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.

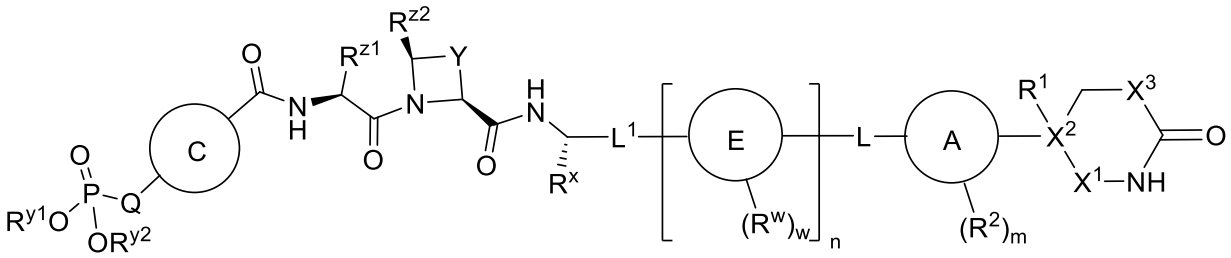
[0006] Aberrations in the process have recently been implicated in the pathogenesis of several diseases, both inherited and acquired. These diseases fall into two major groups: (a) those that result from loss of function with the resultant stabilization of certain proteins, and (b) those that result from gain of function, i.e. abnormal or accelerated degradation of the protein target.

[0007] The UPP is used to induce selective protein degradation, including use of fusion proteins to artificially ubiquitinate target proteins and synthetic small-molecule probes to induce proteasome-dependent degradation. Bifunctional compounds composed of a target protein-binding ligand and an E3 ubiquitin ligase ligand, induced proteasome-mediated degradation of selected proteins via their recruitment to E3 ubiquitin ligase and subsequent ubiquitination. These drug-like molecules offer the possibility of temporal control over protein expression. Such compounds are capable of inducing the inactivation of a protein of interest upon addition to cells or administration to an animal or human, and could be useful as biochemical reagents and lead to a new paradigm for the treatment of diseases by removing pathogenic or oncogenic proteins (Crews C, Chemistry & Biology, 2010, 17(6):551-555; Schnnekloth JS Jr., Chembiochem, 2005, 6(l):40-46).

[0008] An ongoing need exists in the art for effective treatments for disease, especially hyperplasia and cancer, such as breast cancer. 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 signal transducers and activators of transcription ("STAT") hold promise as therapeutic agents. Accordingly, there remains a need to find compounds that are STAT degraders useful as therapeutic agents.

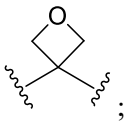
SUMMARY

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



I-a

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is a bivalent moiety selected from a covalent bond, $-CR_2-$, -C(O)-, -C(S)-, $-CR(CF_3)-$, -P(O)OR-, -P(O)R-, $-P(O)NR_2-$, $-S(O)-$, $-S(O)_2-$, or ;

X^2 is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from $-CR_2-$, -NR-, -O-, -S-, or $-SiR_2-$;

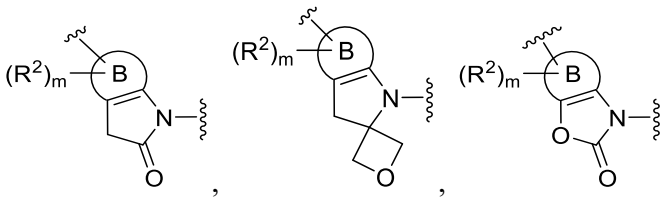
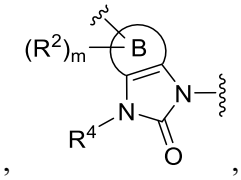
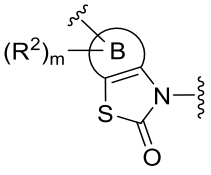
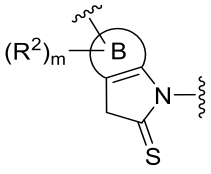
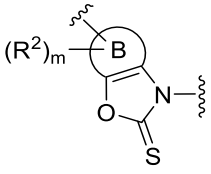
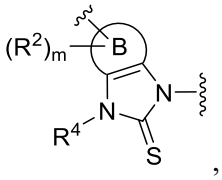
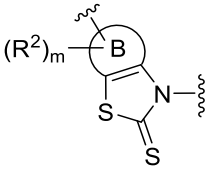
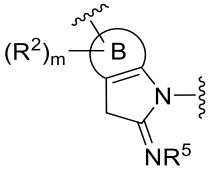
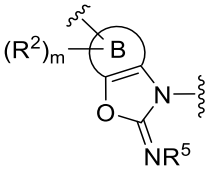
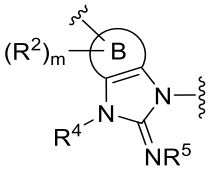
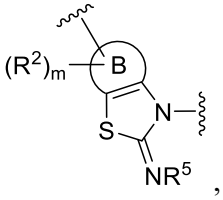
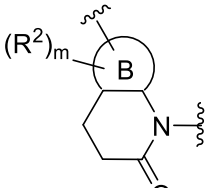
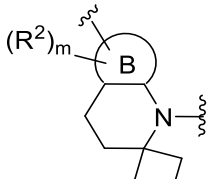
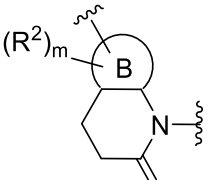
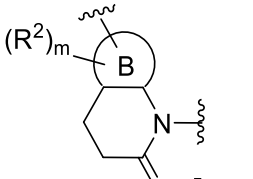
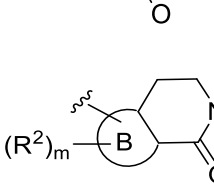
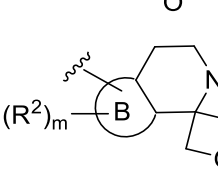
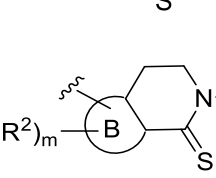
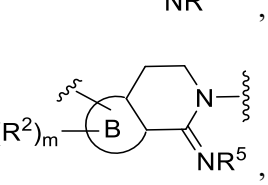
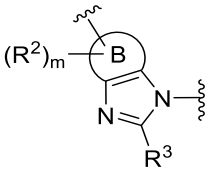
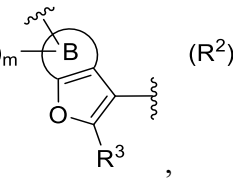
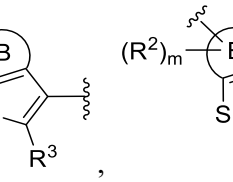
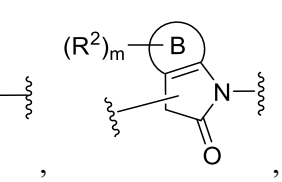
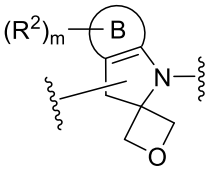
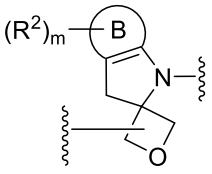
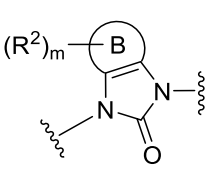
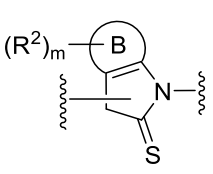
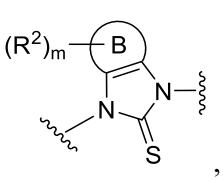
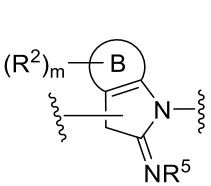
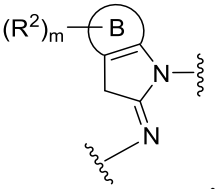
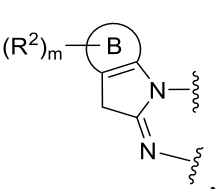
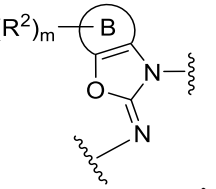
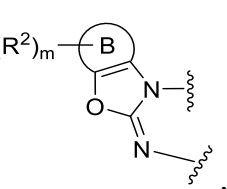
R^1 is hydrogen, halogen, -CN, -OR, -SR, -S(O)R, $-S(O)_2R$, $-NR_2$, $-P(O)(OR)_2$, $-P(O)NR_2OR$, $-P(O)(NR_2)_2$, $-Si(OH)_2R$, $-Si(OH)R_2$, $-SiR_3$, or an optionally substituted C_{1-4} aliphatic;

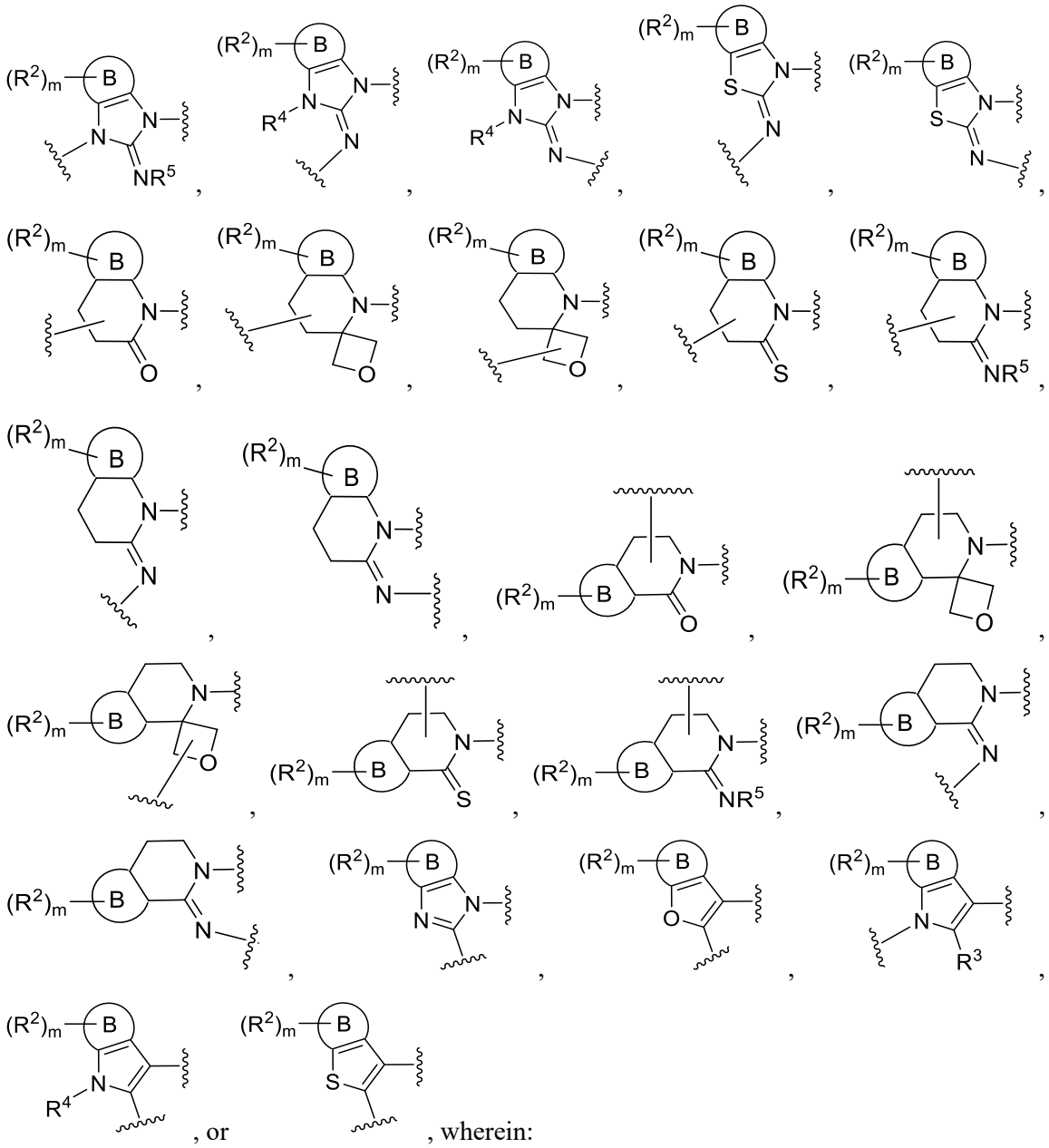
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^2 is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)NR_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, or $-NRS(O)_2R$;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or 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 bicyclic or tricyclic ring selected from , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , .


