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted with one or more substituents selected from R_a;~~

~~R_2 and R_3 are independently selected from: H, $(C{=}O)_aO_bC_1$-C_{10} alkyl, $(C{=}O)_aO_b$aryl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $(C{=}O)_aO_b$ heterocyclyl, CO_2H, CN, O_bC_1-C_6fluoroalkyl, $O_a(C{=}O)_bNR_5R_6$, CHO, $(N{=}O)R_5R_6$, $S(O)_mNR_5R_6$, SH, $S(O)_m$ $(C_1$-$C_{10})$alkyl, $(C{=}O)_aO_bC_3$-C_8 cycloalkyl, optionally substituted with one or more substituents selected from R_1; or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one or more substituents selected from R_1;~~

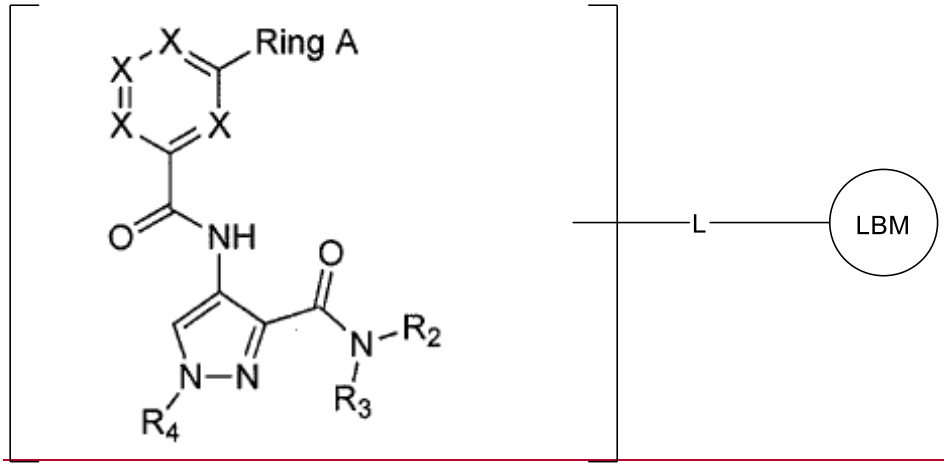
~~R_4 is independently selected from: $(C_1$-$C_6)$alkyl, OH, methoxy, CF_3 and F, said alkyl optionally substituted with OH;~~

~~R_5 and R_6 are independently selected from H, $(C{=}O)_aO_b(C_1$-$C_{10})$alkyl, $(C{=}O)_aO_b$-aryl, $(C{=}O)_aO_b(C_2$-$C_{10})$alkenyl, $(C{=}O)_aO_b(C_2$-$C_{10})$alkynyl, CO_2H, $O_b(C_1$-$C_6)$fluoroalkyl, $(C{=}O)_aN(R_a)_2$, CN, $(C{=}O)_aO_b(C_3$-$C_8)$cycloalkyl, $S(O)_mN(R_a)_2$, SH, $S(O)_m$ $(C_1$-$C_{10})$alkyl and $(C{=}O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted with one or more substituents selected from R_a;~~

~~R_a is independently selected from R_b, OH, $(C_1$-$C_6)$alkoxy, halogen, cyclopropyl, CO_2H, CN, $O_a(C{=}O)_b(C_1$-$C_6)$alkyl, oxo, and $N(R_b)_2$; and~~

~~R_b is independently selected from H and $(C_1$-$C_6)$alkyl; or~~

~~(ii)~~



~~I-nnn-1~~

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

~~X is CH or N;~~

~~a is 0 or 1; b is 0 or 1; m is 0, 1 or 2;~~

~~Ring A is $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkenyl, aryl or heterocycle optionally substituted with one to three substituents independently selected from R_1;~~

~~R_1 is selected from: H, oxo, $(C{=}O)_aO_b(C_1$-$C_{10})$alkyl, $(C{=}O)_aO_b$-aryl, $(C{=}O)_aO_b(C_2$-$C_{10})$alkenyl, $(C{=}O)_aO_b(C_2$-$C_{10})$alkynyl, CO_2H, halo, OH, $O_b(C_1$-$C_6)$fluoroalkyl, $(C{=}O)_aNR_5R_6$, CN, $(C{=}O)_aO_b(C_3$-$C_8)$cycloalkyl, $S(O)_mNR_5R_6$, SH, $S(O)_m$-$(C_1$-$C_{10})$alkyl and $(C{=}O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted with one or more substituents selected from R_a;~~

~~R_2 and R_3 are independently selected from: H, $(C{=}O)_aO_bC_1$-C_{10} alkyl, $(C{=}O)_aO_b$aryl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $(C{=}O)_aO_b$ heterocyclyl, CO_2H, CN, O_bC_1-C_6 fluoroalkyl, $O_a(C{=}O)_bNR_5R_6$, CHO, $(N{=}O)R_5R_6$, $S(O)_mNR_5R_6$, SH, $S(O)_m$-$(C_1$-$C_{10})$alkyl, $(C{=}O)_aO_bC_3$-C_8 cycloalkyl, optionally substituted with one or more substituents selected from R_1; or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one or more substituents selected from R_1;~~

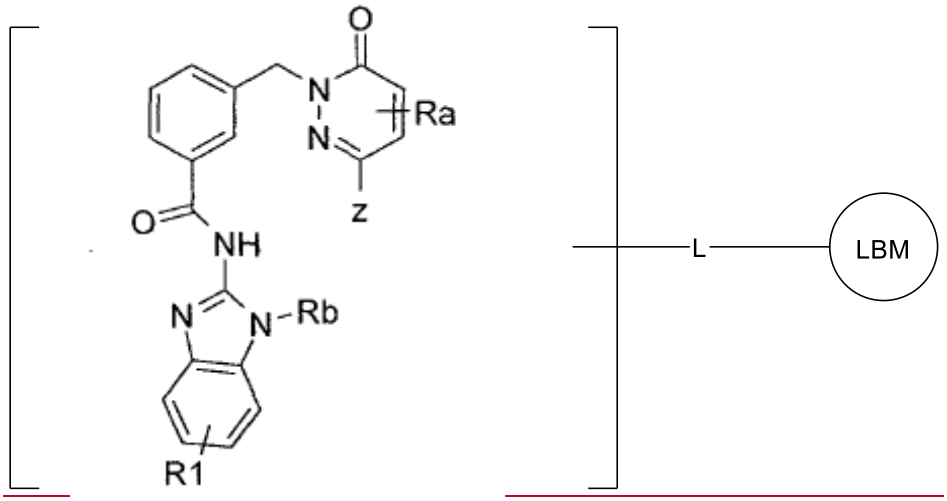
~~R_4 is selected from: $(C_1$-$C_6)$alkyl and $(C_3$-$C_6)$cycloalkyl, optionally substituted with R_a;~~

R_5 and R_6 are independently selected from: H, oxo, $(C{=}O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C{=}O)_aO_b$-aryl, $(C{=}O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C{=}O)_aO_b(C_2\text{-}C_{10})$alkynyl, CO_2H, $O_b(C_1\text{-}C_6)$fluoroalkyl, $(C{=}O)_aN(R_a)_2$, CN, $(C{=}O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mN(R_a)_2$, SH, $S(O)_m$ $(C_1\text{-}C_{10})$alkyl and $(C{=}O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted with one or more substituents selected from R_a;

R_a is independently selected from R_b, OH, $(C_1\text{-}C_6)$alkoxy, halogen, cyclopropyl, CO_2H, CN, $O_a(C{=}O)_b(C_1\text{-}C_6)$alkyl, oxo, and $N(R_b)_2$; and

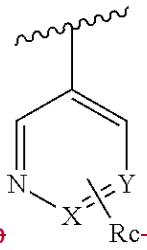
R_b is independently selected from H and $(C_1\text{-}C_6)$alkyl; or

(jj)



I-ooo-1

or a pharmaceutically acceptable salt thereof, wherein:

Z denotes a group  ; wherein

X is CH or N;

Y is CH or N;

Ra, Rc, R1 denote each independently H, Hal or A1;

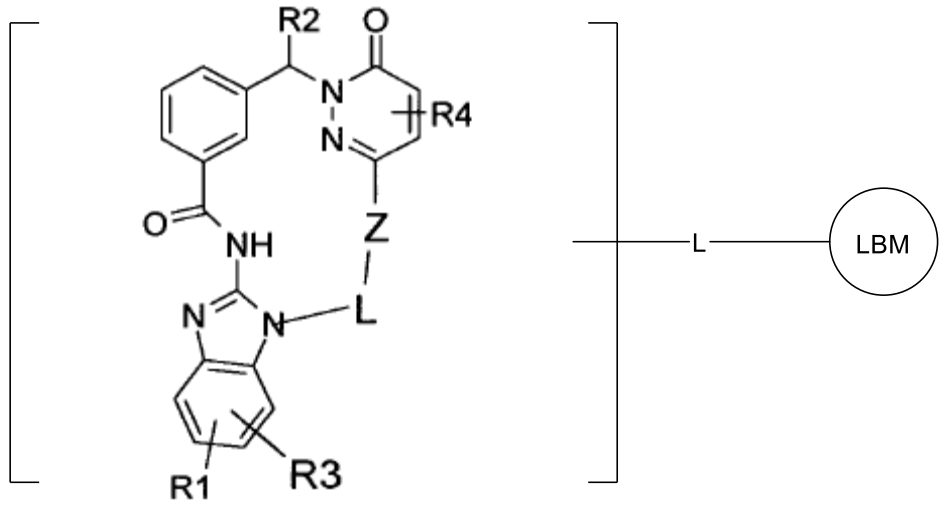
Rb is H or alkyl;

Al is branched or linear alkyl having 1 to 12 C-atoms, wherein one or more, such as 1 to 7, H atoms may be replaced by Hal, ORb, COORb, CN or $N(Rb)_2$ and wherein one or more,

preferably 1 to 5 CH_2-groups may be replaced by O, CO, NRb or S, SO, SO_2, 1,2-, 1,3- or 1,4-phenylen, —CH=CH— or —C≡C—; and

Hal denotes F, Cl, Br, I; or

(kk)



I ppp-1

or a pharmaceutically acceptable salt thereof, wherein:

R1, R3 denote each, independently of one another H, $(CH_2)_pCON(R5)_2$, OA, Hal, COOH, COOA, $(CH_2)_pNHCOA$, $(CH_2)_pHet1$, $(CH_2)_pNR2R5$, or OH;

R2 denotes H or linear or branched alkyl with 1, 2 or 3 C atoms, wherein one or two H atoms of the alkyl group are optionally replaced by OR6, NR5R6, NHCOR5, CONR5R6;

R4 denotes H or A;

R5 denotes H or linear or branched alkyl with 1, 2 or 3 C atoms;

R6 denotes H or linear or branched alkyl with 1, 2 or 3 C atoms;

Z is absent or denotes Ar-diyl or Het-diyl;

L denotes $(CH_2)_n$ wherein one or two CH_2 groups are optionally replaced by O and/or a CH=CH-group, and/or wherein one or two H atoms are optionally replaced by OR2, NR2R5 or Het1;

Ar-diyl denotes 1,2-, 1,3- or 1,4-phenylen optionally substituted with from 1 to 5 groups independently selected from the group consisting of Hal, CN, CF_3, OCF_3, OH, O-A, SO_2-A, COOH, COOA, CO-A, O-phenyl, SO_2-phenyl, SO_2-CF_3, Het2 and A;

Het-diyl denotes an unsaturated, saturated or aromatic 5- or 6-membered heterocycle comprising 1 to 2 N, O and/or S atoms, which are optionally unsubstituted or mono-, di- or trisubstituted by Hal, CN, CF_3, OCF_3, O-A, SO_2-A, COOH, COOA, CO-A, O-phenyl, SO_2-phenyl, SO_2-CF_3, Het2 and/or A;

A denotes an unbranched or branched alkyl comprising 1 to 10 C atoms, in which 1 to 5 H atoms are optionally replaced by F and/or in which one or two non-adjacent CH_2 groups are optionally replaced by O;

Het1 denotes morpholinyl, piperidinyl or pyrrolidinyl;

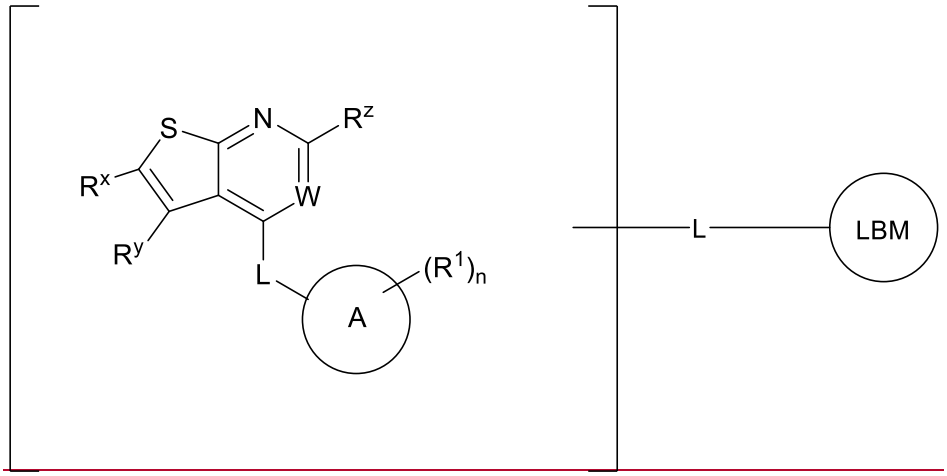
Het2 denotes morpholinyl, piperidinyl or pyrrolidinyl;

Hal denotes F, Cl, Br, I;

n denotes 1, 2, 3, 4, 5 or 6;

p denotes 0, 1 or 2; or

(ll)



I-qqq-1

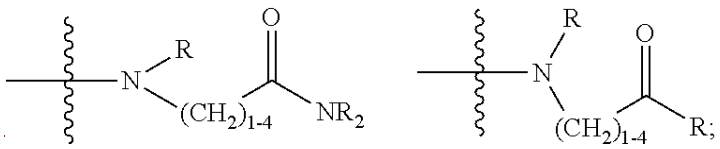
or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

n is 0-4;

each R^1 is independently R, halogen, CN, NO_2, OR, CH_2OR, SR, $N(R)_2$, SO_2R, $SO_2N(R)_2$, SOR, C(O)R, CO_2R, $C(O)N(R)_2$, C(O)N(R) OR,

~~$NRC(O)R$, $NRC(O)N(R)_2$, Cy, or $NRSO_2R$; or R^1 is selected from one of the following formulas:~~



~~or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;~~

~~each Cy is an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;~~

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

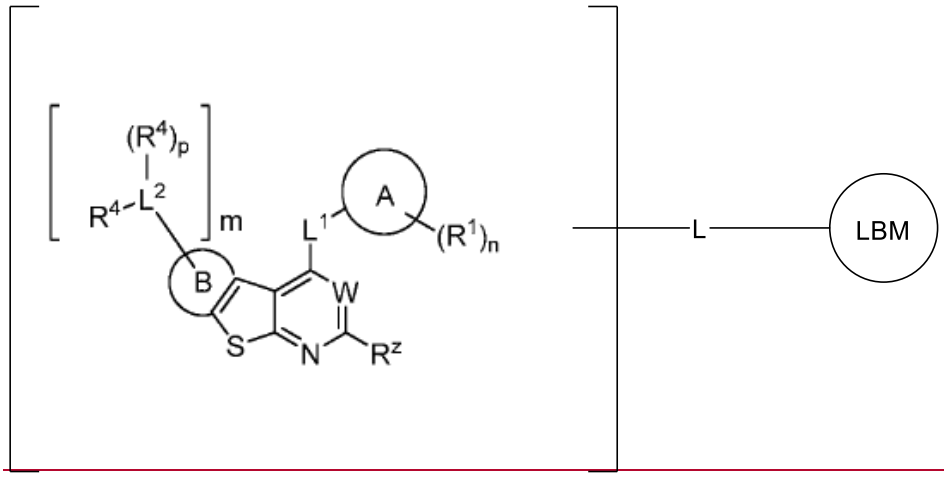
~~two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, or sulfur;~~

~~R^z is R, CN, NO_2, halogen, $C(O)N(R)_2$, C(O)OR, C(O)R, $N(R)_2$, OR, or $SO^2N(R)_2$;~~

~~Ring B is an unsubstituted 4-8 membered partially unsaturated carbocyclic fused ring; and~~

~~L is a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by NR , N(R)C(O) , C(O)N(R) , $N(R)SO_2$, $SO_2N(R)$, O , C(O) , OC(O) , C(O)O , S , SO or SO_2 ; or~~

~~(mm)~~



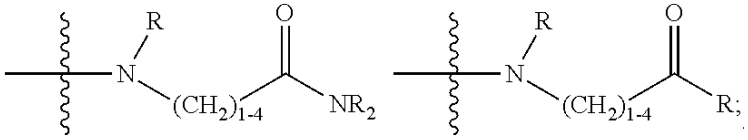
I-rrr-1

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

n is 0-4;

each R^1 is independently R, halogen, CN, NO_2, OR, CH_2OR, SR, $N(R)_2$, SO_2R, $SO_2N(R)_2$, SOR, C(O)R, CO_2R, $C(O)N(R)_2$, C(O)N(R) OR, NRC(O)OR, $NRC(O)N(R)_2$, Cy, or $NRSO_2R$; or R^1 is selected from one of the following formulas:



or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Cy is an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

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

~~heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:~~

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

~~Ring B is a cyclopento or cyclohexo fused ring;~~

~~m is 1-2;~~

~~p is 0-2;~~

~~W is N;~~

~~R^z is R, CN, NO_2, halogen, $C(O)N(R)_2$, C(O)OR, C(O)R, N(R)C(O)OR, $NRC(O)N(R)_2$, OR, or $SO_2N(R)_2$;~~

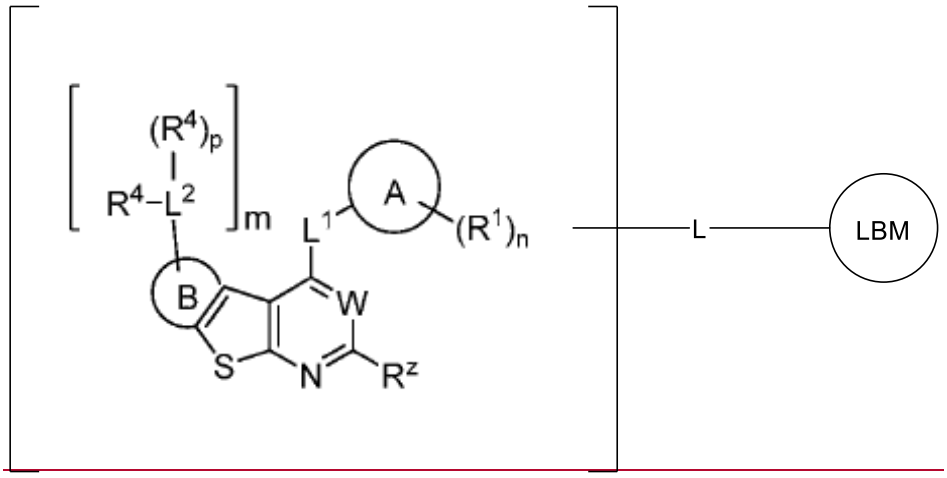
~~L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by NR, N(R)C(O), C(O)N(R), $N(R)SO_2$, $SO_2N(R)$, O, C(O), OC(O), C(O)O, S, SO or SO_2;~~

~~each L^2 is independently a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by NR, N(R)C(O), C(O)N(R), $N(R)SO_2$, $SO_2N(R)$, O, C(O), OC(O), C(O)O, S, SO or SO_2;~~

~~each R^4 is independently halogen, CN, NO_2, OR, SR, $N(R)_2$, SO_2R, $SO_2N(R)_2$, SOR, C(O)R, CO_2R, $C(O)N(R)_2$, NRC(O)R, $NRC(O)N(R)_2$, C(O)N(R)OR, N(R)C(O)OR, $N(R)S(O)_2N(R)_2$, $NRSO_2R$, or an optionally substituted group selected from C_{1-6}aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:~~

~~two $L^2(R^4)_p$ R^4 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or~~

~~(nn)~~



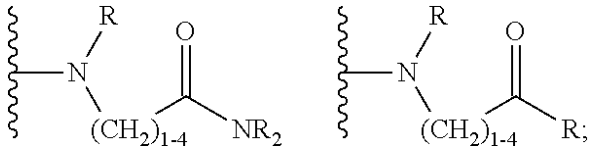
I-sss-1

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

n is 0-4;

each R^1 is independently R, halogen, CN, NO_2, OR, CH_2OR, SR, $N(R)_2$, $S(O)_2R$, $S(O)_2N(R)_2$, SOR, C(O)R, CO_2R, $C(O)N(R)_2$, C(O)N(R)OR, N(R)C(O)R, N(R)C(O)OR, $N(R)C(O)N(R)_2$, Cy, or $N(R)S(O)_2R$, or R^1 is selected from one of the following formulas:



or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each Cy is an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

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

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

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

Ring B is selected from a benzo fused ring and a 5-6 membered heteroaromatic fused ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said Ring B may be optionally substituted by one or more oxo, thiono, or imino groups;

m is 0-4;

p is 0-2;

W is N or $C(R^3)$;

R^2 is R, CN, NO_2, halogen, $C(O)N(R)_2$, C(O)OR, C(O)R, $N(R)_2$, N(R)C(O)OR, $N(R)C(O)N(R)_2$, OR, or $S(O)_2N(R)_2$;

R^3 is hydrogen, halogen, CN, C_{1-4} aliphatic, C_{1-4} haloaliphatic, OR, C(O)R, or $C(O)N(R)_2$;

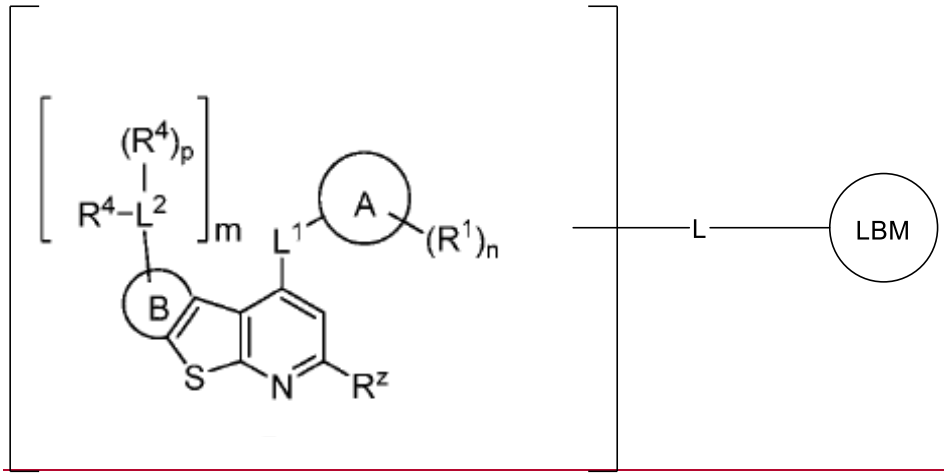
L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by N(R), N(R)C(O), C(O)N(R), $N(R)S(O)_2$, $S(O)_2N(R)$, O, C(O), OC(O), C(O)O, S, S(O) or $S(O)_2$;

each L^2 is independently a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by N(R), N(R)C(O), C(O)N(R), $N(R)S(O)_2$, $S(O)_2N(R)$, O, C(O), OC(O), C(O)O, S, S(O) or $S(O)_2$; and

each R^4 is independently halogen, CN, NO_2, OR, SR, $N(R)_2$, $S(O)_2R$, $S(O)_2N(R)_2$, S(O)R, C(O)R, CO_2R, $C(O)N(R)_2$, N(R)C(O)R, $N(R)C(O)N(R)_2$, C(O)N(R)OR, N(R)C(O)OR, $N(R)S(O)_2N(R)_2$, $N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two -$L^2(R^4)_p$- R^4 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

(oo)



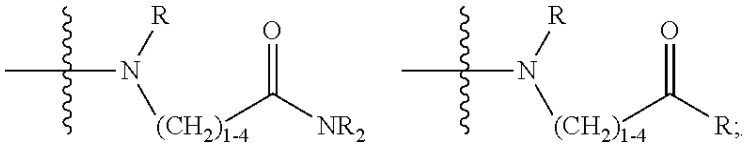
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or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

n is 0-4;

each R^1 is independently R, halogen, CN, NO_2, OR, CH_2OR, SR, $N(R)_2$, $S(O)_2R$, $S(O)_2N(R)_2$, S(O)R, C(O)R, C(O)OR, $C(O)N(R)_2$, C(O)N(R)OR, N(R)C(O)R, N(R)C(O)OR, $N(R)C(O)N(R)_2$, Cy, or $N(R)S(O)_2R$; or R^1 is selected from one of the following formulas:



two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each Cy is an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated

heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

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

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

Ring B is selected from a 4-8 membered partially unsaturated carbocyclic fused ring and a 4-7 membered partially unsaturated heterocyclic fused ring having 1-2 heteroatoms selected from nitrogen, oxygen, and sulfur; wherein said Ring B may be optionally substituted by one or more oxo, thiono, or imino groups;

m is 0-4;

p is 0-2;

R^z is R, CN, NO_2, halogen, $C(O)N(R)_2$, C(O)OR, C(O)R, $N(R)_2$, N(R)C(O)OR, $N(R)C(O)N(R)_2$, OR, or $S(O)_2N(R)_2$;

R^3 is hydrogen, halogen, CN, C_{1-4} aliphatic, C_{1-4} haloaliphatic, OR, C(O)R, or $C(O)N(R)_2$;

L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by N(R), N(R)C(O), C(O)N(R), $N(R)S(O)_2$, $S(O)_2N(R)$, O, C(O), OC(O), C(O)O, S, S(O) or $S(O)_2$;

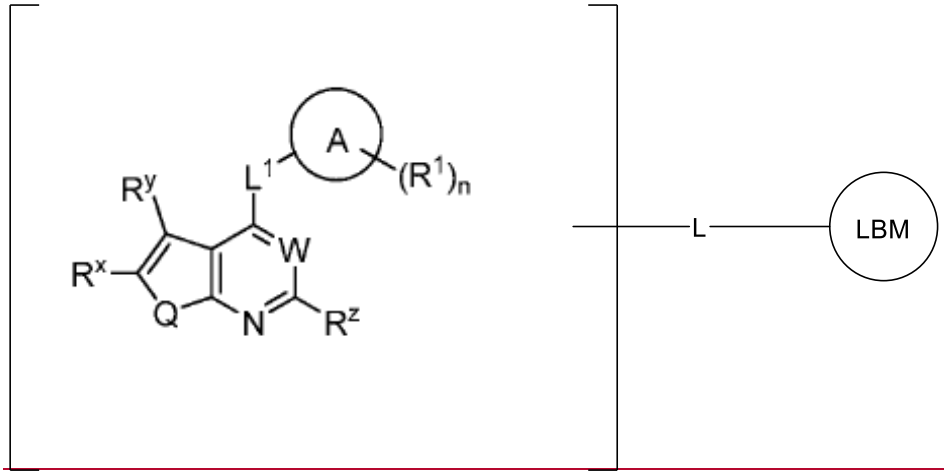
each L^2 is independently a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by N(R), N(R)C(O), C(O)N(R), $N(R)S(O)_2$, $S(O)_2N(R)$, O, C(O), OC(O), C(O)O, S, S(O) or $S(O)_2$; and

each R^4 is independently halogen, CN, NO_2, OR, SR, $N(R)_2$, $S(O)_2R$, $S(O)_2N(R)_2$, S(O)R, C(O)R, C(O)OR, $C(O)N(R)_2$, N(R)C(O)R, $N(R)C(O)N(R)_2$, C(O)N(R)OR, N(R)C(O)OR, $N(R)S(O)_2N(R)_2$, $N(R)S(O)_2R$,

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

two $-L^2(R^4)_p-R^4$ groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

(pp)



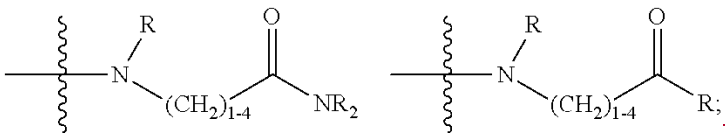
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or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

n is 0-4;

each R^1 is independently R, halogen, CN, NO_2, OR, CH_2OR, SR, $N(R)_2$, $S(O)_2R$, $S(O)_2N(R)_2$, S(O)R, C(O)R, C(O)OR, $C(O)N(R)_2$, C(O)N(R)OR, N(R)C(O)R, N(R)C(O)OR, $N(R)C(O)N(R)_2$, Cy, or $N(R)S(O)_2R$; or R^1 is selected from one of the following formulas:



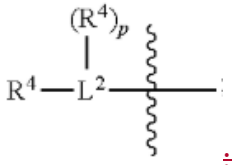
or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each Cy is an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

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

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

each of R^x and R^y is independently R, halogen, CN, NO_2, OR, SR, $N(R)_2$, $S(O)_2R$, $S(O)_2N(R)_2$, S(O)R, C(O)R, C(O)OR, $C(O)N(R)_2$, N(R)C(O)R, $N(R)C(O)N(R)_2$, or $N(R)S(O)_2R$, or:

R^x and R^y are taken together with their intervening atoms to form Ring B substituted with m occurrences of  ;

Ring B is selected from a benzo fused ring, a 4-8 membered partially unsaturated carbocyclic fused ring, a 4-8 membered partially unsaturated heterocyclic fused ring having one or two heteroatoms independently selected from nitrogen oxygen and sulfur, and a 5-6 membered heteroaromatic fused ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said Ring B may be optionally substituted by one or more oxo, thiono, or imino groups;

m is 0-4;

p is 0-2;

Q is O or N(R)

W is N or $C(R^3)$;

R^z is R, CN, NO_2, halogen, $C(O)N(R)_2$, C(O)OR, C(O)R, $N(R)_2$, N(R)C(O)OR, $N(R)C(O)N(R)_2$, OR, or $S(O)_2N(R)_2$;

R^3 is hydrogen, halogen, CN, C_{1-4} aliphatic, C_{1-4} haloaliphatic, OR, C(O)R, or $C(O)N(R)_2$;

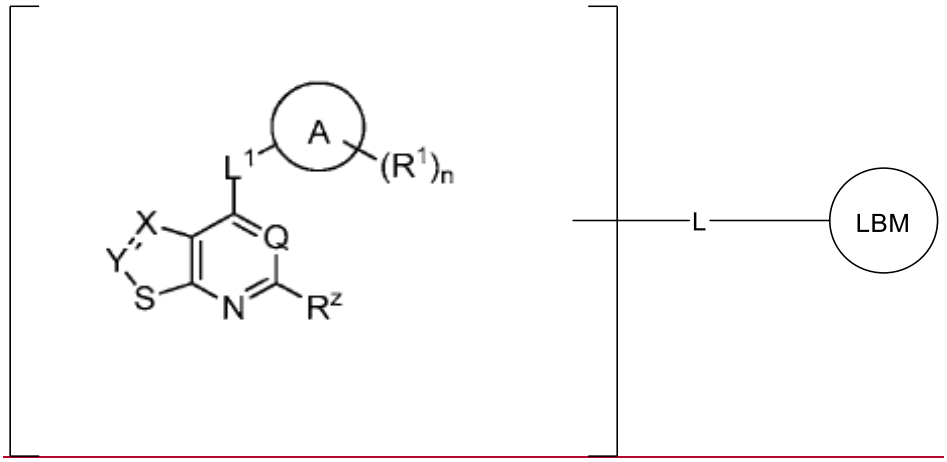
L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by N(R), N(R)C(O), C(O)N(R), $N(R)S(O)_2$, $S(O)_2N(R)$, O, C(O), OC(O), C(O)O, S, S(O) or $S(O)_2$;

each L^2 is independently a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by N(R), N(R)C(O), C(O)N(R), $N(R)S(O)_2$, $S(O)_2N(R)$, O, C(O), OC(O), C(O)O, S, S(O) or $S(O)_2$; and

each R^4 is independently halogen, CN, NO_2, OR, SR, $N(R)_2$, $S(O)_2R$, $S(O)_2N(R)_2$, S(O)R, C(O)R, C(O)OR, $C(O)N(R)_2$, N(R)C(O)R, $N(R)C(O)N(R)_2$, C(O)N(R)OR, N(R)C(O)OR, $N(R)S(O)_2N(R)_2$, $N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

two $L^2(R^4)_p$ R^4 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

(qq)



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or a pharmaceutically acceptable salt thereof, wherein:

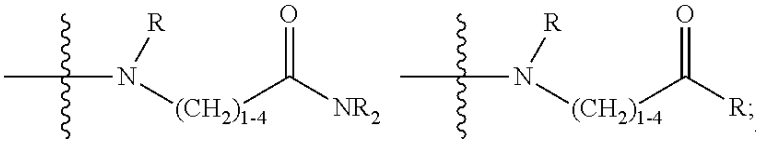
Q is CH, C—CN, or N;

X is C-L^2(R^4)$_p$—R^x and Y is N; or

X is N and Y is C—Rx;

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^1 and R$^{1'}$ is independently —R^2, halogen, —CN, —NO$_2$, —OR, —SR, —N(R)$_2$, —S(O)$_2$R, —S(O)$_2$N(R)$_2$, —S(O)R, —C(O)R, —C(O)OR, —C(O)N(R)$_2$, —C(O)N(R)OR, —N(R)C(O)OR, —N(R)C(O)N(R)$_2$, Cy, or —N(R)S(O)$_2$R; or R^1 is selected from one of the following formulas:



or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Cy is an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-10 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

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

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

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

each R^4 is independently halogen, CN, NO_2, OR, SR, $N(R)_2$, $S(O)_2R$, $S(O)_2N(R)_2$, S(O)R, C(O)R, C(O)OR, $C(O)N(R)_2$, N(R)C(O)R, $N(R)C(O)N(R)_2$, C(O)N(R)OR, N(R)C(O)OR, $N(R)S(O)_2N(R)_2$, $N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^x is hydrogen, R^2, CN, NO_2, halogen, $C(O)N(R)_2$, C(O)OR, C(O)R, $N(R)_2$, NH[Ar], OR, or $S(O)_2N(R)_2$;

R^z is hydrogen, R^2, CN, NO_2, halogen, $C(O)N(R)_2$, C(O)OR, C(O)R, $N(R)_2$, NH[Ar], OR, or $S(O)_2N(R)_2$;

[Ar] is a phenyl or heteroaromatic ring substituted by m instances of $R^{1'}$;

L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by N(R), N(R)C(O), C(O)N(R), $N(R)S(O)_2$, $S(O)_2N(R)$, O, C(O), OC(O), C(O)O, S, S(O) or $S(O)_2$;

L^2 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by N(R), N(R)C(O),

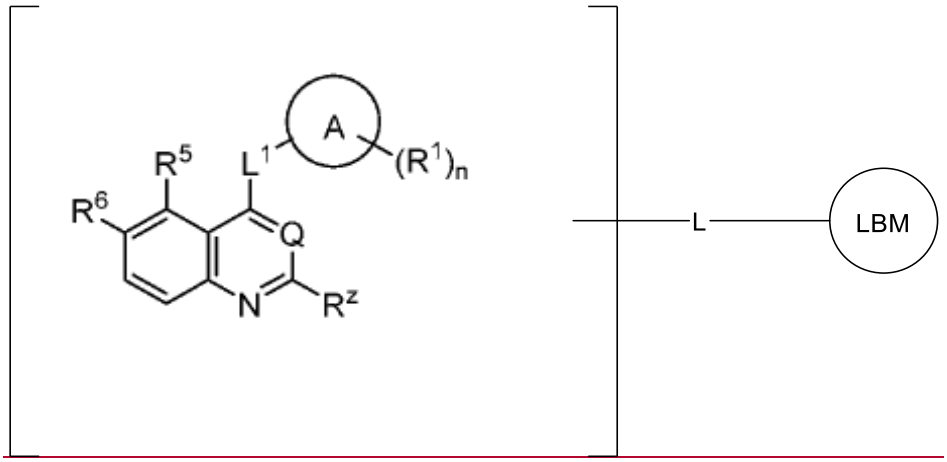
~~$C(O)N(R)$, $N(R)S(O)_2$, $S(O)_2N(R)$, O, C(O), OC(O), C(O)O, S, S(O) or $S(O)_2$;~~

~~m is 0-4;~~

~~n is 0-4; and~~

~~p is 0-2; or~~

~~(rr)~~



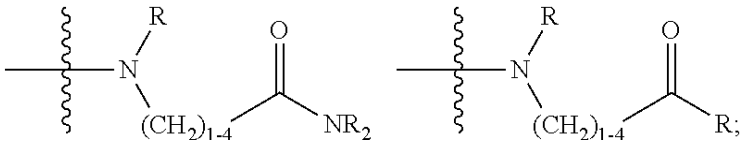
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~~or a pharmaceutically acceptable salt thereof, wherein:~~

~~Q is =N- or =CH-;~~

~~Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;~~

~~each R^1 is independently R^2, 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, N(R)C(O)OR, $N(R)C(O)NR_2$, Cy, or $N(R)S(O)_2R$; or R^1 is selected from one of the following formulas:~~



~~or two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;~~

each Cy is independently an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-10 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

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

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

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

each of R^5 and R^6 is independently hydrogen or $-L^2(R^4)_p-R^x$; or

R^5 and R^6 are taken together with their intervening atoms to form a 4-7 membered partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^4 is independently halogen, CN, NO_2, OR, SR, NR_2, $S(O)_2R$, $S(O)_2NR_2$, S(O)R, C(O)R, C(O)OR, $C(O)NR_2$, N(R)C(O)R, $N(R)C(O)NR_2$, C(O)N(R)OR, N(R)C(O)OR, $N(R)S(O)_2NR_2$, $N(R)S(O)_2R$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^x is hydrogen, R^2, CN, NO_2, halogen, $C(O)NR_2$, C(O)OR, C(O)R, NR_2, NH[Ar], OR, or $S(O)_2NR_2$;

R^z is hydrogen, R^2, CN, NO_2, halogen, $C(O)NR_2$, C(O)OR, C(O)R, NR_2, NH[Ar], OR, or $S(O)_2NR_2$;

[Ar] is an optionally substituted phenyl or an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by N(R), N(R)C(O), C(O)N(R), $N(R)S(O)_2$, $S(O)_2N(R)$, O, C(O), OC(O), C(O)O, S, S(O) or $S(O)_2$;

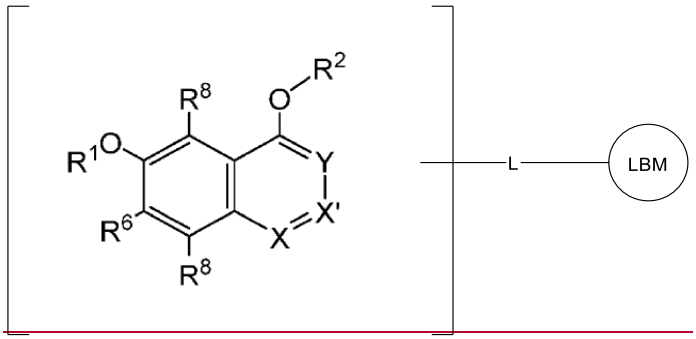
L^2 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by N(R), N(R)C(O), C(O)N(R), $N(R)S(O)_2$, $S(O)_2N(R)$, O, C(O), OC(O), C(O)O, S, S(O) or $S(O)_2$;

m is 0-4;

n is 0-4; and

p is 0-2; or

(ss)



