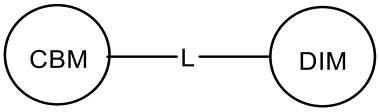
biochemical reagents and lead to a new paradigm for the treatment of diseases by removing pathogenic or oncogenic proteins (Crews C, Chemistry & Biology, 2010, 17(6):551-555; Schnnekloth JS Jr., Chembiochem, 2005, 6(l):40-46).

[0006] An ongoing need exists in the art for effective treatments for disease, especially cancers. Cyclin-dependent kinases (CDKs) are a family of serine/threonine kinases. Heterodimerized with regulatory subunits known as cyclins, such as cyclin E1 ("CCNE1"), CDKs become fully activated and regulate key cellular processes including cell cycle progression and cell division. Uncontrolled proliferation is a hallmark of cancer cells. The deregulation of the CDK activity is associated with abnormal regulation of cell-cycle, and is detected in virtually all forms of human cancers. As such, small molecule therapeutic agents that leverage UPP mediated protein degradation to target cancer-associated proteins such as cyclin-dependent kinase 2 ("CDK2") or CDK2 and CCNE1 protein hold promise as therapeutic agents. Accordingly, there remains a need to find compounds that are CDK2 or CDK2 and CCNE1 degraders useful as therapeutic agents.

SUMMARY

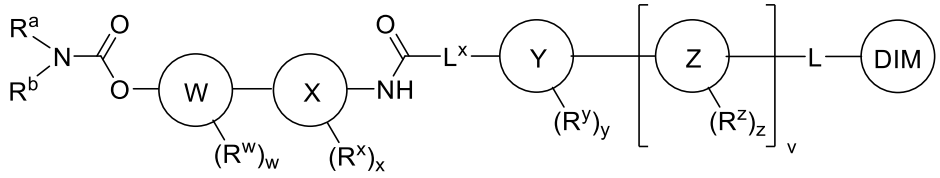
[0006a] In an aspect of the present disclosure, there is provided a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

CBM is a CDK binding moiety capable of binding to CDK2 protein, said compound of formula **I** is a compound of formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

R^a and R^b are independently hydrogen or R^A, or

R^a and R^b are taken together with the nitrogen to which they are attached to form to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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 W, Ring X, and Ring Y are independently a ring selected from phenyl, a 4 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5 to 6-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring Z is a 4 to 8-membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w, R^x, R^y, and R^z are independently selected from 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, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, and $-NRS(O)_2R$;

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

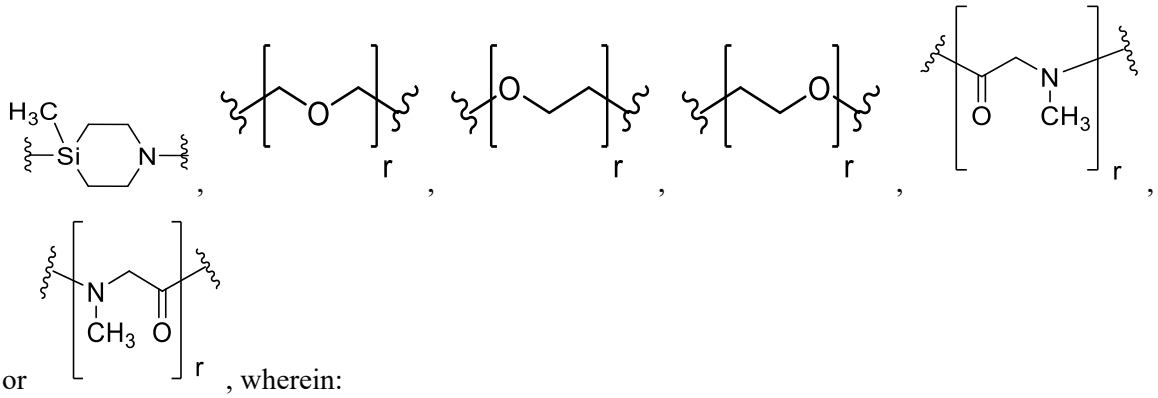
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen atom to which they are attached, independently selected from nitrogen, oxygen, and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

L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-CF_2$-, -CRF-, -NR-, -S-, -S(O)-, $-S(O)_2$- or -CR=CR-;

v is 0 or 1;

w, x, y, and z are independently 0, 1, 2, 3, or 4;

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, $–SiR_2–$, $–Si(OH)R–$, $–Si(OH)_2–$, $–P(O)OR–$, $–P(O)R–$, $–P(O)NR_2–$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2$-, $-NRS(O)_2$-, $-S(O)_2NR$-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, –NRC(O)O-,



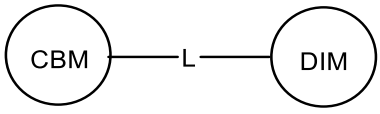
or , wherein:

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

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

DIM is a degradation inducing moiety, wherein DIM is a ligase binding moiety (LBM), lysine mimetic, or hydrogen atom.

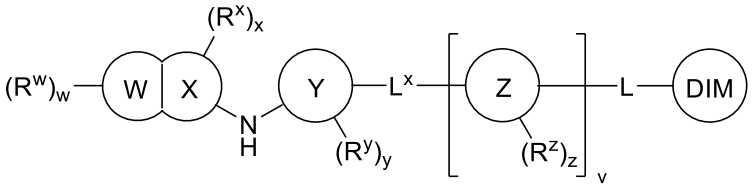
[0006b] In another aspect of the present disclosure, there is provided a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

CBM is a CDK binding moiety capable of binding to CDK2 protein, said compound of formula **I** is a compound of formula **I-b**:



I-b

or a pharmaceutically acceptable salt thereof, wherein:

Ring W and Ring X are independently fused rings selected from benzo, a 4 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5 to 6-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

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

Ring Z is a 4 to 8-membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w, R^x, R^y, and R^z are independently selected from 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, -$NRC(O)N(R)_2$, -$NRS(O)_2R$, -$NP(O)R_2$, -$NRP(O)(OR)_2$, -$NRP(O)(OR)NR_2$, -$NRP(O)(NR_2)_2$, and -$NRS(O)_2R$; or

two R^w groups attached to the same carbon atom are optionally taken together to form a spiro fused ring selected from a 3-5 membered saturated or partially unsaturated carbocyclyl and a 3-5 membered saturated or partially unsaturated heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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;

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

or:

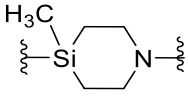
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen atom to which they are attached, independently selected from nitrogen, oxygen, and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

L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-CF_2-$, -CRF-, -NR-, -S-, -S(O)-, $-S(O)_2-$ or -CR=CR-;

v is 0 or 1;

w, x, y, and z are independently 0, 1, 2, 3, or 4;

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, $–SiR_2–$, $–Si(OH)R–$, $–Si(OH)_2–$, $–P(O)OR–$, $–P(O)R–$, $–P(O)NR_2–$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2-$, $-NRS(O)_2-$, $-S(O)_2NR-$, -NRC(O)-, -C(O)NR-, -OC(O)NR-, –NRC(O)O-,



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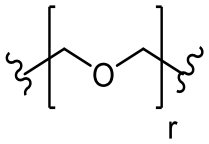

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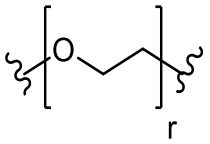

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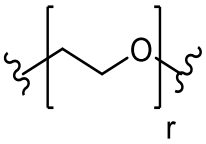

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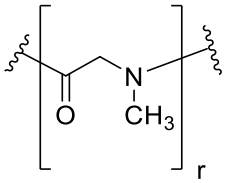

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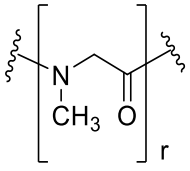
or


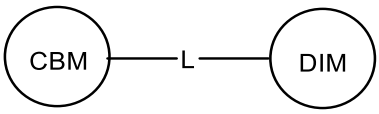
, wherein:

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

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

DIM is a degradation inducing moiety, wherein DIM is a ligase binding moiety (LBM), lysine mimetic, or hydrogen atom.

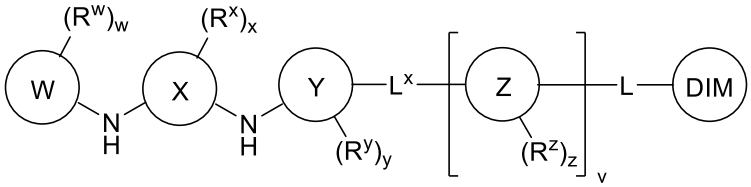
[0006c] In a further aspect of the present disclosure, there is provided a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

CBM is a CDK binding moiety capable of binding to CDK2 protein, said compound of formula **I** is a compound of formula **I-c**:



I-c

or a pharmaceutically acceptable salt thereof, wherein:

Ring W, Ring X, and Ring Y are independently a ring selected from phenyl, a 4 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5 to 6-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring Z is phenyl or a 4 to 8-membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w, R^x, R^y, and R^z are independently selected from 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, -$NRC(O)N(R)_2$, -$NRS(O)_2R$, -$NP(O)R_2$, -$NRP(O)(OR)_2$, -$NRP(O)(OR)NR_2$, -$NRP(O)(NR_2)_2$, and -$NRS(O)_2R$;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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;

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

a 4-7 membered saturated or partially unsaturated 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, or:

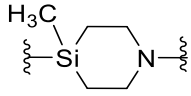
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen atom to which they are attached, independently selected from nitrogen, oxygen, and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

L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-CF_2-$, -CRF-, -NR-, -S-, -S(O)-, $-S(O)_2-$ or -CR=CR-;

v is 0 or 1;

w, x, y, and z are independently 0, 1, 2, 3, or 4;

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, $–SiR_2–$, $–Si(OH)R–$, $–Si(OH)_2–$, $–P(O)OR–$, $–P(O)R–$, $–P(O)NR_2–$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2-$, $-NRS(O)_2-$, $-S(O)_2NR-$, -NRC(O)-, -C(O)NR-, -OC(O)NR-, –NRC(O)O-,



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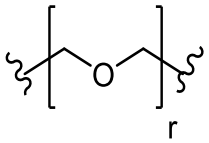

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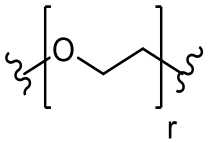

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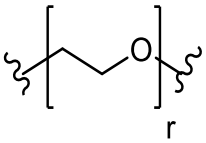

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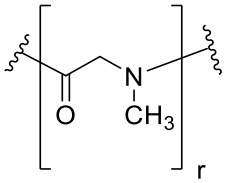

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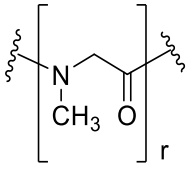


or , wherein:

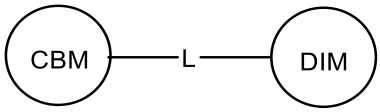
each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated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

1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

DIM is a degradation inducing moiety, wherein DIM is a ligase binding moiety (LBM), lysine mimetic, or hydrogen atom.

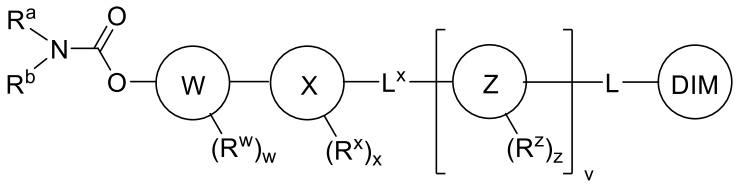
[0006d] In another aspect of the present disclosure, there is provided a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

CBM is a CDK binding moiety capable of binding to CDK2 protein, said compound of formula **I** is a compound of formula **I-d**:



I-d

or a pharmaceutically acceptable salt thereof, wherein:

R^a and R^b are independently hydrogen or R^A, or

R^a and R^b are taken together with the nitrogen to which they are attached to form to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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 W is a ring selected from phenyl, a 4 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5 to 6-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring X is a bicyclic ring selected from naphthyl, a 9 to 10-membered saturated or partially unsaturated

carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 9 to 10-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring Z is phenyl or a 4 to 8-membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w, R^x, and R^z are independently selected from 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, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, and $-NRS(O)_2R$;

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

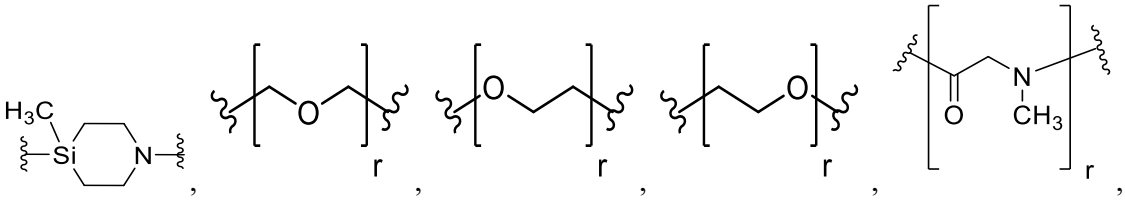
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen atom to which they are attached, independently selected from nitrogen, oxygen, and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

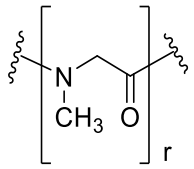
L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-CF_2$-, -CRF-, -NR-, -S-, -S(O)-, $-S(O)_2$- or -CR=CR-;

v is 0 or 1;

w, x, and z are independently 0, 1, 2, 3, or 4;

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, $–SiR_2–$, $–Si(OH)R–$, $–Si(OH)_2–$, $–P(O)OR–$, $–P(O)R–$, $–P(O)NR_2–$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2$-, $-NRS(O)_2$-, $-S(O)_2NR$-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, –NRC(O)O-,



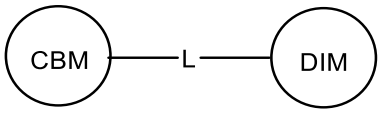
or  , wherein:

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

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

DIM is a degradation inducing moiety, wherein DIM is a ligase binding moiety (LBM), lysine mimetic, or hydrogen atom.

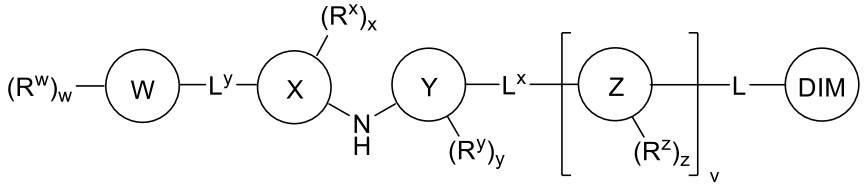
[0006e] In a further aspect of the present disclosure, there is provided a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

CBM is a CDK binding moiety capable of binding to CDK2 protein, said compound of formula **I** is a compound of formula **I-e**:



I-e

or a pharmaceutically acceptable salt thereof, wherein:

Ring W and Ring X are independently rings selected from phenyl, a 4 to 7-membered saturated or partially

unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5 to 6-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

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

Ring Z is phenyl or a 4 to 8-membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w, R^x, R^y, and R^z are independently selected from 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, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, and $-NRS(O)_2R$; or

two R^w groups attached to the same carbon atom are optionally taken together to form a spiro fused ring selected from a 3-5 membered saturated or partially unsaturated carbocyclyl and a 3-5 membered saturated or partially unsaturated heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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;

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

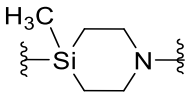
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen atom to which they are attached, independently selected from nitrogen, oxygen, and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

L^x and L^y are independently, a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-CF_2$-, -CRF-, -NR-, -S-, -S(O)-, $-S(O)_2$- or -CR=CR-;

v is 0 or 1;

w, x, y, and z are independently 0, 1, 2, 3, or 4;

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, $–SiR_2–$, –Si(OH)R–, $–Si(OH)_2–$, –P(O)OR–, –P(O)R–, $–P(O)NR_2–$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2-$, $-NRS(O)_2-$, $-S(O)_2NR-$, -NRC(O)-, -C(O)NR-, -OC(O)NR-, –NRC(O)O-,



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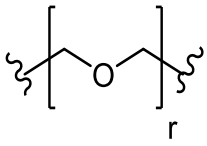

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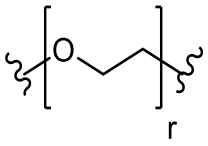

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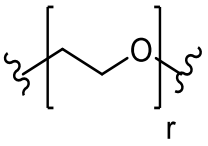

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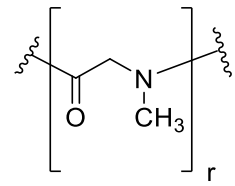

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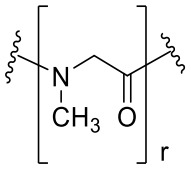


, wherein:

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

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

DIM is a degradation inducing moiety, wherein DIM is a ligase binding moiety (LBM), lysine mimetic, or hydrogen atom.

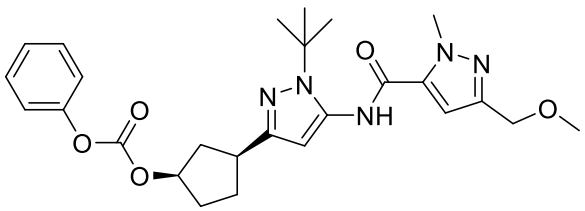
[0006f] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

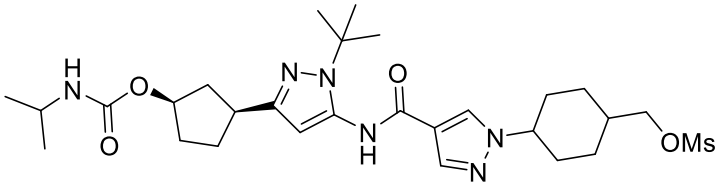
[0006g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutical composition thereof, in the manufacture of a medicament for inhibiting or degrading CDK2 in a patient or biological sample.