, wherein:

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

R^3 is selected from hydrogen, halogen, -OR, -NR_2, or -SR;

each R^4 is independently hydrogen, R^A, 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)NROR, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)NR_2$, or -$NRS(O)_2R$;

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

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

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -CRF-, -CF_2-, -C(O)-, -S-, -S(O)-, -$S(O)_2$-, -SiR_2-, -Si(OH)R-, -$Si(OH)_2$-, -P(O)OR-, -P(O)R-, or -$P(O)NR_2$-, wherein:

each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-3 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;

L^1 is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^1 are independently replaced by -O-, -NR-, -CRF-, -CF_2-, -C(O)-, -S-, -S(O)-, or -$S(O)_2$-;

Q is a bivalent moiety selected from -O-, -CR_2-, -CF_2-, -CFR-, -C(O)-, -OCR_2-, and -C(S)-;

Y is an optionally substituted -$(CH_2)_y$-, wherein:

y is 1, 2, or 3;

R^x is hydrogen, R^A, -$(CR_2)_{1-3}OCONR_2$, or -$(CR_2)_{1-3}CONR_2$;

R^{y1} and R^{y2} are each independently hydrogen, R^A, -CH_2CO_2R, or -CH_2OCO_2R;

R^{z1} and R^{z2} are each independently hydrogen or R^A, or:

R^{z1} and R^{z2} are cyclically linked to form an optionally substituted fused 5-8 membered heterocyclic ring;

Ring C is an optionally substituted bivalent ring selected from phenylenyl, naphthylenyl, a 5-10 membered heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring E is a bivalent ring selected from phenylenyl, a 4-7 membered saturated or partially unsaturated

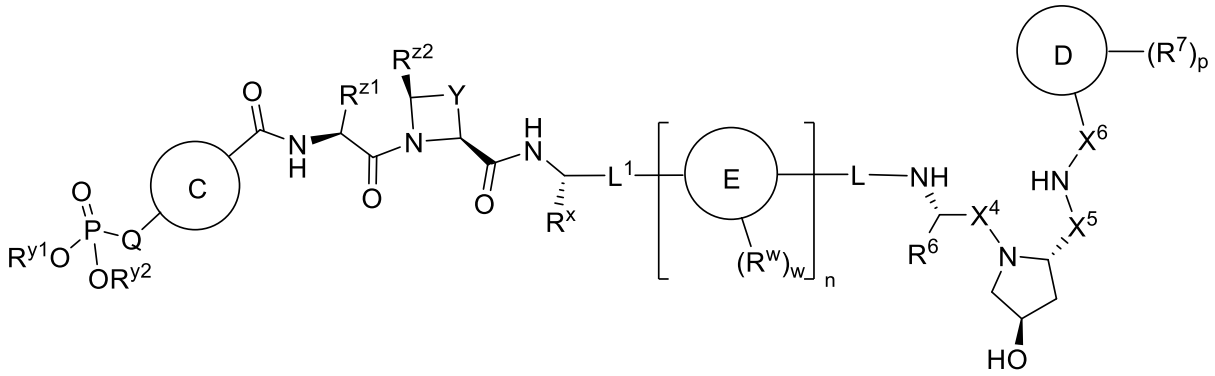
carbocyclylenyl or heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w is hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)NROR, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)NR_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, or $-NRS(O)_2R$;

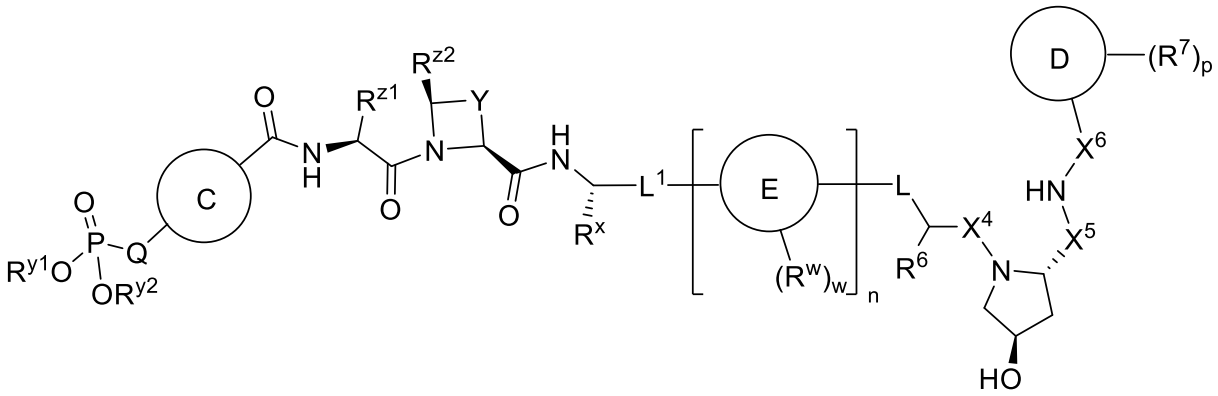
w is 0, 1, 2, 3, or 4; and

n is 0 or 1.

[0008b] In another aspect of the present disclosure, there is provided a compound according to formula **I-b** or **I-f**:



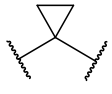
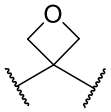
I-b



I-f

or a pharmaceutically acceptable salt thereof, wherein:

X^4, X^5, and X^6 are each independently a bivalent moiety selected from a covalent bond, $-CR_2-$, -C(O)-, -

C(S)-, -O-, -S(O)-, -S(O)$_2$-,  , or  ;

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

two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

R^6 is hydrogen or R^A;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or 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 D is selected from phenyl, a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

R^7 is hydrogen, R^A, 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)NROR, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)NR_2$, or -$NRS(O)_2R$;

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

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -CRF-, -CF_2-, -C(O)-, -S-, -S(O)-, -$S(O)_2$-, -SiR_2-, -Si(OH)R-, -$Si(OH)_2$-, -P(O)OR-, -P(O)R-, or -$P(O)NR_2$-, wherein:

each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially

unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-3 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;

L^1 is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^1 are independently replaced by -O-, -NR-, -CRF-, -CF_2-, -C(O)-, -S-, -S(O)-, or -$S(O)_2$-;

Q is a bivalent moiety selected from -O-, -CR_2-, -CF_2-, -CFR-, -C(O)-, -OCR_2-, and -C(S)-;

Y is an optionally substituted -$(CH_2)_y$-, wherein:

y is 1, 2, or 3;

R^x is hydrogen, R^A, -$(CR_2)_{1-3}OCONR_2$, or -$(CR_2)_{1-3}CONR_2$;

R^{y1} and R^{y2} are each independently hydrogen, R^A, -CH_2CO_2R, or -CH_2OCO_2R;

R^{z1} and R^{z2} are each independently hydrogen or R^A, or:

R^{z1} and R^{z2} are cyclically linked to form an optionally substituted fused 5-8 membered heterocyclic ring;

Ring C is an optionally substituted bivalent ring selected from phenylenyl, naphthylenyl, a 5-10 membered heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

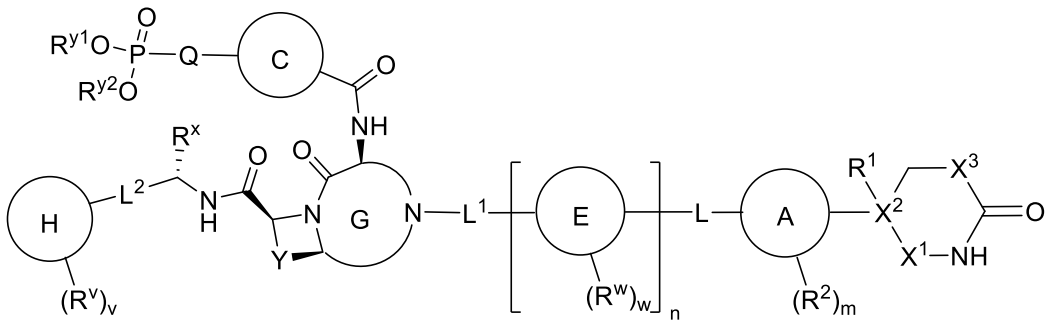
Ring E is a bivalent ring selected from phenylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w is hydrogen, R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -SiR_3, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, –$C(O)NR_2$, -C(O)NROR, -$CR_2NRC(O)R$, -$CR_2NRC(O)NR_2$, -OC(O)R, -$OC(O)NR_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)NR_2$, -$NRS(O)_2R$, -$NP(O)R_2$, -$NRP(O)(OR)_2$, -$NRP(O)(OR)NR_2$, -$NRP(O)(NR_2)_2$, or -$NRS(O)_2R$;

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

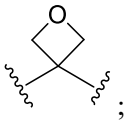
n is 0 or 1.

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



I-d

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is a bivalent moiety selected from a covalent bond, $-CR_2-$, -C(O)-, -C(S)-, $-CR(CF_3)-$, -P(O)OR-, -P(O)R-, $-P(O)NR_2-$, -S(O)-, $-S(O)_2-$, or ;

X^2 is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from $-CR_2-$, -NR-, -O-, -S-, or $-SiR_2-$;

R^1 is hydrogen, halogen, -CN, -OR, -SR, -S(O)R, $-S(O)_2R$, $-NR_2$, $-P(O)(OR)_2$, $-P(O)NR_2OR$, $-P(O)(NR_2)_2$, $-Si(OH)_2R$, $-Si(OH)R_2$, $-SiR_3$, or an optionally substituted C_{1-4} aliphatic;

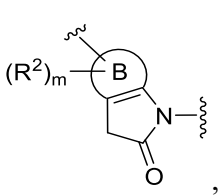
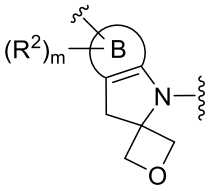
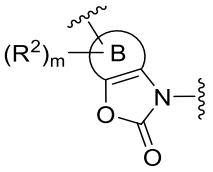
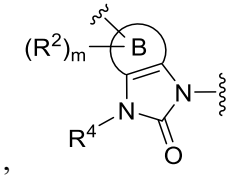
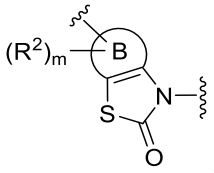
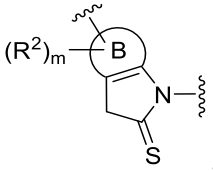
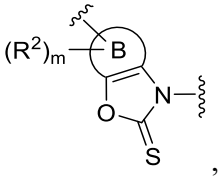
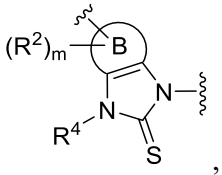
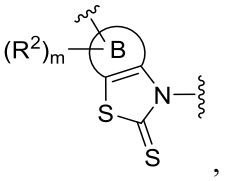
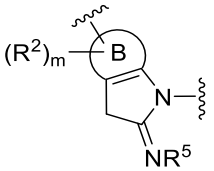
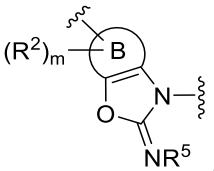
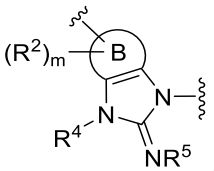
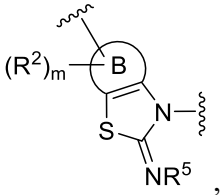
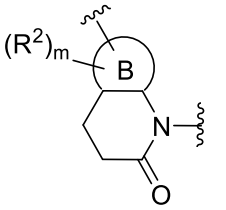
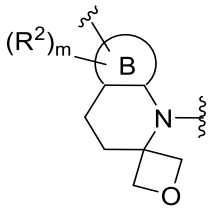
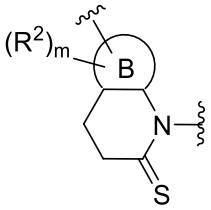
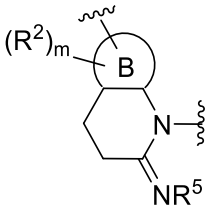
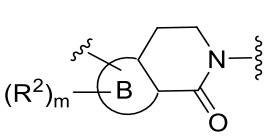
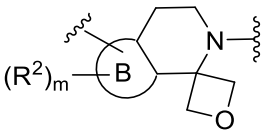
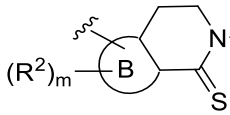
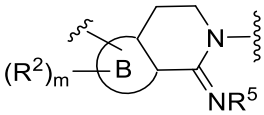
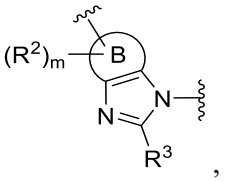
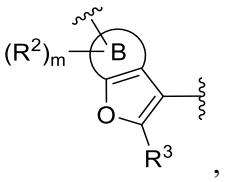
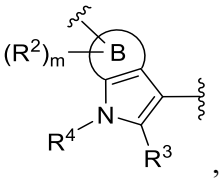
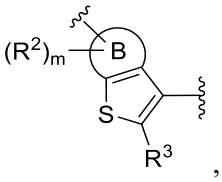
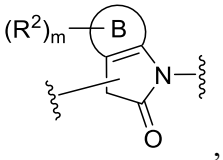
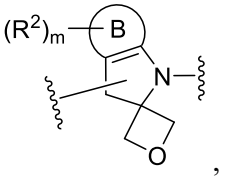
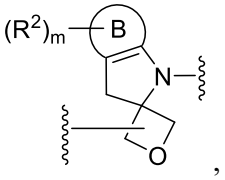
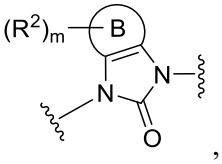
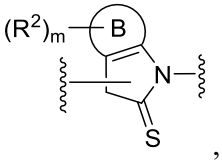
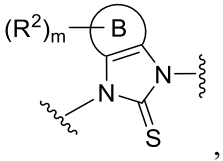
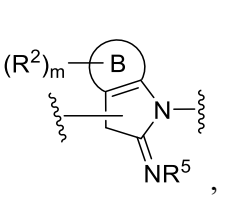
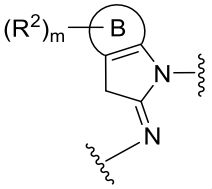
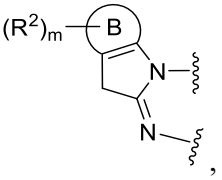
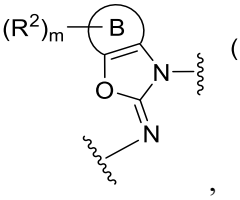
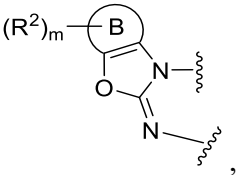
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