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or a pharmaceutically acceptable salt thereof, wherein:

X and X′ are each independently CR^8, N or N^+-O^-; Y is independently N, N^+-O^- or $CR^{8'}$; provided that at least one of X, X′ or Y is neither N nor N^+-O^- and that no more than one of X, X′ or Y is N^+-O^-;

R^1 is C_1-C_6alkyl; C_2-C_6alkenyl; C_2-C_6alkynyl; $(CR^{3a}R^{3b})_m$-(3- to 7-membered cycloalkyl); $(CR^{3a}R^{3b})_m$-(3- to 7-membered heterocycloalkyl) having one to three heteroatoms; $(CR^{3a}R^{3b})_m$-(5- to 10-membered heteroaryl), having one to three heteroatoms; or $(CR^{3a}R^{3b})_m$ C_6-C_{12}aryl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, heteroaryl or aryl is optionally substituted with one to five halogen,

deuterium, OR^5, SR^5, $NR^{11a}R^{11b}$, cyano, C_1-C_6alkyl, C_3-C_6cycloalkyl or C_1-C_6alkoxy;

R^2 is $(CR^{3a}R^{3b})_m$-(3- to 10-membered cycloalkyl); $(CR^{3a}R^{3b})_m$-(3- to 10-membered heterocycloalkyl) having one to three heteroatoms; $(CR^{3a}R^{3b})_m$-(5- to 10-membered heteroaryl) having one to three heteroatoms; or $(CR^{3a}R^{3b})_m$-C_6-C_{12}aryl; wherein said cycloalkyl, heterocycloalkyl, heteroaryl or aryl is optionally substituted with one to five R^4; and wherein, if the heteroatom on said heterocycloalkyl and heteroaryl is N, said N is optionally substituted with $R^{4'}$; or R^2 is C_1-C_6alkyl, wherein said alkyl is optionally substituted with NH_2, OH or cyano;

R^{3a} and R^{3b} for each occurrence are independently hydrogen or C_1-C_3alkyl;

R^4 for each occurrence is independently a bond, deuterium halogen, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, oxo, OR^5, SR^5, $S(O)R^9$, $S(O)_2R^9$, $NR^{11a}R^{11b}$, $C(O)R^{10}$, $(CR^{3a}R^{3b})_n$-(3- to 7-membered cycloalkyl), $(CR^{3a}R^{3b})_n$-(4- to 10-membered heterocycloalkyl), having one to three heteroatoms, $(CR^{3a}R^{3b})_n$-(5- to 10-membered heteroaryl), having one to three heteroatoms, or $(CR^{3a}R^{3b})_n$-C_6-C_{12}aryl wherein said alkyl, cycloalkyl, heterocycloalkyl, heteroaryl or aryl is each optionally and independently substituted with one to five deuterium, halogen, OR^5, SR^5, $NR^{11a}R^{11b}$, cyano, C_1-C_6alkyl, C_3-C_6cycloalkyl or C_1-C_6alkoxy; or two R^4 taken together with the respective carbons to which each are bonded form a 3- to 6-membered cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl is optionally substituted with one to three halogen, deuterium, OR^5, SR^5, $NR^{11a}R^{11b}$, cyano or C_1-C_6alkyl or C_1-C_6alkoxy, wherein the alkyl or alkoxy is optionally substituted with halogen, deuterium, OR^5, SR^5, $NR^{11a}R^{11b}$, or cyano; and wherein, if a heteroatom on said heterocycloalkyl is N, said N is optionally substituted with $R^{4'}$;

$R^{4'}$ is independently C_1-C_6alkyl, C_2-C_6alkenyl, $C(O)R^{10}$, $S(O)_2R^9$, $(CR^{3a}R^{3b})_n$-(3- to 7-membered cycloalkyl), $(CR^{3a}R^{3b})_n$-(4- to 10-membered heterocycloalkyl) or $C(O)(CH_2)_tCN$; wherein said alkyl, alkenyl, cycloalkyl, or heterocycloalkyl is each optionally and independently substituted with one to five deuterium, halogen, OH, cyano or C_1-C_6alkoxy; or R^4 and $R^{4'}$ taken together with the respective atoms to which each are bonded form a 3- to 6-membered cycloalkyl or 4- to 6-membered heterocycloalkyl, wherein said cycloalkyl or heterocycloalkyl is optionally substituted with one to three

halogen, deuterium, $-OR^5$, $-SR^5$, $-NR^{11a}R^{11b}$, cyano, C_1-C_6alkyl or C_1-C_6alkoxy, wherein the alkyl or alkoxy is optionally substituted with halogen, deuterium, $-OR^5$, $-SR^5$, $-NR^{11a}R^{11b}$, or cyano;

R^5 is independently hydrogen or C_1-C_6alkyl, wherein said alkyl is optionally substituted with halogen, deuterium, C_1-C_6alkoxy, C_1-C_6alkylthiolyl, $-NR^{11a}R^{11b}$, cyano, C_1-C_6alkyl or C_3-C_6cycloalkyl; or two R^5 taken together with the oxygen atoms to which they are bonded form a 5- or 6-membered heterocycloalkyl;

R^6 is $-C(O)NHR^7$, $-CO_2R^7$ or cyano;

R^7 is hydrogen or C_1-C_6alkyl;

each R^8 is independently hydrogen, halogen, cyano, $-OR^5$, $-SR^5$, $-NR^{11a}R^{11b}$, C_6alkyl, C_3-C_6cycloalkyl, 3- to 10-membered heterocycloalkyl or 5- to 6-membered heteroaryl or aryl, wherein said alkyl, cycloalkyl, heterocycloalkyl, heteroaryl or aryl is optionally substituted with one to three halogen, $-NR^{11a}R^{11b}$, $-OR^5$, $-SR^5$, cyano, C_1-C_3 alkyl, $-C(O)R^{10}$ or oxo;

$R^{8'}$ is hydrogen, deuterium, halogen, cyano, $-OR^5$, $-SR^5$ or $-NR^{11a}R^{11b}$;

R^9 is $-(CR^{3a}R^{3b})_p$-(C_1-C_3alkyl), $-(CR^{3a}R^{3b})_p$-(4- to 6-membered cycloalkyl), $-(CR^{3a}R^{3b})_p$-(4- to 6-membered heterocycloalkyl) or $-(CR^{3a}R^{3b})_p$-(C_5-C_9aryl), wherein said alkyl, cycloalkyl, heterocycloalkyl or aryl are each optionally substituted with fluoro or C_1-C_3alkyl;

R^{10} is C_1-C_6alkyl, wherein said alkyl is optionally substituted with deuterium, halogen, OH, C_1-C_6alkoxy or cyano;

R^{11a} and R^{11b} are each independently hydrogen or C_1-C_6alkyl, wherein said alkyl is optionally substituted with deuterium, C_1-C_6alkoxy or cyano; and if C_2-C_6alkyl, said alkyl is optionally substituted with deuterium, C_1-C_6alkoxy, cyano, halogen or OH;

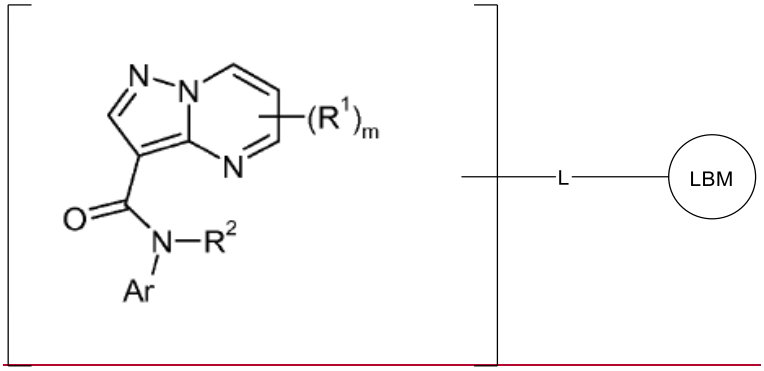
m is independently 0, 1, 2 or 3;

n is independently 0, 1, 2 or 3;

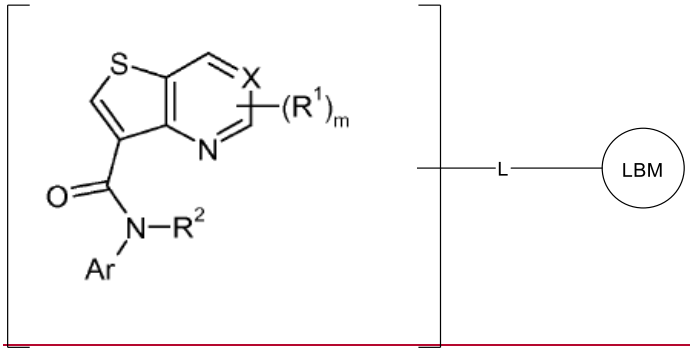
p is independently 0 or 1; and

t is 1, 2 or 3; or

(tt)



~~I-yyy-1~~



~~I-yyy-2~~

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

~~X is N or CH~~

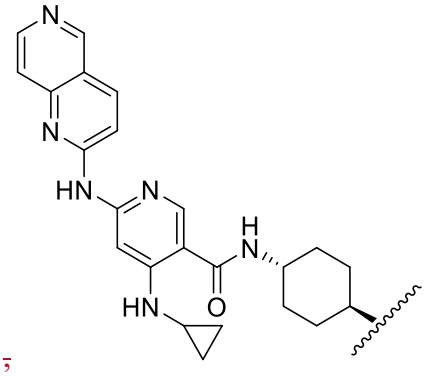
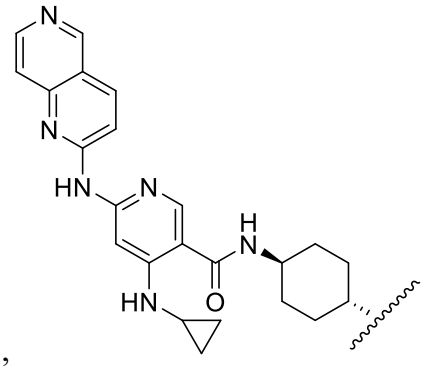
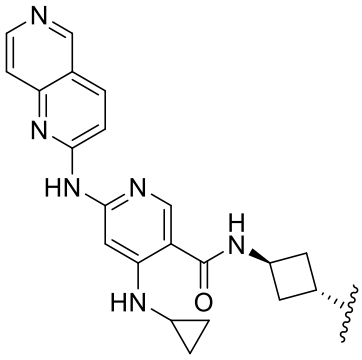
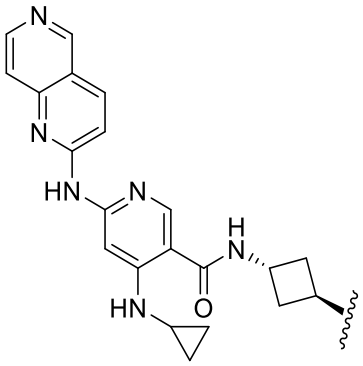
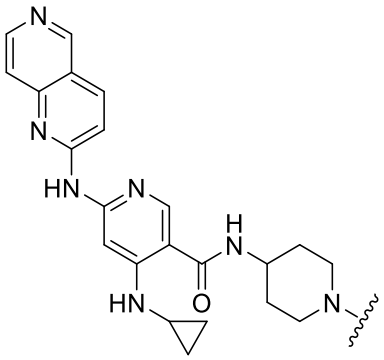
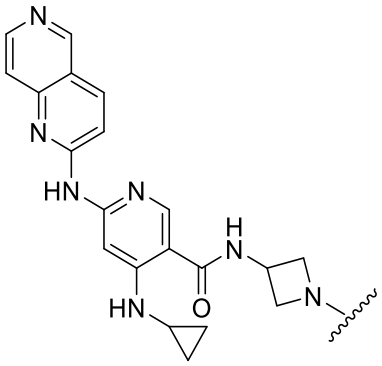
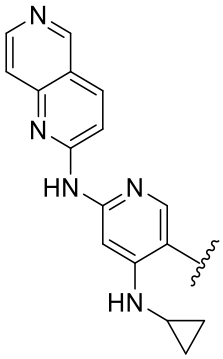
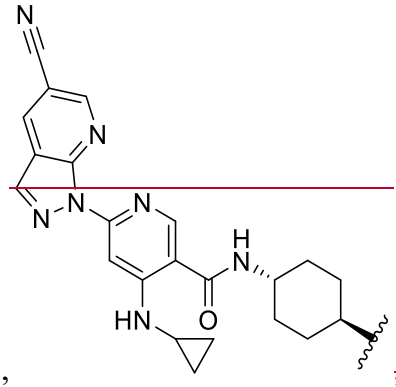
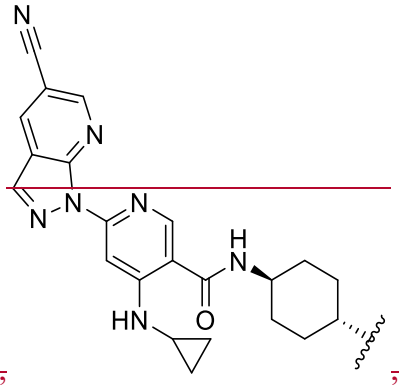
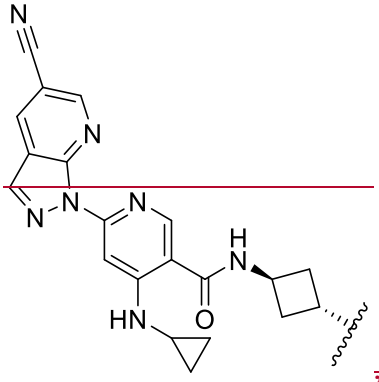
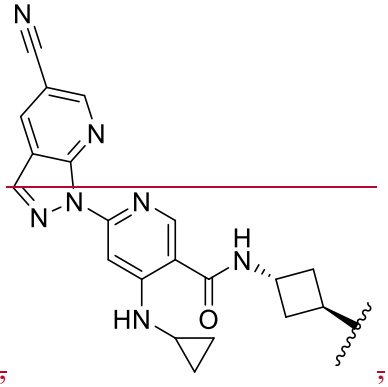
~~m is 1 or 2;~~

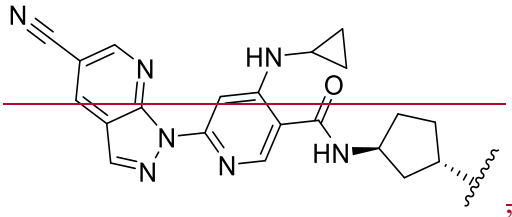
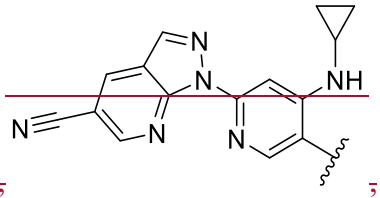
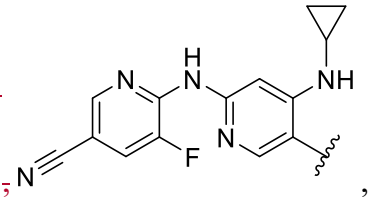
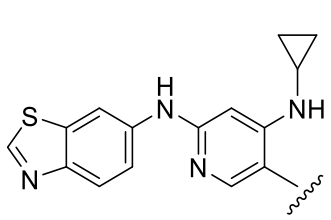
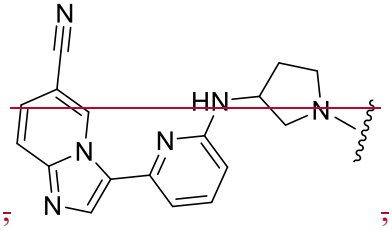
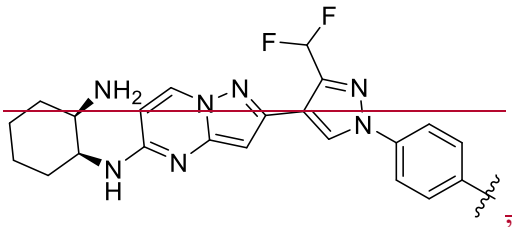
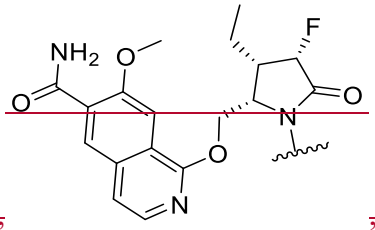
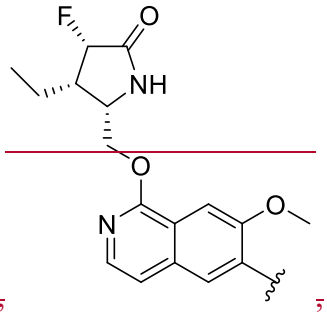
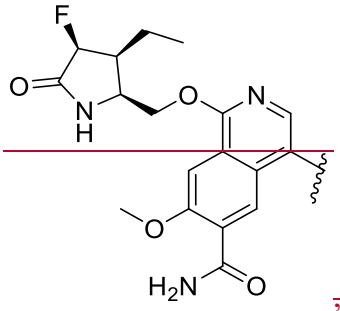
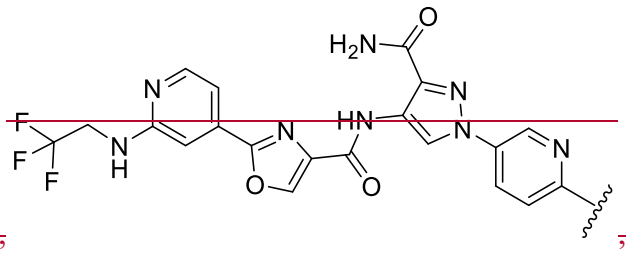
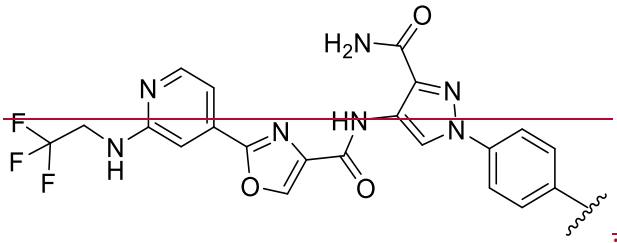
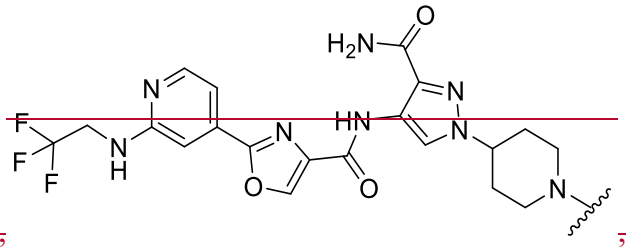
~~Ar is optionally substituted aryl or optionally substituted heteroaryl;~~

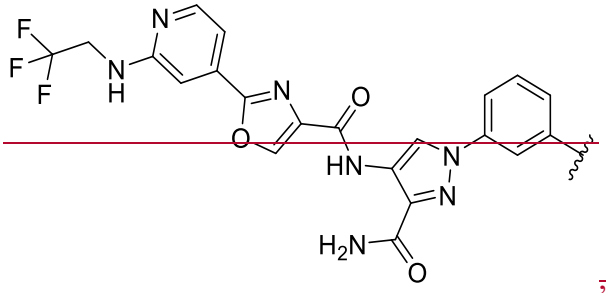
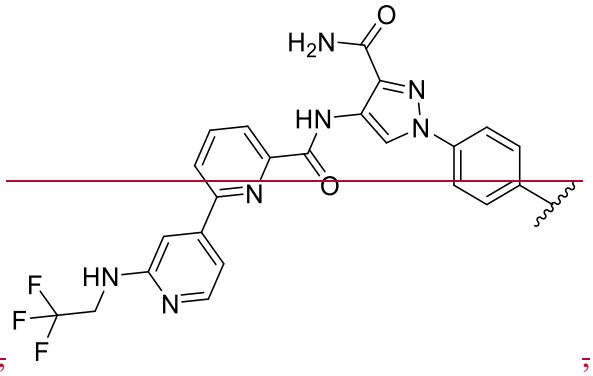
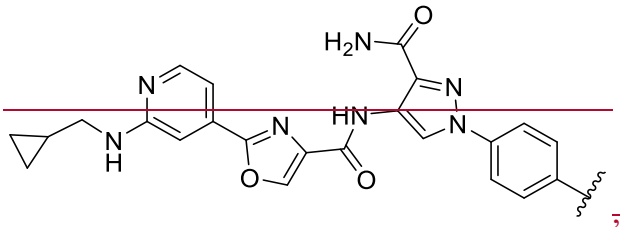
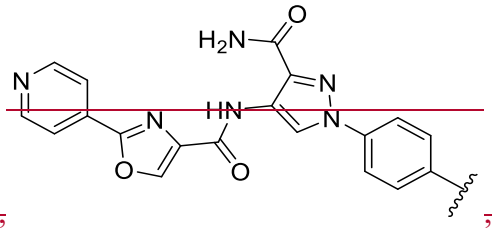
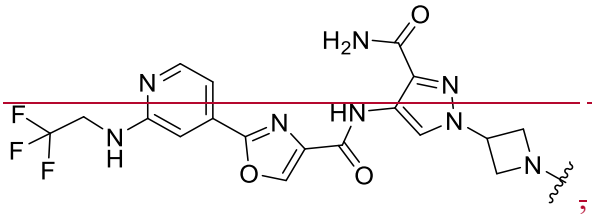
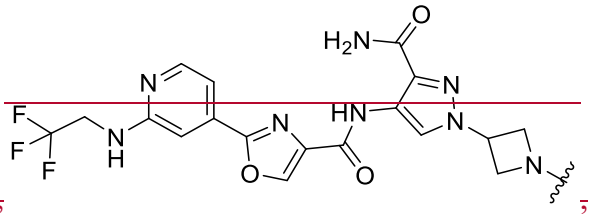
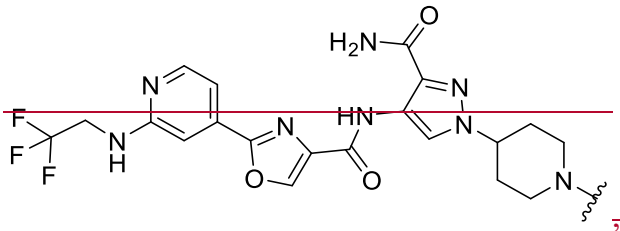
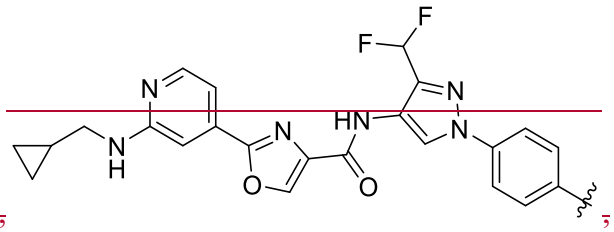
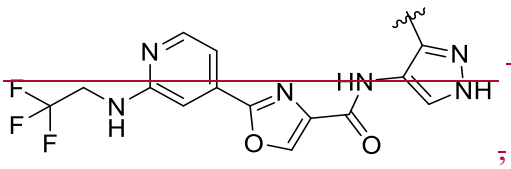
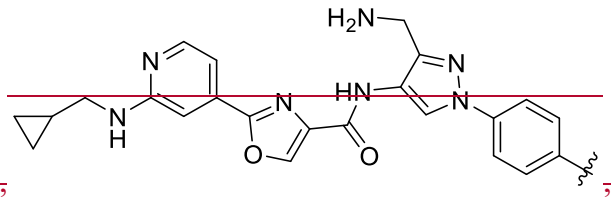
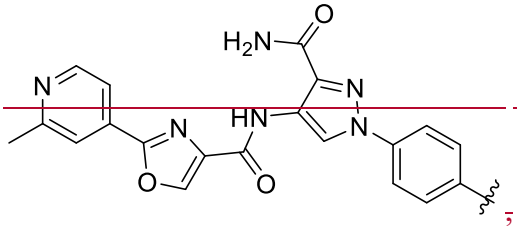
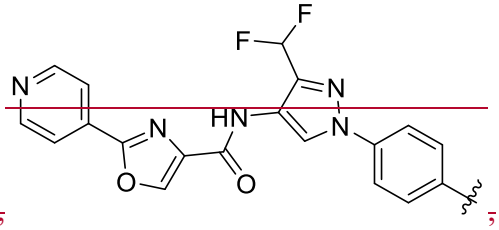
~~R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyl, hydroxy-C_{1-6}alkyl, C_{1-6}alkyl-amino, amino-C_{1-6}alkyl, amino-C_{1-6}alkyl-amino, hydroxy-C_{1-6}alkylamino, C_{3-6}cycloalkylamino, amino-C_{3-6}cycloalkylamino, amino-C_{3-6}heterocycloalkylamino, aminocarbonyl, halo, hydroxy-C_{1-6}alkyl, or hydroxy-C_{1-6}alkoxy; and~~

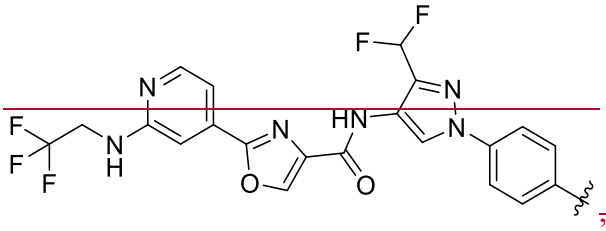
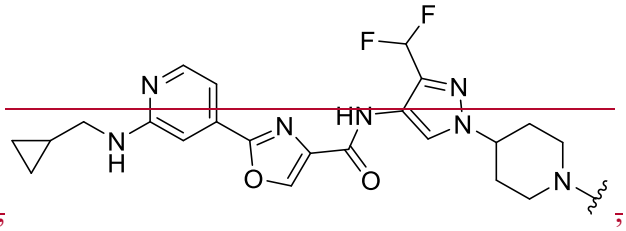
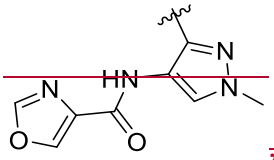
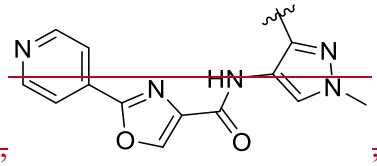
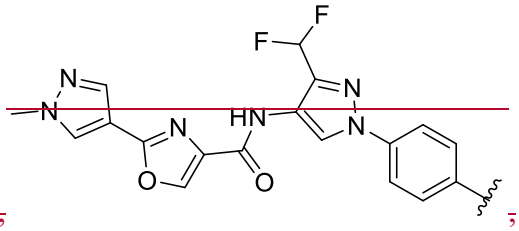
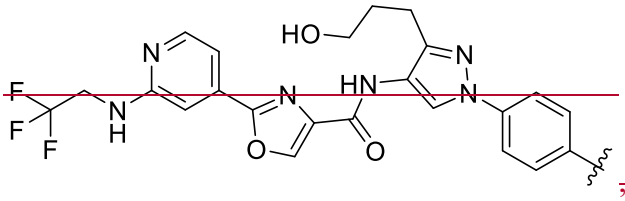
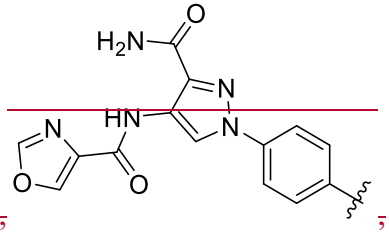
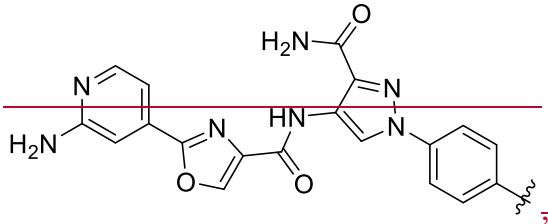
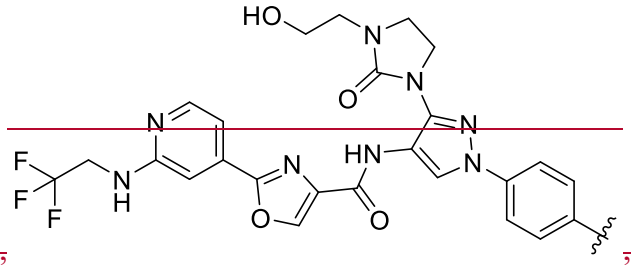
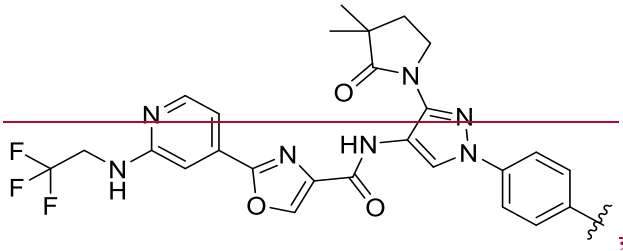
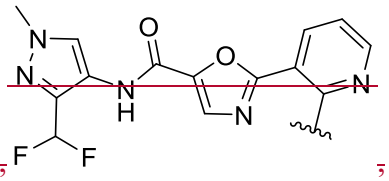
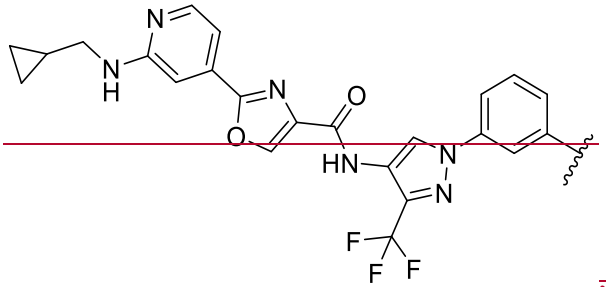
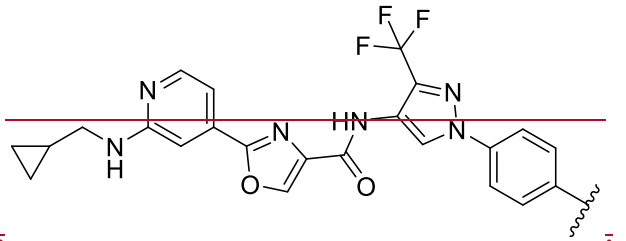
~~R^2 is hydrogen or C_{1-6}alkyl.~~

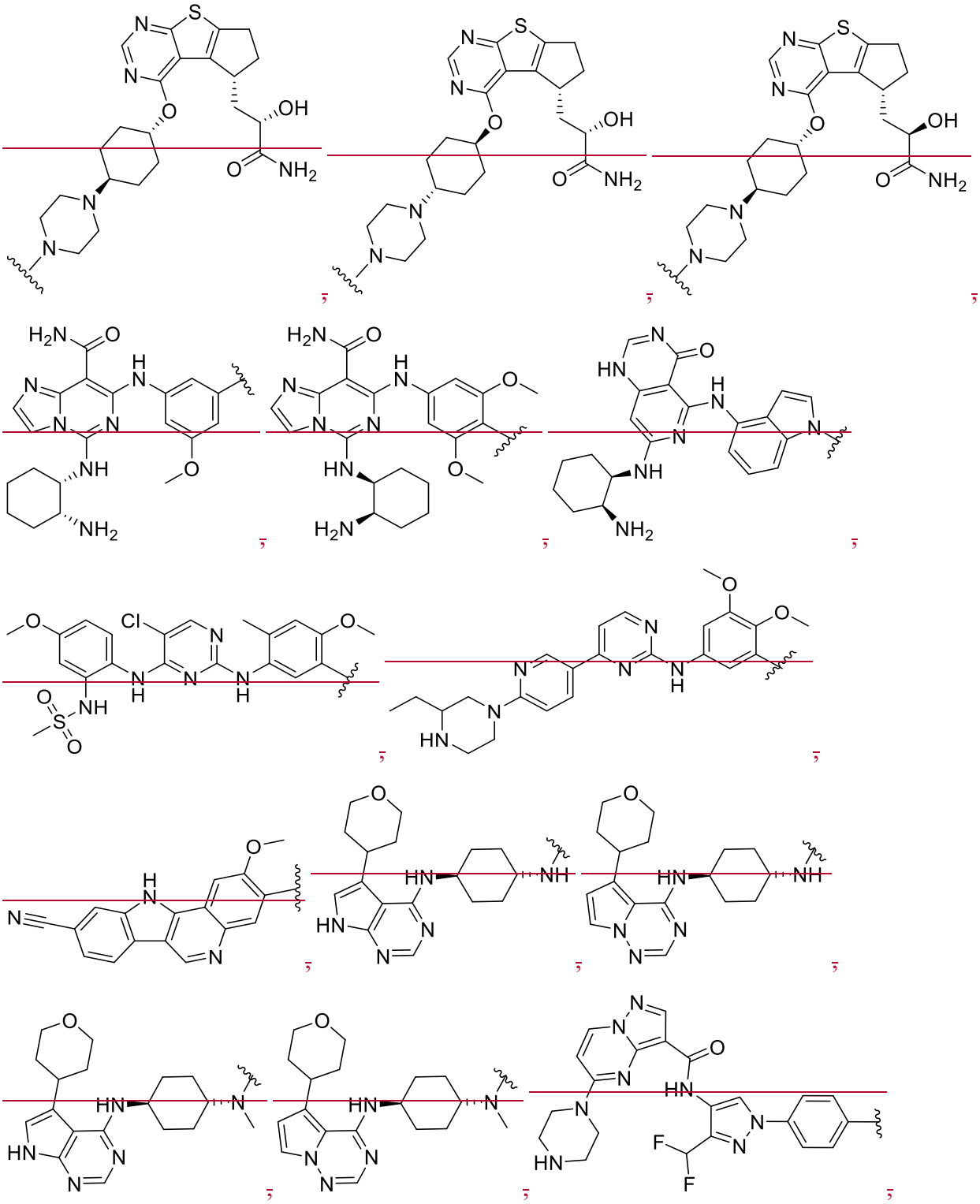
~~11~~3. The compound according to claim ~~9~~1, wherein the IRAK4 binding moiety is selected from ~~the group consisting of~~:

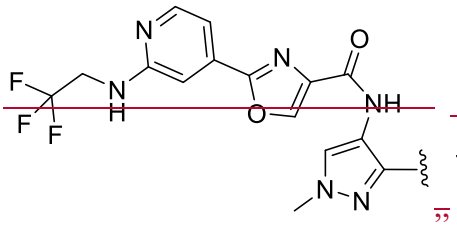

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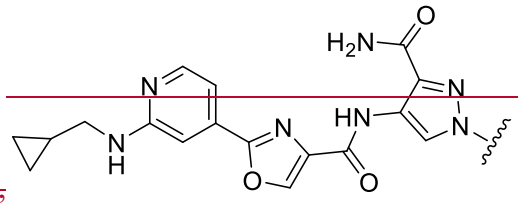

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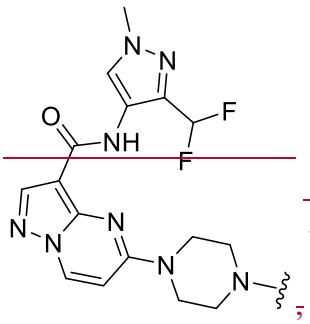













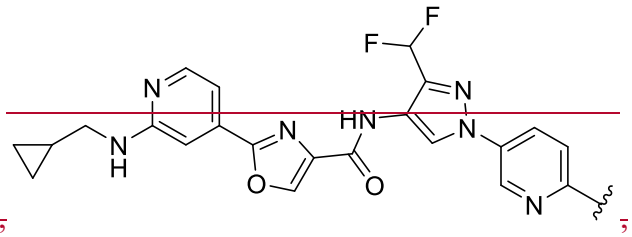














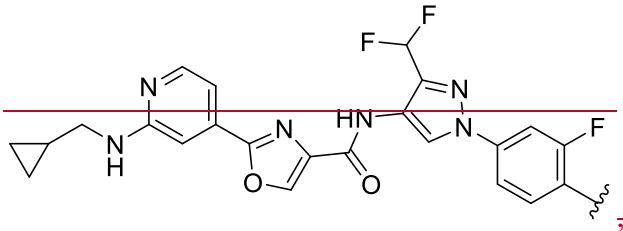


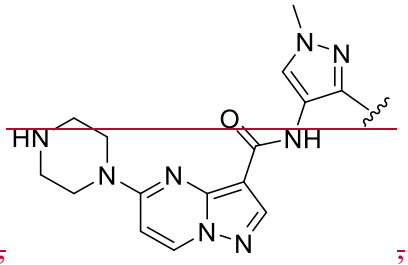


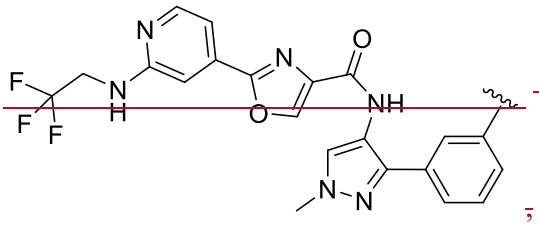


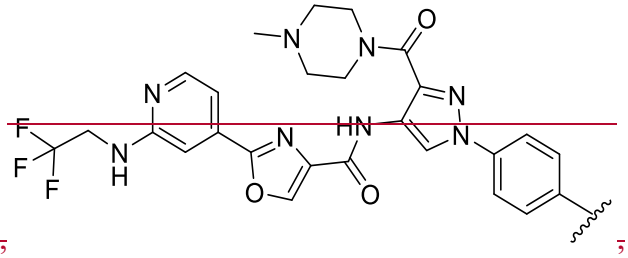


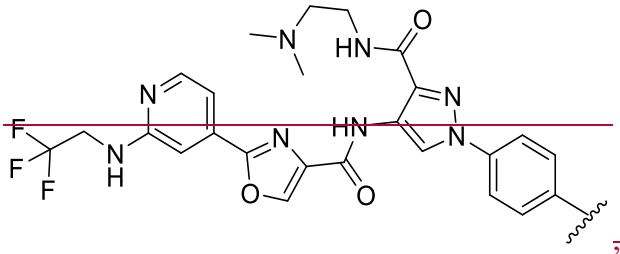


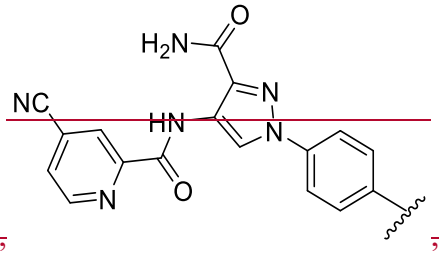


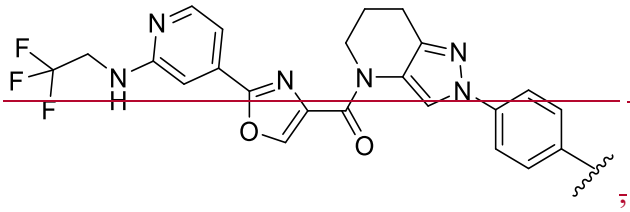


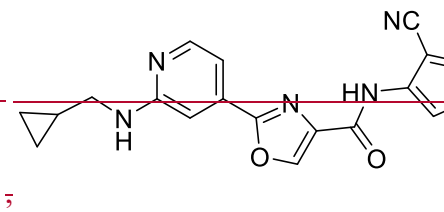


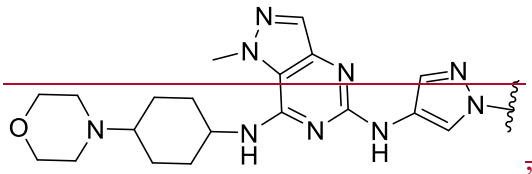
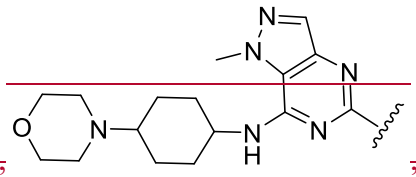


