by an E3 ubiquitin ligase that binds to a protein and adds ubiquitin molecules to the protein. The E3 ubiquitin ligase is part of a pathway that includes E1 and E2 ubiquitin ligases, which make ubiquitin available to the E3 ubiquitin ligase to add to the protein.

To harness this degradation pathway, molecular constructs known as chemical inducers of degradation (CIDEs) bring together an E3 ubiquitin ligase with a protein that is to be targeted for degradation. To facilitate a protein for degradation by the proteasome, the CIDE is comprised of a group that binds to an E3 ubiquitin ligase and a group that binds to the protein target for degradation. These groups are typically connected with a linker. This CIDE can bring the E3 ubiquitin ligase in proximity with the protein so that it is ubiquitinated and marked for degradation. However, the relatively large size of the CIDE can be problematic for targeted delivery, as well as contribute to undesirable properties, such as fast metabolism/clearance, short half-life, and low bioavailability.

There is an ongoing need in the art for improving CIDEs, including enhancing targeted delivery of CIDEs to cells that contain the protein target. The subject matter described herein addresses this and other shortcomings in the art.

BRIEF SUMMARY

In one ~~aspect~~example, the subject matter described herein is directed to conjugated or covalently linked Ab-CIDEs, wherein the positions of the covalent bonds that connect the components of the Ab-CIDE: Antibody (Ab), Linker 1 (L1), Linker 2 (L2), protein binding group (PB) and the E3 ligase binding group (E3LB), can be tailored as desired to prepare Ab-CIDEs having desirable properties, such as potency, in vivo pharmacokinetics, stability and solubility.

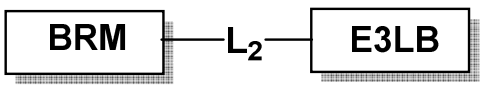
In one ~~aspect~~example, the subject matter described herein is directed to an Ab-CIDE having the chemical structure:

$$Ab\text{-}(L1\text{-}D)_p,$$

wherein,

Ab is an antibody;

D is a CIDE, or prodrug thereof, having the structure:



wherein,

BRM is a residue of a BRM-binding compound,

E3LB is a residue of an E3 ligase-binding compound, and
L2 is a moiety covalently linking BRM with E3LB;
L1 is a linker-1 covalently linking Ab to one of BRM, E3LB or L2; and
p is 1 to 16.

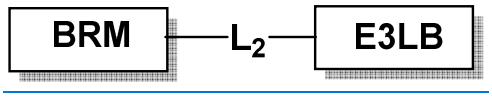
In one aspect, the disclosure provides a conjugate having the structure:

$$Ab\text{-}(L1\text{-}D)_p,$$

wherein,

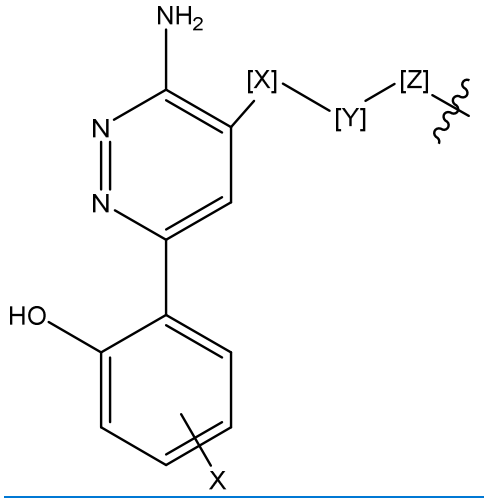
Ab is an antibody;

D is a CIDE, or prodrug thereof, the CIDE having the structure:

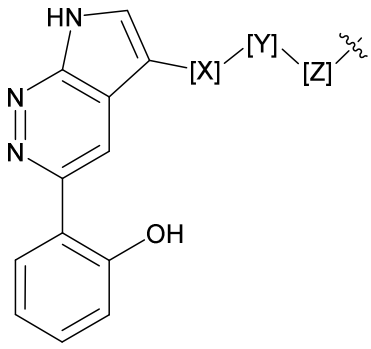


wherein,

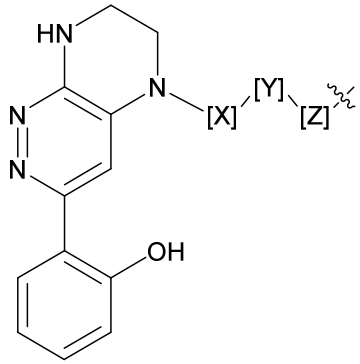
BRM is a residue of a BRM-binding compound, wherein the residue of a BRM-binding compound is a compound of formula (I-A), formula (I-B), formula (I-C), formula (I-D), or formula (I-E):



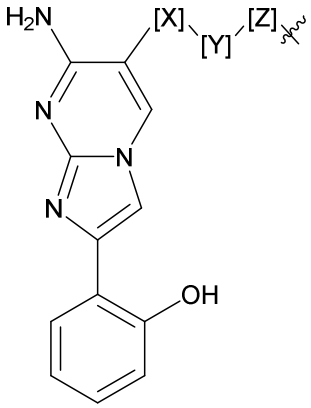
(I-A),



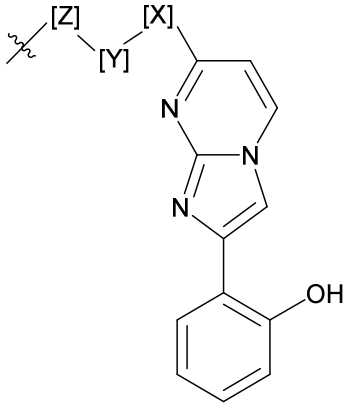
(I-B),



(I-C),



(I-D), wherein X is hydrogen or halogen; or



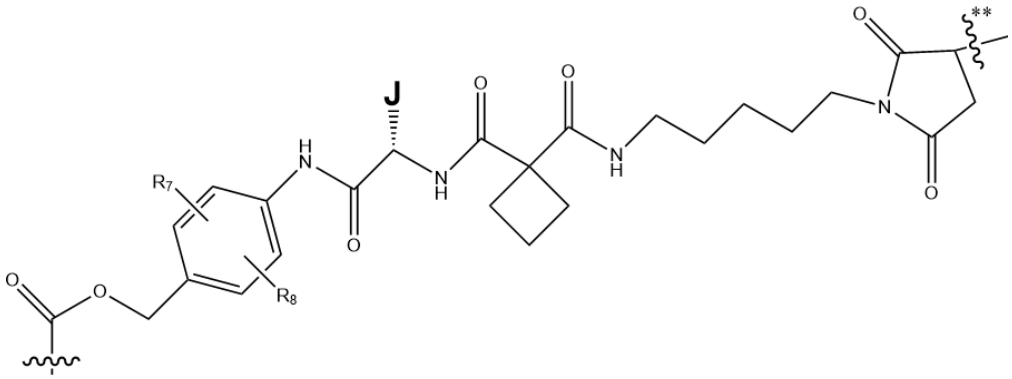
(I-E);

E3LB is a residue of an E3 ligase-binding compound, and

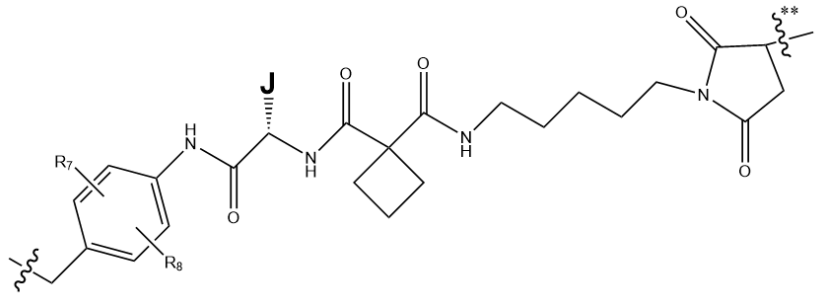
L2 is a linker covalently linking BRM and E3LB;

L1 is a linker covalently linking Ab to BRM, E3LB or L2;

wherein L1 is selected from the group consisting of:



, and



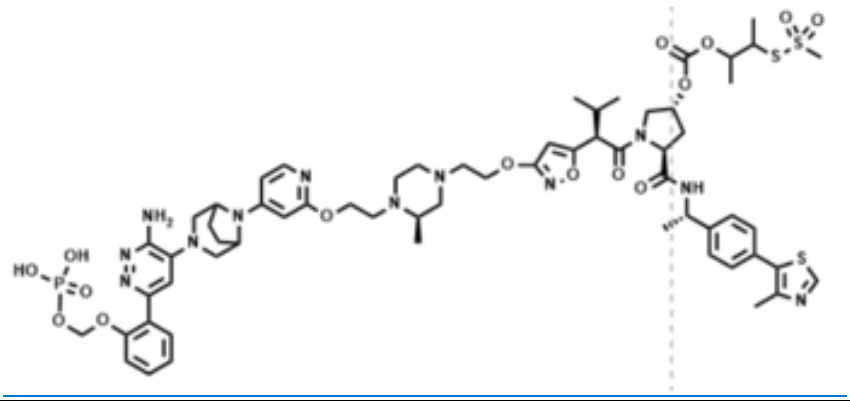
wherein,

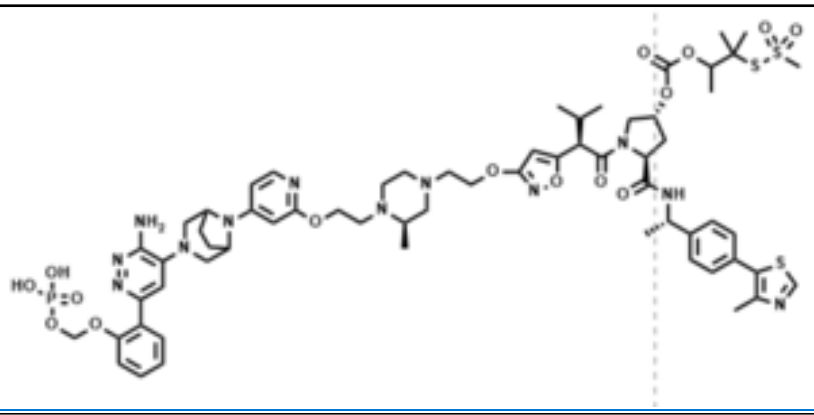
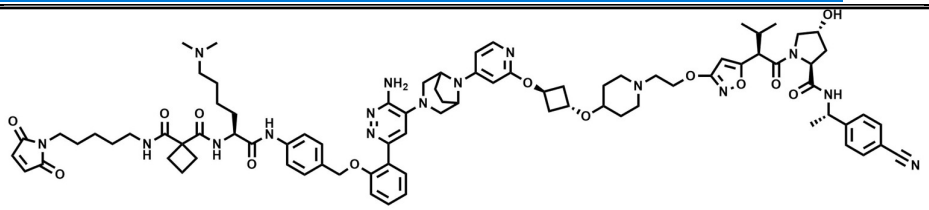
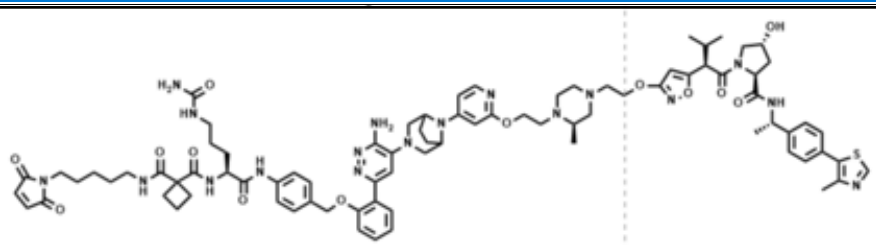
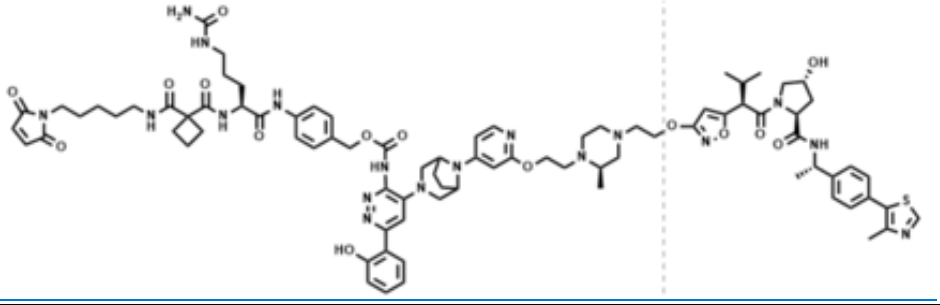
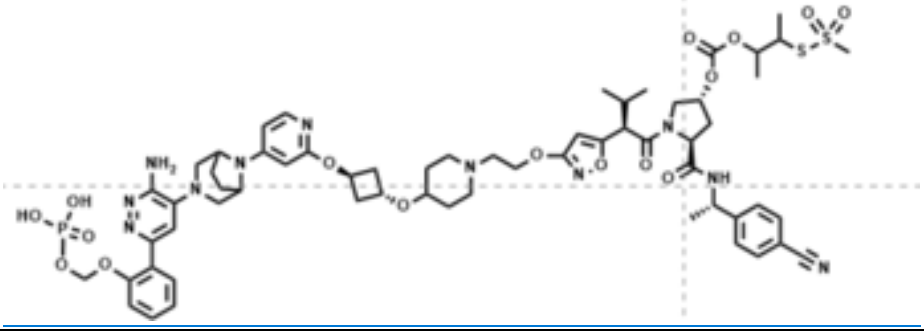
J is —CH_2-CH_2-CH_2-NH-C(O)-NH_2; —CH_2-CH_2-CH_2-CH_2-NH_2; —CH_2-CH_2-CH_2-CH_2-NH-CH_3; or —CH_2-CH_2-CH_2-CH_2-$N(CH_3)_2$; and

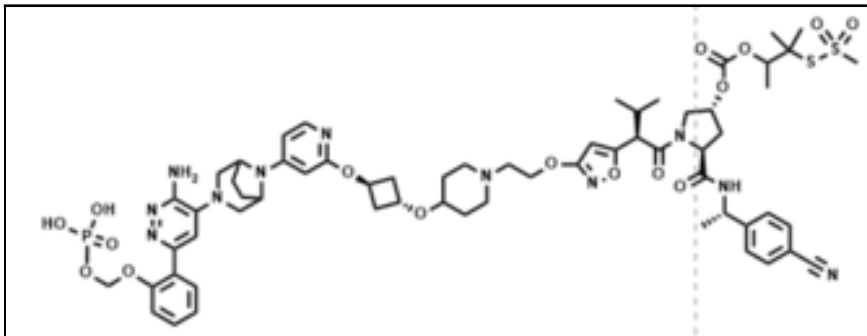
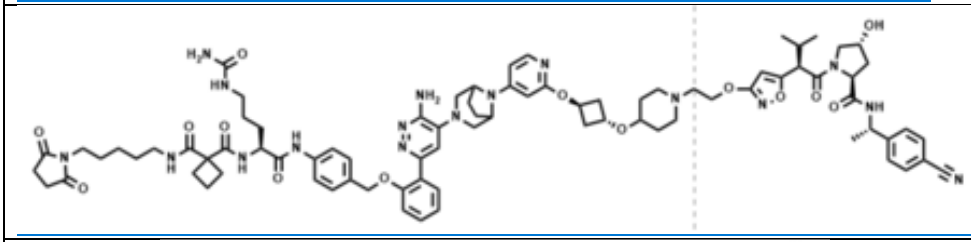
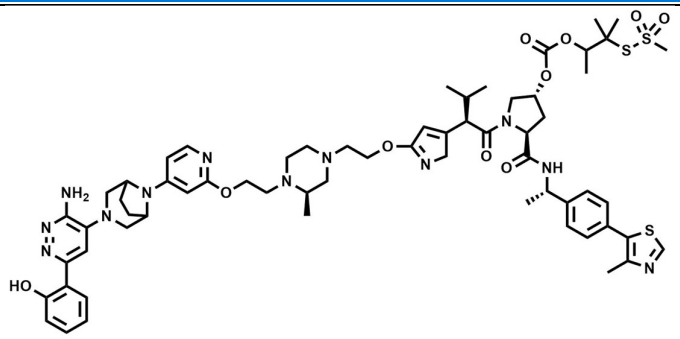
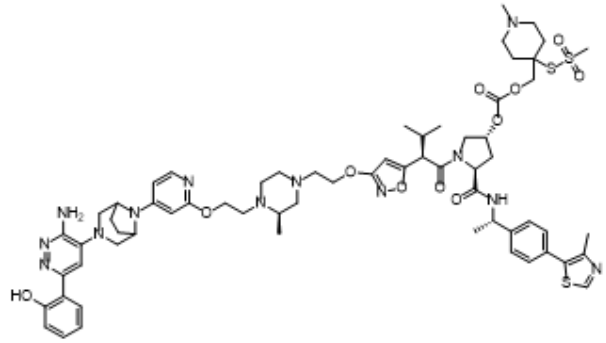
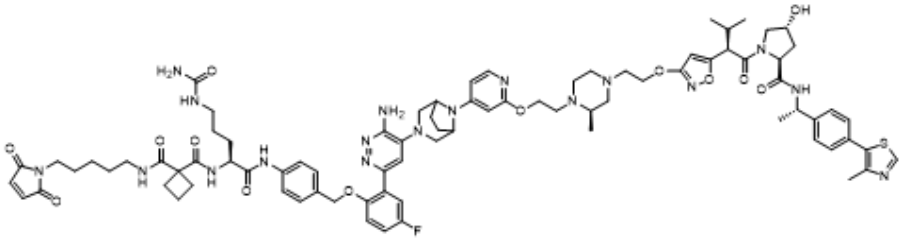
R_7 and R_8 are each independently hydrogen, halo, C_{1-5} alkyl, C_{1-5} alkoxy or hydroxy; and

