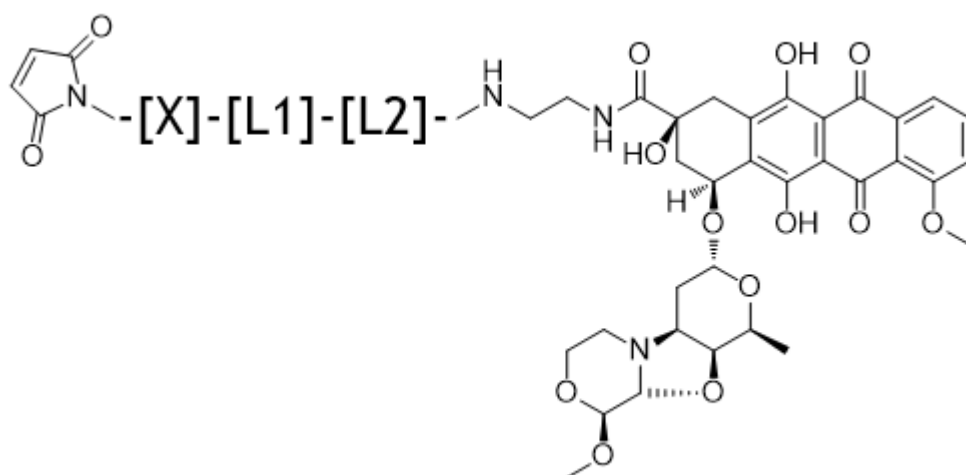


CLAIMS

1. An anthracycline (PNU) derivative of formula (I):

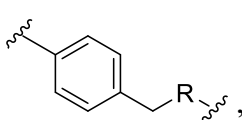
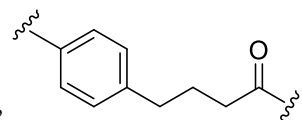


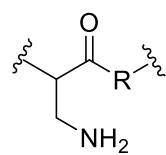
(I)

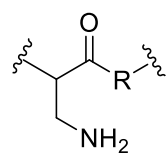
in which [X] is an optional spacer selected from the group comprising substituted or
 5 unsubstituted alkyl groups, substituted or unsubstituted heteroalkyl groups, substituted
 or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, one or more
 heteroatoms, polyethylene glycol, or a combination thereof;

[L1] and [L2] are optional linkers selected from the group consisting of valine (Val),
 citrulline (Cit), alanine (Ala), asparagine (Asn), a peptide, $-(CH_2)_n-$, $-(CH_2CH_2O)_n-$, p-
 10 aminobenzyloxycarbonyl (PAB), Val-Cit-PAB, Val-Ala-PAB, Ala-Ala-Asn-PAB, any
 amino acid except glycine, and combinations thereof, in which the anthracycline (PNU)
 derivative of formula (I) comprises [L1], [L2] or [L1] and [L2].