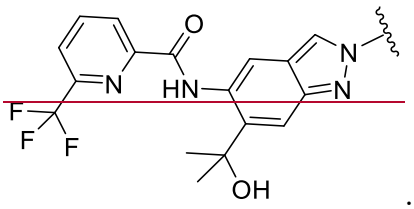




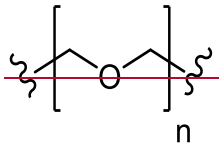




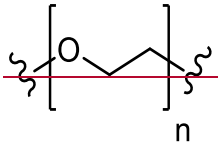


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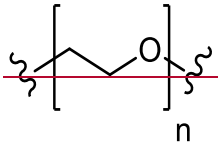

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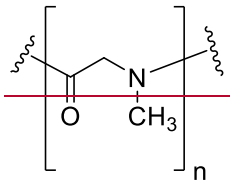
12. The compound according to claim 1, wherein L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -

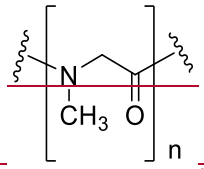

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-$NRS(O)_2$-, -$S(O)_2NR$-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, -NRC(O)O-,


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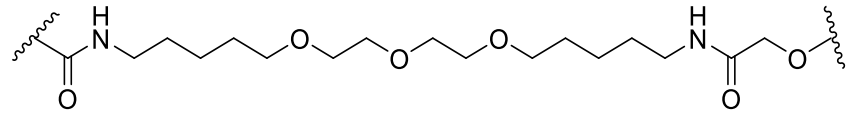

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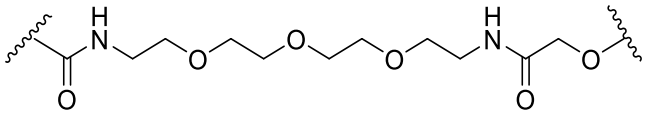

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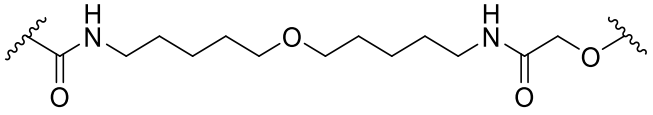

, wherein:

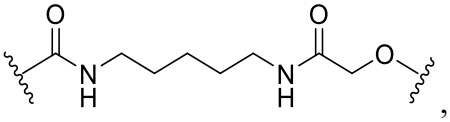
each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated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

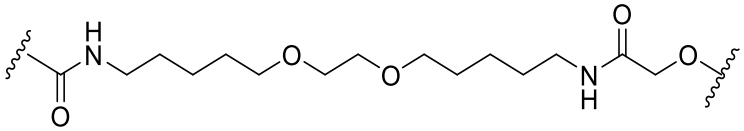
~~134~~. The compound of claim ~~121~~1, wherein L is selected from:

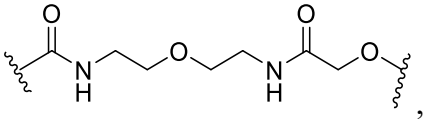
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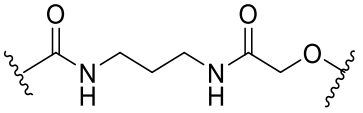
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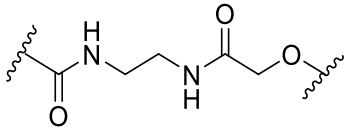
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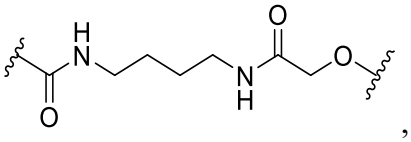
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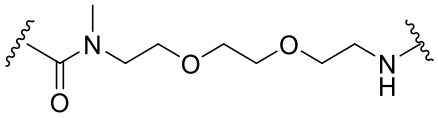
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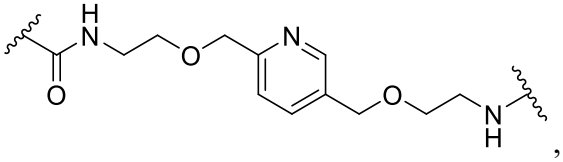
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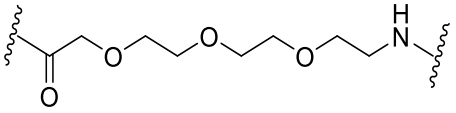
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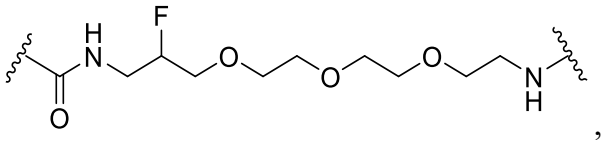
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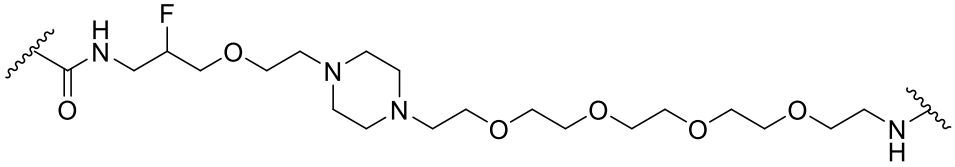
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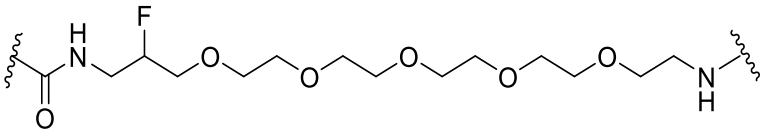
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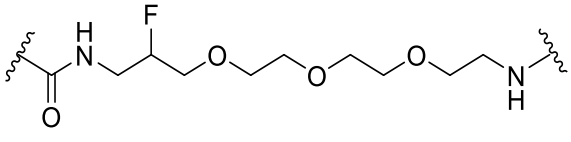
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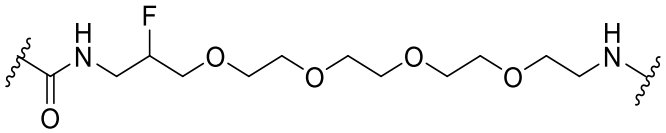
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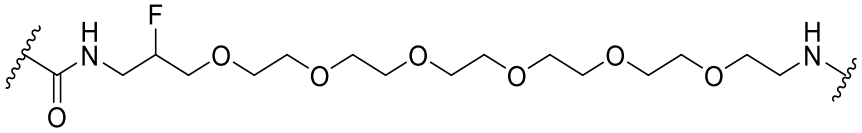
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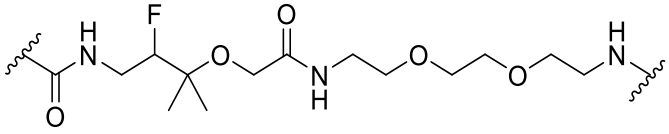
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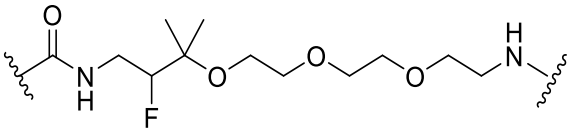
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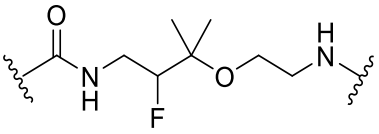
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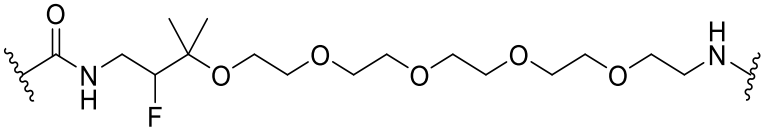

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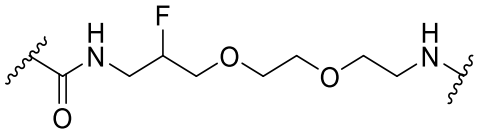

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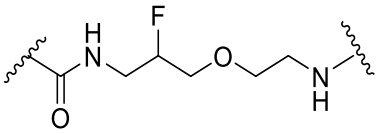

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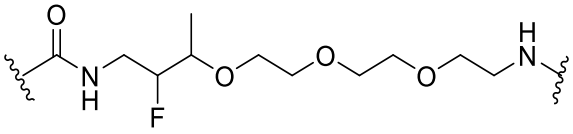

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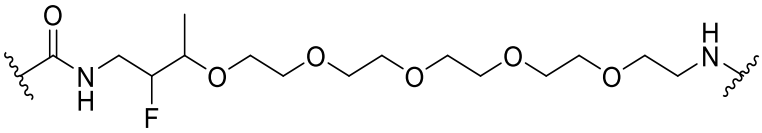

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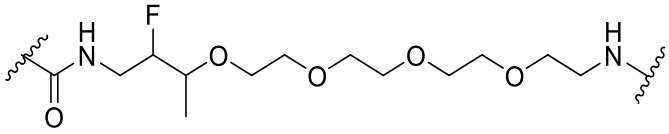

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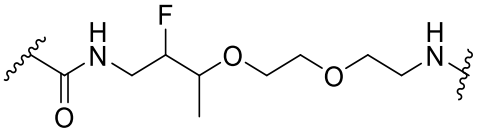

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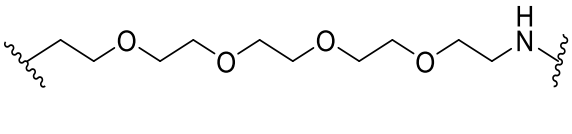

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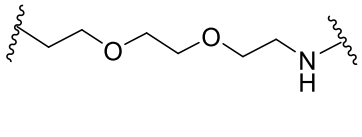

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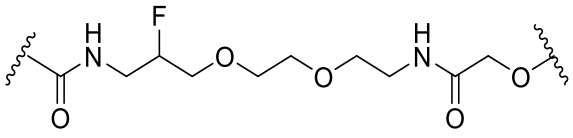
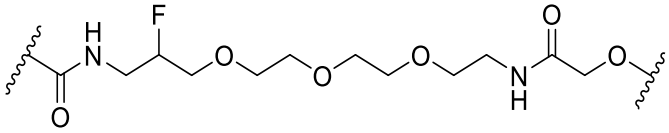
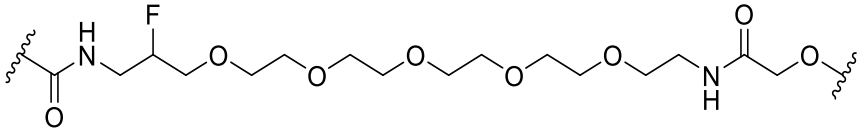
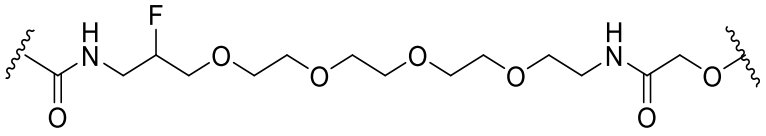
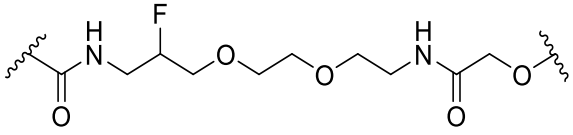
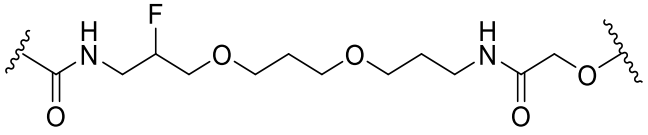
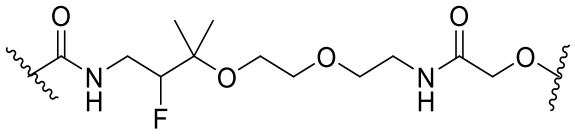
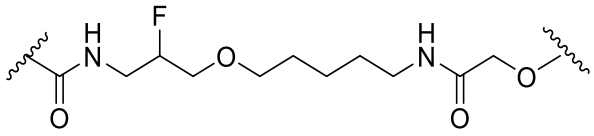
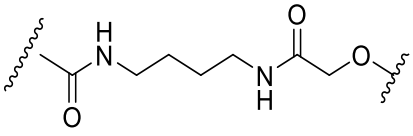
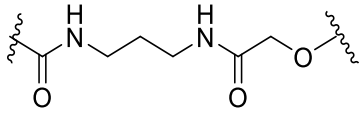
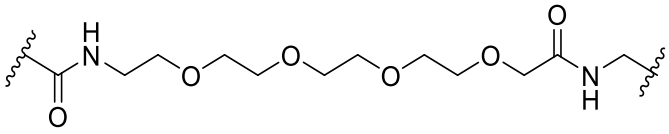
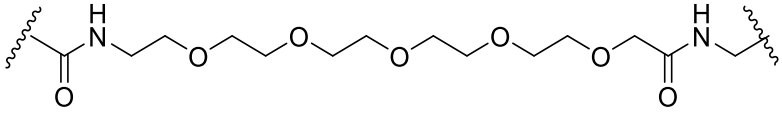
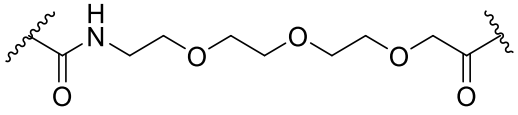
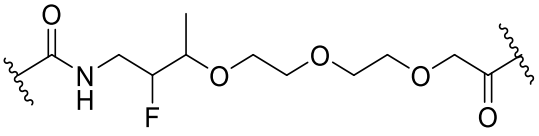
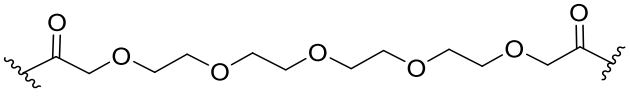

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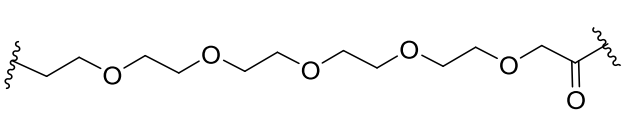
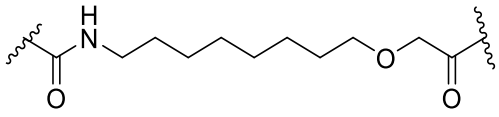
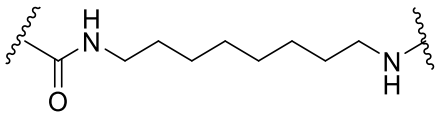
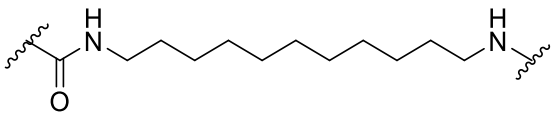
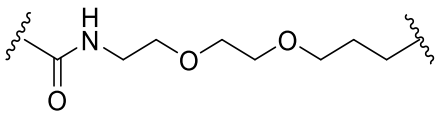
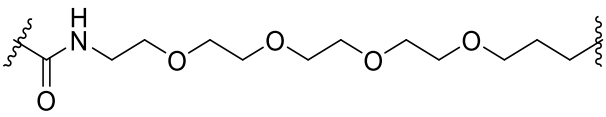
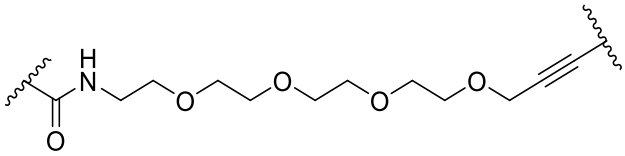
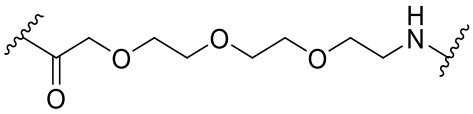
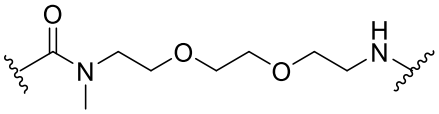
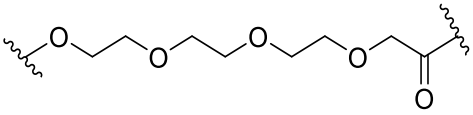
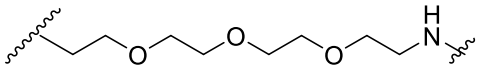
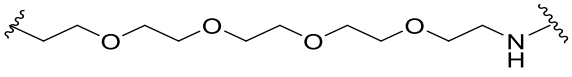
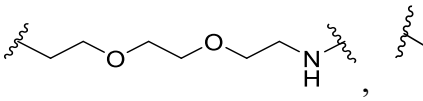
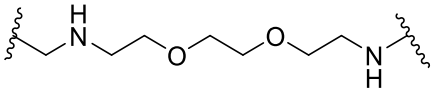
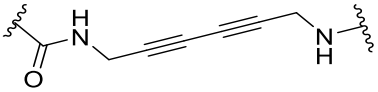

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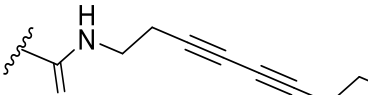
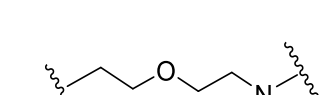
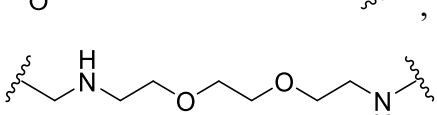

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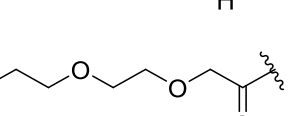
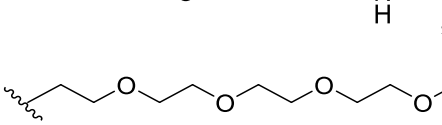
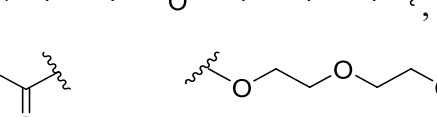
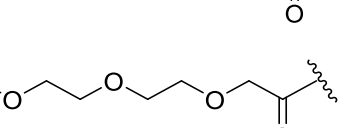

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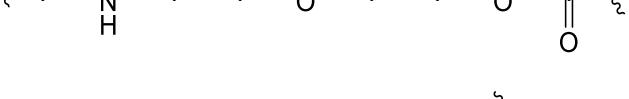
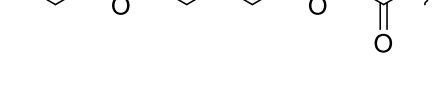
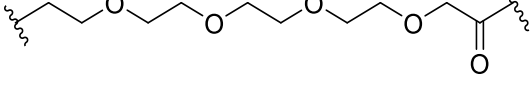
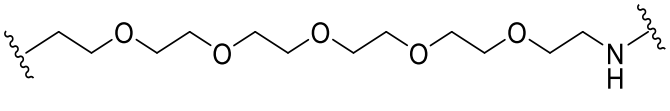

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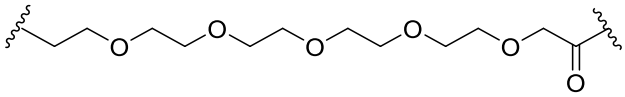
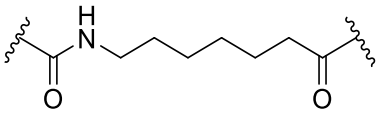
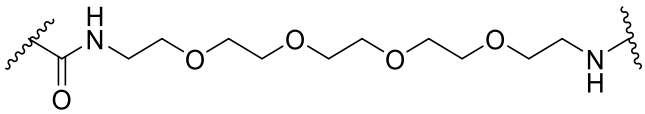
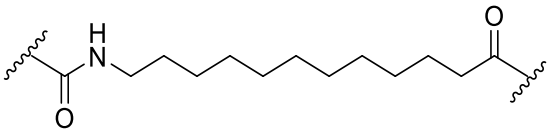
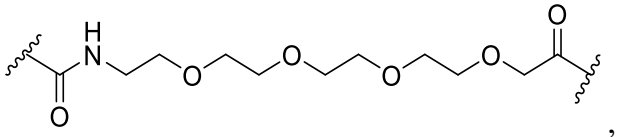
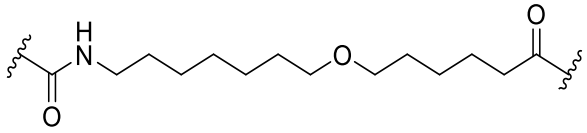
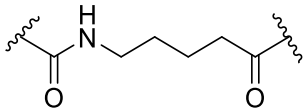
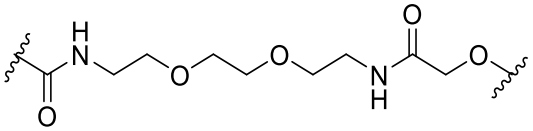
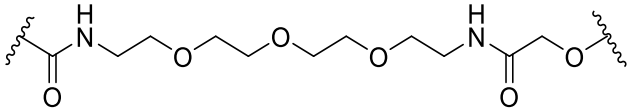
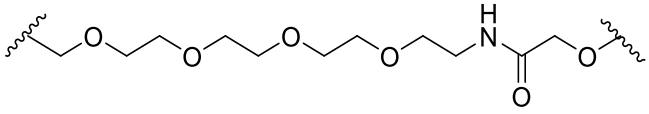
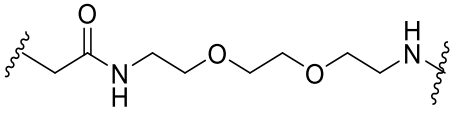
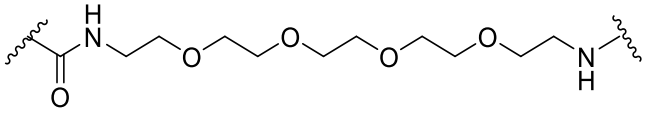
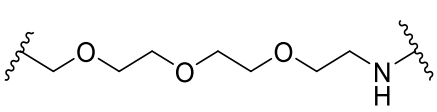
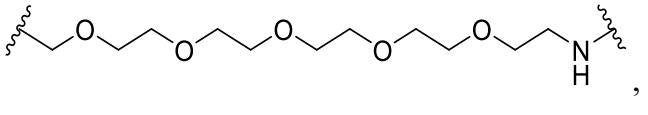

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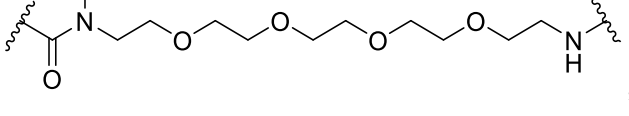
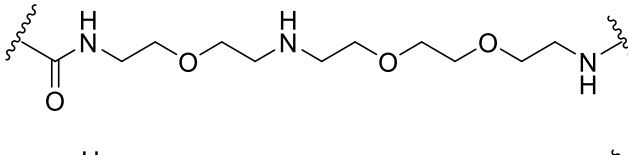
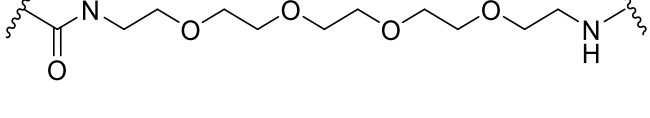
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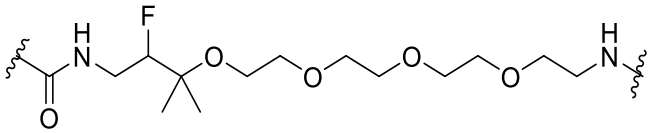
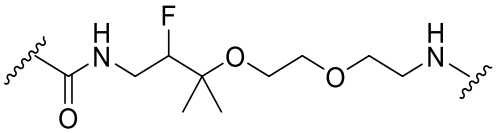
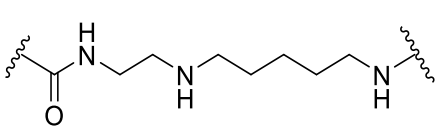
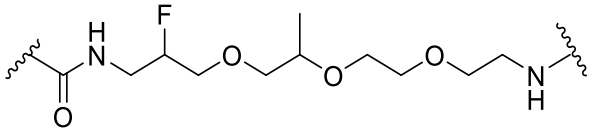
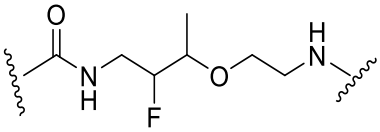
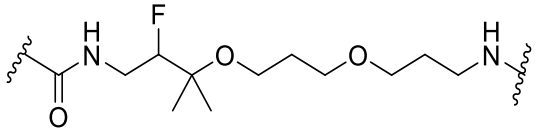
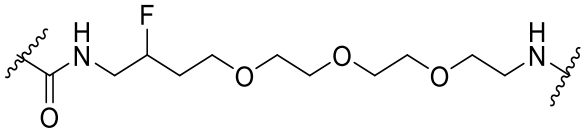
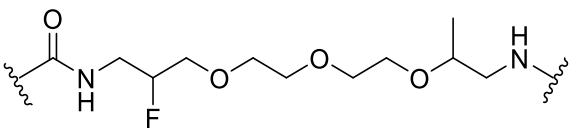
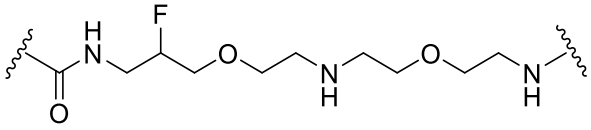
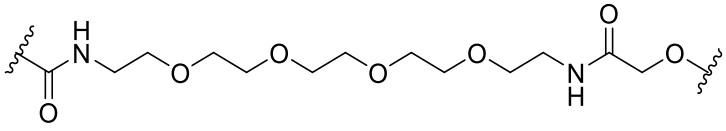
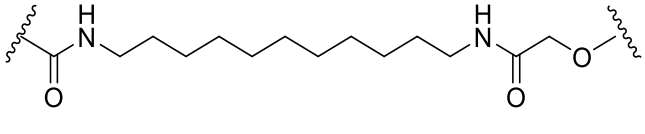
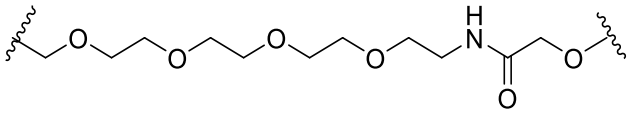
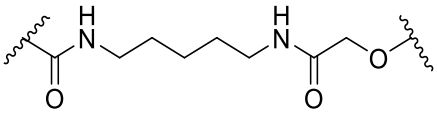
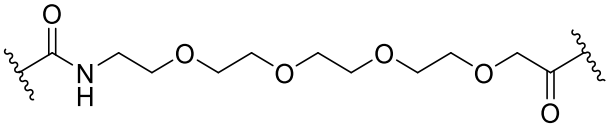
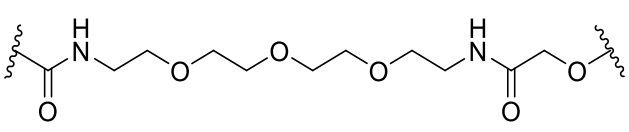
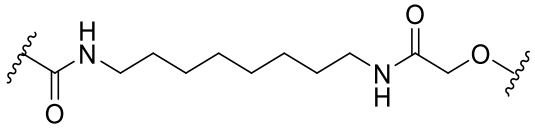
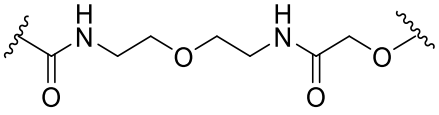
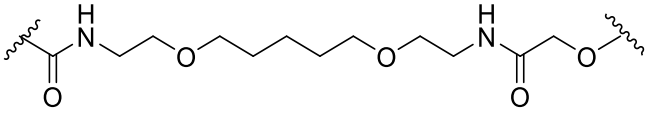
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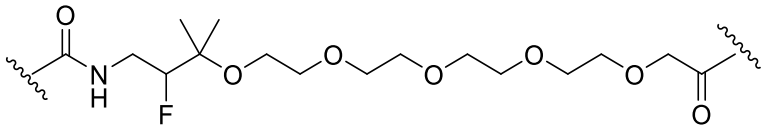
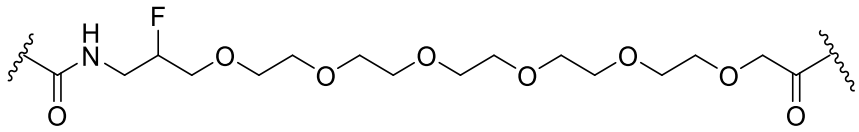
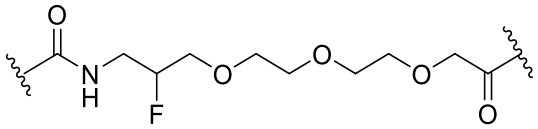
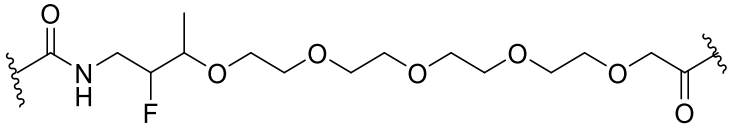
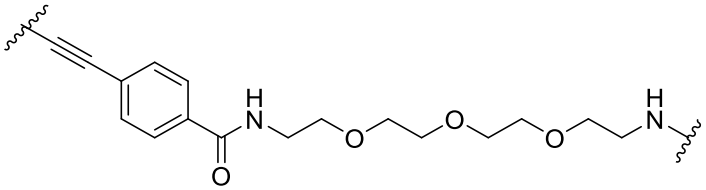
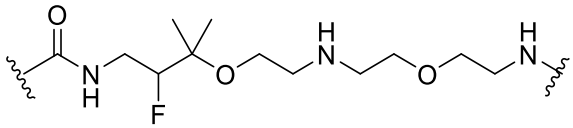
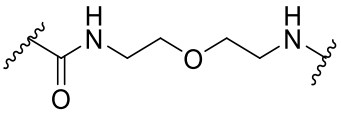
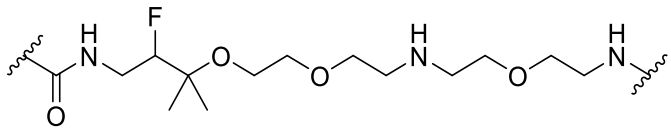

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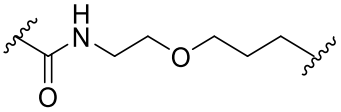
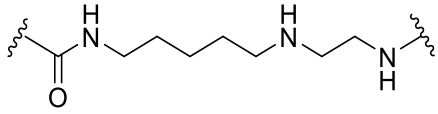
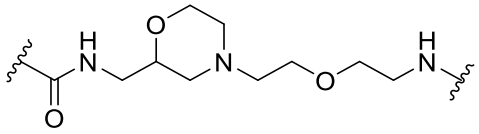
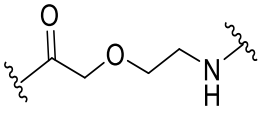
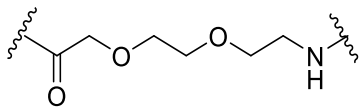
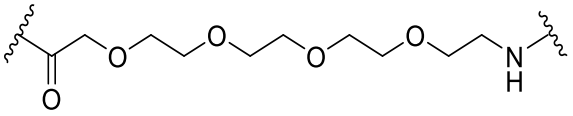
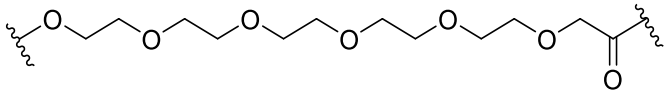
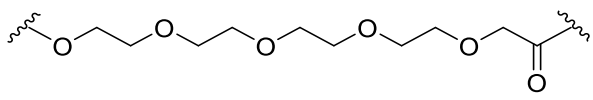
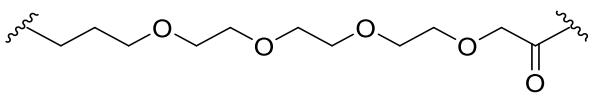
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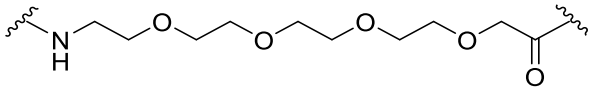
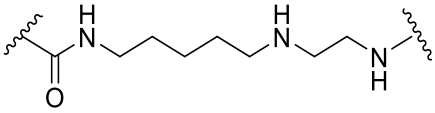
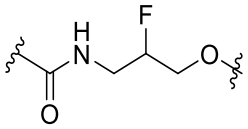
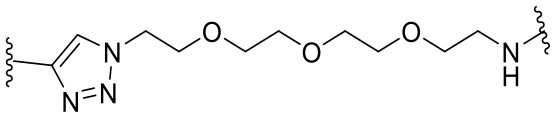
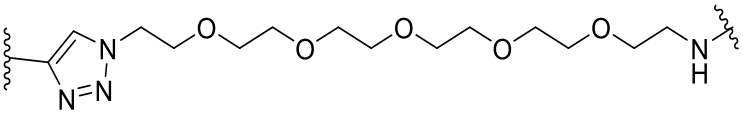
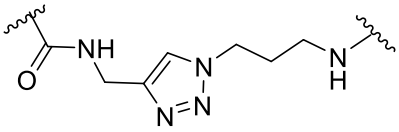
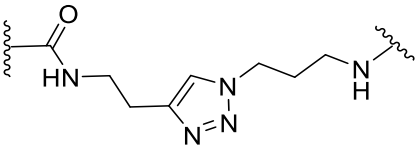
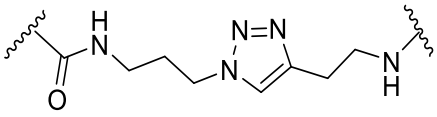
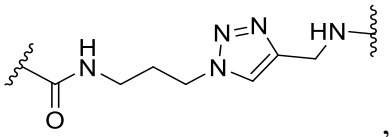
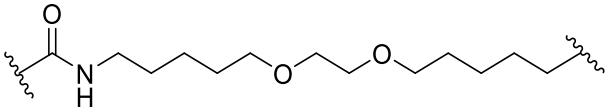
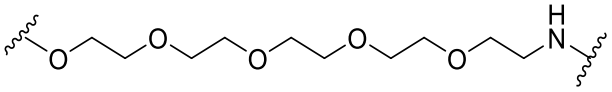
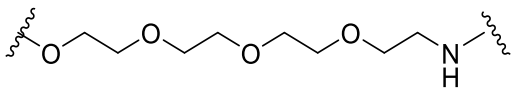
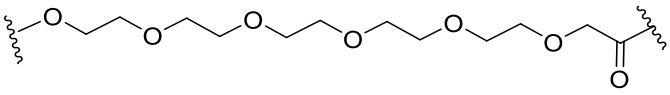
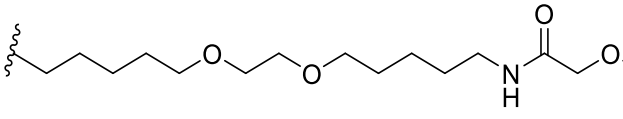
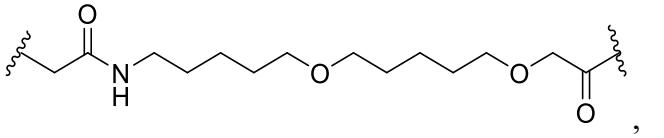
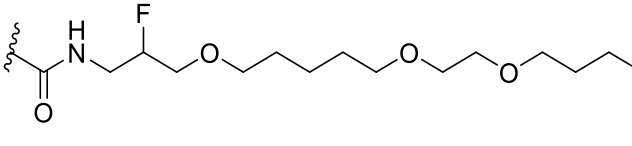
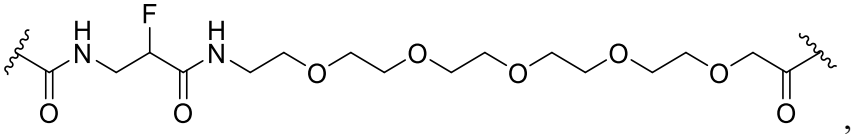
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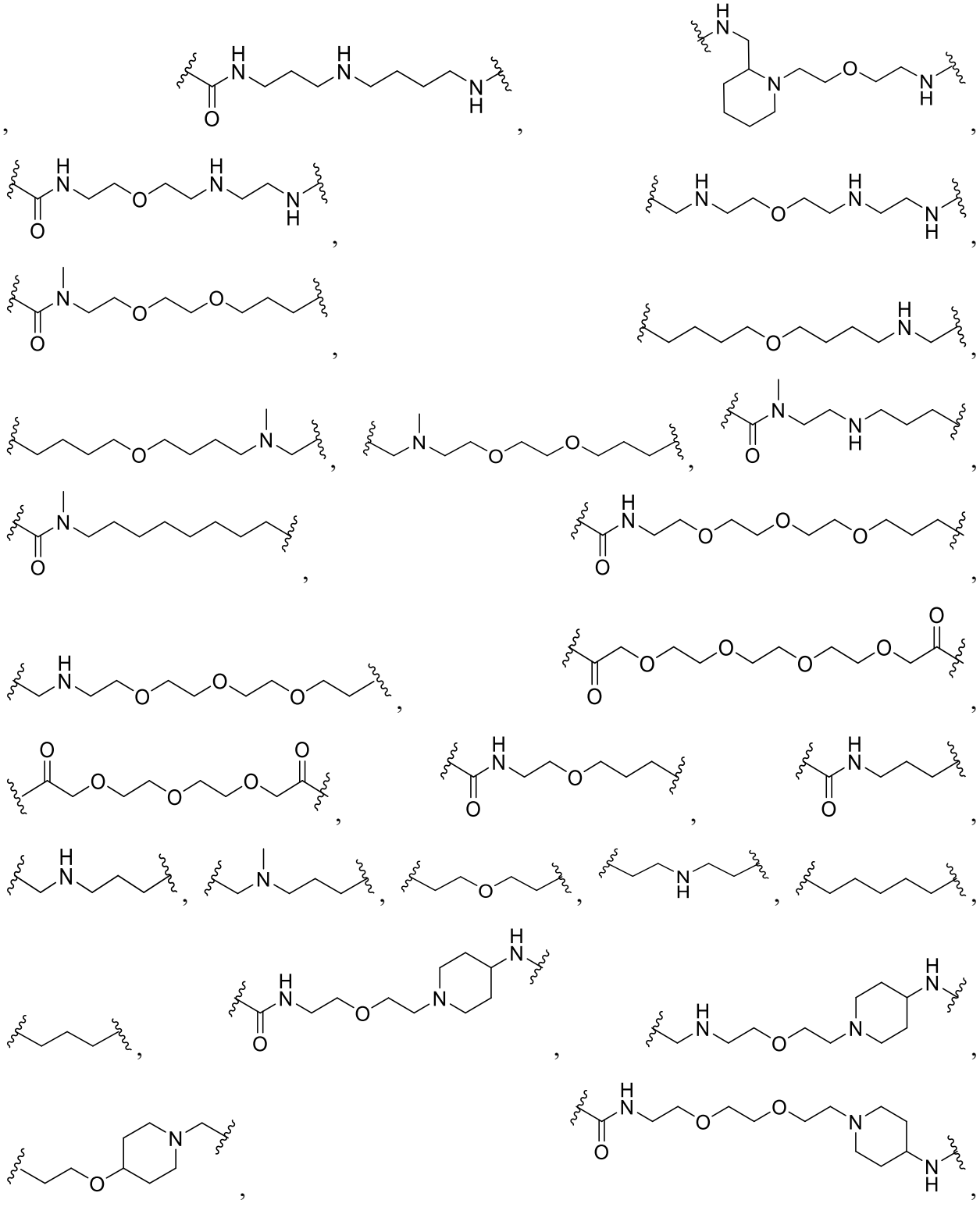