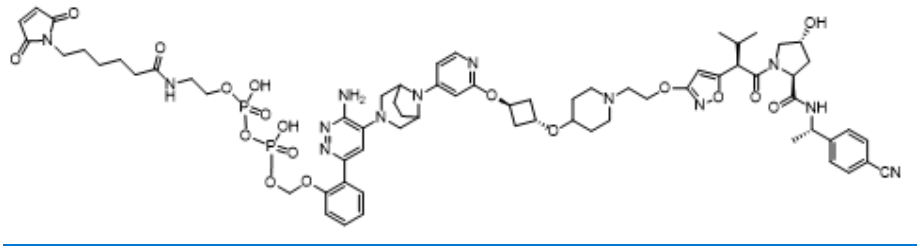
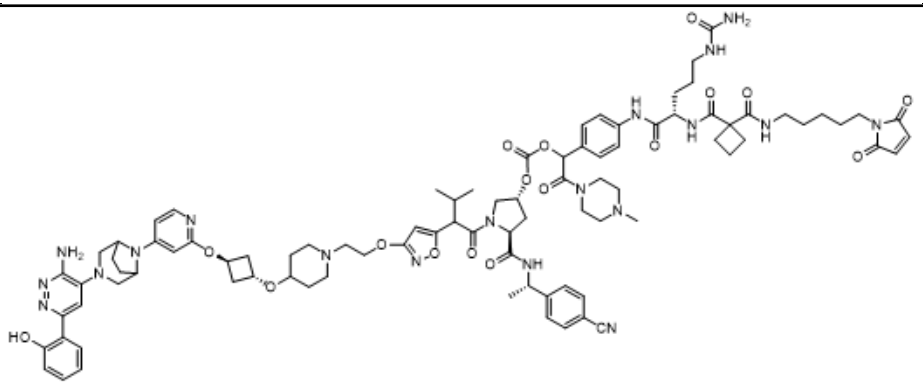
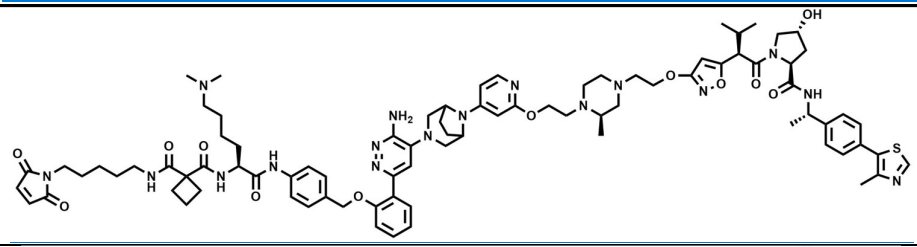
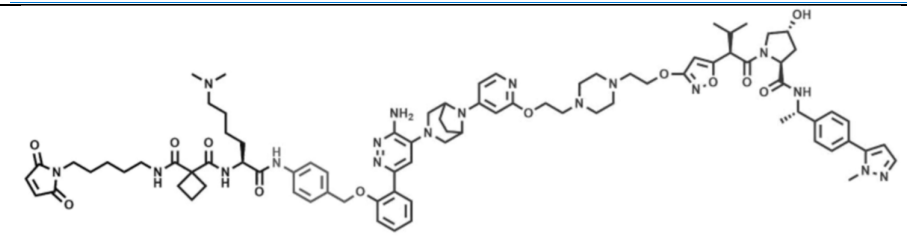
p has a value from about 1 to about 16.

In another aspect, the diclsoure provides a compound, selected from the group consisting of:

	L1-CIDE-BRM1-10

	L1-CIDE-BRM1-9
	L1-CIDE-BRM1-19
	L1-CIDE-BRM1-13
	L1-CIDE-BRM1-20
	L1-CIDE-BRM1-11

	L1-CIDE-BRM1-12
	L1-CIDE-BRM1-14
	L1-CIDE-BRM1-7
	L1-CIDE-BRM1-8
	L1-CIDE-BRM1-16

	L1-CIDE-BRM1-17
	L1-CIDE-BRM1-18
	L1-CIDE-BRM1-21
	L1-CIDE-BRM1-22

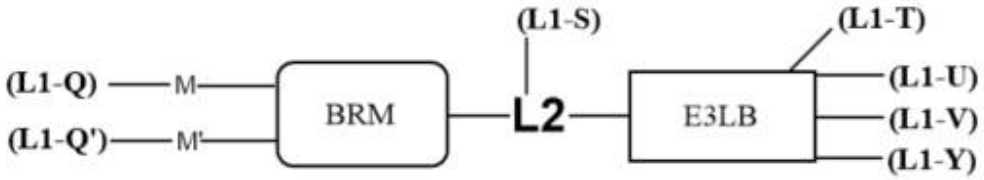
In another ~~aspect~~example, the subject matter described herein is directed to an Ab-CIDE having the chemical structure:

$$Ab\text{-}(L1\text{-}D)_p,$$

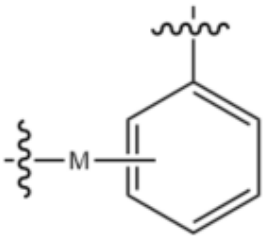
wherein,

Ab is an antibody;

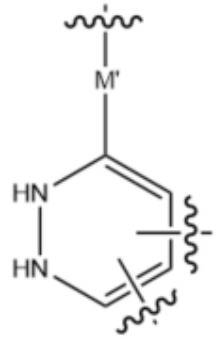
D is a CIDE, or prodrug thereof, having the structure:



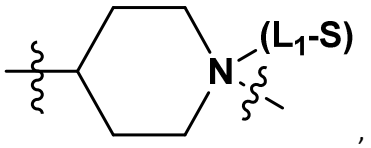
wherein L1 is attached at one attachment point selected from L1-Q, L1-Q', L1-S, L1-T, and optionally L1-U, L1-V and L1-Y, if present, wherein

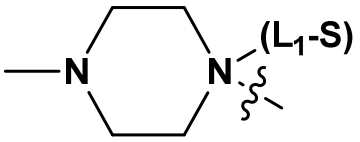
L1Q is at 

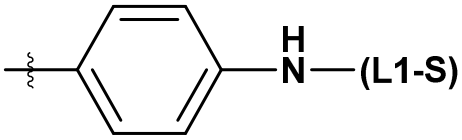
on BRM, wherein M is O;

L1-Q’ is at 

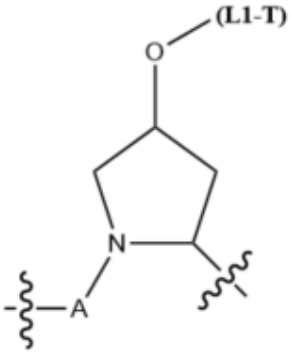
on BRM, wherein M’ is -NH;

L1-S is at 

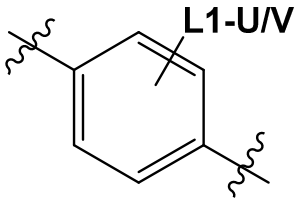
, 

or 

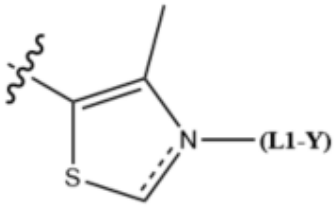
on L2;

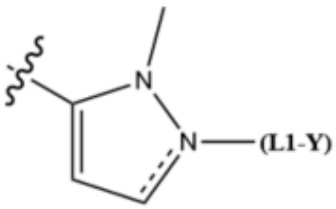
L1-T is at 

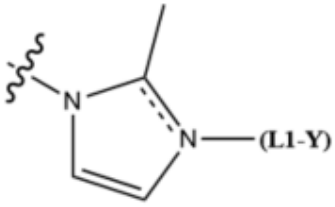
on E3LB, wherein, A is a group covalently bound to L2;

L1-U and L1-V are at 

on E3LB; and

L1-Y is at 

, 

or 

on E3LB, wherein, ---- is a single or double bond.

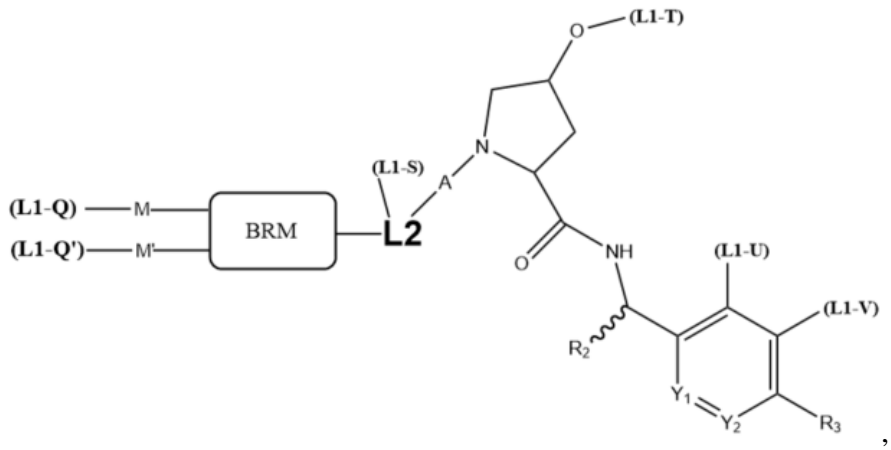
In another ~~aspect~~example, the subject matter described herein is directed to an ABCIDE having the chemical structure:

$$Ab\text{-}(L1\text{-}D)_p,$$

wherein,

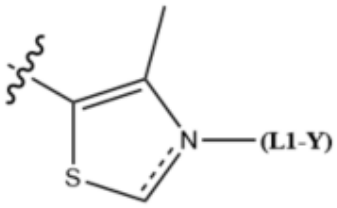
Ab is an antibody;

D is a CIDE, or prodrug thereof, having the structure:

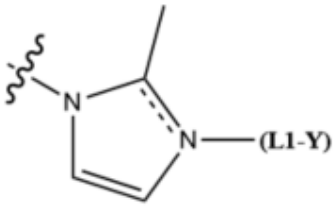


,

wherein:

R_3 is cyano, 

, or



,

wherein, ---- is a single or double bond.

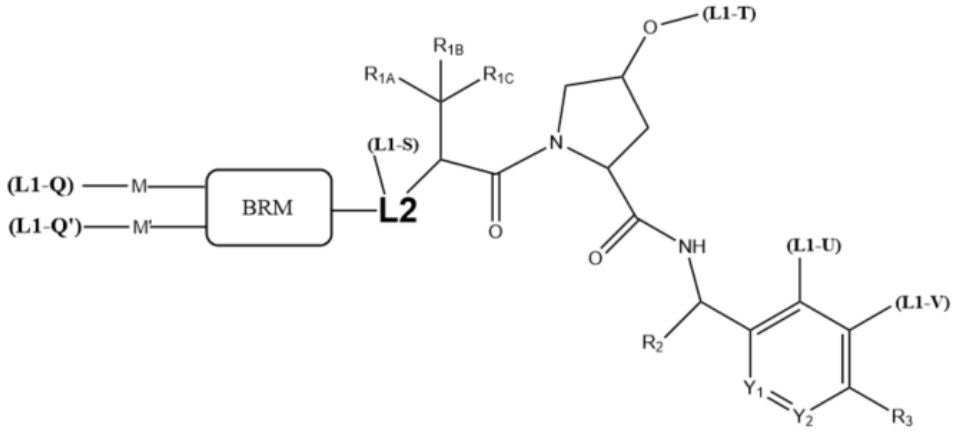
In another ~~aspect~~example, the subject matter described herein is directed to an Ab-CIDE having the chemical structure:

$$Ab\text{-}(L1\text{-}D)_p,$$

wherein,

Ab is an antibody;

D is a CIDE, or prodrug thereof, having the structure:



,

wherein, R_{1A}, R_{1B} and R_{1C} are each independently hydrogen, or $C_{1\text{-}5}$ alkyl; or two of R_{1A} , R_{1B} and R_{1C} together with the carbon to which each is attached form a $C_{1\text{-}5}$ cycloalkyl.

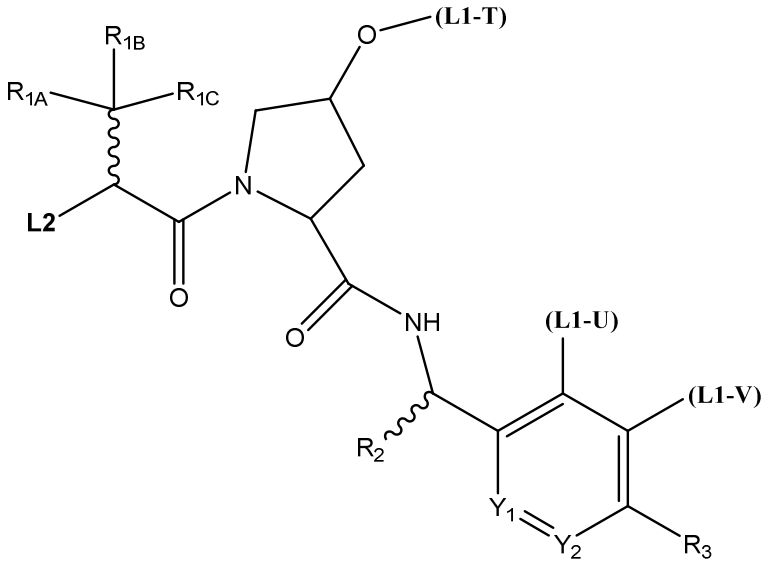
In another ~~aspect~~example, the subject matter described herein is directed to an ABCIDE having the chemical structure:

$$Ab—(L1—D)_p,$$

wherein,

D is a CIDE having the structure E3LB—L2—PB;

E3LB is covalently bound to L2, said E3LB having the formula:



E3LB

wherein,

R_{1A}, R_{1B} and R_{1C} are each independently hydrogen, or $C_{1\text{-}5}$ alkyl; or two of R_{1A} , R_{1B} and R_{1C} together with the carbon to which each is attached form a $C_{1\text{-}5}$ cycloalkyl;

p has a value from about 1 to about 8.

Another ~~aspect~~example of the subject matter described herein is a pharmaceutical composition comprising an Ab-CIDE, and one or more pharmaceutically acceptable excipients. In one aspect, the disclosure provides a pharmaceutical composition comprising the conjugate as disclosed herein, and one or more pharmaceutically acceptable excipients.

Another ~~aspect~~example of the subject matter described herein is the use of an Ab-CIDE in methods of treating conditions and diseases by administering to a subject a pharmaceutical composition comprising an Ab-CIDE. In one aspect, the disclosure provides use of the conjugate as disclosed herein or the pharmaceutical composition as disclosed herein in the preparation of a medicament for treating a disease in a subject in need thereof, wherein the disease is a cancer. In another aspect, the disclosure provides use of the conjugate as disclosed herein or the pharmaceutical composition as disclosed herein in the preparation of a medicament for reducing the level of BRM protein in a subject.

Another ~~aspect~~example of the subject matter described herein is a method of making an Ab-CIDE.

Another ~~aspect~~example of the subject matter described herein is an article of manufacture comprising a pharmaceutical composition comprising an Ab-CIDE, a container, and a package insert or label indicating that the pharmaceutical composition can be used to treat a disease or condition.

Yet other ~~embodiment~~examples are also fully described herein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1A and 1B shows an exemplary Ab-CIDE Ab-L1a-CIDE-BRM1-1 is active in cell-based assays.

Figure 2A and 2B shows an exemplary Ab-CIDE Ab-L1a-CIDE-BRM1-3 is active in cell-based assays.

Figure 3A-3L shows dose and antigen-dependent anti-tumor activity of an exemplary Ab-CIDE Ab-L1a-CIDE-BRM1-1.

Figure 4A-4L shows dose and antigen-dependent anti-tumor activity of an exemplary Ab-CIDE Ab-L1a-CIDE-BRM1-3. The data are in relative contrast to those of Ab-CIDE Ab-L1a-CIDE-BRM1-1.

Figure 5 shows that BRM and BRG1 degradation correlate with anti-tumor activity of an exemplary Ab-CIDE Ab-L1a-CIDE-BRM1-1.

Figure 6 shows that BRM and BRG1 degradation with anti-tumor activity of an exemplary Ab-CIDE Ab-L1a-CIDE-BRM1-3 is less correlative. All lanes are for Ab-CIDE Ab-L1a-CIDE-BRM1-3 except ** indicates the lane for Ab-CIDE-L1a-BRM1-1.

