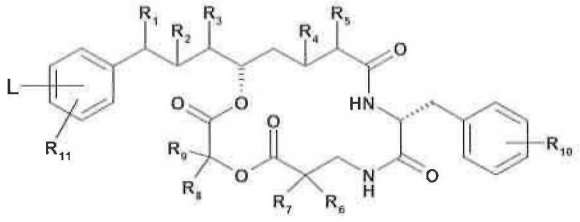
CLAIMS

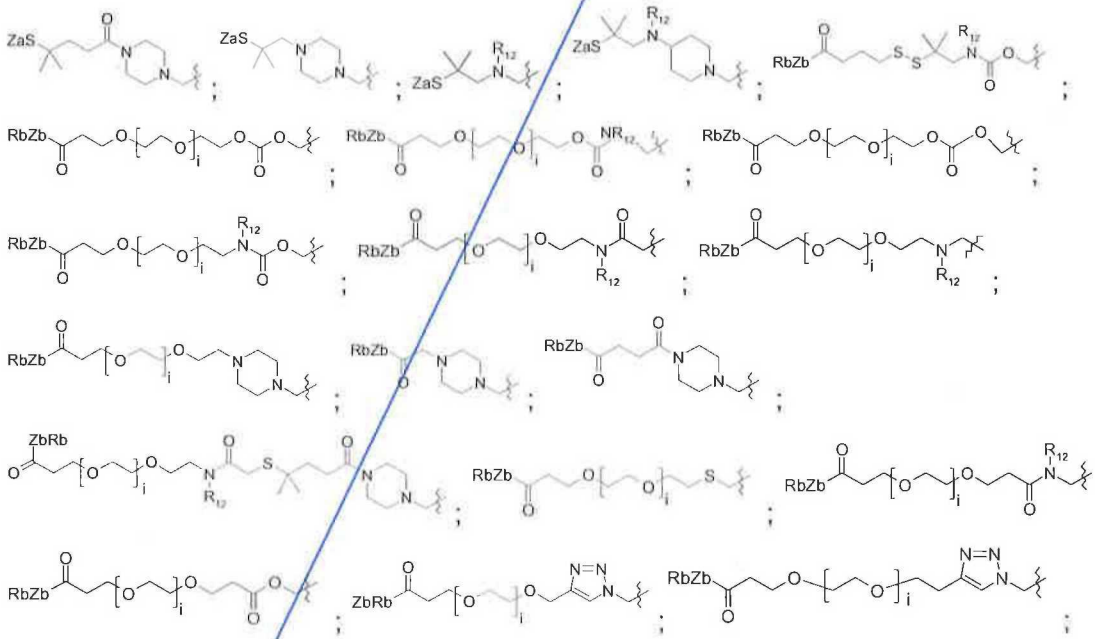
1. Cryptophycin derivative of formula (II):

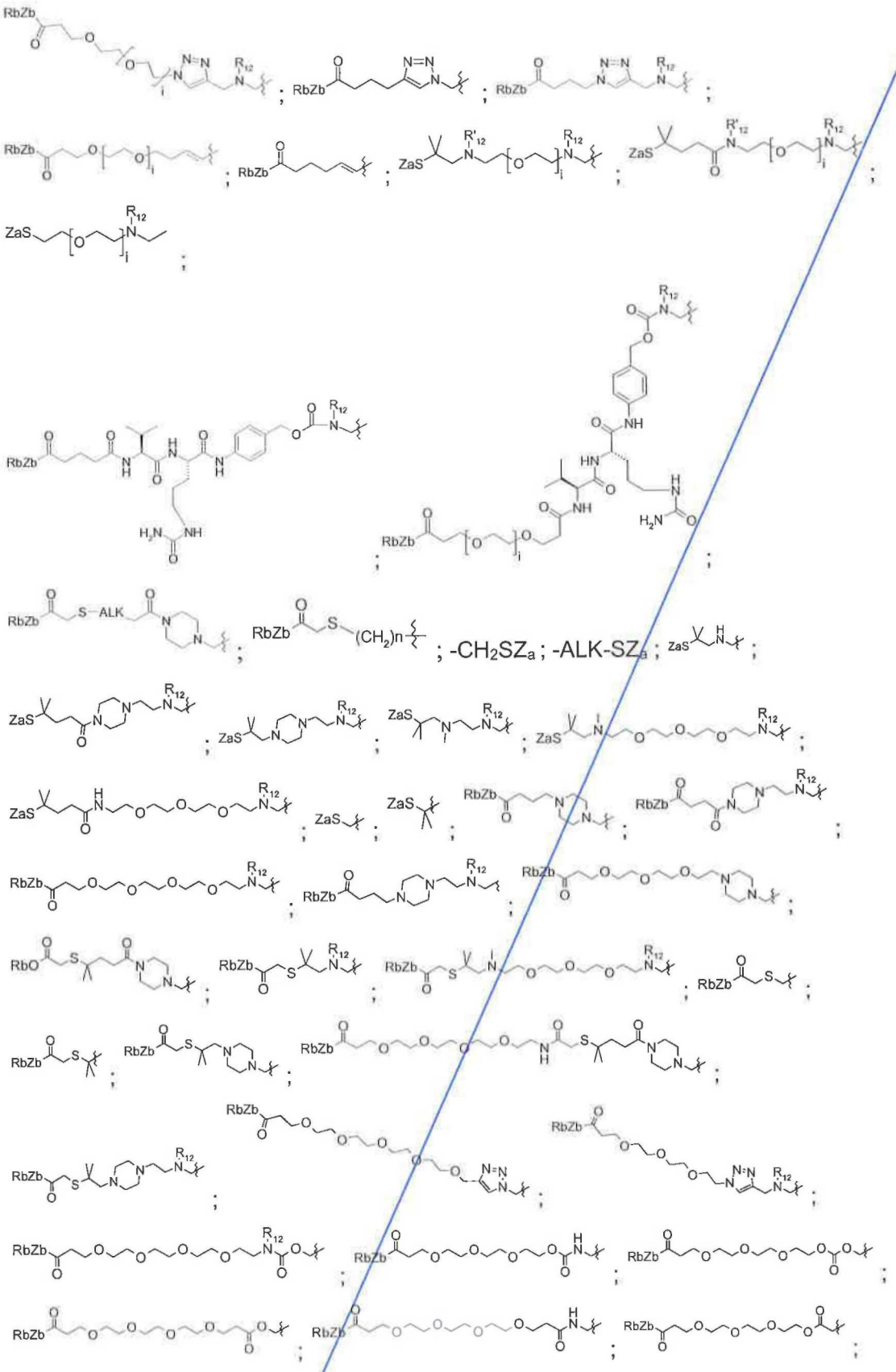


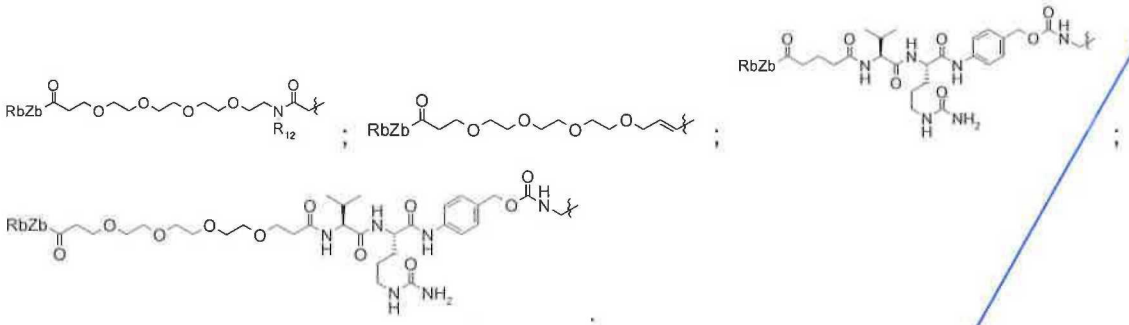
(II)

in which:

- **R_1** represents a halogen atom and **R_2** represents a group –OH, an acyl group derived from an amino acid **AA** or a group (C_1-C_4)alkanoyloxy;
  or alternatively **R_1** and **R_2** form an epoxide unit;
- **AA** denotes a natural or unnatural amino acid;
- **R_3** represents a group (C_1-C_6)alkyl;
- **R_4** and **R_5** both represent H or together form a double bond CH=CH between C13 and C14;
- **R_6** and **R_7** represent, independently of each other, H or a group (C_1-C_6)alkyl;
- **R_8** and **R_9** represent, independently of each other, H or a group (C_1-C_6)alkyl;
- **R_{10}** represents at least one substituent of the phenyl nucleus chosen from: H, a group OH, (C_1-C_4)alkoxy, a halogen atom or a group -NH_2, -NH(C_1-C_6)alkyl or -N(C_1-C_6)alkyl$_2$;
- **R_{11}** represents at least one substituent of the phenyl nucleus chosen from H and a group (C_1-C_4)alkyl;
- **L** represents a linker in the ortho (o), meta (m) or para (p) position, preferably in the para position, of the phenyl nucleus wherein L is chosen from:




RbZb
ZaS
; -CH2SZa ; -ALK-SZa ;



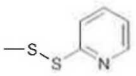
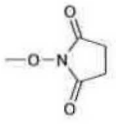
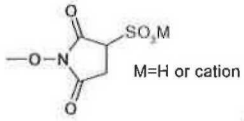
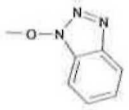
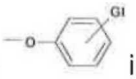
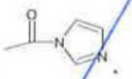
- R_{12} and R'_{12} represent, independently of each other, H or a group $(C_1\text{-}C_6)$alkyl, more particularly a methyl group;
- **i** represents an integer ranging from 1 to 20, more particularly from 1 to 10, even more particularly from 1 to 8, or from 1 to 6, and even more particularly from 2 to 5;
- Z_a represents H or a group $-SR_a$, R_a representing a group $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, heteroaryl or $(C_3\text{-}C_7)$heterocycloalkyl;
- Z_b represents a single bond, -O- or -NH-, R_b representing H or a group $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, heteroaryl or $(C_3\text{-}C_7)$heterocycloalkyl.

2. Cryptophycin derivative according to Claim 1, in which R_{10} represents at least one substituent on the phenyl nucleus chosen from: H, a group OH, (C_1-C_4)alkoxy, a halogen atom.