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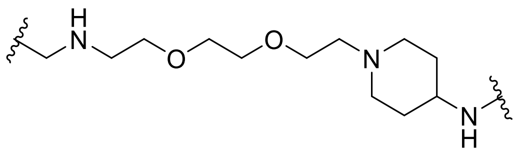

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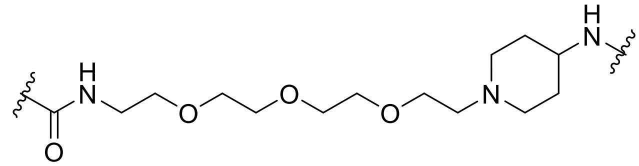
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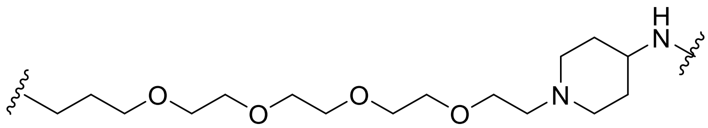

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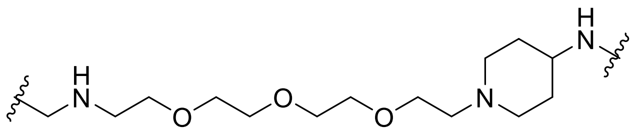
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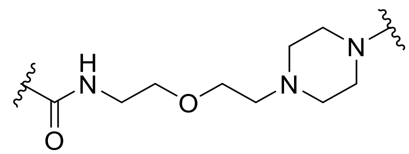


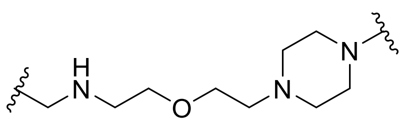
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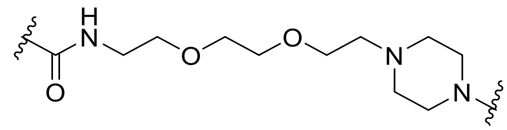
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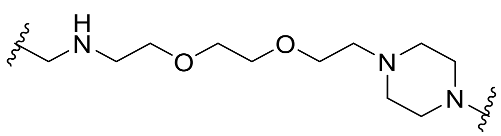
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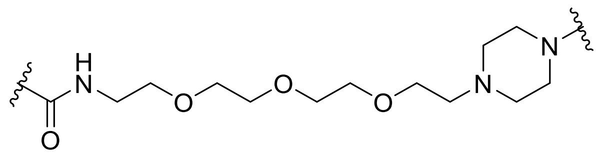
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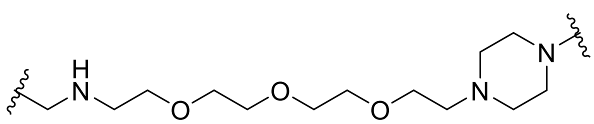
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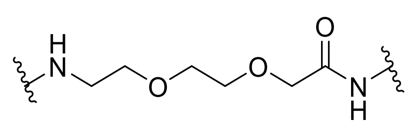
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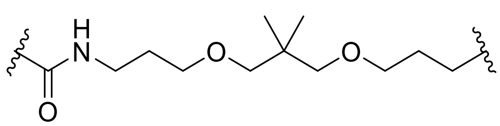
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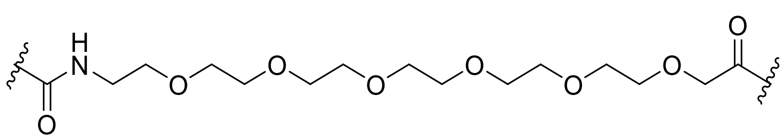
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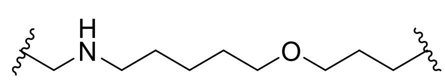
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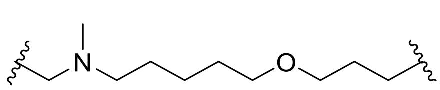
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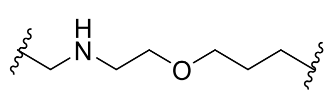
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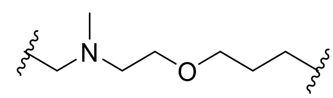
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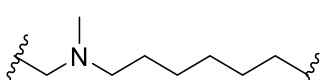
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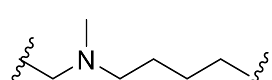
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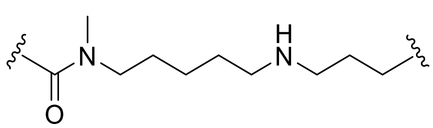
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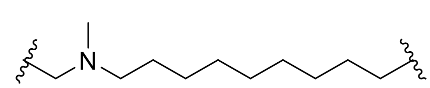
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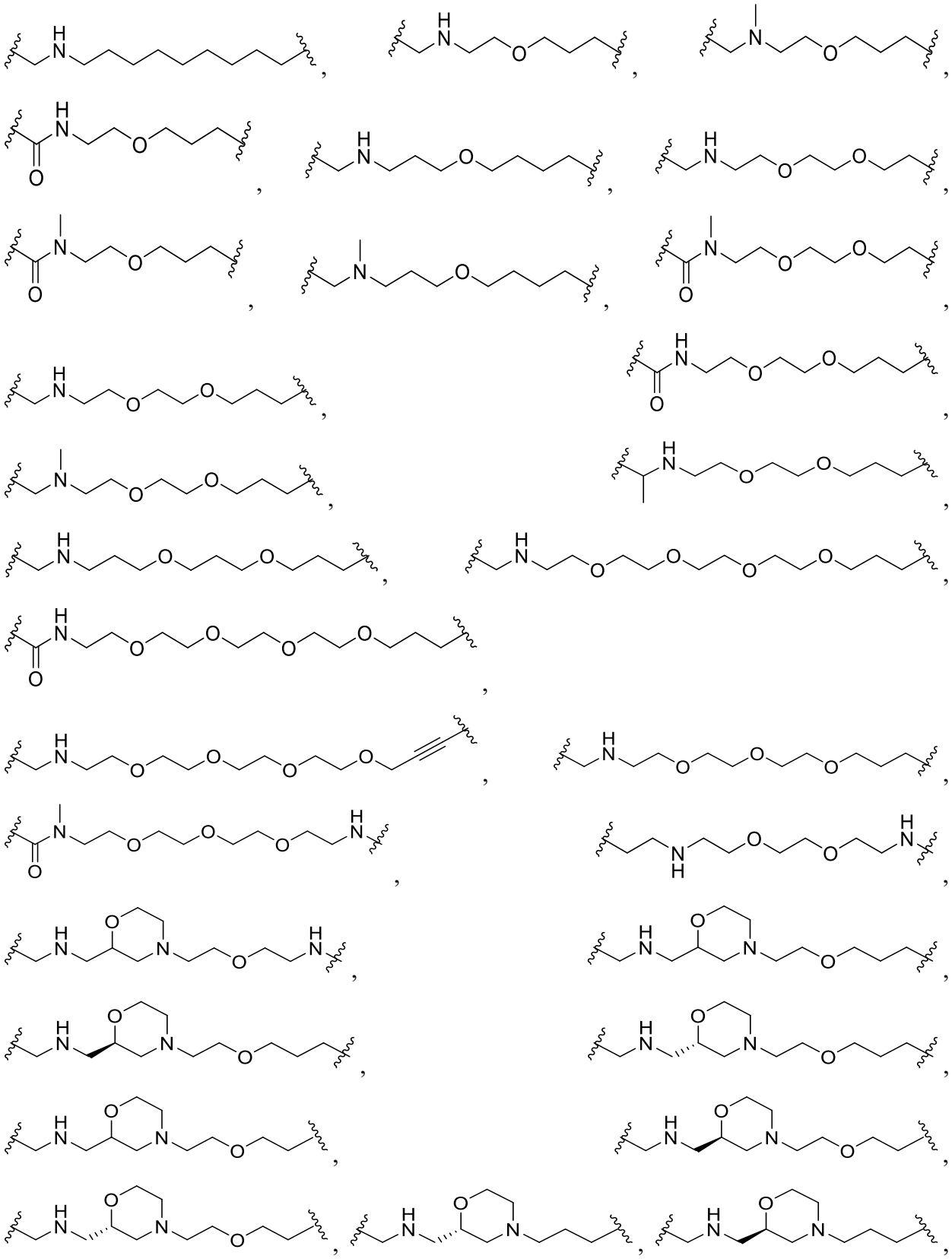
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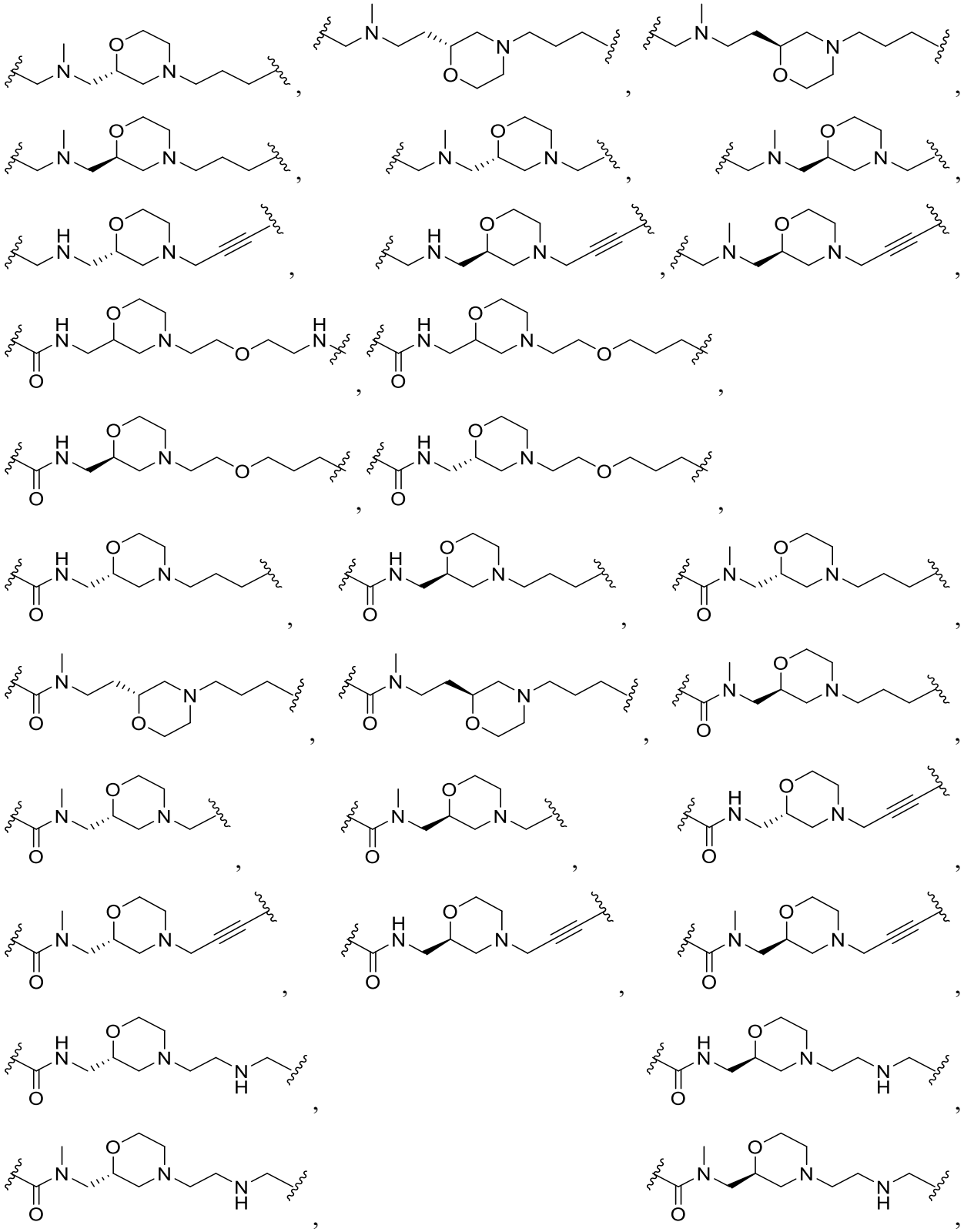
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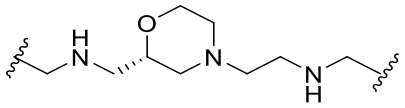
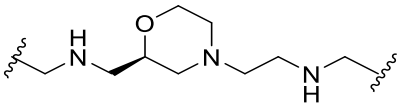
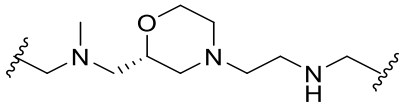
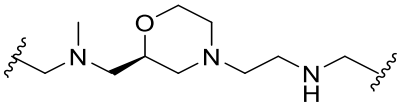
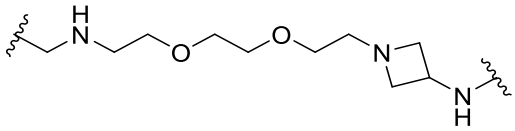
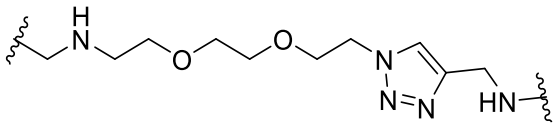
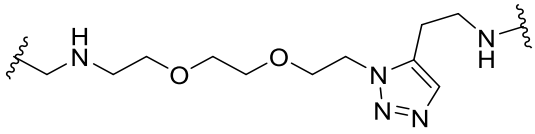
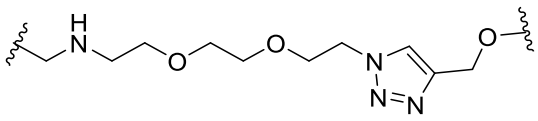
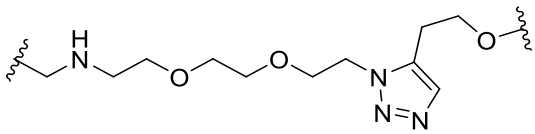
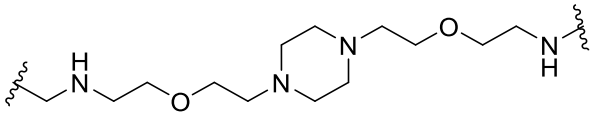
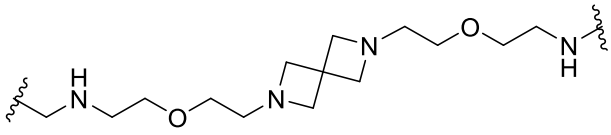
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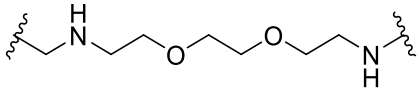
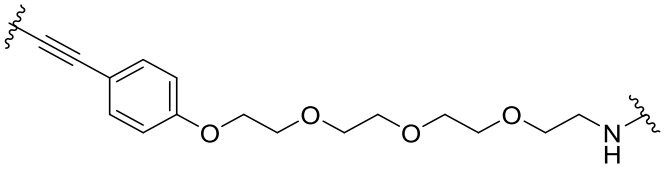
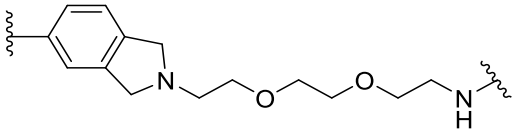
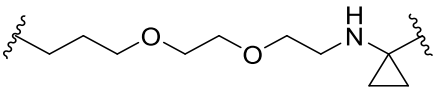
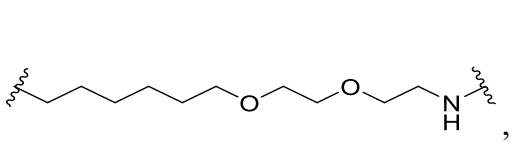
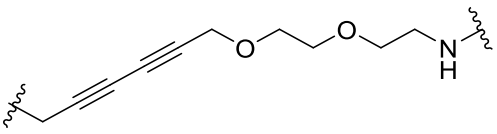
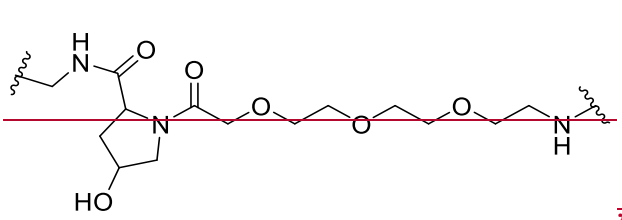
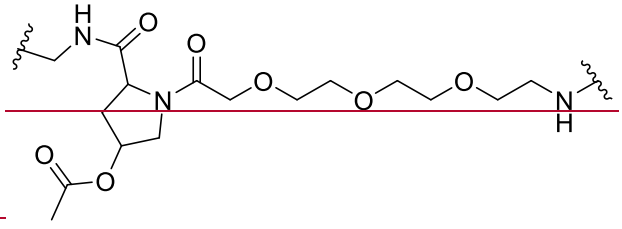
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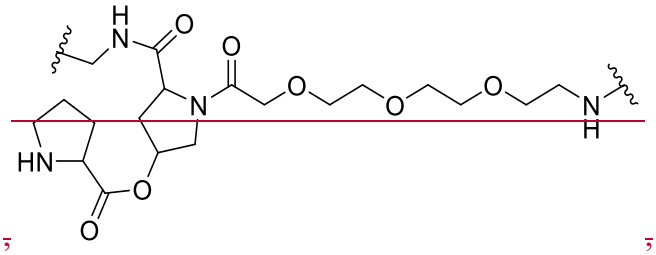
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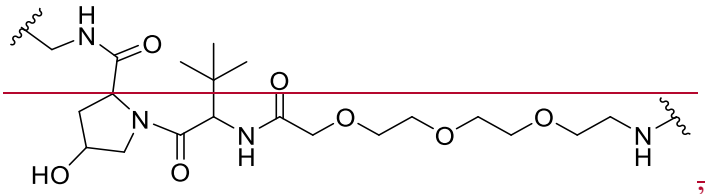


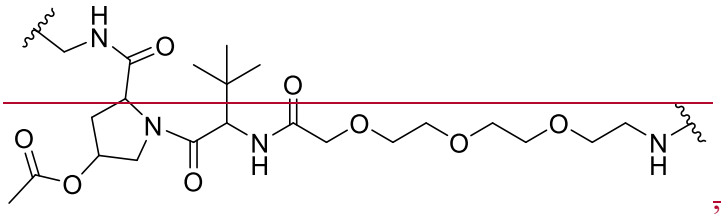


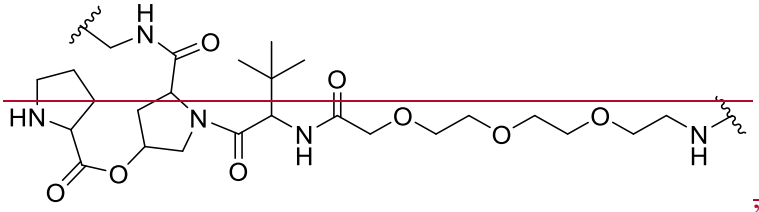

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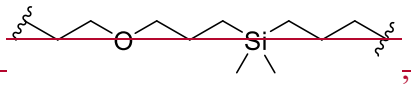
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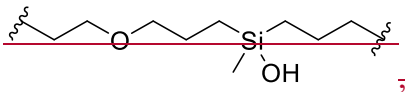


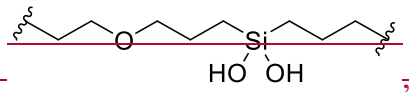




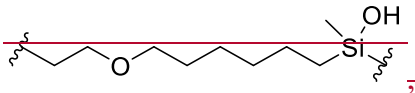


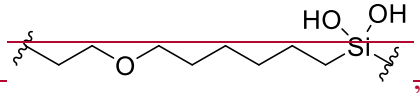


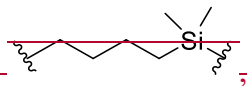


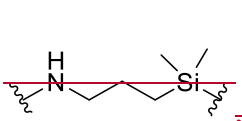


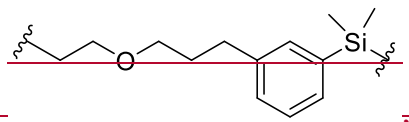


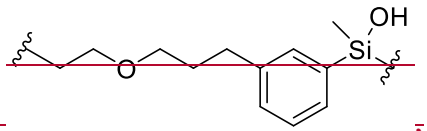


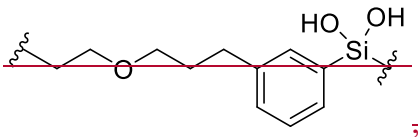


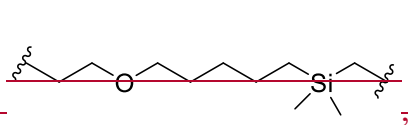


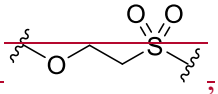


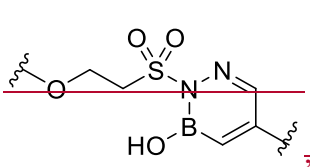


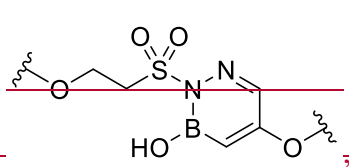


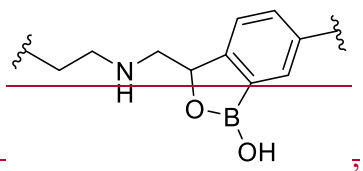


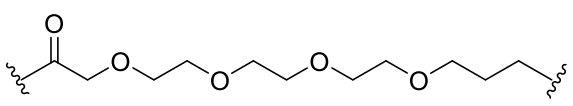
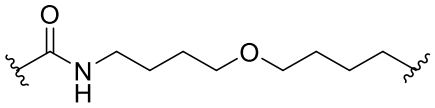
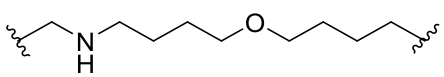
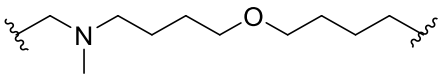
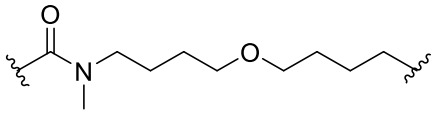
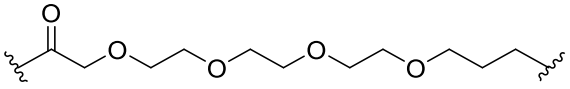
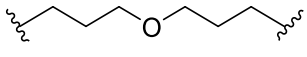
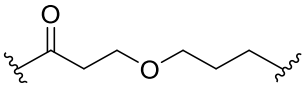
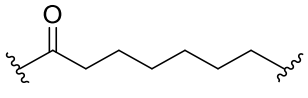
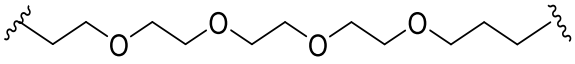
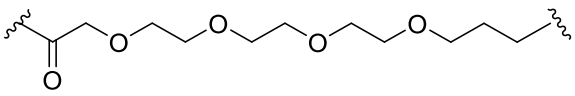
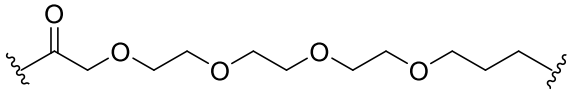
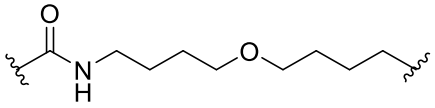
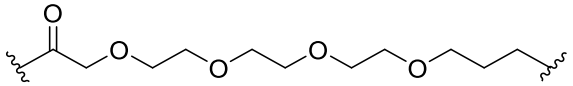
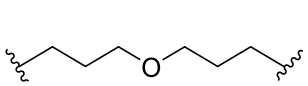
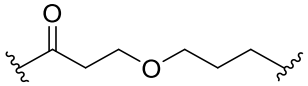
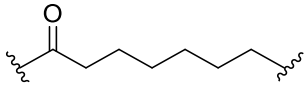
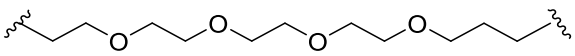
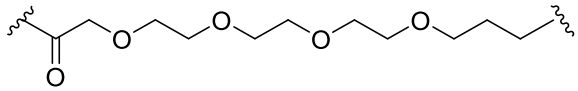
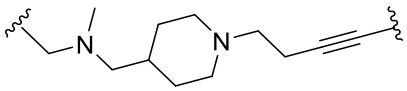
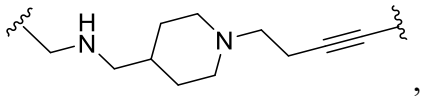
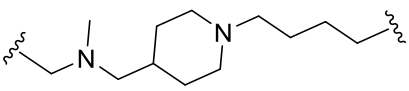
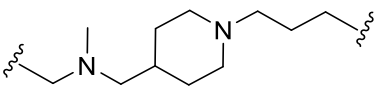
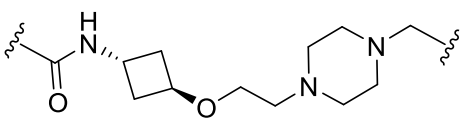
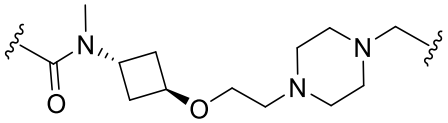
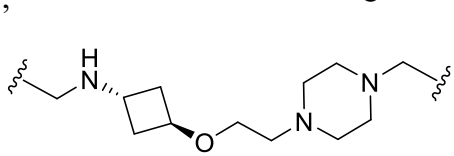
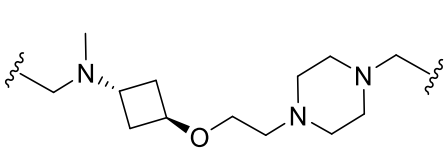
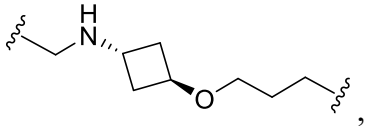
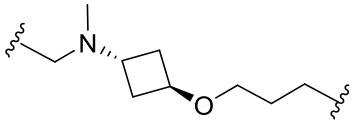
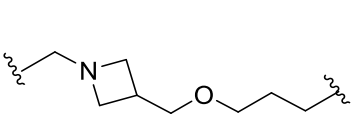


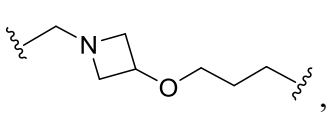
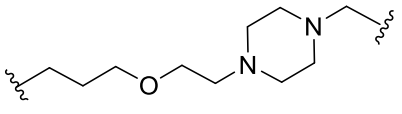
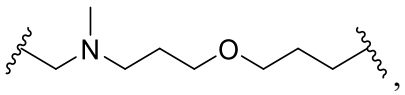
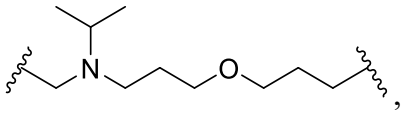
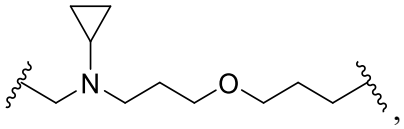
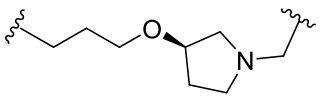
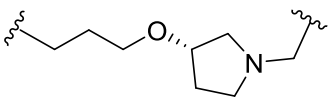
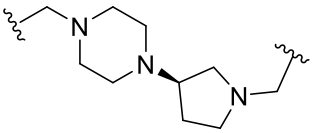
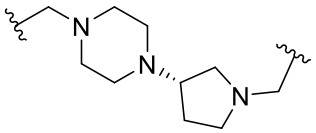
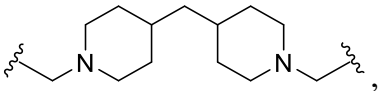
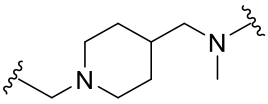
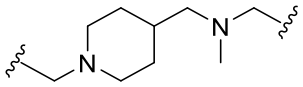
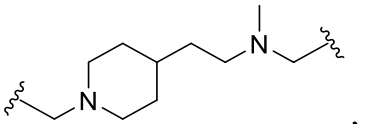
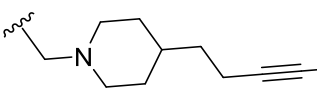
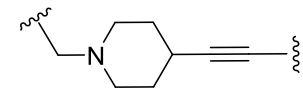






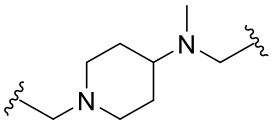
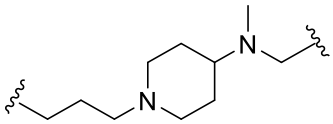
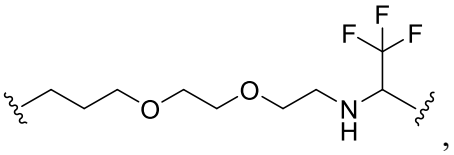
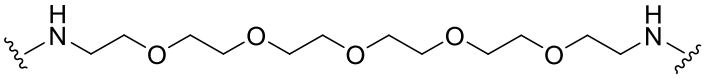
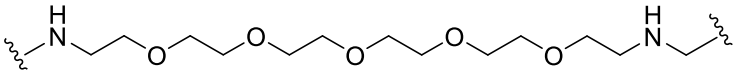
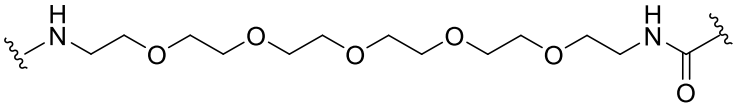
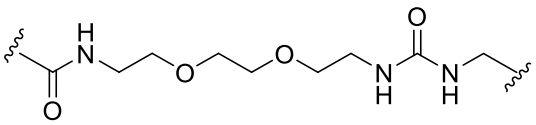
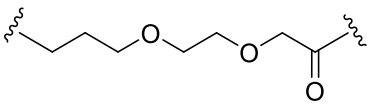
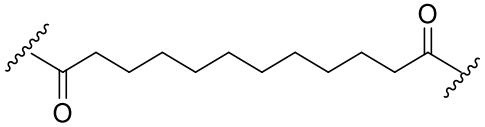
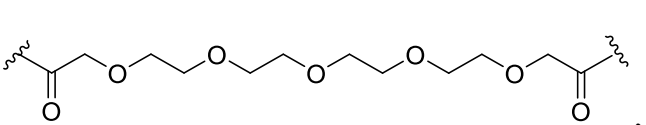
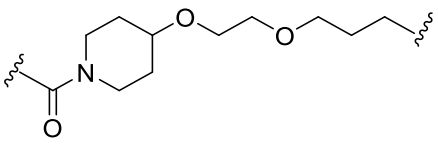
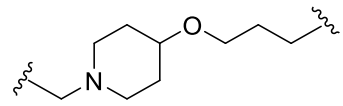
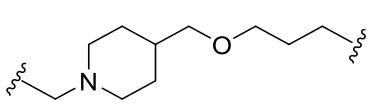


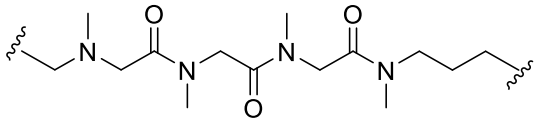
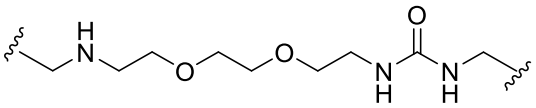
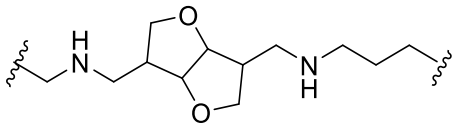
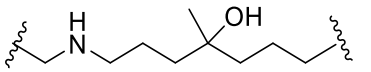
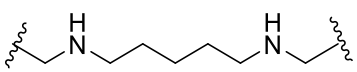
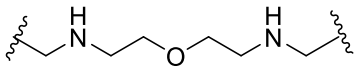
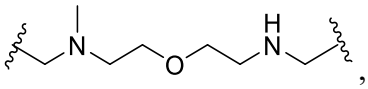
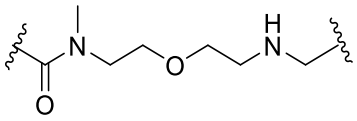
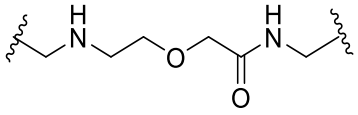
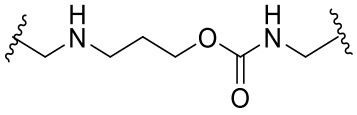
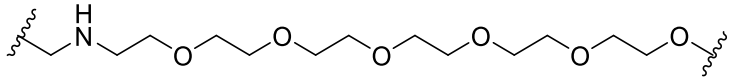
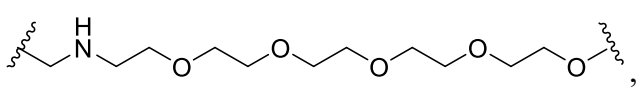
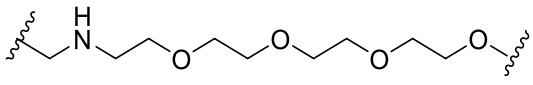
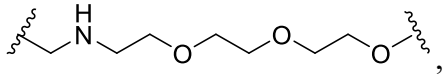
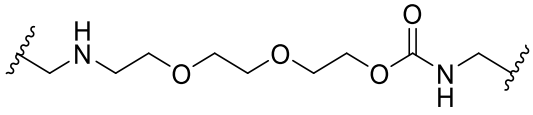
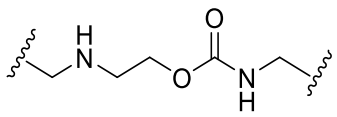
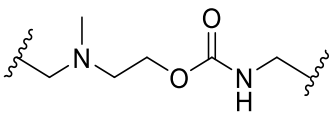
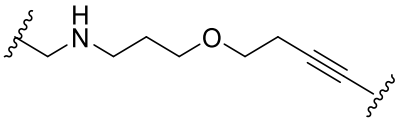
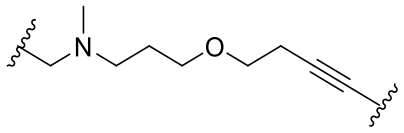
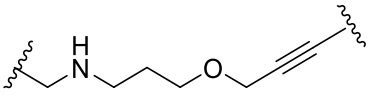
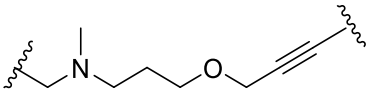
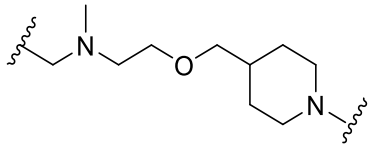
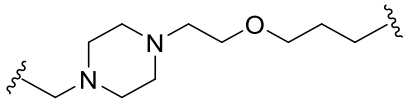
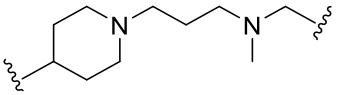
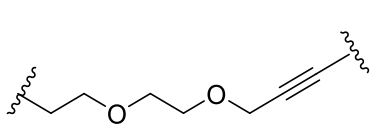
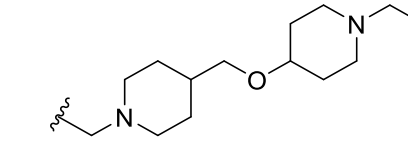
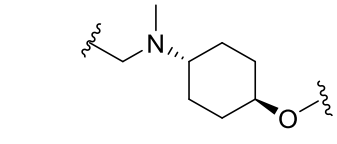

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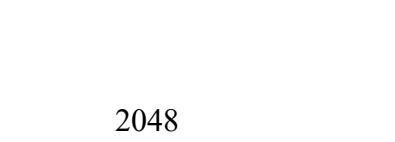