2. An anthracycline derivative according to Claim 1, in which [X] is selected from the

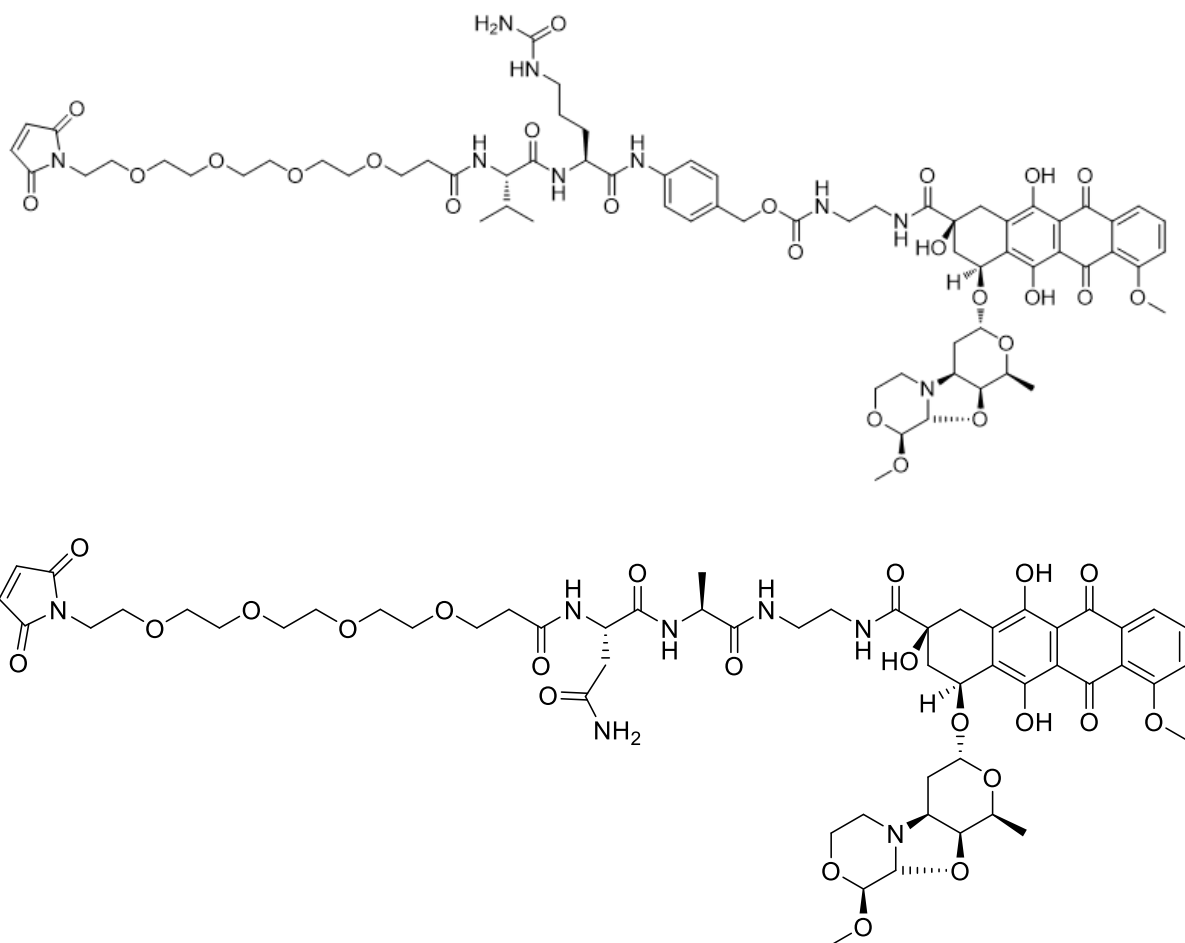
group comprising polyethylene glycol, , , and

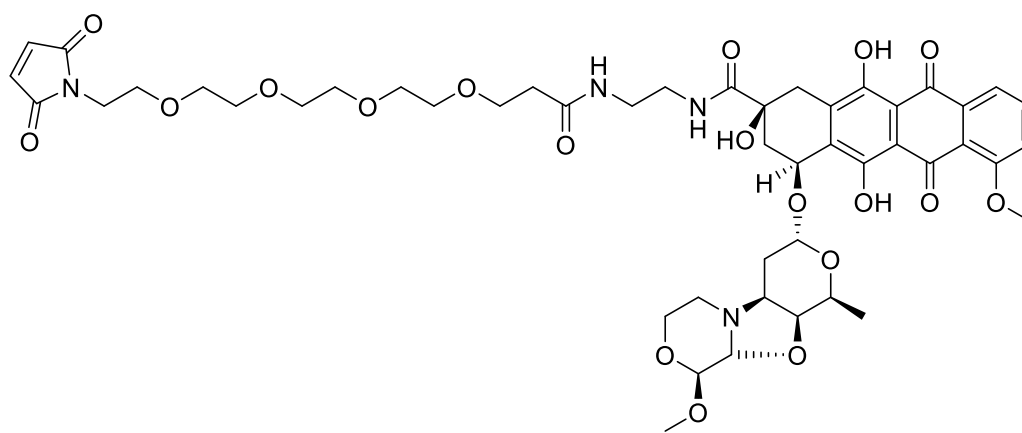
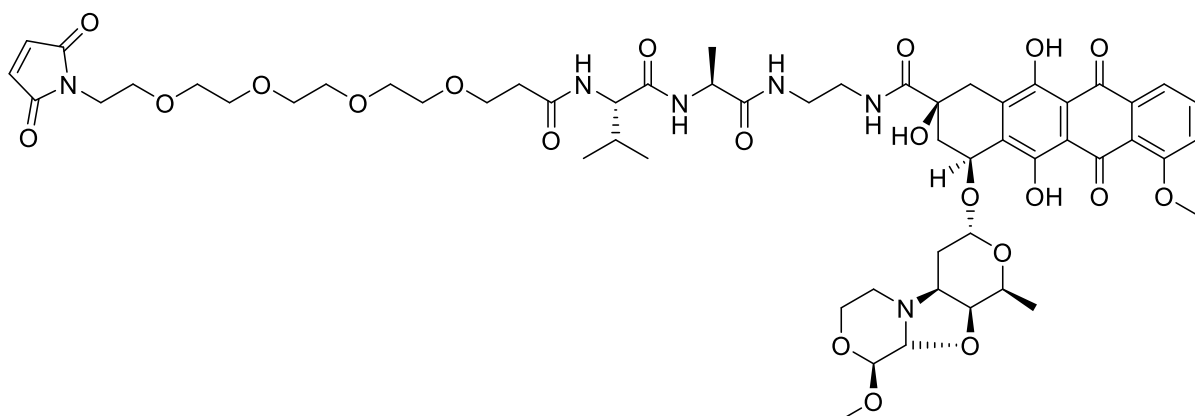