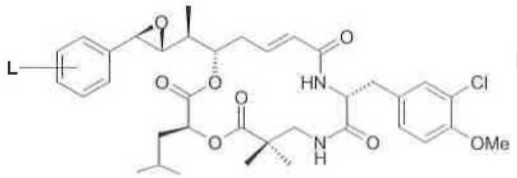
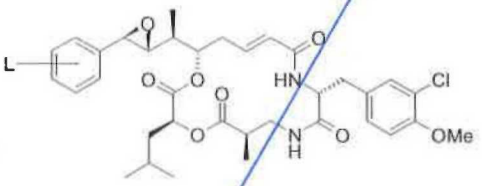
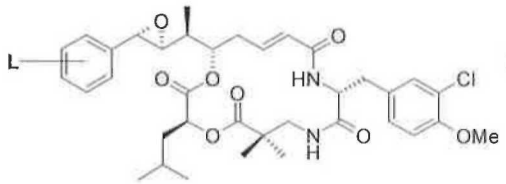
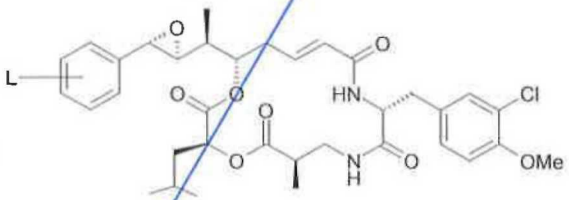
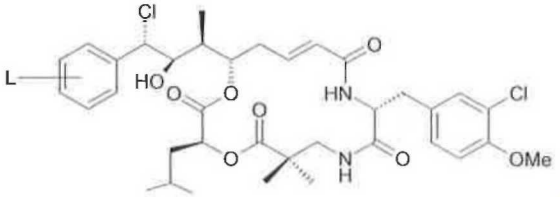
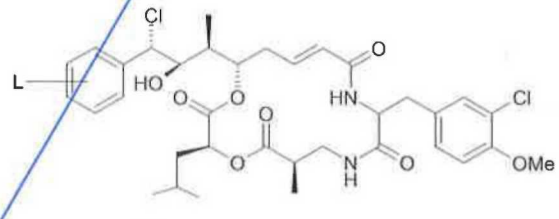
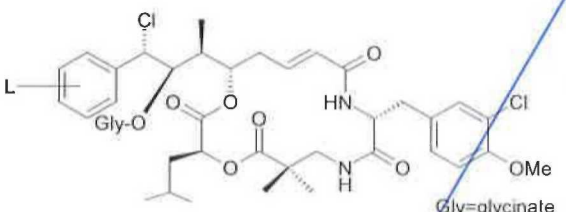
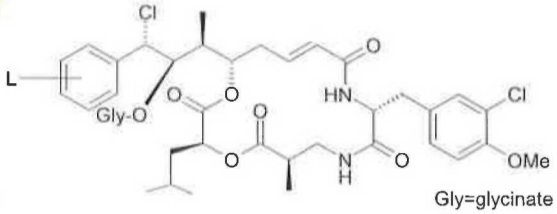
3. Cryptophycin derivative according to Claim 1, in which R_{12} represents H.

4. Cryptophycin derivative according to Claim 1, in which R_{12} represents $(C_1\text{-}C_6)$alkyl, more particularly a methyl group.

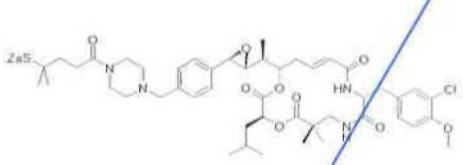
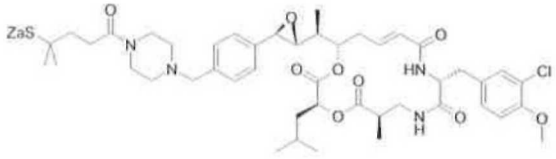
5. Cryptophycin derivative according to Claims 1 to 4, in which $\mathbf{Z_a}$ represents H or

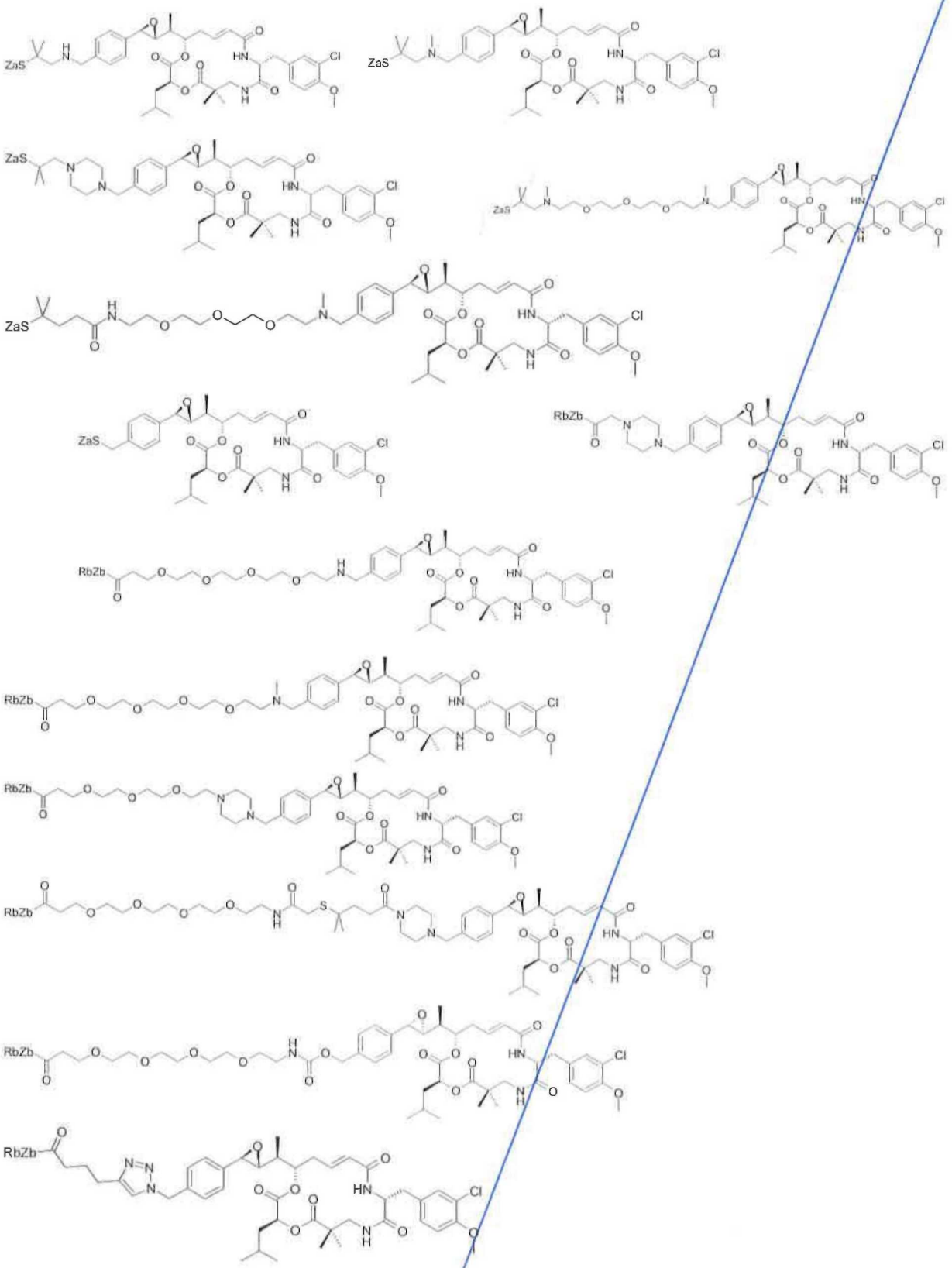
–S(C_1-C_6)alkyl, especially –SMe, ou –S-heteroaryl, especially  or Z_bR_b represents –O(C_1-C_6)alkyl, -OH, -OCH_3, -$OCH_2CH=CH_2$,  or   or the group  in which **Gl** represents at least one electroinductive group, or alternatively in which –C(=O)Z_bR_b represents .

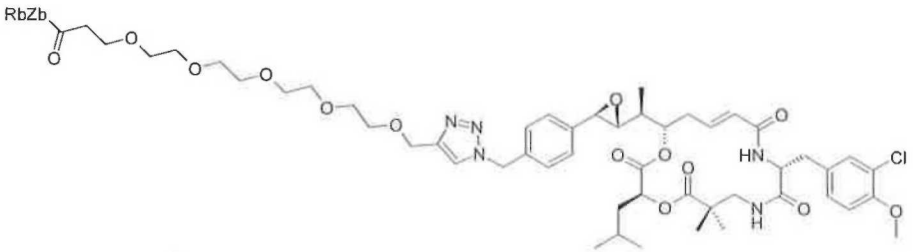
6. Cryptophycin derivative according to one of Claims 1 to 5 defined according to one of the following formulae, **L** preferably being in the para position:

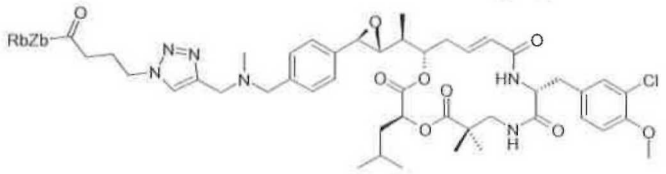







Gly=glycinate

Gly=glycinate

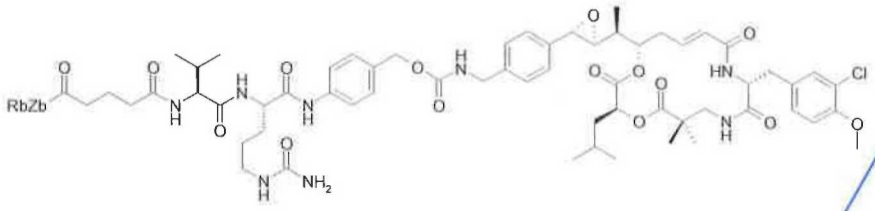
7. Cryptophycin derivative according to Claim 1, chosen from:

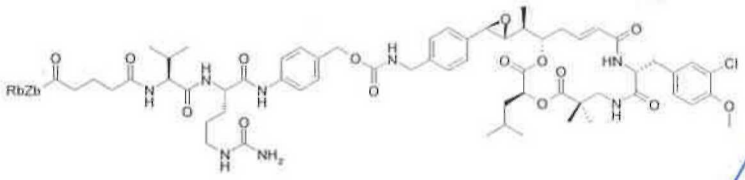




ZaS
RbZb
Cl
HN
O
N
H



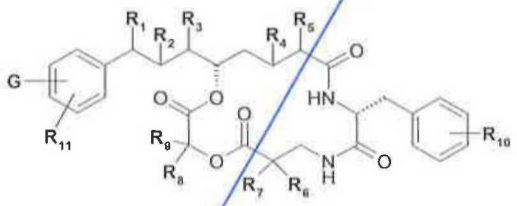




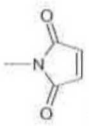
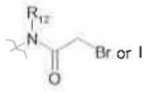


Z_a, Z_b and R_b being as defined in Claim 1 or 5.