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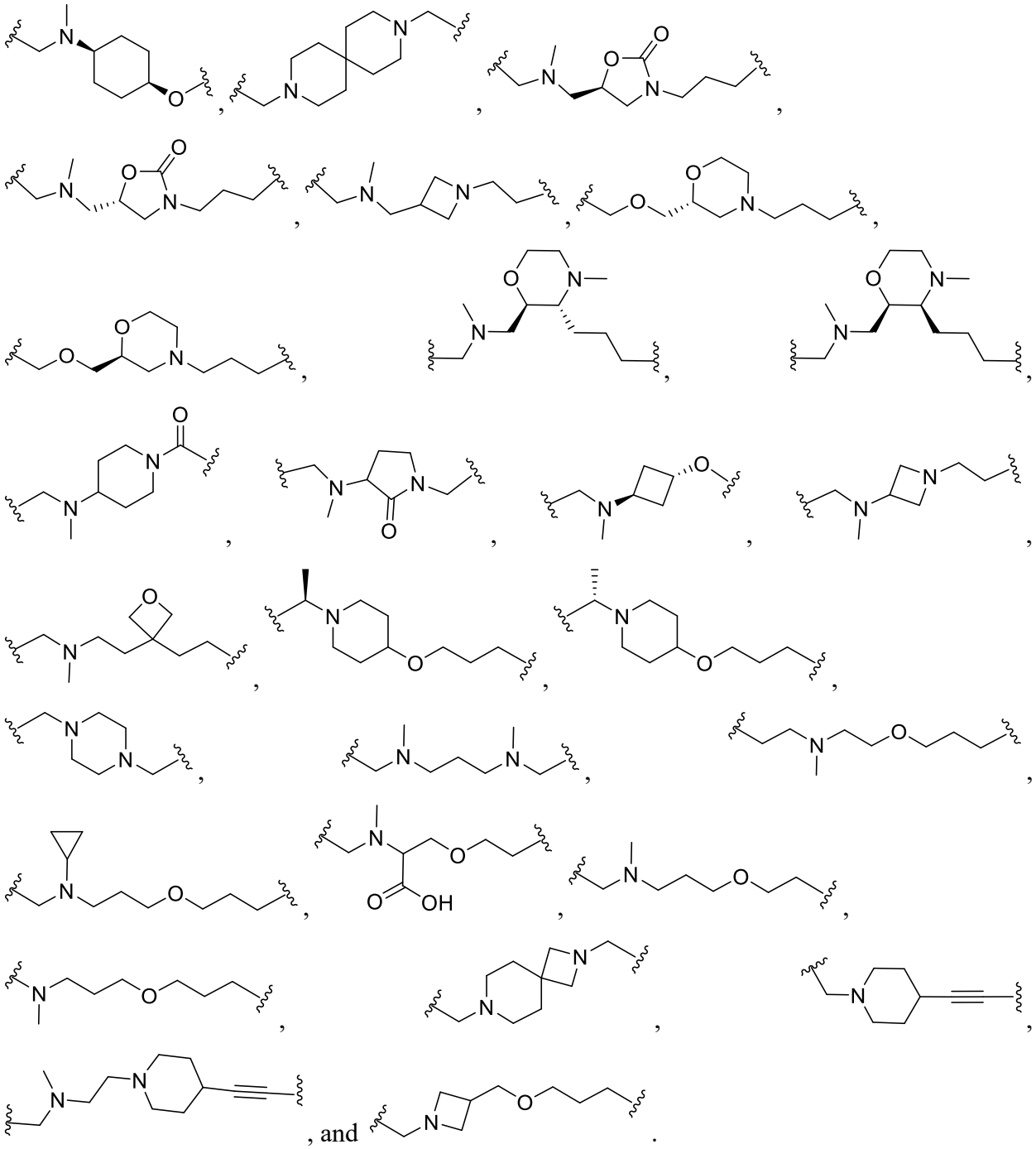
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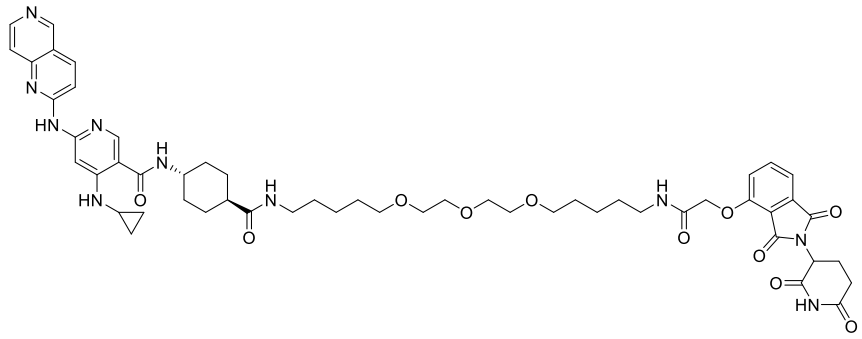
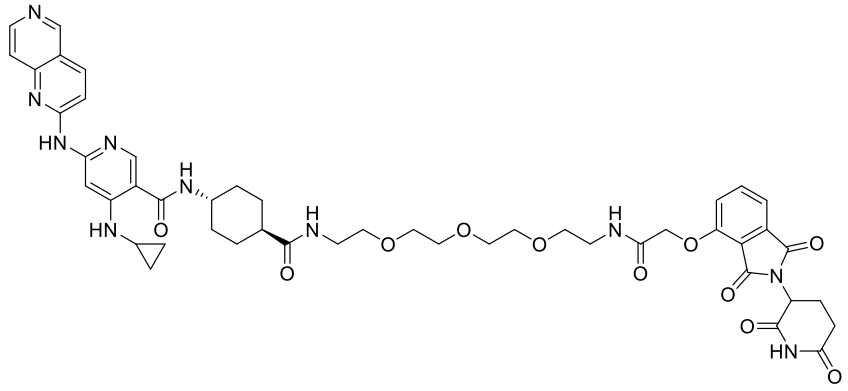
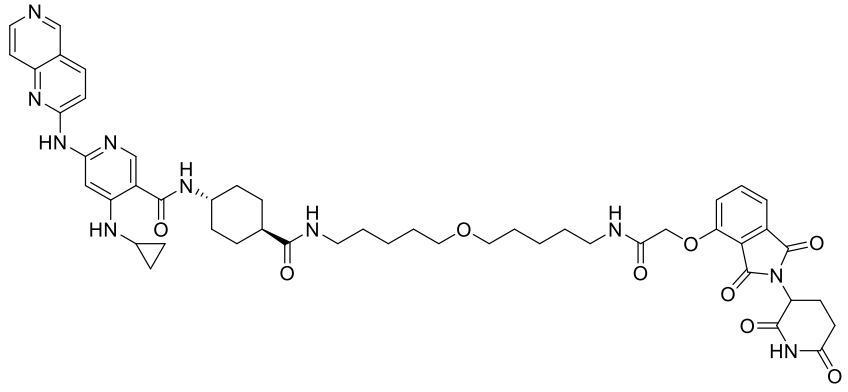
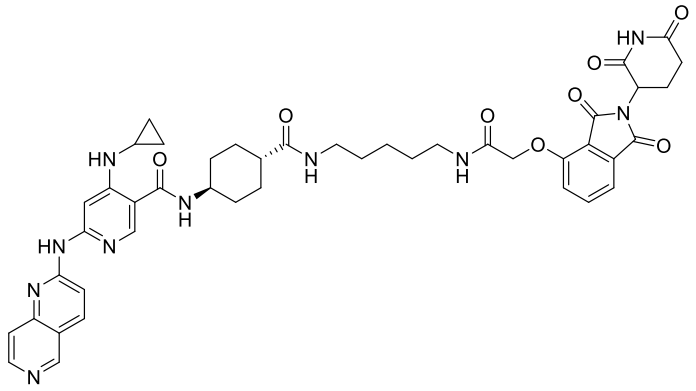
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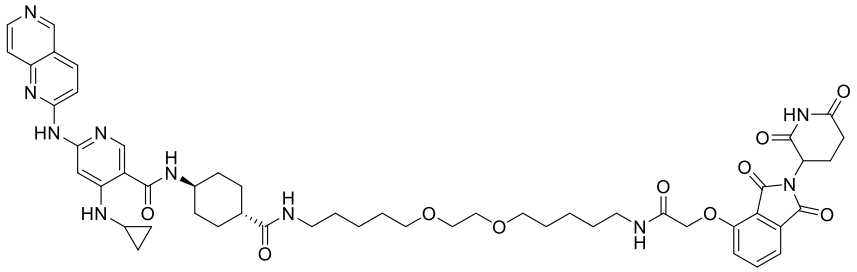
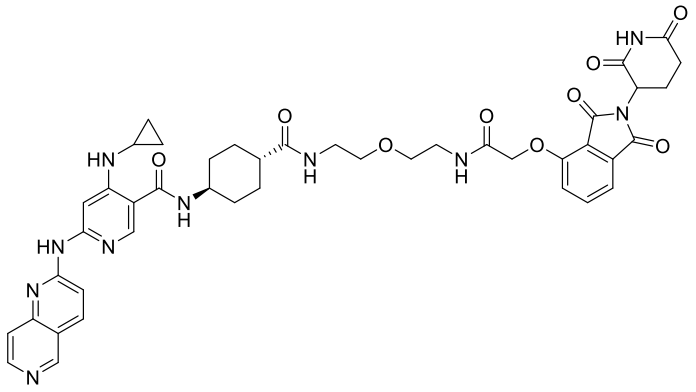
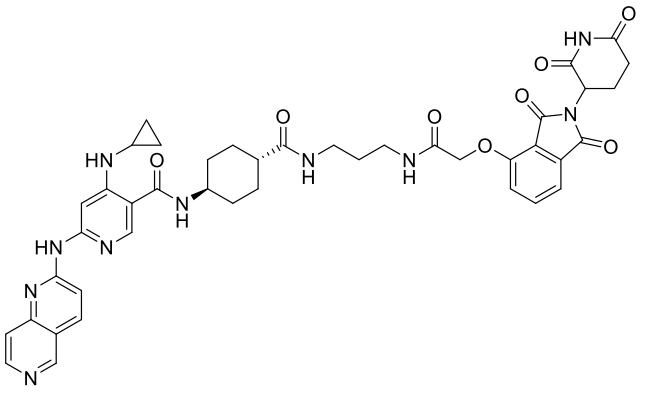
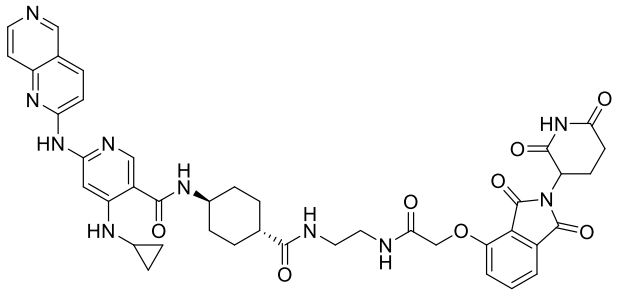
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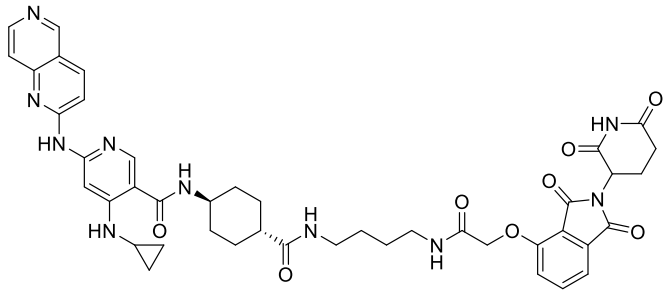
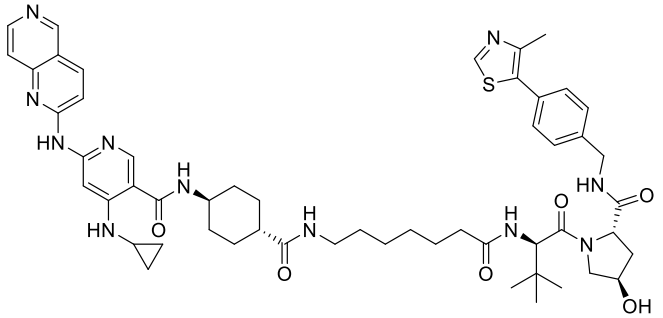
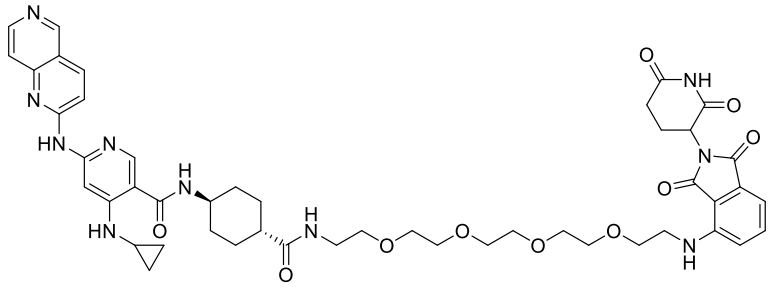
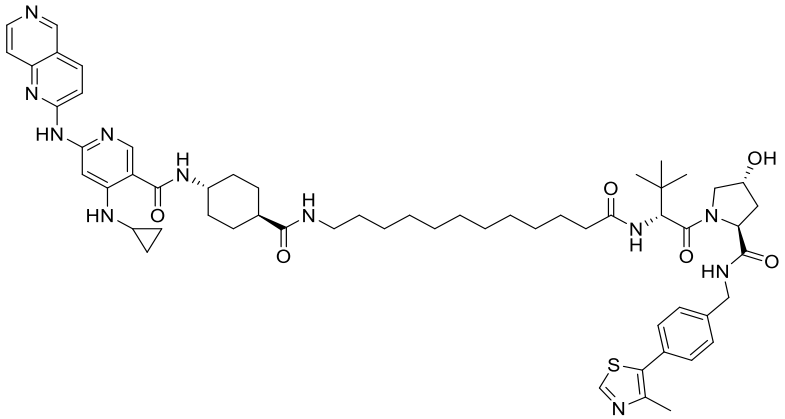


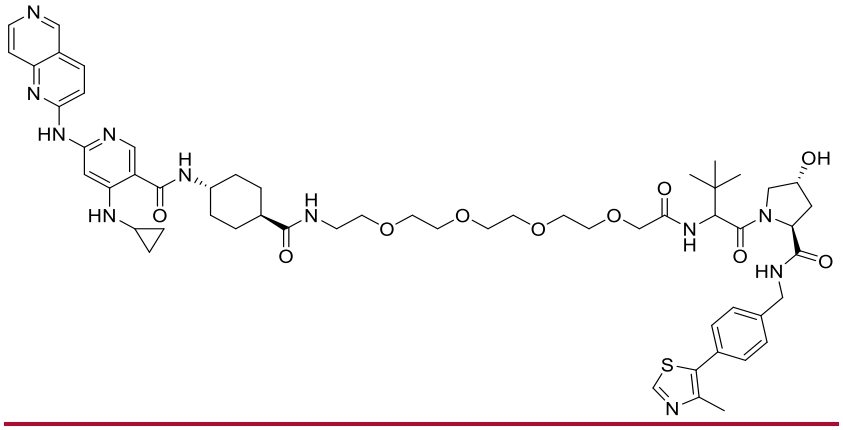
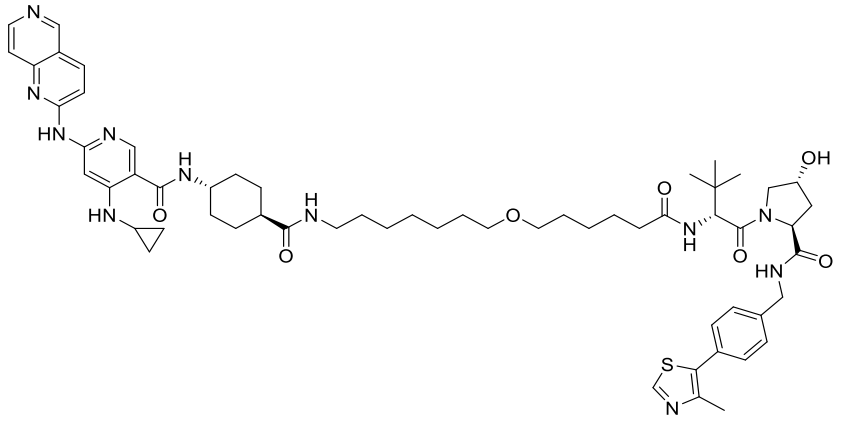
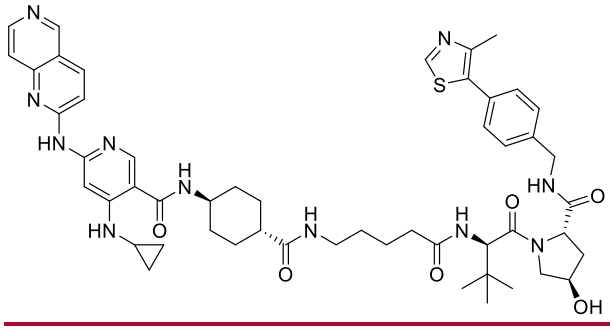
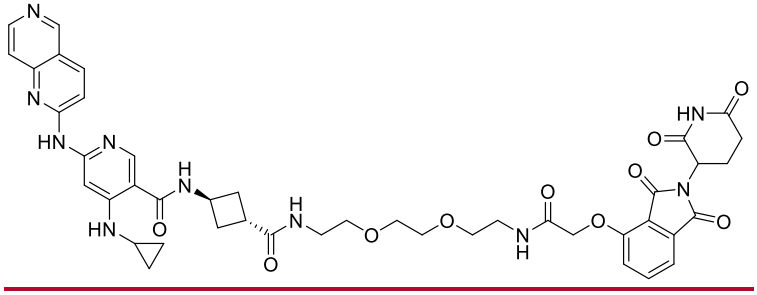
~~145~~. The compound of claim 1, wherein said compound is selected from any one of the following compounds ~~depicted in **Table 1**~~, or a pharmaceutically acceptable salt thereof.

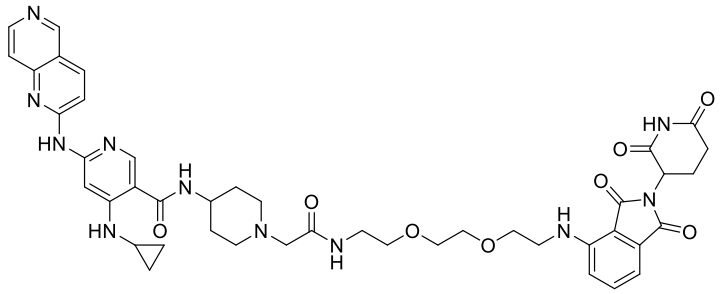
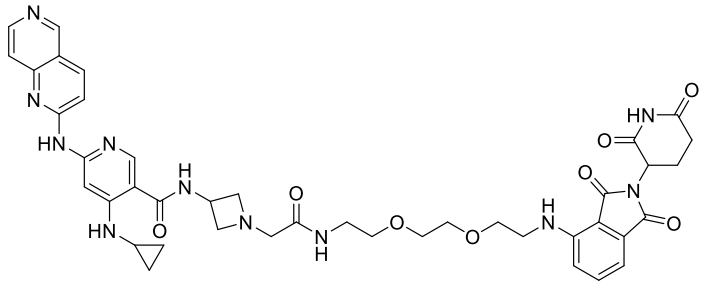
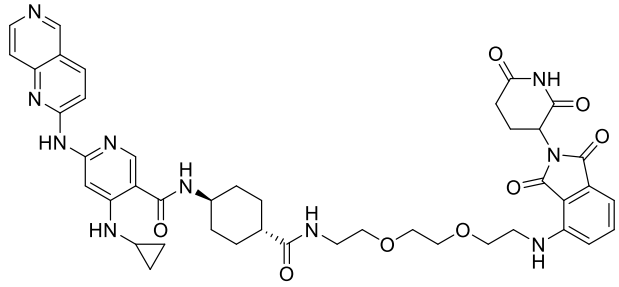
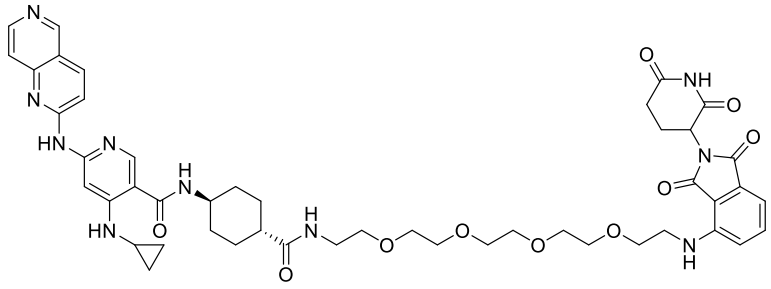
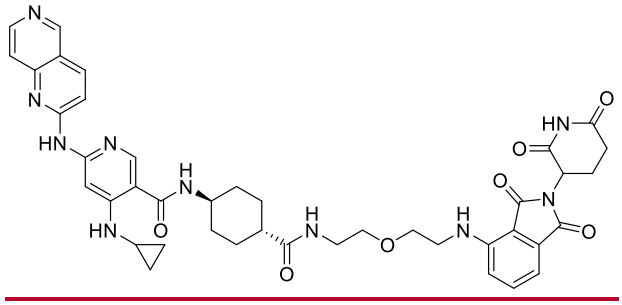
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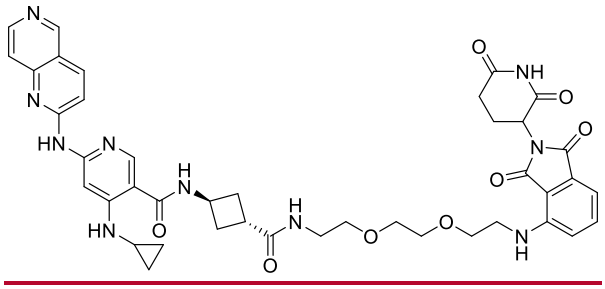
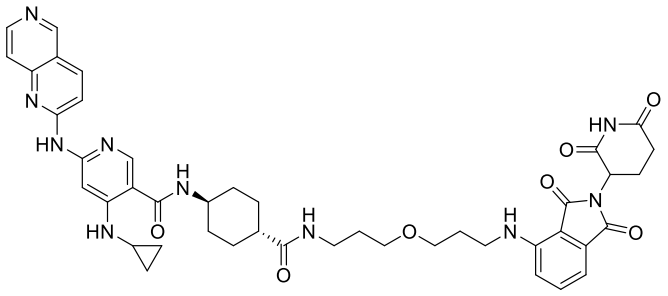
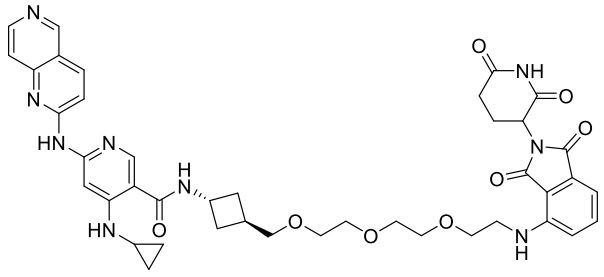
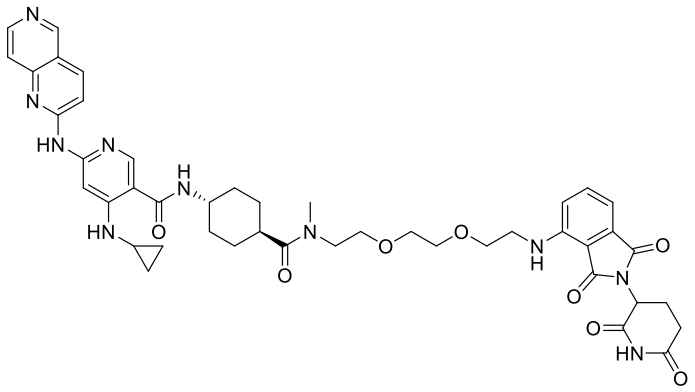
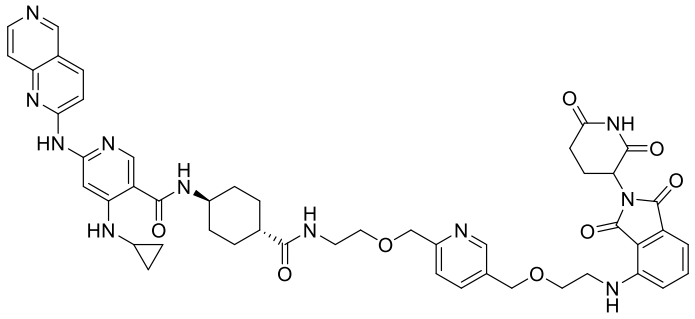
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I-4	

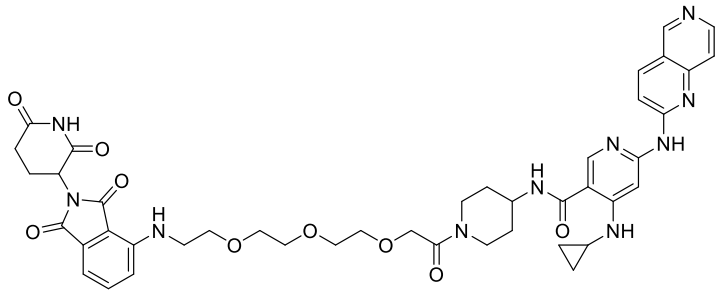
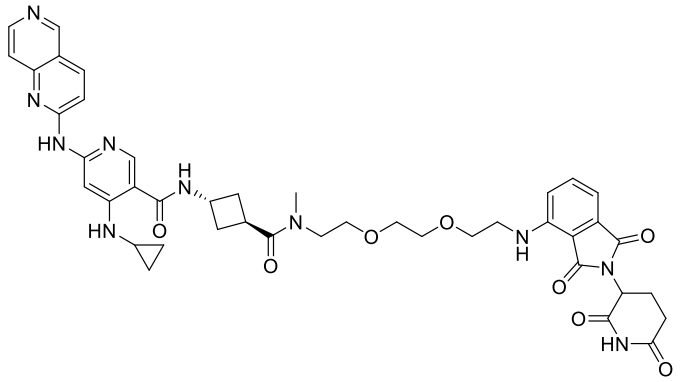
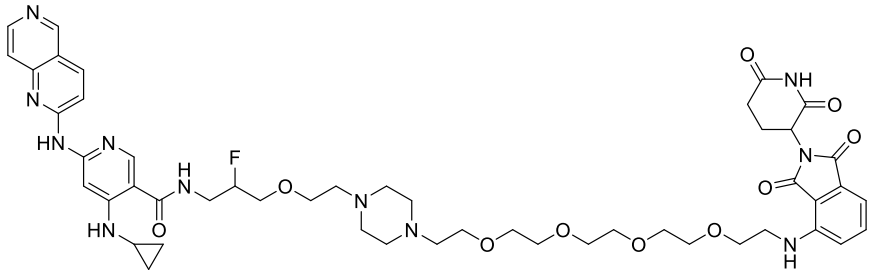
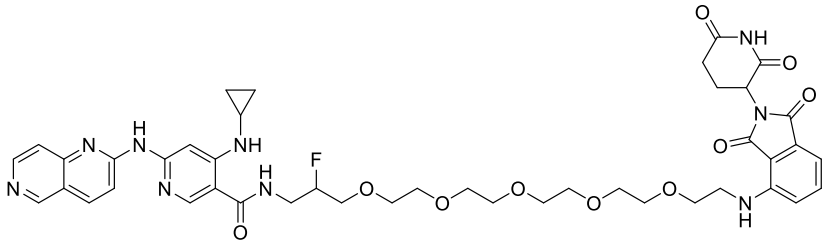
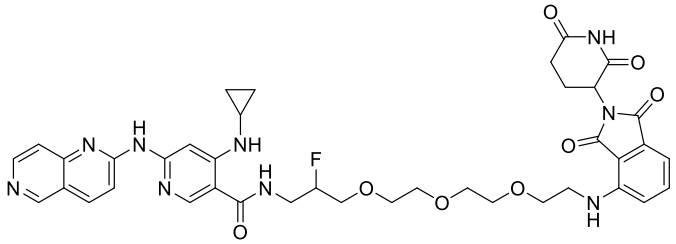
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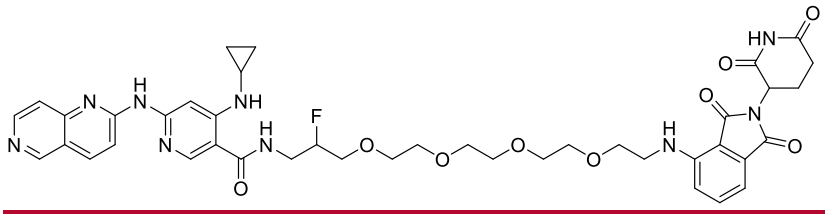
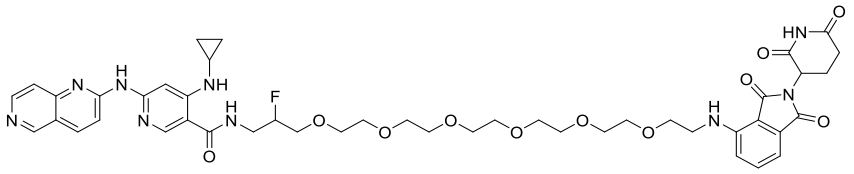
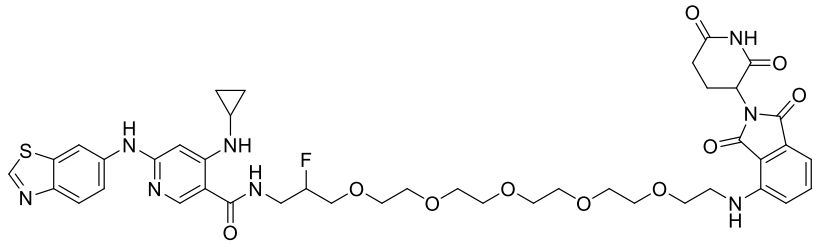
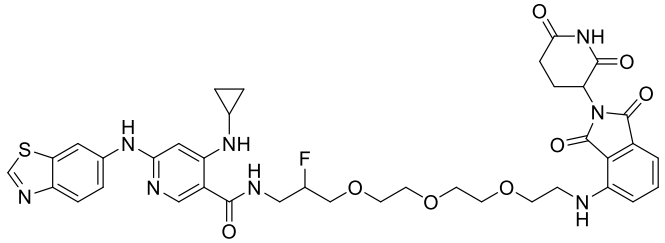
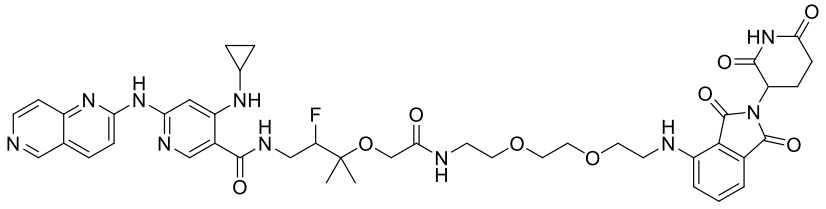
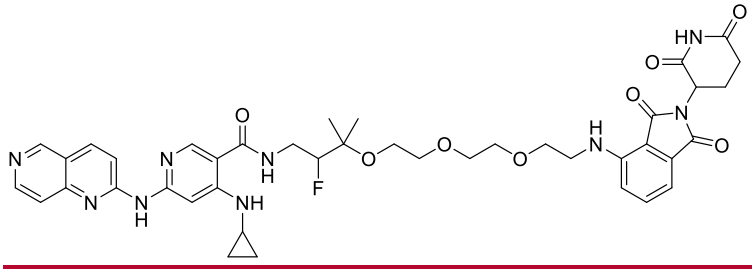
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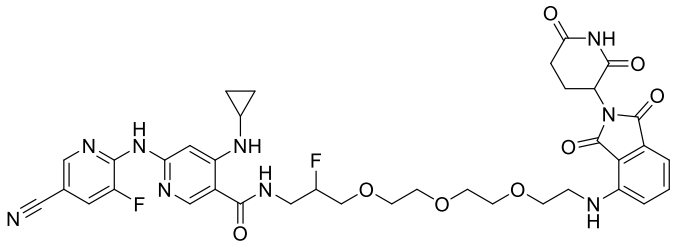
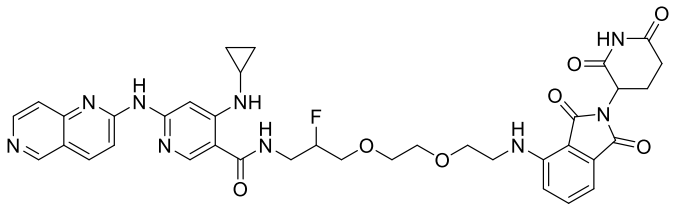
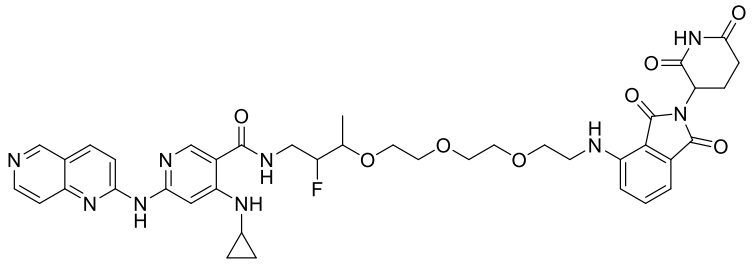
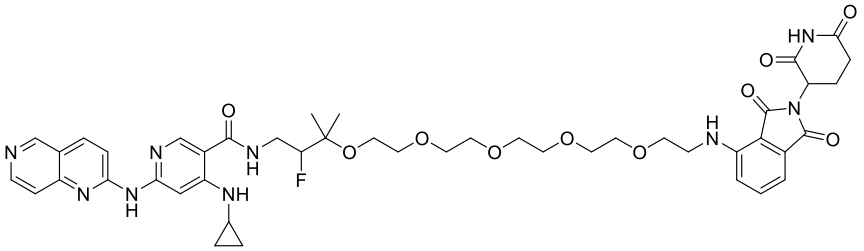
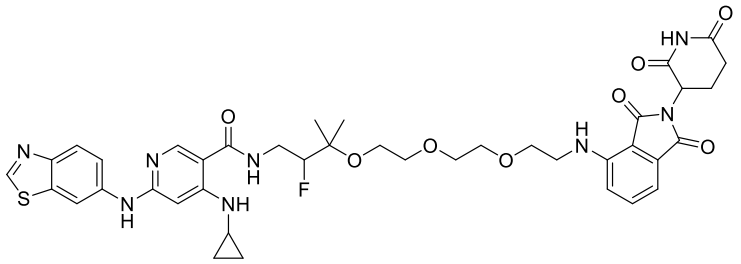
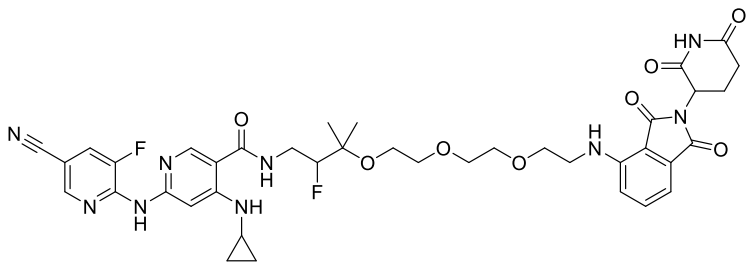
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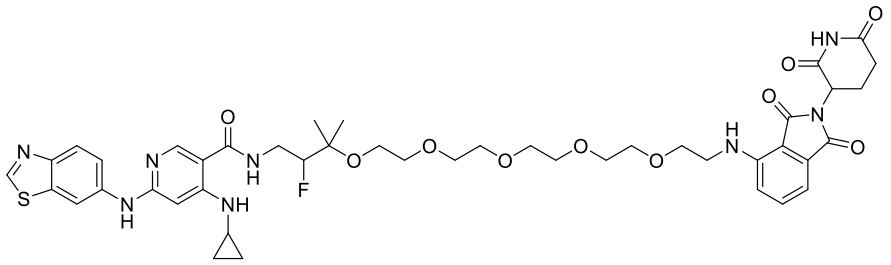
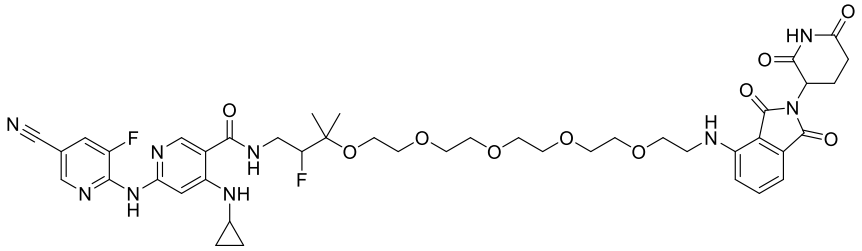
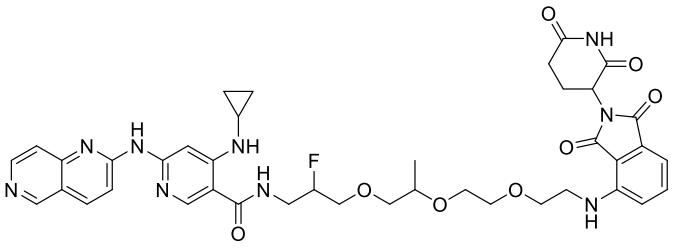
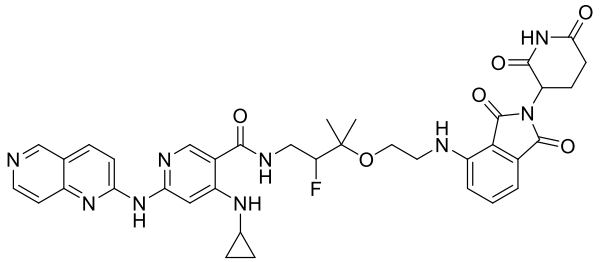
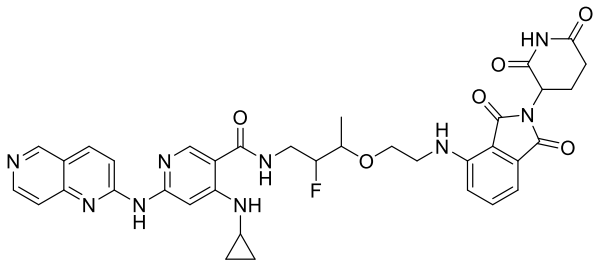
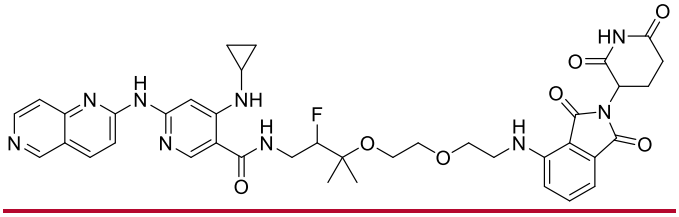
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I-24	
I-25	

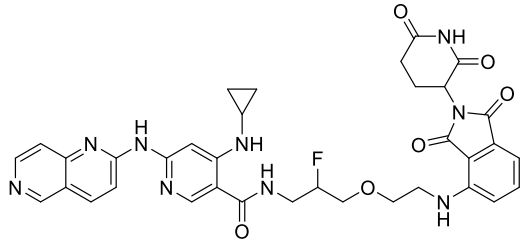
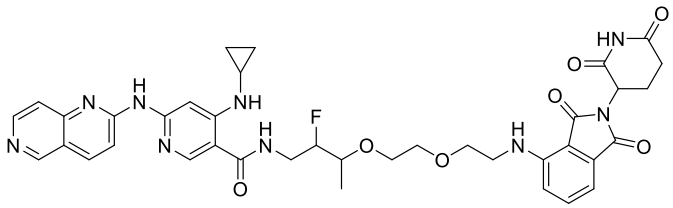
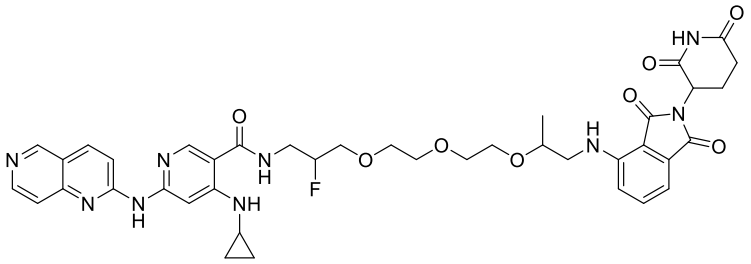
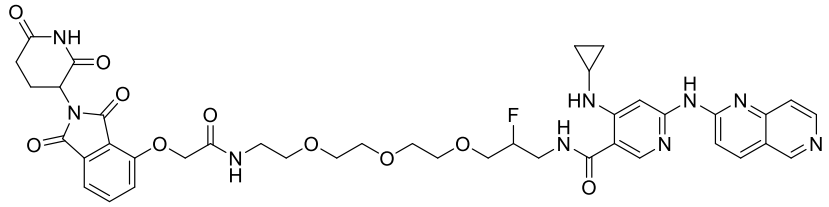
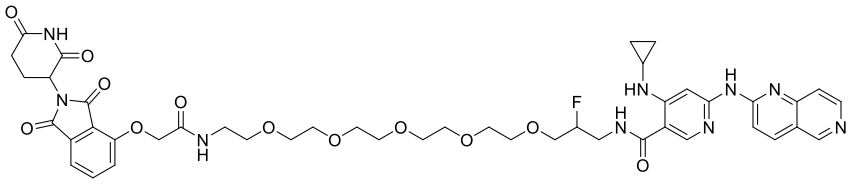
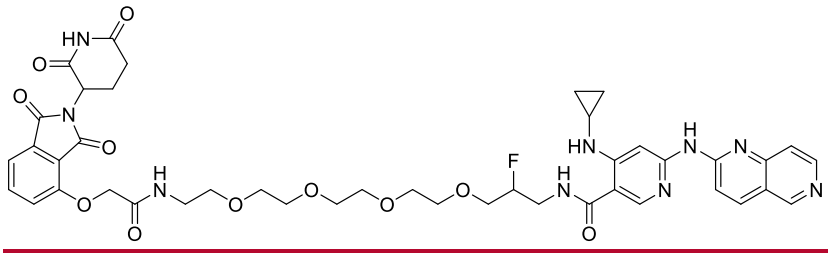
I-#	Structure
I-26	
I-30	
I-31	
I-40	
I-41	

