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.

[006] 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.

[007] 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).

[008] 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.

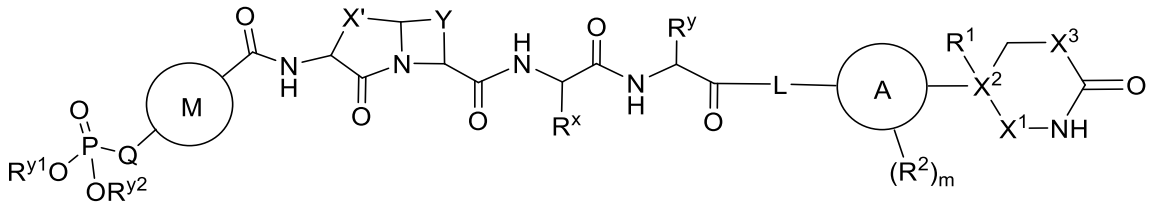
SUMMARY ~~OF THE INVENTION~~

[009] 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.

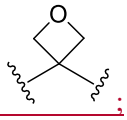
[0010] The present application further relates to targeted degradation of STAT proteins through the use of bifunctional molecules, including bifunctional molecules that link a cereblon-binding moiety to a ligand that binds STAT proteins.

[0010a] In an aspect of the present disclosure, there is provided a compound of formula **I-bbb**:



I-bbb

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;

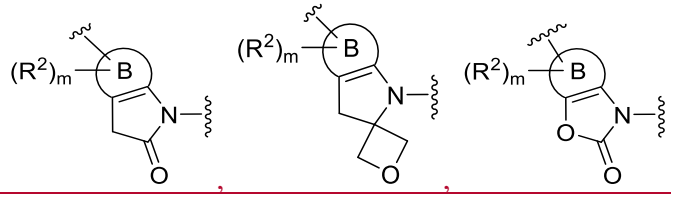
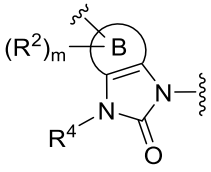
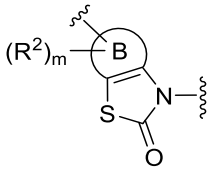
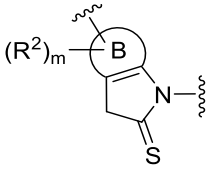
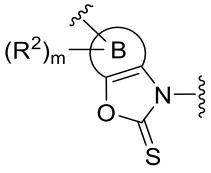
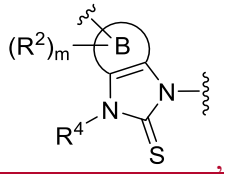
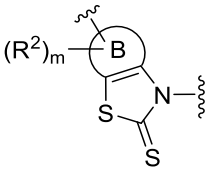
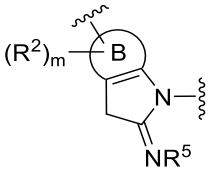
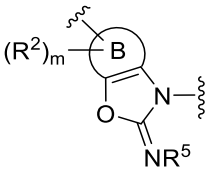
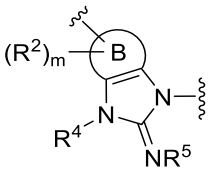
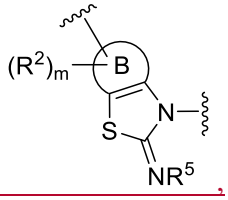
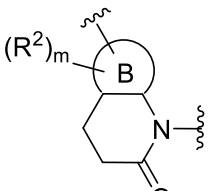
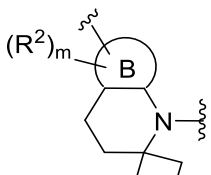
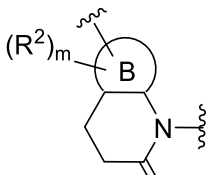
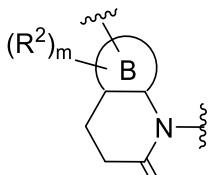
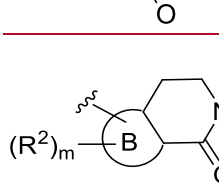
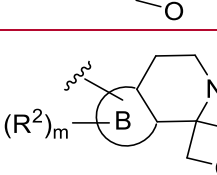
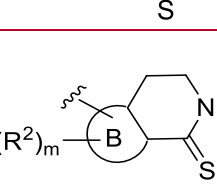
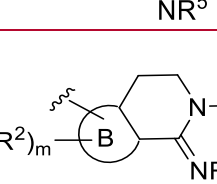
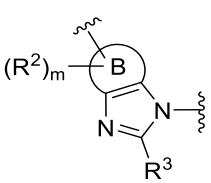
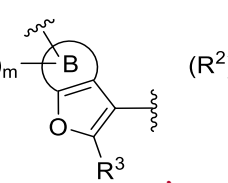
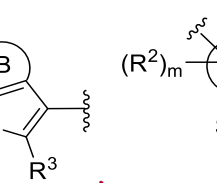
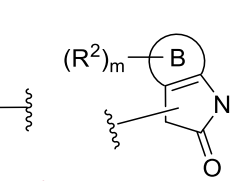
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

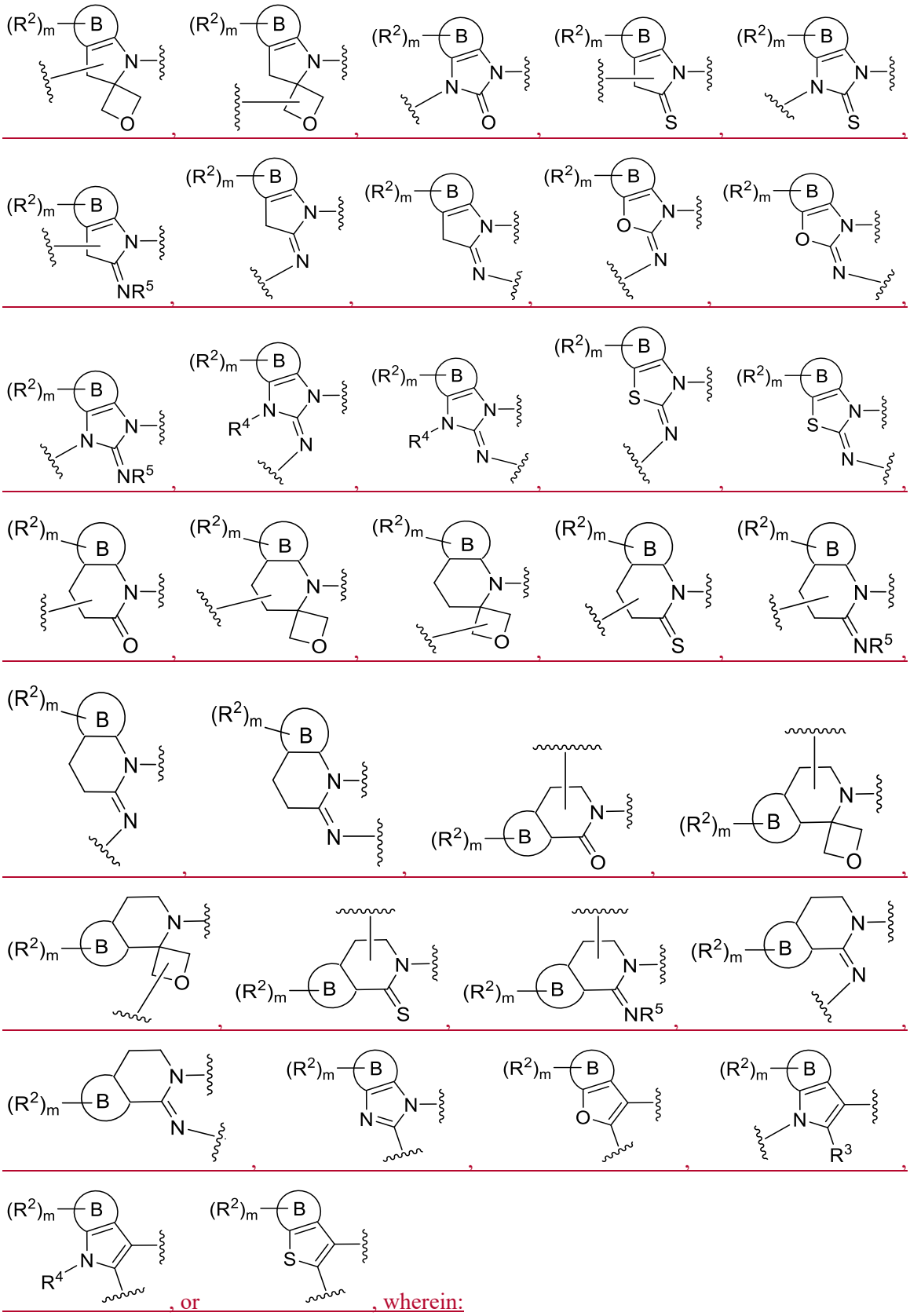
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in 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^6, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)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^6 and 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^6, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)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;