8. Cryptophycin derivative of formula (III):



in which the groups **R_1** to **R_{11}** have the same meanings as in Claim 1, 6 or 7 and **G** represents a group $-(CH_2)_nY$, which is in an ortho (o), meta (m) or para (p) position on the phenyl nucleus bearing the unit CR_1, preferably in the para position,

n being an integer ranging from 1 to 6 and Y denoting $-N_3$; $-NR_{12}-CH_2-C\equiv CH$ in which **R_{12}** represents H or a group (C_1-C_6)alkyl; -OMs; -OC(=O)-O-(4-nitrophenyl),  or 

, R_{12} representing H or (C_1-C_6)alkyl, more particularly a methyl group.

9. Cryptophycin derivative according to Claim 8, in which Y represents $-N_3$; $-NR_{12}-CH_2-C\equiv CH$ in which R_{12} represents H or a group (C_1-C_6)alkyl; -OMs or $-OC(=O)-O-$(4-nitrophenyl).

10. Cryptophycin derivative according to one of Claims 1 to 7 or according to formula (III) of Claim 8 with G= $-(CH_2)_nY$ with Y= -Cl, $-N_3$, -OH, $-NH_2$, maleimido, haloacetamido intended to be conjugated to a binding agent.

11. Cryptophycin derivative according to Claim 10, in which the binding agent is a ligand, a protein, an antibody, more particularly a monoclonal antibody, a protein or antibody fragment, a peptide, an oligonucleotide or an oligosaccharide.

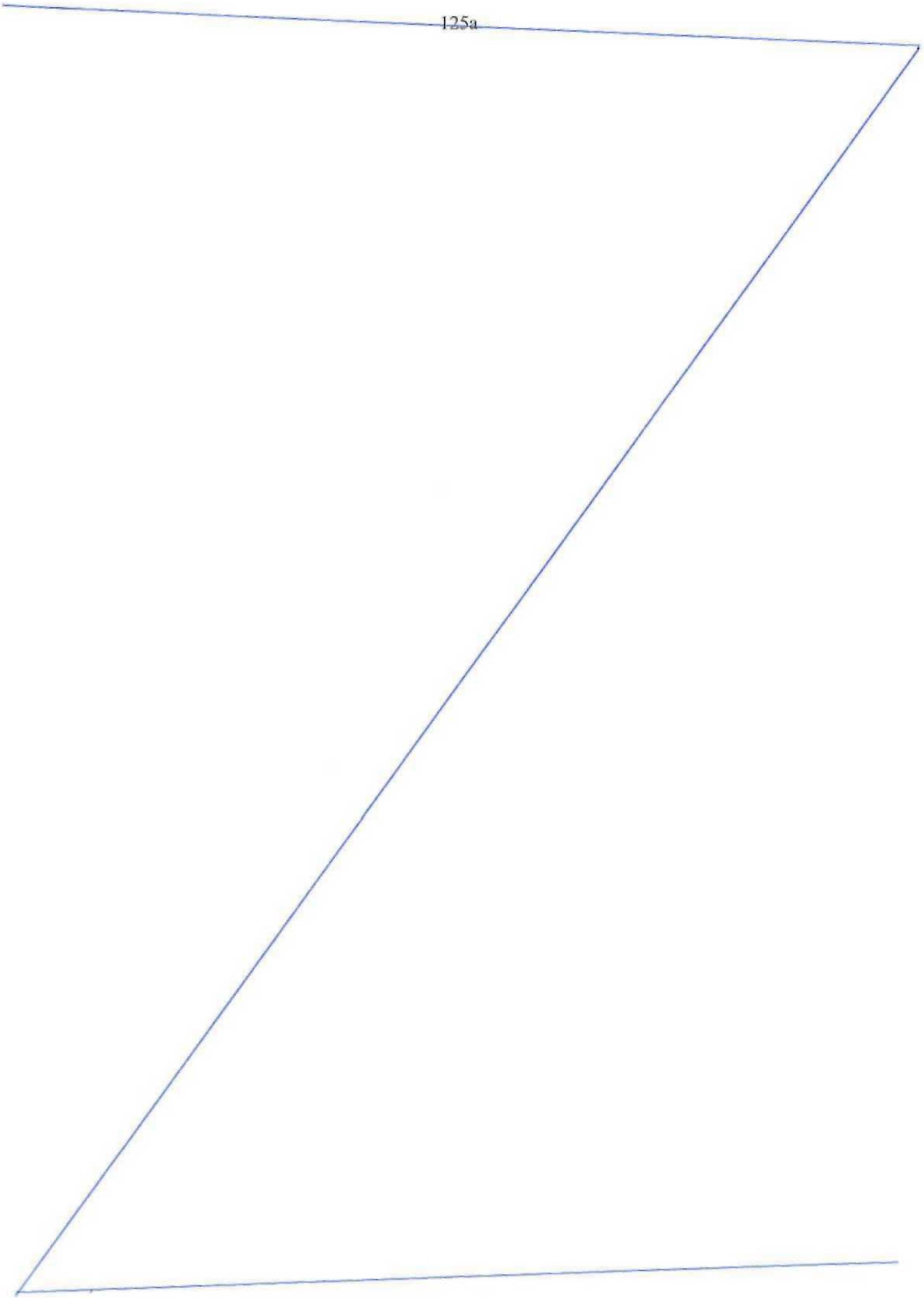
12. Process for preparing a binding agent to which is attached at least one cryptophycin derivative, referred to as a conjugate, which consists in:

(i) placing in contact and leaving to react an aqueous solution of an optionally buffered binding agent and a solution of the cryptophycin derivative as defined in one of Claims 1 to 11;

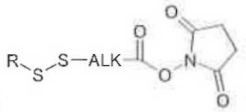
(ii) and then in optionally separating the conjugate formed in step (i) from the cryptophycin derivative and/or the unreacted binding agent and/or any aggregates formed,

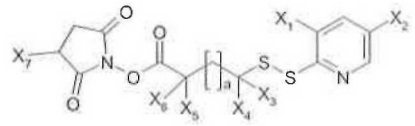
wherein

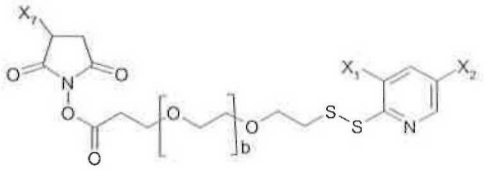
- in the presence of a cryptophycin derivative comprising a reactive chemical group of the type $-SZ_a$ in the linker L, the binding agent comprises:
  - disulfide chemical groups in the case where $-SZ_a$ represents –SH;
  - thiol chemical groups in the case where $Z_a \neq H$;
  - maleimido or iodoacetamido chemical groups in the case where $-SZ_a$ represents –SH;
- in the presence of a cryptophycin derivative comprising a reactive chemical group of the type $-C(=O)-Z_bR_b$ in the linker L, the cryptophycin derivative is reacted with the amino functions of the binding agent, especially the ε-amino groups borne by the side chains of the lysine residues (Lys) of an antibody;
- in the presence of a cryptophycin derivative of formula (III) with G= $-(CH_2)_nY$, the binding agent comprises groups –SH when Y= -Cl or -maleimido, groups $-C\equiv CH$ when Y= $-N_3$ or carboxylic acid groups when Y= -OH or $-NH_2$.

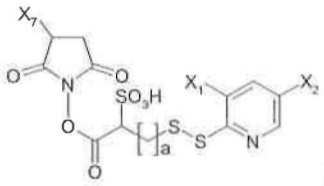
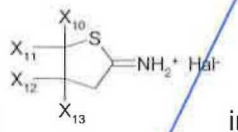


13. Process according to Claim 12, in which:

- in the presence of a cryptophycin derivative comprising a reactive chemical group of the type -SZ_a in the linker L, the binding agent is modified with a modifying agent chosen from a compound of formula:  in which R represents a group (C_1-C_6)alkyl, aryl, heteroaryl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl and ALK represents a group (C_1-C_6)alkylene;

, a pegylated analogue of formula:

 or a sulfonic analogue of formula

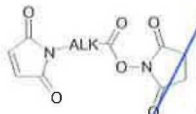
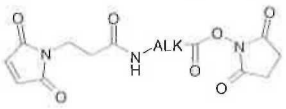
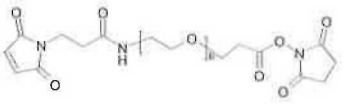
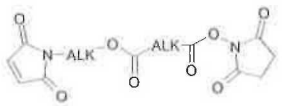
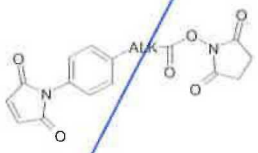
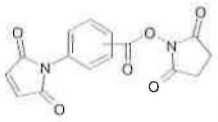
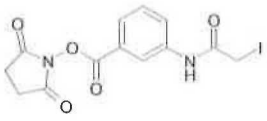
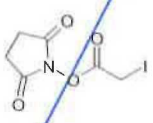
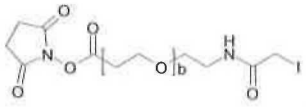
 in which X_3, X_4, X_5 and X_6 represent H or a group (C_1-C_6)alkyl, X_1 and X_2 represent -H, -$CONX_8X_9$, -NO_2, X_8 and X_9 representing H or a group (C_1-C_6)alkyl, X_7 represents -$SO_3^-M^+$ or H or alternatively a quaternary ammonium group and a denotes an integer ranging from 0 to 4 and b denotes an integer ranging from 0 to 2000;  in which:

- Hal represents a halogen atom;
- X_{10} represents a halogen atom or a group $COOX_{14}$, nitro, unsubstituted or halogenated (C_1-C_8)alkyl, unsubstituted or halogenated (C_1-C_8)alkoxy, unsubstituted or halogenated (C_2-C_8)alkenyl, unsubstituted or halogenated (C_2-C_8)alkynyl, unsubstituted (C_3-C_8)cycloalkyl, aryl that is unsubstituted or substituted with one to three substituents selected from amino, halogen atom, unsubstituted or halogenated (C_1-C_8)alkyl group, unsubstituted or halogenated (C_1-C_8)alkoxy;
- each of the X_{11}, X_{12} and X_{13} independently represents a hydrogen atom or may represent X_3;

or X_{10} and X_{11} together form a ring (C_2-C_5)alkylene, which is unsubstituted or substituted with one to five groups (C_1-C_4)alkyl;

or X_{10} and X_{11} form, together with X_{12}, a ring (C_1-C_5)alkylene, which is unsubstituted or substituted with one to five groups (C_1-C_4) alkyl;

and X_{14} is –H or a group (C_1-C_8)alkyl;

- in the presence of a cryptophycin derivative comprising a reactive chemical group of the type –SH in the linker L, the binding agent is modified with a modifying agent chosen from succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate; ; sulfosuccinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate; ; ; ; ; ; ALK denoting a group (C_1-C_{12})alkylene and b being an integer between 0 and 2000; ; ; succinimidyl-N-bromoacetate; succinimidyl-3-(N-bromoacetamido)propionate; , b being an integer between 0 and 2000.