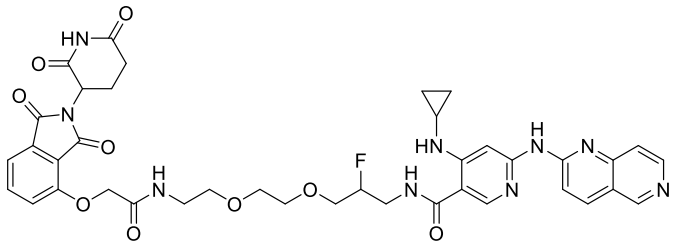
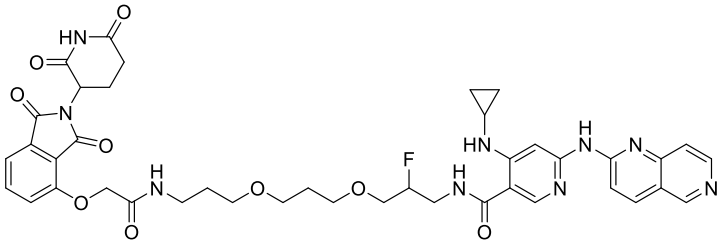
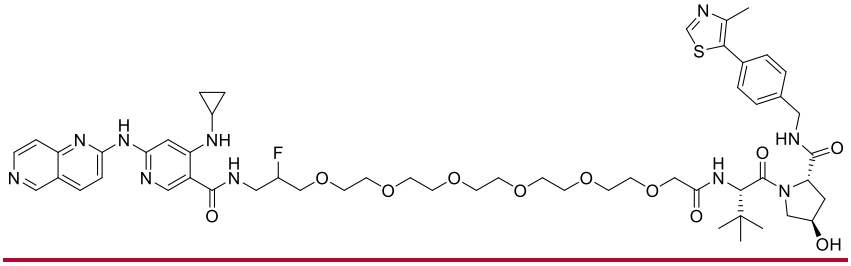
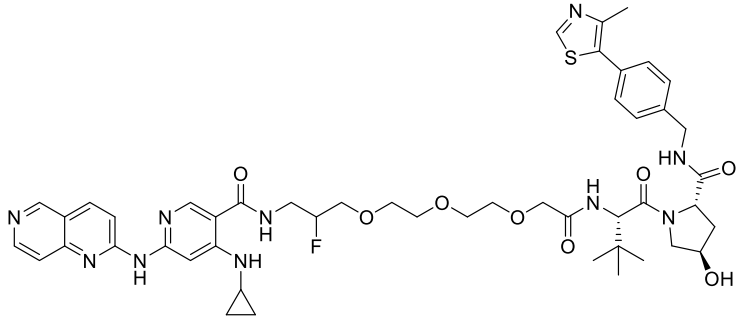
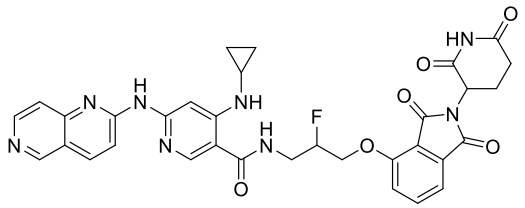
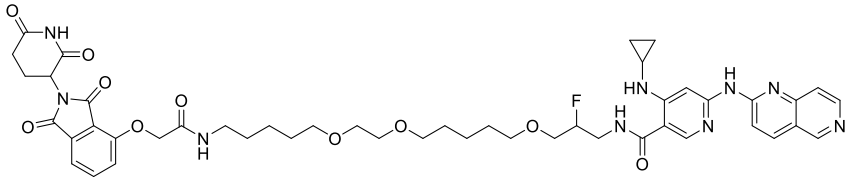
I-#	Structure
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I-44	
I-47	
I-48	
I-49	

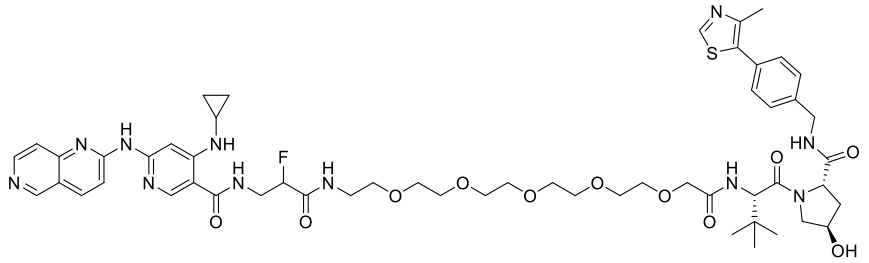
I-#	Structure
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I-51	
I-52	
I-54	
I-55	
I-56	

I-#	Structure
I-58	
I-61	
I-62	
I-64	
I-65	
I-67	

I-#	Structure
I-68	
I-69	
I-70	
I-74	
I-77	
I-80	

I-#	Structure
I-81	
I-84	
I-93	
I-96	
I-97	
I-98	

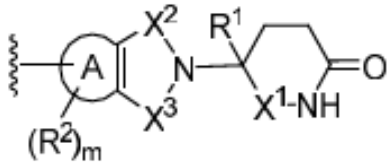
I-#	Structure
I-99	
I-100	
I-119	
I-120	
I-174	
I-206	

I-#	Structure
I-207	

~~156~~. A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

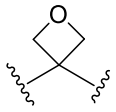
~~167~~. The pharmaceutical composition according to claim ~~156~~, further comprising an additional therapeutic agent.

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;

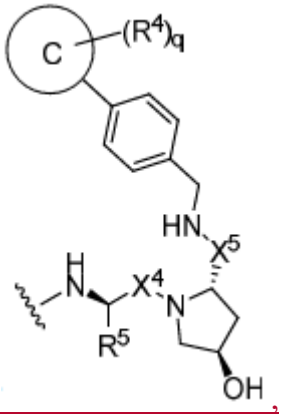
each R^2 is hydrogen, $–R^6$, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

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;

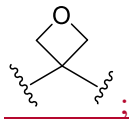
Ring A is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5 to 7-membered partially saturated carbocyclyl, 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 5-membered heteroaryl with 1-3 heteroatoms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

;

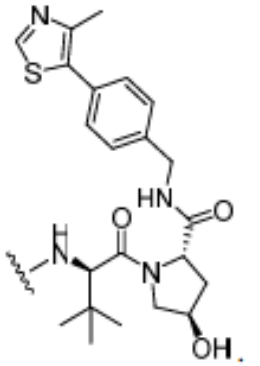
each R^4 is independently hydrogen, $–R^6$, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

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

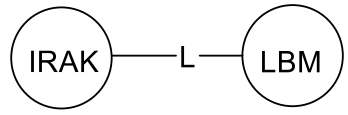
each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

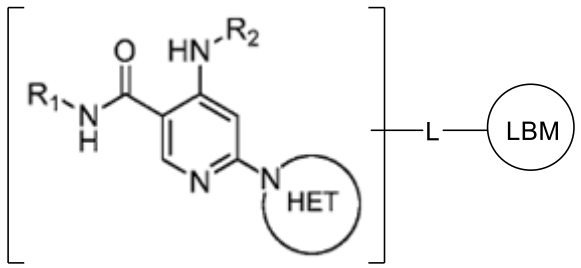
11. A compound of formula **I**:



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)$_2$OH, —OCH_3, —C(O)CH_2CN, —S(O)$_2$$CH_3$, —S(O)$_2$$NH_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);

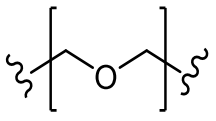
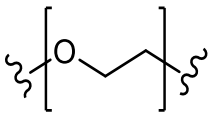
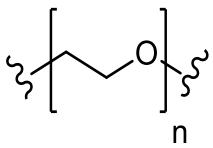
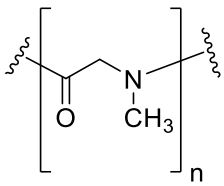
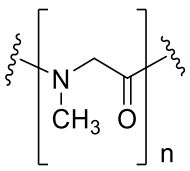
(ii) —(C_{1-4} alkylenyl)R_y wherein R_y is C_{3-6} cycloalkyl, azetidinyl, oxetanyl, oxazolyl, pyridinyl, tetrahydropyranyl, or morpholinyl, each substituted with zero to 2 substituents independently selected from F, —OH, and C_{1-3} alkyl;

(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_{1-3} 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:

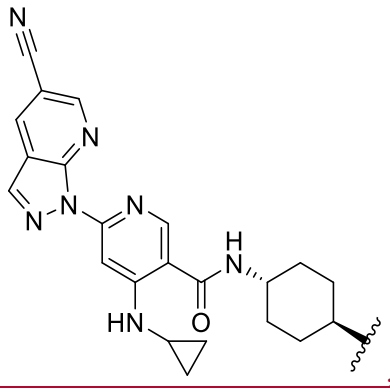
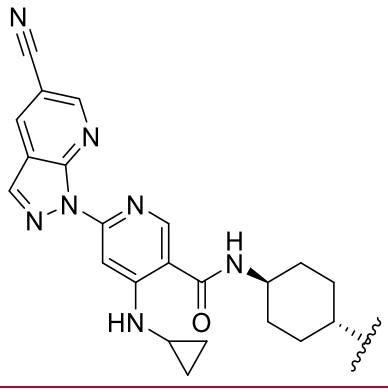
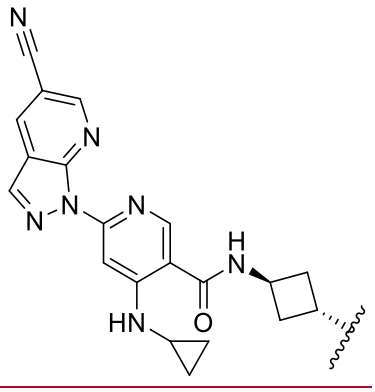
each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated

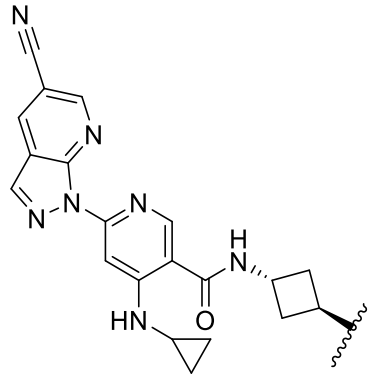
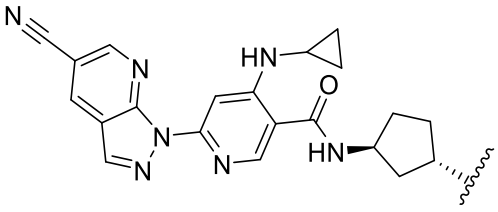
carbocyclylenyl, a 4-7 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, 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

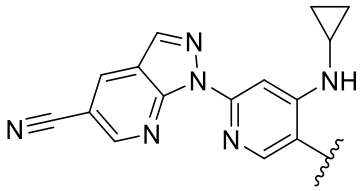
each of n is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

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;

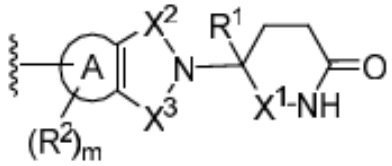
LBM is a ligase binding moiety selected from a cereblon E3 ubiquitin ligase binding moiety and a VHL E3 ubiquitin ligase binding moiety.

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

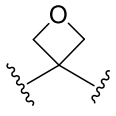


and



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

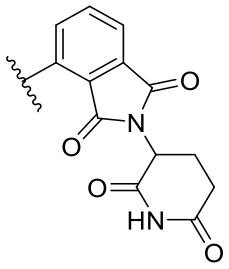
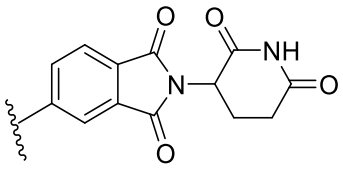
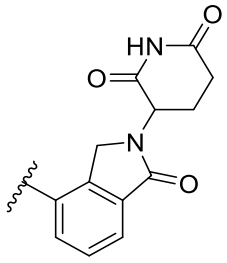
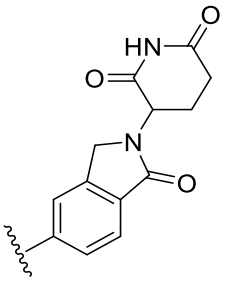
each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms

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;

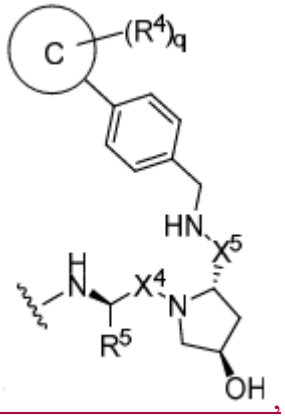
Ring A is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5 to 7-membered partially saturated carbocyclyl, 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 5-membered heteroaryl with 1-3 heteroatoms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

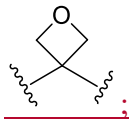



, and

.

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


;

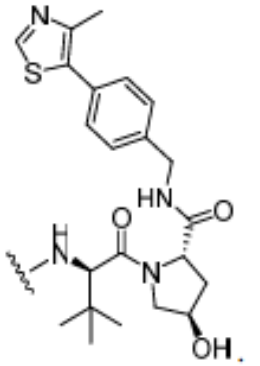
each R^4 is independently hydrogen, $–R^6$, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, or $-N(R)S(O)_2R$;

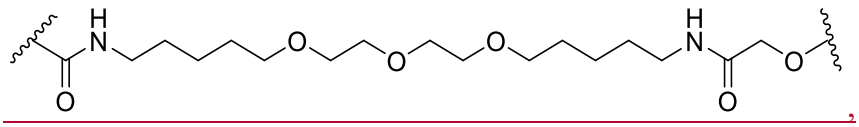
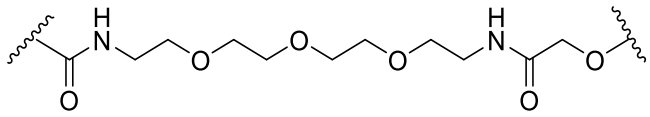
R^5 is hydrogen or C_{1-6} aliphatic;

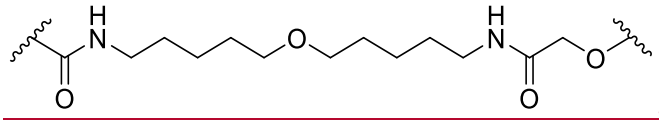
each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

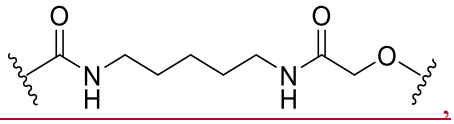
Ring C is a selected from 6-membered aryl containing 0-2 nitrogen atoms or a 5-membered heteroaryl with 1-3 heteroatoms independently selected from nitrogen, oxygen or sulfur; and

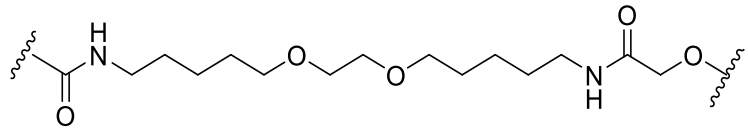
q is 0, 1, 2, 3 or 4.

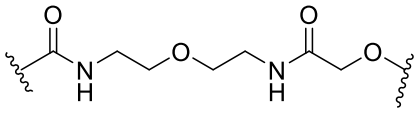
16. The compound according to claim 11, wherein the VHL E3 ubiquitin ligase binding moiety is  .

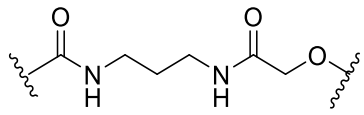
17. The compound according to claim 11, wherein L is selected from:  ,  , ,