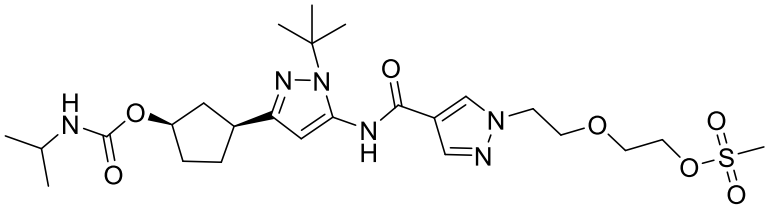
[0006h] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating a CDK2-mediated disorder, disease, or condition in a patient.

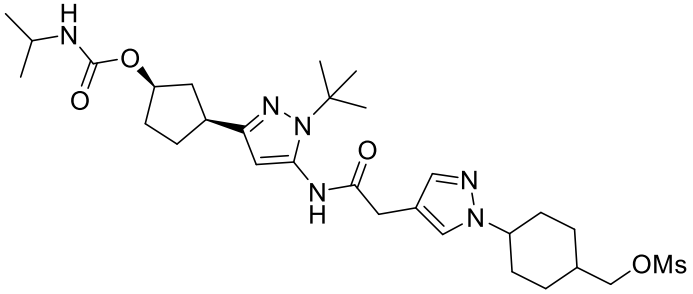
[0006i] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutical composition thereof, for use in therapy.

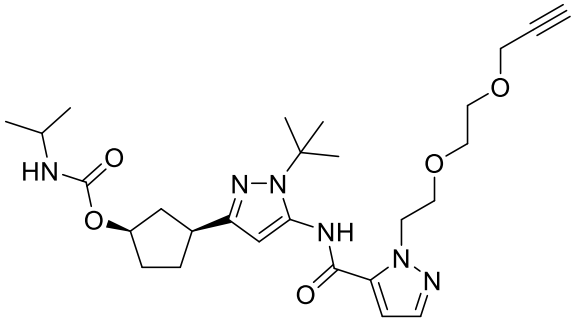
[0006j] In another aspect of the present disclosure, there is provided a compound of any of the following formulae:

P 

R 

BR 

V 

X 

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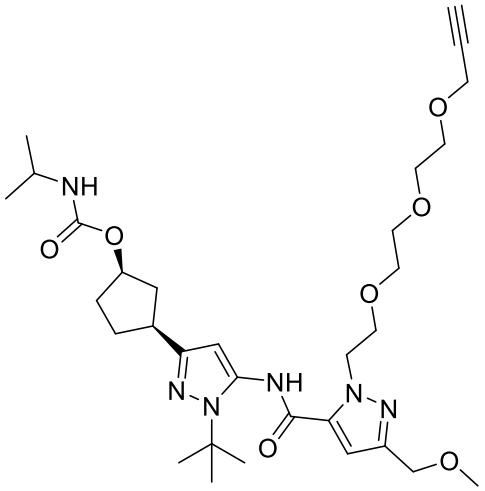

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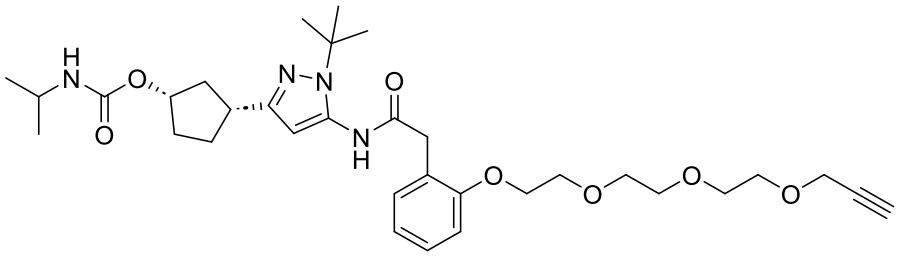

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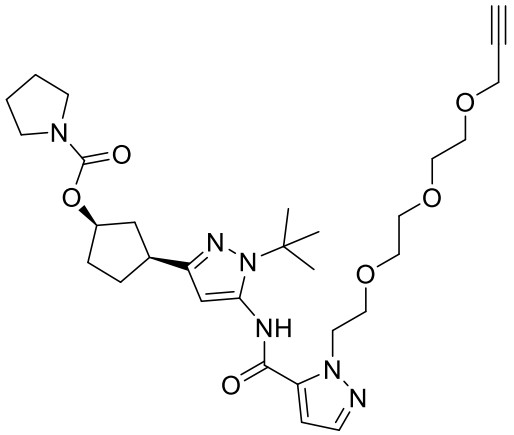

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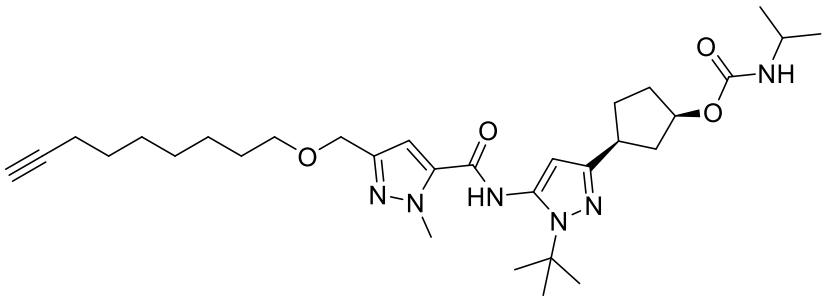

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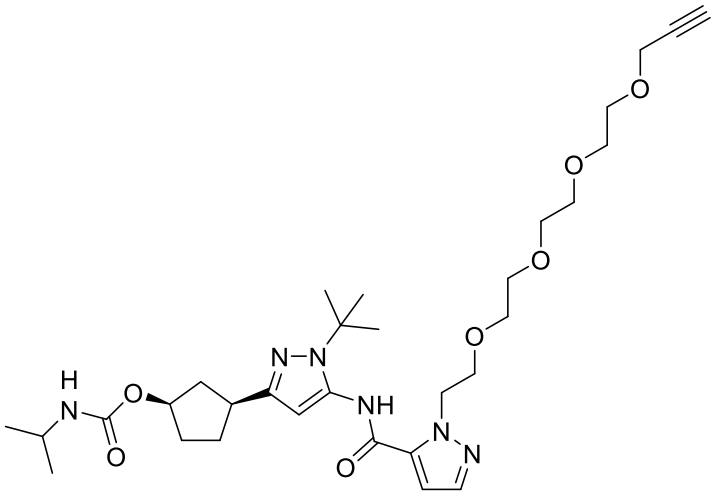

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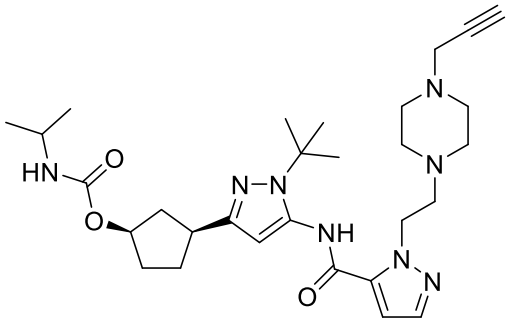

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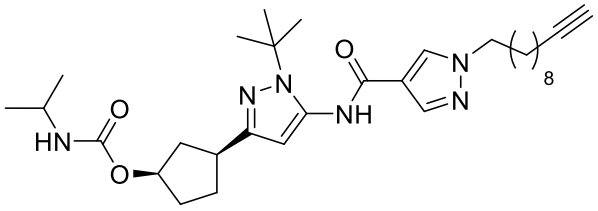

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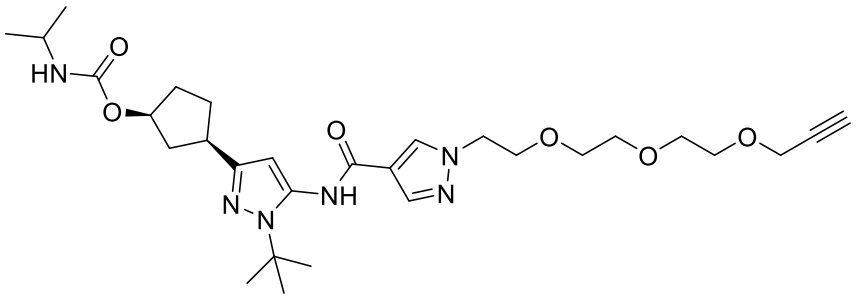

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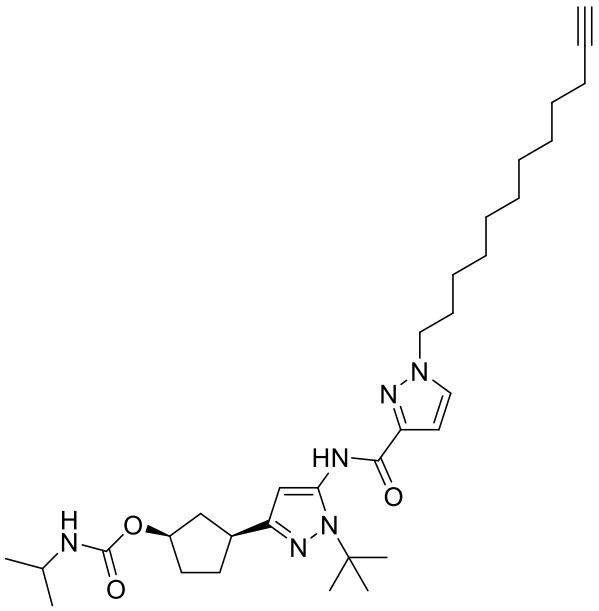

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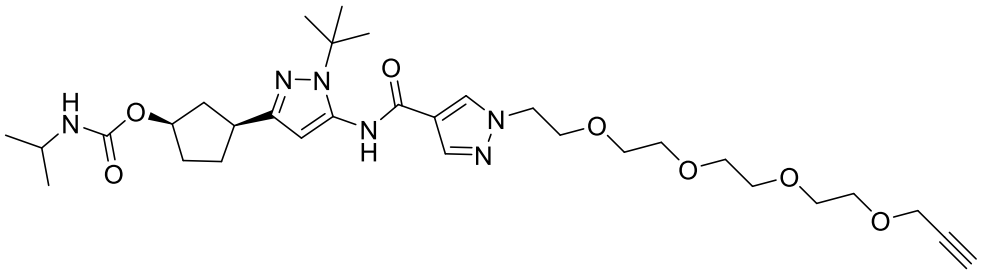

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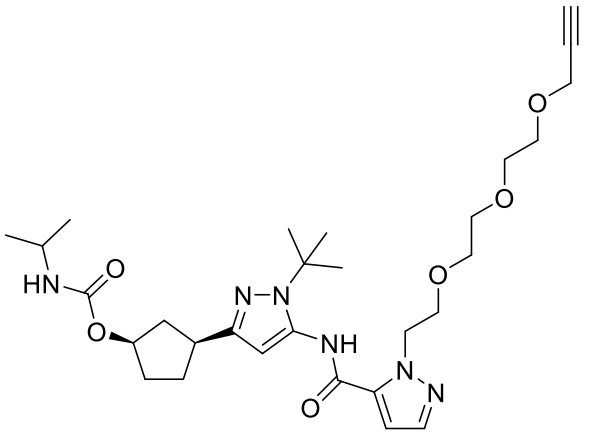

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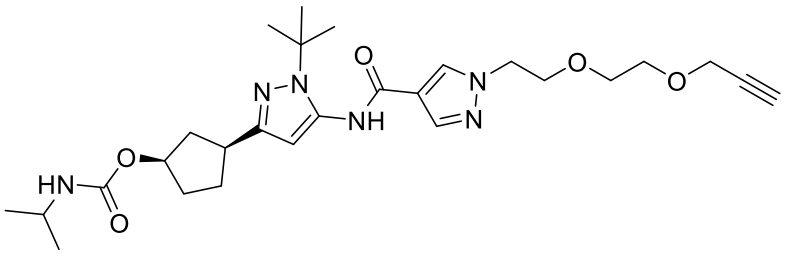

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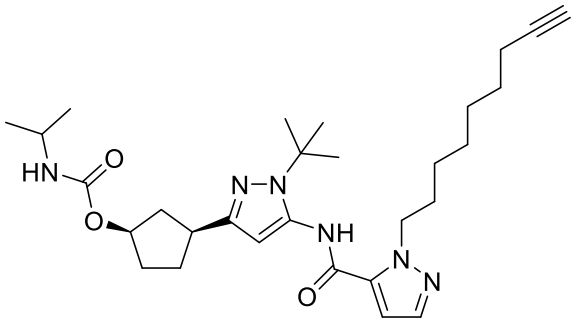

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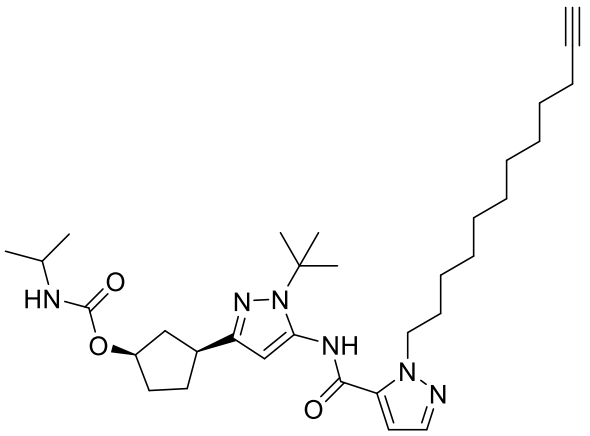

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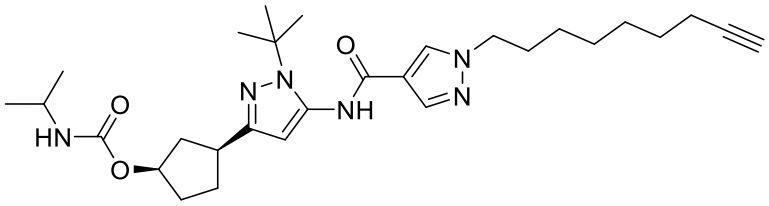

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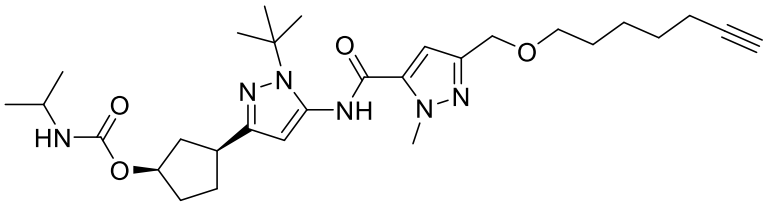

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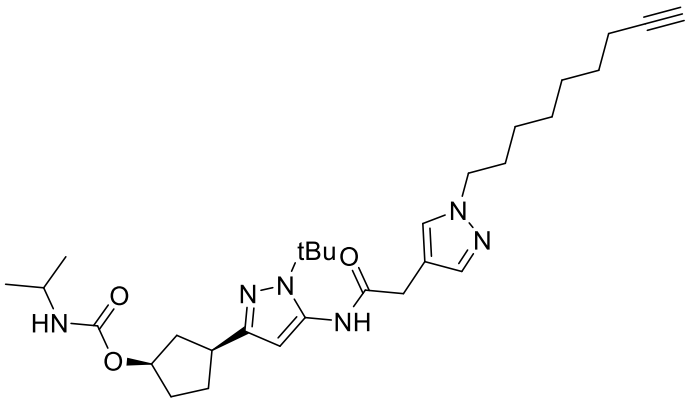

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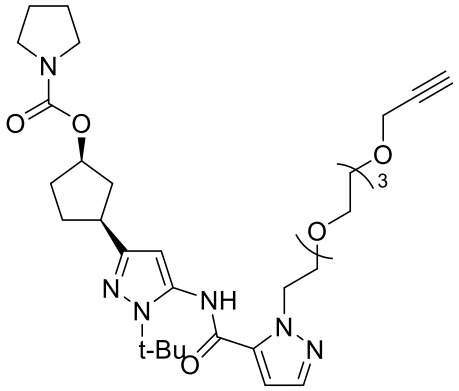
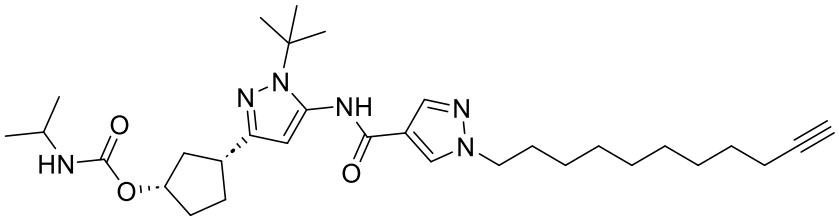
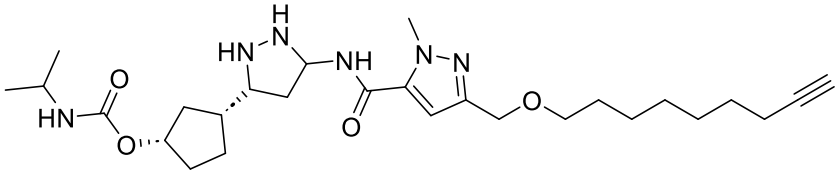
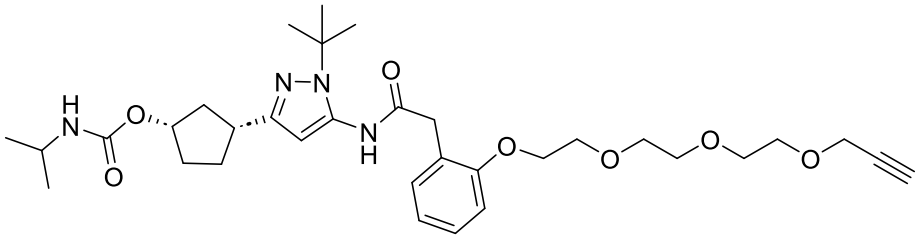
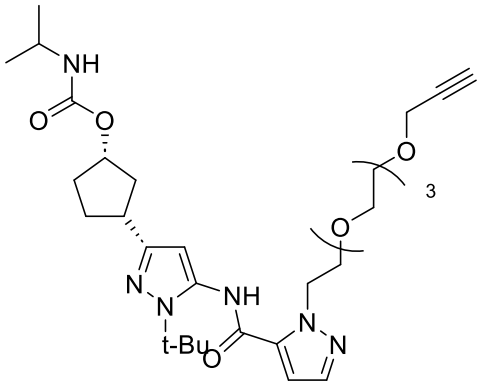
FV 