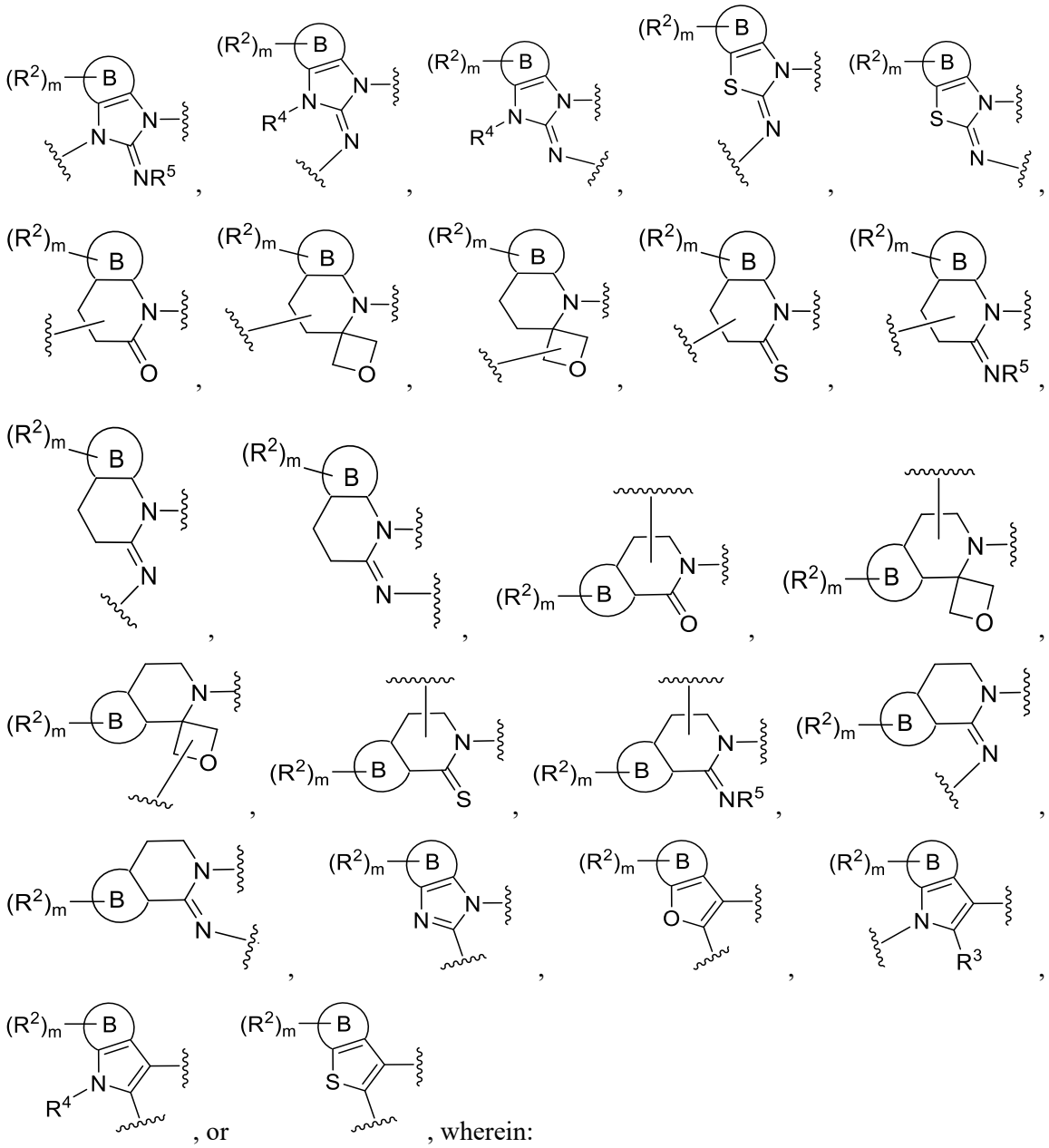
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^2 is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, –C(O)NR_2, -C(O)NROR, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)NR_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, or $-NRS(O)_2R$;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or 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 bicyclic or tricyclic ring selected from , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , .


, wherein:

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

R^3 is selected from hydrogen, halogen, -OR, -NR_2, or -SR;

each R^4 is independently hydrogen, R^A, 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)NROR, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)NR_2$, or -$NRS(O)_2R$;

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

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

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -CRF-, -CF_2-, -C(O)-, -S-, -S(O)-, -$S(O)_2$-, -SiR_2-, -Si(OH)R-, -$Si(OH)_2$-, -P(O)OR-, -P(O)R-, or -$P(O)NR_2$-, wherein:

each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-3 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;

L^1 is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^1 are independently replaced by -O-, -NR-, -CRF-, -CF_2-, -C(O)-, -S-, -S(O)-, or -$S(O)_2$-;

L^2 is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^2 are independently replaced by -O-, -NR-, -CRF-, -CF_2-, -C(O)-, , -S-, -S(O)-, or -$S(O)_2$-;

R^x is hydrogen, R^A, -$(CR_2)_{1-3}OCONR_2$, or -$(CR_2)_{1-3}CONR_2$;

Ring C is an optionally substituted bivalent ring selected from phenylenyl, naphthylenyl, a 5-10 membered heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Q is a bivalent moiety selected from -O-, -CR_2-, -CF_2-, -CFR-, -C(O)-, -OCR_2-, and -C(S)-;

R^{y1} and R^{y2} are each independently hydrogen or R^A;

Y is an optionally substituted -$(CH_2)_y$-, wherein:

y is 1, 2, or 3;

Ring G is an optionally substituted ring selected from a 5-9 membered saturated or partially unsaturated heterocyclyl;

Ring H is a ring selected from phenyl, a 5-9 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^v is hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)NROR, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)NR_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, or $-NRS(O)_2R$;

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

Ring E is a bivalent ring selected from phenylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w is hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)NROR, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)NR_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, or $-NRS(O)_2R$;

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

n is 0 or 1.

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

[0008e] In a further aspect of the present disclosure, there is provided a compound disclosed herein or a pharmaceutical composition thereof, for use in degrading STAT3 protein in a patient or biological sample.

[0008f] In another aspect of the present disclosure, there is provided a compound disclosed herein or a pharmaceutical composition thereof, for use in treating an STAT3-mediated disorder, disease, or condition in a patient.

[0008g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating an STAT3-mediated disorder, disease, or condition in a patient.

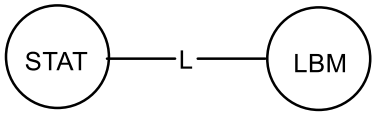
[0009] The present application relates novel bifunctional compounds, which function to recruit STAT

proteins 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 STAT proteins, which are then degraded and/or otherwise inhibited by the bifunctional compounds as described herein. Also provided are monovalent compounds, which find utility as inducers of targeted ubiquitination of STAT proteins, which are then degraded and/or otherwise inhibited by the monovalent compounds as described herein. An advantage of the compounds provided herein is that a

broad range of pharmacological activities is possible, consistent with the degradation/inhibition of STAT proteins. 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., breast cancer.

[0010] The present application further relates to targeted degradation of STAT proteins through the use of bifunctional molecules, including bifunctional molecules that link a cereblon-binding moiety to a ligand that binds STAT proteins.

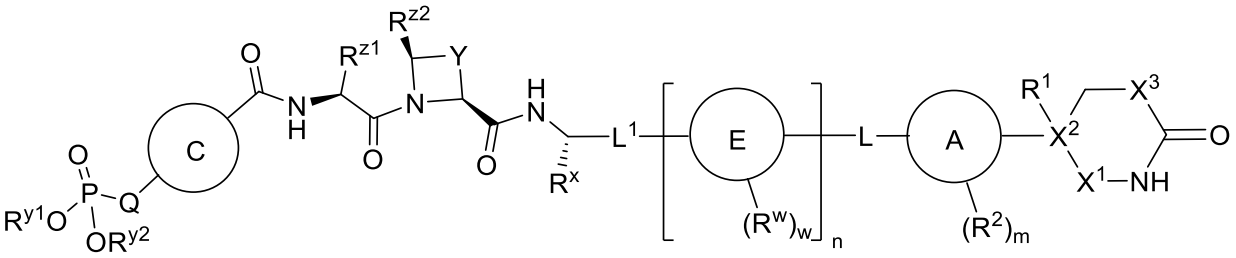
[0011] It has now been found that compounds of this present disclosure, and pharmaceutically acceptable compositions thereof, are effective as degraders of STAT proteins. Such compounds have the general formula **I**:



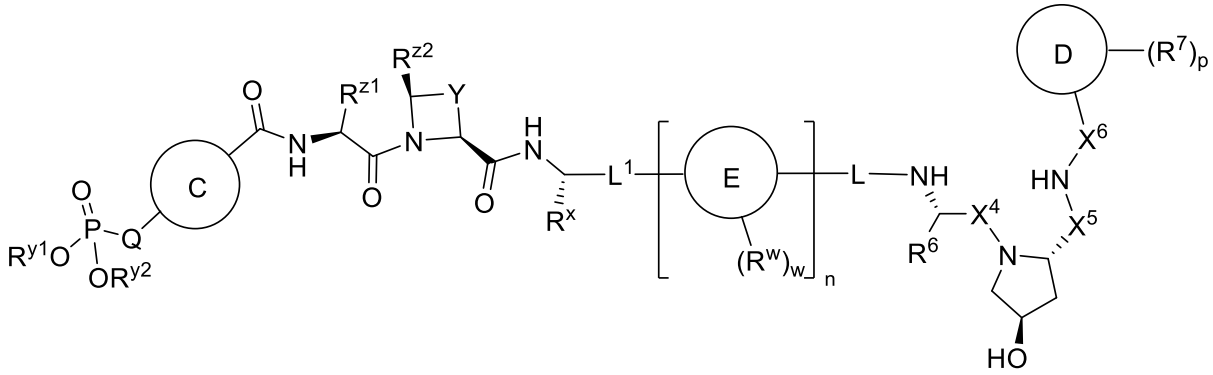
I

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

[0012] It has now been found that compounds of this present disclosure, and pharmaceutically acceptable compositions thereof, are effective for the modulation of targeted ubiquitination. Such compounds have the formula **I-a** to **I-f**:



I-a



I-b

I-f

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

[0013] Compounds of the present present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of signaling pathways implicating STAT proteins. Such diseases, disorders, or conditions include those described herein.

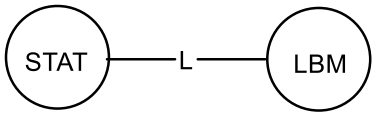
[0014] Compounds provided by this present disclosure are also useful for the study of STAT proteins in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new STAT inhibitors or STAT degraders or other regulators of cell cycling, metastasis, angiogenesis, and immune cell evasion, *in vitro* or *in vivo*.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Certain Embodiments of the Invention:

[0015] Compounds of the present invention, and compositions thereof, are useful as degraders and/or inhibitors of one or more STAT proteins. In some embodiments, a provided compound degrades and/or inhibits one or more of STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6.

[0016] In certain embodiments, the present invention provides a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

STAT is a STAT binding moiety capable of binding to STAT3;

L is a bivalent moiety that connects STAT to LBM; and

LBM is a E3 ubiquitin ligase binding moiety.