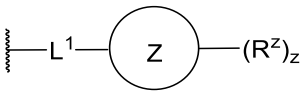
X' is an optionally substituted $-(CH_2)_x-$, wherein 1-2 methylenes of X is optionally replaced with a bivalent group selected from -NR-, -N(COR)-, $-N(CO_2R)-$, $-N(SO_2R)-$, $-N(CONR_2)-$, and $-N(SO_2NR_2)-$, wherein:

x is 1, 2, 3, 4, or 5;

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^y is hydrogen, R^A, or 

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 $-S(O)_2-$;

Ring Z is a ring selected from phenyl, naphthyl, a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^z 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 $-NRS(O)_2R$;

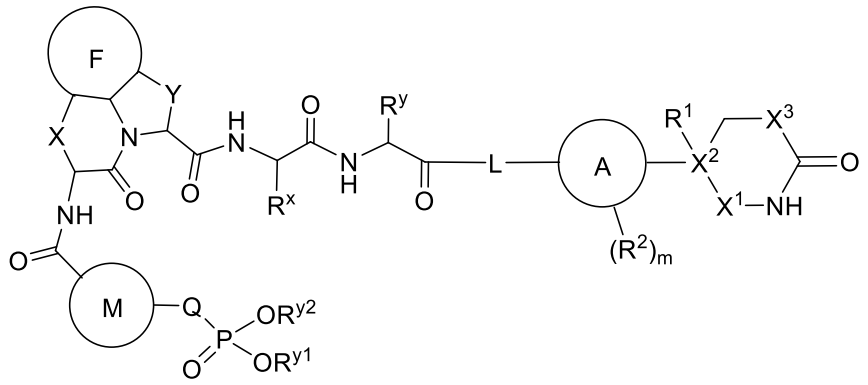
z is 0, 1, 2, 3, or 4;

Ring M 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)-; and

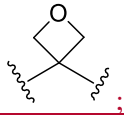
R^{y1} and R^{y2} are each independently hydrogen, R^A, $-CH_2CO_2R$, or $-CH_2OCO_2R$.

[0010b] In another aspect of the present disclosure, there is provided a compound of formula **I-ddd**:



I-ddd

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 $-SiR_2-$;

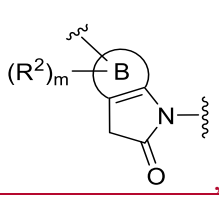
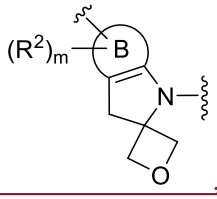
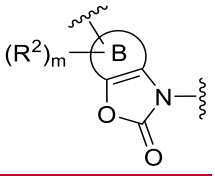
R^1 is hydrogen, halogen, -CN, -OR, -SR, -S(O)R, $-S(O)_2R$, $-NR_2$, $-P(O)(OR)_2$, $-P(O)NR_2OR$, $-P(O)(NR_2)_2$, $-Si(OH)_2R$, $-Si(OH)R_2$, $-SiR_3$, or an optionally substituted C_{1-4} aliphatic;

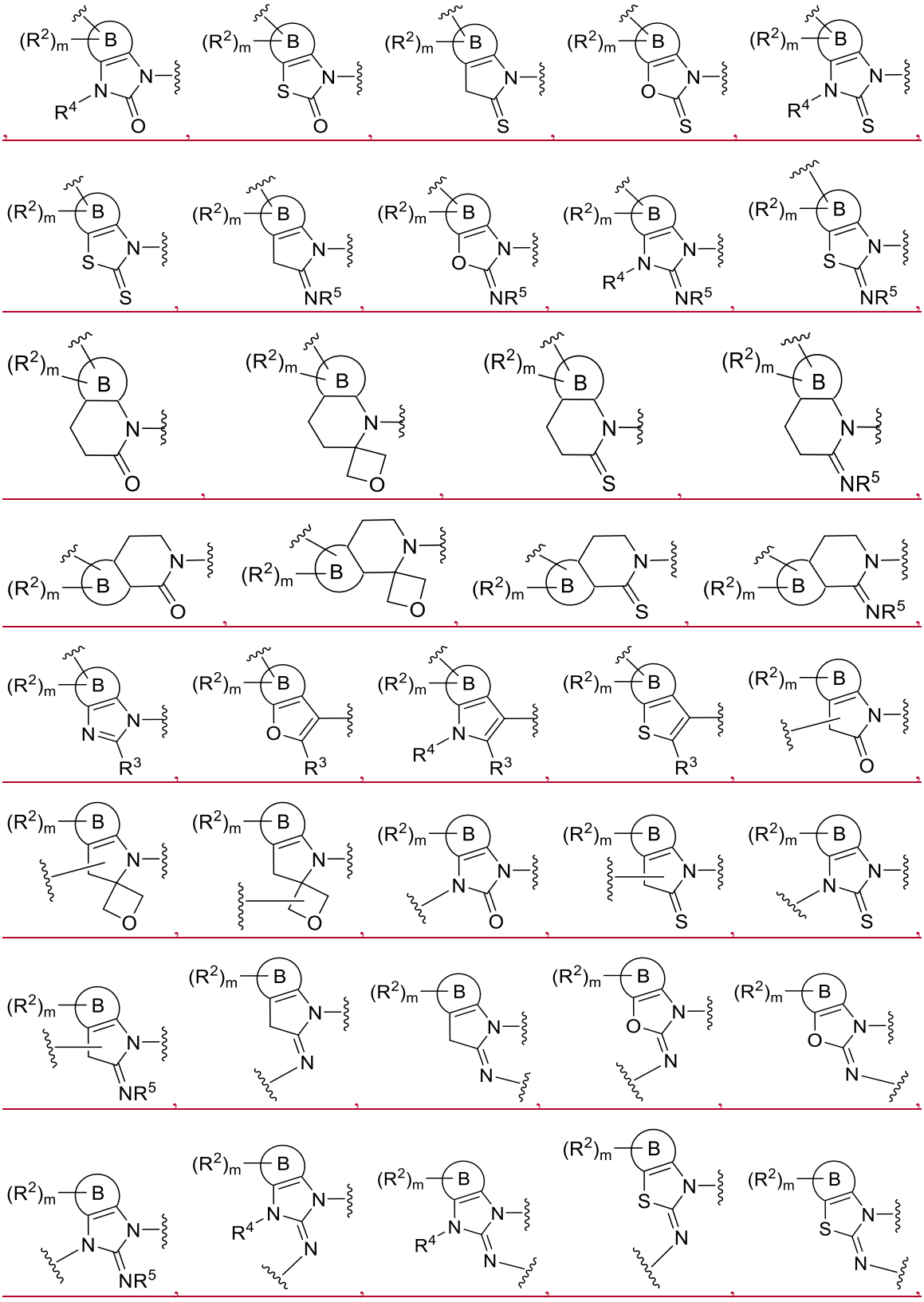
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