15 , in which  represents the point of attachment to the rest of the molecule and in
 which [R] is an optional spacer selected from the group comprising substituted or
 unsubstituted alkyl groups, substituted or unsubstituted heteroalkyl groups, substituted or

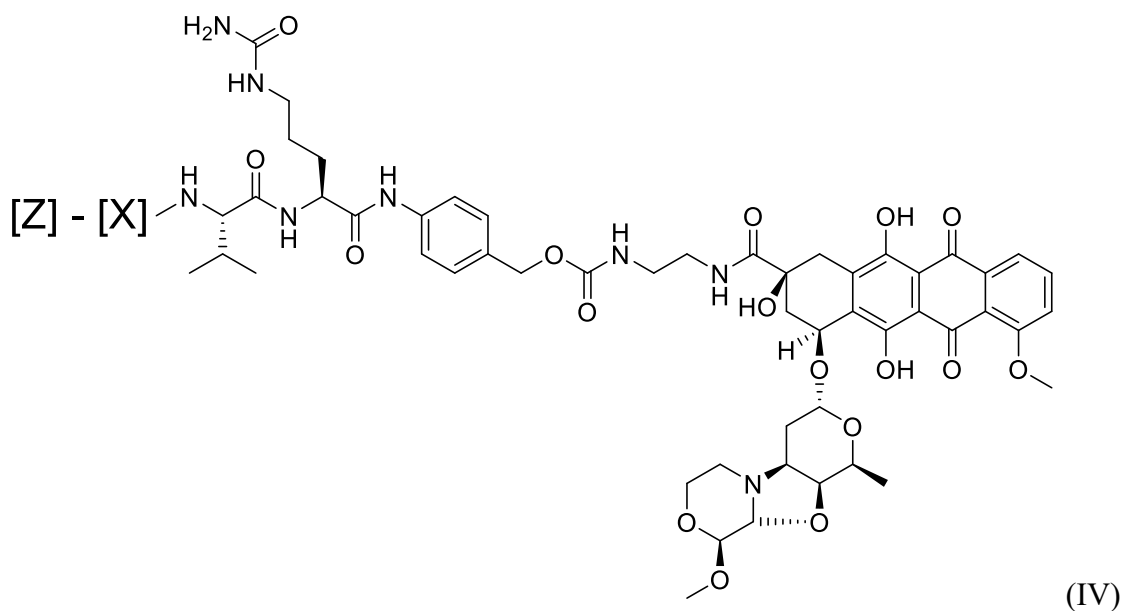
unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, one or more heteroatoms, polyethylene glycol, or a combination thereof.

3. An anthracycline derivative according to Claim 1, in which [X] is polyethylene glycol.
4. An anthracycline derivative according to Claim 1, 2 or 3, in which [L2] is p-aminobenzyloxycarbonyl (PAB) or alanine.
5. An anthracycline derivative according to Claim 1, in which the PNU derivative has a structure selected from:





6. An anthracycline (PNU) derivative of formula (IV):



5 in which [X] is an optional spacer selected from the group comprising substituted or unsubstituted alkyl groups, substituted or unsubstituted heteroalkyl groups, substituted

or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, one or more heteroatoms, polyethylene glycol, or a combination thereof;

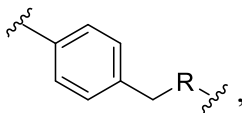
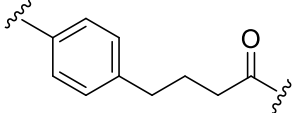
and in which [Z] is a reactive group suitable for use in a conjugation reaction.

7. An anthracycline derivative according to Claim 6, in which [Z] is selected from the group consisting of a maleimide, an alkyl halide, a sulphydryl group, an activated disulphide, an amino group, an alkyne group, an azido group, an aminoxy group, an aldehyde group and a ketone group.

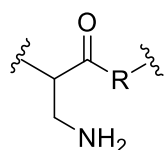
8. An anthracycline derivative according to Claim 6, in which [Z] is selected from the group consisting of polyGly and a primary amine.