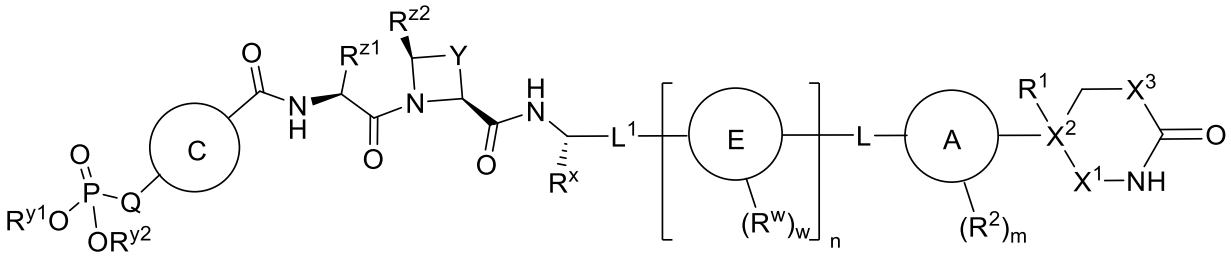
2. Compounds and Definitions:

[0017] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which

CLAIMS

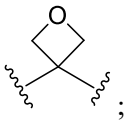
We claim:

1. A compound according to formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is a bivalent moiety selected from a covalent bond, $-CR_2-$, -C(O)-, -C(S)-, $-CR(CF_3)-$, -P(O)OR-, -P(O)R-, $-P(O)NR_2-$, $-S(O)-$, $-S(O)_2-$, or ;

X^2 is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from $-CR_2-$, -NR-, -O-, -S-, or $-SiR_2-$;

R^1 is hydrogen, halogen, -CN, -OR, -SR, -S(O)R, $-S(O)_2R$, $-NR_2$, $-P(O)(OR)_2$, $-P(O)NR_2OR$, $-P(O)(NR_2)_2$, $-Si(OH)_2R$, $-Si(OH)R_2$, $-SiR_3$, or an optionally substituted C_{1-4} aliphatic;

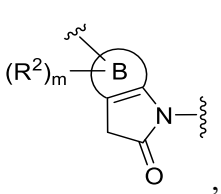
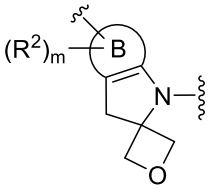
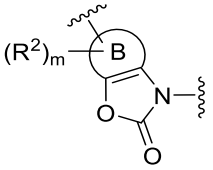
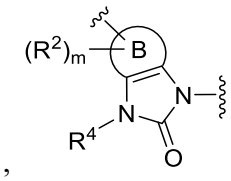
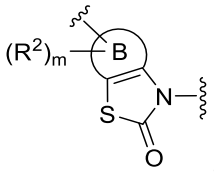
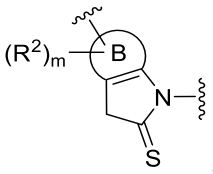
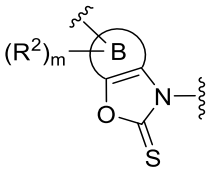
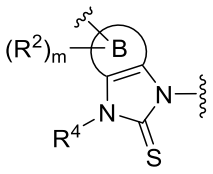
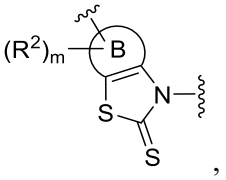
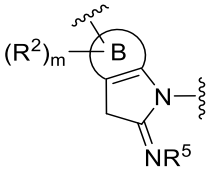
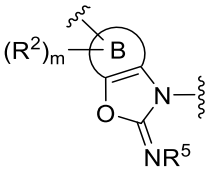
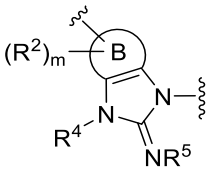
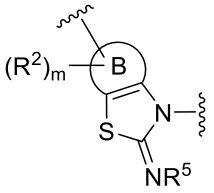
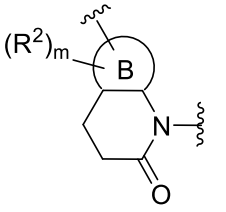
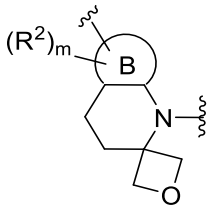
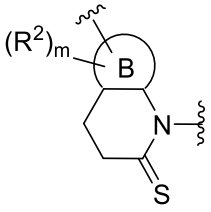
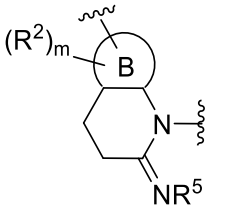
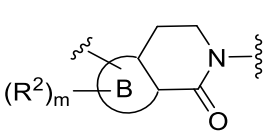
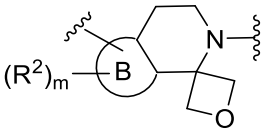
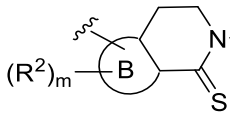
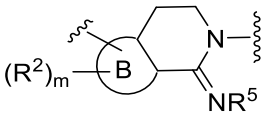
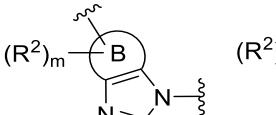
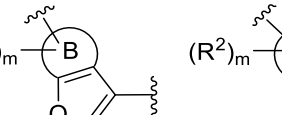
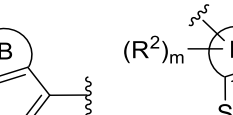
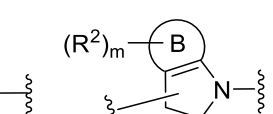
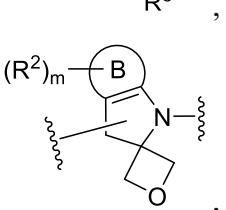
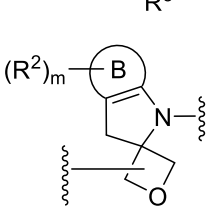
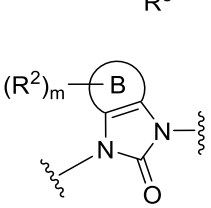
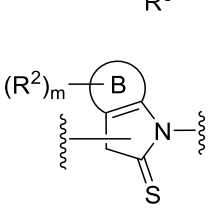
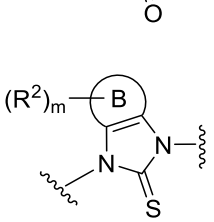
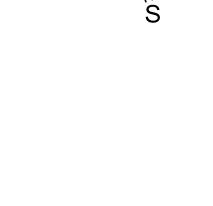
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

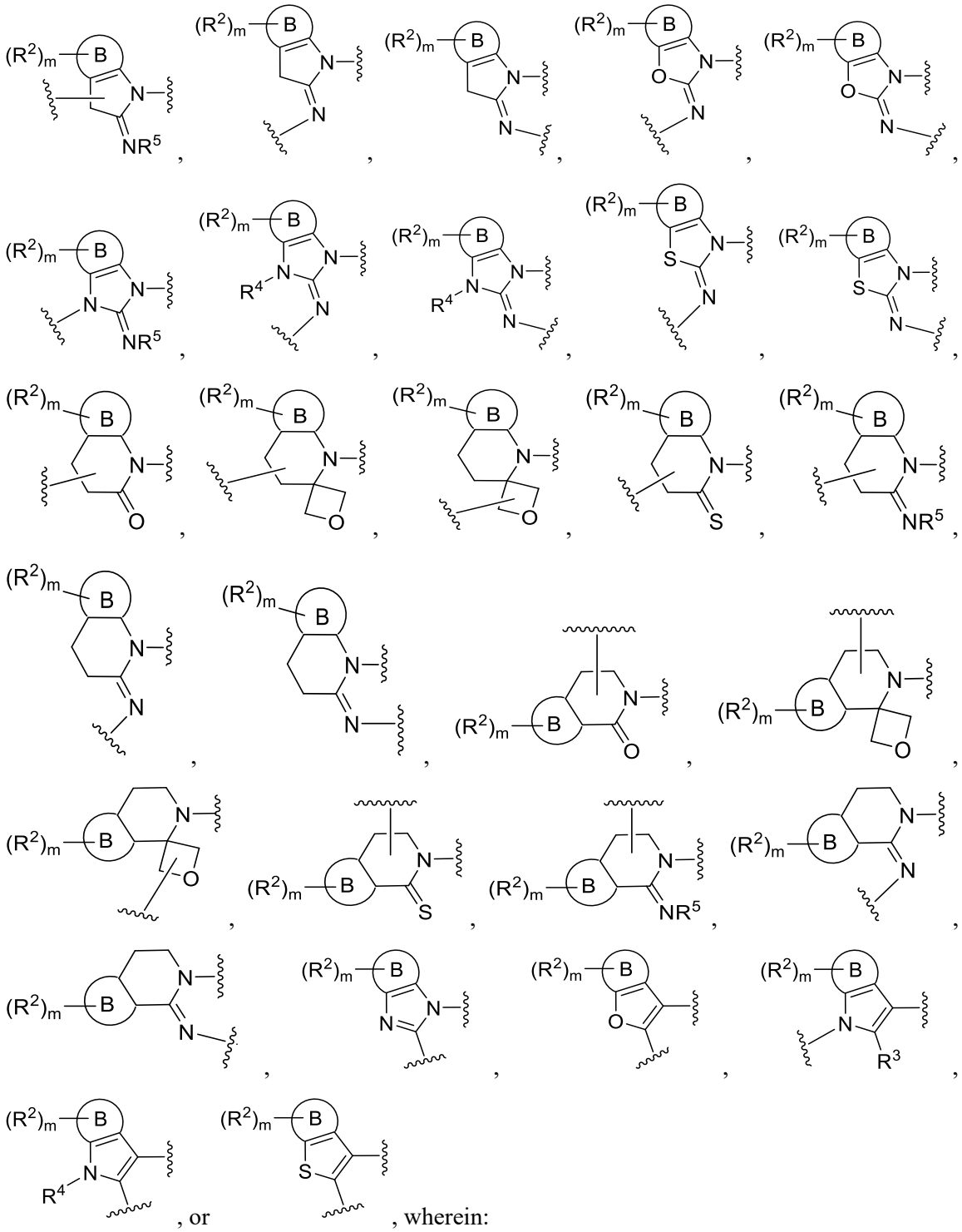
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^2 is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)NROR, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)NR_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, or $-NRS(O)_2R$;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7

membered saturated or partially unsaturated carbocyclic or 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 bicyclic or tricyclic ring selected from , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , .


, or , wherein:

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

R^3 is selected from hydrogen, halogen, -OR, -NR_2, or -SR;

each R^4 is independently hydrogen, R^A, 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)NROR, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)NR_2$, or -$NRS(O)_2R$;

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

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

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -CRF-, -CF_2-, -C(O)-, -S-, -S(O)-, -$S(O)_2$-, -SiR_2-, -Si(OH)R-, -$Si(OH)_2$-, -P(O)OR-, -P(O)R-, or -$P(O)NR_2$-, wherein:

each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-3 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;

L^1 is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^1 are independently replaced by -O-, -NR-, -CRF-, -CF_2-, -C(O)-, -S-, -S(O)-, or -$S(O)_2$-;

Q is a bivalent moiety selected from -O-, -CR_2-, -CF_2-, -CFR-, -C(O)-, -OCR_2-, and -C(S)-;

Y is an optionally substituted -$(CH_2)_y$-, wherein:

y is 1, 2, or 3;

R^x is hydrogen, R^A, -$(CR_2)_{1-3}OCONR_2$, or -$(CR_2)_{1-3}CONR_2$;

R^{y1} and R^{y2} are each independently hydrogen, R^A, -CH_2CO_2R, or -CH_2OCO_2R;

R^{z1} and R^{z2} are each independently hydrogen or R^A, or:

R^{z1} and R^{z2} are cyclically linked to form an optionally substituted fused 5-8 membered heterocyclic ring;

Ring C is an optionally substituted bivalent ring selected from phenylenyl, naphthylenyl, a 5-10 membered heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

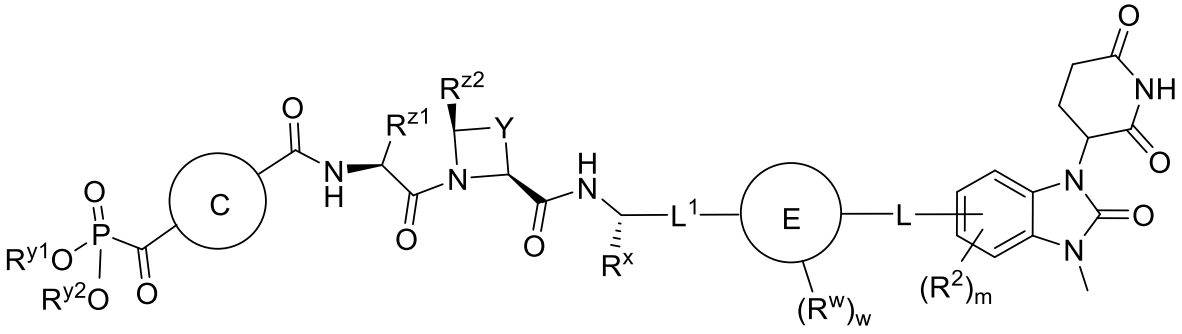
Ring E is a bivalent ring selected from phenylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w is hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)NROR, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)NR_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, or $-NRS(O)_2R$;

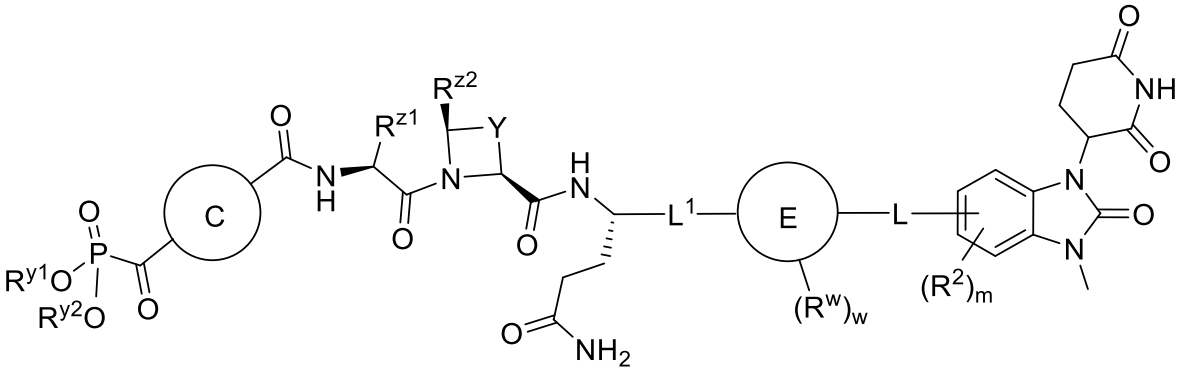
w is 0, 1, 2, 3, or 4; and

n is 0 or 1.