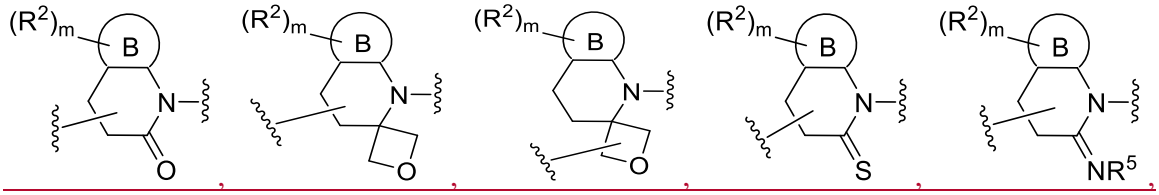
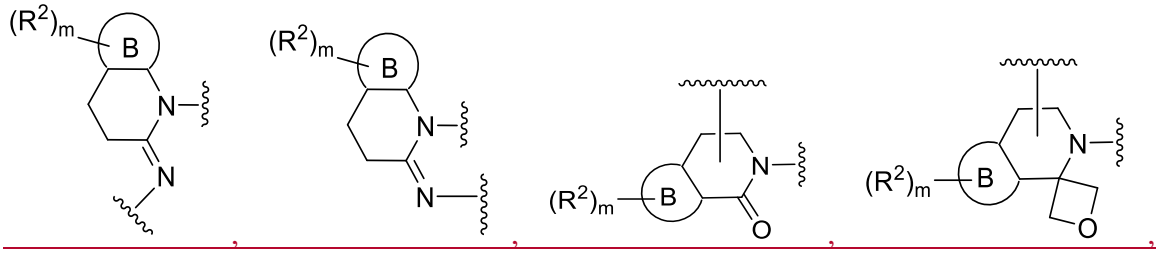
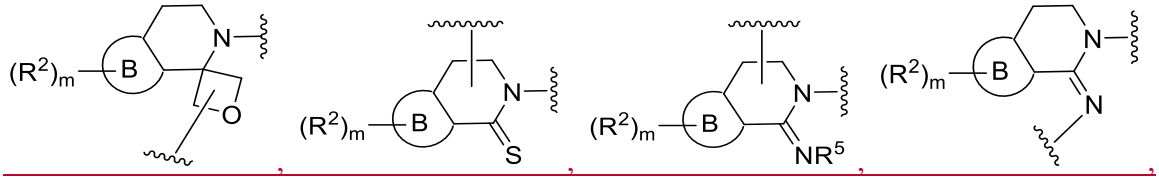
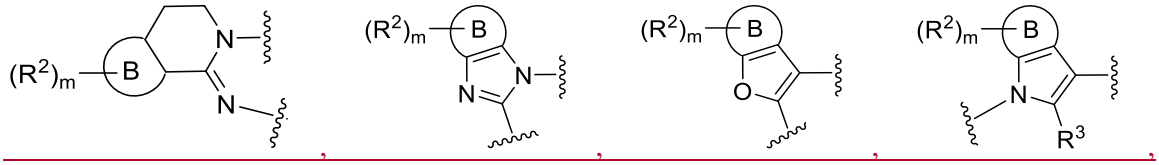
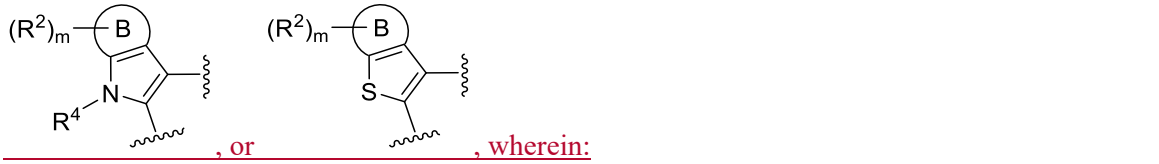
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in 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^6, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)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^6 and 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^6, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)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;

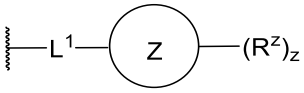
m is 0, 1, 2, 3 or 4;

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;

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

R^y is hydrogen, R^A, or 

;

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 -$S(O)_2$-;

Ring Z is a ring selected from phenyl, naphthyl, a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^z 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 -$NRS(O)_2R$;

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

Ring F is an optionally substituted fused ring selected from a 6-membered aryl, a 5-6 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;

X is an optionally substituted $-(CH_2)_x-$, wherein:

x is 0, 1, 2, or 3;

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

y is 0, 1, 2, or 3;

Ring M 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)-; and

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

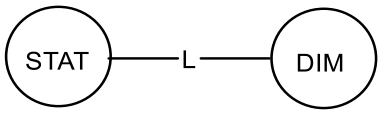
[0010c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0010d] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutical composition thereof, for degrading STAT3 protein in a patient or biological sample.

[0010e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an STAT3-mediated disorder, disease, or condition in a patient.

[0010f] In another aspect of the present disclsosure, there is provided a compound disclosed herein, or a pharmaceutical composition thereof, for use in therapy.

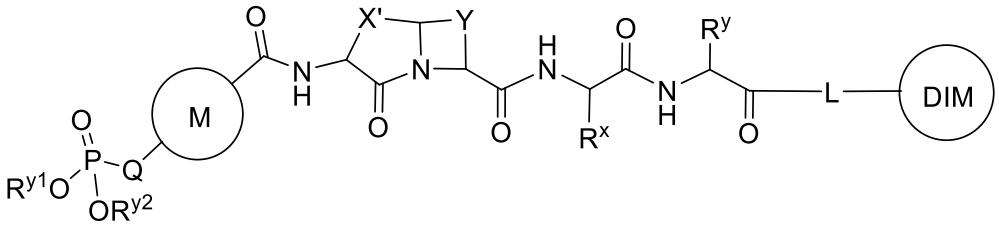
[0011] It has now been found that compounds of this ~~invention~~disclosure, and pharmaceutically acceptable compositions thereof, are effective as degraders of STAT proteins. Such compounds have the general formula **I**:



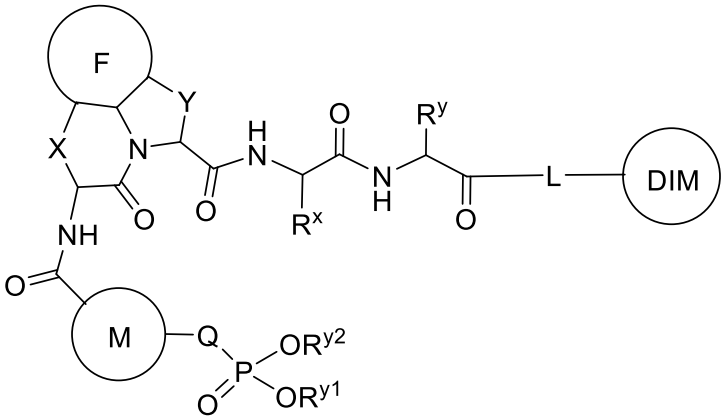
I

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

[~~0001~~0011a] It has now been found that compounds of this ~~invention~~disclosure, and pharmaceutically acceptable compositions thereof, are effective for the modulation of targeted ubiquitination. Such compounds have the formula **I-aaa** and **I-ccc**:



I-aaa



I-ccc

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

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

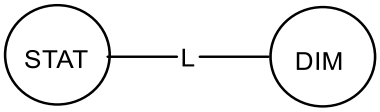
[0013] Compounds provided by this ~~invention~~disclosure are also useful for the study of STAT proteins in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new STAT inhibitors or STAT degraders 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:

[0014] 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.

[0015] 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 one or more of STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, or STAT6, preferably STAT3;

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

DIM is a degradation inducing moiety selected from an E3 ubiquitin ligase binding moeity (LBM), lysine mimetic, and hydrogen.

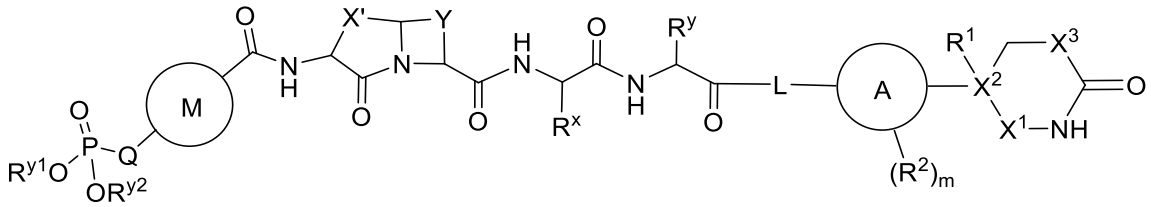
2. Compounds and Definitions:

[0016] 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",

CLAIMS

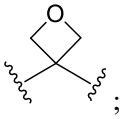
We claim:

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



I-bbb

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;

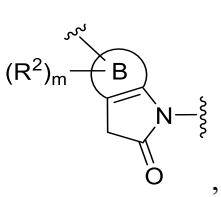
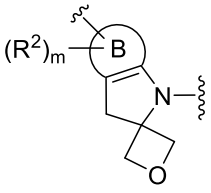
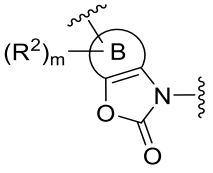
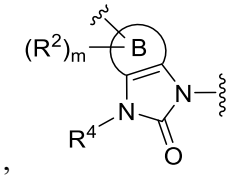
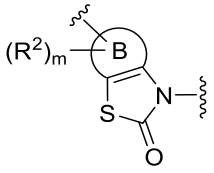
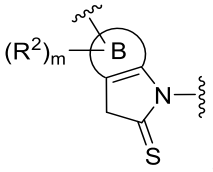
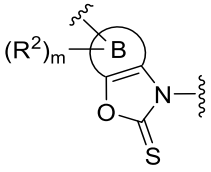
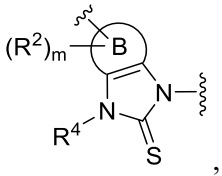
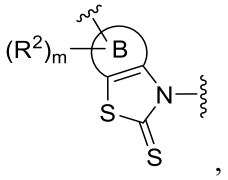
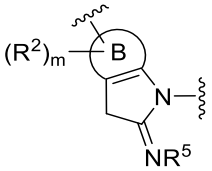
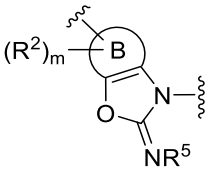
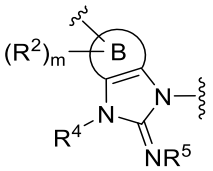
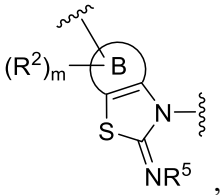
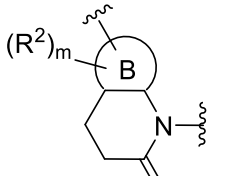
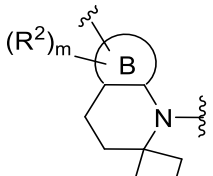
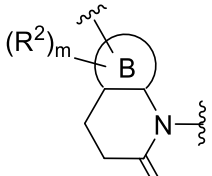
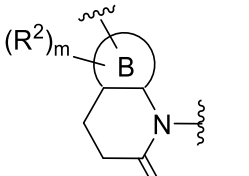
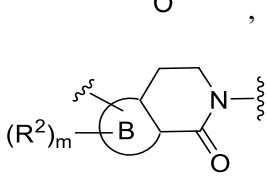
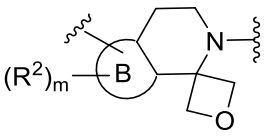
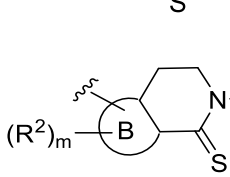
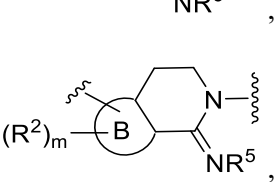
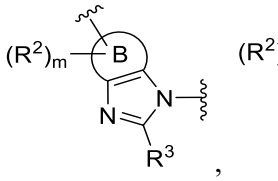
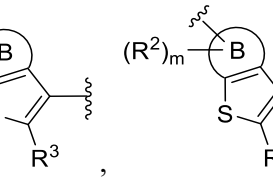
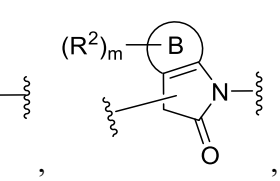
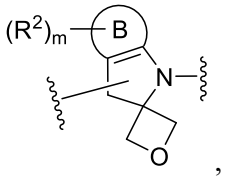
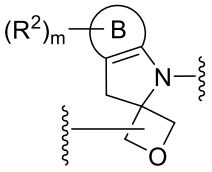
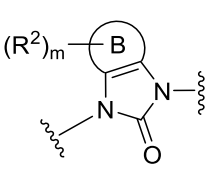
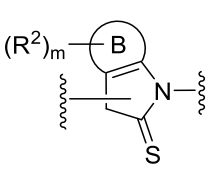
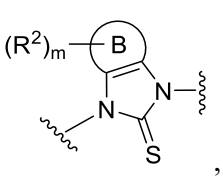
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