Figure 7 shows that the antibody linking strategy can modulate the activity of the CIDE. The data show that the exemplary Ab-CIDE Ab-L1a-CIDE-BRM1-1 provides stronger BRM degradation than unconjugated CIDE-BRM1-3, although CIDE-BRM1-3 is

What is Claimed is:

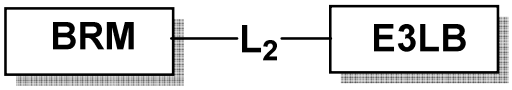
1. A conjugate having the structure:

$$Ab\text{-}(L1\text{-}D)_p,$$

wherein,

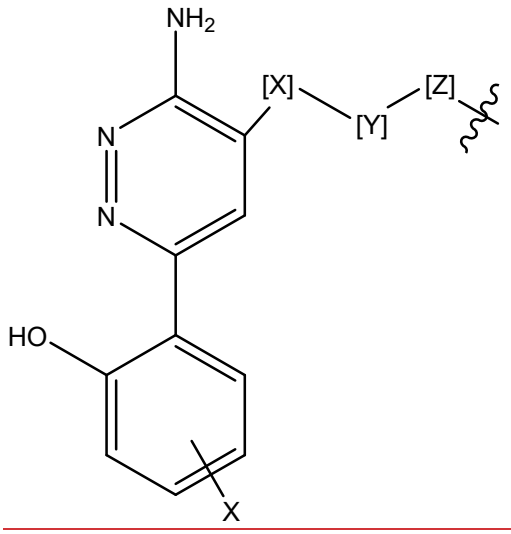
Ab is an antibody;

D is a CIDE, or prodrug thereof, the CIDE having the structure:

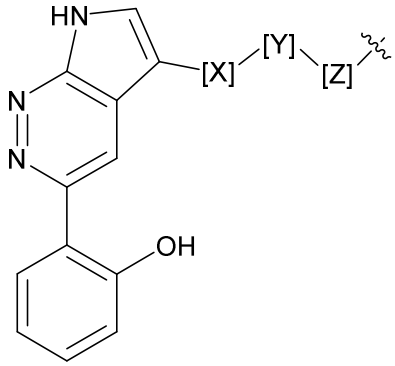


wherein,

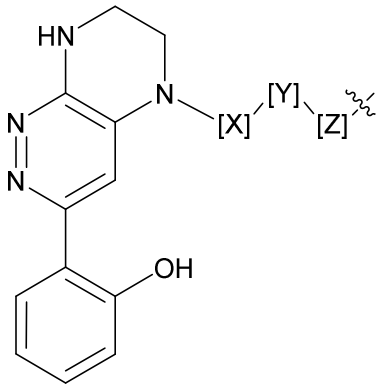
BRM is a residue of a BRM-binding compound, wherein the residue of a BRM-binding compound is a compound of formula (I-A), formula (I-B), formula (I-C), formula (I-D), or formula (I-E):



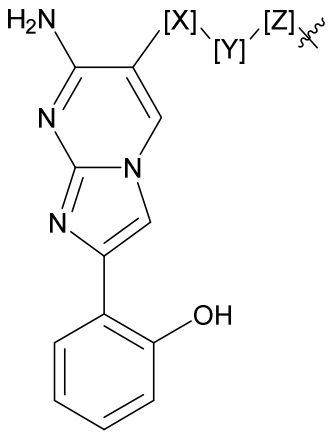
(I-A),



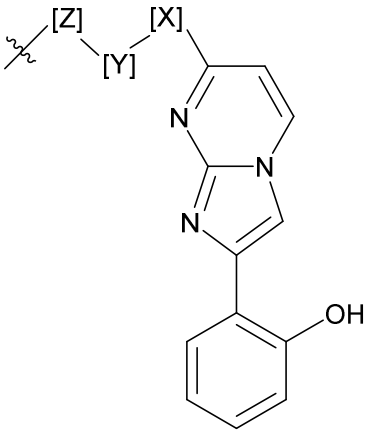
(I-B),



(I-C),



(I-D), wherein X is hydrogen or halogen; or



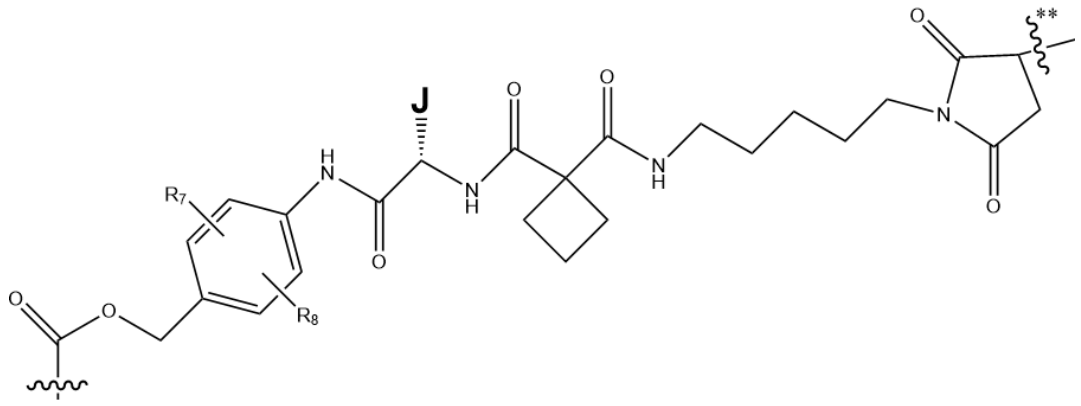
(I-E);

E3LB is a residue of an E3 ligase-binding compound, and

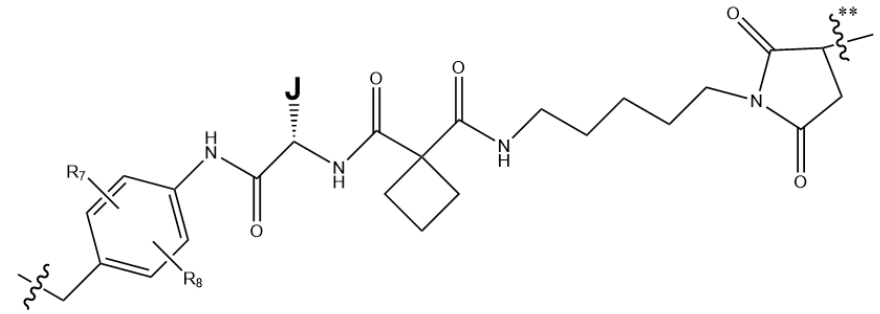
L2 is a ~~moiety~~ linker covalently linking BRM ~~with~~ and E3LB;

L1 is a linker~~-1~~ covalently linking Ab to ~~one of~~ BRM, E3LB or L2;

wherein L1 is selected from the group consisting of:



, and



wherein,

J is —CH_2-CH_2-CH_2-NH-C(O)-NH_2; —CH_2-CH_2-CH_2-CH_2-NH_2; —CH_2-CH_2-CH_2-CH_2-NH-CH_3; or —CH_2-CH_2-CH_2-CH_2-N(CH_3)$_2$; and

R_7 and R_8 are each independently hydrogen, halo, C_{1-5} alkyl, C_{1-5} alkoxy or hydroxy; and

p has a value from about~~is~~ 1 to about 16.

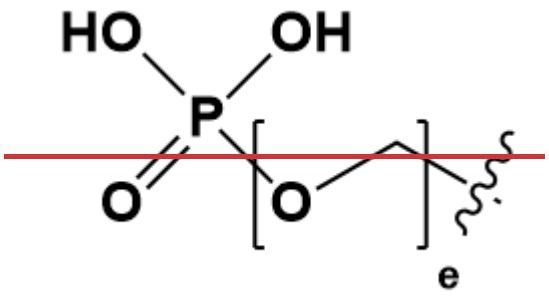
2. The conjugate of claim 1, wherein L1 is covalently bound to E3LB.

3. The conjugate of claim 2, wherein the prodrug is a CIDE having a phosphate moiety covalently bound to BRM.

4. The conjugate of claim 1, wherein L1 is covalently bound to BRM.

5. The conjugate of claim 4, wherein the prodrug is a CIDE having a phosphate moiety is covalently bound to E3LB.

~~6. The conjugate of any one of claims 3 or 5, wherein the phosphate moiety has the structure:~~

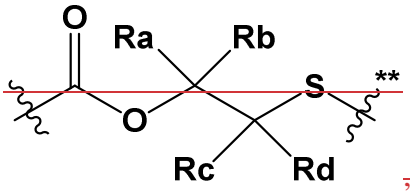


~~, wherein e is 0 or 1.~~

~~7. The conjugate of claim 1, wherein L1 is covalently bound to L2.~~

~~8. The conjugate of claim 1, wherein L1 is selected from the group consisting of~~

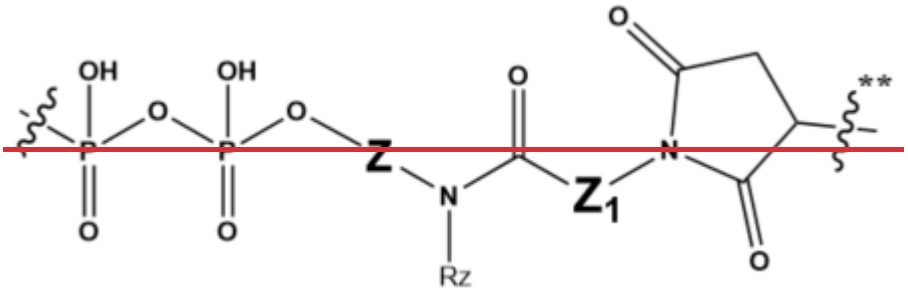
~~i) L1a~~



~~, wherein~~

~~wherein R^a, R^b, R^c, and R^d are independently selected from the group consisting of H, optionally substituted branched or linear C_1–C_5 alkyl, and optionally substituted C_3–C_6 cycloalkyl, or R^a and R^b taken together or R^c and R^d taken together with the carbon atom to which they are bound form an optionally substituted C_3-C_6 cycloalkyl ring or a 3 to 6 membered heterocycloalkyl ring;~~

ii) L1b

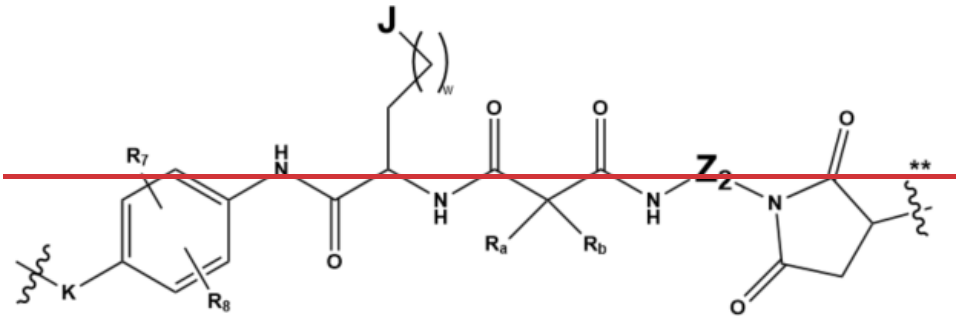


, wherein,

Z and Z_1 are each independently a C_{1-12} alkylene or $[CH_2]_g[O\ CH_2]_h$, wherein g is 0, 1 or 2, and h is 1-5;

R_z is H or C_{1-3}alkyl; and,

iii) L1c



, wherein

Z_2 is a C_{1-12} alkylene or $[CH_2]_g[O\ CH_2]_h$, wherein g is 0, 1 or 2, and h is 1-5;

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

J is $N(R_x)(R_y)$, $C(O)NH_2$, $NH\text{-}C(O)\text{-}NH_2$, $NH\text{-}NH\text{-}NH_2$, wherein, R_x and R_y are each independently selected from hydrogen and C_{1-3}alkyl;

K is selected from CH_2, CH(R), CH(R)O^, C(O), ^C(O)O CH(R), CH_2-O C(O)^, CH_2-O C(O) NH^, ^O C(L1c) C(O) NR_xR_y, ^C(L1c) C(O) NR_xR_y, CH_2-O C(O) NH CH_2, CH_2-O C(O) R $[CH_2]_q$-O^, CH_2-O C(O) R $[CH_2]_q$-^, wherein ^ indicates the attachment to CIDE, wherein R is hydrogen, C_{1-3}alkyl, $N(R_x)(R_y)$, O $N(R_x)(R_y)$ or C(O) $N(R_x)(R_y)$, wherein q is 0, 1, 2, or 3, and R_x and R_y are each independently selected from hydrogen and C_{1-3}alkyl, or R_x and R_y together with the nitrogen to which each is attached form an optionally substituted 5- to 7-member heterocyclyl;

~~Ra and Rb are each independently selected from hydrogen and C_{1-3}alkyl or Ra and Rb together with the nitrogen to which each is attached form an optionally substituted C_{3-6}cycloalkyl; and~~

~~R_7 and R_8 are each independently hydrogen, halo, C_{1-5} alkyl, C_{1-5} alkoxy or hydroxyl.~~

~~9. The conjugate of claim 8, wherein L1a is covalently bound to E3LB.~~

~~10. The conjugate of claim 8, wherein L1b is covalently bound to E3LB or BRM.~~

~~11. The conjugate of claim 8, wherein L1c is covalently bound to E3LB, BRM or L2.~~

~~12. The conjugate of claim 8, wherein L1b is covalently bound to E3LB.~~

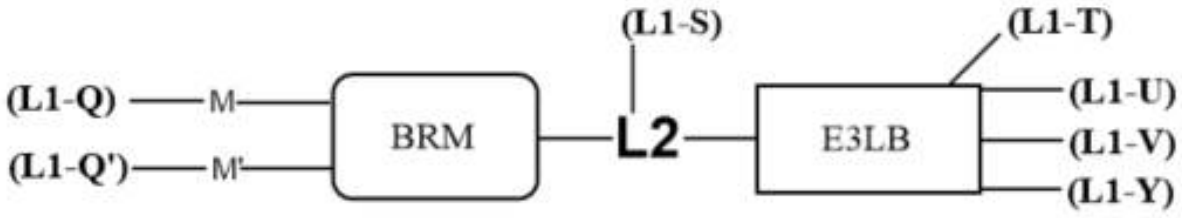
~~13. The conjugate of claim 8, wherein L1b is covalently bound to BRM.~~

~~14. The conjugate of claim 8, wherein L1c is covalently bound to E3LB.~~

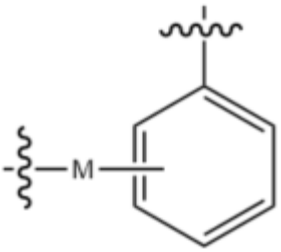
~~15. The conjugate of claim 8, wherein L1c is covalently bound to BRM.~~

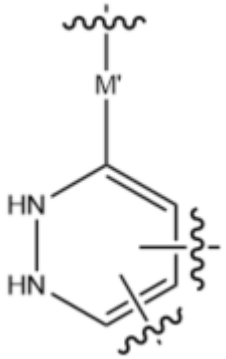
~~16. The conjugate of claim 8, wherein L1c is covalently bound to L2.~~

~~17.~~ 6. The conjugate of claim 1, wherein D has the structure

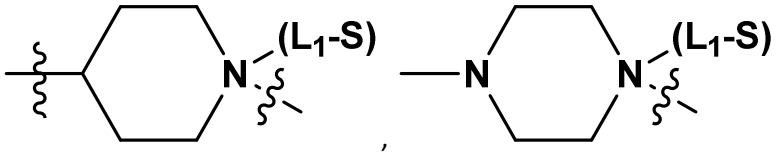


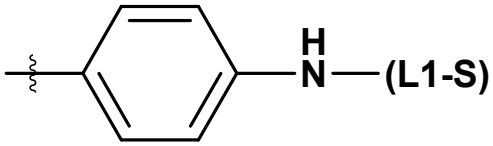
wherein L1 is attached at one attachment point selected from L1-Q, L1-Q', L1-S, L1-T, and optionally L1-U, L1-V and L1-Y, if present, wherein

L1Q is at  on BRM, wherein M is O;

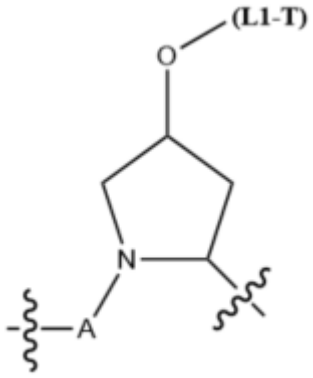


L1-Q' is at on BRM, wherein M' is -NH;

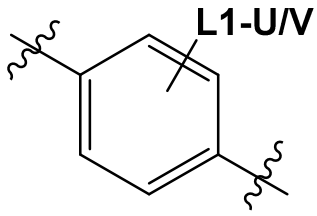
L1-S is at  , or



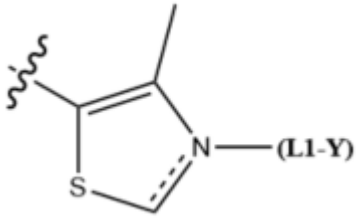
on L2;

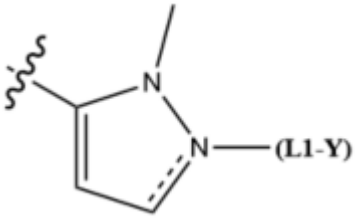


L1-T is at on E3LB, wherein, A is a group covalently bound to L2;

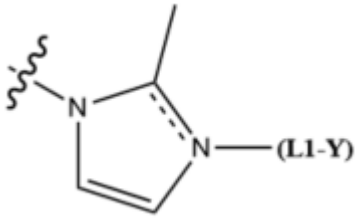
L1-U and L1-V are at 

on E3LB; and

L1-Y is at 

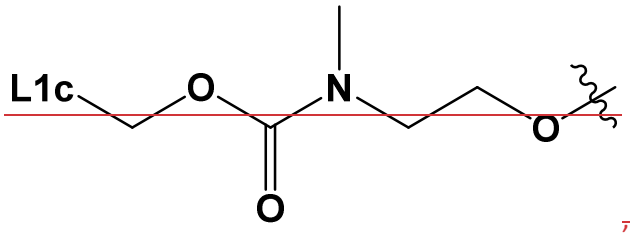
, 

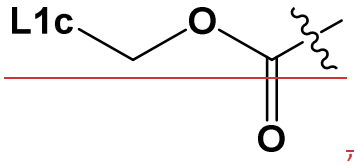
or

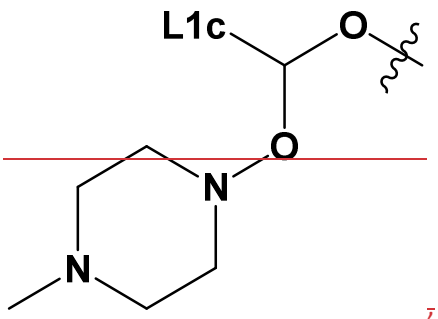


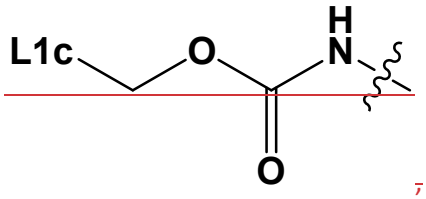
on E3LB, wherein, ---- is a single or double bond.