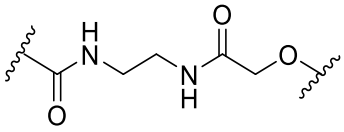


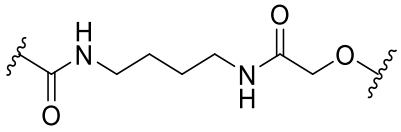


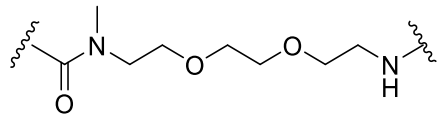


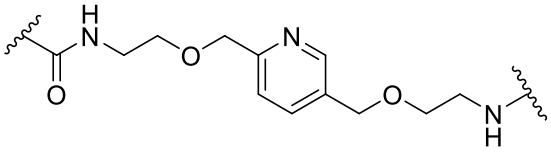


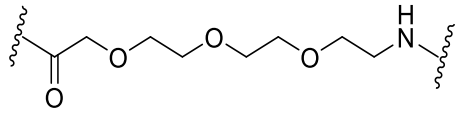


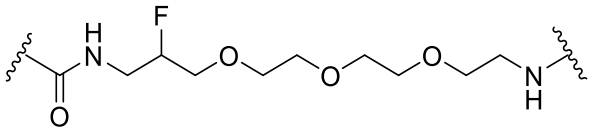


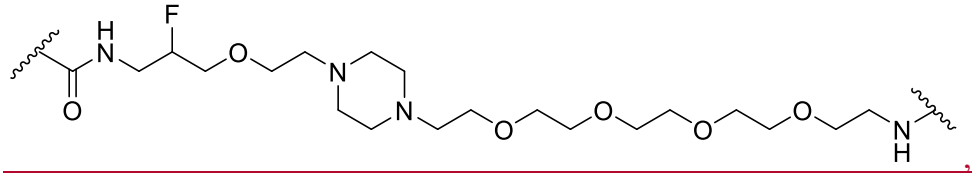


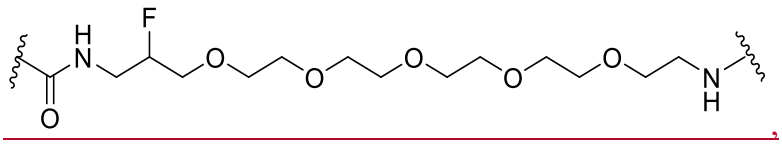


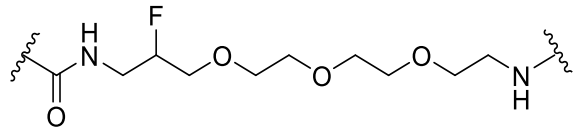


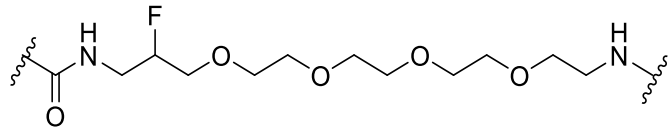


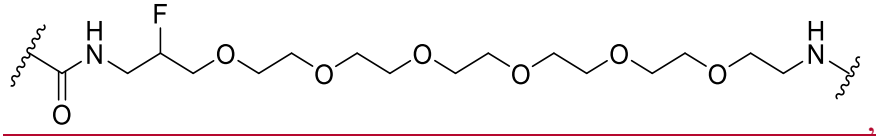


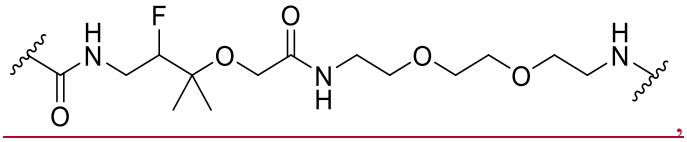


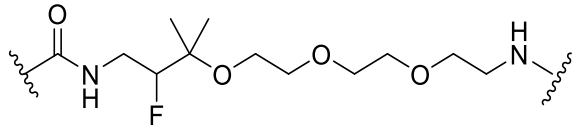


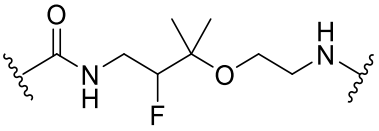


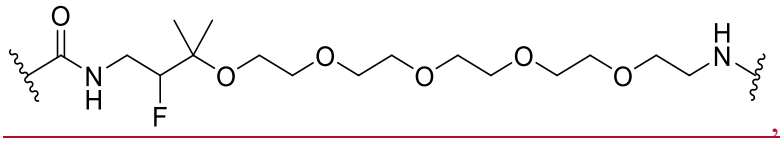


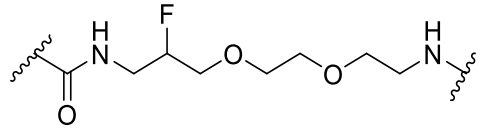


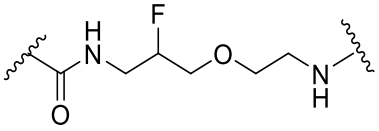


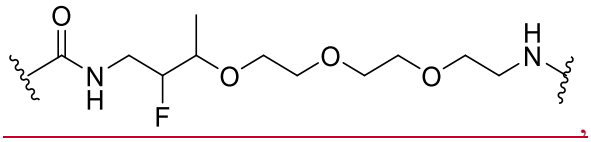


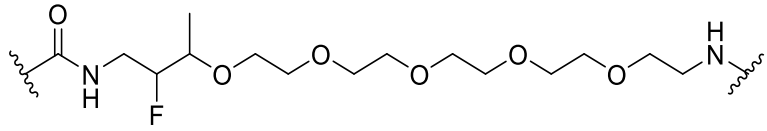


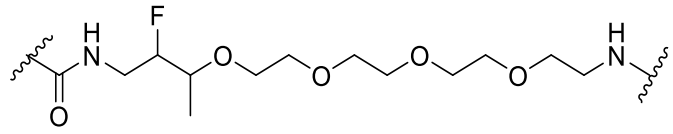


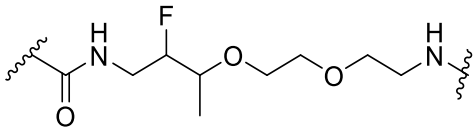


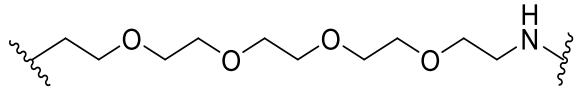


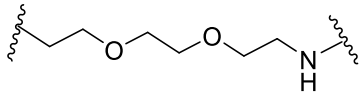


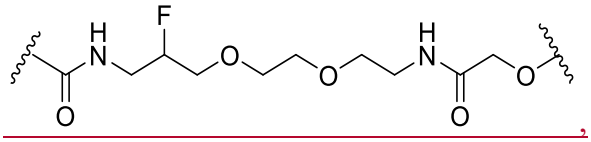


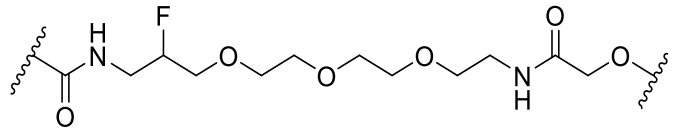


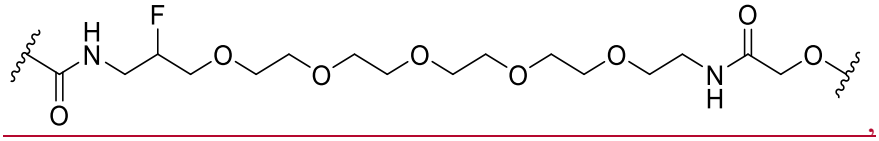


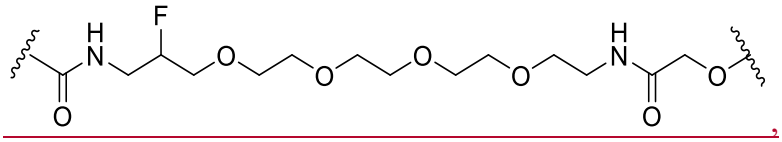


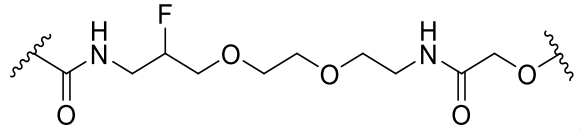


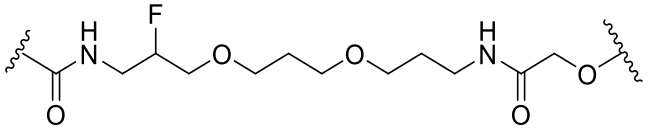


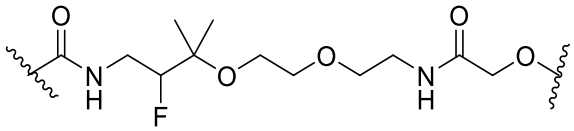


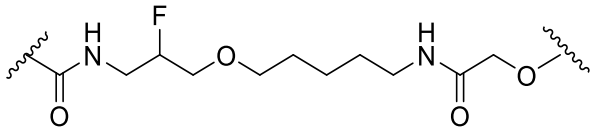


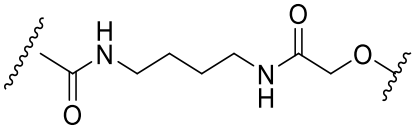


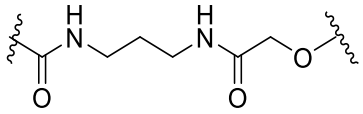


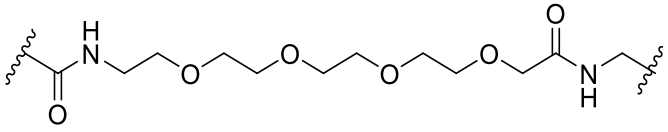


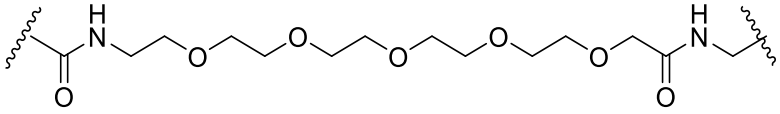


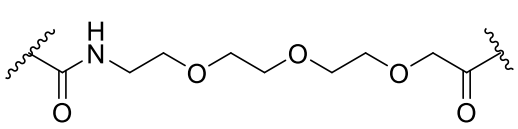


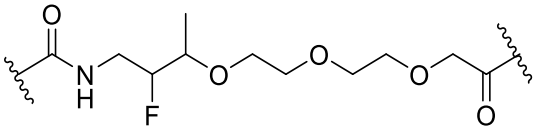


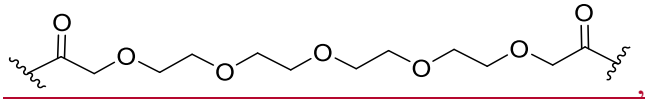


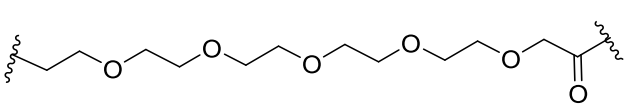


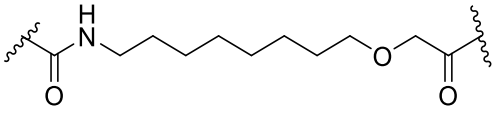


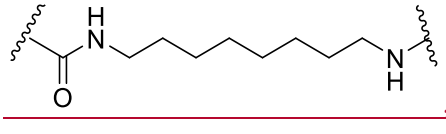


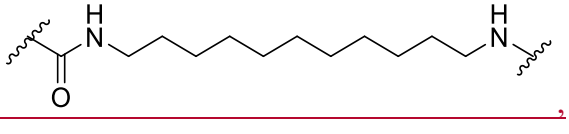


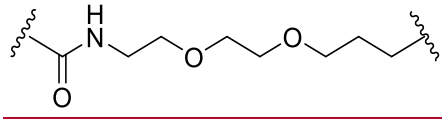


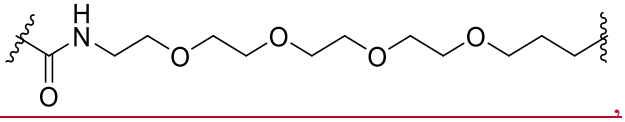


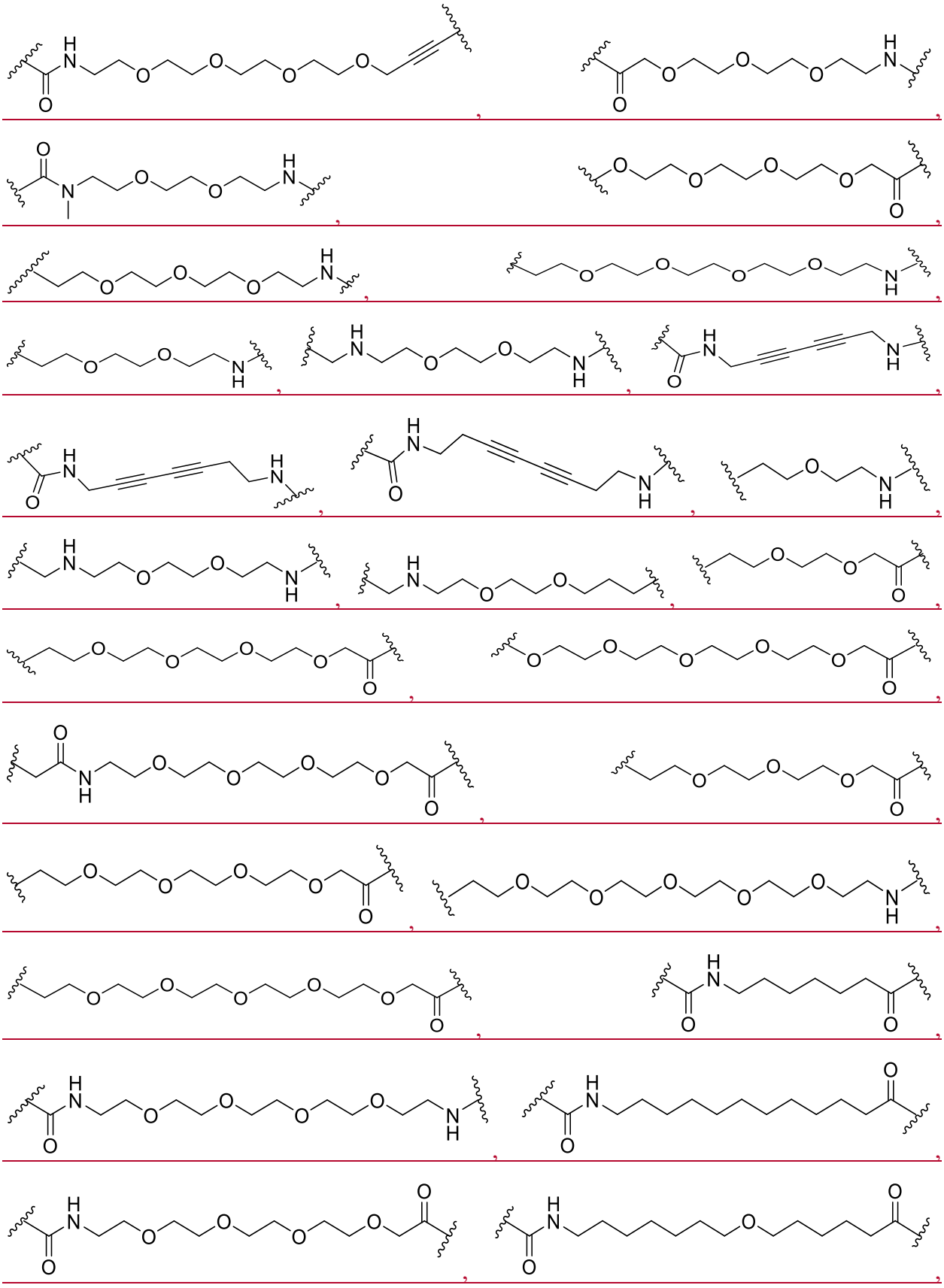


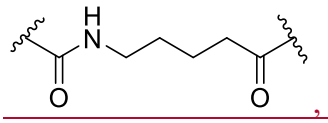


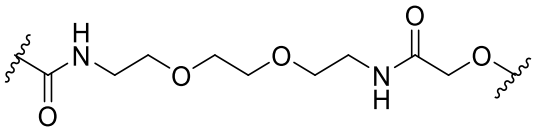


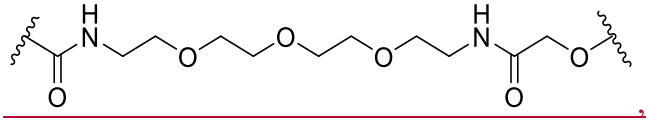


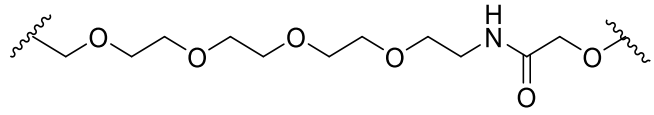


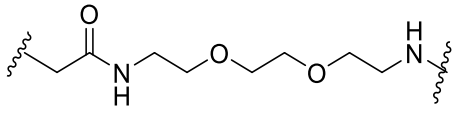


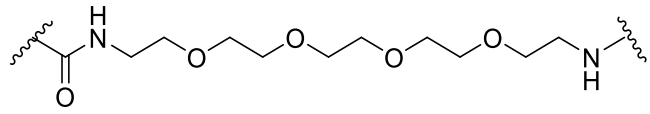


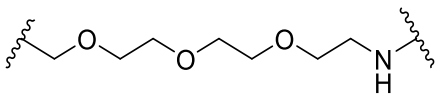


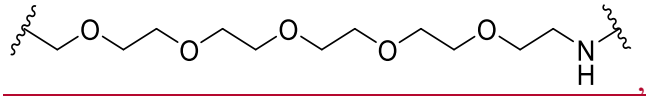


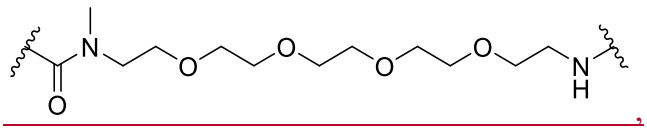


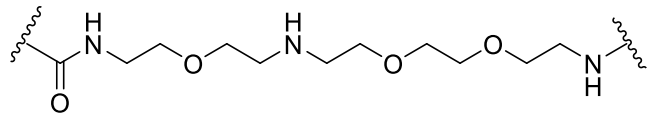


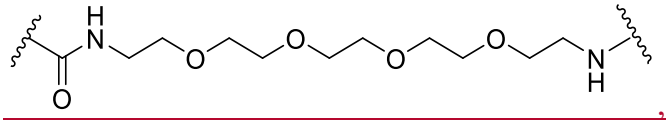


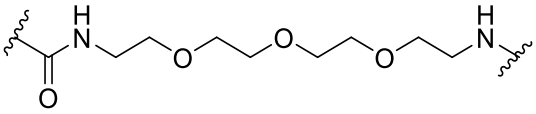


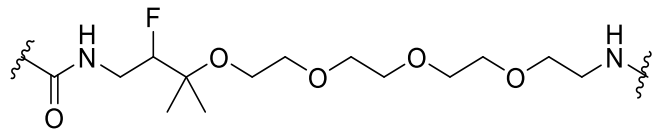


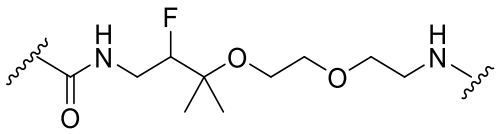


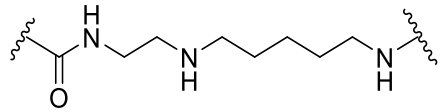


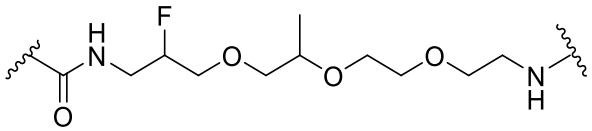


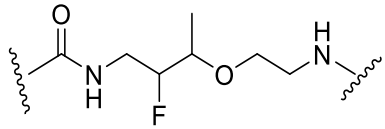


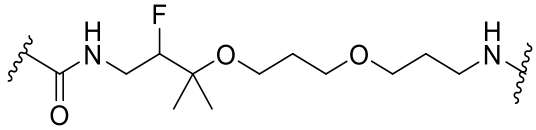


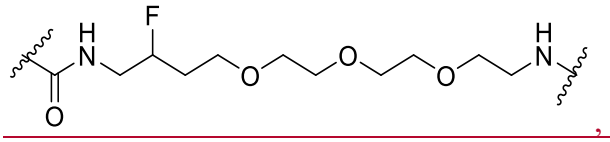


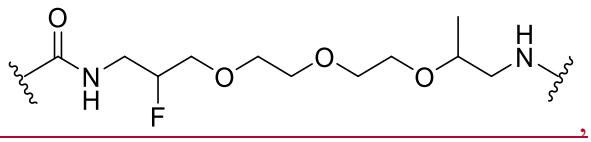


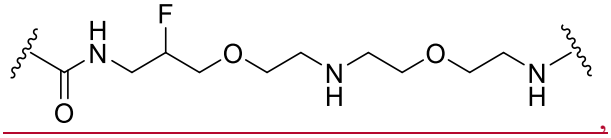


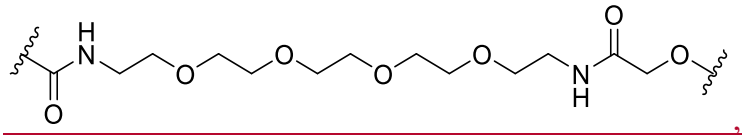


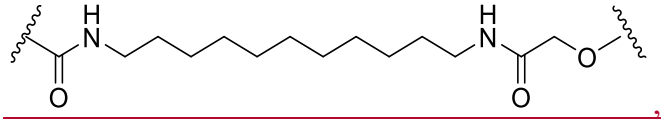


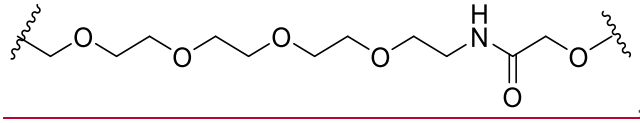


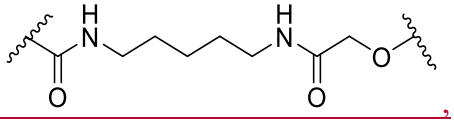


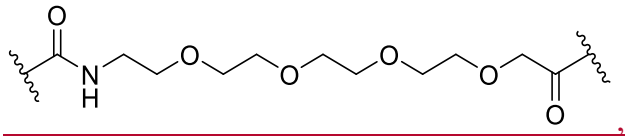


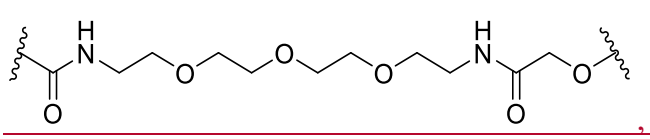


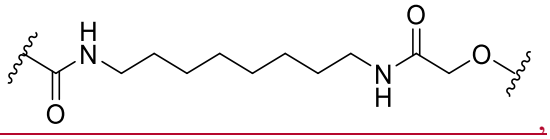


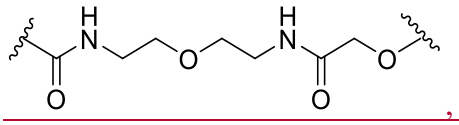


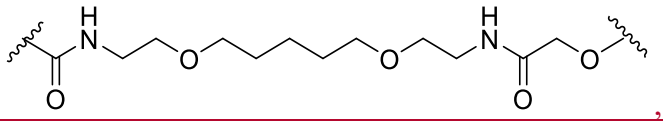


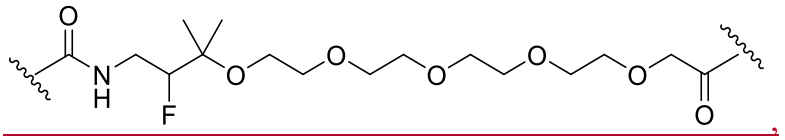


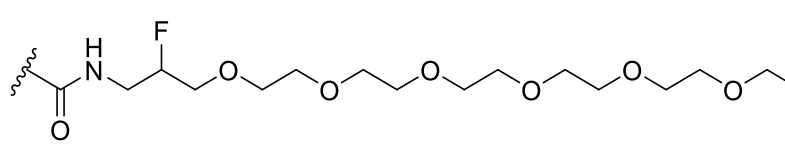


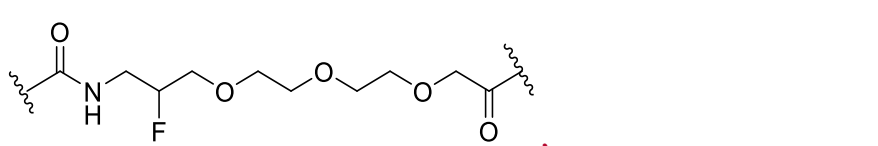


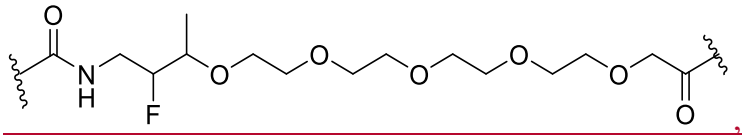


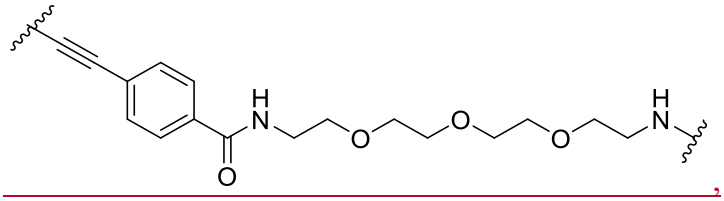


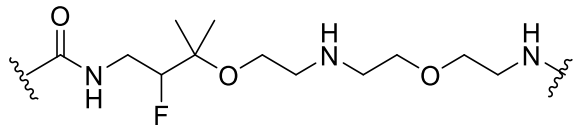


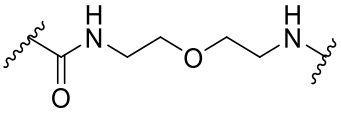


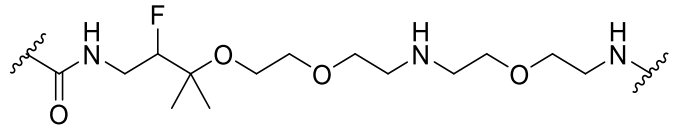


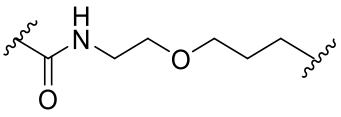


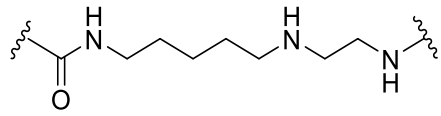


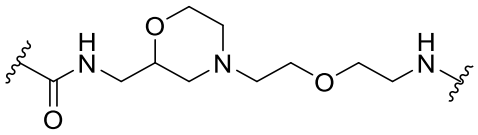


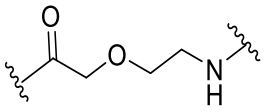


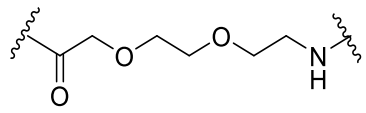


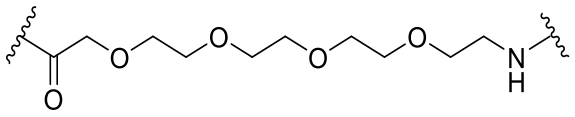


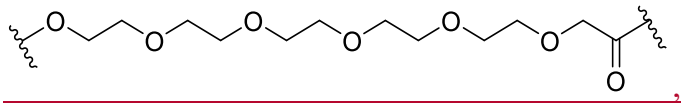


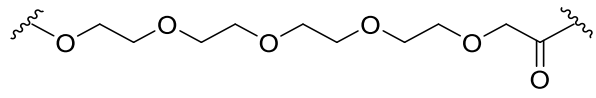


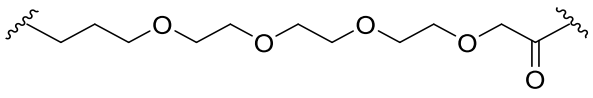


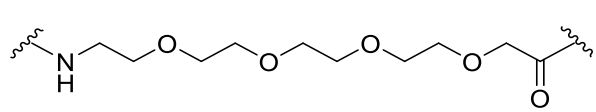


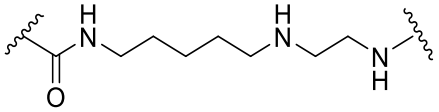


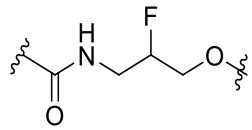


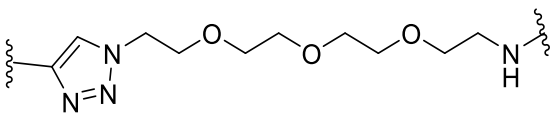


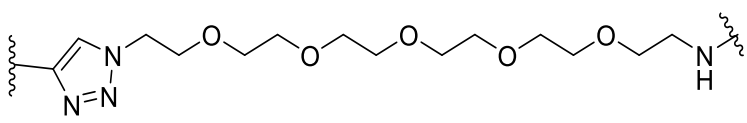


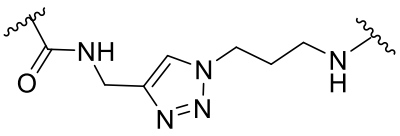


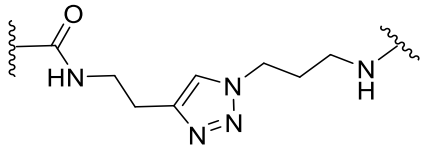


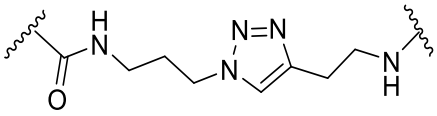


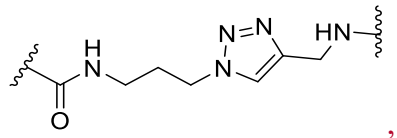


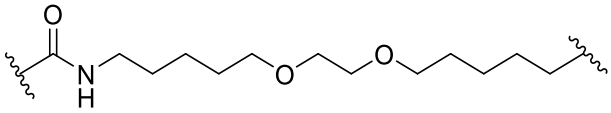


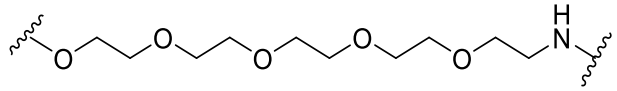


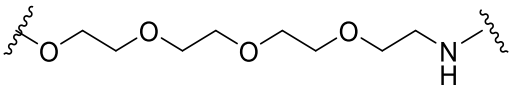


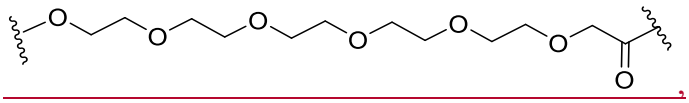


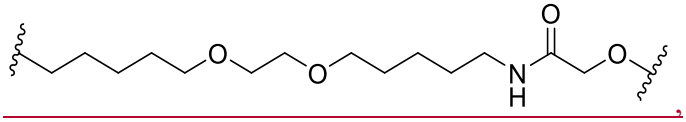


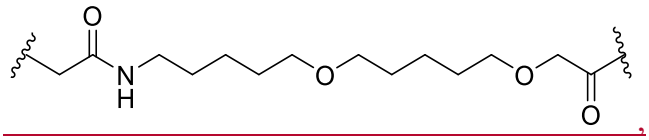


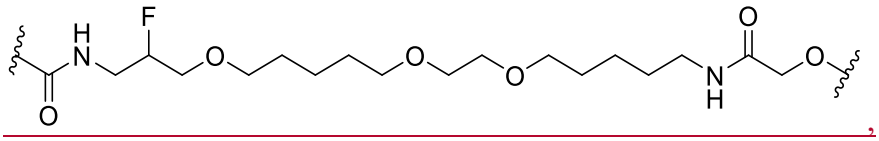


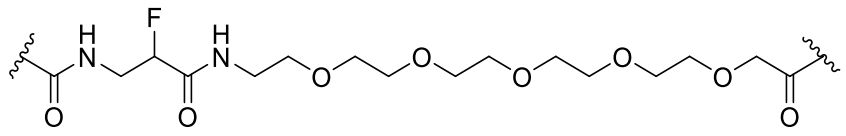


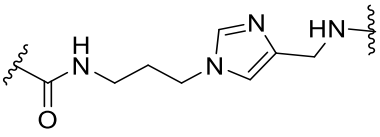


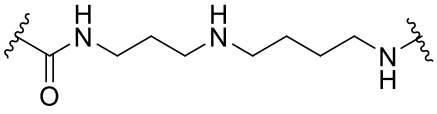


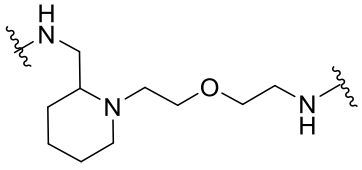


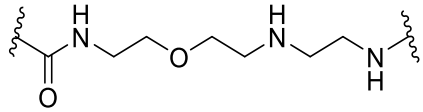


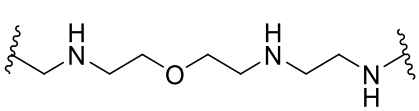


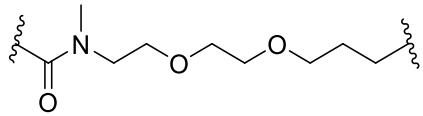


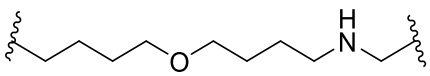


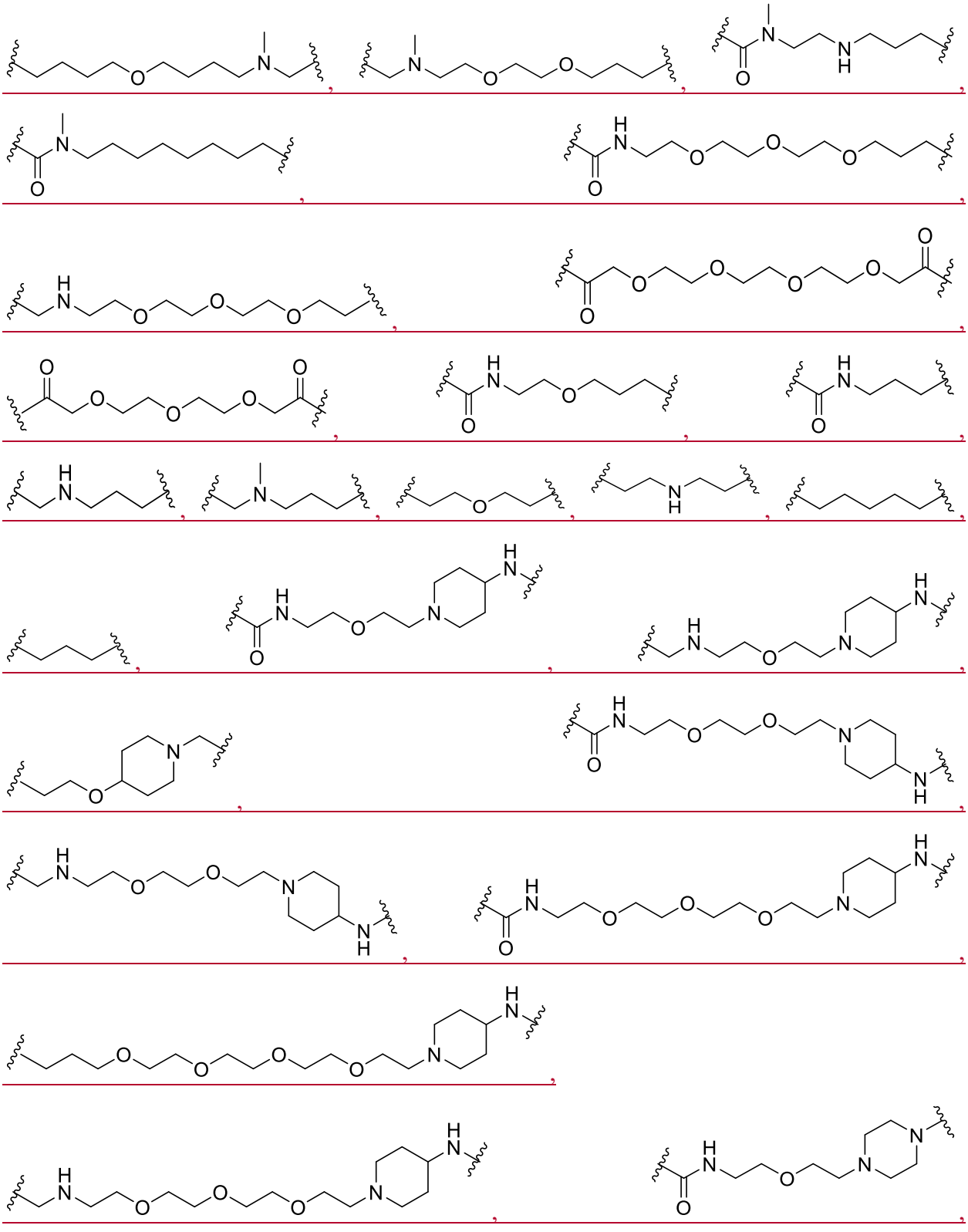


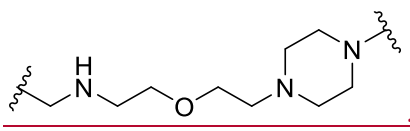
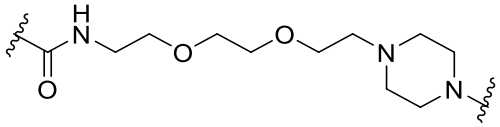
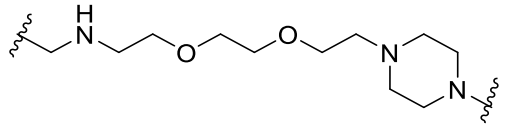
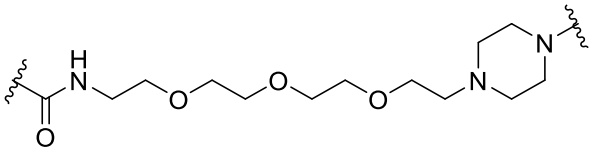
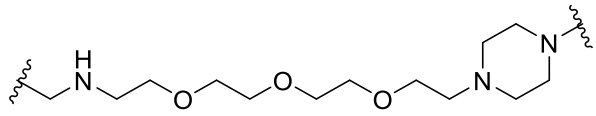
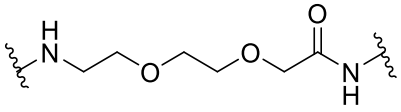
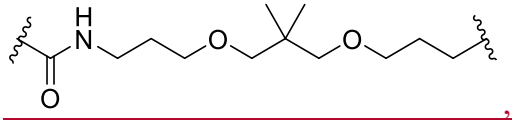
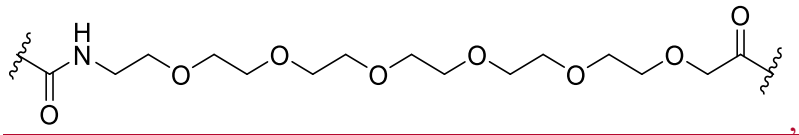
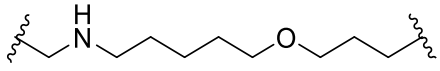
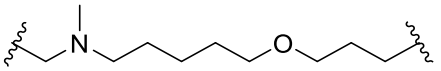
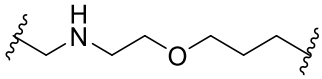
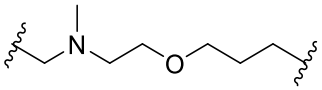
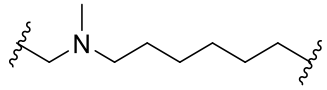
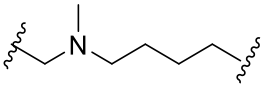
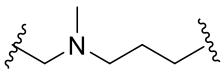
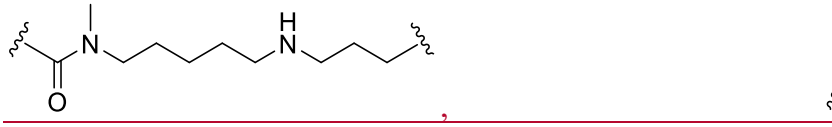
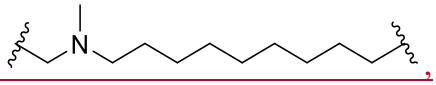
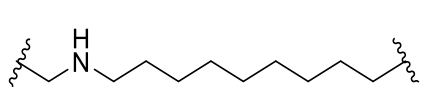
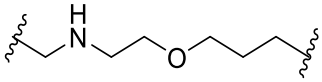
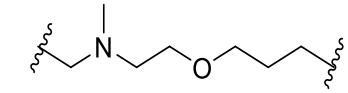


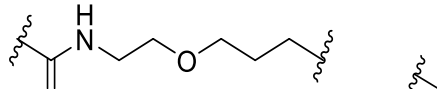
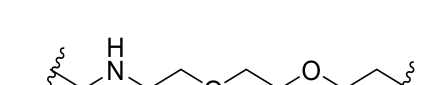
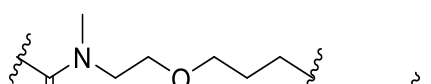


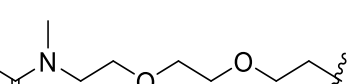


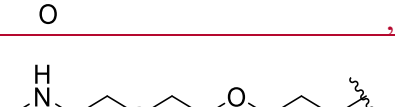
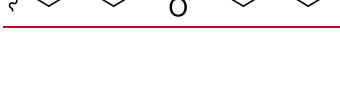




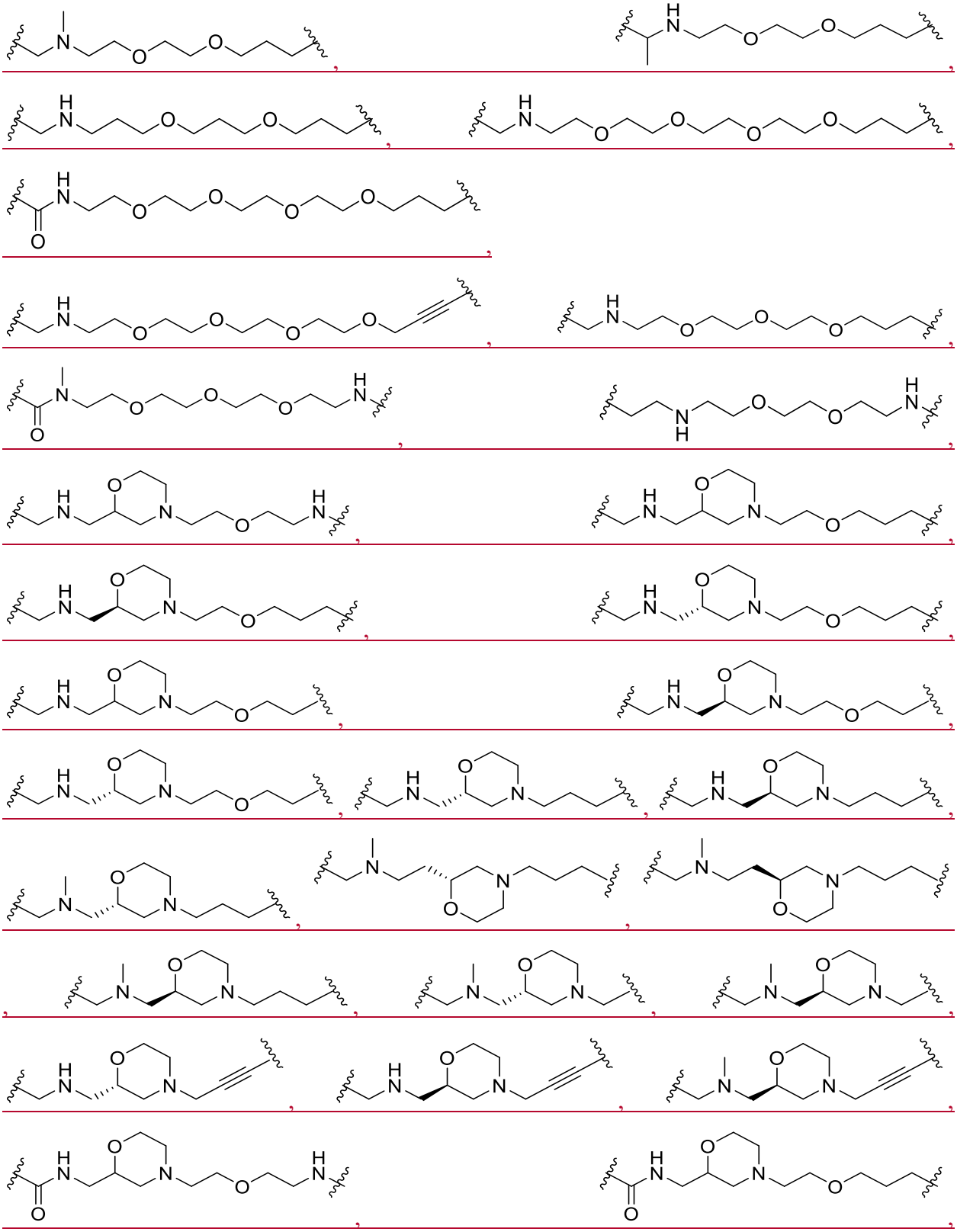





















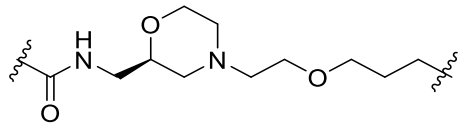
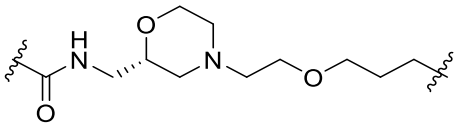
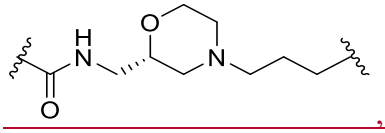
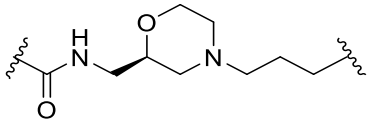
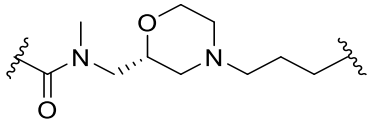
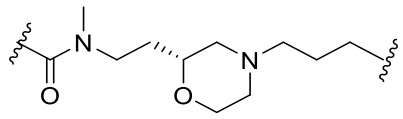
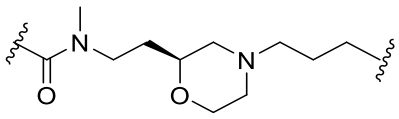
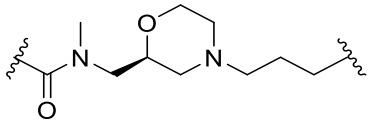
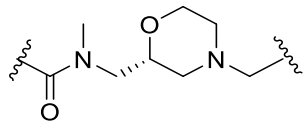
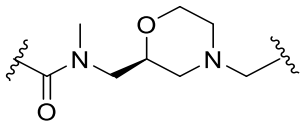
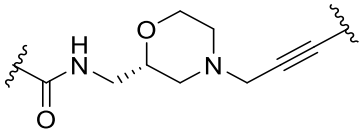
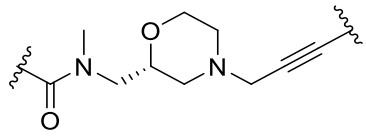
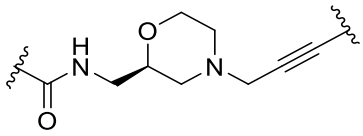
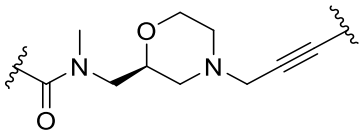
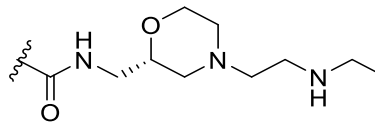




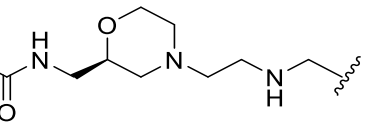


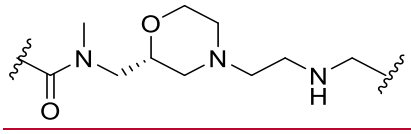
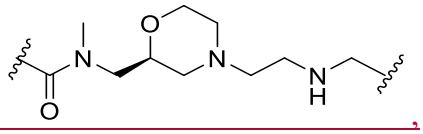
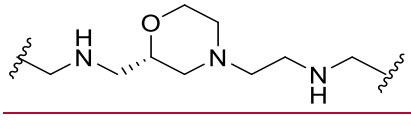
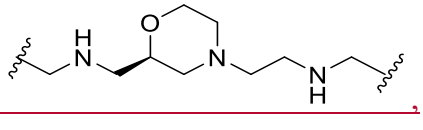
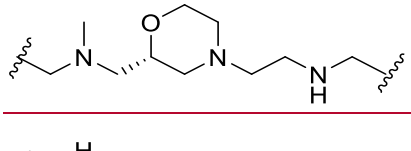
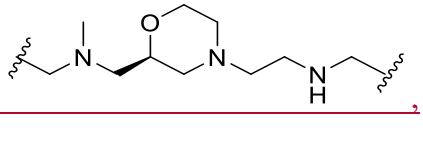
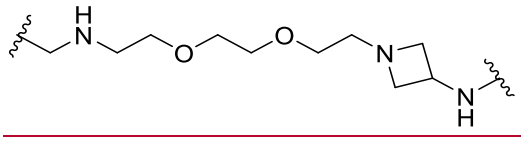
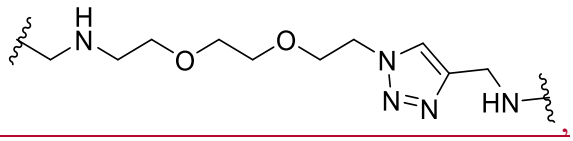
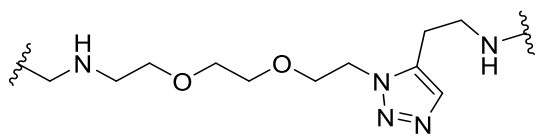
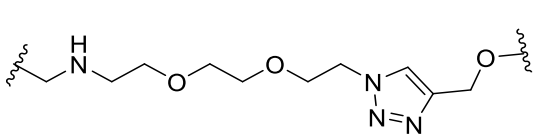




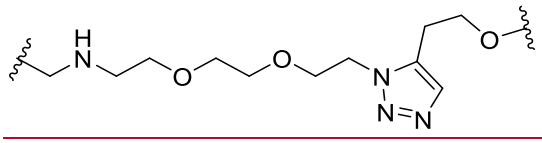
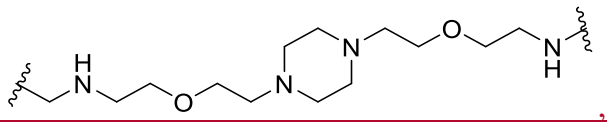
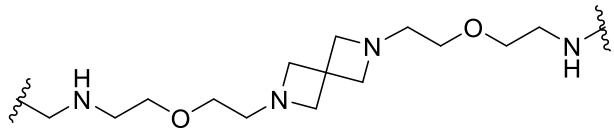
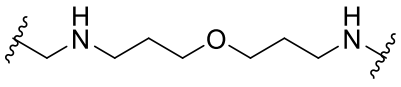
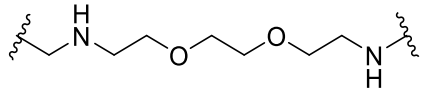
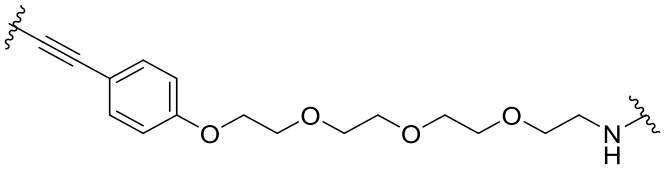
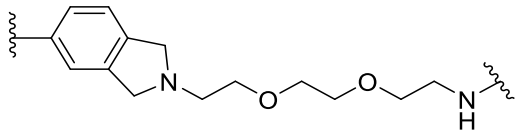
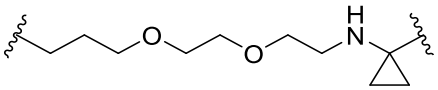
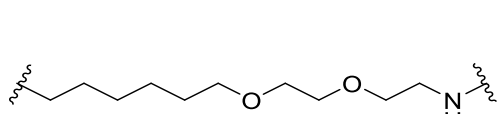


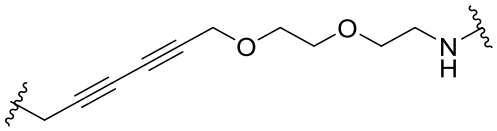
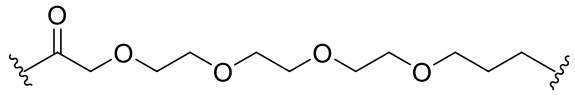
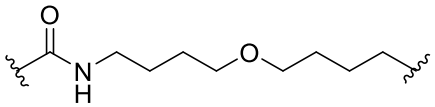
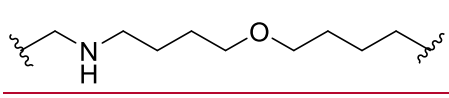
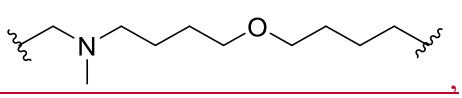
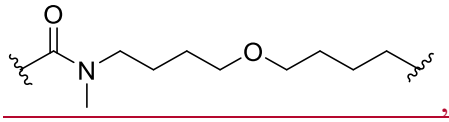
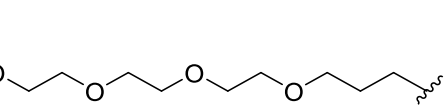
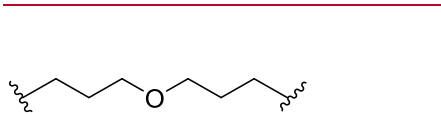


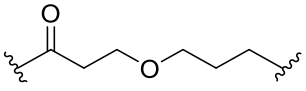
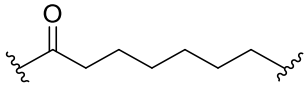
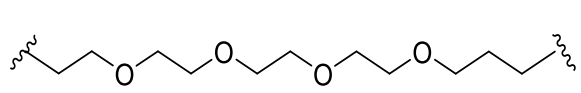
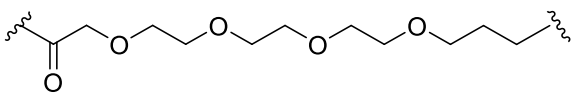
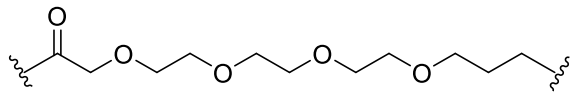
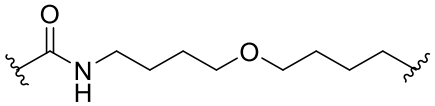
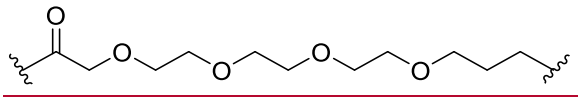
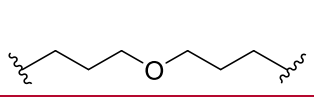
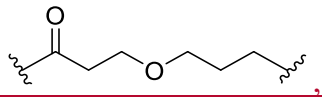
