9. An anthracycline derivative according to Claim 6, 7 or 8, in which [X] is selected from

the group comprising polyethylene glycol,

, and

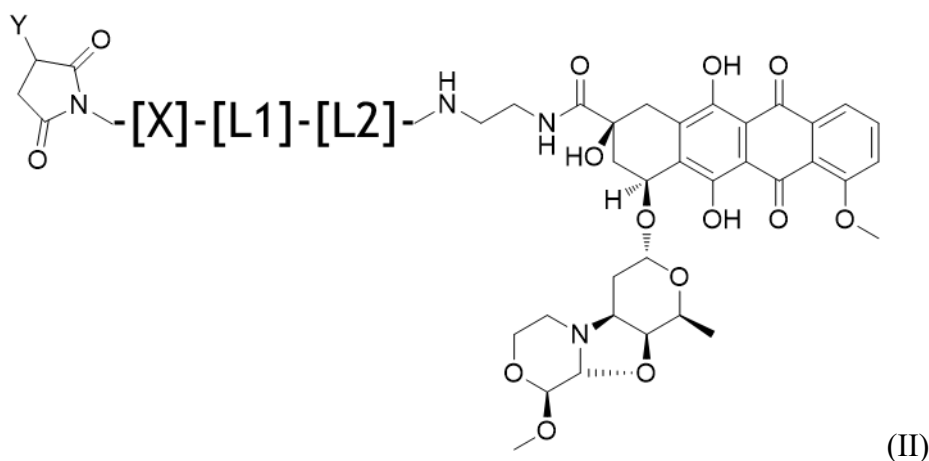


, in which  represents the point of attachment to the rest of the molecule and in

which [R] is an optional spacer selected from the group comprising substituted or unsubstituted alkyl groups, substituted or unsubstituted heteroalkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, one or more heteroatoms, polyethylene glycol, or a combination thereof.

10. An anthracycline derivative according to Claim 6, 7 or 8, in which [X] is polyethylene glycol.

11. A target-binding molecule-drug conjugate, comprising a specific antigen binding protein and an anthracycline (PNU) derivative, in which the target-binding molecule-drug conjugate has the structure of formula (II):

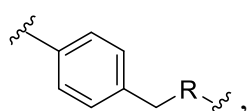


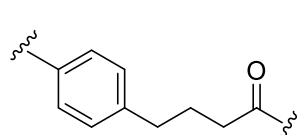
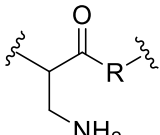
in which [X] is an optional spacer selected from the group comprising substituted or unsubstituted alkyl groups, substituted or unsubstituted heteroalkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, one or more heteroatoms, polyethylene glycol, or a combination thereof;

[L1] and [L2] are optional linkers selected from the group consisting of valine (Val), citrulline (Cit), alanine (Ala), asparagine (Asn), a peptide, $-(CH_2)_n-$, $-(CH_2CH_2O)_n-$, p-aminobenzyloxycarbonyl (PAB), Val-Cit-PAB, Val-Ala-PAB, Ala-Ala-Asn-PAB, any amino acid except glycine, and combinations thereof.; and

Y is a target-binding molecule, in which the target-binding molecule-drug conjugate of formula (II) comprises [L1], [L2] or [L1] and [L2].

12. A target-binding molecule-drug conjugate according to Claim 11, in which [X] is

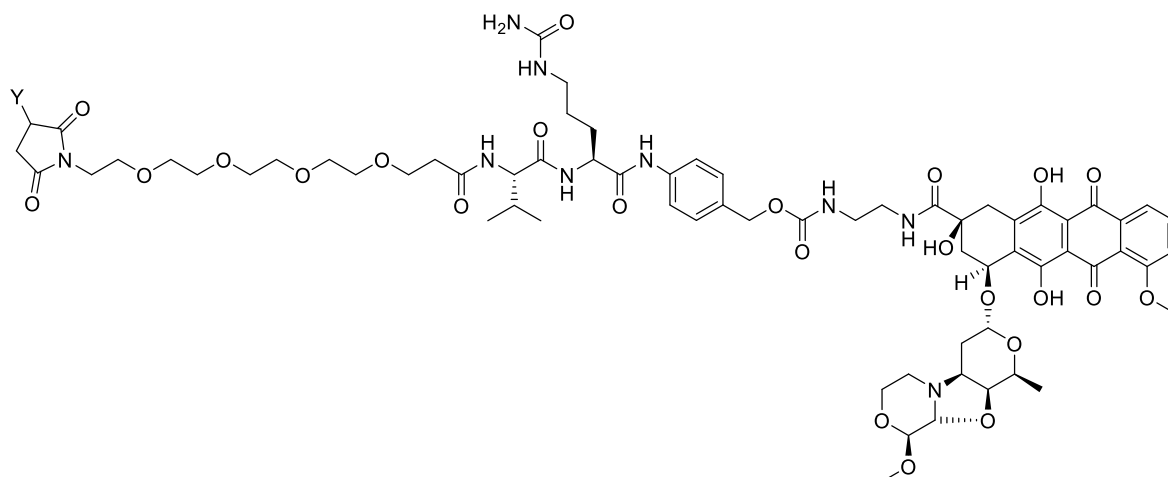
selected from the group comprising polyethylene glycol, ,