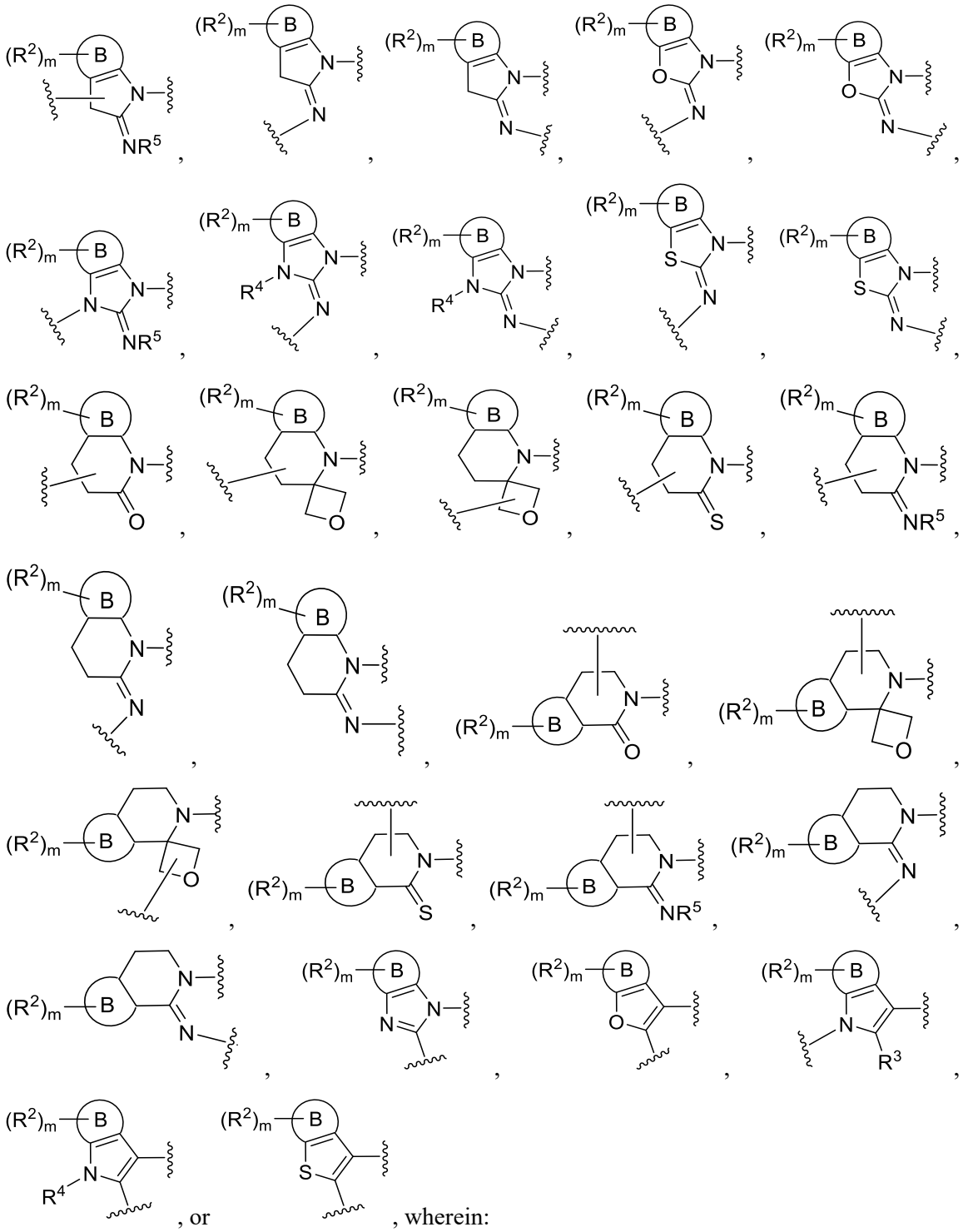
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in 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^6, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)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^6 and 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^6, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)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;

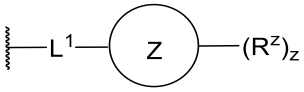
X' is an optionally substituted $-(CH_2)_x-$, wherein 1-2 methylenes of X is optionally replaced with a bivalent group selected from -NR-, -N(COR)-, $-N(CO_2R)-$, $-N(SO_2R)-$, $-N(CONR_2)-$, and $-N(SO_2NR_2)-$, wherein:

x is 1, 2, 3, 4, or 5;

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^y is hydrogen, R^A, or 

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 -$S(O)_2$-;

Ring Z is a ring selected from phenyl, naphthyl, a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^z 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 -$NRS(O)_2R$;

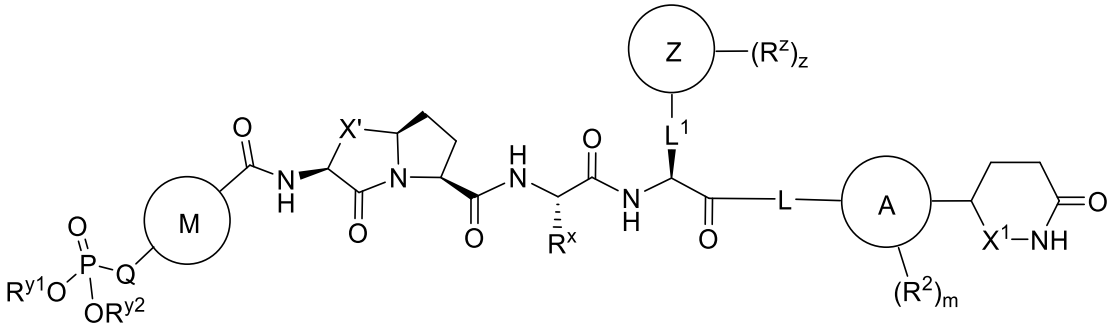
z is 0, 1, 2, 3, or 4;

Ring M 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;

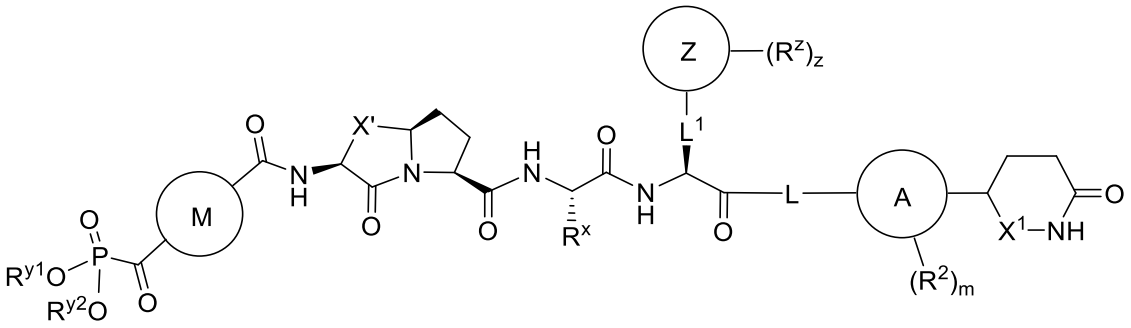
Q is a bivalent moiety selected from -O-, -CR_2-, -CF_2-, -CFR-, -C(O)-, -OCR_2-, and -C(S)-; and