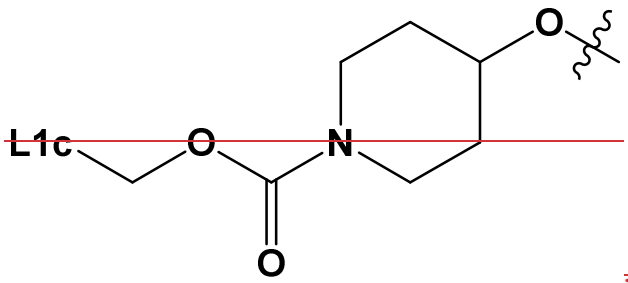
~~18. The conjugate of claim 8, wherein K of L1c is selected from the group consisting of:~~

~~L1c-CH2-,~~ 

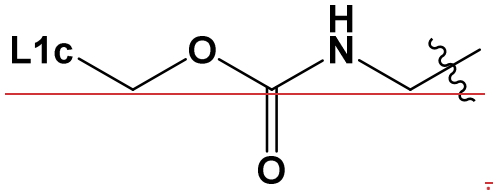




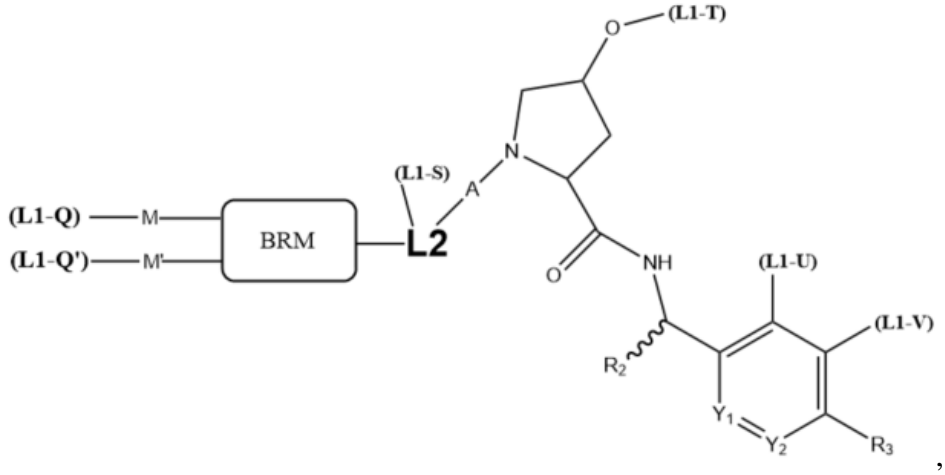




~~, and~~

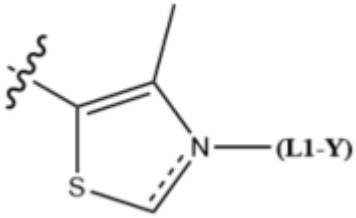


~~197~~. The conjugate of claim ~~176~~, ~~having~~ wherein D has the structure:

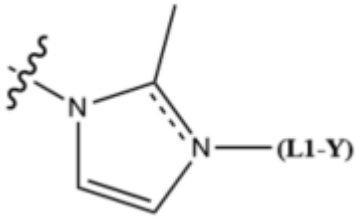


,

wherein:

R_3 is cyano, 

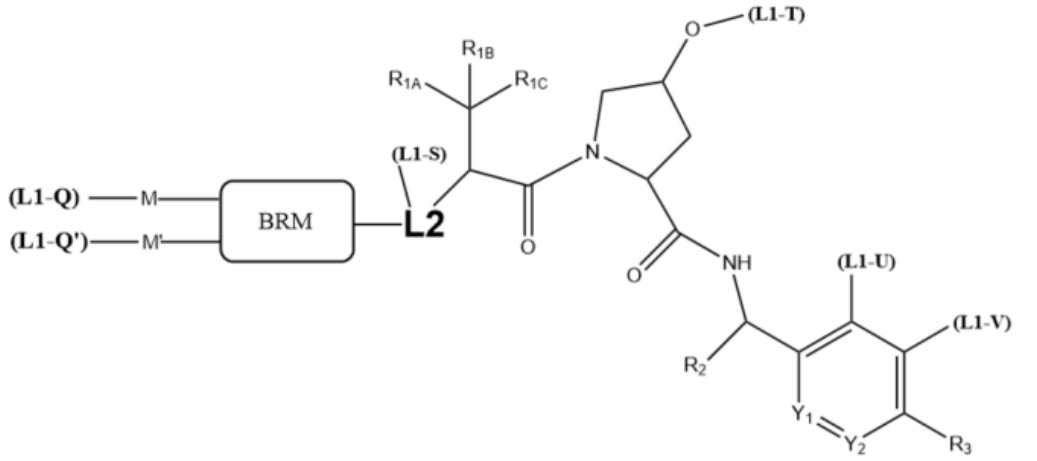
, or



,

wherein, ---- is a single or double bond.

208. The conjugate of claim 196, having wherein D has the structure:



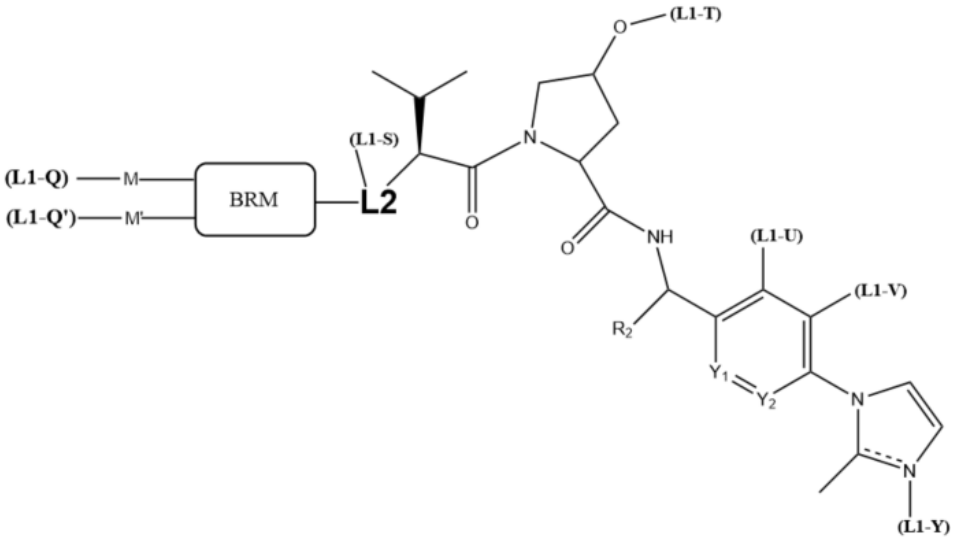
,

wherein, R_{1A}, R_{1B} and R_{1C} are each independently hydrogen or methylhydrogen, or C_{1-5} alkyl; or two of R_{1A}, R_{1B} and R_{1C} together with the carbon to which each is attached form a C_{1-5} cycloalkyl.

21. The conjugate of claim 20, wherein R_{1A}, R_{1B} and R_{1C} are each independently hydrogen or methyl.

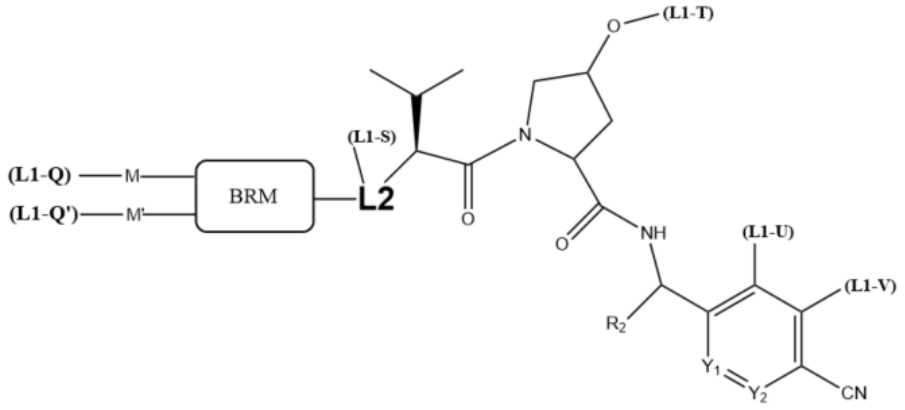
22. The conjugate of claim 21, wherein R_{1A} and R_{1B} are each methyl.

239. The conjugate of claim 226, having wherein D has the structure:



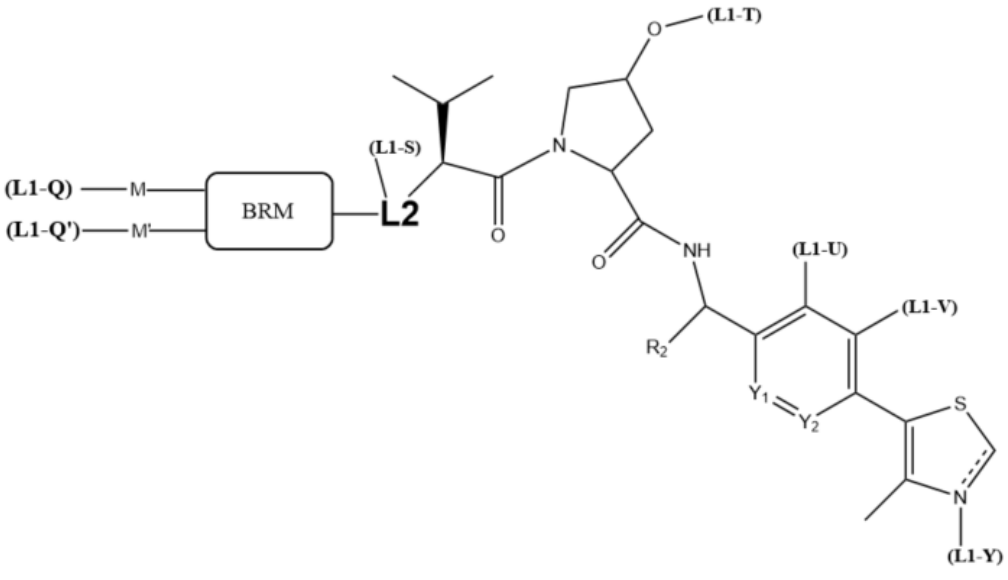
DAC4

,



DAC5

, or



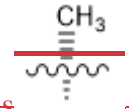
DAC6

;

and wherein R_2 is methyl and Y_1 and Y_2 are each -CH.

~~24. The conjugate of claim 23, wherein R_2 is hydrogen, methyl, ethyl or propyl.~~

~~25. The conjugate of claim 24, wherein R_2 is methyl.~~

~~26. The conjugate of claim 25, wherein R_2 is bound to E3LB as~~  ~~.~~

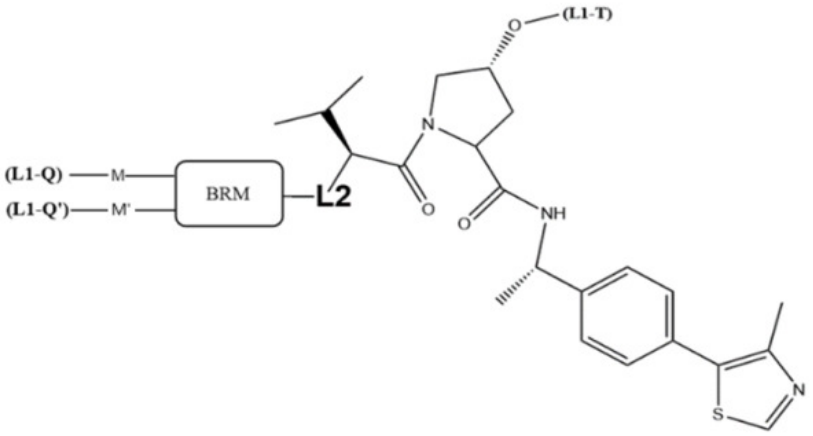
~~27. The conjugate of claim 23, wherein Y_1 and Y_2 are each -CH.~~

~~28. The conjugate of claim 23, wherein Y_1 is N and Y_2 is -CH.~~

~~29. The conjugate of claim 23, wherein Y_1 is -CH and Y_2 is N.~~

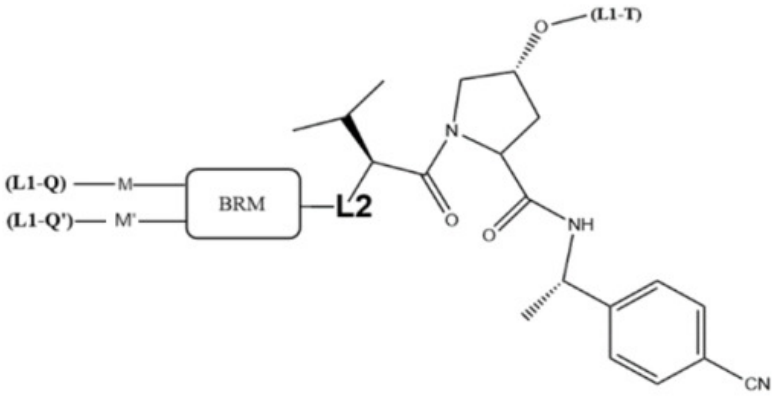
~~30. The conjugate of claim 23, wherein L1 is attached at L1-Q, L1-Q' or L1-T.~~

~~31~~10. The conjugate of claim ~~30~~6, ~~having~~ wherein D has the structure:



DAC7

, or

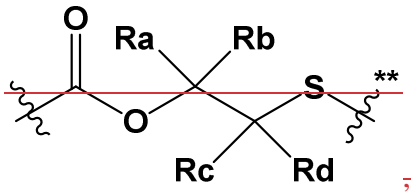


DAC8

.

~~32. The conjugate of claim 17, wherein:~~

~~L1 is attached at L1-T and is~~

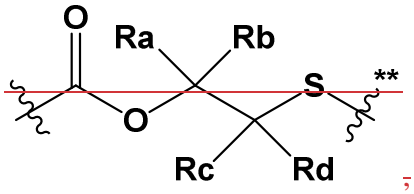


~~,~~

~~wherein, Ra, Rb, Rc and Rd are each independently selected from hydrogen and C_{1-3}alkyl.~~

~~33. The conjugate of claim 17, wherein:~~

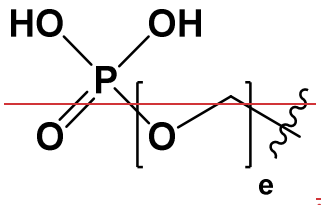
~~L1 is attached at L1-T and is~~



~~,~~

~~wherein, Ra, Rb, Rc and Rd are each independently selected from hydrogen and C_{1-3}alkyl; and,~~

~~a phosphate moiety having the structure:~~



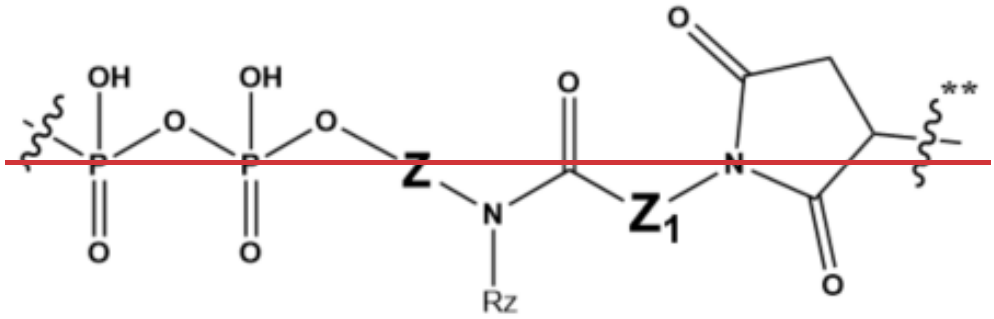
~~, wherein e is 0 or 1,~~

~~is covalently bound to BRM.~~

~~34. The conjugate of claim 17, wherein:~~

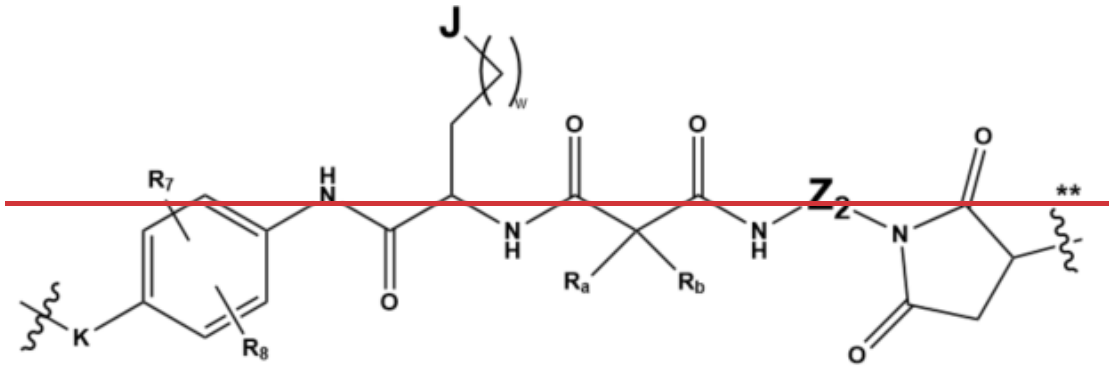
~~L1 is attached at L1-T and is selected from the group consisting of:~~

~~ii) L1b~~



~~and,~~

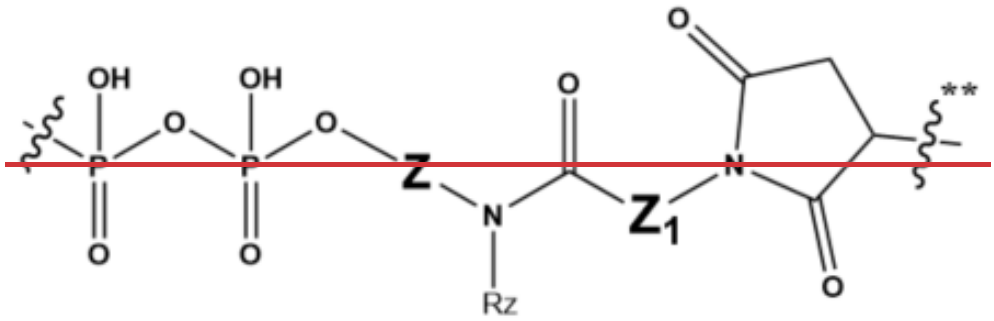
~~iii) L1c~~



~~35. The conjugate of claim 17, wherein:~~

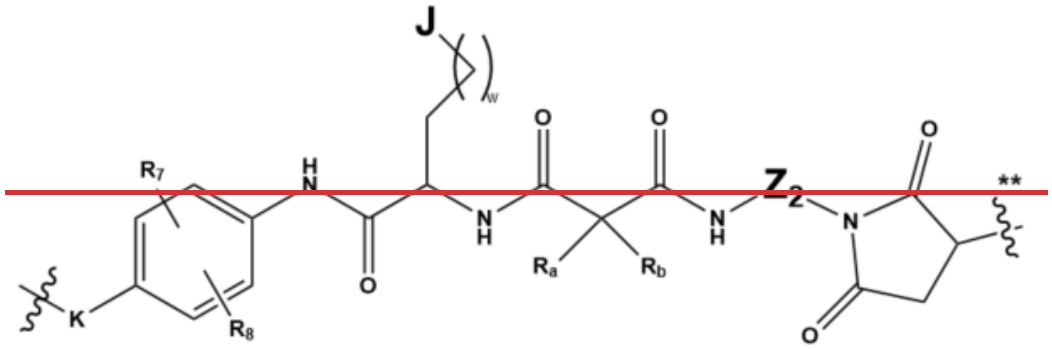
~~L1 is attached at L1-T and is selected from the group consisting of:~~

~~ii) L1b~~



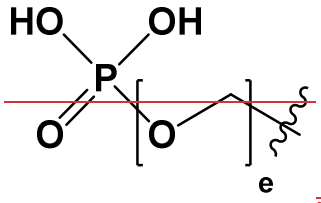
and,

iii) L1c



; and,

a phosphate moiety having the structure:



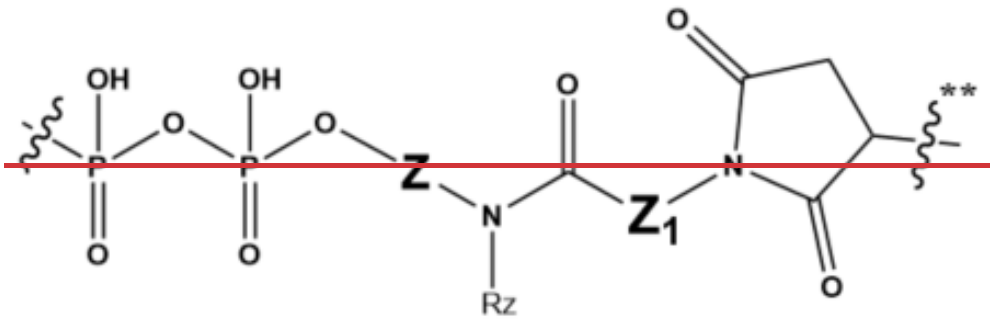
, wherein e is 0 or 1,

is covalently bound to BRM.