FA 

EW 

EV 

EQ 

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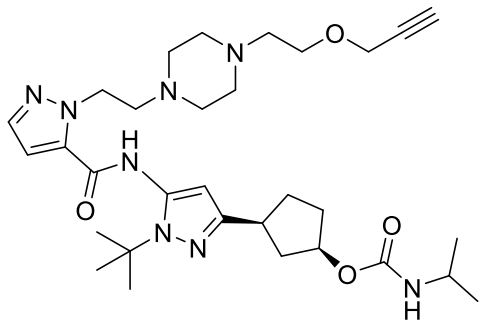

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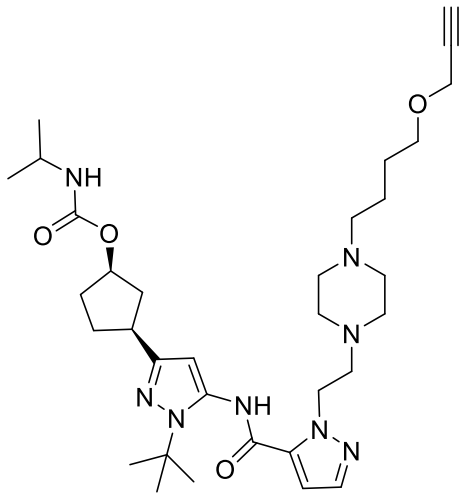
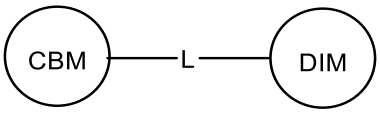


[0007] The present application relates novel bifunctional compounds, which function to recruit CDK2 or CDK2 and CCNE1 protein to E3 ubiquitin ligase for degradation, and methods of preparation and uses thereof. In particular, the present disclosure provides bifunctional compounds, which find utility as modulators of targeted ubiquitination of CDK2 or CDK2 and CCNE1, which is 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 CDK2 or CDK2 and CCNE1, 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 CDK2 or CDK2 and CCNE1. 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 those caused by aberrant CDK2 or CDK2 and CCNE1 activity.

[0008] The present application further relates to targeted degradation of CDK2 or CDK2 and CCNE1 protein through the use of bifunctional molecules, including bifunctional molecules that link a cereblon-binding moiety to a ligand that binds CDK2 or CDK2 and CCNE1.

[0009] It has now been found that compounds of this disclosure, and pharmaceutically acceptable compositions thereof, are effective as degraders of CDK2 or CDK2 and CCNE1 protein. Such compounds have the general formula **I**:



I

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

[0010] Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of CDK2 protein. Such diseases, disorders, or conditions include those described herein.

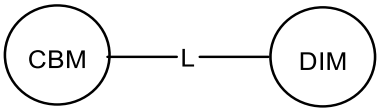
[0011] Compounds provided by this disclosure are also useful for the study of CDK2 protein in biological and pathological phenomena; and the comparative evaluation of new CDK2 inhibitors or CDK2 degraders, *in vitro* or *in vivo*.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Certain Embodiments of the Invention:

[0012] Compounds of the present invention, and compositions thereof, are useful as degraders and/or inhibitors of CDK protein. In some embodiments, a provided compound degrades and/or inhibits CDK2 protein. In some embodiments, a provided compound degrades and/or inhibits CDK2 and CCNE1 protein.

[0013] In certain embodiments, the present invention provides a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

CBM is a CDK binding moiety capable of binding CDK2 or CDK2 and CCNE1;

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

DIM is a degradation inducing moiety, such as a ligase binding moiety (LBM), lysine mimetic, or hydrogen atom.

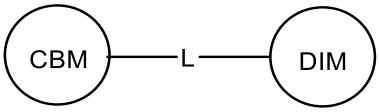
2. Compounds and Definitions:

[0014] 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",

CLAIMS

We claim:

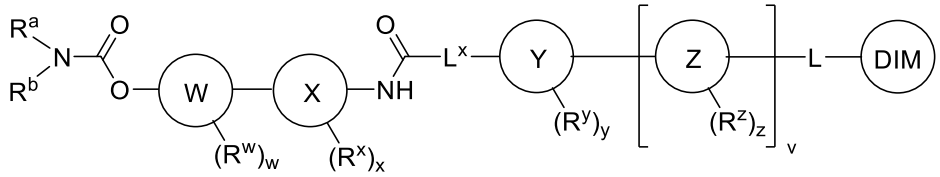
1. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

CBM is a CDK binding moiety capable of binding to CDK2 protein, said compound of formula **I** is a compound of formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

R^a and R^b are independently hydrogen or R^A, or

R^a and R^b are taken together with the nitrogen to which they are attached to form to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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 W, Ring X, and Ring Y are independently a ring selected from phenyl, a 4 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5 to 6-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring Z is a 4 to 8-membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w, R^x, R^y, and R^z are independently selected from 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, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, and $-NRS(O)_2R$;

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

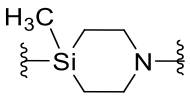
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen atom to which they are attached, independently selected from nitrogen, oxygen, and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

L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-CF_2$-, -CRF-, -NR-, -S-, -S(O)-, $-S(O)_2$- or -CR=CR-;

v is 0 or 1;

w, x, y, and z are independently 0, 1, 2, 3, or 4;

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, $–SiR_2–$, $–Si(OH)R–$, $–Si(OH)_2–$, $–P(O)OR–$, $–P(O)R–$, $–P(O)NR_2–$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2$-, $-NRS(O)_2$-, $-S(O)_2NR$-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, –NRC(O)O-,



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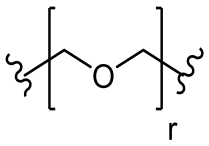

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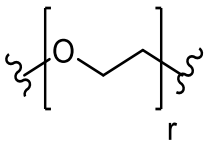

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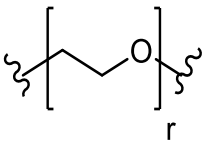

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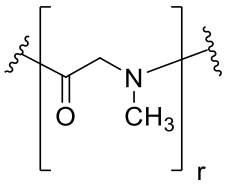

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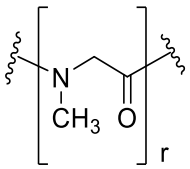
or


, wherein:

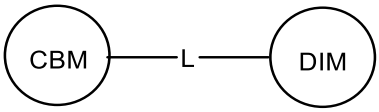
each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated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

oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

DIM is a degradation inducing moiety, wherein DIM is a ligase binding moiety (LBM), lysine mimetic, or hydrogen atom.

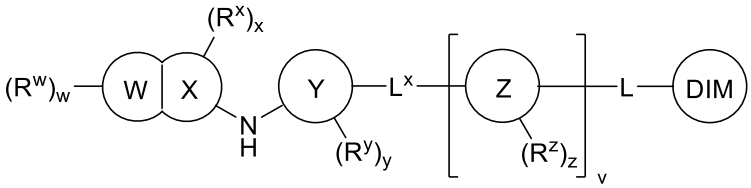
2. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

CBM is a CDK binding moiety capable of binding to CDK2 protein, said compound of formula **I** is a compound of formula **I-b**:



I-b

or a pharmaceutically acceptable salt thereof, wherein:

Ring W and Ring X are independently fused rings selected from benzo, a 4 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5 to 6-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

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

and sulfur;

Ring Z is a 4 to 8-membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w, R^x, R^y, and R^z are independently selected from 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, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, and $-NRS(O)_2R$; or

two R^w groups attached to the same carbon atom are optionally taken together to form a spiro fused ring selected from a 3-5 membered saturated or partially unsaturated carbocyclyl and a 3-5 membered saturated or partially unsaturated heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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;

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

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

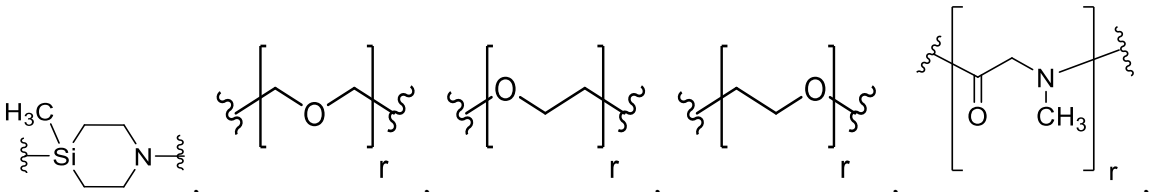
L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-CF_2$-, -CRF-, -NR-, -S-, -S(O)-, $-S(O)_2$- or -CR=CR-;

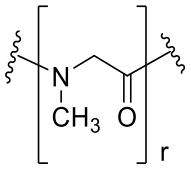
v is 0 or 1;

w, x, y, and z are independently 0, 1, 2, 3, or 4;

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, $–SiR_2–$, $–Si(OH)R–$, $–Si(OH)_2–$, –P(O)OR–, –P(O)R–, $–P(O)NR_2–$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-,

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





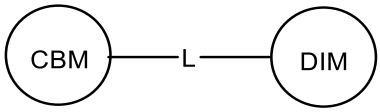
, wherein:

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

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

DIM is a degradation inducing moiety, wherein DIM is a ligase binding moiety (LBM), lysine mimetic, or hydrogen atom.

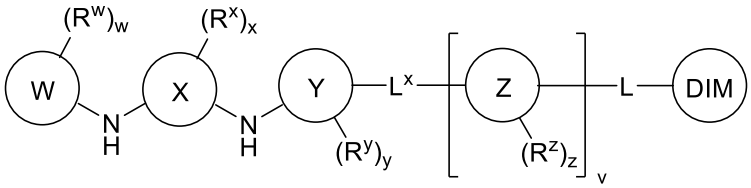
3. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

CBM is a CDK binding moiety capable of binding to CDK2 protein, said compound of formula **I** is a compound of formula **I-c**:



I-c

or a pharmaceutically acceptable salt thereof, wherein:

Ring W, Ring X, and Ring Y are independently a ring selected from phenyl, a 4 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5 to 6-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring Z is phenyl or a 4 to 8-membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w, R^x, R^y, and R^z are independently selected from 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, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, and $-NRS(O)_2R$;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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;

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

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

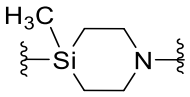
L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-

, -C(S)-, -CF_2-, -CRF-, -NR-, -S-, -S(O)-, -$S(O)_2$- or -CR=CR-;

v is 0 or 1;

w, x, y, and z are independently 0, 1, 2, 3, or 4;

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, –SiR_2–, –Si(OH)R–, –$Si(OH)_2$–, –P(O)OR–, –P(O)R–, –$P(O)NR_2$–, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -$NRS(O)_2$-, -$S(O)_2$NR-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, –NRC(O)O-,



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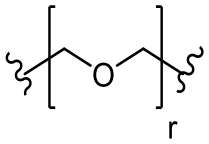

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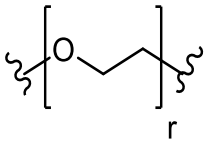

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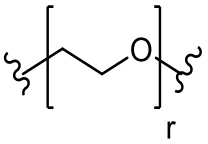

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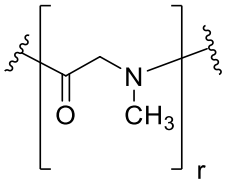

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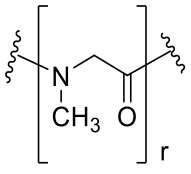


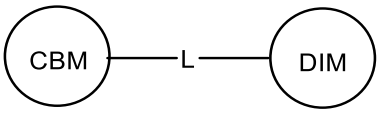
, wherein:

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

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

DIM is a degradation inducing moiety, wherein DIM is a ligase binding moiety (LBM), lysine mimetic, or hydrogen atom.

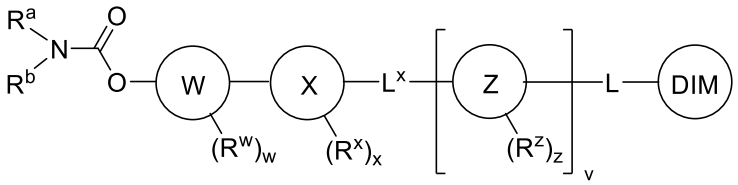
4. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

CBM is a CDK binding moiety capable of binding to CDK2 protein, said compound of formula **I** is a compound of formula **I-d**:



I-d

or a pharmaceutically acceptable salt thereof, wherein:

R^a and R^b are independently hydrogen or R^A, or

R^a and R^b are taken together with the nitrogen to which they are attached to form to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen atom to which they are attached, independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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 W is a ring selected from phenyl, a 4 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5 to 6-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring X is a bicyclic ring selected from naphthyl, a 9 to 10-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 9 to 10-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

Ring Z is phenyl or a 4 to 8-membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w, R^x, and R^z are independently selected from hydrogen, R^A, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, -

SiR_3, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $–C(O)NR_2$, $-C(O)NROR$, $-CR_2NRC(O)R$, $-CR_2NRC(O)NR_2$, $-OC(O)R$, $-OC(O)NR_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$-, $-NRC(O)OR$, $-NRC(O)R$, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, and $-NRS(O)_2R$;

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

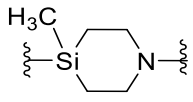
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen atom to which they are attached, independently selected from nitrogen, oxygen, and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

L^x is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-CF_2$-, -CRF-, -NR-, -S-, -S(O)-, $-S(O)_2$- or -CR=CR-;

v is 0 or 1;

w, x, and z are independently 0, 1, 2, 3, or 4;

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, $–SiR_2–$, –Si(OH)R–, $–Si(OH)_2–$, –P(O)OR–, –P(O)R–, $–P(O)NR_2–$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2$-, $-NRS(O)_2$-, $-S(O)_2NR$-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, –NRC(O)O-,



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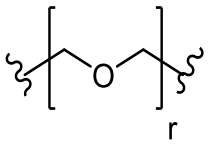

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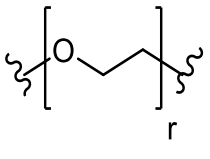

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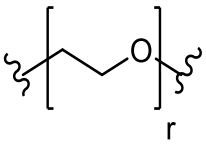

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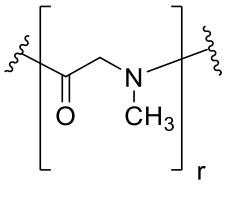

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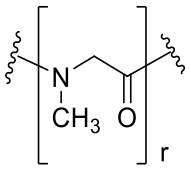
or


, wherein:

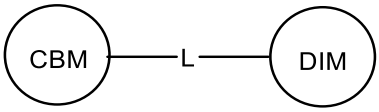
each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated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

unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-11 membered saturated or partially unsaturated spiro heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic saturated or partially unsaturated heterocyclylenyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur,

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

DIM is a degradation inducing moiety, wherein DIM is a ligase binding moiety (LBM), lysine mimetic, or hydrogen atom.