14. Conjugate that may be obtained via the process according to one of Claims 12 to 13.

15. Conjugate according to Claim 14, characterized by a DAR determined from the deconvolution of the HRMS spectrum of greater than 1, preferably between 2 and 10 and more particularly between 2 and 7.

16. Conjugate according to Claim 14, characterized by a DAR determined using a UV spectrophotometer of greater than 0.5, preferably greater than 1, more particularly between 1 and 10 and even more particularly between 2 and 7, the DAR being calculated by the equation:

$DAR = c_D / c_A$

in which:

$c_D = [(\varepsilon_{A\,\lambda1} \times A_{\lambda2}) - (\varepsilon_{A\,\lambda2} \times A_{\lambda1})] / [(\varepsilon_{D\,\lambda2} \times \varepsilon_{A\,\lambda1}) - (\varepsilon_{A\,\lambda2} \times \varepsilon_{D\,\lambda1})]$

$c_A = [A_{\lambda1} - (c_D \times \varepsilon_{D\,\lambda1})] / \varepsilon_{A\,\lambda1}$

and

$A_{\lambda 1}$ and $A_{\lambda 2}$ denoting, respectively, the absorbances of the conjugate solution, respectively, at the wavelengths $\lambda 1$ and $\lambda 2$;

$\varepsilon_{D\,\lambda 1}$ and $\varepsilon_{D\,\lambda 2}$ denoting, respectively, the molar absorption coefficients of the cryptophycin derivative before conjugation at the wavelengths $\lambda 1$ and $\lambda 2$, these coefficients being measured on the compounds of formula (II) of the type $-SZ_a$ with Z_a = -SMe or of the type $-C(=O)-Z_bR_b$ with Z_bR_b = -OMe or $-OCH_2-CH=CH_2$;

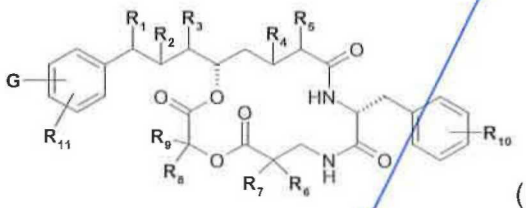
$\varepsilon_{A\,\lambda 1}$ and $\varepsilon_{A\,\lambda 2}$ denoting, respectively, the molar absorption coefficients of the naked antibody before conjugation at the two wavelengths $\lambda 1$ and $\lambda 2$.

17. Conjugate according to Claim 16, in which $\lambda 1$= 280 nm and $\lambda 2$ is chosen within the specific wavelength range 246 nm - 252 nm.

18. Conjugate solution that may be obtained via the process according to one of Claims 12 to 13 or comprising the conjugate as defined in one of Claims 14 to 17.

19. Use of a cryptophycin derivative according to one of Claims 1 to 8, for the preparation of a binding agent to which is attached at least one of the said cryptophycin derivatives.

20. Use of a cryptophycin derivative of formula (III):



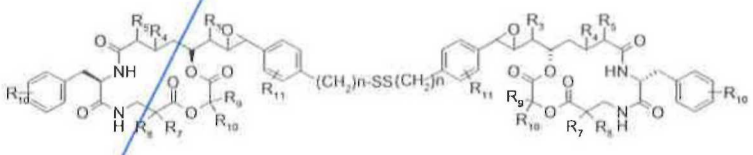
(III)

in which:

G represents a group $-CH=CH_2$ or $-(CH_2)_nY$, which is in an ortho (o), meta (m) or para (p) position on the phenyl nucleus bearing the unit CR_1, preferably in the para position;

Y represents –OH; -Cl; $-N_3$; $-NH_2$; -SH; -COOH; $-NR_{12}-CH_2-C\equiv CH$ in which $\mathbf{R_{12}}$ represents H or a group (C_1-C_6)alkyl, more particularly a methyl group; -OLG in which LG represents a leaving group; -OC(=O)-O-(4-nitrophenyl); maleimido,

or of formula:

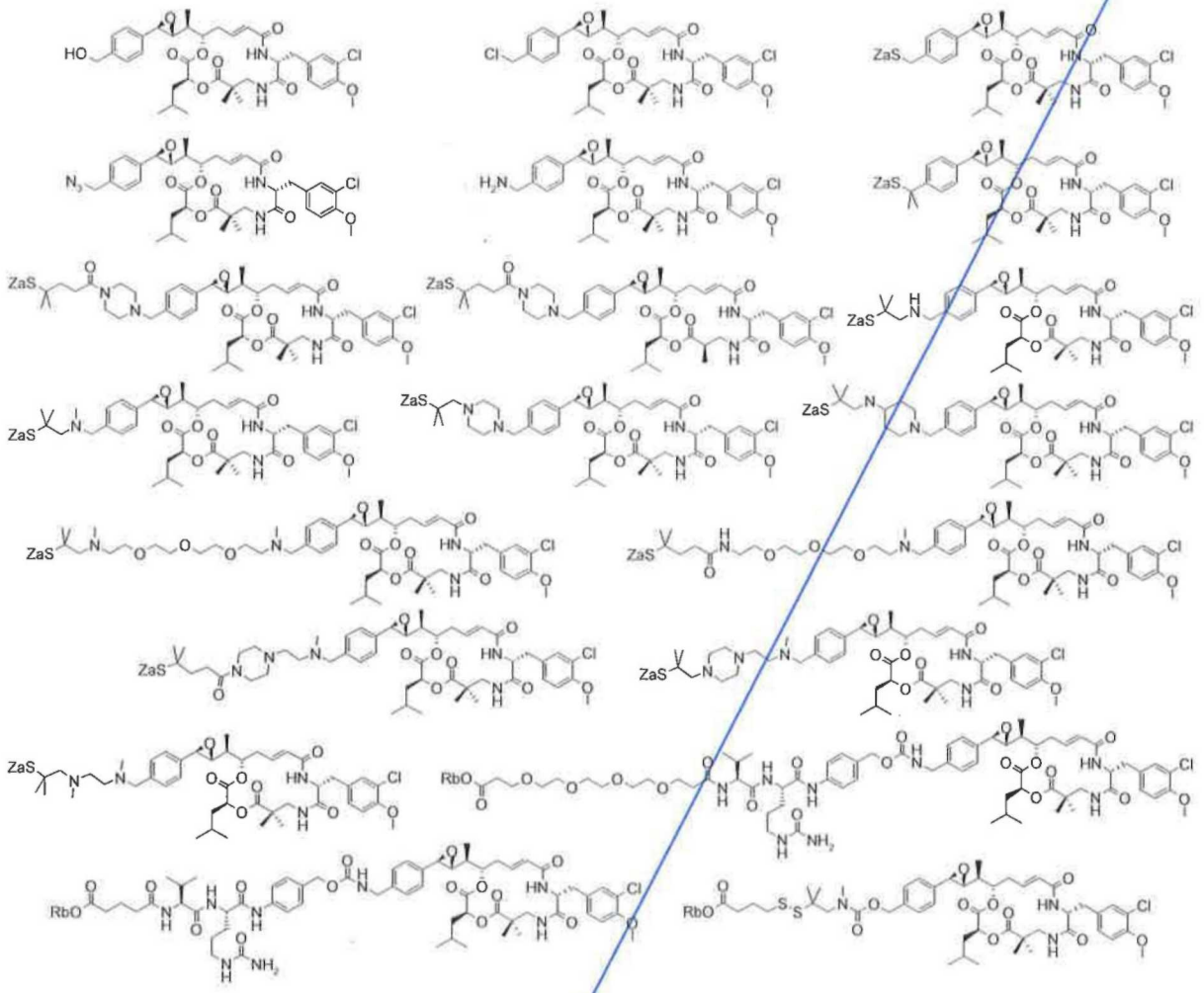


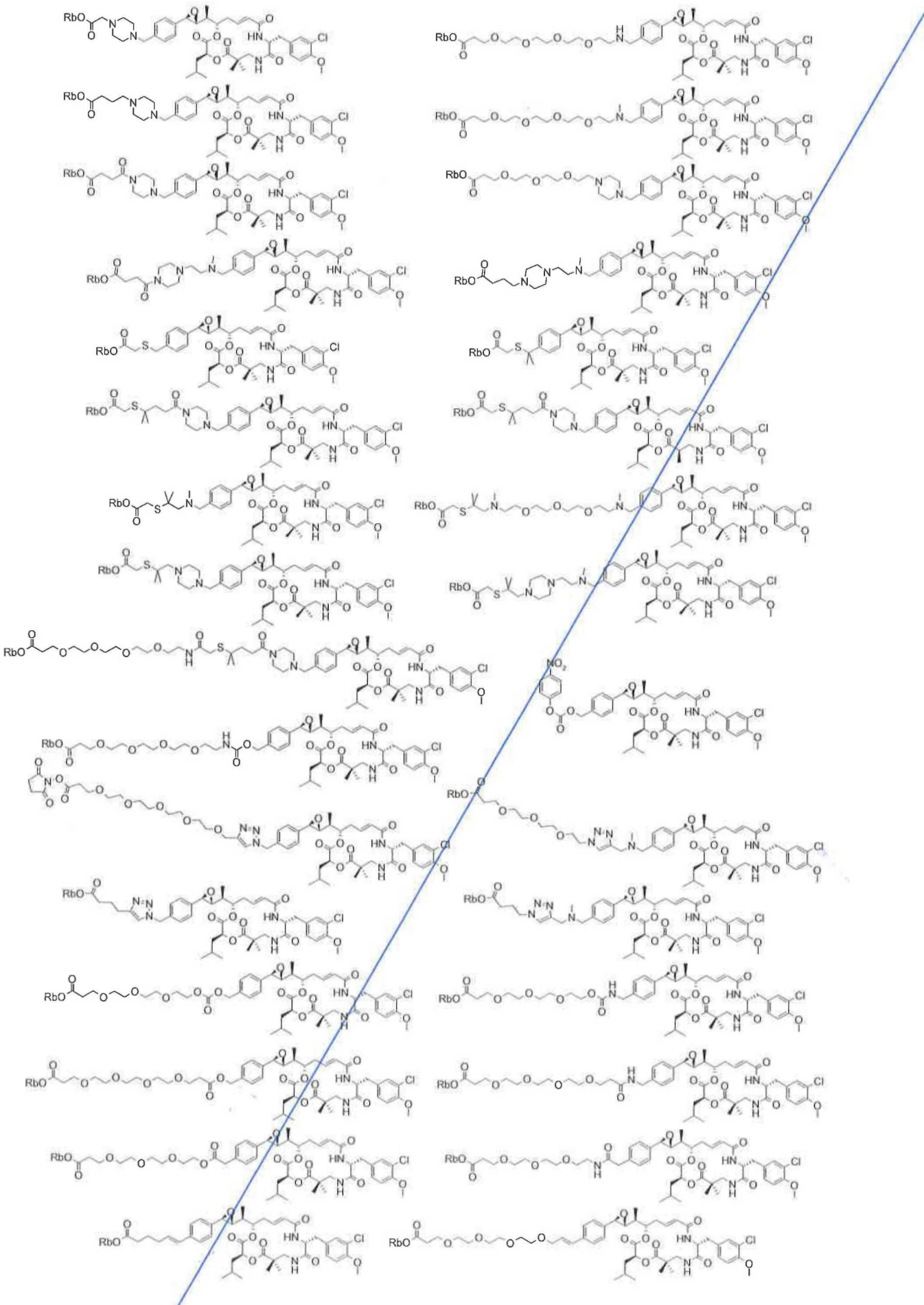
the groups $\mathbf{R_1}$ to $\mathbf{R_{11}}$ having the same meaning as in Claim 1, 6 or 7 and n being an

integer ranging from 1 to 6,

for the preparation of a binding agent to which is attached at least one of the said cryptophycin derivatives.

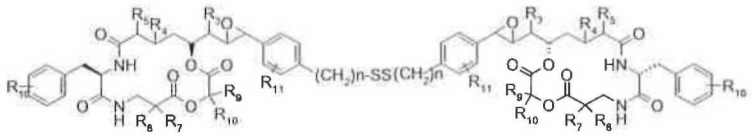
21. Use of a cryptophycin derivative chosen from one of the following:





Z_a, Z_b and R_b being as defined in Claim 1 or 5, for the preparation of a binding agent to which is attached at least one cryptophycin derivative.

22. Cryptophycin derivative of formula:



the groups **R_1** to **R_{11}** having the same meanings as in Claim 1, 6 or 7 and n being an integer ranging from 1 to 6.

23. Cryptophycin derivative according to one of Claims 1 to 10, for use as an anticancer agent.

24. Conjugate according to Claims 14 to 17, for use as an anticancer agent.

25. Conjugate solution according to Claim 18, for use as an anticancer agent.

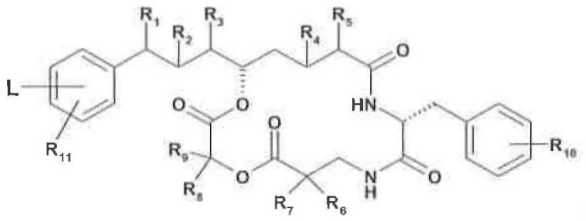
26. Use of a cryptophycin derivative according to one of Claims 1 to 10, for the preparation of an anticancer medicament.

27. Use of a conjugate according to Claims 14 to 17, for the preparation of an anticancer medicament.

28. Use of a conjugate solution according to Claim 18, for the preparation of an anticancer medicament.

CLAIMS

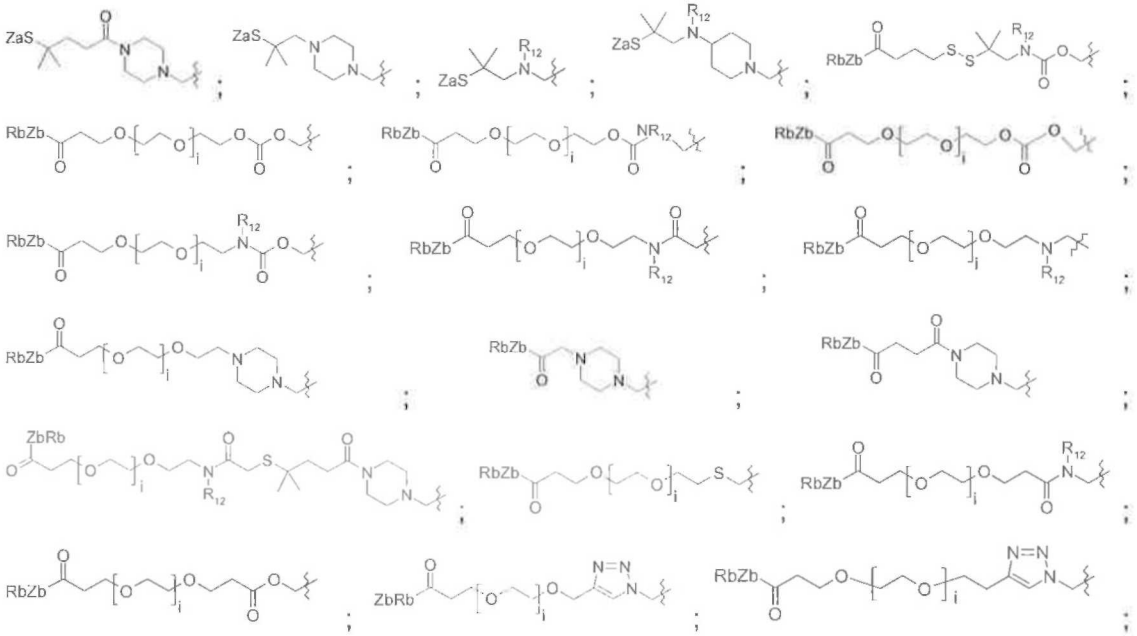
1. Cryptophycin derivative of formula (II):

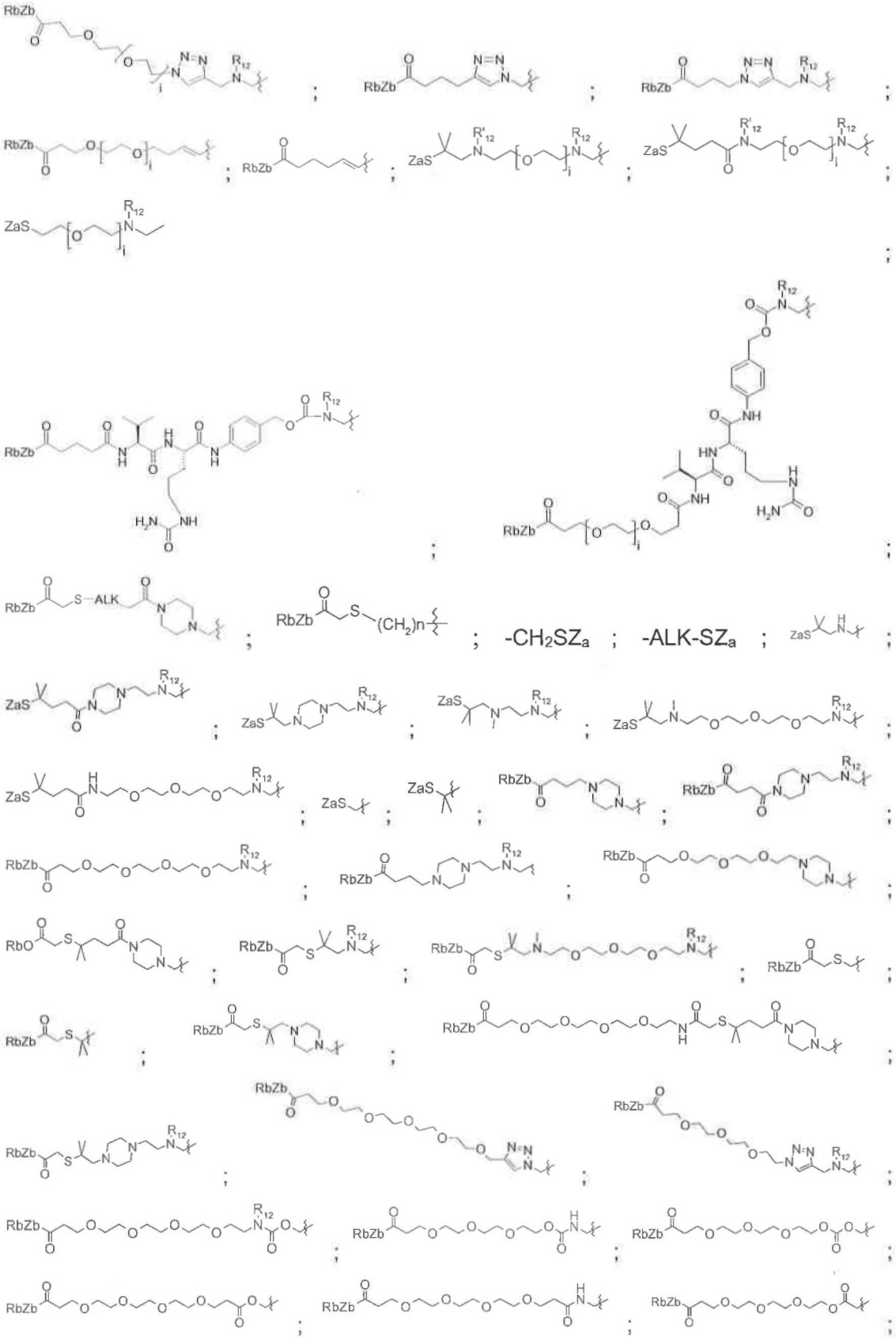


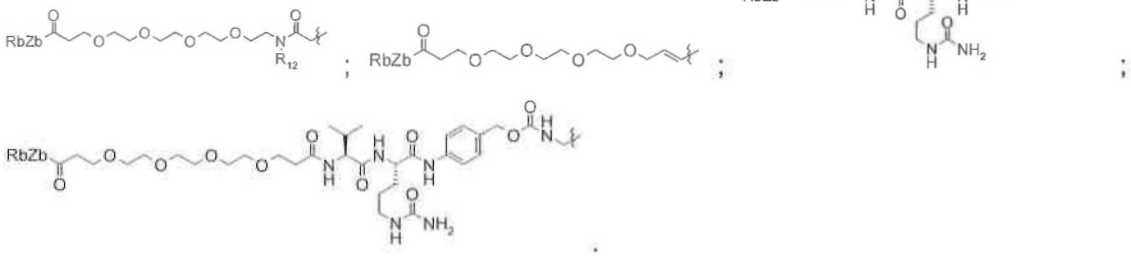
(II)

in which:

- **R_1** represents a halogen atom and **R_2** represents a group –OH, an acyl group derived from an amino acid **AA** or a group (C_1-C_4)alkanoyloxy;
  or alternatively **R_1** and **R_2** form an epoxide unit;
- **AA** denotes a natural or unnatural amino acid;
- **R_3** represents a group (C_1-C_6)alkyl;
- **R_4** and **R_5** both represent H or together form a double bond CH=CH between C13 and C14;
- **R_6** and **R_7** represent, independently of each other, H or a group (C_1-C_6)alkyl;
- **R_8** and **R_9** represent, independently of each other, H or a group (C_1-C_6)alkyl;
- **R_{10}** represents at least one substituent of the phenyl nucleus chosen from: H, a group OH, (C_1-C_4)alkoxy, a halogen atom or a group -NH_2, -NH(C_1-C_6)alkyl or -N(C_1-C_6)alkyl$_2$;
- **R_{11}** represents at least one substituent of the phenyl nucleus chosen from H and a group (C_1-C_4)alkyl;
- **L** represents a linker in the ortho (o), meta (m) or para (p) position, preferably in the para position, of the phenyl nucleus wherein L is chosen from:




RbZb
ZaS
-CH2SZa
-ALK-SZa

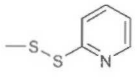
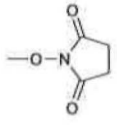
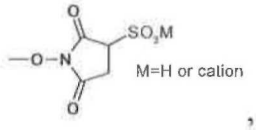


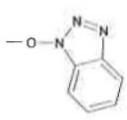
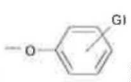
- R_{12} and R'_{12} represent, independently of each other, H or a group $(C_1\text{-}C_6)$alkyl, more particularly a methyl group;
- **i** represents an integer ranging from 1 to 20, more particularly from 1 to 10, even more particularly from 1 to 8, or from 1 to 6, and even more particularly from 2 to 5;
- Z_a represents H or a group $-SR_a$, R_a representing a group $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, heteroaryl or $(C_3\text{-}C_7)$heterocycloalkyl;
- Z_b represents a single bond, -O- or -NH-, R_b representing H or a group $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, heteroaryl or $(C_3\text{-}C_7)$heterocycloalkyl.

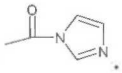
2. Cryptophycin derivative according to Claim 1, in which R_{10} represents at least one substituent on the phenyl nucleus chosen from: H, a group OH, $(C_1\text{-}C_4)$alkoxy, a halogen atom.

3. Cryptophycin derivative according to Claim 1, in which R_{12} represents H.

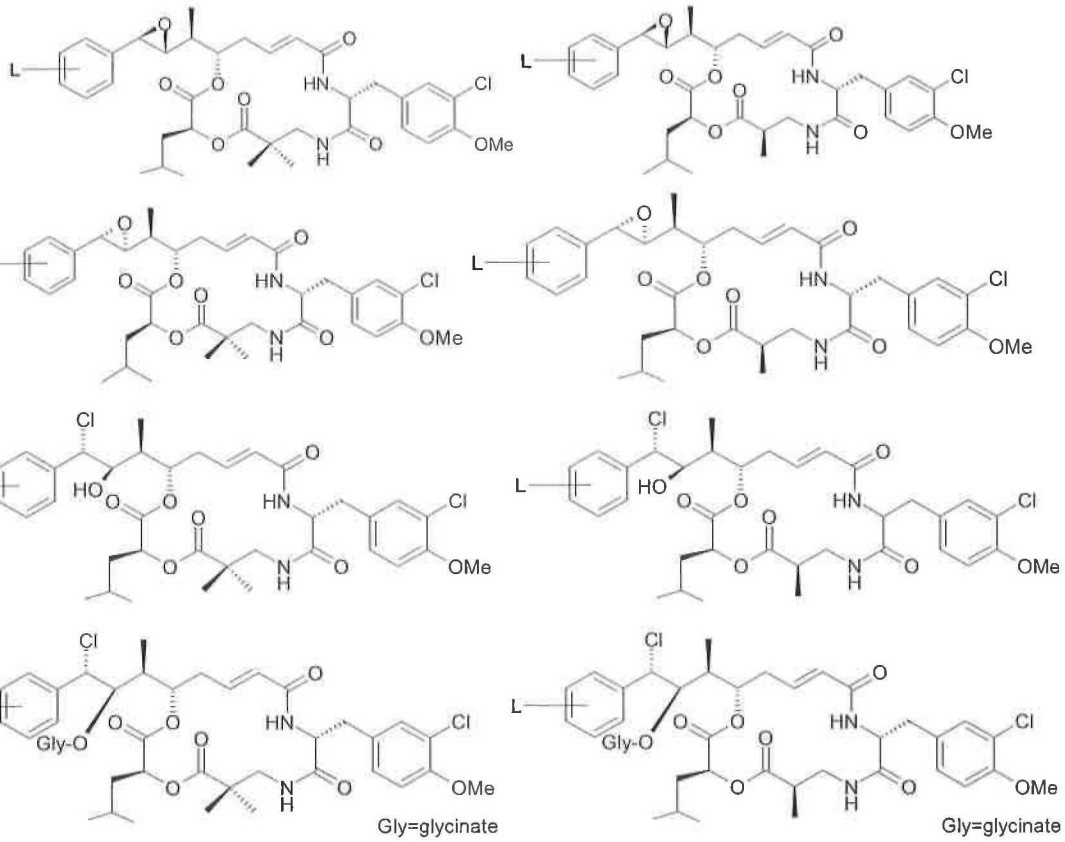
4. Cryptophycin derivative according to Claim 1, in which R_{12} represents $(C_1\text{-}C_6)$alkyl, more particularly a methyl group.

5. Cryptophycin derivative according to Claims 1 to 4, in which Z_a represents H or $-S(C_1\text{-}C_6)$alkyl, especially –SMe, ou –S-heteroaryl, especially  or Z_bR_b represents $-O(C_1\text{-}C_6)$alkyl, -OH, $-OCH_3$, $-OCH_2CH{=}CH_2$,  or 