36. The conjugate of claim 17, wherein:

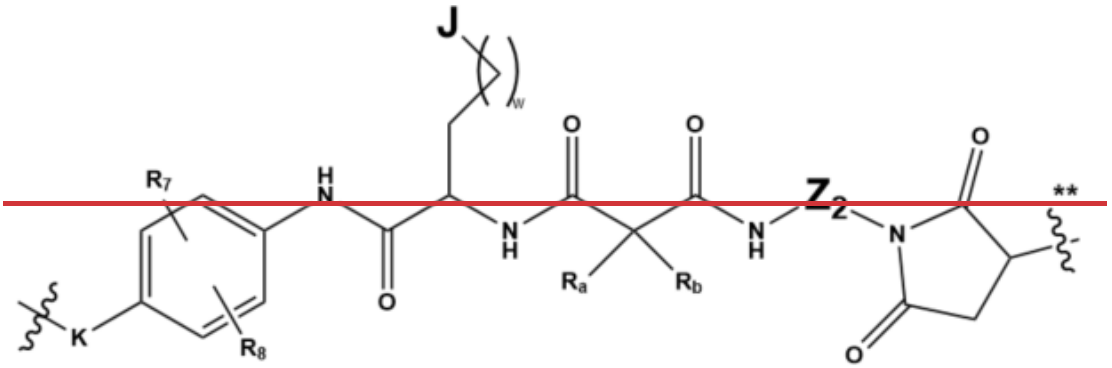
L1 is attached at L1-Q and is selected from the group consisting of:

ii) L1b



and,

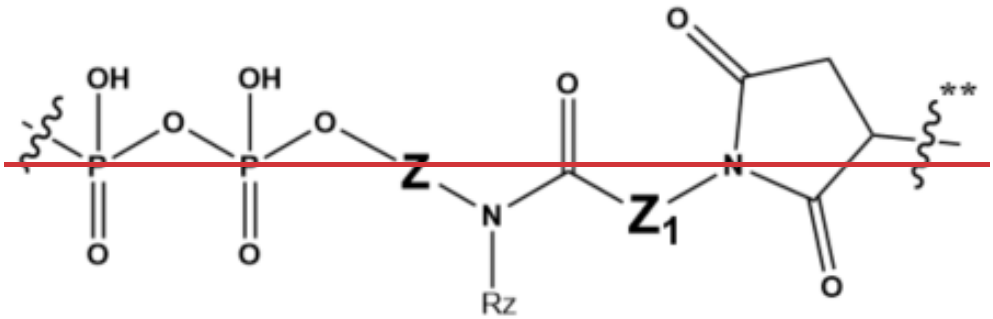
iii) L1c



37. The conjugate of claim 17, wherein:

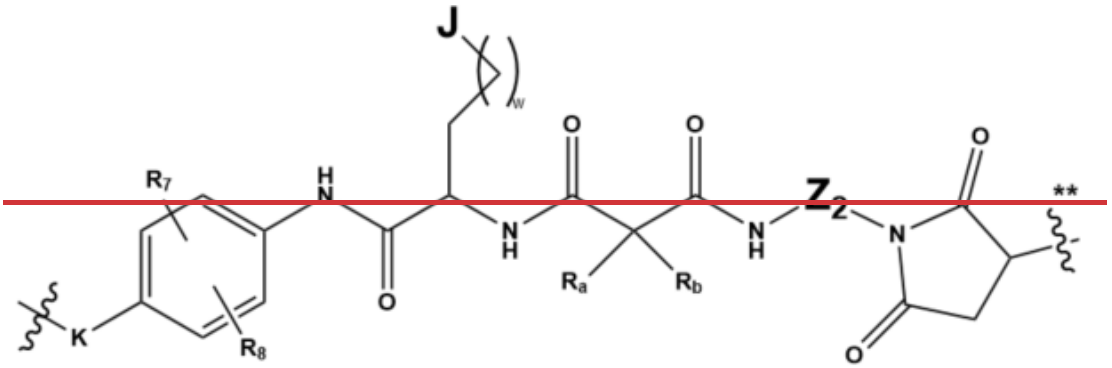
L1 is attached at L1-Q and is selected from the group consisting of:

ii) L1b



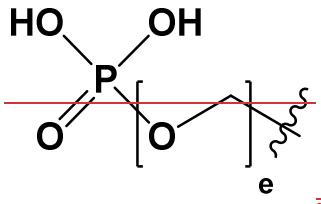
and,

iii) L1c



; and,

a phosphate moiety having the structure:



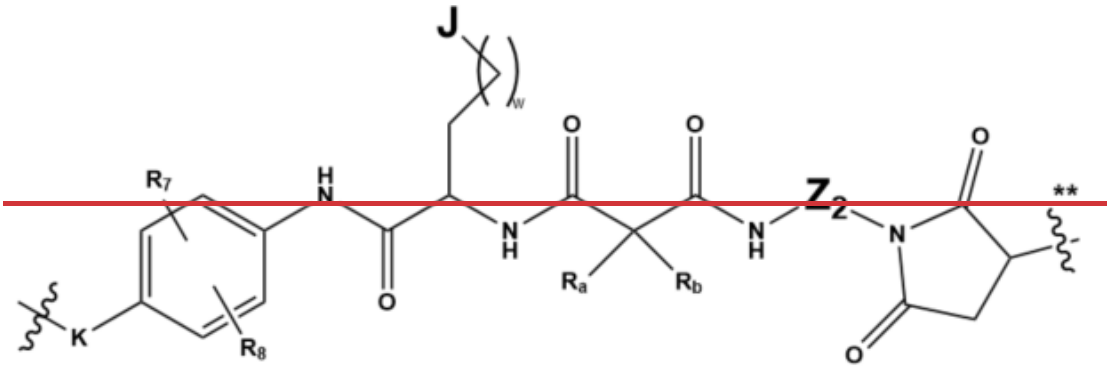
, wherein e is 0 or 1,

is covalently bound to BRM.

38. The conjugate of claim 17, wherein:

L1 is attached at L1-Q' and has the structure:

iii) L1c

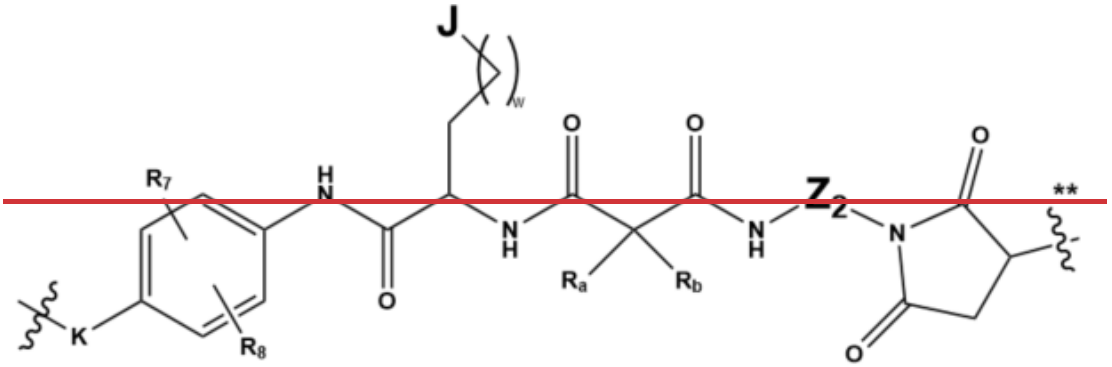


.

39. The conjugate of claim 17, wherein:

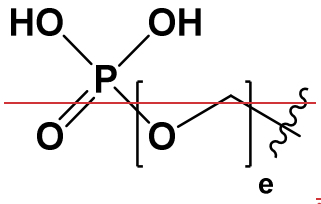
L1 is attached at L1-Q' and has the structure:

iii) L1c



; and,

a phosphate moiety having the structure:



, wherein e is 0 or 1,

is covalently bound to E3LB.

40. The conjugate of claim 8, wherein:

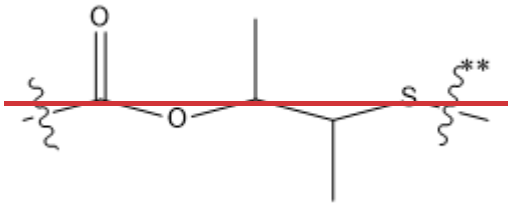
Z and Z_1 are each independently selected from $-(CH_2)_{1-6}-$ and $-[CH_2]_g-[-O-CH_2]_h-$, wherein g is 0, 1 or 2, and h is 1-5.

41. The conjugate of claim 8, wherein:

Z_2 is selected from $-(CH_2)_{1-6}-$ and $-[CH_2]_g-[-O-CH_2]_h-$, wherein g is 0, 1 or 2, and h is 1-5.

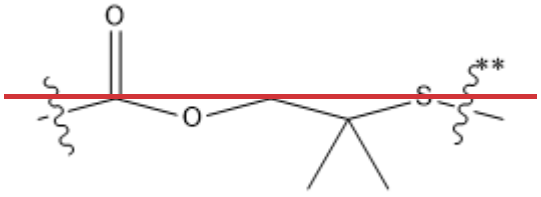
42. The conjugate of claim 8, wherein L1 is selected from the group consisting of:

L1a i)



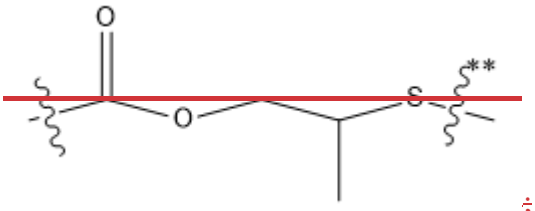
;

L1a ii)



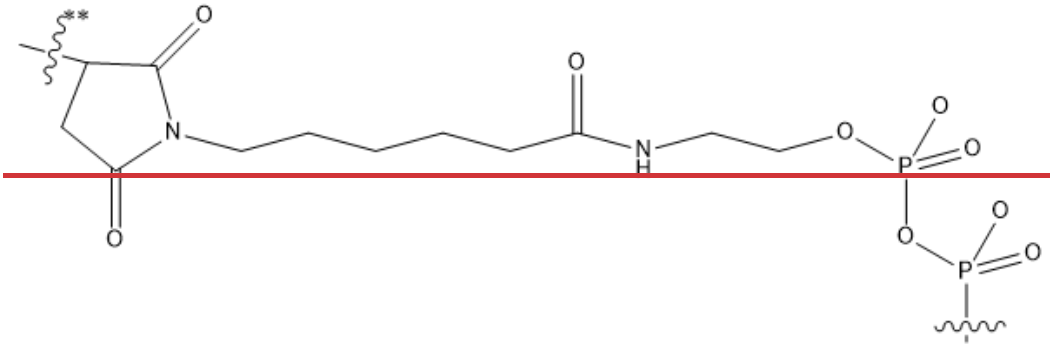
;

L1a iii)



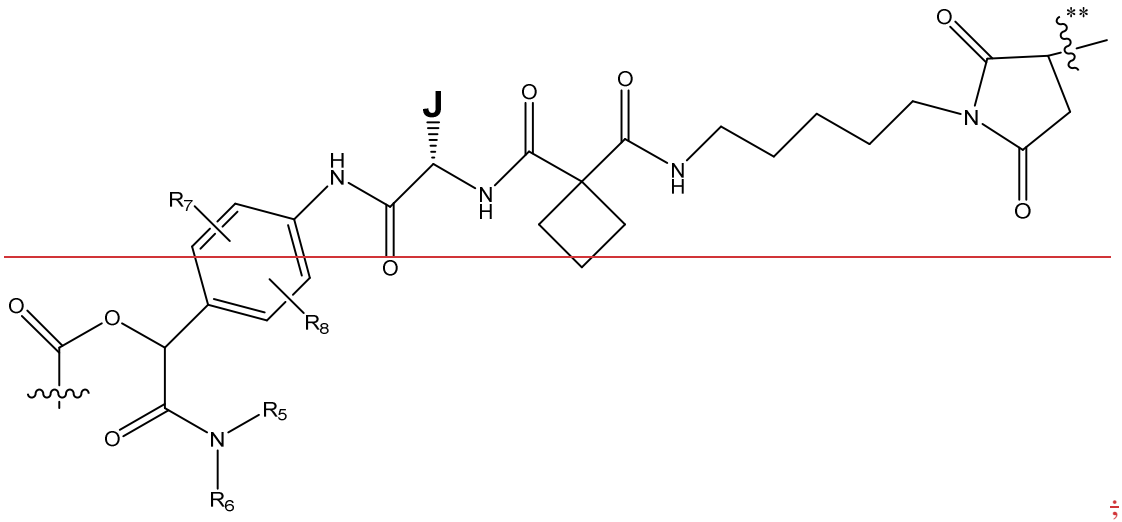
;

~~L1b i)~~



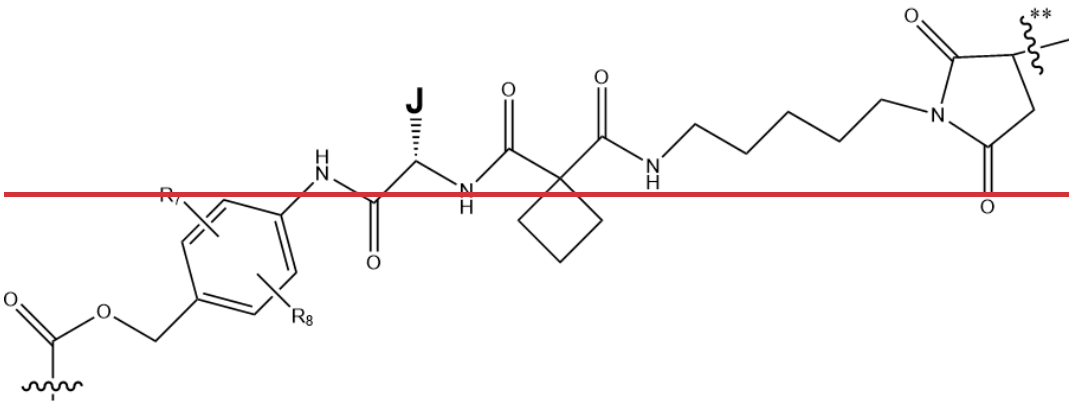
;

~~L1c i)~~



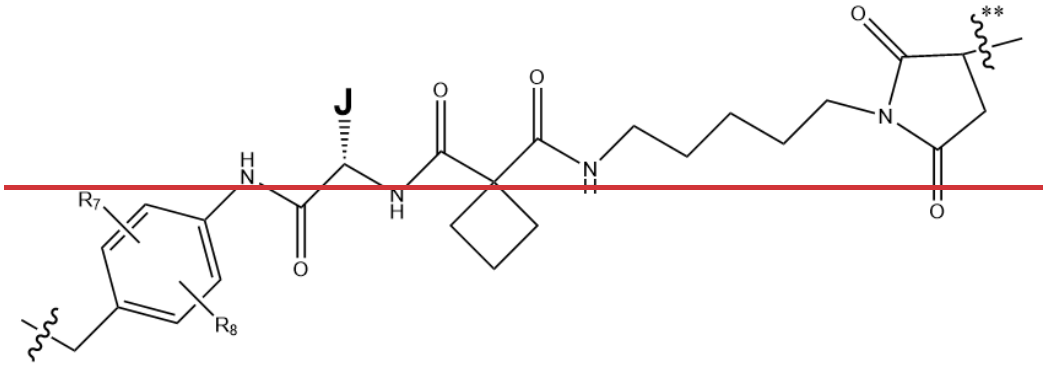
;

~~L1c ii)~~



;

L1c-iii)



;

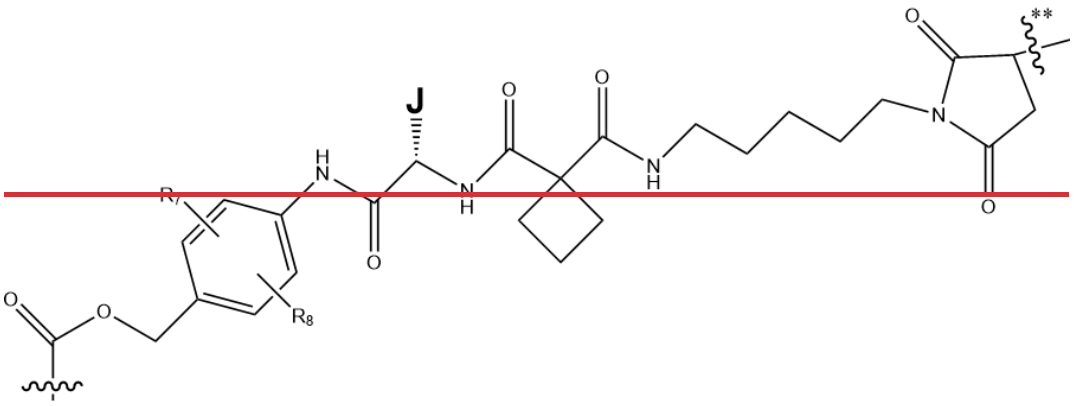
wherein,

J is $-CH_2-CH_2-CH_2-NH-C(O)-NH_2$; $-CH_2-CH_2-CH_2-CH_2-NH_2$; $-CH_2-CH_2-CH_2-CH_2-NH-CH_3$; or $-CH_2-CH_2-CH_2-CH_2-N(CH_3)_2$;

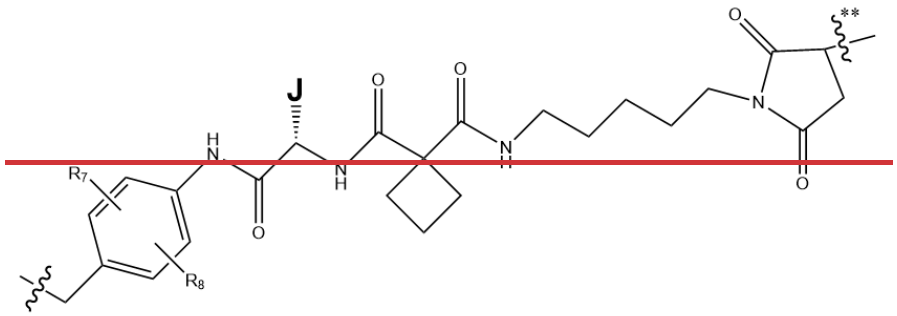
R_5 and R_6 are independently hydrogen or C_{1-5} alkyl; or R_5 and R_6 together with the nitrogen to which each is attached form an optionally substituted 5- to 7-member heterocyclyl; and

R_7 and R_8 are each independently hydrogen, halo, C_{1-5} alkyl, C_{1-5} alkoxy or hydroxy.