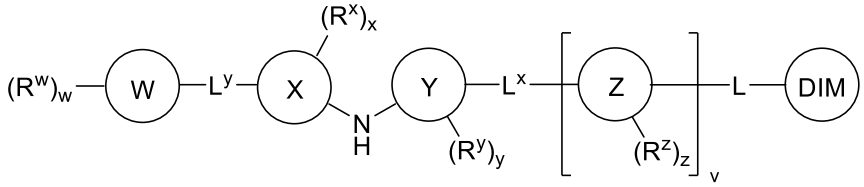
5. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

CBM is a CDK binding moiety capable of binding to CDK2 protein, said compound of formula **I** is a compound of formula **I-e**:



I-e

or a pharmaceutically acceptable salt thereof, wherein:

Ring W and Ring X are independently rings selected from phenyl, a 4 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5 to 6-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

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

Ring Z is phenyl or a 4 to 8-membered saturated or partially unsaturated monocyclic, bicyclic, bridged bicyclic, or spirocyclic carbocyclyl or heterocyclyl with 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^w, R^x, R^y, and R^z are independently selected from 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, $-NRC(O)N(R)_2$, $-NRS(O)_2R$, $-NP(O)R_2$, $-NRP(O)(OR)_2$, $-NRP(O)(OR)NR_2$, $-NRP(O)(NR_2)_2$, and $-NRS(O)_2R$; or

two R^w groups attached to the same carbon atom are optionally taken together to form a spiro fused ring selected from a 3-5 membered saturated or partially unsaturated carbocyclyl and a 3-5 membered saturated or partially unsaturated heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R^A is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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;

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

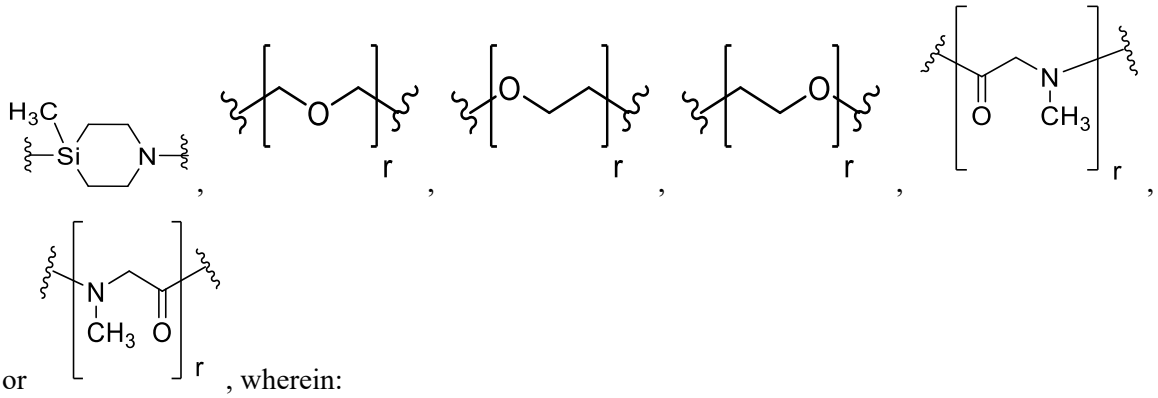
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen atom to which they are attached, independently selected from nitrogen, oxygen, and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

L^x and L^y are independently, a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-CF_2$-, -CRF-, -NR-, -S-, -S(O)-, $-S(O)_2$- or -CR=CR-;

v is 0 or 1;

w, x, y, and z are independently 0, 1, 2, 3, or 4;

L is a covalent bond or a bivalent, saturated or partially unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -Cy-, -O-, -NR-, $–SiR_2–$, –Si(OH)R–, $–Si(OH)_2–$, –P(O)OR–, –P(O)R–, $–P(O)NR_2–$, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2$-, $-NRS(O)_2$-, $-S(O)_2NR$-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, –NRC(O)O-,



or , wherein:

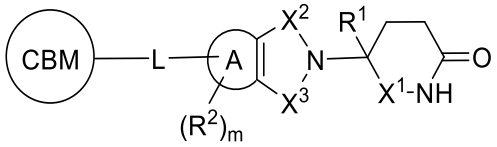
each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated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

r is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

DIM is a degradation inducing moiety, wherein DIM is a ligase binding moiety (LBM), lysine mimetic, or hydrogen atom.

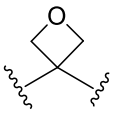
6. The compound of any one of claims 1-5, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety, a VHL E3 ubiquitin ligase binding moiety, an IAP E3 ubiquitin ligase binding moiety, or an MDM2 E3 ubiquitin ligase binding moiety.

7. The compound of claim 6, wherein LBM is an cereblon E3 ubiquitin ligase binding moiety and said compound is of formula **I-nn-1**:



I-nn-1

or a pharmaceutically acceptable salt thereof, wherein:

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

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

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

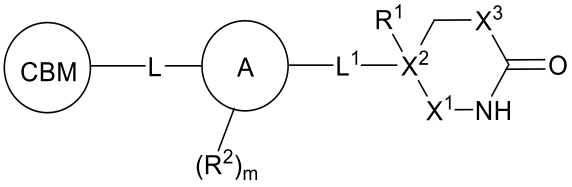
Ring A is a fused ring selected from 6-membered aryl containing 0-2 nitrogen atoms, 5 to 7-membered partially saturated carbocyclyl, 5 to 7-membered partially saturated heterocyclyl with 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur, or 5-membered heteroaryl with 1-3 heteroatoms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

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

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

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

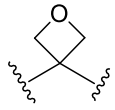
8. The compound of claim 6, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety and said compound is of formula **I-aa**:



I-aa

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is a bivalent moiety selected from a covalent bond, $–CH_2–$, $–CHCF_3–$, $–SO_2–$, –S(O)–, –P(O)R–, –

P(O)OR–, –P(O)NR$_2$–, –C(O)–, –C(S)–, or  ;

X^2 is a carbon atom or silicon atom;

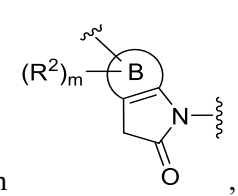
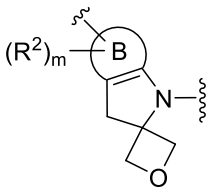
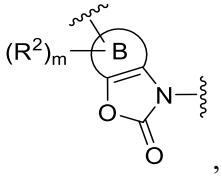
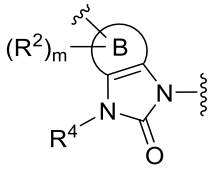
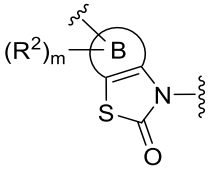
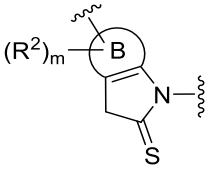
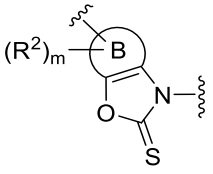
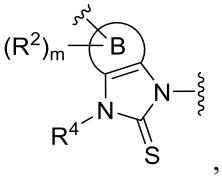
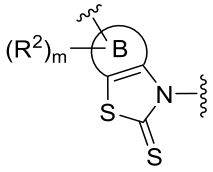
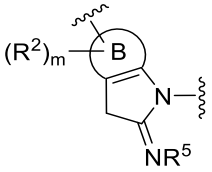
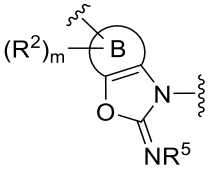
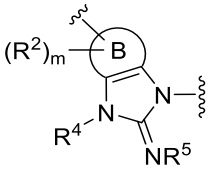
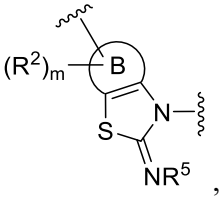
X^3 is a bivalent moiety selected from –CR$_2$–, –NR–, –O–, –S–, or –SiR$_2$–;

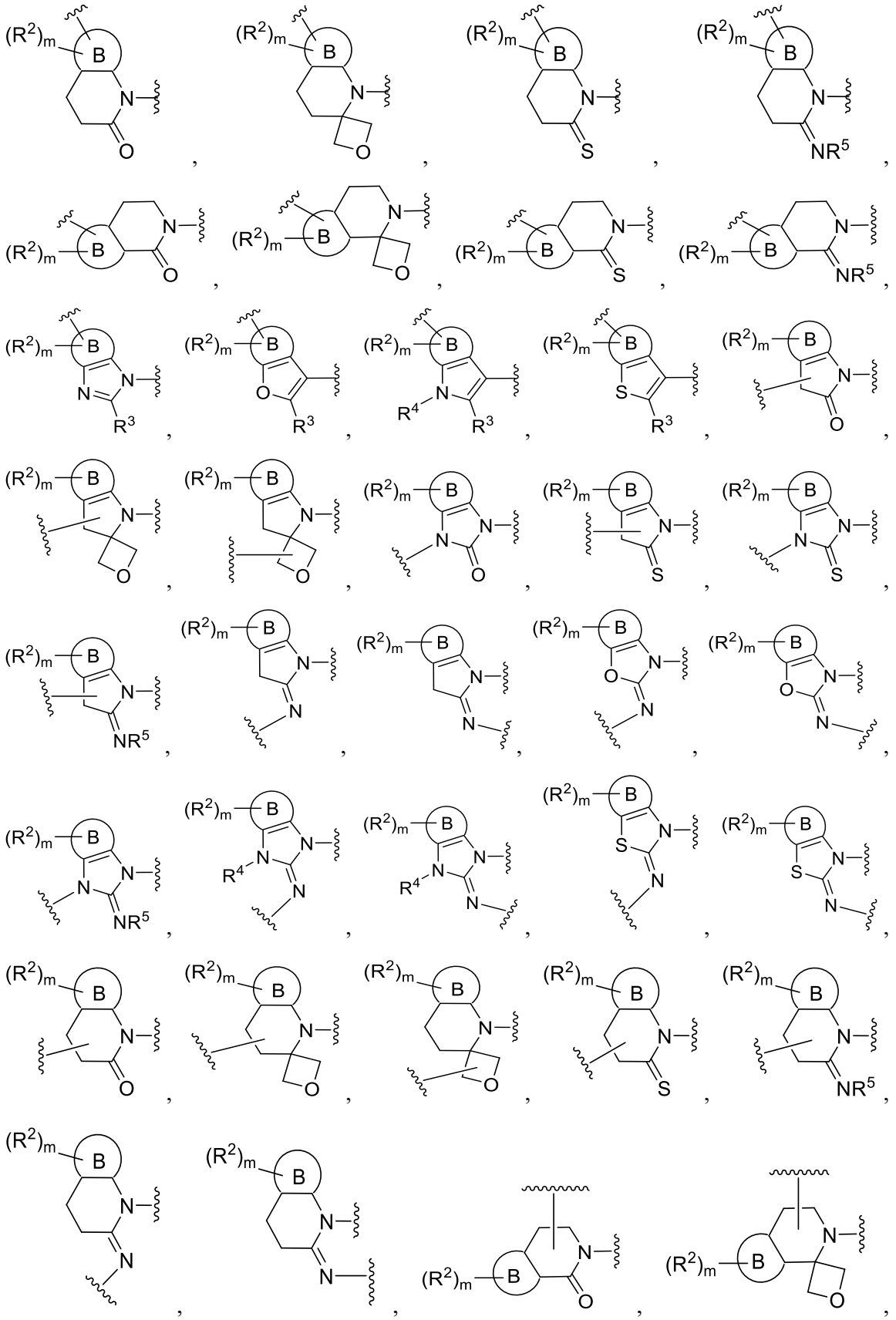
each R is independently hydrogen, or an optionally substituted group selected from C$_{1-6}$ aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4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

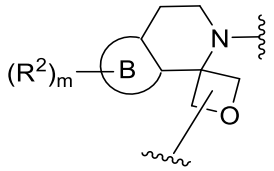
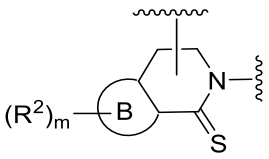
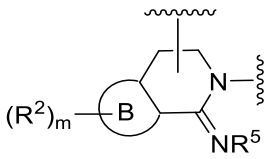
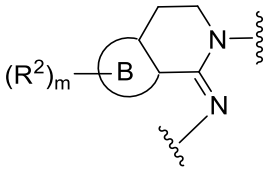
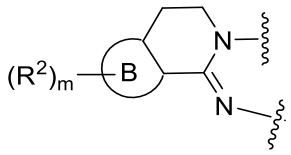
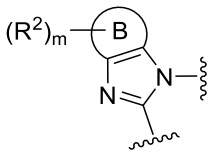
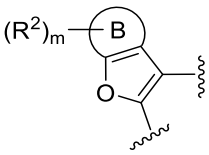
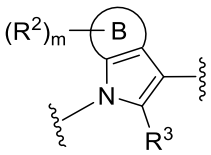
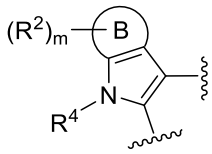
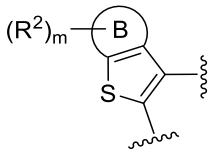
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

R^1 is hydrogen, halogen, –CN, –OR, –SR, –S(O)R, –S(O)$_2$R, –NR$_2$, –P(O)(OR)$_2$, –P(O)(NR$_2$)OR, –P(O)(NR$_2$)$_2$, –Si(OH)$_2$R, –Si(OH)R$_2$, –SiR$_3$, or an optionally substituted C$_{1-4}$ aliphatic;

each R^2 is independently hydrogen, R^6, halogen, –CN, –NO$_2$, –OR, -SR, -N(R)$_2$, -Si(R)$_3$, -S(O)$_2$R, -S(O)$_2$N(R)$_2$, -S(O)R, -C(O)R, -C(O)OR, –C(O)N(R)$_2$, -C(O)N(R)OR, -C(R)$_2$N(R)C(O)R, -C(R)$_2$N(R)C(O)N(R)$_2$, -OC(O)R, -OC(O)N(R)$_2$, -OP(O)R$_2$, -OP(O)(OR)$_2$, -OP(O)(OR)(NR$_2$), -OP(O)(NR$_2$)$_2$-, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)N(R)$_2$, –N(R)S(O)$_2$R, -NP(O)R$_2$, -N(R)P(O)(OR)$_2$, -N(R)P(O)(OR)(NR$_2$), -N(R)P(O)(NR$_2$)$_2$, or –N(R)S(O)$_2$R;

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




, 
, 
, 
, 
, 
, 
, 
, 
, 
, wherein

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

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

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

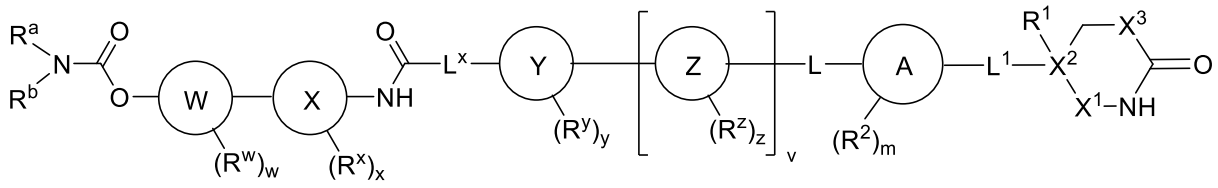
R^5 is hydrogen, C_{1-4} aliphatic, or –CN;

each R^6 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 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;

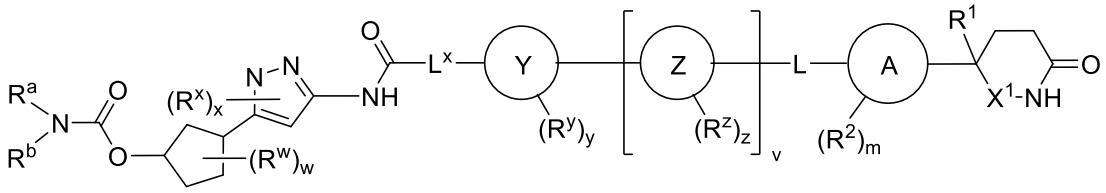
L^1 is a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, $-S(O)_2-$ or -(C)=CH-; and

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

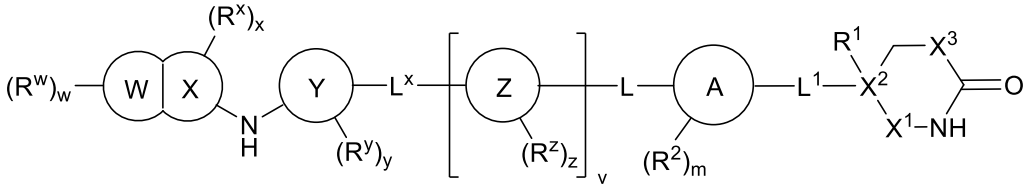
9. The compound of claim 8, wherein said compound is a compound of any of the following formulae:



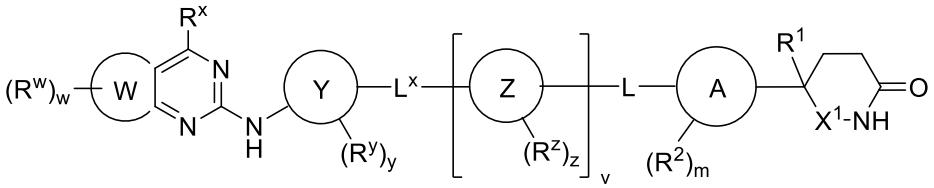
I-a-1



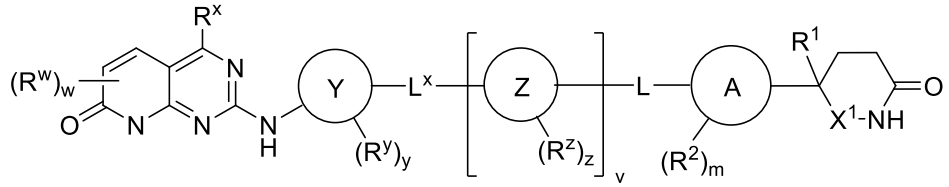
I-a-2



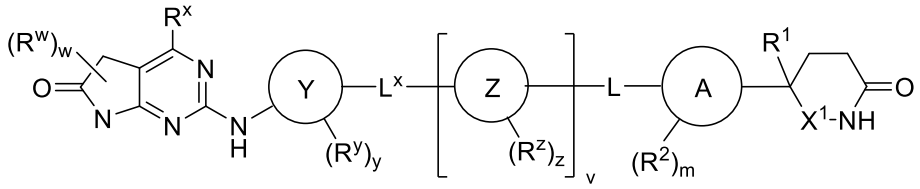
I-b-1



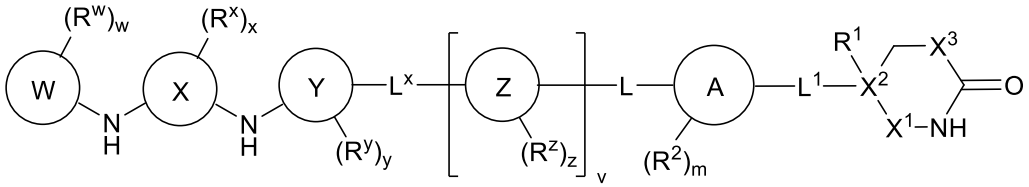
I-b-2



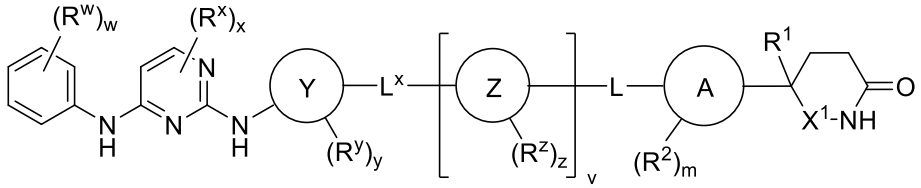
I-b-3



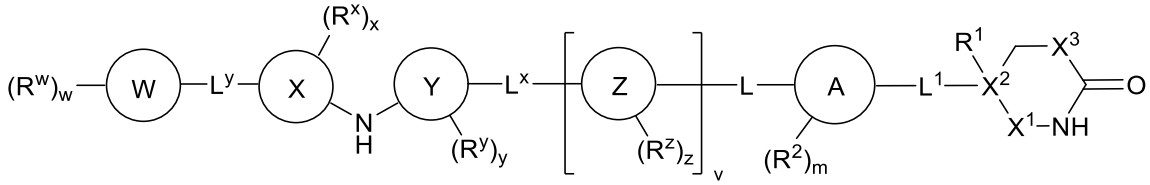
I-b-4



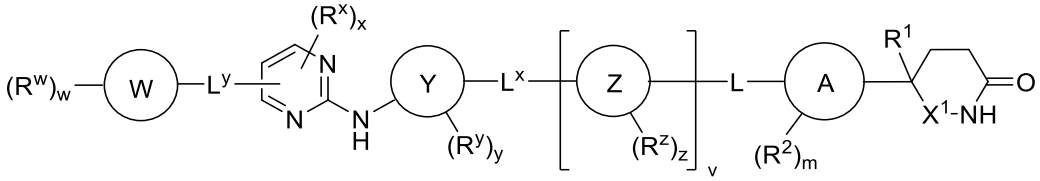
I-c-1



I-c-2



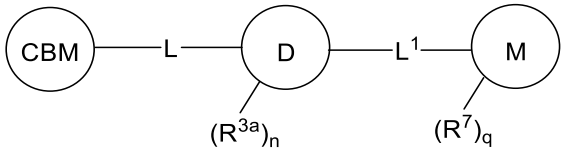
I-e-1



I-e-2

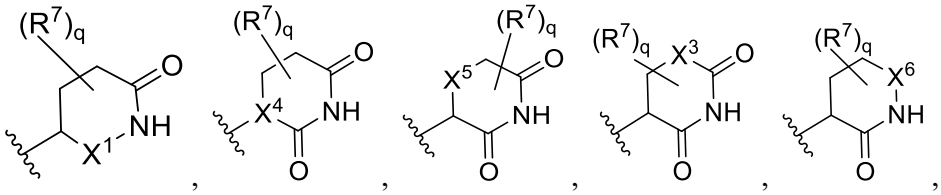
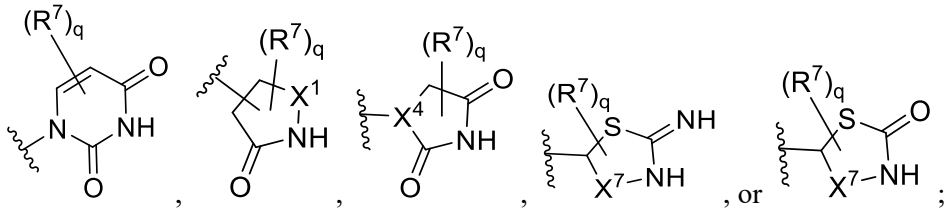
or pharmaceutically acceptable salt thereof.

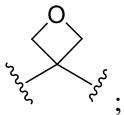
10. The compound of claim 6, wherein LBM is a cereblon E3 ubiquitin ligase binding moiety and said compound is of formula **I-nn**:



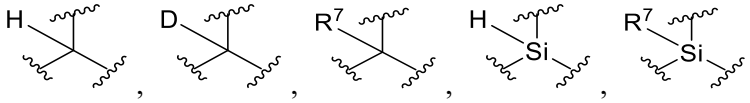
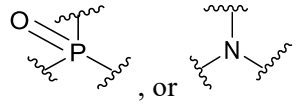
I-nn

or a pharmaceutically acceptable salt thereof, wherein:

Ring M is selected from  ,  , or ;

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

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

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

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

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

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

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

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

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

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

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

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

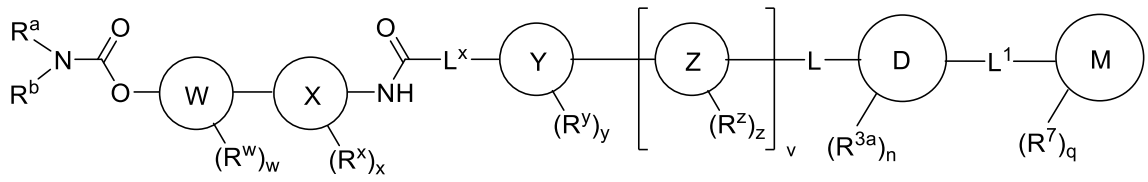
Ring D is selected from 6 to 10-membered aryl or heteroaryl containing 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 5 to 7-membered saturated or partially unsaturated carbocyclyl, 5 to 7-membered saturated or partially unsaturated heterocyclyl with 1-3 heteroatoms independently selected from boron, nitrogen, oxygen, silicon, and sulfur, or 5-membered heteroaryl with 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur;

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

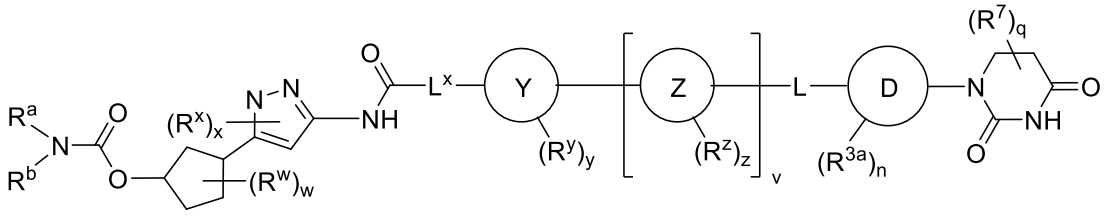
n is 0, 1, 2, 3, or 4; and

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

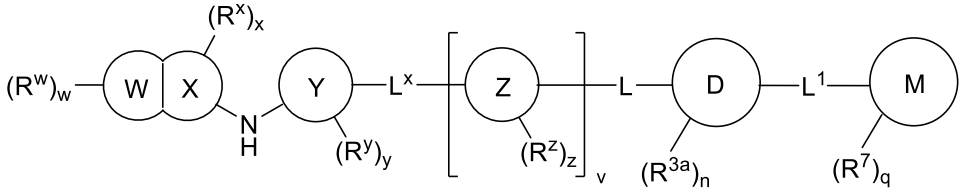
11. The compound of claim 10, wherein said compound is a compound of any of the following formulae:



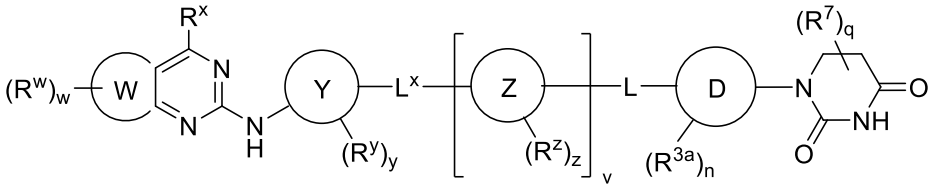
I-a-3



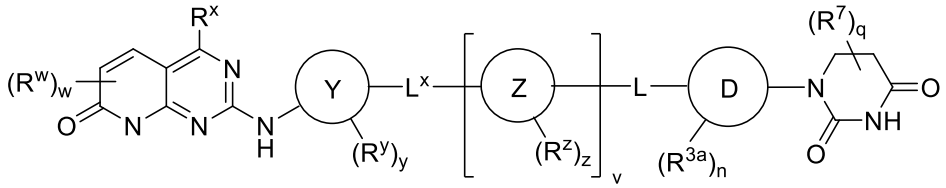
I-a-4



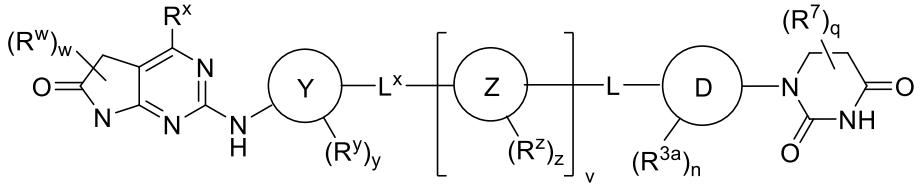
I-b-5



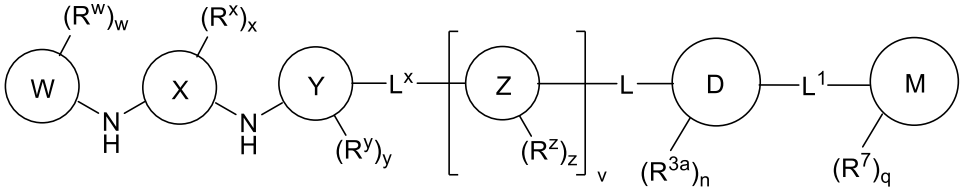
I-b-6



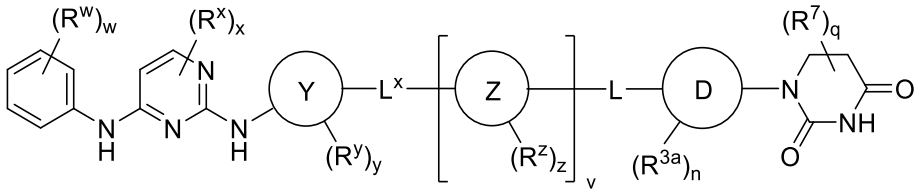
I-b-7



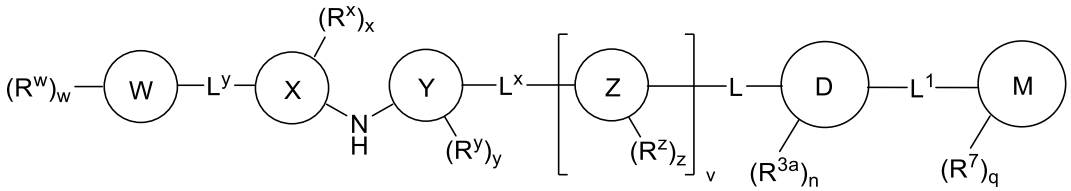
I-b-8



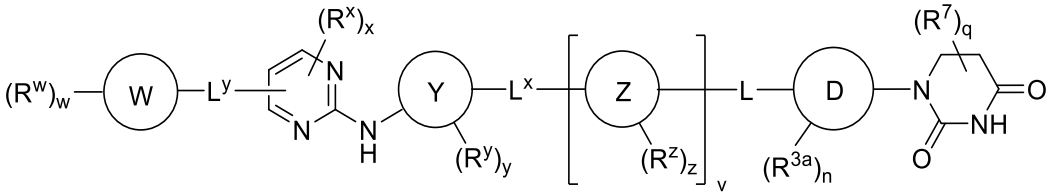
I-c-3



I-c-4



I-e-3

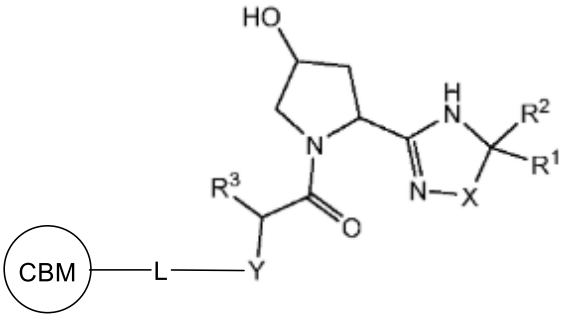


I-e-4

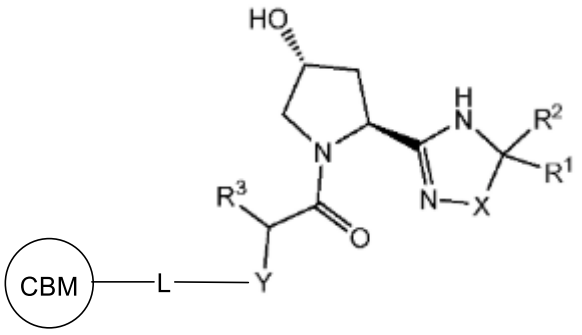
or pharmaceutically acceptable salt thereof.

12. The compound of claim 6, wherein LBM is a VHL E3 ubiquitin ligase binding moiety and said compound is selected from any of the following formulae:

(i)



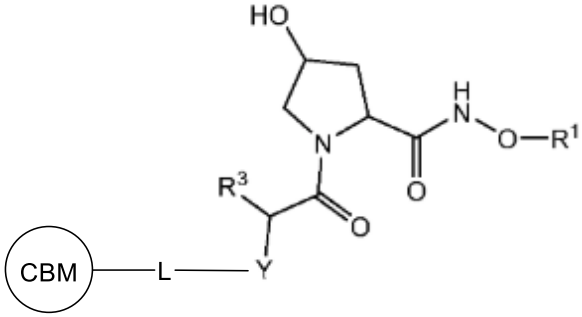
I-nnn-1



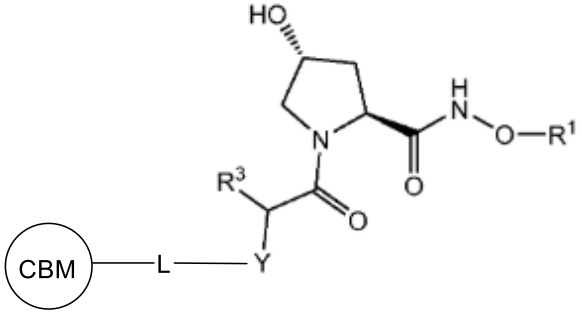
I-nnn-2

or a pharmaceutically acceptable salt thereof, wherein each of the variables R^1, R^2, R^3, X, and Y is as defined and described in WO 2019/084026;

(ii)



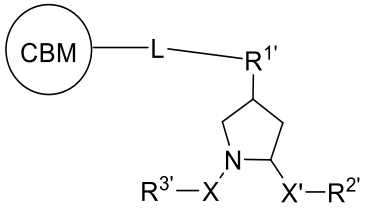
I-ooo-1



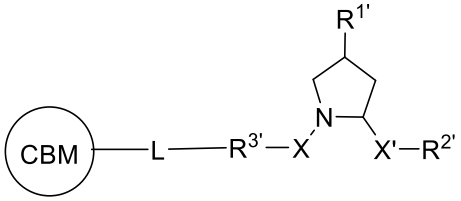
I-ooo-2

or a pharmaceutically acceptable salt thereof, wherein each of the variables R^1, R^3, and Y is as defined and described in WO 2019/084030;

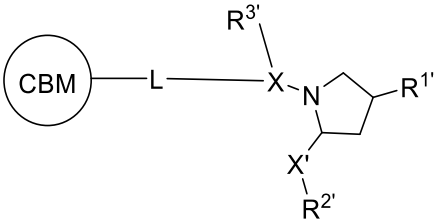
(iii)



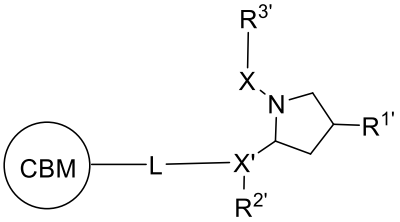
I-ww-1



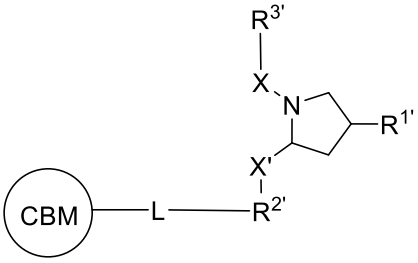
I-ww-2



I-ww-3



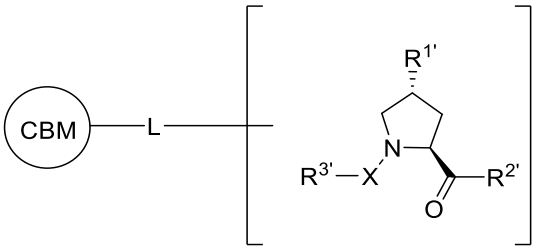
I-ww-4



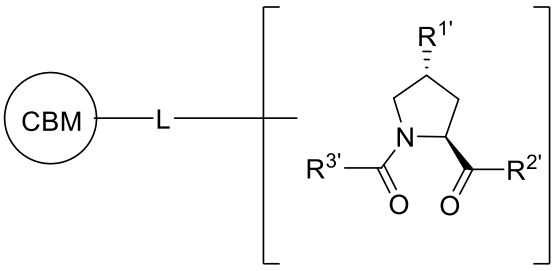
I-ww-5

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

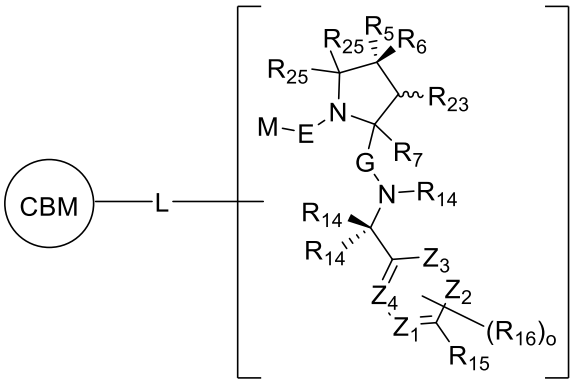
(iv)