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

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



I-bbb-1



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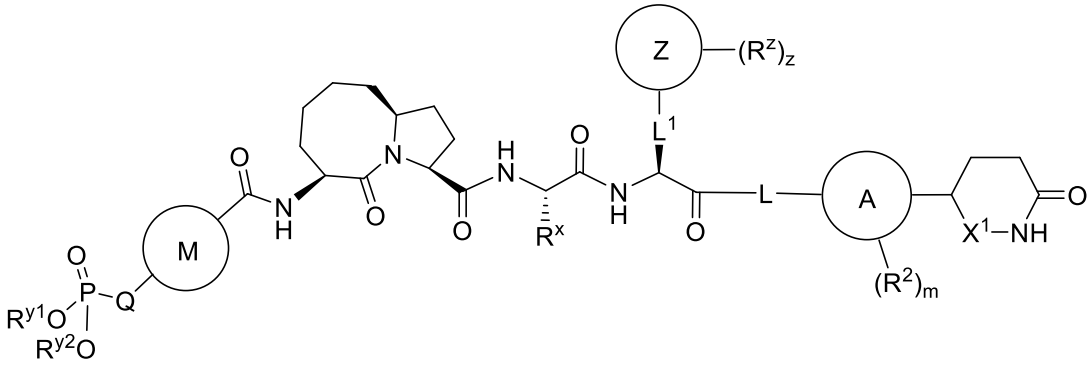
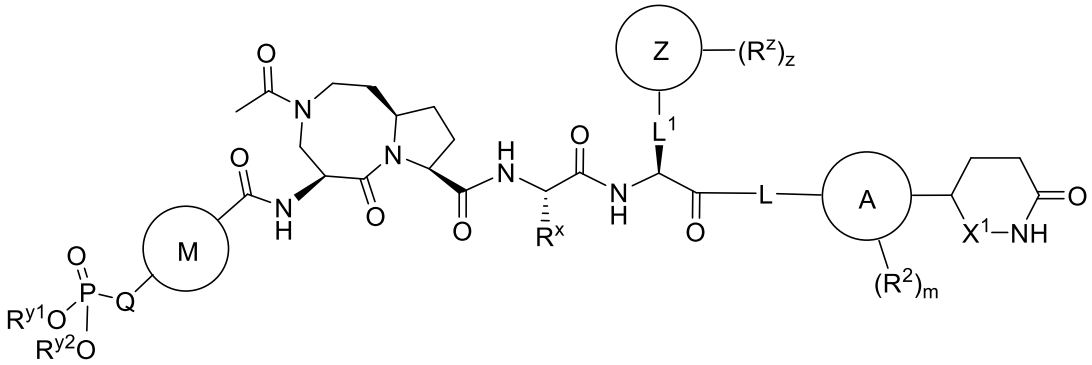
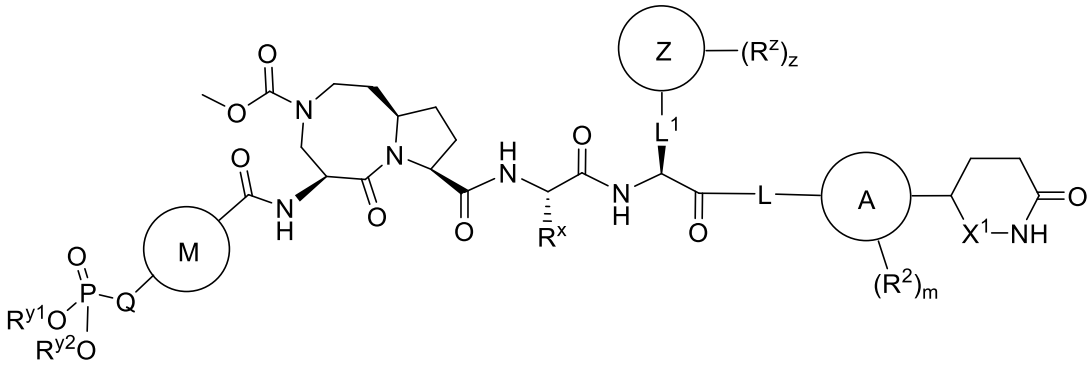


I-bbb-3



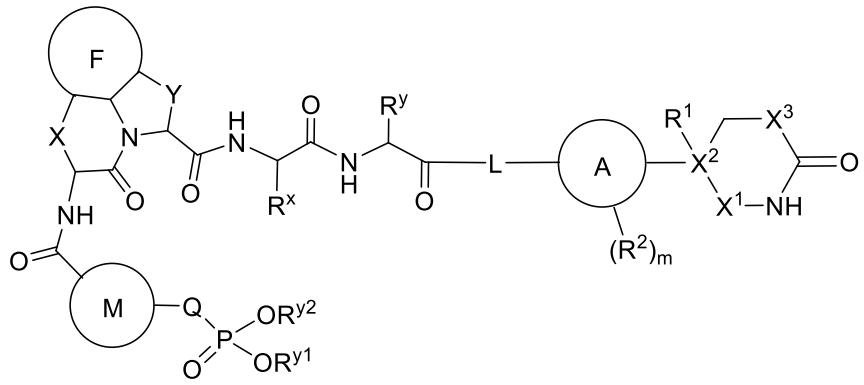
I-bbb-4



I-bbb-5

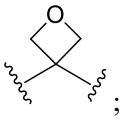
or a pharmaceutically acceptable salt thereof.

3. A compound of formula **I-ddd**:



I-ddd

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;

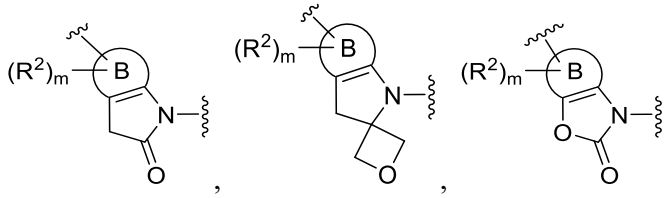
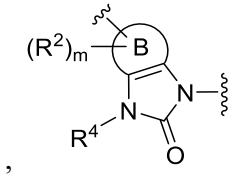
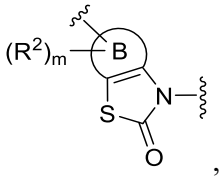
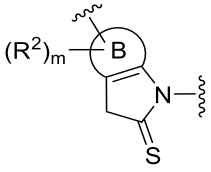
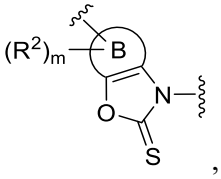
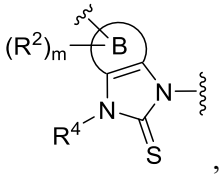
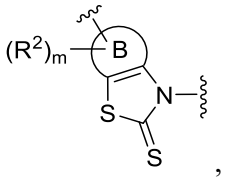
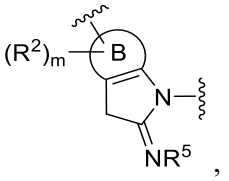
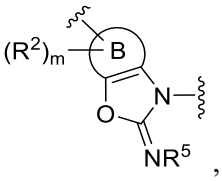
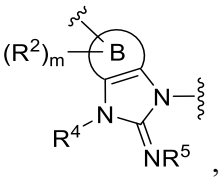
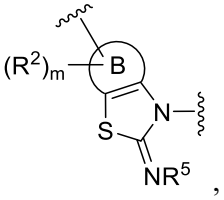
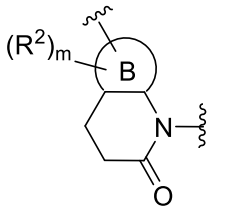
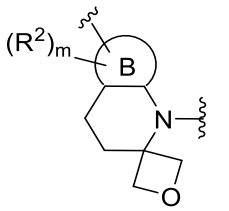
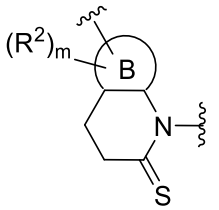
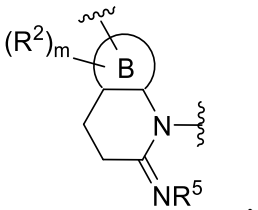
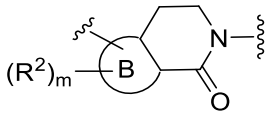
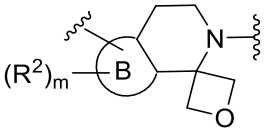
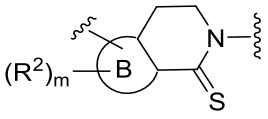
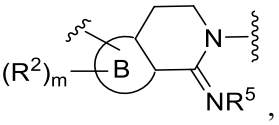
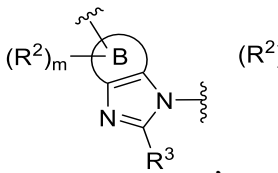
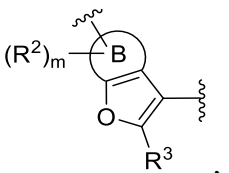
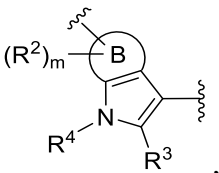
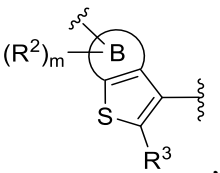
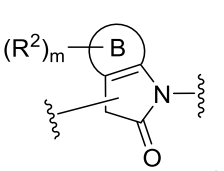
each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms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