43. The conjugate of claim 42, wherein L1 is selected from the group consisting of:



, or



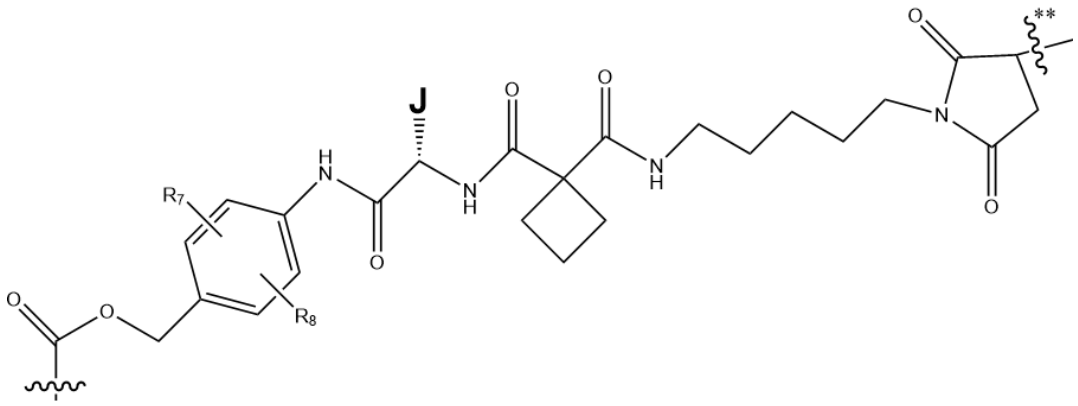
wherein,

J is —CH_2-CH_2-CH_2-NH-C(O)-NH_2; —CH_2-CH_2-CH_2-CH_2-NH_2; —CH_2-CH_2-CH_2-CH_2-NH-CH_3; or —CH_2-CH_2-CH_2-CH_2-$N(CH_3)_2$; and

R_7 and R_8 are each independently hydrogen, halo, C_{1-5} alkyl, C_{1-5} alkoxy or hydroxy.

4411. The conjugate of claim 431, wherein J is —CH_2-CH_2-CH_2-NH-C(O)-NH_2 or —CH_2-CH_2-CH_2-CH_2-$N(CH_3)_2$.

4512. The conjugate of claim 431, wherein L1 has the structure:



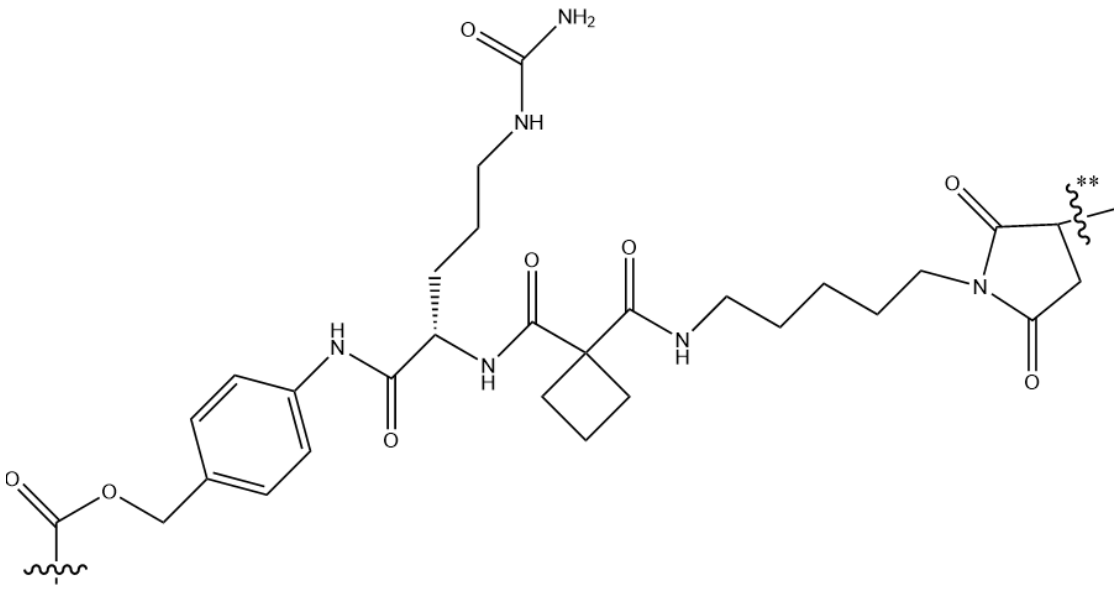
,

wherein,

J is —CH_2-CH_2-CH_2-NH-C(O)-NH_2; —CH_2-CH_2-CH_2-CH_2-NH_2; —CH_2-CH_2-CH_2-CH_2-NH-CH_3; or —CH_2-CH_2-CH_2-CH_2-N(CH_3)$_2$; and

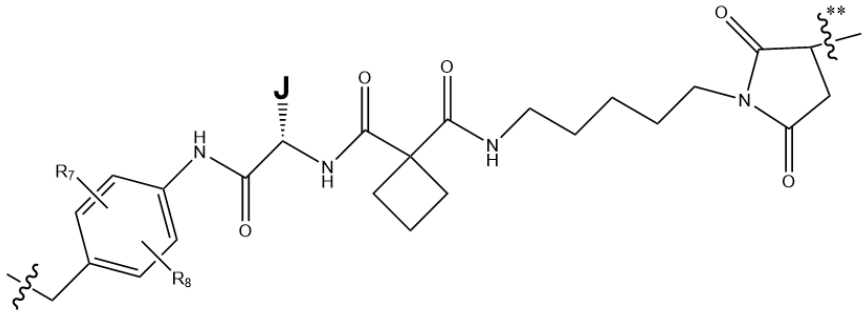
R_7 and R_8 are each independently hydrogen, halo, C_{1-5} alkyl, C_{1-5} alkoxy or hydroxy.

~~46~~13. The conjugate of claim ~~45~~12, wherein L1 has the structure:



.

~~47~~14. The conjugate of claim ~~43~~1, wherein ~~linker-1~~L1 has the structure:

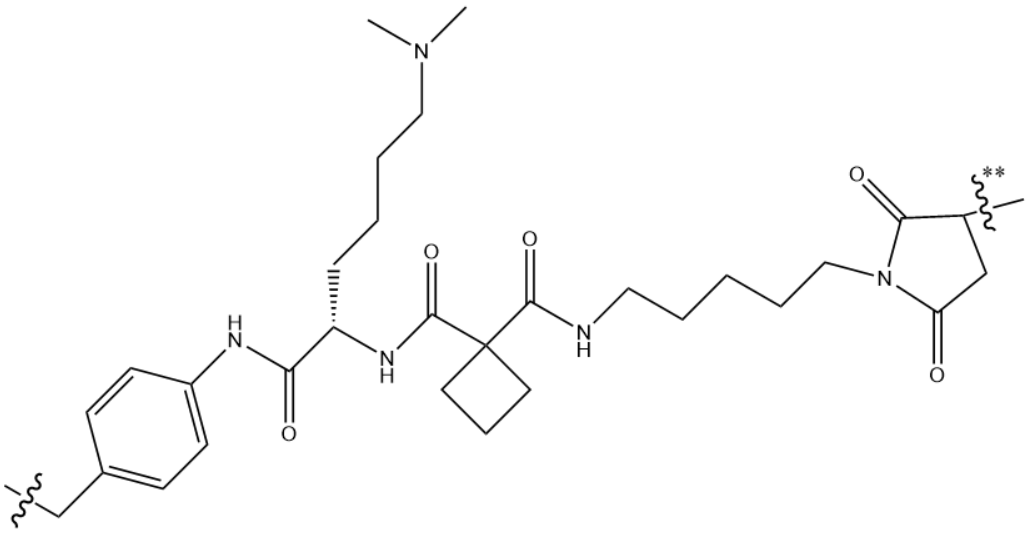


wherein,

J is —CH_2-CH_2-CH_2-NH-C(O)-NH_2; —CH_2-CH_2-CH_2-CH_2-NH_2; —CH_2-CH_2-CH_2-CH_2-NH-CH_3; or —CH_2-CH_2-CH_2-CH_2-N(CH_3)$_2$; and

R_7 and R_8 are each independently hydrogen, halo, C_{1-5} alkyl, C_{1-5} alkoxy or hydroxy.

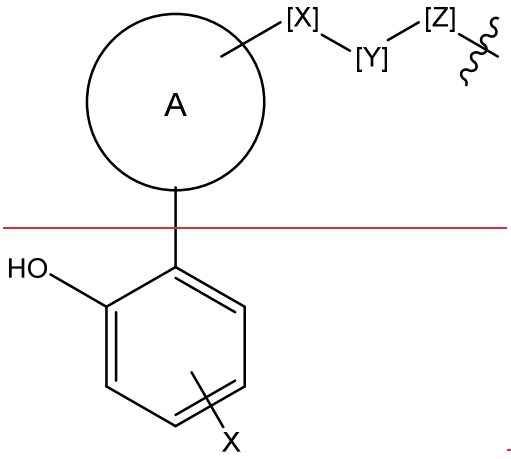
~~48~~15. The conjugate of claim ~~47~~14, wherein L1 has the structure:



~~49. The conjugate of claim 1, wherein:~~



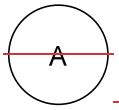
is a residue of a BRM-binding compound having a structure of Formula I:



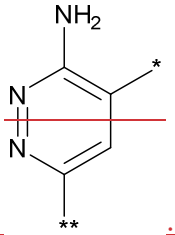
(I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

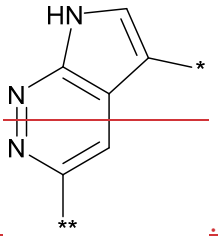
wherein X is hydrogen or halogen;



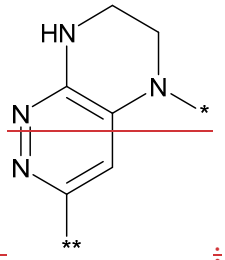
is selected from the group consisting of:

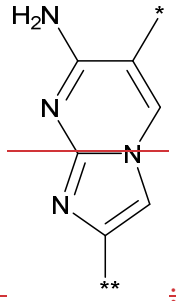


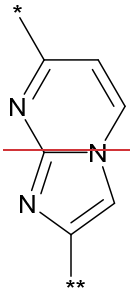
(a) ;



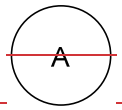
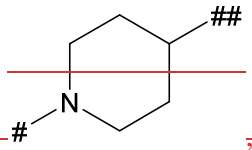
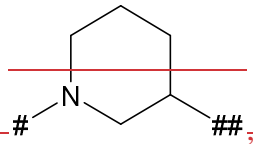
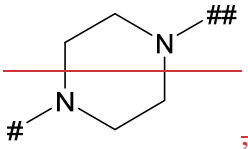
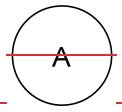
(b) ;

(c)  ;

(d)  ; and

(e)  ;

wherein, for (a)-(e), * denotes the point of attachment to [X], or, if [X] is absent, * denotes the point of attachment to [Y], and ** denotes the point of attachment to the phenyl ring; and wherein:

(i) [X] is 3-15 membered heterocyclyl or 5-20 membered heteroaryl, provided that, when  is (a), then [X] is not  ,  , or  , wherein # denotes the point of attachment to  and ## denotes the point of attachment to L2,

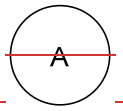
[Y] is absent, and

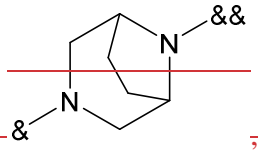
[Z] is absent; or

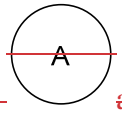
(ii) [X] is 3-15 membered heterocyclyl or 5-20 membered heteroaryl, wherein the 3-15 membered heterocyclyl of [X] is optionally substituted with one or more -OH or C_{1-6}alkyl,

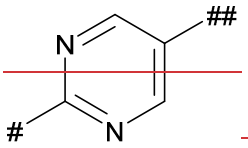
[Y] is absent, and

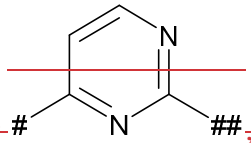
[Z] is 3-15 membered heterocyclyl or 5-20 membered heteroaryl,

provided that, when 

is (a) and [X] is 

, wherein & denotes the point of attachment to 

and && denotes the point of attachment to [Z], then [Z] is not 

or 

, wherein # denotes the point of attachment to [X] and ## denotes the point of attachment to L2; or

(iii) [X] is 3-15 membered heterocyclyl or 5-20 membered heteroaryl,

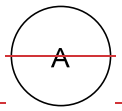
[Y] is methylene, wherein the methylene of [Y] is optionally substituted with one or more methyl group, and

[Z] is 3-15 membered heterocyclyl; or

(iv) [X] is absent,

[Y] is ethenylene, wherein the ethenylene of [Y] is optionally substituted with one or more halo, and

[Z] is 5-20 membered heteroaryl,

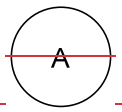
provided that 

is (a), (b), (d), or (e); or

(v) [X] is absent,

[Y] is ethynylene, and

[Z] is 5-20 membered heteroaryl,

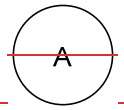
provided that 

is (a), (b), (d), or (e); or

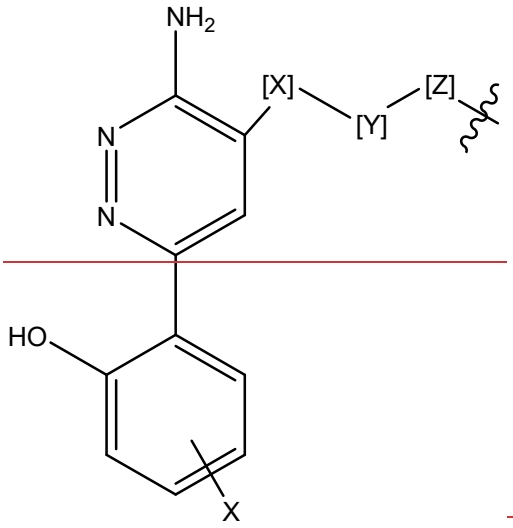
(vi) [X] is absent,

[Y] is cyclopropyl or cyclobutyl, and

~~[Z] is 5-20 membered heteroaryl,~~

~~provided that~~  ~~is (a), (b), (d), or (e).~~

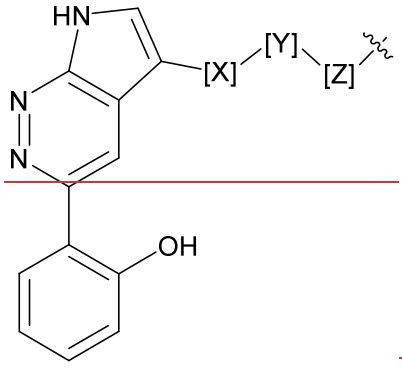
~~50. The conjugate of claim 49, wherein the residue of a BRM-binding compound is a compound of formula (I-A):~~



~~(I-A),~~

~~or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof.~~

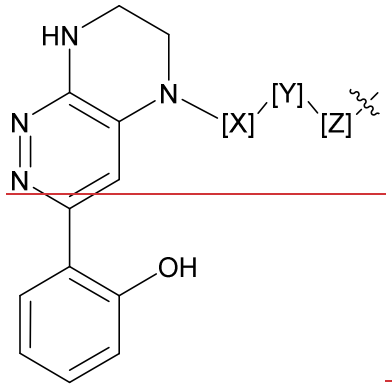
~~51. The conjugate of claim 49, wherein the residue of a BRM-binding compound is a compound of formula (I-B):~~



~~(I-B),~~

~~or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof.~~

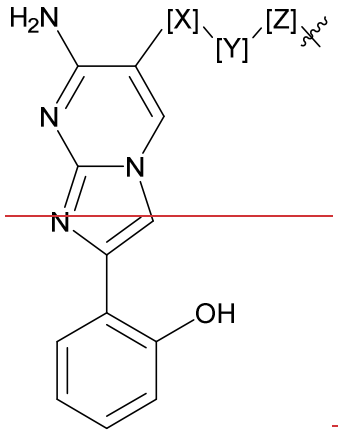
~~52. The conjugate of claim 49, wherein the residue of a BRM-binding compound is a compound of formula (I-C):~~



(I-C),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof.