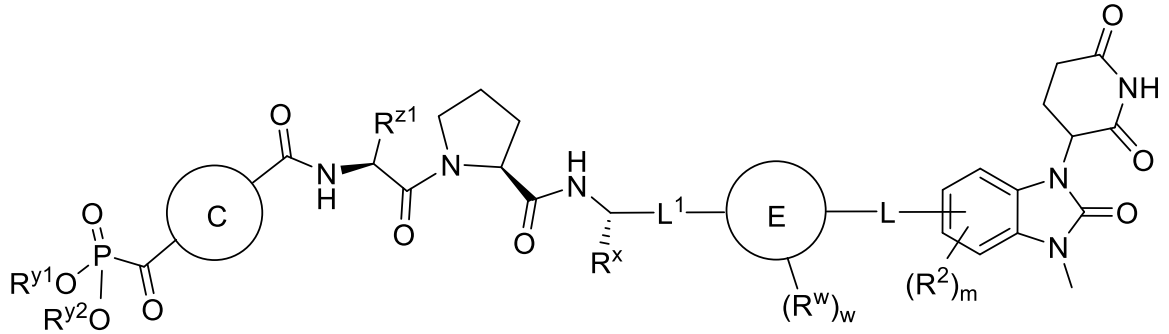
2. The compound according to claim 1, wherein said compound is any one of the following formulae:



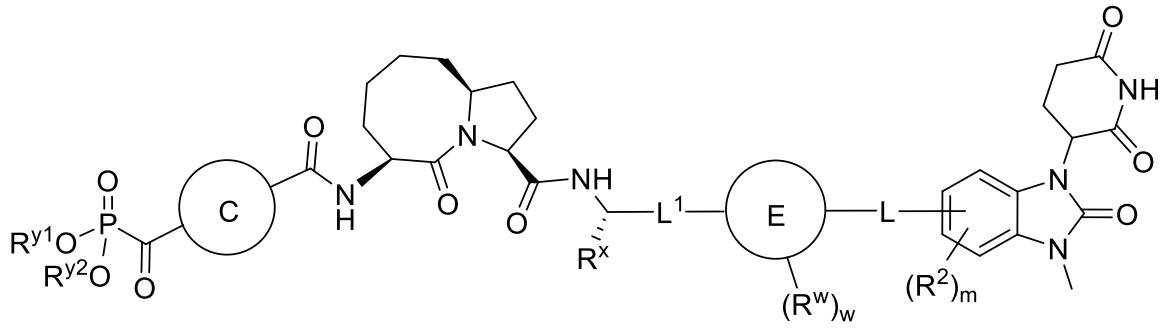
I-a-1



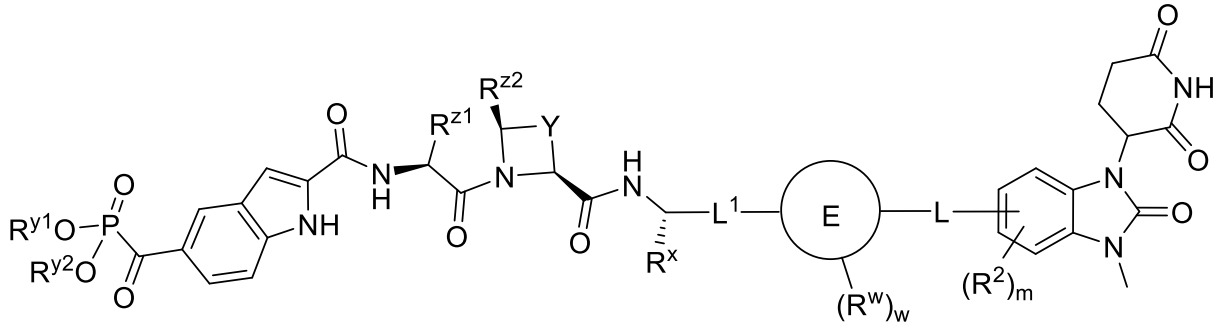
I-a-2



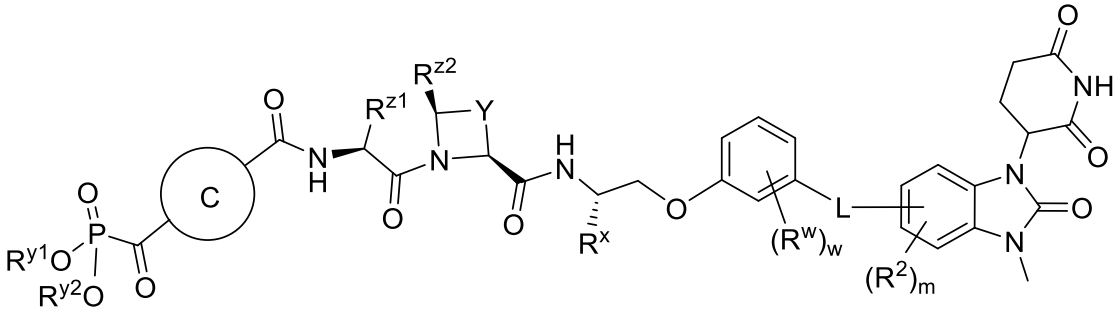
I-a-3



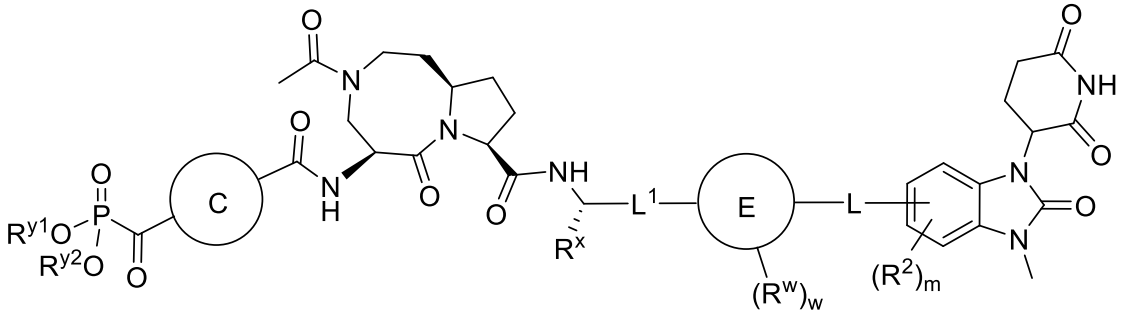
I-a-4



I-a-5



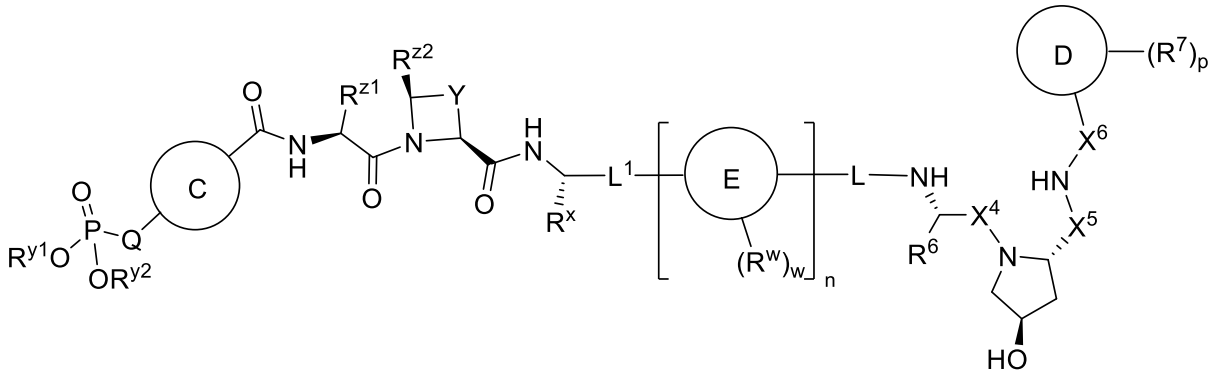
I-a-6



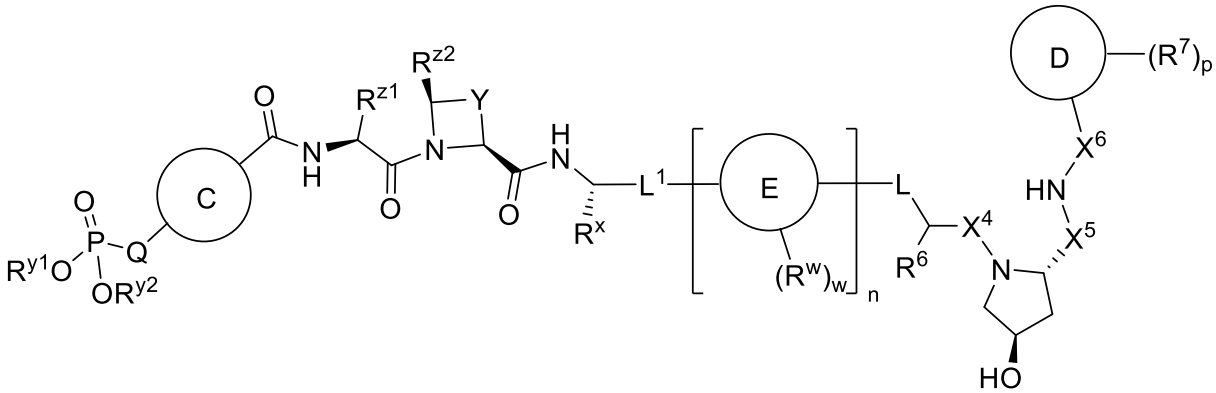
I-a-7

or a pharmaceutically acceptable salt thereof.

3. A compound according to formula **I-b** or **I-f**:

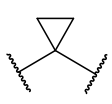
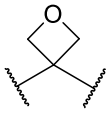


I-b



I-f

or a pharmaceutically acceptable salt thereof, wherein:

X^4, X^5, and X^6 are each independently a bivalent moiety selected from a covalent bond, $-CR_2-$, -C(O)-, -C(S)-, -O-, -S(O)-, $-S(O)_2-$, , or ;

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

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

two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

R^6 is hydrogen or R^A;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated carbocyclic or 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 D is selected from phenyl, a 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen or sulfur;

R^7 is hydrogen, R^A, 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)NROR, -OC(O)R, $-OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)NR_2$, or $-NRS(O)_2R$;

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

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -CRF-, $-CF_2-$, -C(O)-, -S-, -S(O)-, $-S(O)_2-$, $-SiR_2-$, -Si(OH)R-, $-Si(OH)_2-$, -P(O)OR-, -P(O)R-, or $-P(O)NR_2-$, wherein:

each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-3 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;

L^1 is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^1 are independently replaced by -O-, -NR-, -CRF-, -CF_2-, -C(O)-, -S-, -S(O)-, or -$S(O)_2$-;

Q is a bivalent moiety selected from -O-, -CR_2-, -CF_2-, -CFR-, -C(O)-, -OCR_2-, and -C(S)-;

Y is an optionally substituted -$(CH_2)_y$-, wherein:

y is 1, 2, or 3;

R^x is hydrogen, R^A, -$(CR_2)_{1-3}OCONR_2$, or -$(CR_2)_{1-3}CONR_2$;

R^{y1} and R^{y2} are each independently hydrogen, R^A, -CH_2CO_2R, or -CH_2OCO_2R;

R^{z1} and R^{z2} are each independently hydrogen or R^A, or:

R^{z1} and R^{z2} are cyclically linked to form an optionally substituted fused 5-8 membered heterocyclic ring;

Ring C is an optionally substituted bivalent ring selected from phenylenyl, naphthylenyl, a 5-10 membered heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

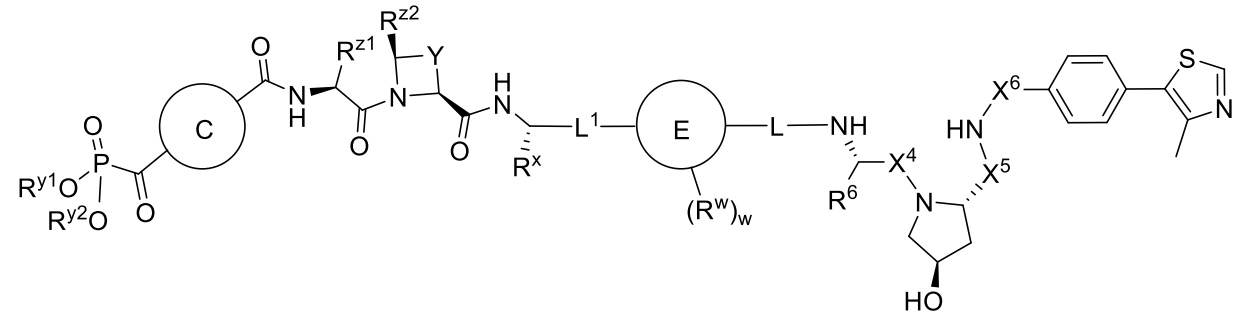
Ring E is a bivalent ring selected from phenylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w is hydrogen, R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -SiR_3, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, –$C(O)NR_2$, -C(O)NROR, -$CR_2NRC(O)R$, -$CR_2NRC(O)NR_2$, -OC(O)R, -$OC(O)NR_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)NR_2$, -$NRS(O)_2R$, -$NP(O)R_2$, -$NRP(O)(OR)_2$, -$NRP(O)(OR)NR_2$, -$NRP(O)(NR_2)_2$, or -$NRS(O)_2R$;

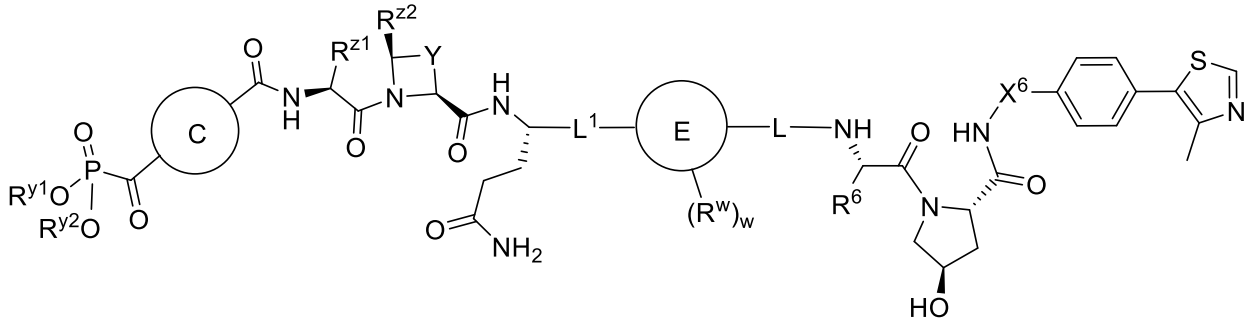
w is 0, 1, 2, 3, or 4; and

n is 0 or 1.