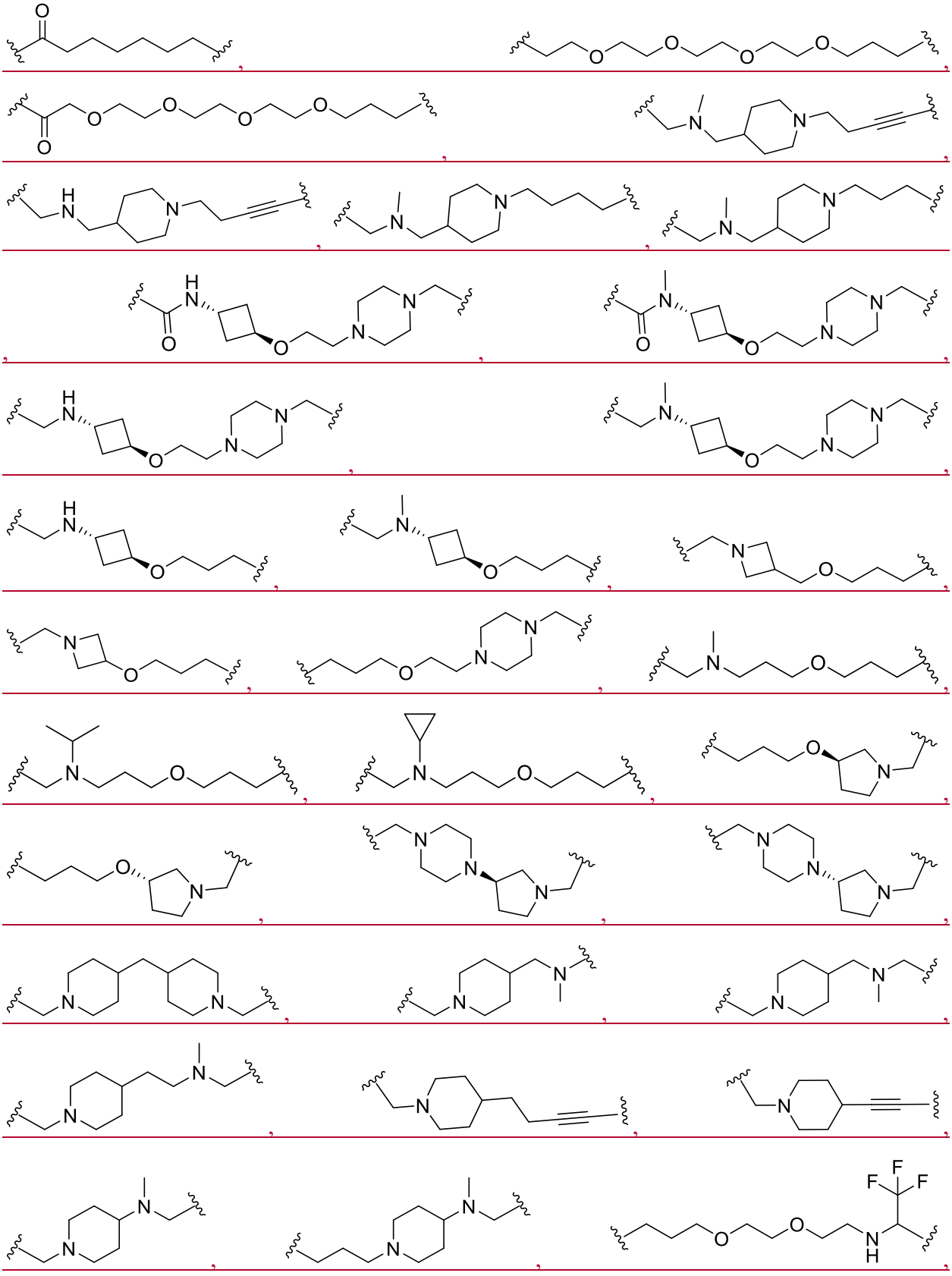


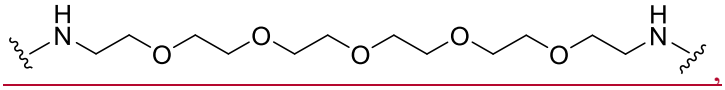











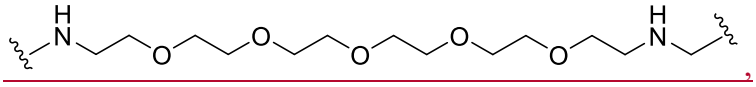










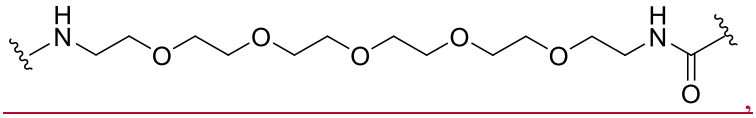









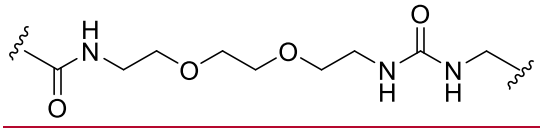










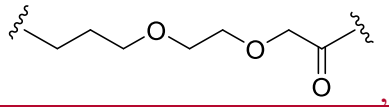


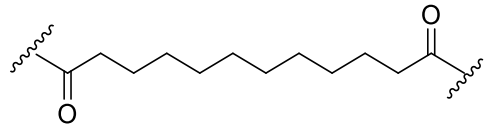


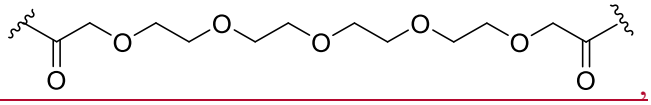


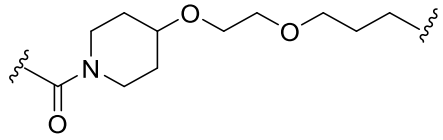


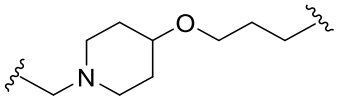


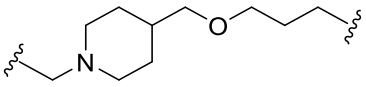


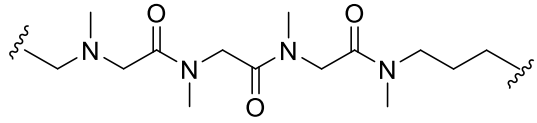


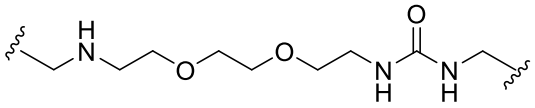


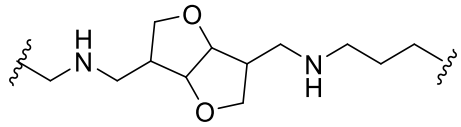


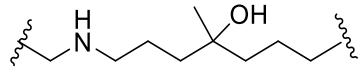


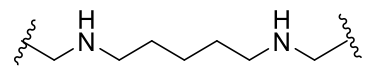


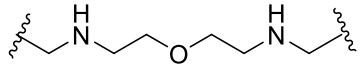


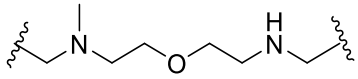


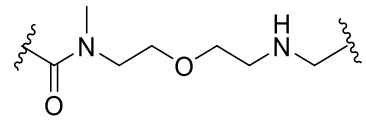


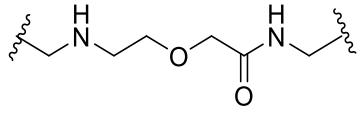


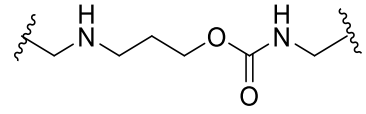


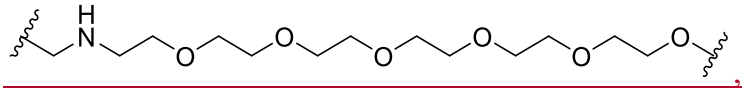


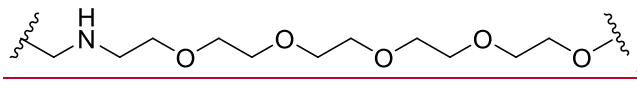


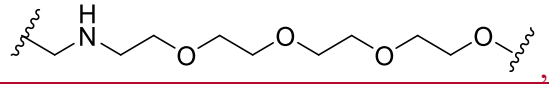


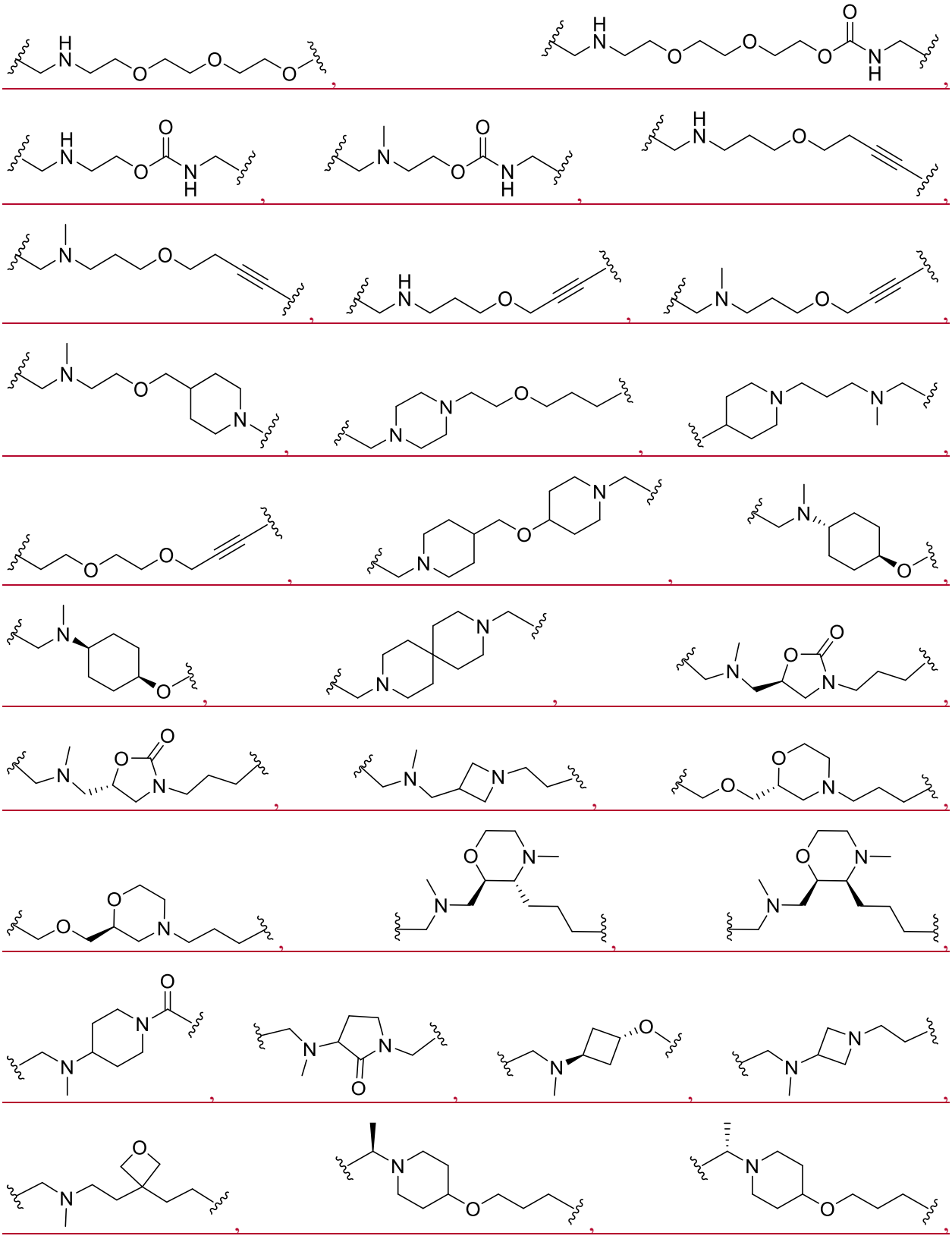


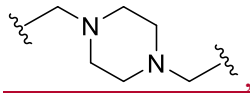
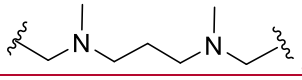
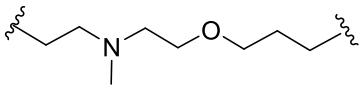


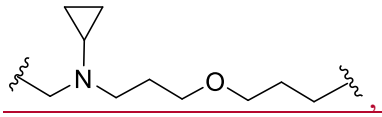
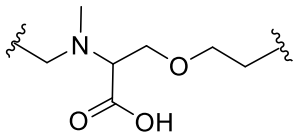
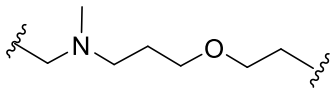


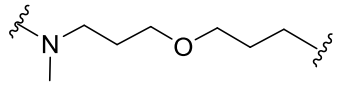
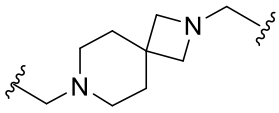
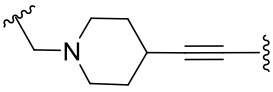


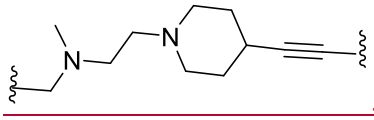
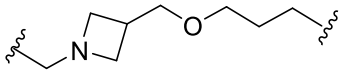




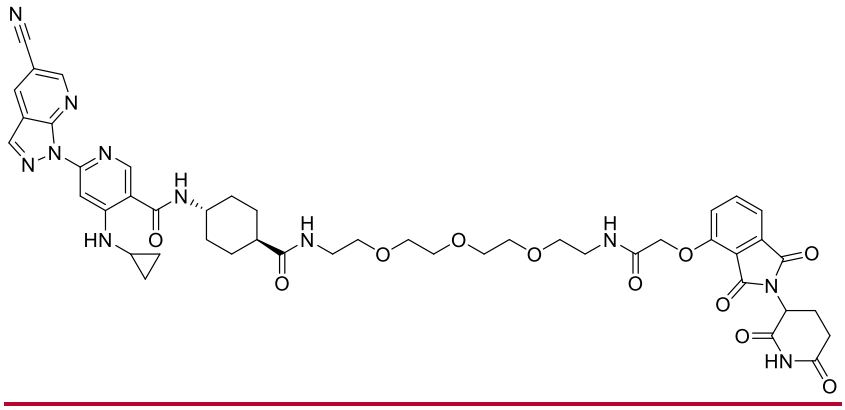
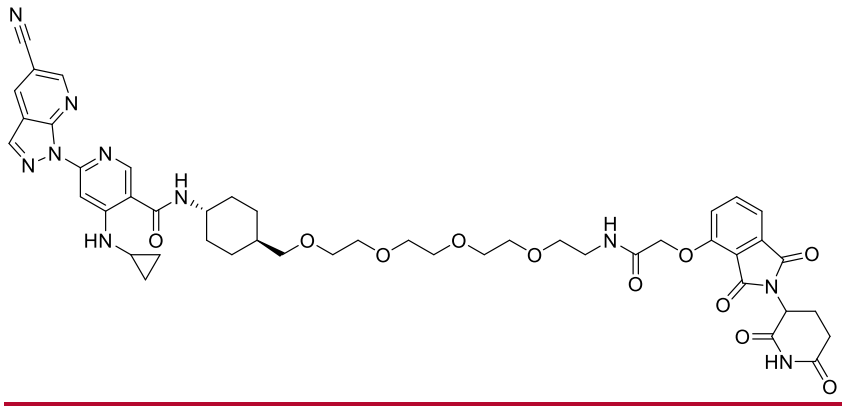
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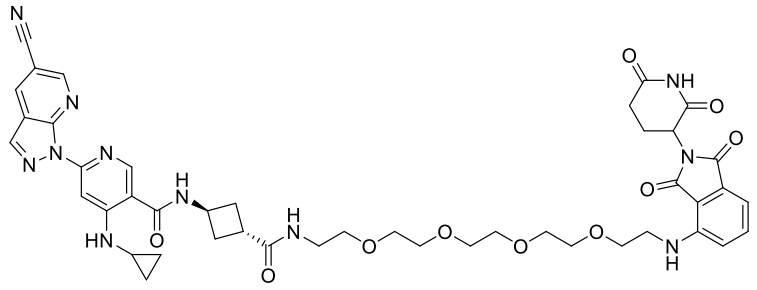
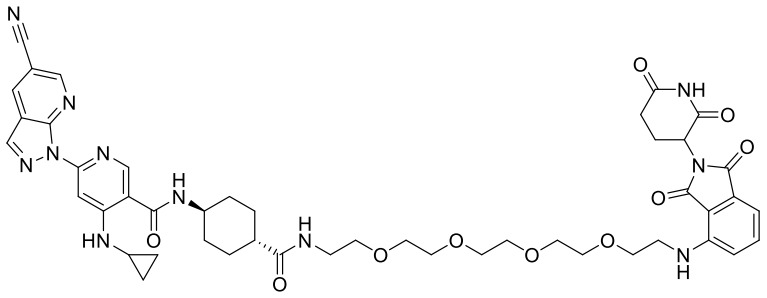
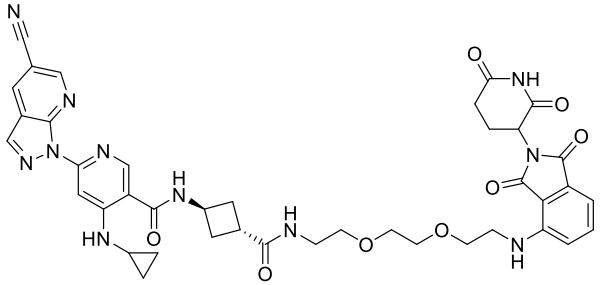
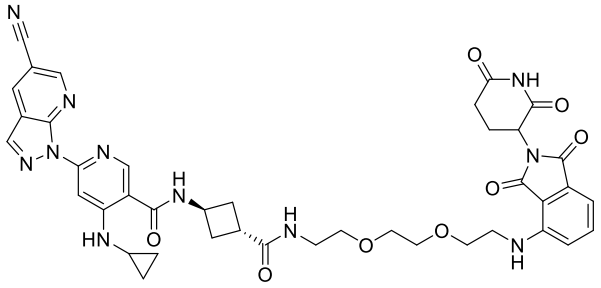
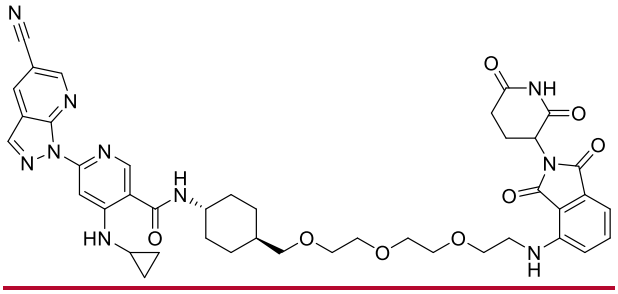
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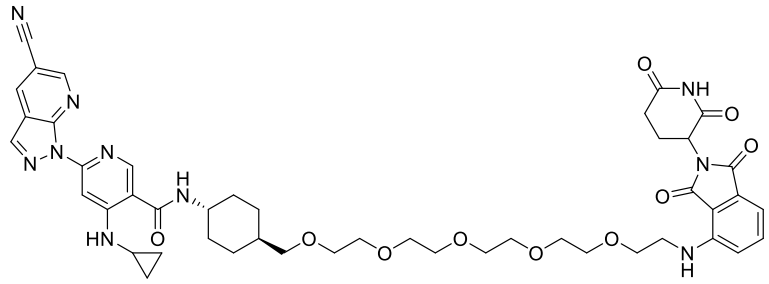
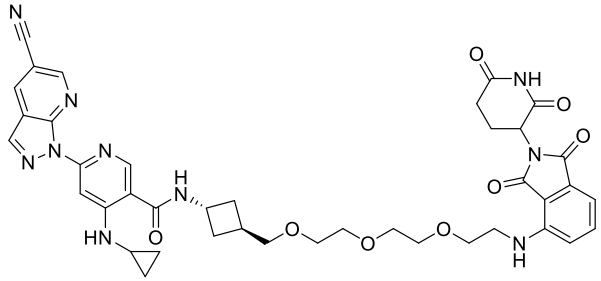
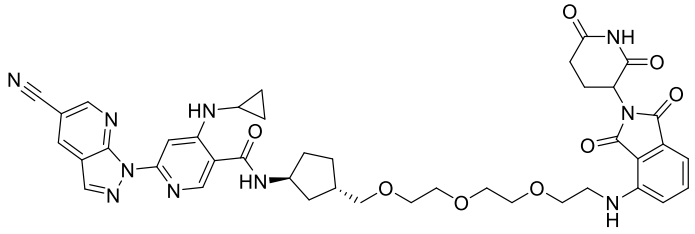
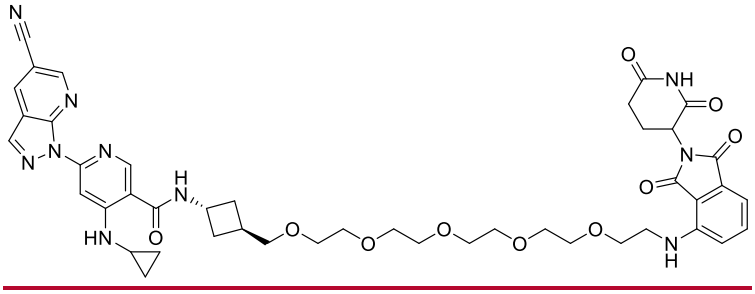
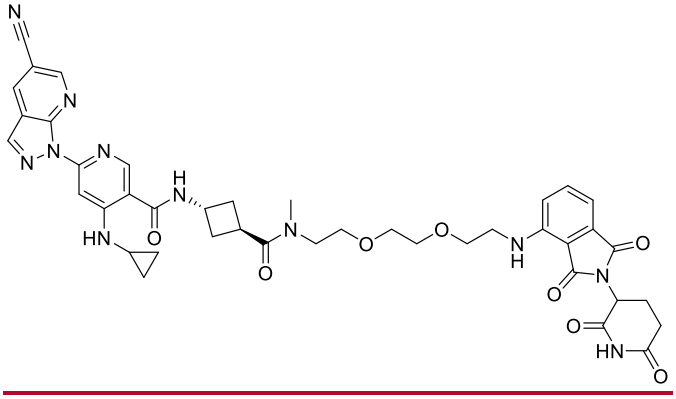
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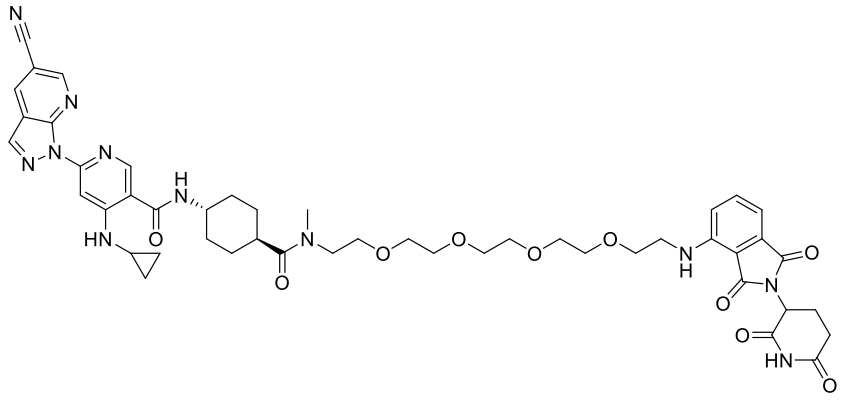
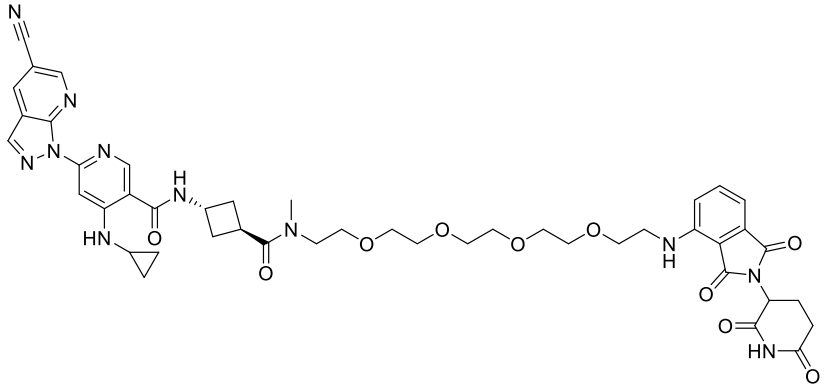
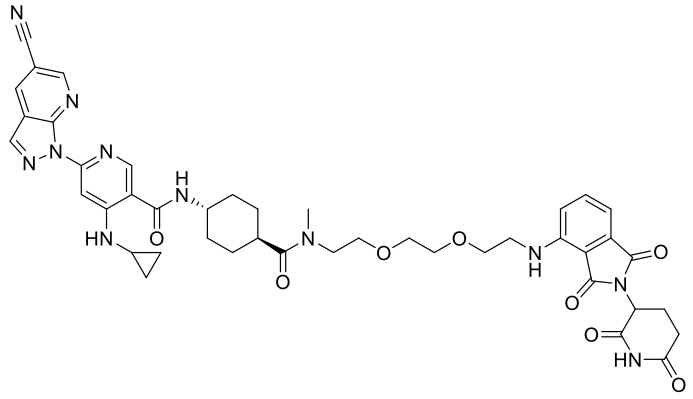
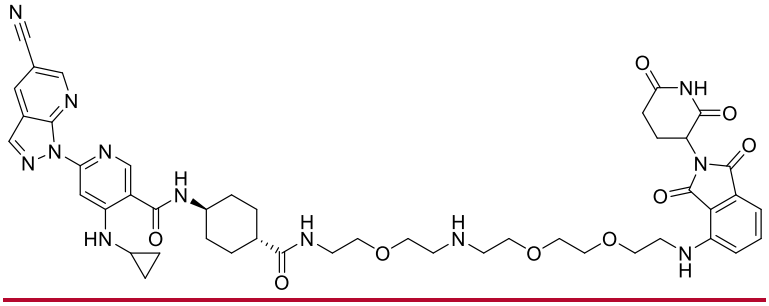
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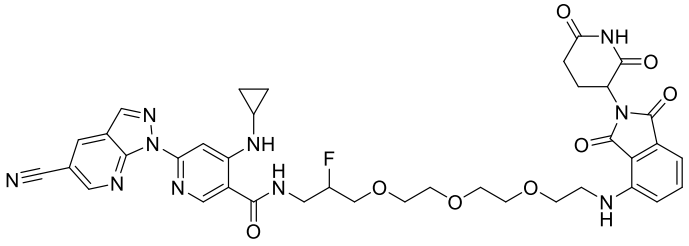
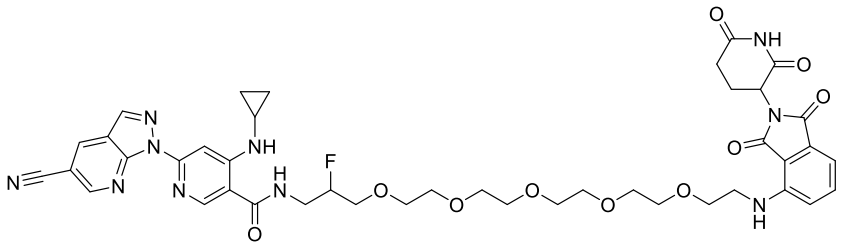
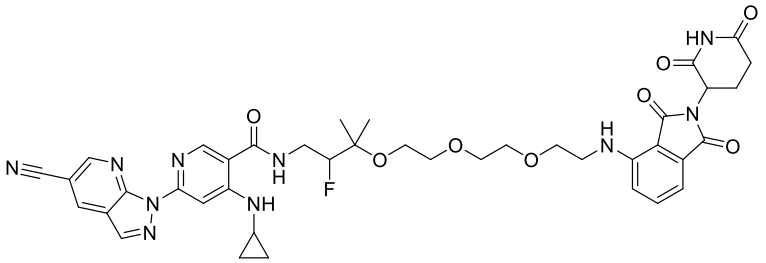
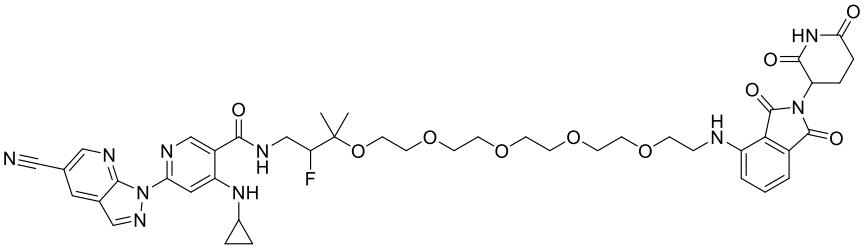
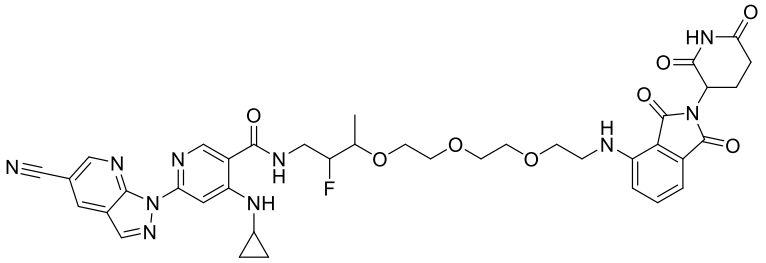
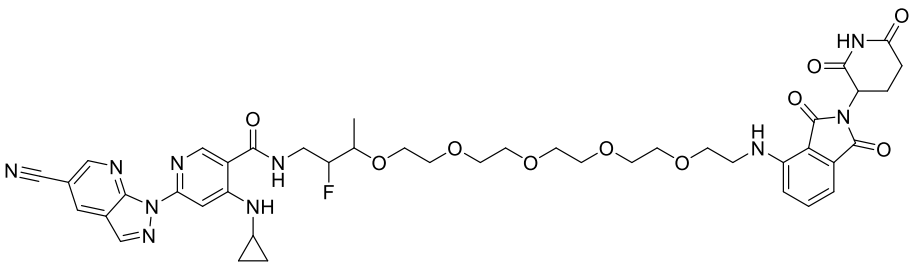
18. The compound according to claim 11, wherein said compound is selected from any one of the following compounds, or a pharmaceutically acceptable salt thereof.

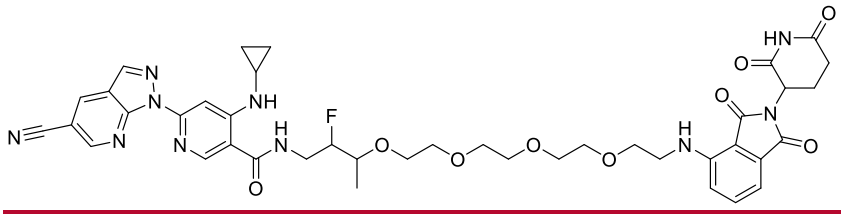
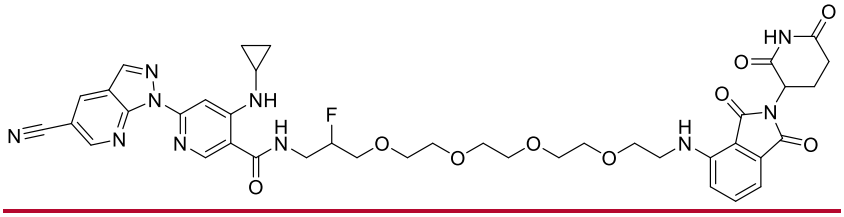
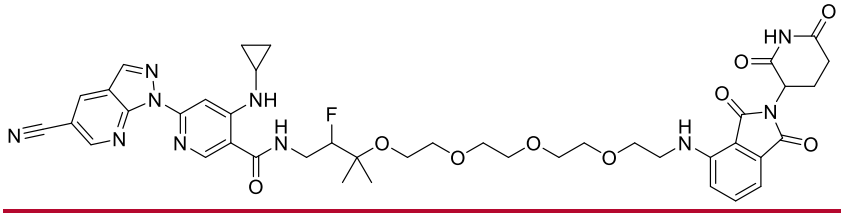
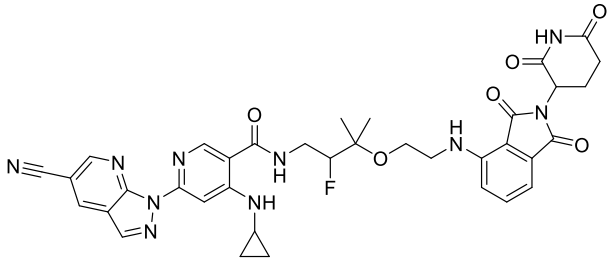
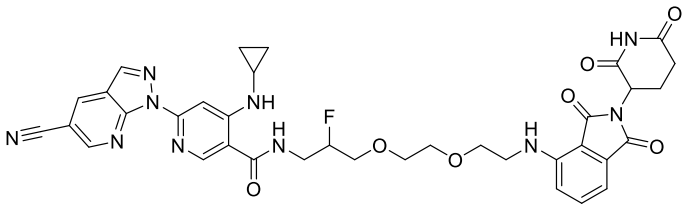
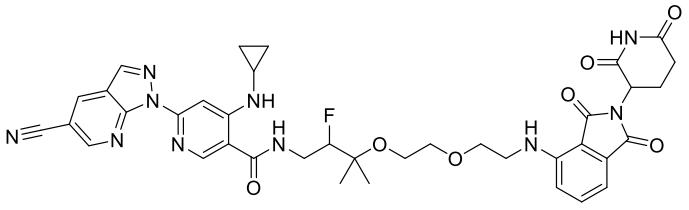
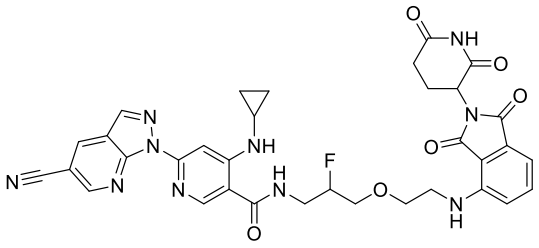
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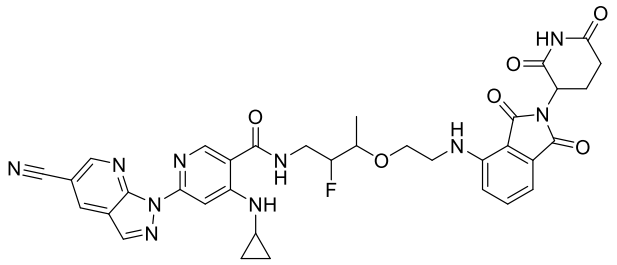
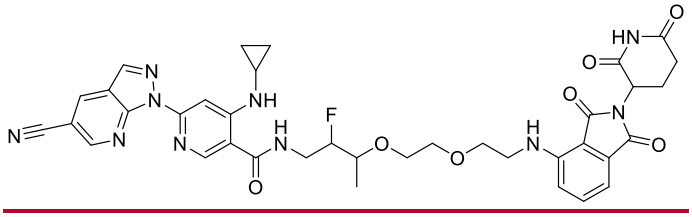
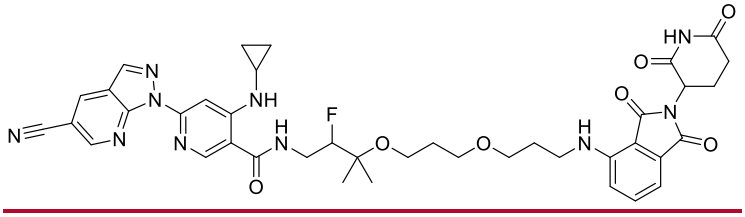
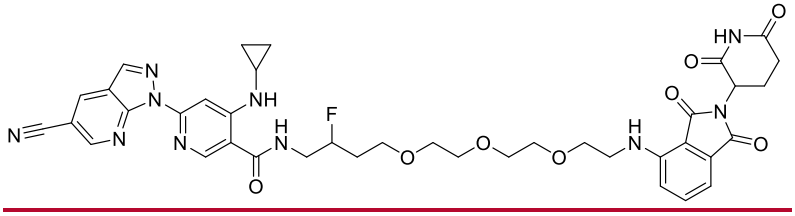
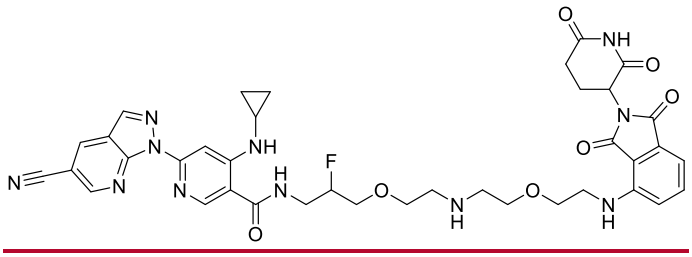
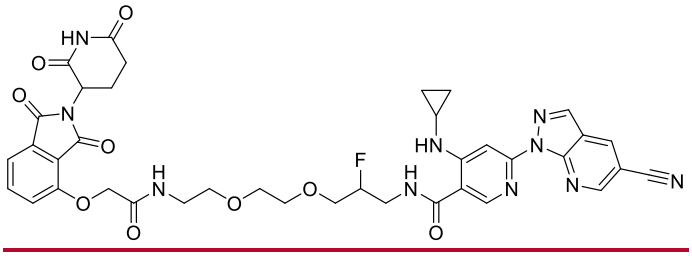
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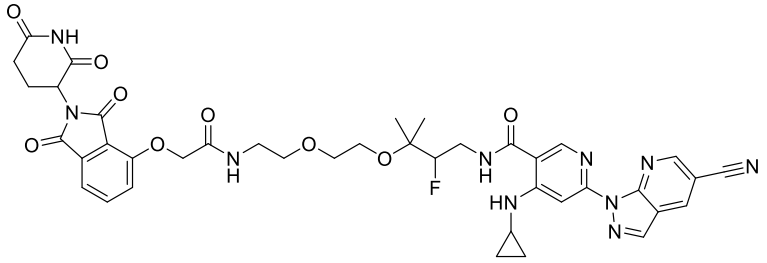
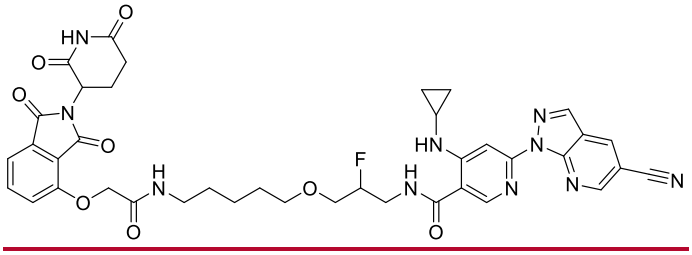
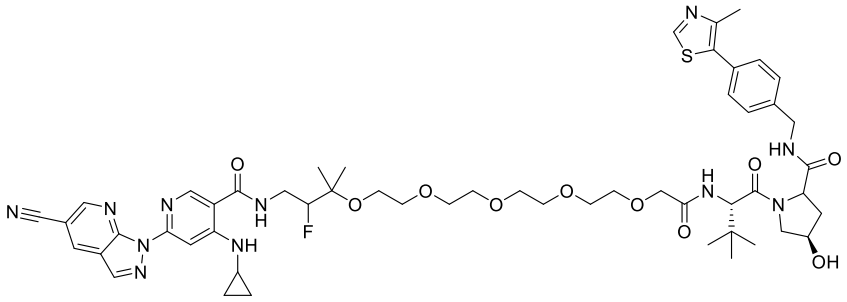
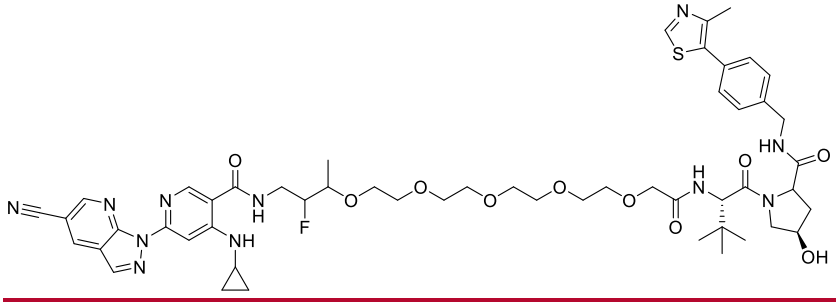
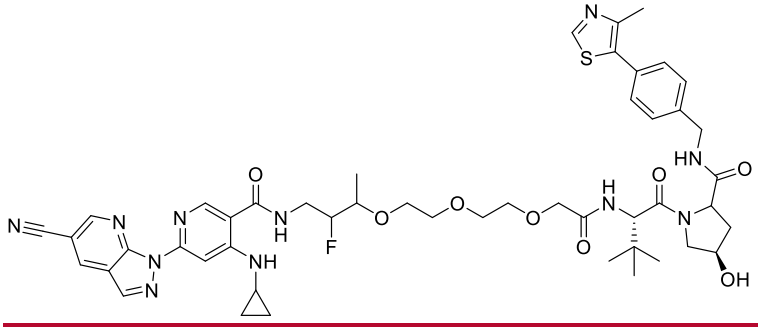
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I-37	

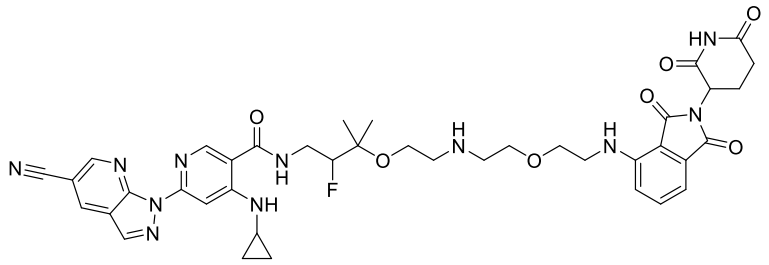
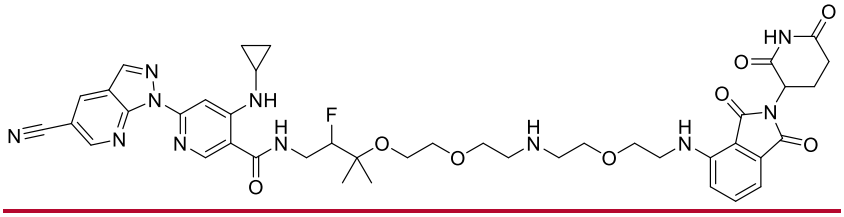
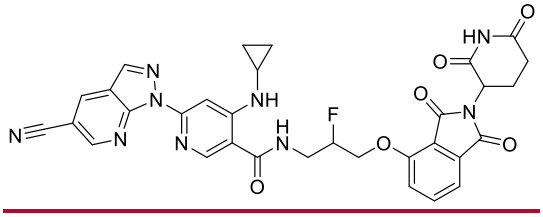
I-#	Structure
I-38	
I-39	
I-42	
I-45	

I-#	Structure
I-46	
I-57	
I-59	
I-60	
I-63	
I-66	

I-#	Structure
I-71	
I-72	
I-73	
I-75	
I-76	
I-79	
I-82	

I-#	Structure
I-83	
I-85	
I-86	
I-88	
I-94	
I-95	

I-#	Structure
I-101	
I-102	
I-118	
I-121	
I-122	

I-#	Structure
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.

~~17. A method of degrading IRAK4 protein kinase in a patient or biological sample comprising administering to said patient, or contacting said biological sample with a compound according to claim 1, or a pharmaceutical composition thereof.~~

~~18. A method of treating an IRAK4-mediated disorder, disease, or condition in a patient comprising administering to said patient a compound according to claim 1, or a pharmaceutical composition thereof.~~

~~19. The method according to claim 18, further comprising administration of an additional therapeutic agent.~~

~~20. The method according to claim 18, wherein the IRAK4-mediated disorder, disease or condition is selected from a cancer, a neurodegenerative disease, a viral disease, an autoimmune disease, an inflammatory disorder, a hereditary disorder, a hormone-related disease, a metabolic disorder, a condition associated with organ transplantation, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T cell activation, a cardiovascular disorder, and a CNS disorder.~~

~~21. The method of claim 10, wherein the IRAK4-mediated disorder, disease or condition is selected from a MyD88 driven disorder.~~

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