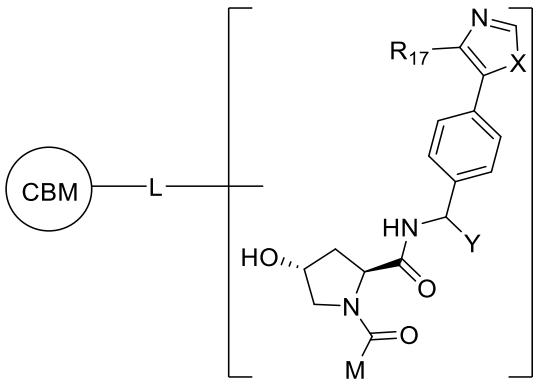
I-xx-1



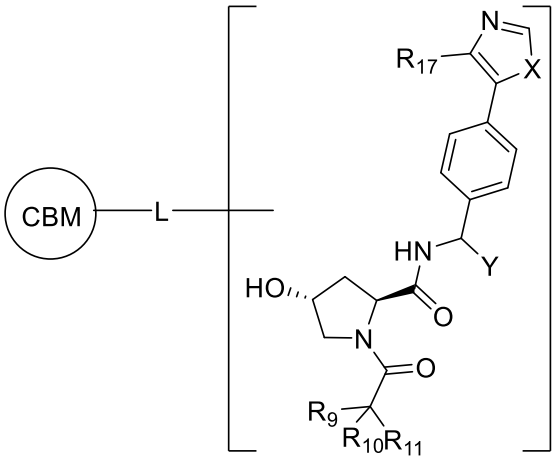
I-xx-2



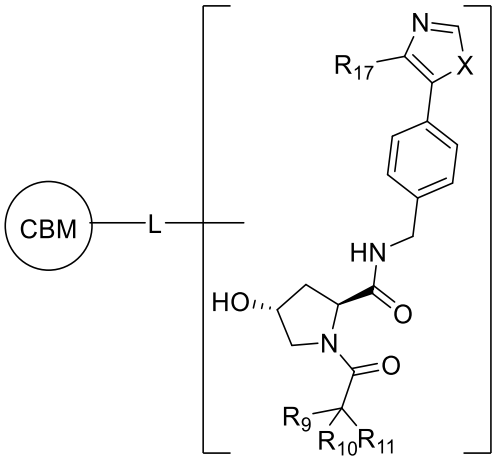
I-xx-3



I-xx-4



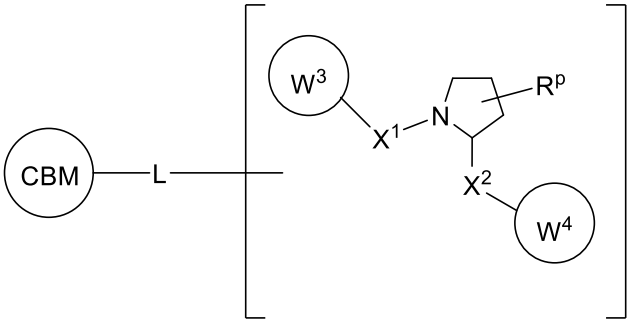
I-xx-5



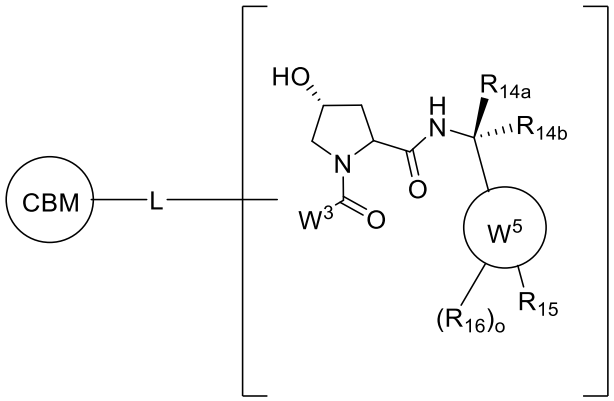
I-xx-6

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

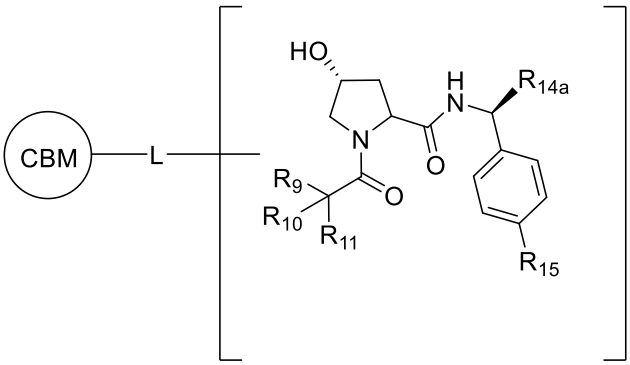
(v)



I-yy-1

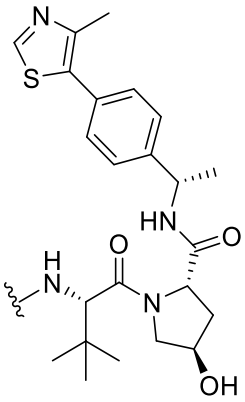
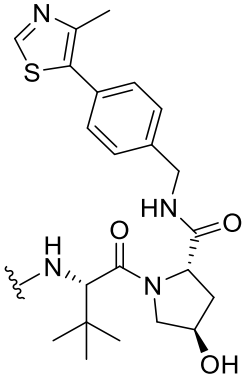
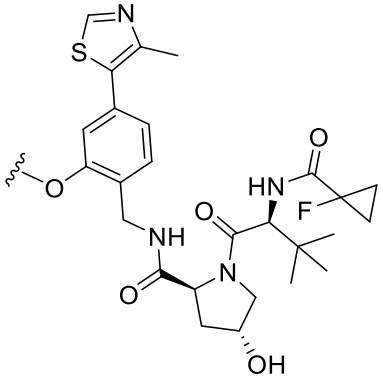


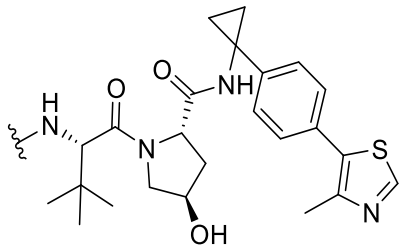
I-yy-2



I-yy-3

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

13. The compound of either claim 6 or claim 12, wherein the VHL E3 ubiquitin ligase binding moiety is selected from  ,  ,  ,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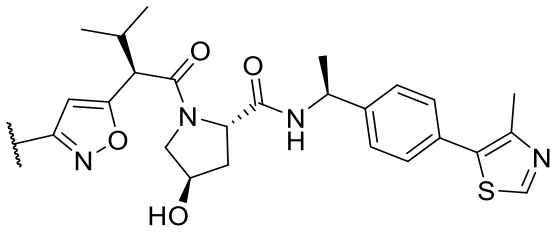
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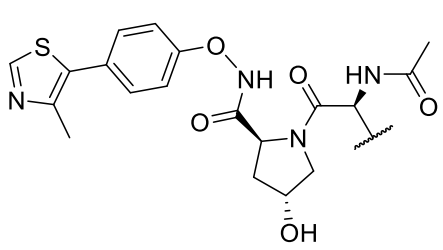
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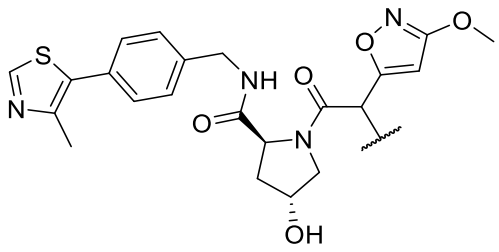
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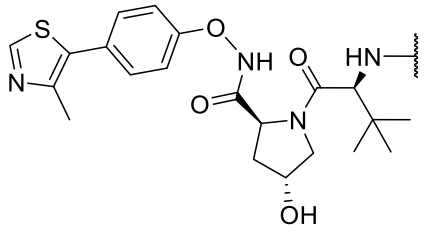
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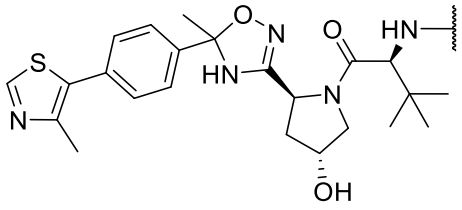
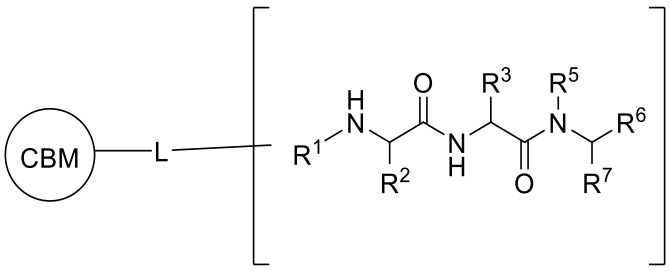
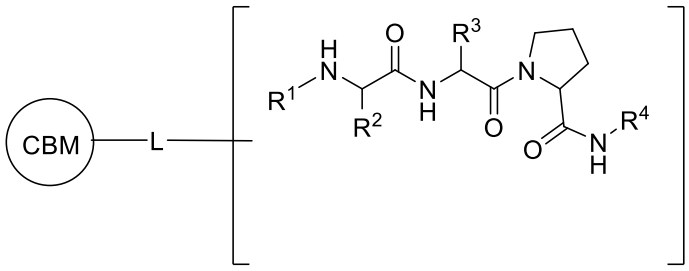

.

14. The compound of claim 6, wherein LBM is a IAP E3 ubiquitin ligase binding moiety and said compound is selected from any one of the following formulae:

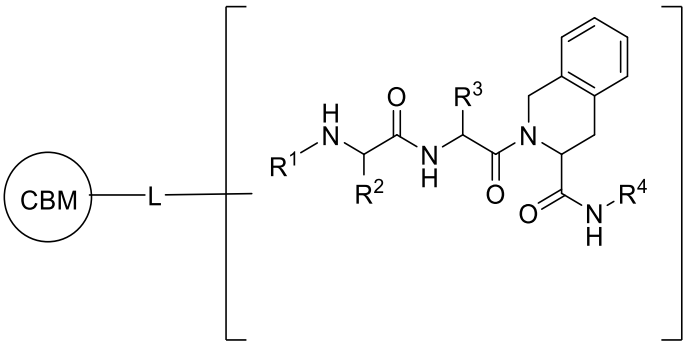
(*i*)



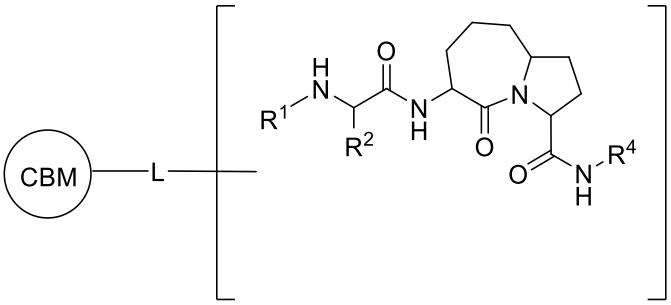
I-bbb-1



I-bbb-2



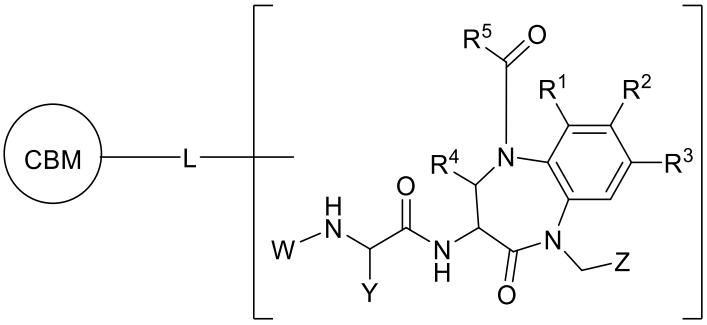
I-bbb-3



I-bbb-4

or a pharmaceutically acceptable salt thereof, wherein each of the variables R^1, R^2, R^3, R^4, R^5, R^6, and R^7, is as defined and described in WO 2017/011590 and US 2007/037004; and

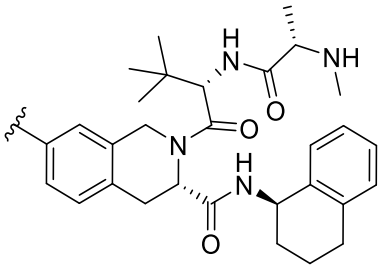
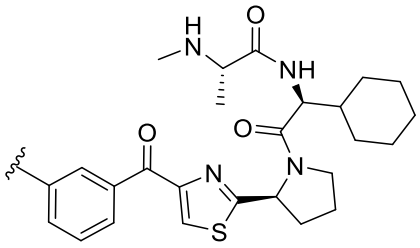
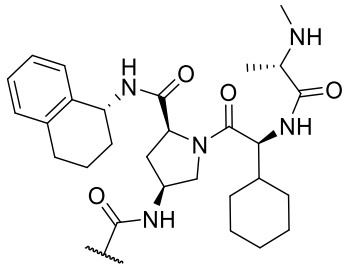
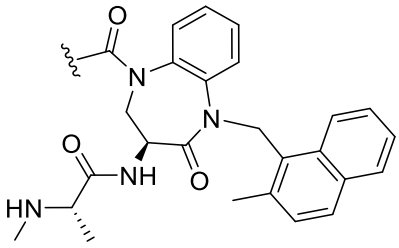
(*ii*)



I-fff

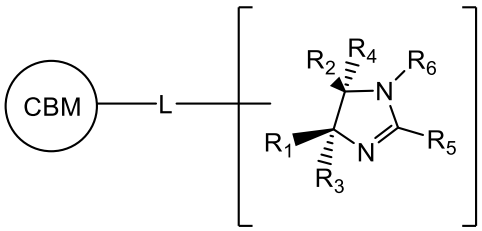
or a pharmaceutically acceptable salt thereof, wherein each of the variables W, Y, Z, R^1, R^2, R^3, R^4, and R^5 is as described and defined in WO 2014/044622, US 2015/0225449. WO 2015/071393, and US 2016/0272596.

15. The compound of claim 6 or claim 14, wherein the IAP E3 ubiquitin ligase binding moiety is

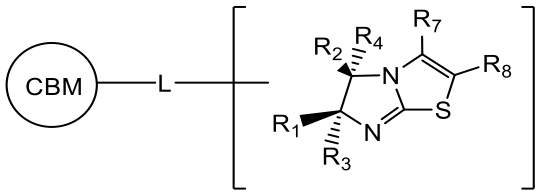
selected from  ,  ,  , and  .