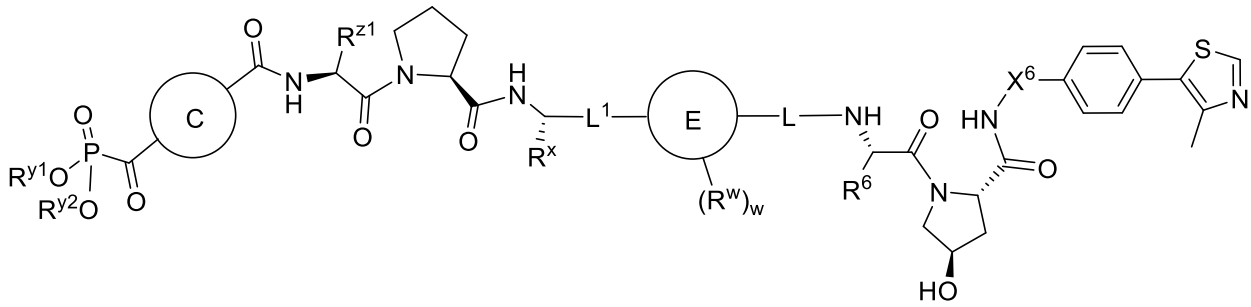
4. The compound according to claim 3, wherein said compound is any one of the following formulae:



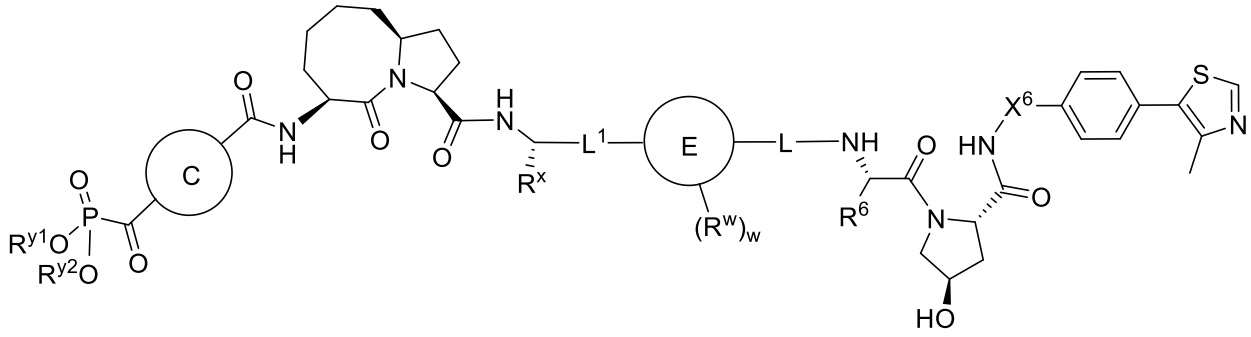
I-b-1



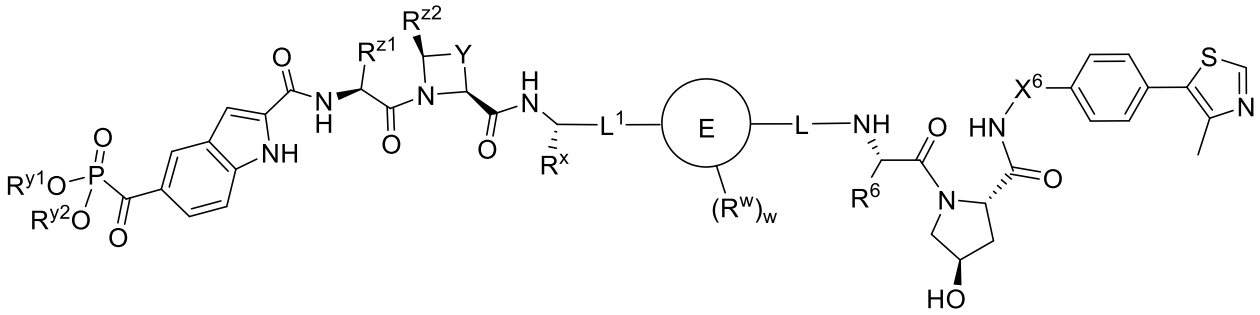
I-b-2



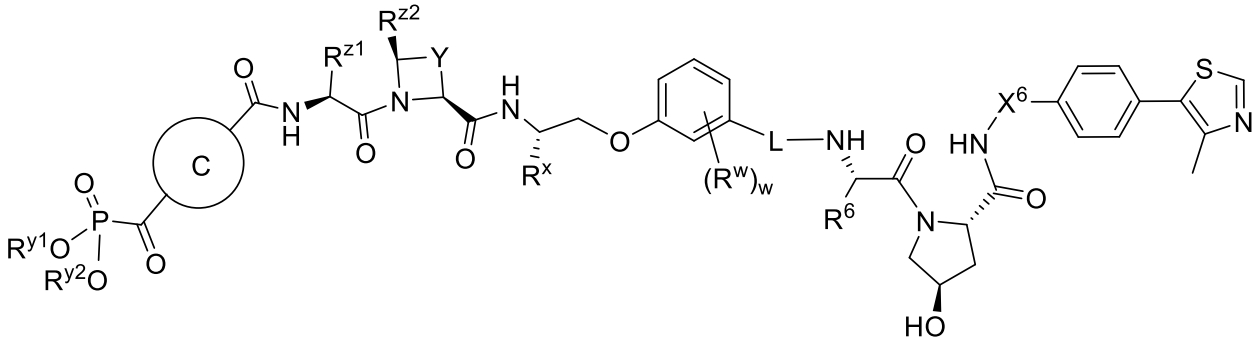
I-b-3



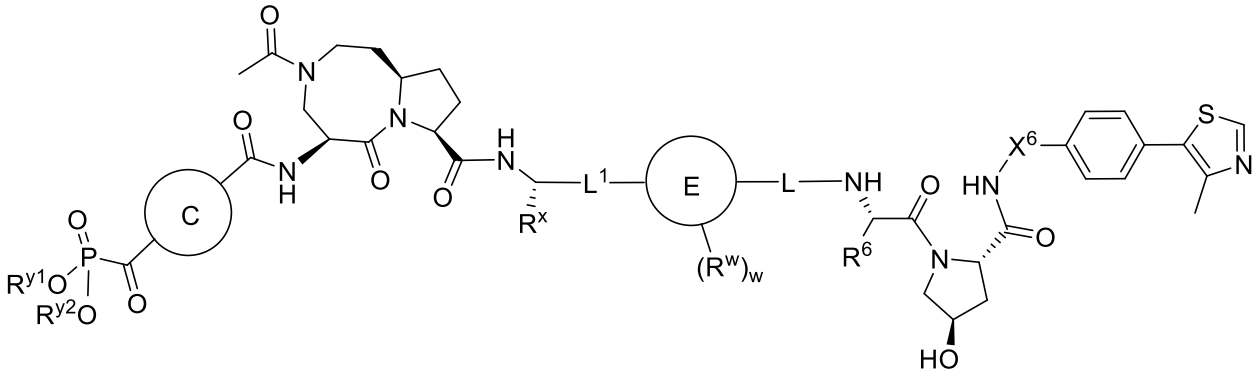
I-b-4



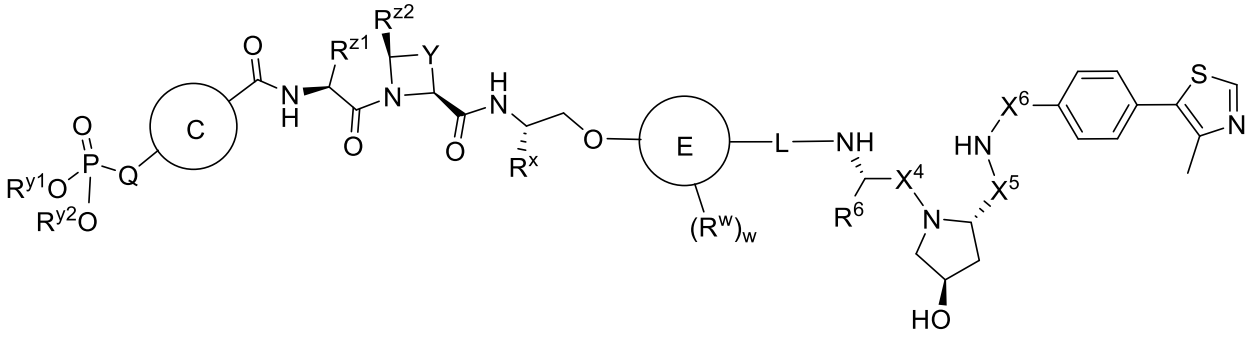
I-b-5



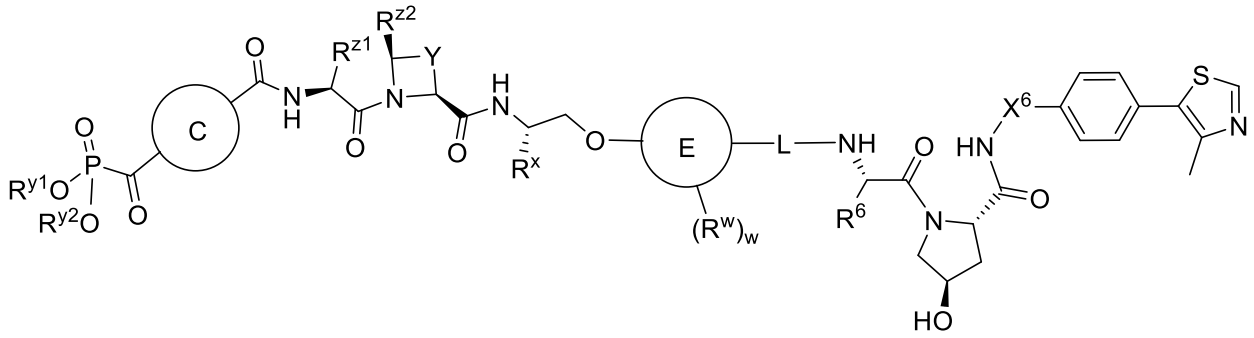
I-b-6



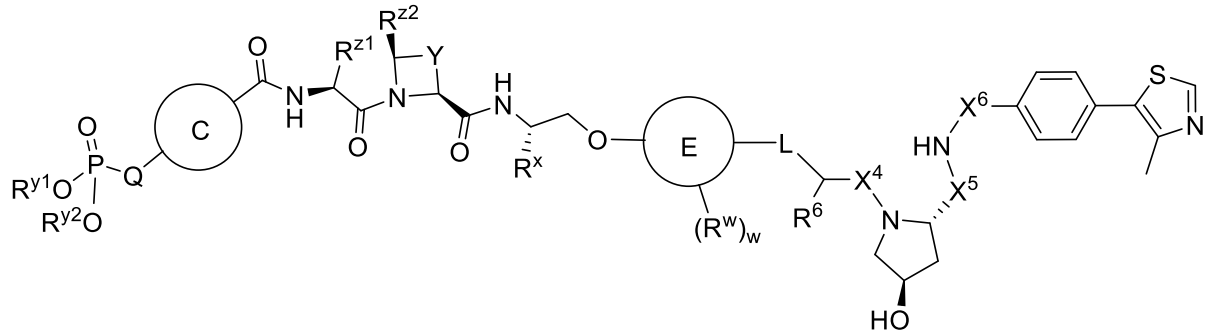
I-b-7



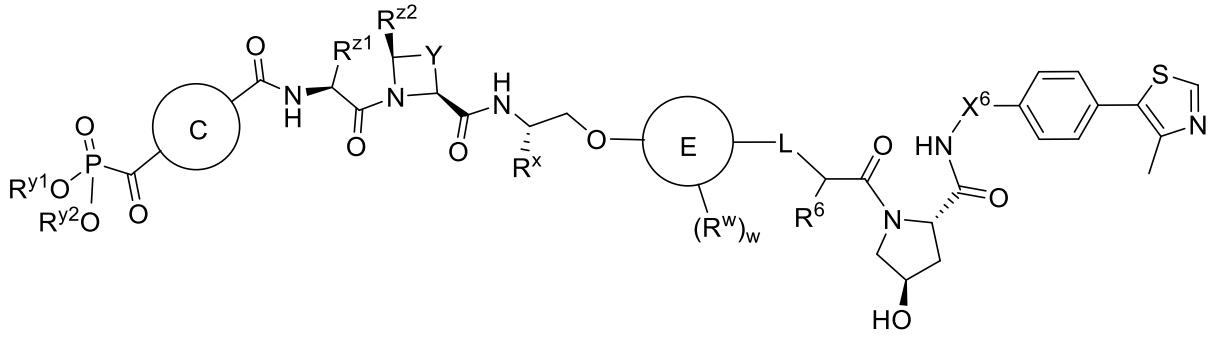
I-b-8



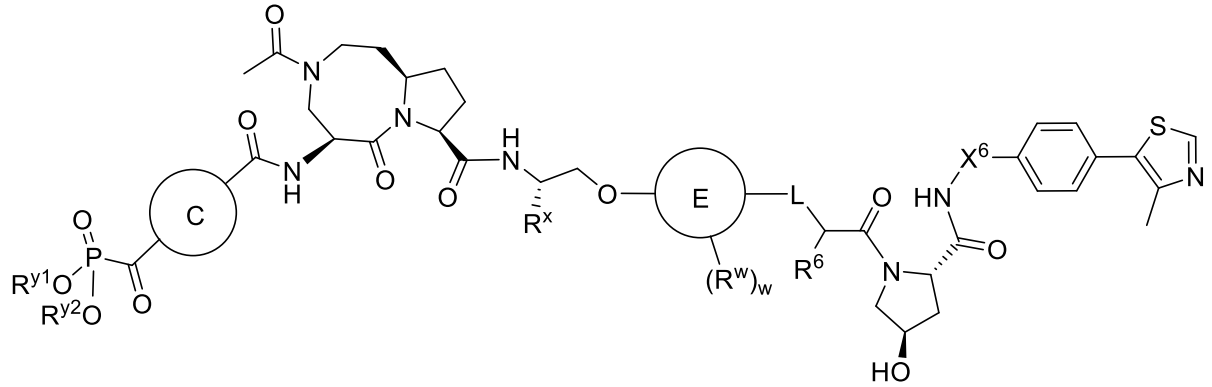
I-b-9



I-f-1



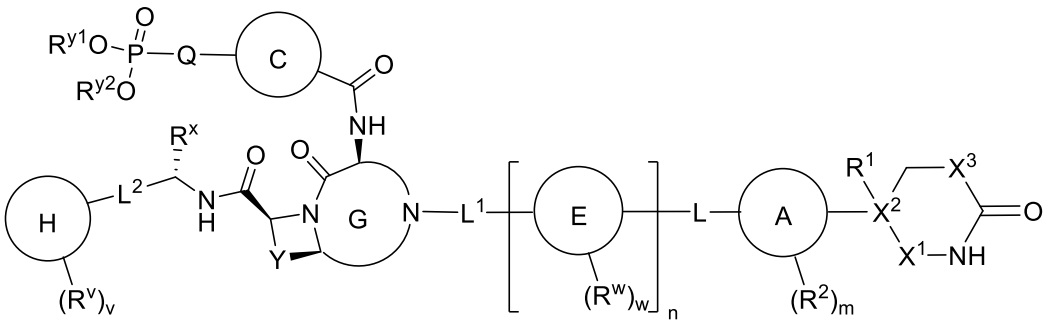
I-f-2



I-f-3

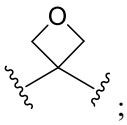
or a pharmaceutically acceptable salt thereof.

5. A compound of formula **I-d**:



I-d

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is a bivalent moiety selected from a covalent bond, $-CR_2-$, -C(O)-, -C(S)-, $-CR(CF_3)-$, -P(O)OR-, -P(O)R-, $-P(O)NR_2-$, -S(O)-, $-S(O)_2-$, or ;

X^2 is a carbon atom or silicon atom;

X^3 is a bivalent moiety selected from $-CR_2-$, -NR-, -O-, -S-, or $-SiR_2-$;

R^1 is hydrogen, halogen, -CN, -OR, -SR, -S(O)R, $-S(O)_2R$, $-NR_2$, $-P(O)(OR)_2$, $-P(O)NR_2OR$, $-P(O)(NR_2)_2$, $-Si(OH)_2R$, $-Si(OH)R_2$, $-SiR_3$, or an optionally substituted C_{1-4} aliphatic;

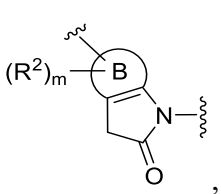
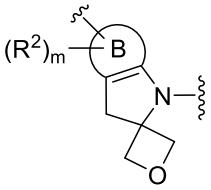
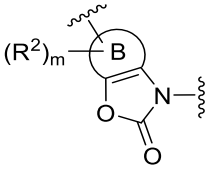
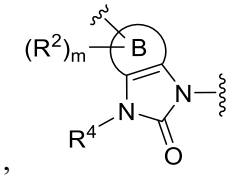
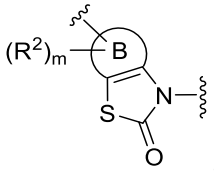
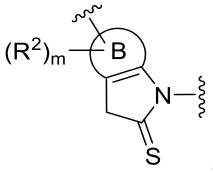
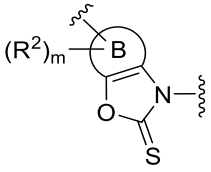
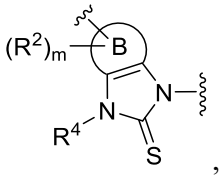
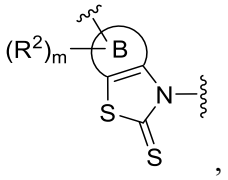
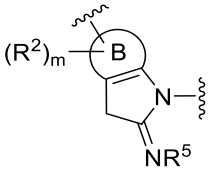
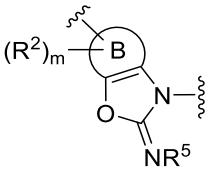
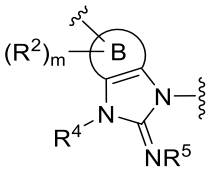
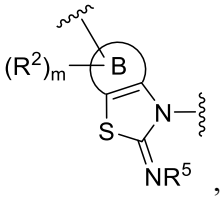
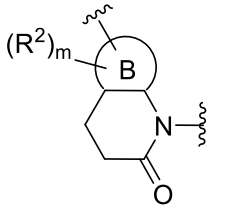
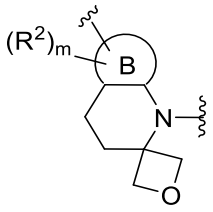
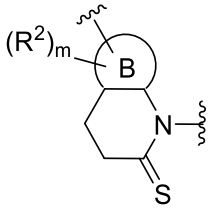
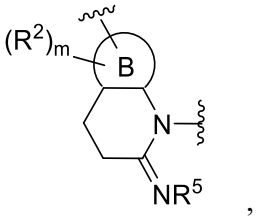
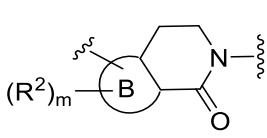
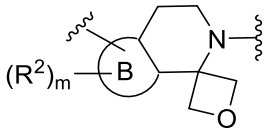
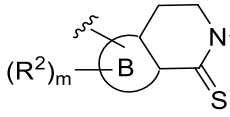
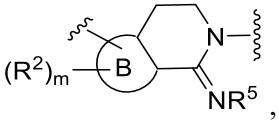
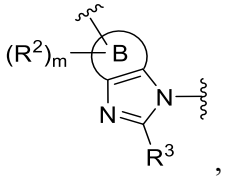
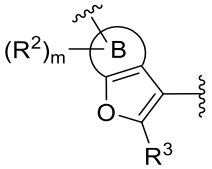
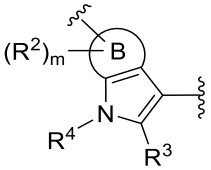
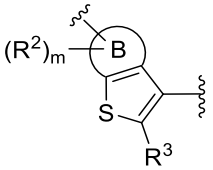
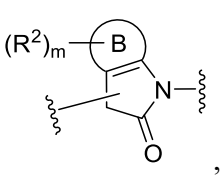
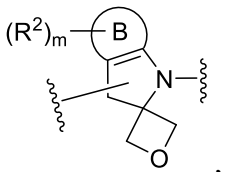
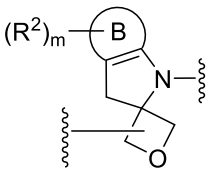
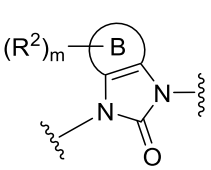
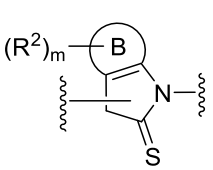
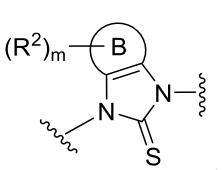
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in addition to the carbon or nitrogen from which the two R groups are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^2 is independently hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, -OC(O)R, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)NR_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, or $-NRS(O)_2R$;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7

membered saturated or partially unsaturated carbocyclic or 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 bicyclic or tricyclic ring selected from , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , 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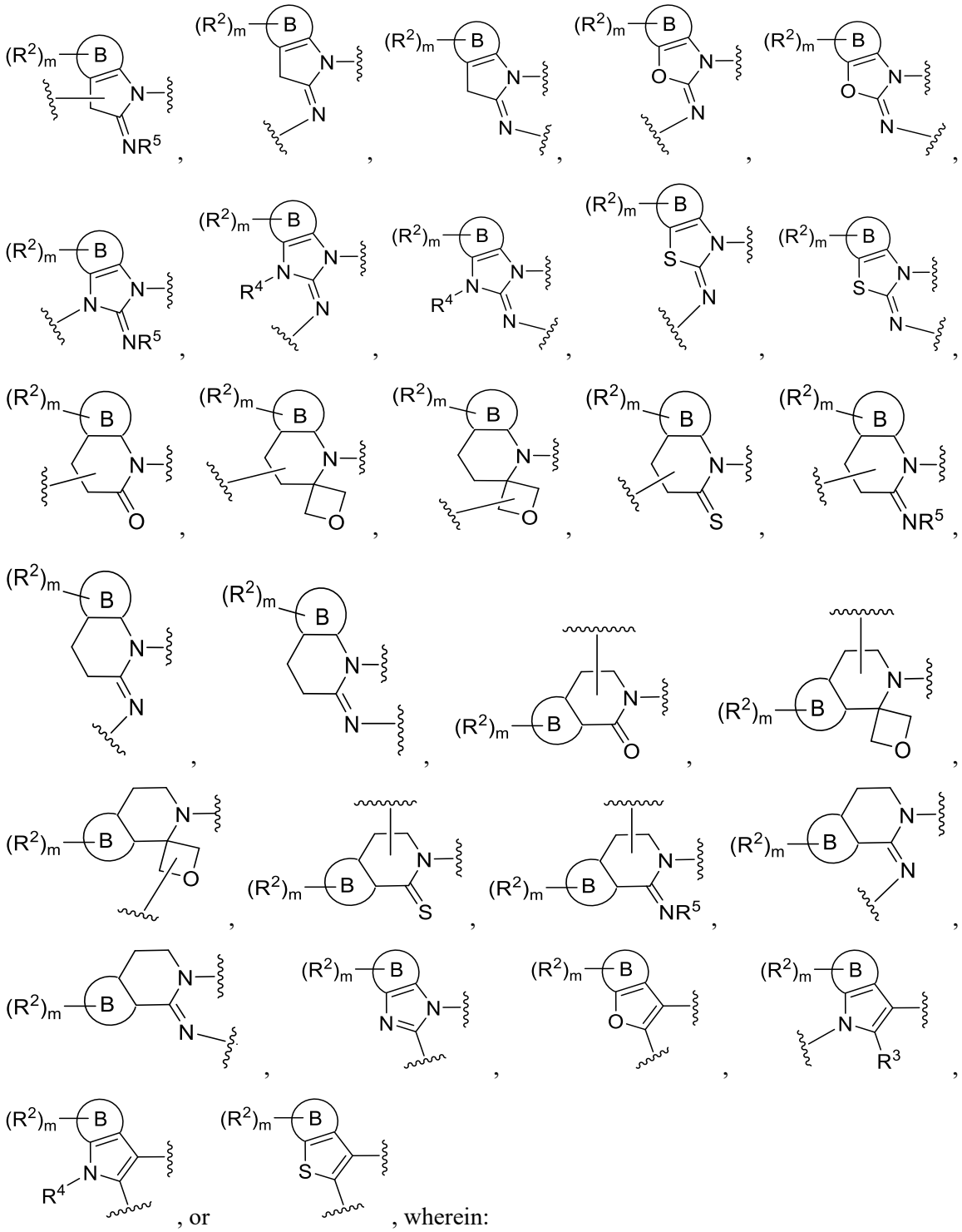