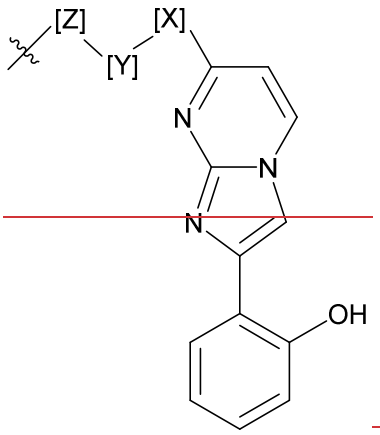
53. The conjugate of claim 49, wherein the residue of a BRM-binding compound is a compound of formula (I-D):



(I-D), wherein X is hydrogen or halogen,

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof.

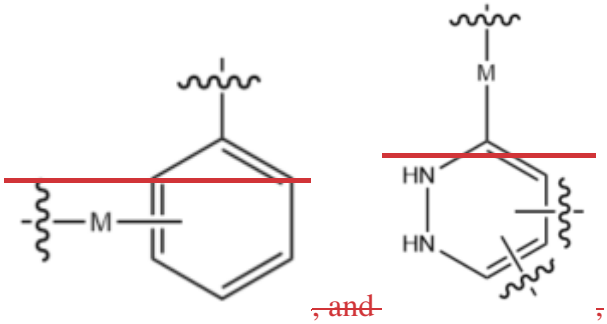
54. The conjugate of claim 49, wherein the residue of a BRM-binding compound is a compound of formula (I-E):



~~(I-E),~~

~~or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof.~~

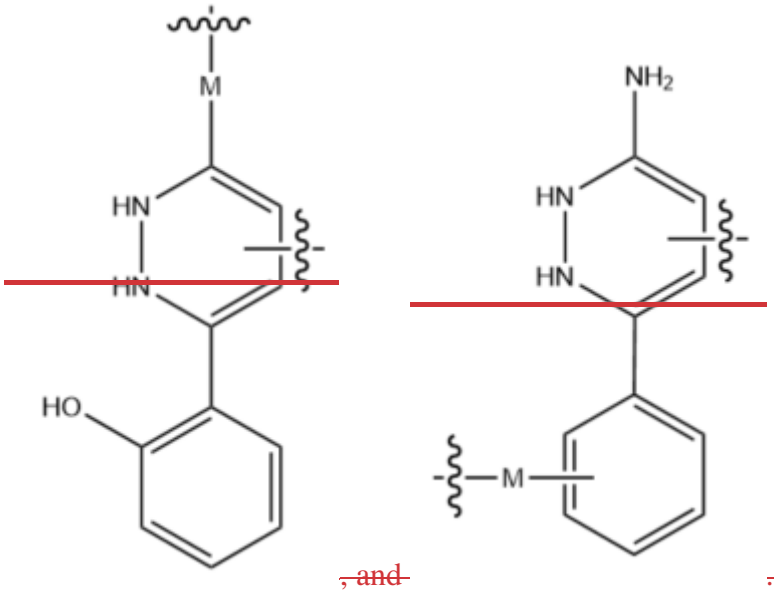
~~55. The conjugate of claim 49, wherein the residue of a BRM-binding compound comprises at least one moiety selected from the group consisting of:~~



~~, and~~ ;

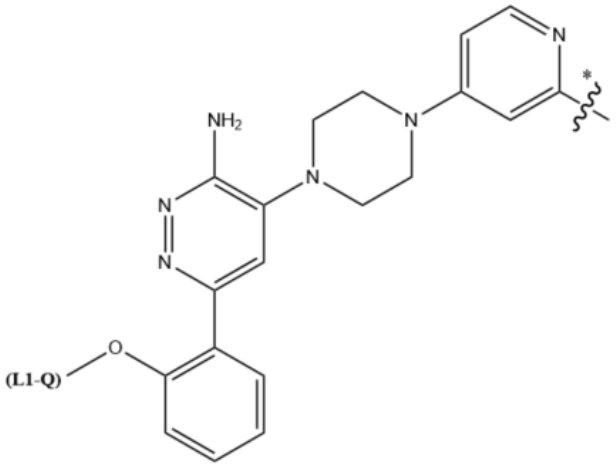
~~wherein, M is -NH or oxygen and is covalently bound to L1-Q.~~

~~56. The conjugate of claim 55, wherein the residue of a BRM-binding compound comprises a moiety selected from the group consisting of:~~

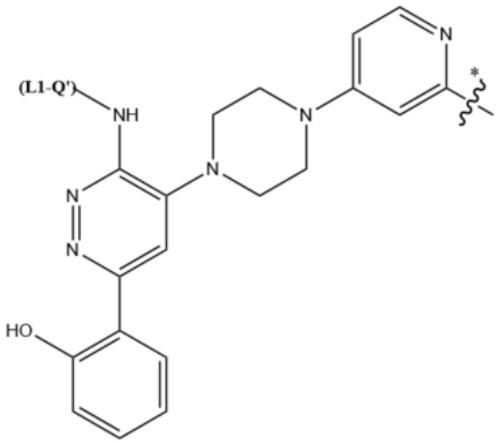


~~, and~~ ~~.~~

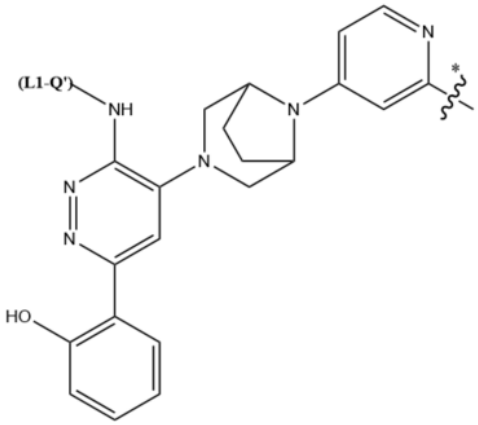
~~57~~16. The conjugate of claim ~~56~~1, wherein BRM is a residue of:



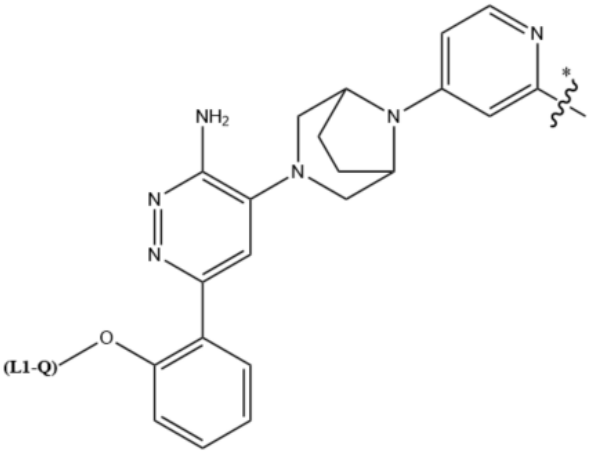
,



,



, and

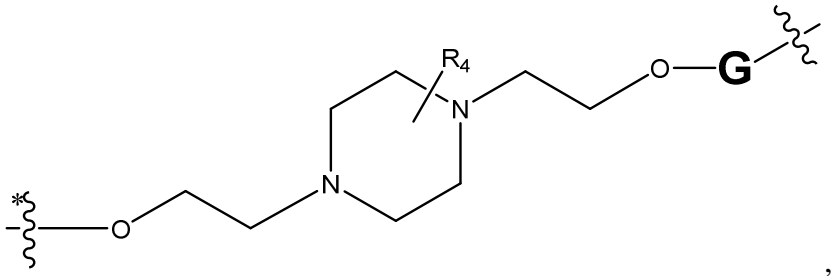


,

wherein~~,~~  is the point of attachment to L2.

~~58~~17. The conjugate of claim 1, wherein:

~~L2 is a linker 2 covalently bound to E3LB and BRM, said~~ L2 ~~having~~ has the formula of structure L2a, L2b, or L2c:

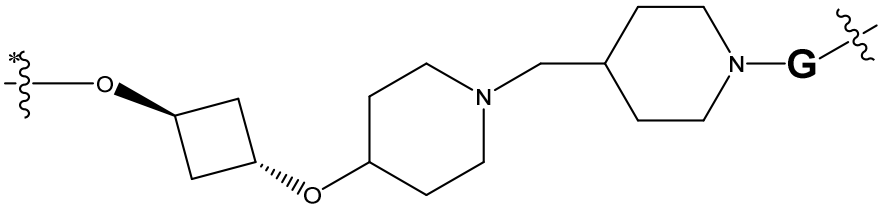


L2a

,

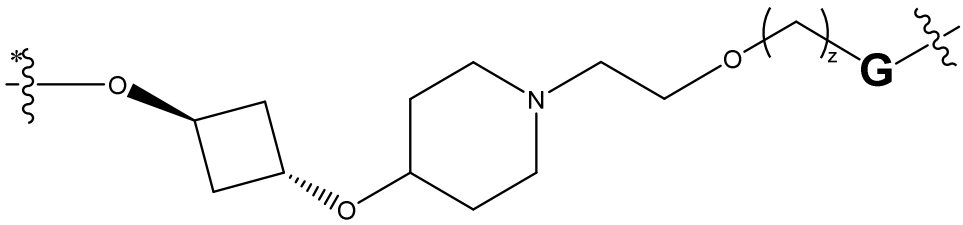
wherein,

R_4 is hydrogen or methyl,



L2b

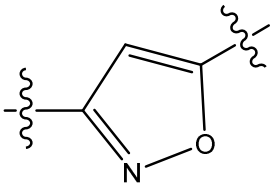
, or



L2c

wherein,

z is one or zero,

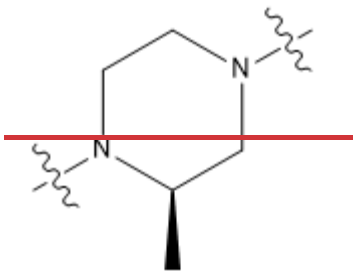
G is  or —C(O)NH—; and,

 is the point of attachment to BRM.

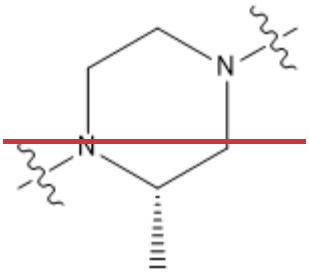
~~59~~18. The conjugate of claim ~~58~~17, wherein R_4 is hydrogen.

~~60~~19. The conjugate of claim ~~58~~17, wherein R_4 is methyl.

~~61. The conjugate of claim 60, wherein R_4 is a methyl as follows:~~

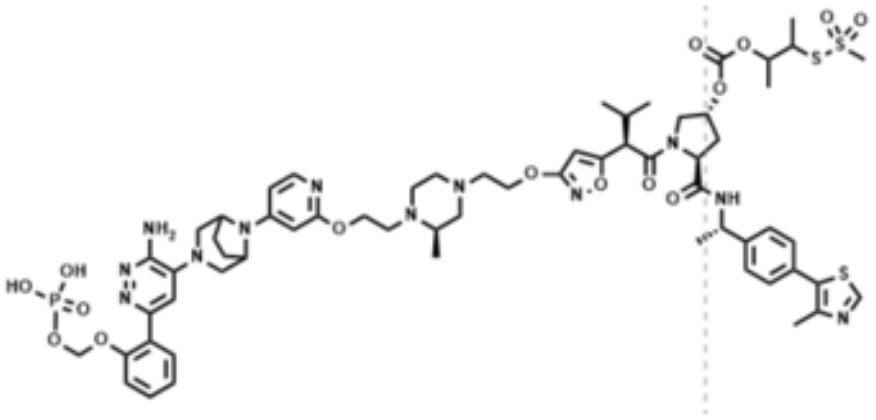
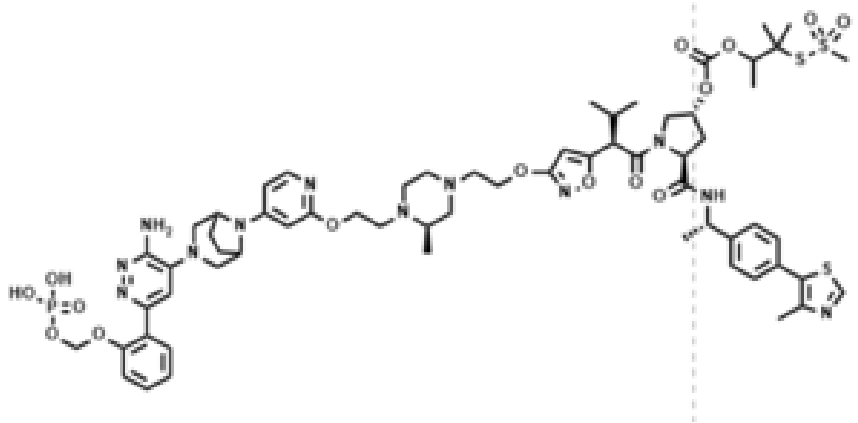


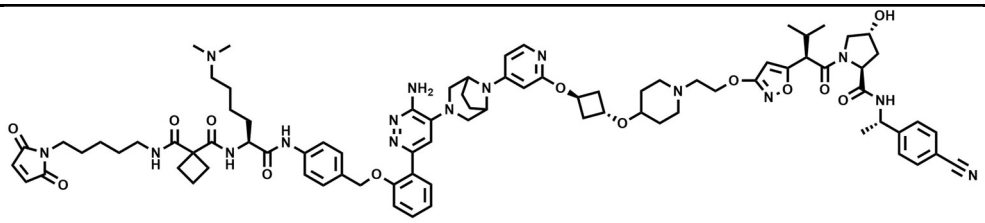
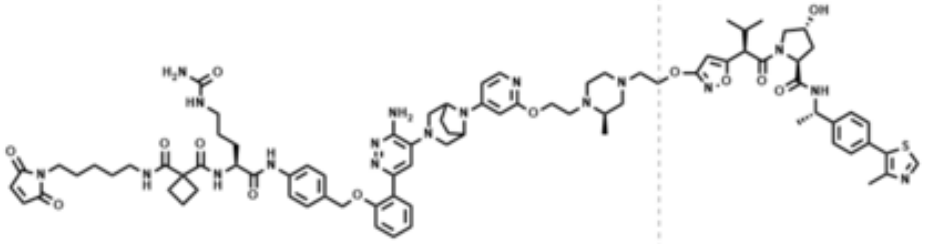
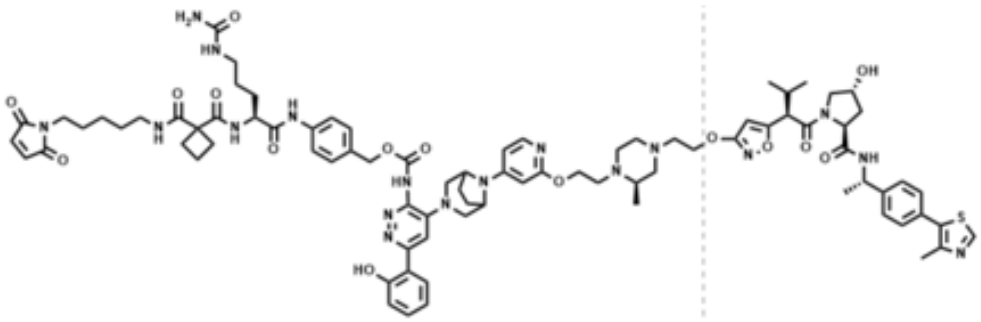
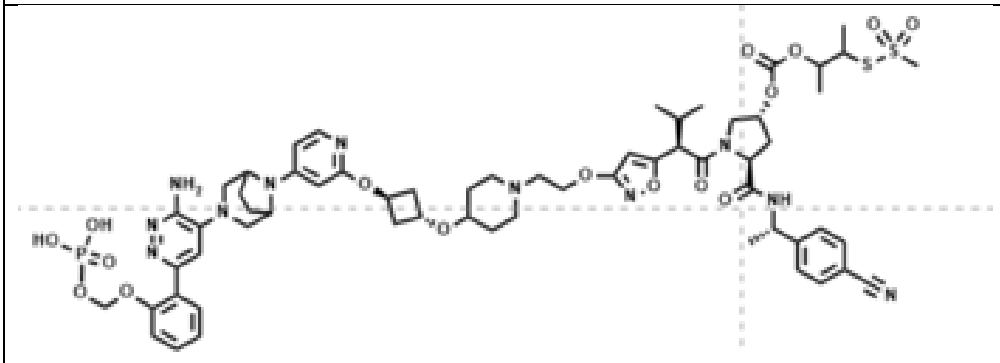
~~or~~