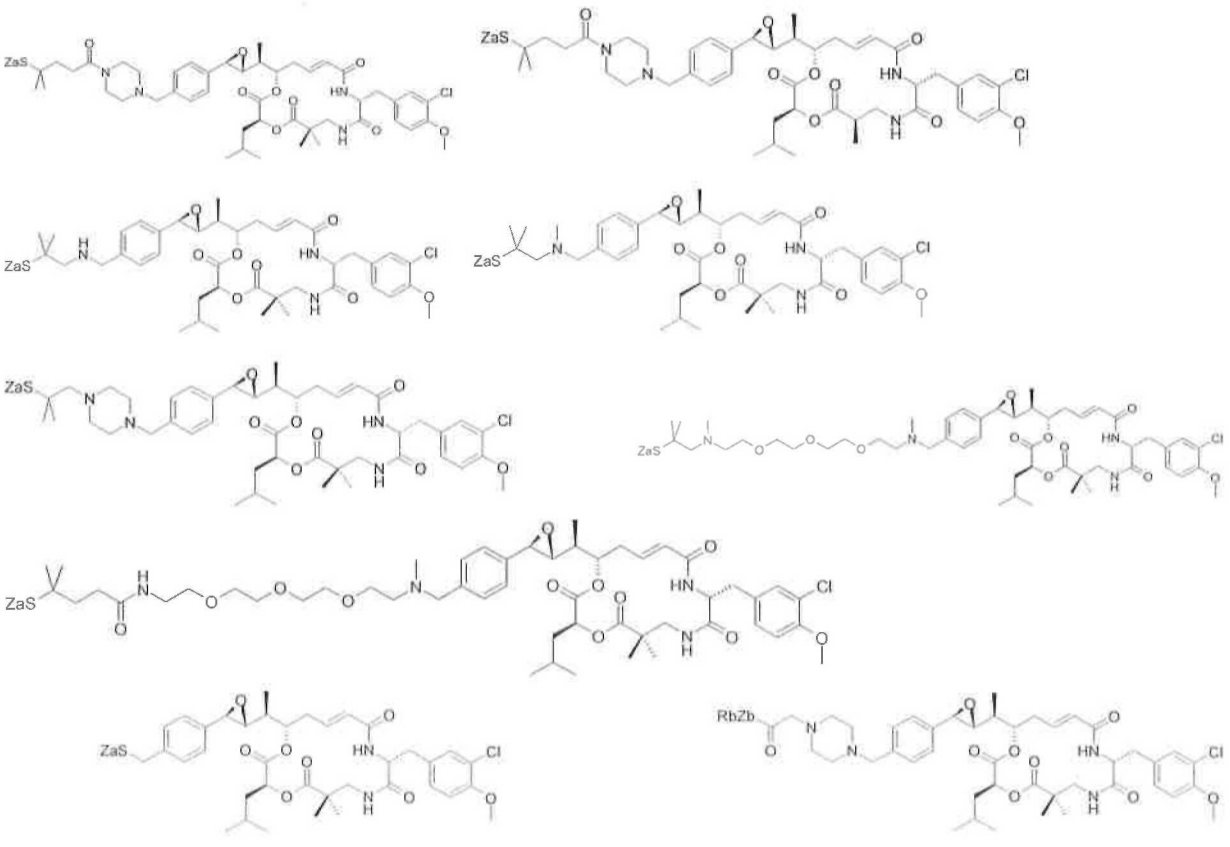
,  or the group 

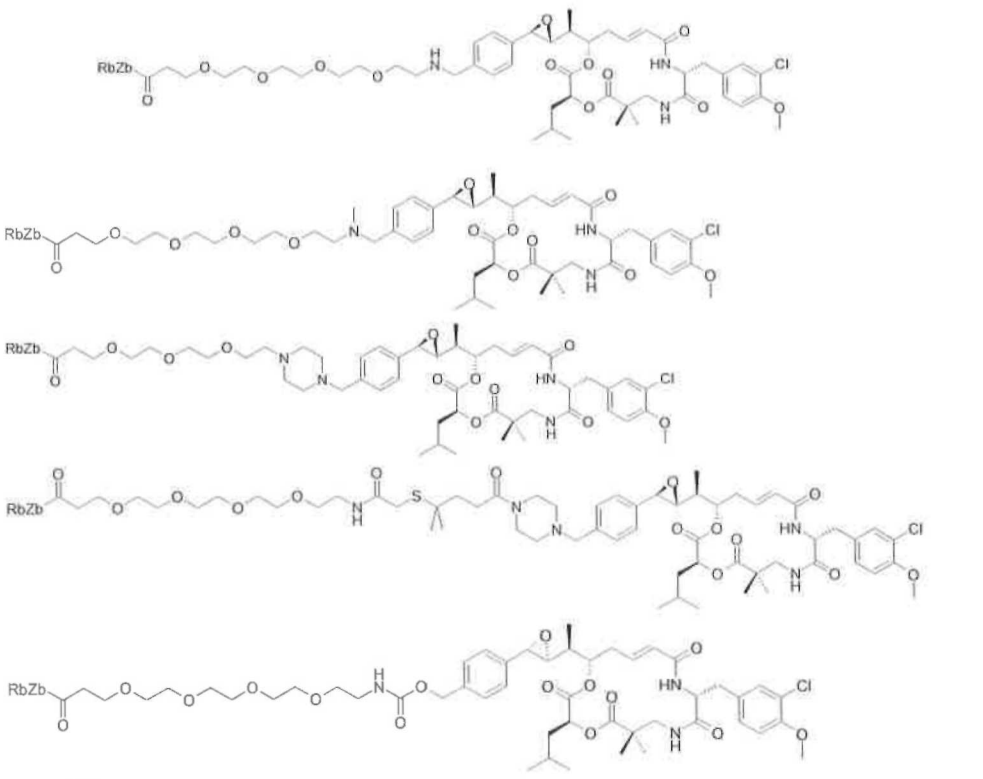
in which **GI** represents at least one electroinductive group, or alternatively in which $-C(=O)Z_bR_b$ represents .

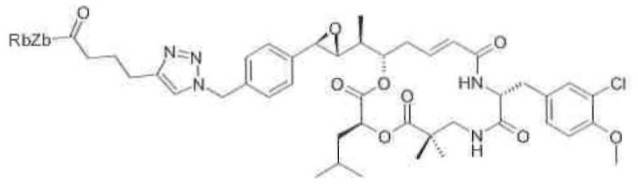
6. Cryptophycin derivative according to one of Claims 1 to 5 defined according to one of the following formulae, **L** preferably being in the para position:

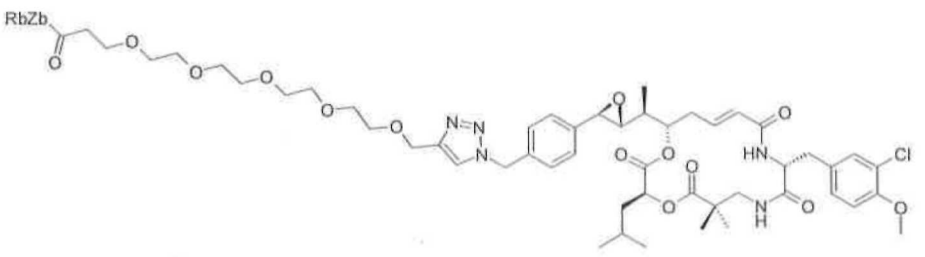


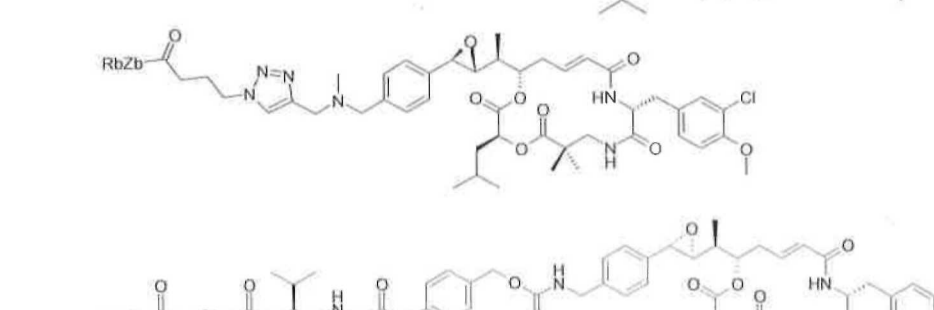
7. Cryptophycin derivative according to Claim 1, chosen from:

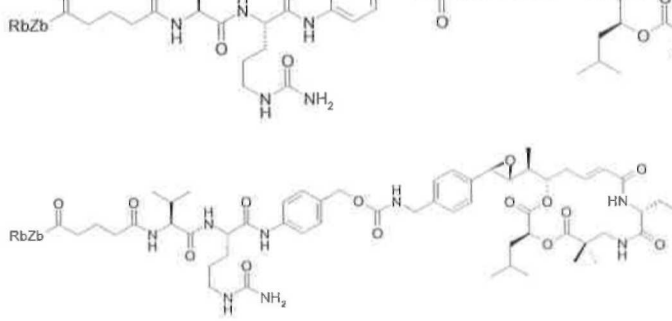






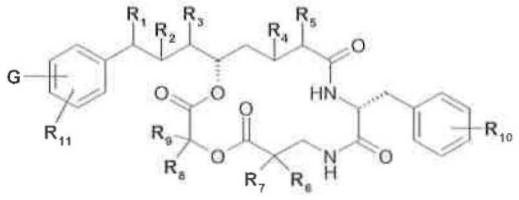




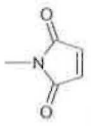
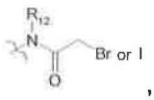


Z_a, Z_b and R_b being as defined in Claim 1 or 5.

8. Cryptophycin derivative of formula (III):



in which the groups **R_1** to **R_{11}** have the same meanings as in Claim 1, 6 or 7 and **G** represents a group $-(CH_2)_nY$, which is in an ortho (o), meta (m) or para (p) position on the phenyl nucleus bearing the unit CR_1, preferably in the para position,

n being an integer ranging from 1 to 6 and Y denoting $-N_3$; -Cl; -OH; $-NH_2$; $-NR_{12}-CH_2-C\equiv CH$ in which **R_{12}** represents H or a group (C_1-C_6)alkyl; -OMs; -OC(=O)-O-(4-nitrophenyl),  or 

, R_{12} representing H or (C_1-C_6)alkyl, more particularly a methyl group.

9. Cryptophycin derivative according to Claim 8, in which Y represents $-N_3$; $-NR_{12}-CH_2-C\equiv CH$ in which R_{12} represents H or a group (C_1-C_6)alkyl; -OMs or -OC(=O)-O-(4-nitrophenyl).

10. Cryptophycin derivative according to one of Claims 1 to 7 or according to formula (III) of Claim 8 with G= $-(CH_2)_nY$ with Y= -Cl, $-N_3$, -OH, $-NH_2$, maleimido or haloacetamido.

11. Cryptophycin derivative according to one of Claims 1 to 7 or according to formula (III) of Claim 8, wherein said cryptophycin derivative is conjugated to a binding agent.

12. Cryptophycin derivative according to Claim 11, in which the binding agent is a ligand, a protein, an antibody, more particularly a monoclonal antibody, a protein or antibody fragment, a peptide, an oligonucleotide or an oligosaccharide.

13. Process for preparing a binding agent to which is attached at least one cryptophycin derivative, referred to as a conjugate, which consists in:

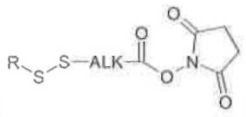
(i) placing in contact and leaving to react an aqueous solution of an optionally buffered binding agent and a solution of the cryptophycin derivative as defined in one of Claims 1 to 10;

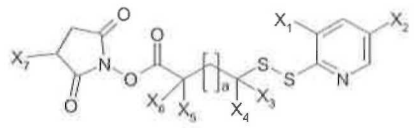
(ii) and then in optionally separating the conjugate formed in step (i) from the cryptophycin derivative and/or the unreacted binding agent and/or any aggregates formed,

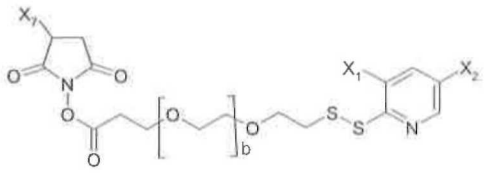
wherein

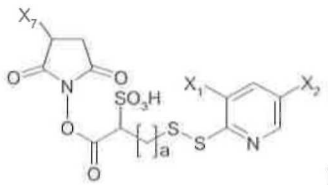
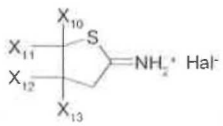
- in the presence of a cryptophycin derivative comprising a reactive chemical group of the type $-SZ_a$ in the linker L, the binding agent comprises:
  - disulfide chemical groups in the case where $-SZ_a$ represents –SH;
  - thiol chemical groups in the case where $Z_a \neq H$;
  - maleimido or iodoacetamido chemical groups in the case where $-SZ_a$ represents –SH;
- in the presence of a cryptophycin derivative comprising a reactive chemical group of the type $-C(=O)-Z_bR_b$ in the linker L, the cryptophycin derivative is reacted with the amino functions of the binding agent, especially the ε-amino groups borne by the side chains of the lysine residues (Lys) of an antibody;
- in the presence of a cryptophycin derivative of formula (III) with $G= -(CH_2)_nY$, the binding agent comprises groups –SH when Y= -Cl or -maleimido, groups $-C\equiv CH$ when Y= $-N_3$ or carboxylic acid groups when Y= -OH or $-NH_2$.