16. The compound of claim 6, wherein LBM is an MDM2 E3 ubiquitin ligase binding moiety and said compound is selected from any one of the following formulae:

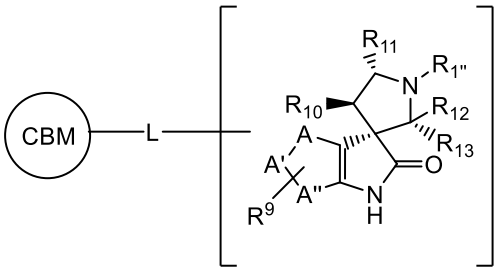
(*i*)



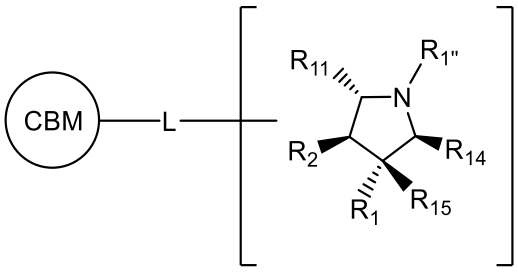
I-aaa-1



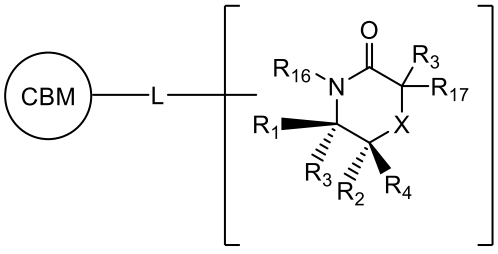
I-aaa-2



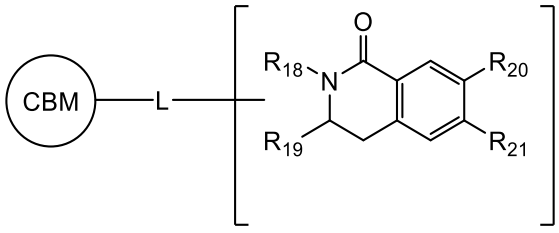
I-aaa-3



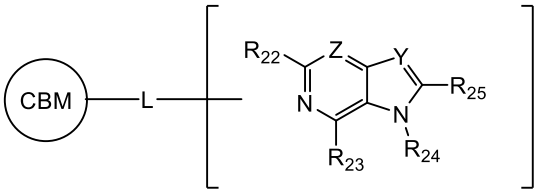
I-aaa-4



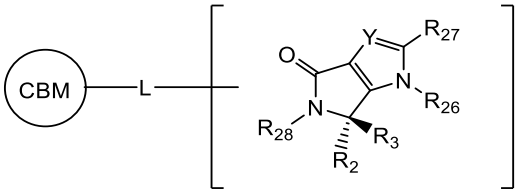
I-aaa-5



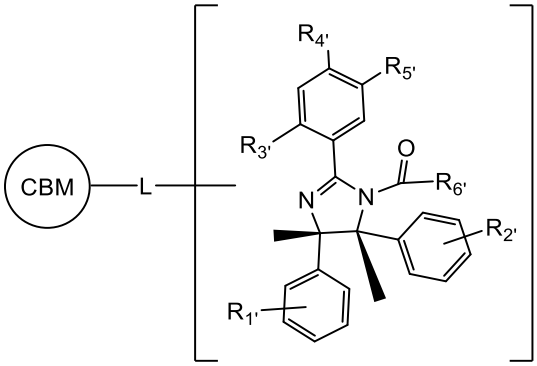
I-aaa-6



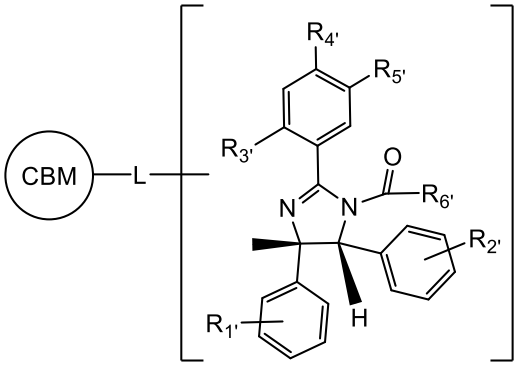
I-aaa-7



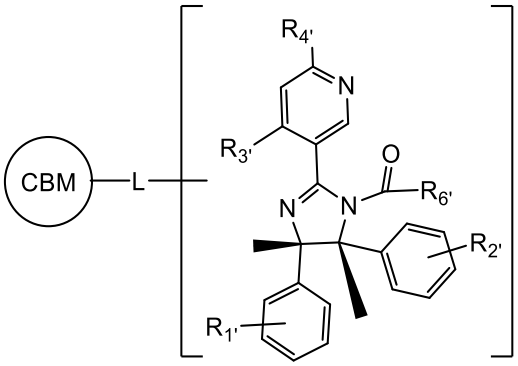
I-aaa-8



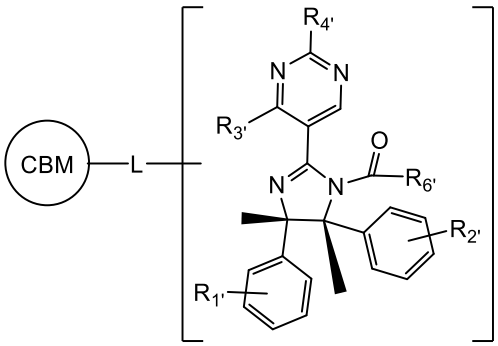
I-aaa-9



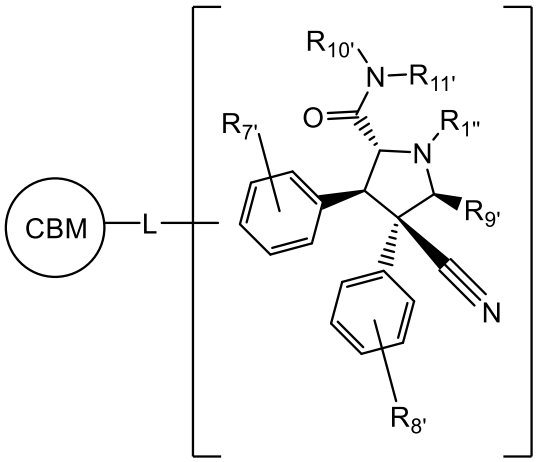
I-aaa-10



I-aaa-11



I-aaa-12



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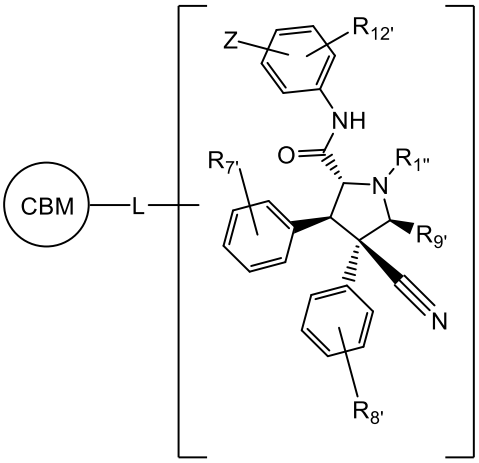

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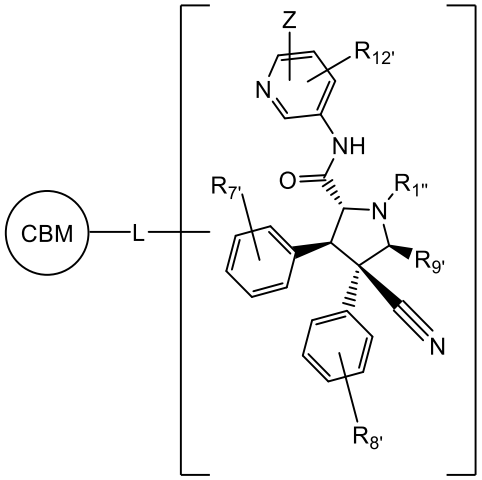

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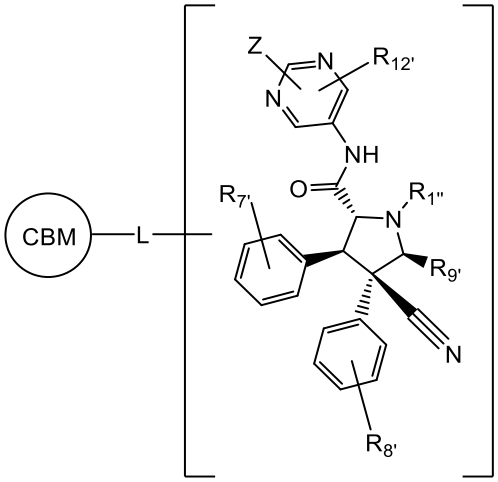

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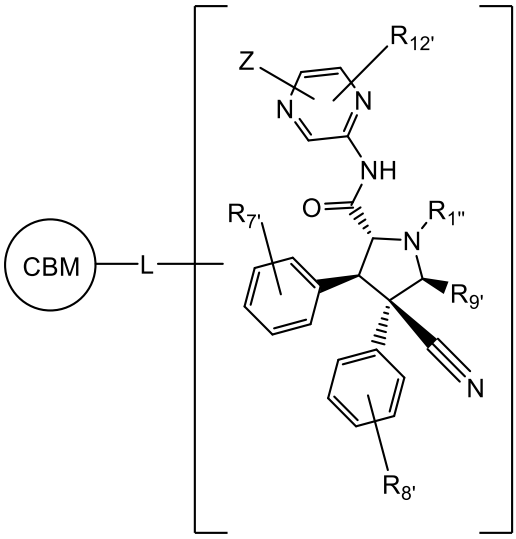

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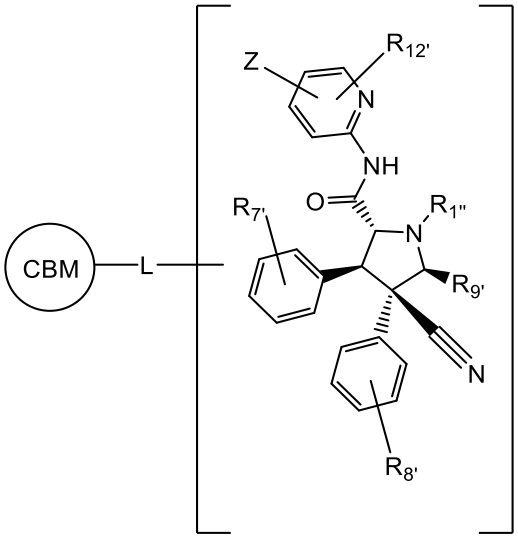
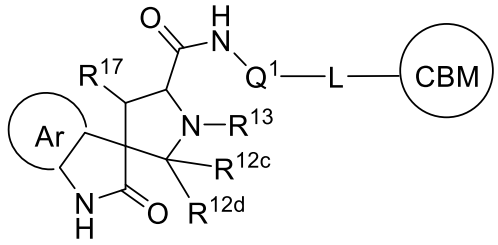


I-aaa-18

or a pharmaceutically acceptable salt thereof, wherein each of the variables R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, $R_{1'}$, $R_{2'}$, $R_{3'}$, $R_{4'}$, $R_{5'}$, $R_{6'}$, $R_{7'}$, $R_{8'}$, $R_{9'}$, $R_{10'}$, $R_{11'}$, $R_{12'}$, $R_{1''}$, A, A', A'', X, Y, and Z is as defined and described in WO 2017/011371 and US 2017/008904; and

(*ii*)



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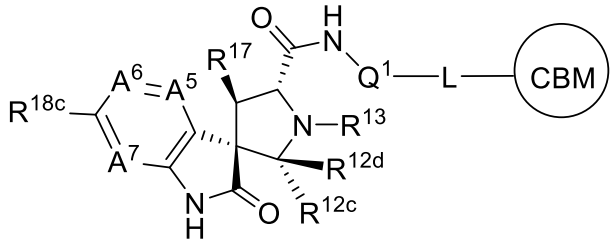
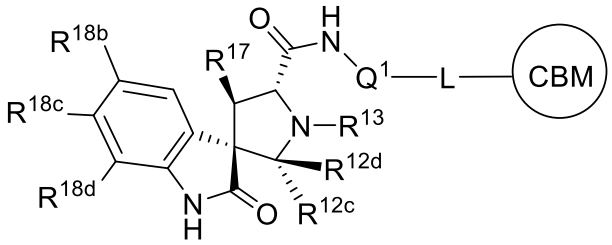
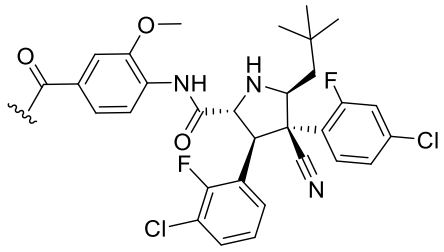
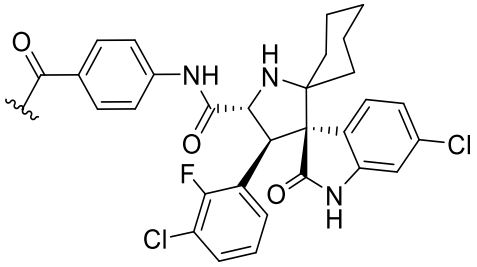
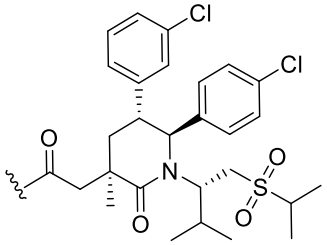
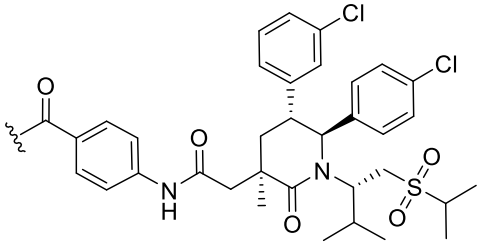
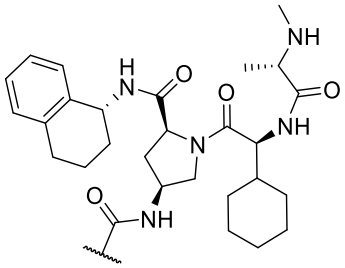
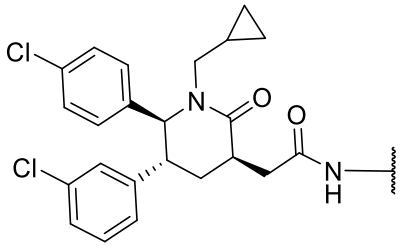
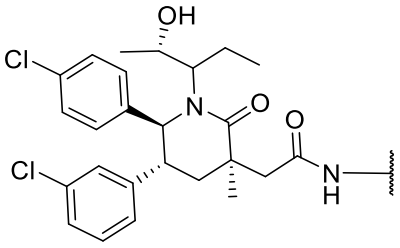
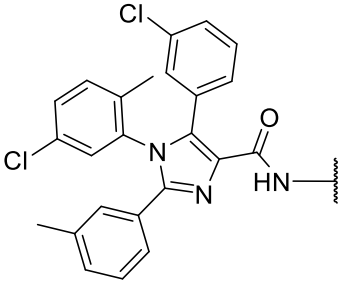


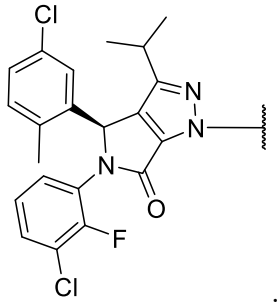
I-aaa-20



I-aaa-21

or a pharmaceutically acceptable salt thereof, wherein each of the variables R^{12c}, R^{12d}, R^{13}, R^{17}, R^{18b}, R^{18c}, R^{18d}, A^5, A^6, A^7, Q^1, and Ar is as defined and described in WO 2017/176957 and US2019/127387.

17. The compound of claim 6 or claim 16, wherein the MDM2 E3 ubiquitin ligase binding moiety is selected from  ,  ,  ,  ,  ,  ,  ,  , and



.

18. The compound of any one of claims 1-17, wherein 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-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, $-S(O)_2-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, –N(R)C(O)O-.

19. The compound of any one of claims 1-18, wherein said compound is selected from any one of the compounds depicted in **Table 1**, or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising a compound of any one of claims 1-19, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

21. The pharmaceutical composition of claim 20, further comprising an additional therapeutic agent.

22. Use of a compound of any one of claims 1-19, or a pharmaceutical composition thereof, in the manufacture of a medicament for inhibiting or degrading CDK2 in a patient or biological sample.

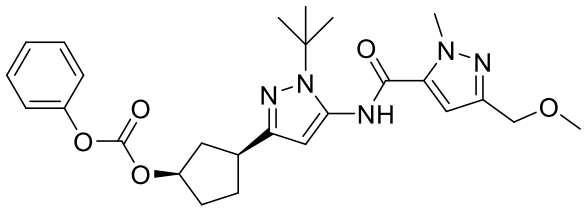
23. Use of a compound of any one claims 1-19, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating a CDK2-mediated disorder, disease, or condition in a patient.

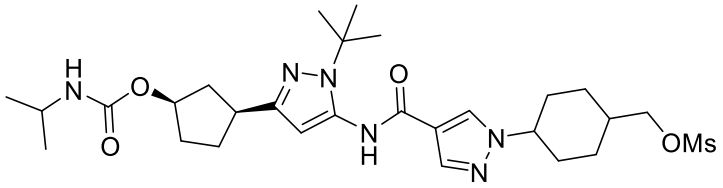
24. The use of claim 23, wherein CDK2-mediated disorder, disease, or condition is cancer.

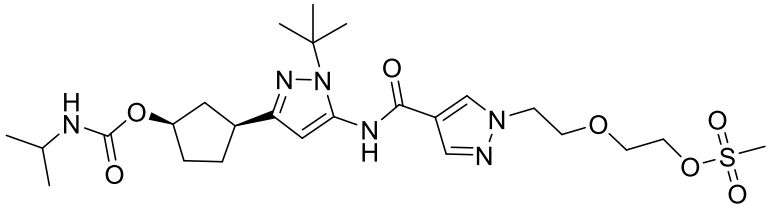
25. The use of claim 24, wherein the cancer is characterized by amplification or overexpression of CCNE1.

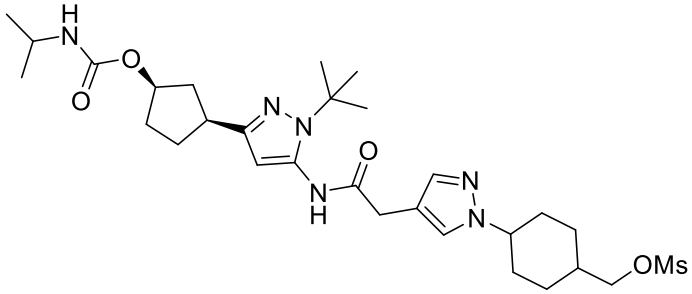
26. A compound of any one claims 1-19, or a pharmaceutical composition thereof, for use in therapy.