, and , in which  represents the point of attachment to

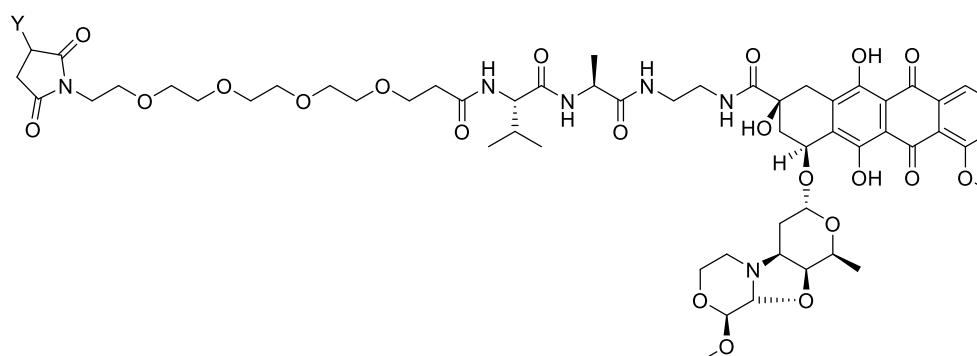
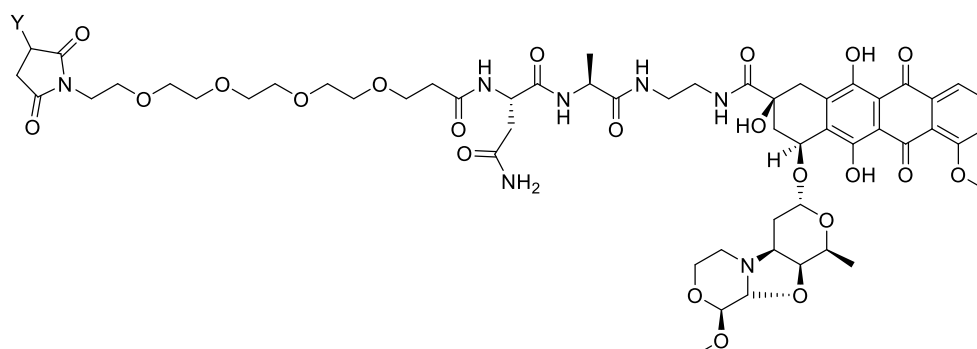
the rest of the molecule and in which [R] is an optional spacer selected from the group comprising substituted or unsubstituted alkyl groups, substituted or unsubstituted heteroalkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, one or more heteroatoms, polyethylene glycol, or a combination thereof.

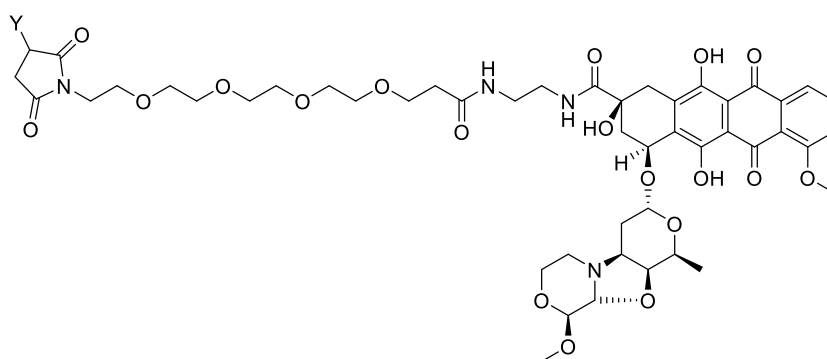
13. A target-binding molecule-drug conjugate according to Claim 11, in which [X] is polyethylene glycol.

14. A target-binding molecule-drug conjugate according to Claim 11, 12 or 13, in which [L2] is p-aminobenzyloxycarbonyl (PAB) or alanine.
15. A target-binding molecule-drug conjugate according to Claim 11, in which the PNU derivative has a structure selected from:

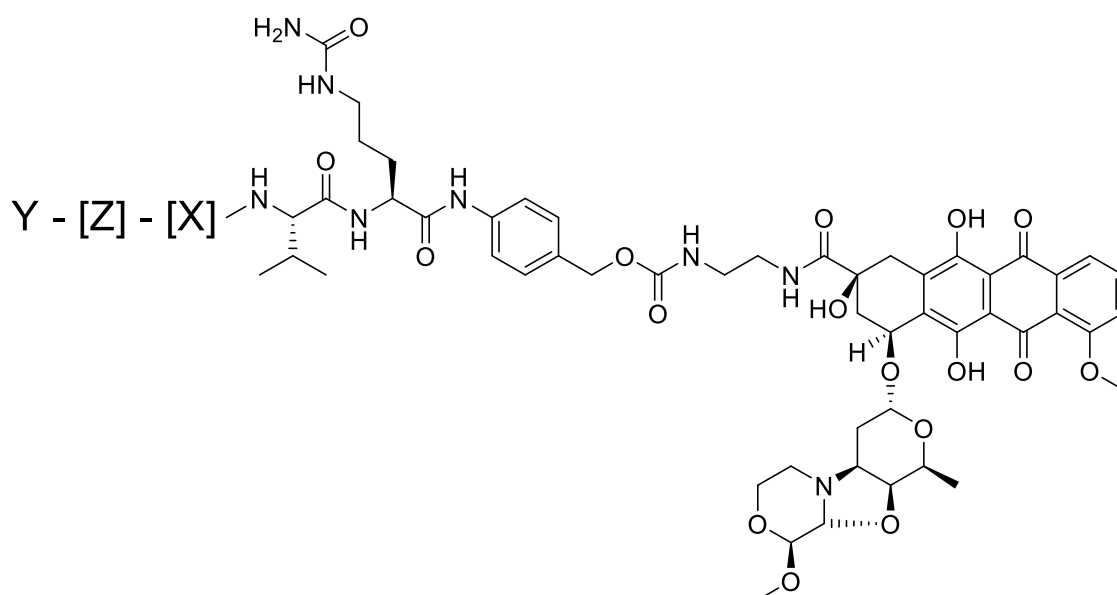


5





16. A target-binding molecule-drug conjugate, comprising a specific antigen binding protein and an anthracycline (PNU) derivative, in which the target-binding molecule-drug conjugate has the structure of formula (V):



(V)

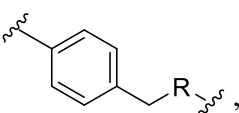
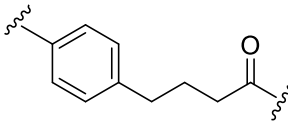
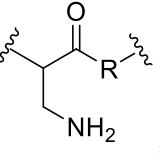
in which [X] is an optional spacer selected from the group comprising substituted or unsubstituted alkyl groups, substituted or unsubstituted heteroalkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, one or more heteroatoms, polyethylene glycol, or a combination thereof;

[Z] is a linker derived from a reactive group used to conjugate the anthracycline (PNU) derivative and the target-binding molecule; and

Y is a target binding molecule.

17. A target-binding molecule-drug conjugate according to Claim 16, in which [Z] is selected from the group consisting of a disulphide bond, an amide bond, an oxime bond, a hydrazone bond, a thioether bond, a 1, 2, 3 triazole and polyGly.

18. A target-binding molecule-drug conjugate according to Claim 16 or 17, in which [X] is

5 selected from the group comprising polyethylene glycol, , , and , in which  represents the point of attachment to the rest of the molecule and in which [R] is an optional spacer selected from the group comprising substituted or unsubstituted alkyl groups, substituted or unsubstituted heteroalkyl groups, substituted or unsubstituted aryl groups, substituted or unsubstituted heteroaryl groups, one or more heteroatoms, polyethylene glycol, or a combination thereof.

10

19. A target-binding molecule-drug conjugate according to Claim 16 or 17, in which [X] is polyethylene glycol.

20. A target-binding molecule-drug conjugate according to any of Claims 11 to 19, in which the target-binding molecule is a protein and anthracycline (PNU) derivative is conjugated to a thiol-containing amino acid residue in the amino acid sequence of the protein or in which the PNU derivative is conjugated via a thiol moiety incorporated by chemical modification at the N-terminus or C-terminus of the amino acid sequence of the protein.

15

21. A target-binding molecule-drug conjugate according to any of Claims 11 to 20, in which the target-binding molecule is a binding protein selected from the group comprising an immunoglobulin or antibody, an immunoglobulin Fc region, an immunoglobulin Fab region, a Fab', a Fv, a Fv-Fc, a single chain Fv (scFv), scFv-Fc, (scFv)₂, a diabody, a triabody, a tetrabody, a bispecific t-cell engager (BiTE), an intein, a VNAR domain, a single domain antibody (sdAb), a VH domain, or a scaffold protein.

20

22. A target-binding molecule-drug conjugate according to any of Claims 11 to 21, where the target-binding molecule binds to receptor tyrosine kinase-like orphan receptor 1 (ROR1).