, or , wherein:

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

R^3 is selected from hydrogen, halogen, -OR, -NR_2, or -SR;

each R^4 is independently hydrogen, R^A, 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)NROR, -OC(O)R, -$OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)NR_2$, or -$NRS(O)_2R$;

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

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

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-20} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, -CRF-, -CF_2-, -C(O)-, -S-, -S(O)-, -$S(O)_2$-, -SiR_2-, -Si(OH)R-, -$Si(OH)_2$-, -P(O)OR-, -P(O)R-, or -$P(O)NR_2$-, wherein:

each -Cy- is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated or partially unsaturated carbocyclylenyl, a 4-7 membered saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-3 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;

L^1 is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^1 are independently replaced by -O-, -NR-, -CRF-, -CF_2-, -C(O)-, -S-, -S(O)-, or -$S(O)_2$-;

L^2 is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-5} hydrocarbon chain, wherein 0-3 methylene units of L^2 are independently replaced by -O-, -NR-, -CRF-, -CF_2-, -C(O)-, , -S-, -S(O)-, or -$S(O)_2$-;

R^x is hydrogen, R^A, -$(CR_2)_{1-3}OCONR_2$, or -$(CR_2)_{1-3}CONR_2$;

Ring C is an optionally substituted bivalent ring selected from phenylenyl, naphthylenyl, a 5-10 membered heteroarylenyl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl with 1-4

heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Q is a bivalent moiety selected from -O-, -CR_2-, -CF_2-, -CFR-, -C(O)-, -OCR_2-, and -C(S)-;

R^{y1} and R^{y2} are each independently hydrogen or R^A;

Y is an optionally substituted -$(CH_2)_y$-, wherein:

y is 1, 2, or 3;

Ring G is an optionally substituted ring selected from a 5-9 membered saturated or partially unsaturated heterocyclyl;

Ring H is a ring selected from phenyl, a 5-9 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-7 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^v is hydrogen, R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -SiR_3, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, –$C(O)NR_2$, -C(O)NROR, -$CR_2NRC(O)R$, -$CR_2NRC(O)NR_2$, -OC(O)R, -$OC(O)NR_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)NR_2$, -$NRS(O)_2R$, -$NP(O)R_2$, -$NRP(O)(OR)_2$, -$NRP(O)(OR)NR_2$, -$NRP(O)(NR_2)_2$, or -$NRS(O)_2R$;

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

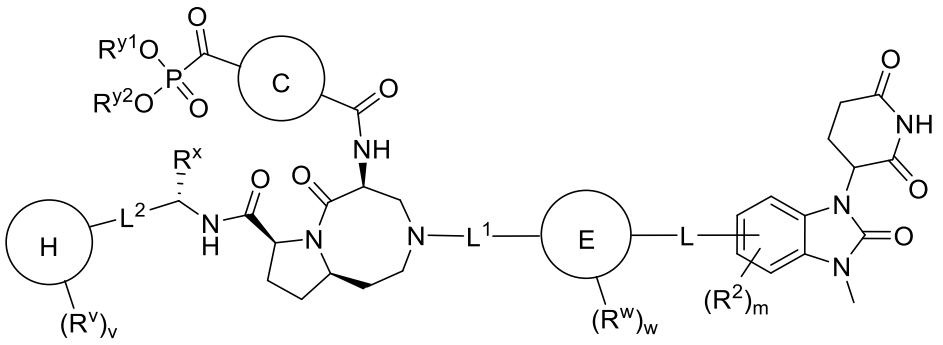
Ring E is a bivalent ring selected from phenylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl or heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w is hydrogen, R^A, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -SiR_3, -$S(O)_2R$, -$S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, –$C(O)NR_2$, -C(O)NROR, -$CR_2NRC(O)R$, -$CR_2NRC(O)NR_2$, -OC(O)R, -$OC(O)NR_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -NRC(O)OR, -NRC(O)R, -$NRC(O)NR_2$, -$NRS(O)_2R$, -$NP(O)R_2$, -$NRP(O)(OR)_2$, -$NRP(O)(OR)NR_2$, -$NRP(O)(NR_2)_2$, or -$NRS(O)_2R$;

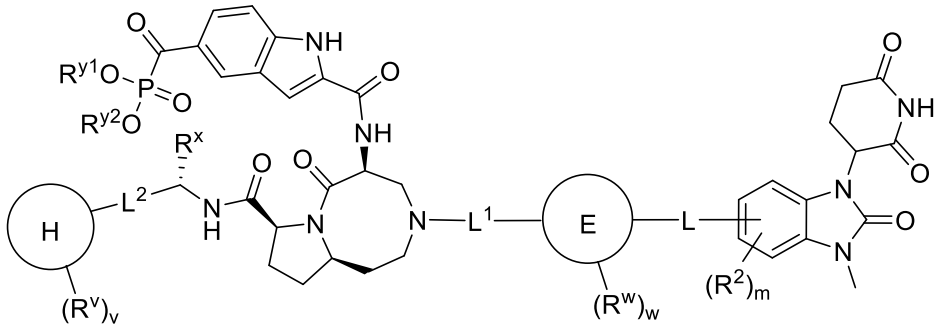
w is 0, 1, 2, 3, or 4; and

n is 0 or 1.

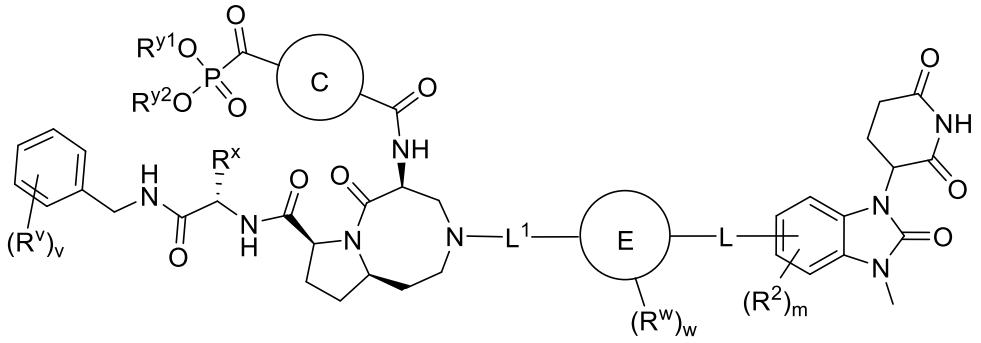
6. The compound of claim 5, wherein said compound is any one of the following formulae:



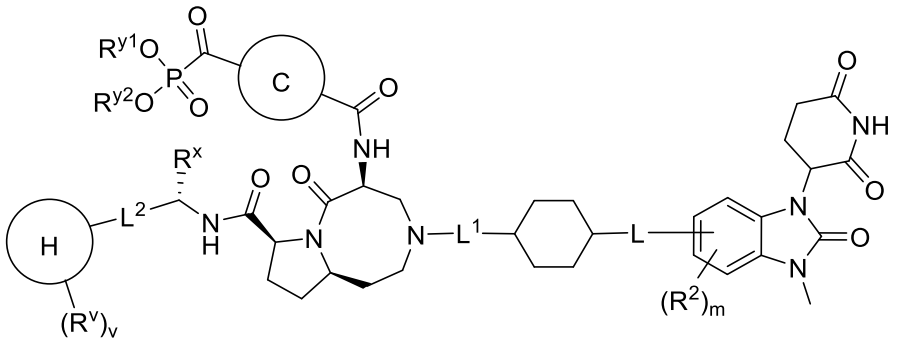
I-d-1



I-d-2



I-d-3

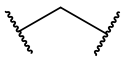
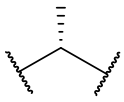


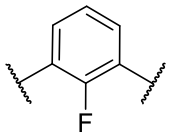
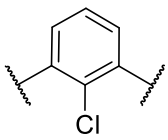
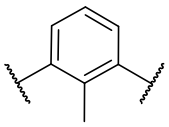
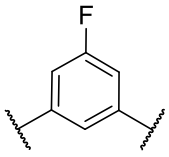
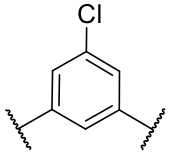
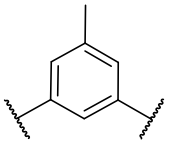
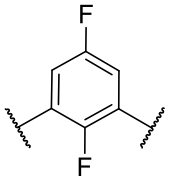
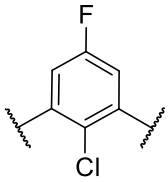
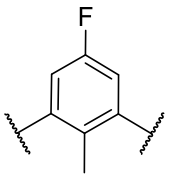
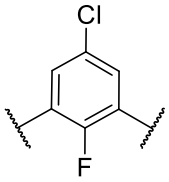
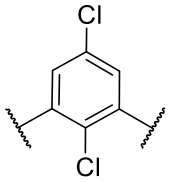
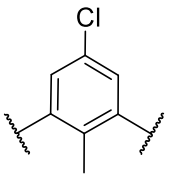
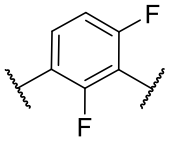
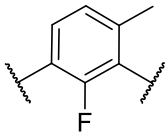
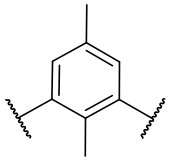
I-d-4

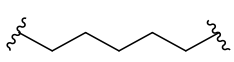
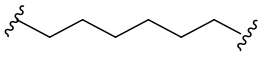
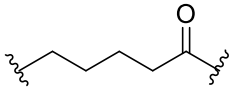
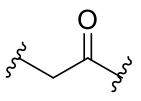
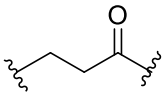
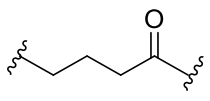
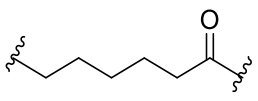
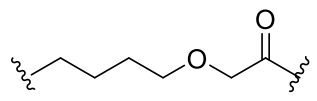
or a pharmaceutically acceptable salt thereof.

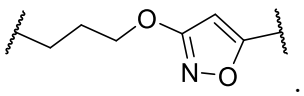
7. The compound of any one of claims 1-4, wherein R^{z1} is selected from hydrogen, methyl, -CH_2CH_2OH, ethyl, isopropyl, neopropyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

8. The compound of claim 3 or claim 4, wherein R^6 is selected from ethyl, isopropyl, neopropyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

9. The compound of claim 3 or claim 4, wherein X^6 is selected from , , and .

10. The compound of any one of claims 1-9, wherein Ring E is selected from , , , , , , , , , , , , , , and .

11. The compound of any one of claims 1-10, wherein L is selected from -CH_2-, -CH_2CH_2-, -CH_2NH-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, , , , , , , , , and



12. The compound of any one of claims 1-11, wherein said compound is selected from any one of the compounds depicted in **Table 1**, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound of any one of claims 1-12, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

14. The pharmaceutical composition according to claim 13, further comprising an additional therapeutic agent.

15. A compound of any one of claims 1-12 or a pharmaceutical composition thereof, for use in degrading STAT3 protein in a patient or biological sample.

16. A compound of any one of claims 1-12 or a pharmaceutical composition thereof, for use in treating an STAT3-mediated disorder, disease, or condition in a patient.

17. The compound for use of claim 16, wherein the STAT3-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.

18. The compound for use of claim 17, wherein the inflammatory disorder is diseases and conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or etiology, including autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's

disease), irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, cryopyrin-associated periodic syndrome, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minal change nephropathy), chronic granulomatous disease, endometriosis, leptospiriosis renal disease, glaucoma, retinal disease, ageing, headache, pain, complex regional pain syndrome, cardiac hypertrophy, musclewasting, catabolic disorders, obesity, fetal growth retardation, hyperchlolesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ecodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic and non-allergic, mild, moderate, severe, bronchitic, and exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, ocular allergy, silica induced diseases, COPD (reduction of damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression), pulmonary disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, or Type 2 diabetes, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, encephalomyelitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, or vulvitis.

19. The compound for use of claim 17, wherein the inflammatory disorder is psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, systemic lupus erythematosus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, or acne vulgaris.

20. Use of a compound of any one of claims 1-12 in the manufacture of a medicament for treating an STAT3-mediated disorder, disease, or condition in a patient.

21. The use of claim 20, wherein the STAT3-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.

22. The use of claim 21, wherein the inflammatory disorder is diseases and conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or etiology, including autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren’s syndrome, keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, cryopyrin-associated periodic syndrome, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minal change nephropathy), chronic granulomatous disease, endometriosis, leptospiriosis renal disease, glaucoma, retinal disease, ageing, headache, pain, complex regional pain syndrome, cardiac hypertrophy, musclewasting, catabolic disorders, obesity, fetal growth retardation, hyperchlolesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ecodermal dysplasia, Behcet’s disease, incontinentia pigmenti, Paget’s disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic and non-allergic, mild, moderate, severe, bronchitic, and exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, ocular allergy, silica induced diseases, COPD (reduction of damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression), pulmonary disease, cystic fibrosis, acid-

induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, or Type 2 diabetes, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, encephalomyelitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, or vulvitis.

23. The use of claim 21, wherein the inflammatory disorder is psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, systemic lupus erythematosus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, or acne vulgaris.