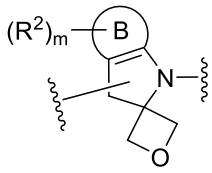
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-11 membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms, in 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^6, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-SiR_3$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, –C(O)NR_2, -C(O)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^6 and 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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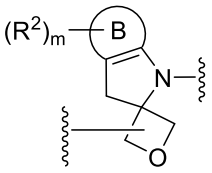
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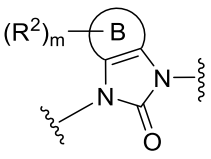
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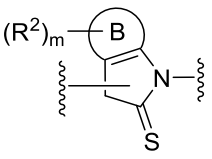
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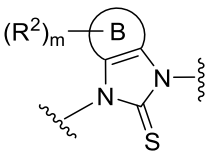
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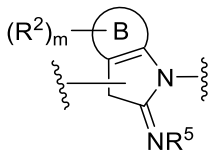
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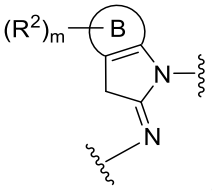
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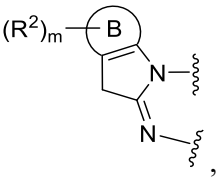
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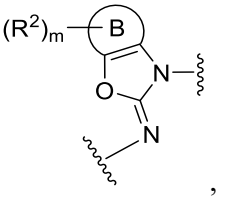
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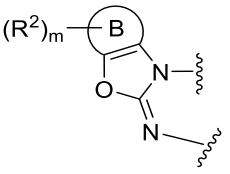
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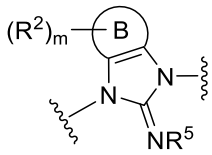
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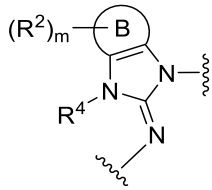
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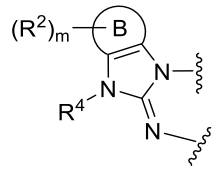
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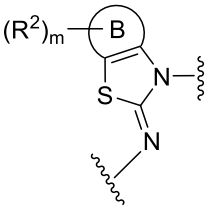
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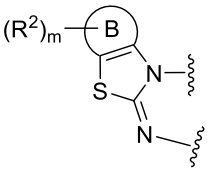
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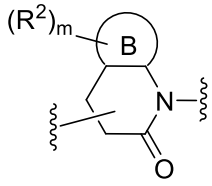
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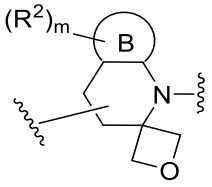
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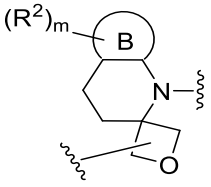
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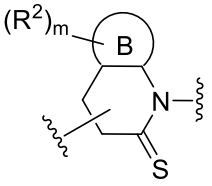
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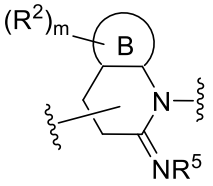
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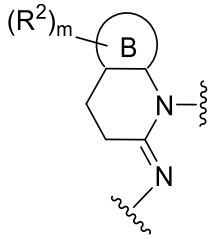
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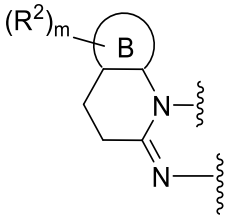
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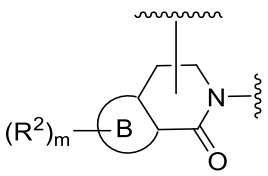
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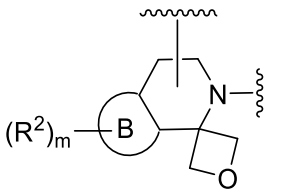
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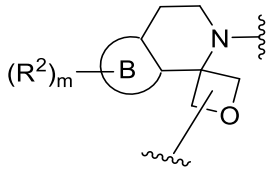
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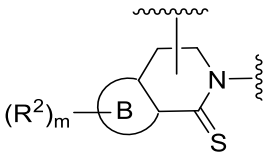
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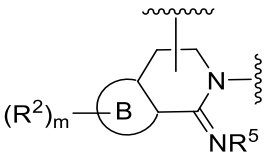
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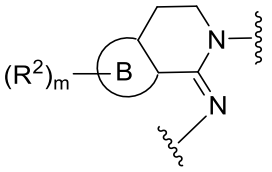
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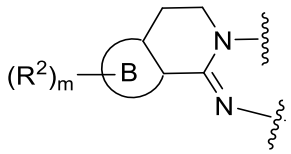
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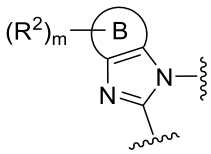
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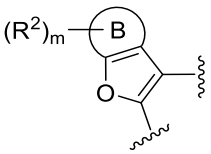
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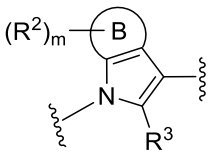
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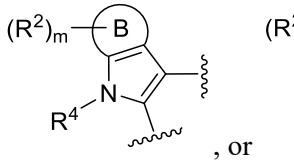
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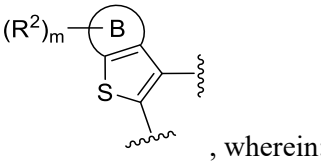
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, or

, 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^6, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)NROR, -OC(O)R, $-OC(O)NR_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)NR_2$, or $-NRS(O)_2R$;