25

23. A target-binding molecule-drug conjugate according to any of Claims 11 to 21, in which the target-binding molecule is a specific antigen binding protein comprising an amino acid sequence represented by the formula (III):



5 in which

FW1 is a framework region

CDR1 is a CDR sequence

FW2 is a framework region

HV2 is a hypervariable sequence

10 FW3a is a framework region

HV4 is a hypervariable sequence

FW3b is a framework region

CDR3 is a CDR sequence

FW4 is a framework region.

15 24. A target-binding molecule-drug conjugate according to Claim 23, in which the specific antigen binding protein binds receptor tyrosine kinase-like orphan receptor 1 (ROR1).

25. A target-binding molecule-drug conjugate according to Claim 24, in which the ROR1-specific antigen binding protein does not bind to receptor tyrosine kinase-like orphan receptor 2 (ROR2).

20 26. A target-binding molecule-drug conjugate according to Claim 24 or 25, in which the ROR1-specific antigen binding protein binds to both human ROR1 and murine ROR1 (mROR1).

27. A target-binding molecule-drug conjugate according to Claim 24, 25 or 26, in which the ROR1-specific antigen binding protein binds to deglycosylated ROR1.

25 28. A target-binding molecule-drug conjugate according to any of Claims 24 to 27, in which the ROR1-specific antigen binding protein does not bind to a linear peptide sequence selected from:

YMESLHMQGEIENQI (SEQ ID NO: 34)

CQPWNSQYPHTHTFTALRFP (SEQ ID NO: 35)

RSTIYGSRLRIRNLDTTDTGYFQ (SEQ ID NO: 36)

QCVATNGKEVVSSTGVLFVKFGPPPTASPGYSDEYE (SEQ ID NO: 37)

- 5 29. A target-binding molecule-drug conjugate according to any of Claims 24 to 28, in which

FW1 is a framework region of from 20 to 28 amino acids

CDR1 is a CDR sequence selected from DTSYGLYS (SEQ ID NO: 1), GAKYGLAA (SEQ ID NO: 2), GAKYGLFA (SEQ ID NO: 3), GANYGLAA (SEQ ID NO: 4), or GANYGLAS (SEQ ID NO: 5)

- 10 FW2 is a framework region of from 6 to 14 amino acids

HV2 is a hypervariable sequence selected from TTDWERMSIG (SEQ ID NO: 6), SSNQERISIS (SEQ ID NO: 7), or SSNKEQISIS (SEQ ID NO: 8)

FW3a is a framework region of from 6 to 10 amino acids

- 15 HV4 is a hypervariable sequence selected from NKRAK (SEQ ID NO: 9), NKRTM (SEQ ID NO: 10), NKGAK (SEQ ID NO: 11), or NKGTK (SEQ ID NO: 12)

FW3b is a framework region of from 17 to 24 amino acids

- 20 CDR3 is a CDR sequence selected from QSGMAISTGSGHGYNWY (SEQ ID NO: 13), QSGMAIDIGSGHGYNWY (SEQ ID NO: 14), YPWAMWGQWY (SEQ ID NO: 15), VFMPQHWHPAAHWY (SEQ ID NO: 16), REARHPWLRQWY (SEQ ID NO: 17), or YPWGAGAPWLVQWY (SEQ ID NO: 18)

FW4 is a framework region of from 7 to 14 amino acids

or a variant thereof with at least 90% sequence identity thereto,

30. A target-binding molecule-drug conjugate according to any of Claims 24 to 29, in which FW1 is selected from: ASVNQTPRTATKETGESLTINCVLT (SEQ ID NO: 19),
 25 AKVDQTPRTATKETGESLTINCVLT (SEQ ID NO: 20),
 TRVDQTPRTATKETGESLTINCVVT (SEQ ID NO: 21),
 TRVDQTPRTATKETGESLTINCVLT (SEQ ID NO: 22),
 ASVNQTPRTATKETGESLTINCVVT (SEQ ID NO: 23),
 TRVDQSPSSLSASVGDRVITITCVLT (SEQ ID NO: 24) or

ASVTQSPRSASKETGESLTITCRVT (SEQ ID NO: 56), FW2 is selected from:
 TSWFRKNPG (SEQ ID NO: 25), or TYWYRKNPG (SEQ ID NO: 26); FW3a is selected
 from: GRYVESV (SEQ ID NO: 27), or GRYSESV (SEQ ID NO: 28), FW3b is selected from:
 SFSRLRIKDLTVADSATYYCKA (SEQ ID NO: 29), SFTLTISSLQPEDSATYYCRA (SEQ
 5 ID NO: 30), SFTLTISSLQPEDFATYYCKA (SEQ ID NO: 31) or
 SFSLRISSLTVEDSATYYCKA (SEQ ID NO: 57), and FW4 is selected from:
 DGAGTVLTVN (SEQ ID NO: 32), DGAGTKVEIK (SEQ ID NO: 33) or DGQGTKLEVK
 (SEQ ID NO: 58); or functional variants thereof with a sequence identity of at least 45%.