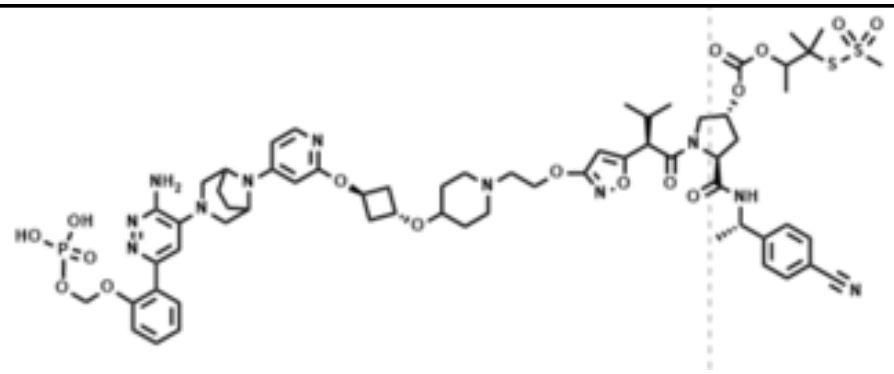
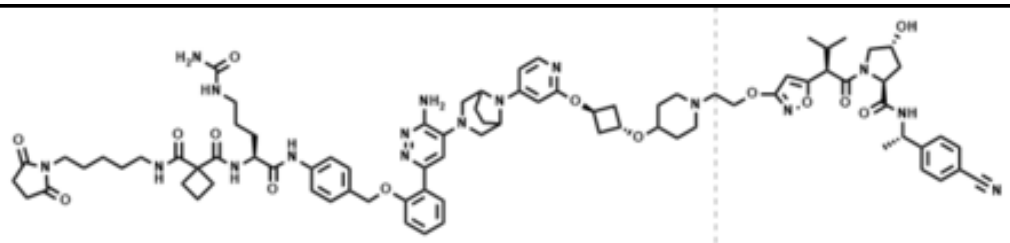
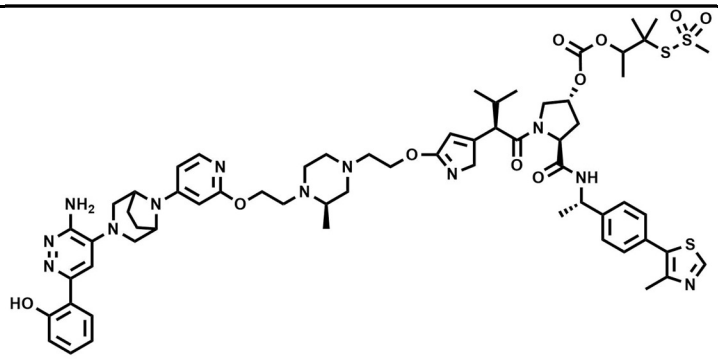
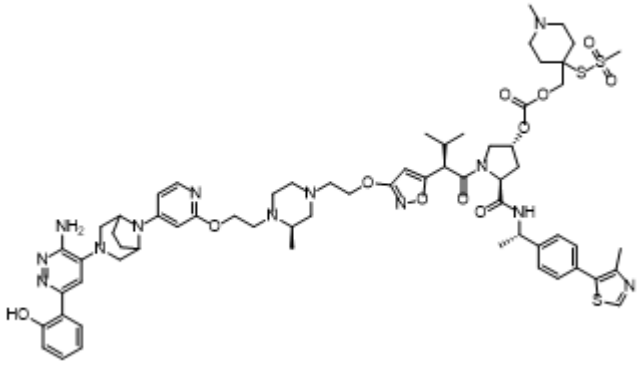


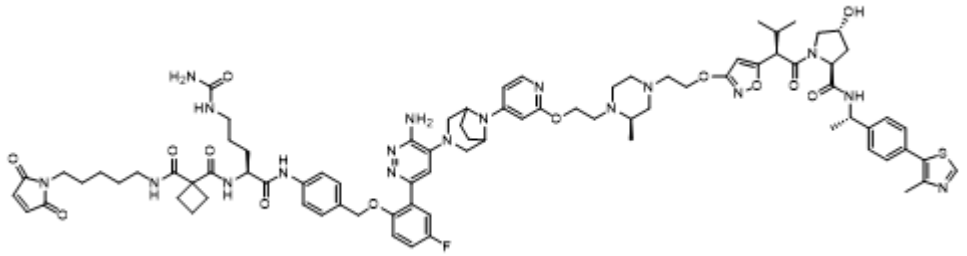
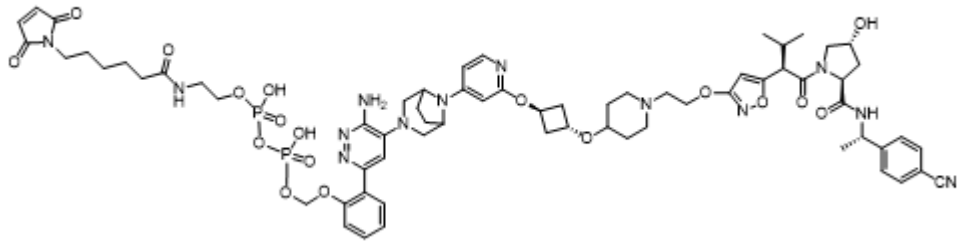
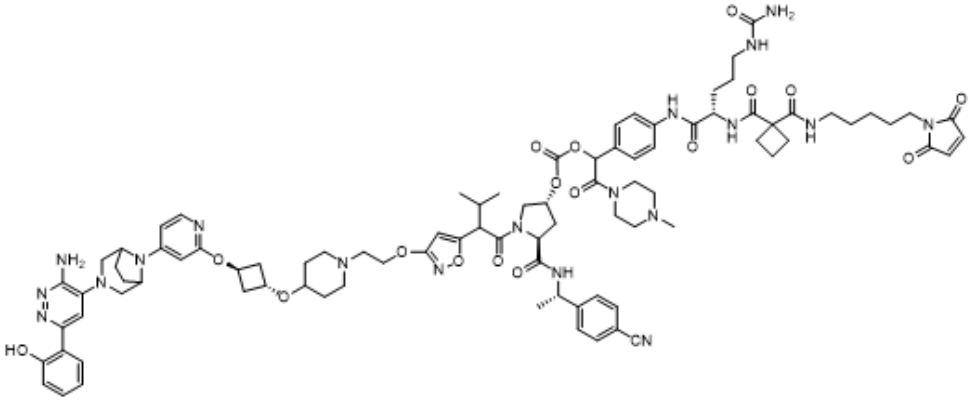
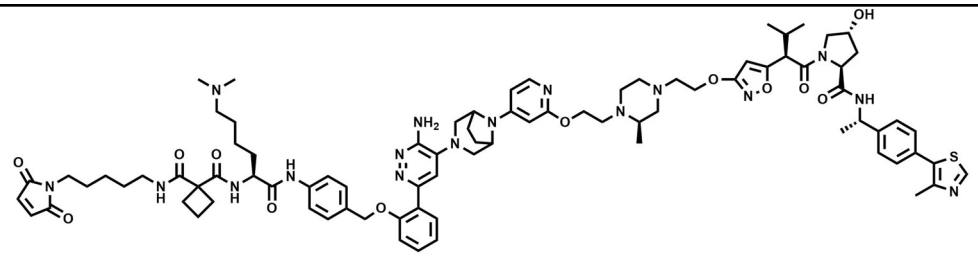
~~.~~

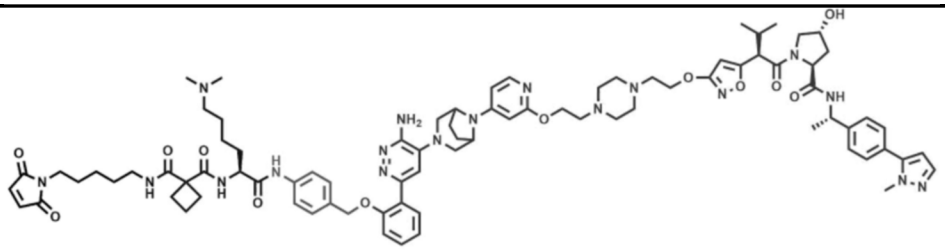
~~62~~20. ~~The conjugate of claim 1~~A compound, selected from the group consisting of:

	L1-CIDE-BRM1-10
	L1-CIDE-BRM1-9

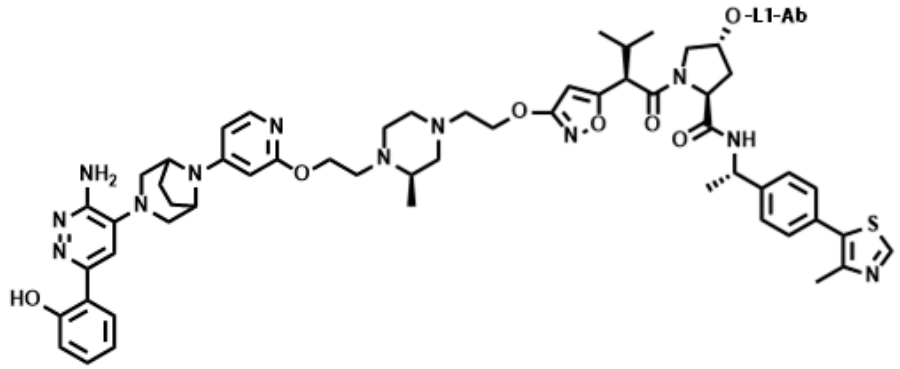
	L1-CIDE-BRM1-19
	L1-CIDE-BRM1-13
	L1-CIDE-BRM1-20
	L1-CIDE-BRM1-11

	L1-CIDE-BRM1-12
	L1-CIDE-BRM1-14
	L1-CIDE-BRM1-7
	L1-CIDE-BRM1-8

	L1-CIDE-BRM1-16
	L1-CIDE-BRM1-17
	L1-CIDE-BRM1-18
	L1-CIDE-BRM1-21

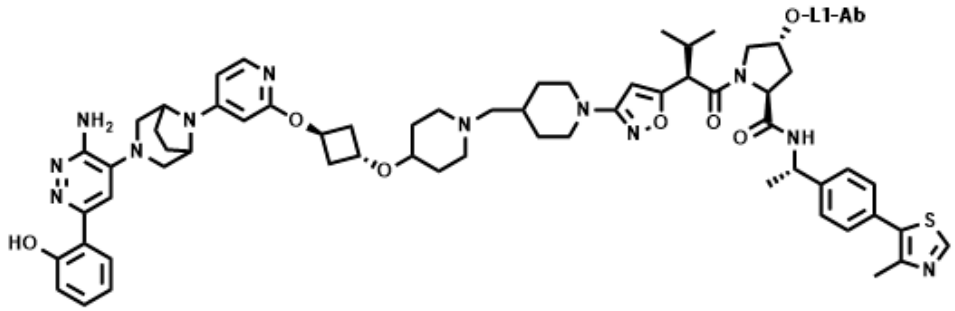
	L1-CIDE-BRM1-22

~~63~~21. The conjugate of claim 1, selected from the group consisting of:



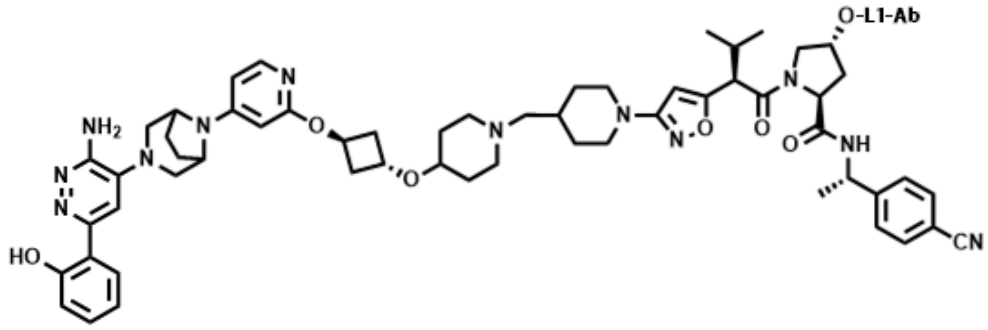
1-L2a

,



2-L2b

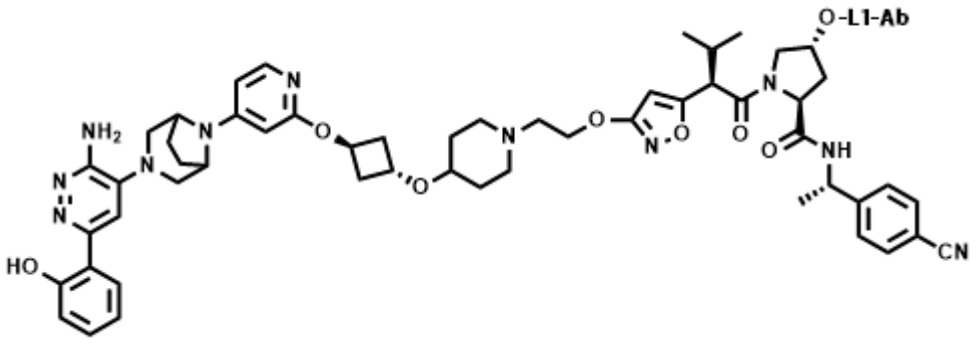
,



3-L2b

,

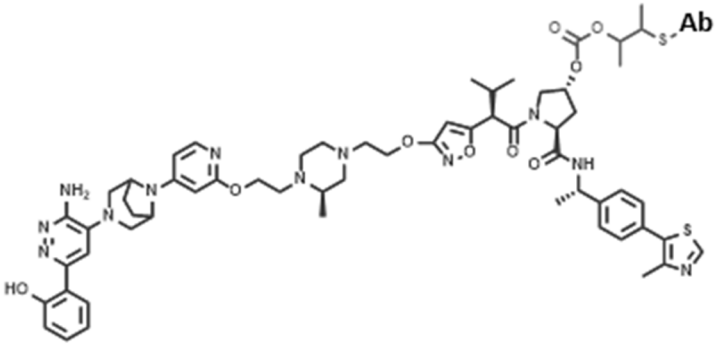
and



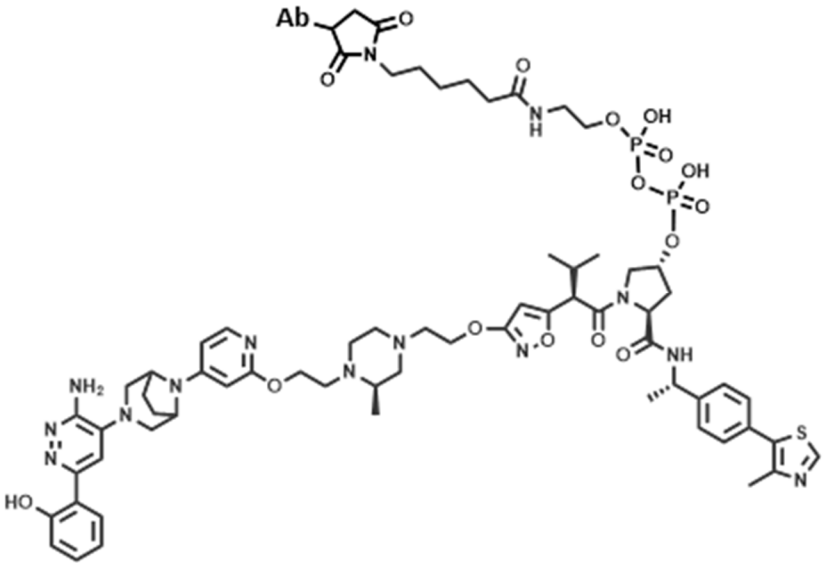
4-L2c

.

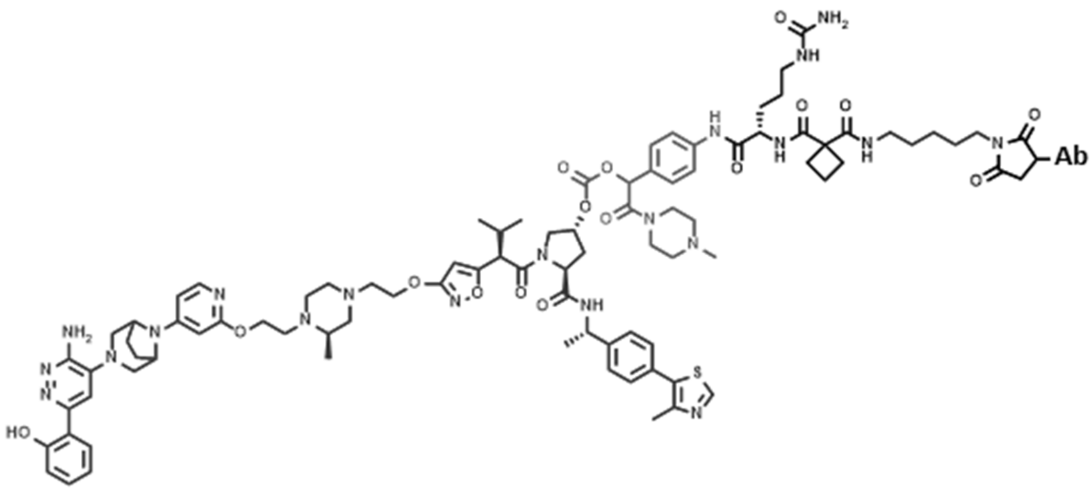
~~64~~22. The conjugate of claim 1, selected from the group consisting of:



,



, and



.

~~65~~23. The conjugate of claim 1, wherein p has a value from about 5 to about 14.

~~66~~24. The conjugate of claim 1, wherein p has a value from about 5 to about 10.

~~67~~25. A pharmaceutical composition comprising ~~a~~ the conjugate of any one of claims 1-19 and 21-24, and one or more pharmaceutically acceptable excipients.

~~68~~26. Use of the conjugate according to any one of claims 1-19 and 21-24 or the pharmaceutical composition of claim 25 ~~A method of~~in the preparation of a medicament for treating a disease in a ~~human~~ subject in need thereof~~, comprising administering to said human an effective amount of a conjugate of claim 1 or a composition of claim 47~~, wherein the disease is a cancer.

~~69. The method of claim 68, wherein said disease is cancer.~~

~~70. The method of claim 68, wherein said cancer is BRM-dependent.~~

~~71. The method of claim 68, wherein said cancer is non-small cell lung cancer.~~

~~72~~27. Use of the conjugate according to any one of claims 1-19 and 21-24 or the pharmaceutical composition of claim 25 in the preparation of a medicament for ~~A method of~~ reducing the level of ~~a target~~ BRM protein in a subject ~~comprising, administering a conjugate of claim 1 or composition of claim 69 to said subject, wherein said BRM portion binds said target BRM protein, wherein ubiquitin ligase effects degradation of said bound target BRM protein, wherein the level of said BRM target protein is reduced~~.