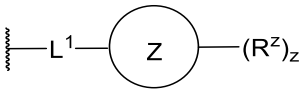
R^5 is hydrogen, C_{1-4} aliphatic, or –CN;

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;

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

R^y is hydrogen, R^A, or 

;

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 $-S(O)_2-$;

Ring Z is a ring selected from phenyl, naphthyl, a 5-10 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-11 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^z 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 $-NRS(O)_2R$;

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

Ring F is an optionally substituted fused ring selected from a 6-membered aryl, a 5-6 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;

X is an optionally substituted $-(CH_2)_x-$, wherein:

x is 0, 1, 2, or 3;

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

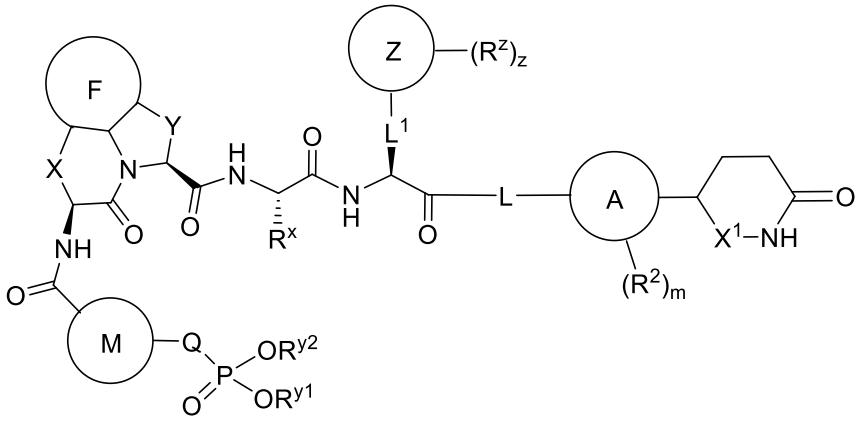
y is 0, 1, 2, or 3;

Ring M 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)-; and

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

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



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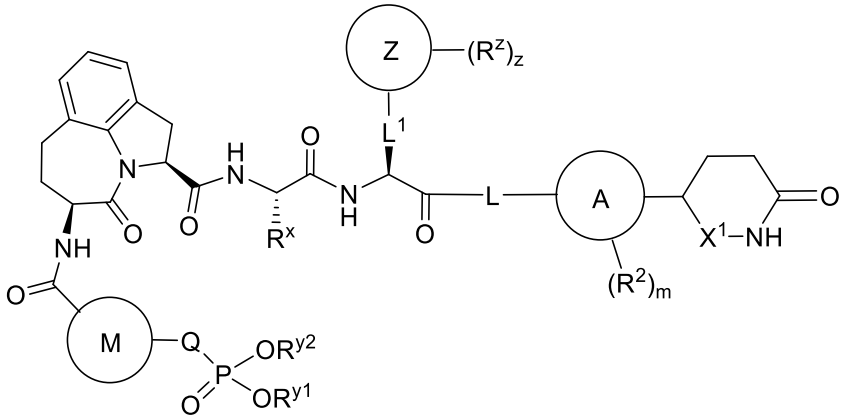

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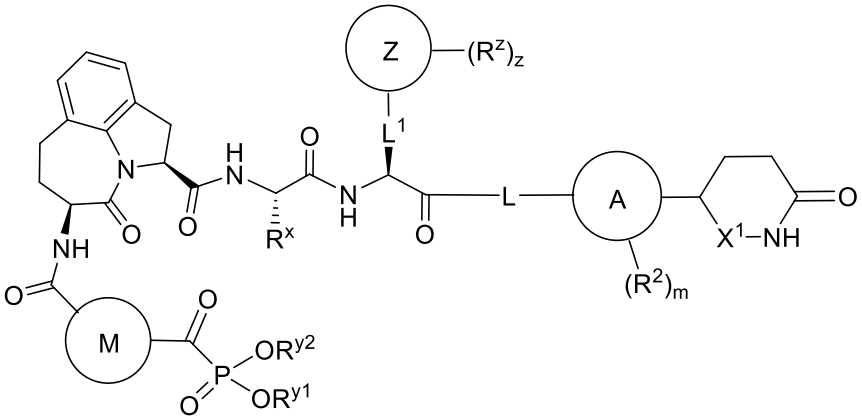

I-ddd-3

or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1-4, wherein Ring B is a fused ring selected from benzo or 5-6 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

6. The compound of any one of claims 1-5, wherein R^x is $-(CH_2)_{1-3}OCONR_2$, or $-(CH_2)_{1-3}CONR_2$;

7. The compound of any one of claims 1-6, wherein Ring Z is a ring selected from phenyl, a 5-6 membered heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and a 5-6 membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

8. The compound of any one of claims 1-7, wherein Ring M 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;

9. The compound of any one of claims 1-8, wherein Q is a bivalent moiety selected from $-CF_2-$ and -C(O)-.

10. The compound of any one of claims 1-9, wherein R^{y1} and R^{y2} are each independently hydrogen, $-CH_2CO_2R$, or $-CH_2OCO_2R$.

11. The compound of any one of claims 1-10, wherein said compound is selected from any one of the compounds depicted in **Table 1**, or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound according to any one of claims 1-11, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

13. The pharmaceutical composition according to claim 12, further comprising an additional therapeutic agent.

14. A ~~method of degrading STAT3 protein in a patient or biological sample comprising administering to said patient, or contacting said biological sample with a~~ compound according to any one of claims 1-11, or a pharmaceutical composition thereof, for degrading STAT3 protein in a patient or biological sample.

15. ~~A method of treating an STAT3-mediated disorder, disease, or condition in a patient comprising administering to said patient~~Use of a compound according to any one of claims 1-11, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an STAT3-mediated disorder, disease, or condition in a patient.

16. The ~~method~~ use according to claim 15, wherein the compound, or a pharmaceutical composition thereof, is to be administered to the patient, and wherein ~~further comprising administration of~~ an additional therapeutic agent is to be further administered.

17. The use ~~method~~ according to claim 15, 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 use ~~method~~ according to claim 17, wherein the cancer is selected from glioma, breast cancer, prostate cancer, head and neck squamous cell carcinoma, skin melanomas, ovarian cancer, malignant peripheral nerve shealth tumors (MPNST), pancreatic cancer, non-small cell lung cancer, urothelial cancer, liver cancer, bile duct cancer, kidney cancer, colon cancer, esophageal cancer, gastric cancer, gastrointestinal stromal tumors, and hematological malignancies include lymphomas, leukemias, myelomas, myeloproliferative neoplasms and myelodysplastic syndromes.

19. The use ~~method~~ according to claim 17, wherein autoimmune disease is selected from systemic sclerosis, idiopathic pulmonary fibrosis, inflammatory bowel disease, atopic dermatitis, rheumatoid arthritis, acute graft versus host disease, chronic graft versus host disease, and tissue fibrosis diseases.

20. The use ~~method~~ according to claim 18, wherein the hematologic malignancy is selected from large granular lymphocytic (LGL) leukemia (T and NK cell), cutaneous T cell lymphoma (CTCL), peripheral T cell lymphomas (PTCL), anaplastic large-cell lymphoma (ALCL), diffuse large B cell lymphoma (DLBCL), acute myelogenous leukemia, multiple myeloma, and myelofibrosis.

21. A compound according to any one of claims 1-11, or a pharmaceutical composition thereof, for use in therapy.