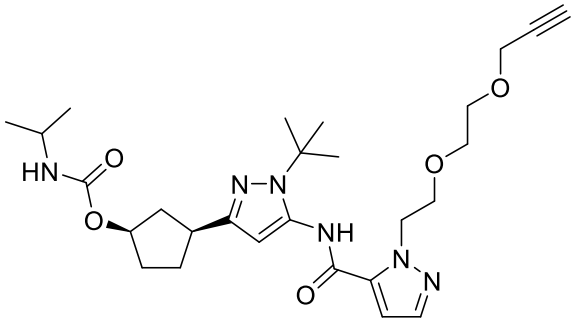
27. A compound of any of the following formulae:

P 

R 

BR 

V 

X 

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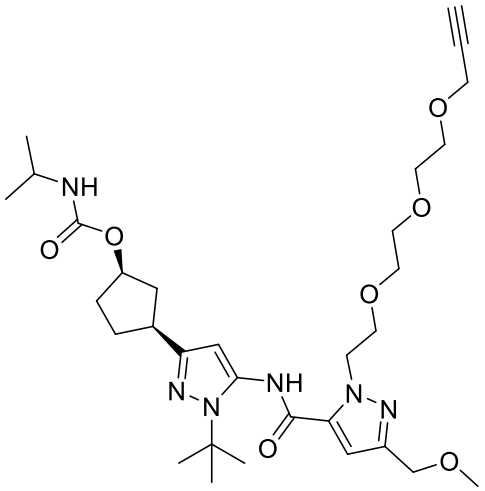

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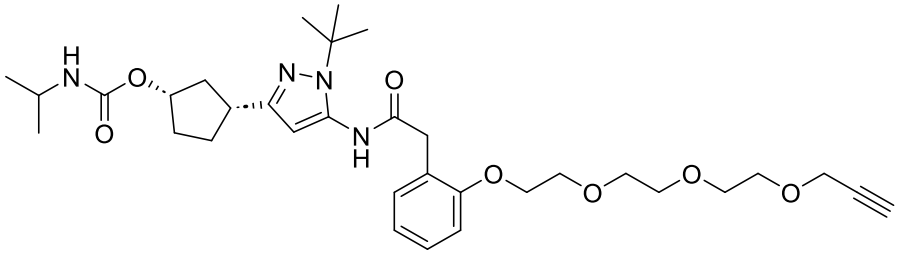

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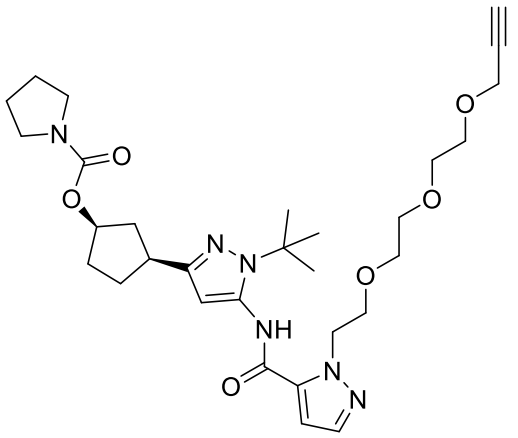

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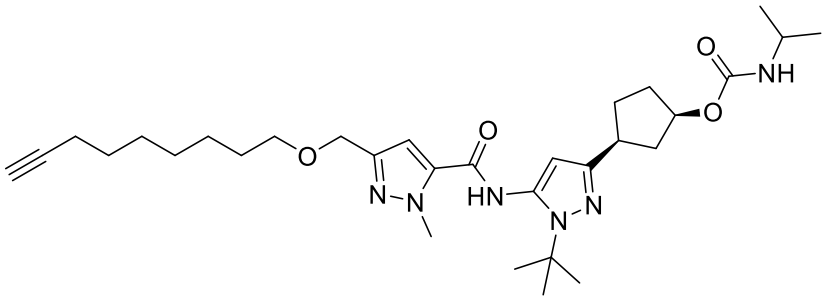

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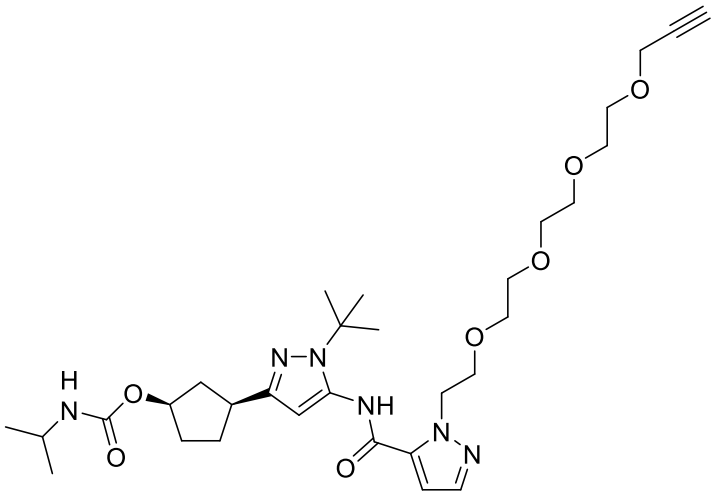

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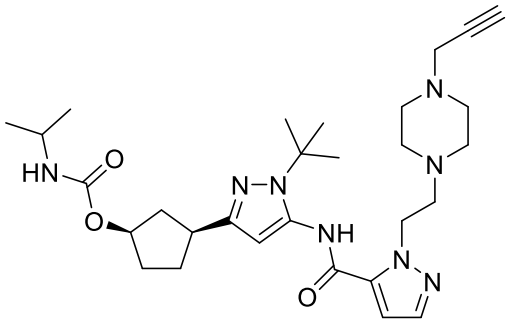

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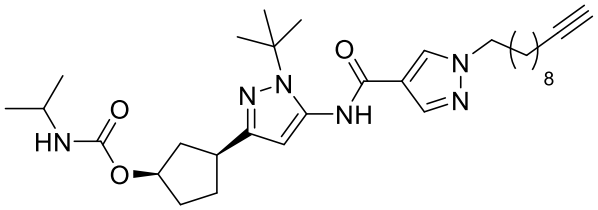

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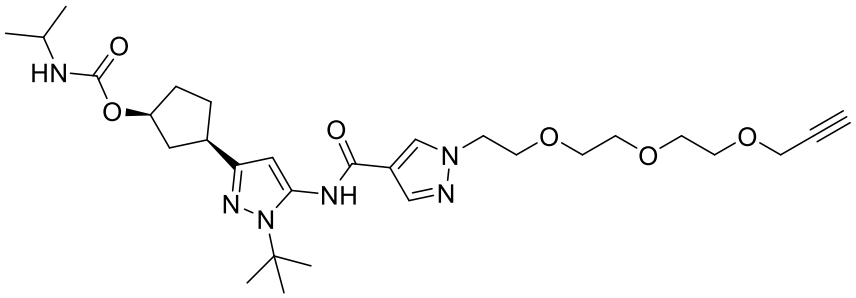

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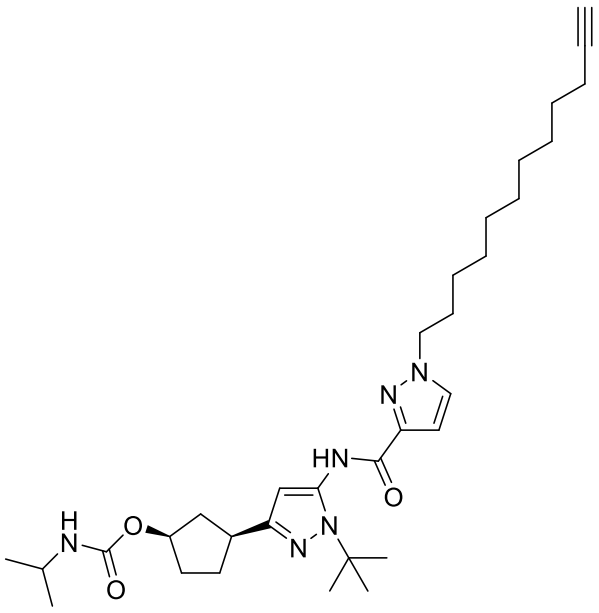

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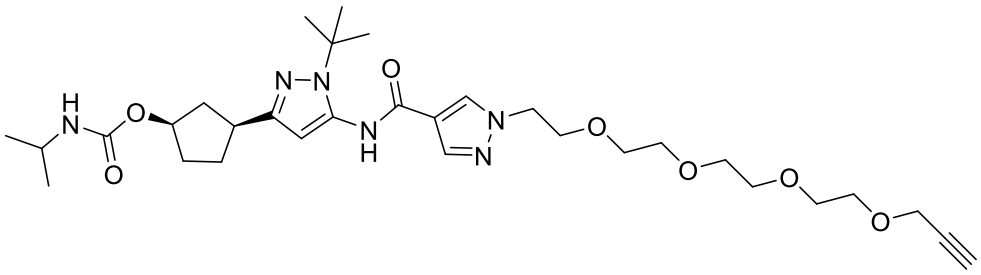

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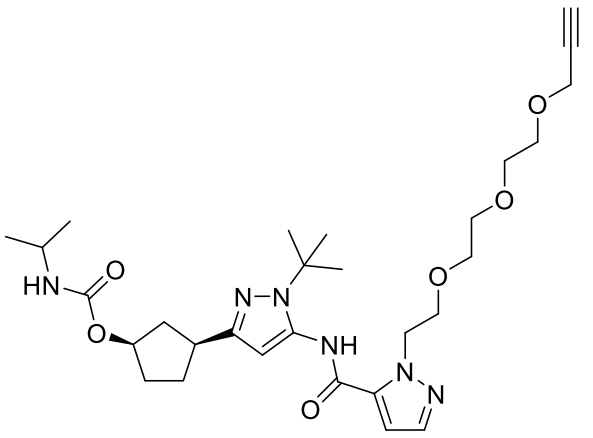

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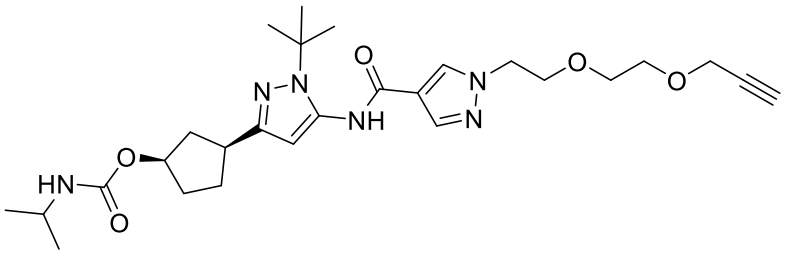
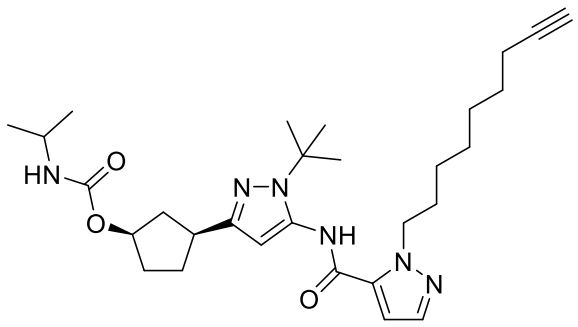
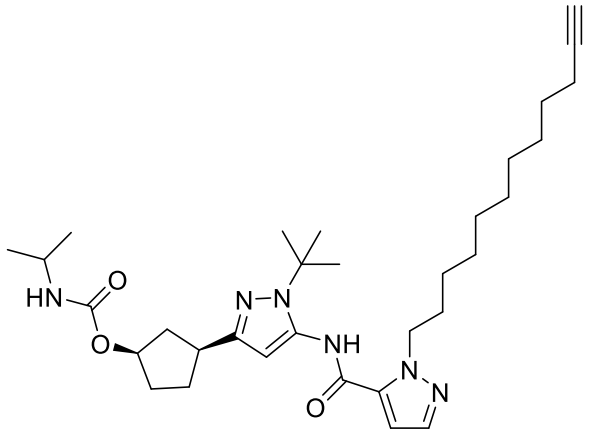
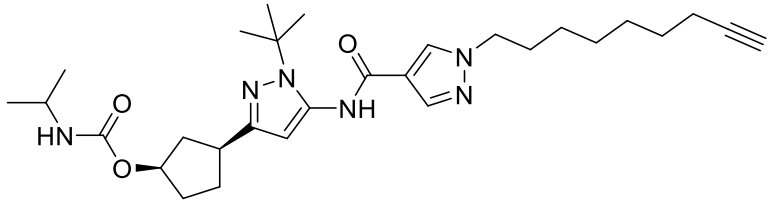
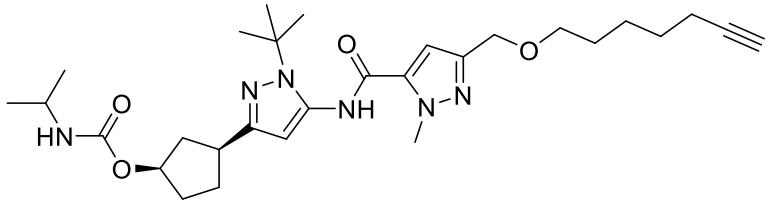
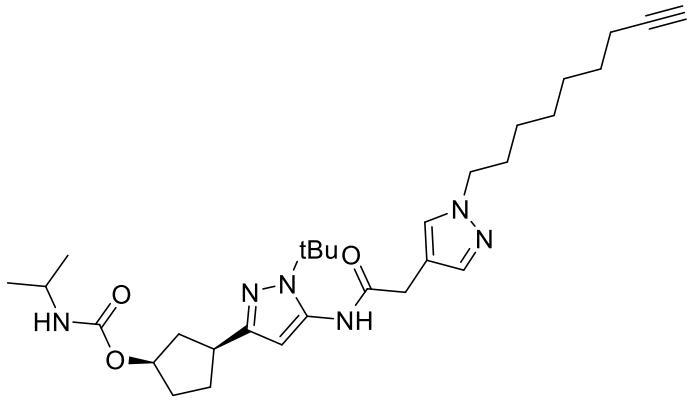


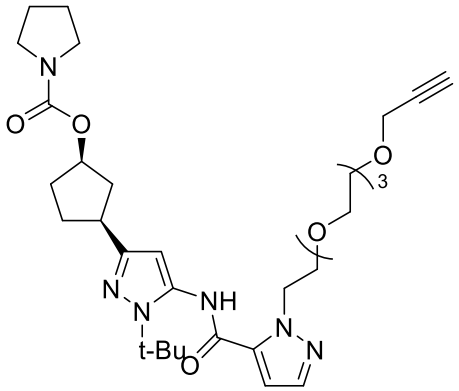
AB 

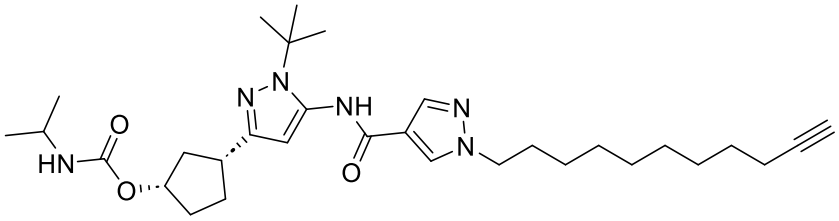
AM 

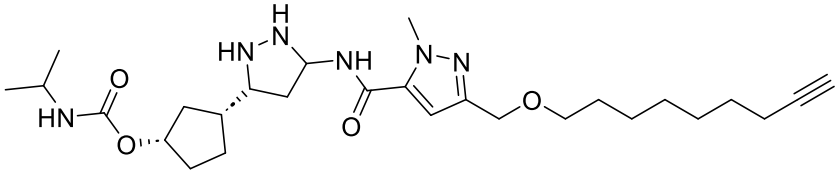
BD 

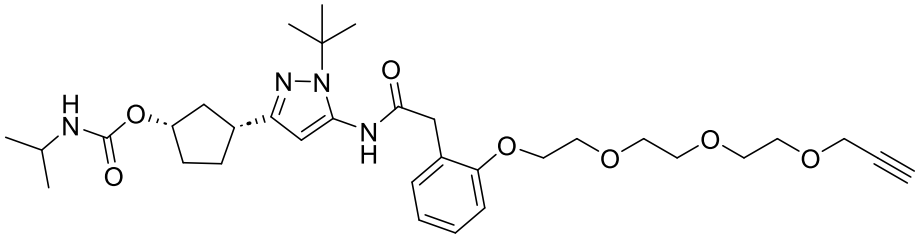
AP 

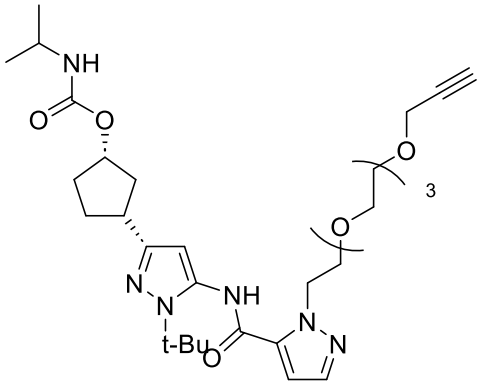
AX 

FV 

FA 

EW 

EV 

EQ 

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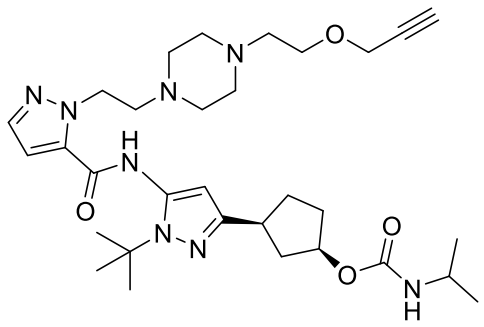

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