31. A target-binding molecule-drug conjugate according to any of Claims 24 to 30, in which
 10 the ROR1-specific antigen binding molecule comprises an amino acid sequence selected from:

ASVNQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERM SIGGR
 YVESVNKRAKSFSRLRIKDLTVADSATYYCKAQSGMAISTGSGHGYNWYDGAG
 TVLTVN (SEQ ID NO: 39);

AKVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERM SIGGR
 15 YVESVNKRAKSFSRLRIKDLTVADSATYYCKAQSGMAIDIGSGHGYNWYDGAGT
 VLTVN (SEQ ID NO: 40);

TRVDQTPRTATKETGESLTINCVTGAKYGLAATYWYRKNPGSSNQERISISGR
 YVESVNKRTMSFSRLRIKDLTVADSATYYCKAYPWAMWGQWYDGAGTVLTVN
 (SEQ ID NO: 41);

20 TRVDQTPRTATKETGESLTINCVTGAKYGLFATYWYRKNPGSSNQERISISGR
 YVESVNKRTMSFSRLRIKDLTVADSATYYCKAVFMPQHWHPAAHWYDGAGTVL
 TVN (SEQ ID NO: 42);

TRVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERM SIGGR
 YVESVNKGAKSFSRLRIKDLTVADSATYYCKAREARHPWLRQWYDGAGTVLTV
 25 N (SEQ ID NO: 43);

ASVNQTPRTATKETGESLTINCVTGANYGLAATYWYRKNPGSSNQERISISGR
 YVESVNKRTMSFSRLRIKDLTVADSATYYCKAYPWGAGAPWLQWYDGAGTV
 LTVN (SEQ ID NO: 44);,

TRVDQSPSSLSASVGDRVTITCVLTGANYGLASTYWYRKNPGSSNKEQISISGRY
 30 SESVNKGTKSFTLTISSLQPEDSATYYCRAYPWGAGAPWLQWYDGAGTKVEI
 K (SEQ ID NO: 45);

TRVDQSPSSLSASVGDRVTITCVLTGANYGLASTYWYRKNPGSSNQERISISGRY
 SESVNKRRTMSFTLTISLQPEDSATYYCRAYPWGAGAPWLVQWYDGAGTKVEI
 K (SEQ ID NO: 46);

5 TRVDQSPSSLSASVGDRVTITCVLTDTSYGLYSTSWFRKNPGTTDWERMSIGGR
 YVESVNKGAKSFTLTISLQPEDFATYYCKAREARHPWLRQWYDGAGTKVEIK
 (SEQ ID NO: 47);

TRVDQSPSSLSASVGDRVTITCVLTDTSYGLYSTYWYRKNPGSSNKEQISISGRY
 SESVNKGTKSFTLTISLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK
 (SEQ ID NO: 48);

10 TRVDQSPSSLSASVGDRVTITCVLTDTSYGLYSTYWYRKNPGTTDWERMSIGGR
 YSESVNKGAKSFTLTISLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK
 (SEQ ID NO: 49);

15 ASVTQSPRSASKETGESLTITCRVTGANYGLAATYWYRKNPGSSNQERISISGRY
 SESVNKRRTMSFSLRISSLTVEDSATYYCKAYPWGAGAPWLVQWYDGQGTKLE
 VK (SEQ ID NO: 59);

or a functional variant thereof with a sequence identity of at least 45%.

32. A target-binding molecule-drug conjugate according to any of Claims 24 to 31, in which the ROR1-specific antigen binding protein is humanized.

20 33. A target-binding molecule-drug conjugate according to any of Claims 24 to 31, in which the ROR1-specific antigen binding protein is de-immunized.

34. A target-binding molecule-drug conjugate according to any of Claims 22 to 33, for use in therapy.

35. A target-binding molecule-drug conjugate according to any of Claims 22 to 33, for use in the treatment of cancer.

25 36. A target-binding molecule-drug conjugate according to any of Claims 11 to 21, in which the target-binding molecule is an antibody.

37. A target-binding molecule-drug conjugate according to Claim 36, in which the antibody is an antibody that binds HER-2.

38. A target-binding molecule-drug conjugate according to Claim 37, in which the antibody is trastuzumab or a derivative thereof.

39. A pharmaceutical composition comprising a target-binding molecule-drug conjugate according to any of Claims 22 to 33 or 36 to 38, and at least one other pharmaceutically

5 acceptable ingredient.