14. Process according to Claim 13, in which:

- in the presence of a cryptophycin derivative comprising a reactive chemical group of the type $-SZ_a$ in the linker L, the binding agent is modified with a modifying agent chosen from a compound of formula:  in which R represents a group (C_1-C_6)alkyl, aryl, heteroaryl, (C_3-C_7)cycloalkyl, (C_3-C_7)heterocycloalkyl and ALK represents a group (C_1-C_6)alkylene;

, a pegylated analogue of formula:

 or a sulfonic analogue of formula

 in which X_3, X_4, X_5 and X_6 represent H or a group (C_1-C_6)alkyl, X_1 and X_2 represent -H, $-CONX_8X_9$, $-NO_2$, X_8 and X_9 representing H or a group (C_1-C_6)alkyl, X_7 represents $-SO_3^-M^+$ or H or alternatively a quaternary ammonium group and a denotes an integer ranging from 0 to 4 and b denotes an integer ranging from 0 to 2000;  in which:

- Hal represents a halogen atom;

- X_{10} represents a halogen atom or a group $COOX_{14}$, nitro, unsubstituted or halogenated $(C_1\text{-}C_8)$alkyl, unsubstituted or halogenated $(C_1\text{-}C_8)$alkoxy, unsubstituted or halogenated $(C_2\text{-}C_8)$alkenyl, unsubstituted or halogenated $(C_2\text{-}C_8)$alkynyl, unsubstituted $(C_3\text{-}C_8)$cycloalkyl, aryl that is unsubstituted or substituted with one to three substituents selected from amino, halogen atom, unsubstituted or halogenated $(C_1\text{-}C_8)$alkyl group, unsubstituted or halogenated $(C_1\text{-}C_8)$alkoxy;

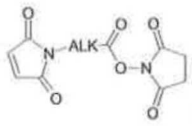
- each of the X_{11}, X_{12} and X_{13} independently represents a hydrogen atom or may represent X_3;

or X_{10} and X_{11} together form a ring $(C_2\text{-}C_5)$alkylene, which is unsubstituted or substituted with one to five groups $(C_1\text{-}C_4)$alkyl;

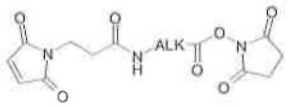
or X_{10} and X_{11} form, together with X_{12}, a ring $(C_1\text{-}C_5)$alkylene, which is unsubstituted or substituted with one to five groups $(C_1\text{-}C_4)$ alkyl;

and X_{14} is –H or a group $(C_1\text{-}C_8)$alkyl;

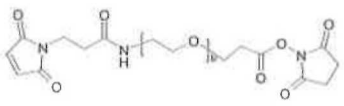
➢ in the presence of a cryptophycin derivative comprising a reactive chemical group of the type –SH in the linker L, the binding agent is modified with a modifying agent chosen from succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate;



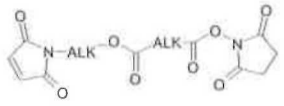
sulfosuccinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate; ;



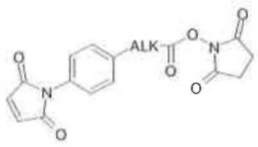
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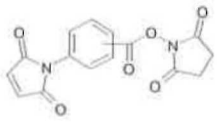
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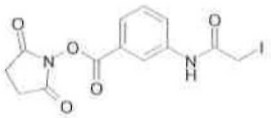
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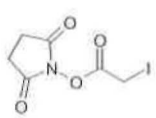
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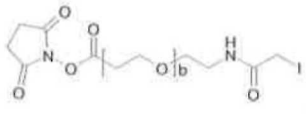
ALK denoting a group $(C_1\text{-}C_{12})$alkylene and b being an integer between 0 and 2000;



;



; succinimidyl-N-bromoacetate; succinimidyl-3-(N-bromoacetamido)propionate;



, b being an integer between 0 and 2000.

15. Cryptophycin derivative in conjugation with a binding agent according to Claim 11, characterized by a DAR determined from the deconvolution of the HRMS spectrum of greater than 1, preferably between 2 and 10 and more particularly between 2 and 7.

16. Cryptophycin derivative in conjugation with a binding agent according to Claim 11, characterized by a DAR determined using a UV spectrophotometer of greater than 0.5, preferably greater than 1, more particularly between 1 and 10 and even more particularly between 2 and 7, the DAR being calculated by the equation:

$DAR = c_D / c_A$

in which:

$c_D = [(\varepsilon_{A\,\lambda1} \times A_{\lambda2}) - (\varepsilon_{A\,\lambda2} \times A_{\lambda1})] / [(\varepsilon_{D\,\lambda2} \times \varepsilon_{A\,\lambda1}) - (\varepsilon_{A\,\lambda2} \times \varepsilon_{D\,\lambda1})]$

$c_A = [A_{\lambda1} - (c_D \times \varepsilon_{D\,\lambda1})] / \varepsilon_{A\,\lambda1}$

and

$A_{\lambda1}$ and $A_{\lambda2}$ denoting, respectively, the absorbances of the conjugate solution, respectively, at the wavelengths $\lambda1$ and $\lambda2$;

$\varepsilon_{D\,\lambda1}$ and $\varepsilon_{D\,\lambda2}$ denoting, respectively, the molar absorption coefficients of the cryptophycin derivative before conjugation at the wavelengths $\lambda1$ and $\lambda2$, these coefficients being measured on the compounds of formula (II) of the type $-SZ_a$ with Z_a = -SMe or of the type $-C(=O)-Z_bR_b$ with Z_bR_b = -OMe or $-OCH_2-CH=CH_2$;

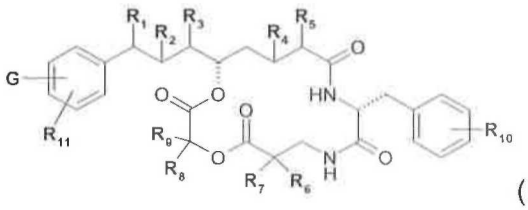
$\varepsilon_{A\,\lambda1}$ and $\varepsilon_{A\,\lambda2}$ denoting, respectively, the molar absorption coefficients of the naked antibody before conjugation at the two wavelengths $\lambda1$ and $\lambda2$.

17. Cryptophycin derivative in conjugation with a binding agent according to Claim 16, in which $\lambda1$= 280 nm and $\lambda2$ is chosen within the specific wavelength range 246 nm - 252 nm.

18. Conjugate solution that may be obtained via the process according to one of Claims 13 to 14 or comprising the cryptophycin derivative in conjugation with a binding agent as defined in one of Claims 15 to 17.

19. Use of a cryptophycin derivative according to one of Claims 1 to 8, for the preparation of a binding agent to which is attached at least one of the said cryptophycin derivatives.

20. Use of a cryptophycin derivative of formula (III):



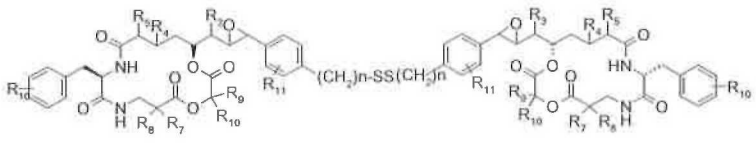
(III)

in which:

G represents a group -CH=CH_2 or -$(CH_2)_nY$, which is in an ortho (o), meta (m) or para (p) position on the phenyl nucleus bearing the unit CR_1, preferably in the para position;

Y represents –OH; -Cl; -N_3; -NH_2; -SH; -COOH; -NR_{12}-CH_2-C≡CH in which $\mathbf{R_{12}}$ represents H or a group (C_1-C_6)alkyl, more particularly a methyl group; -OLG in which LG represents a leaving group; -OC(=O)-O-(4-nitrophenyl); maleimido,

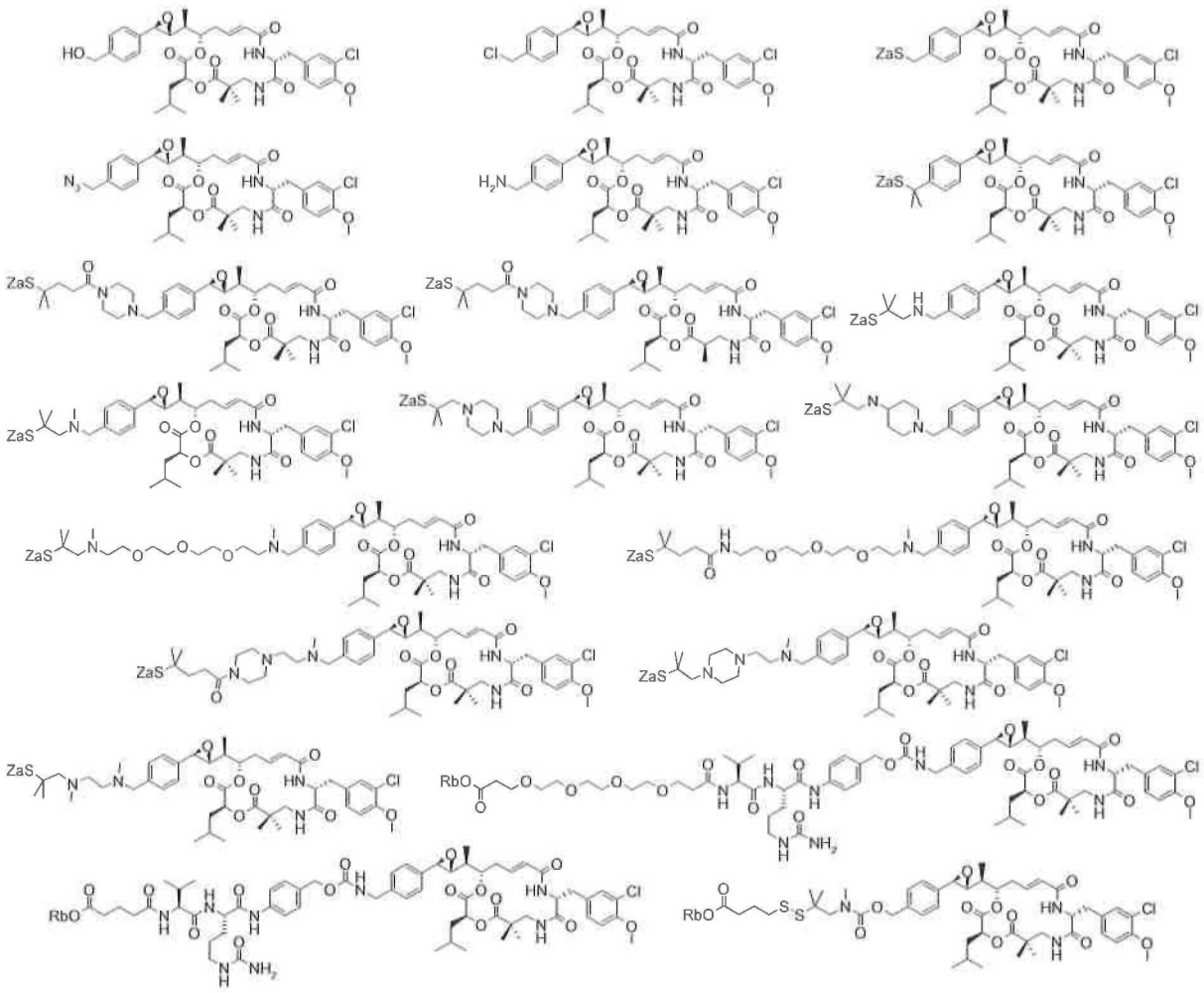
or of formula:

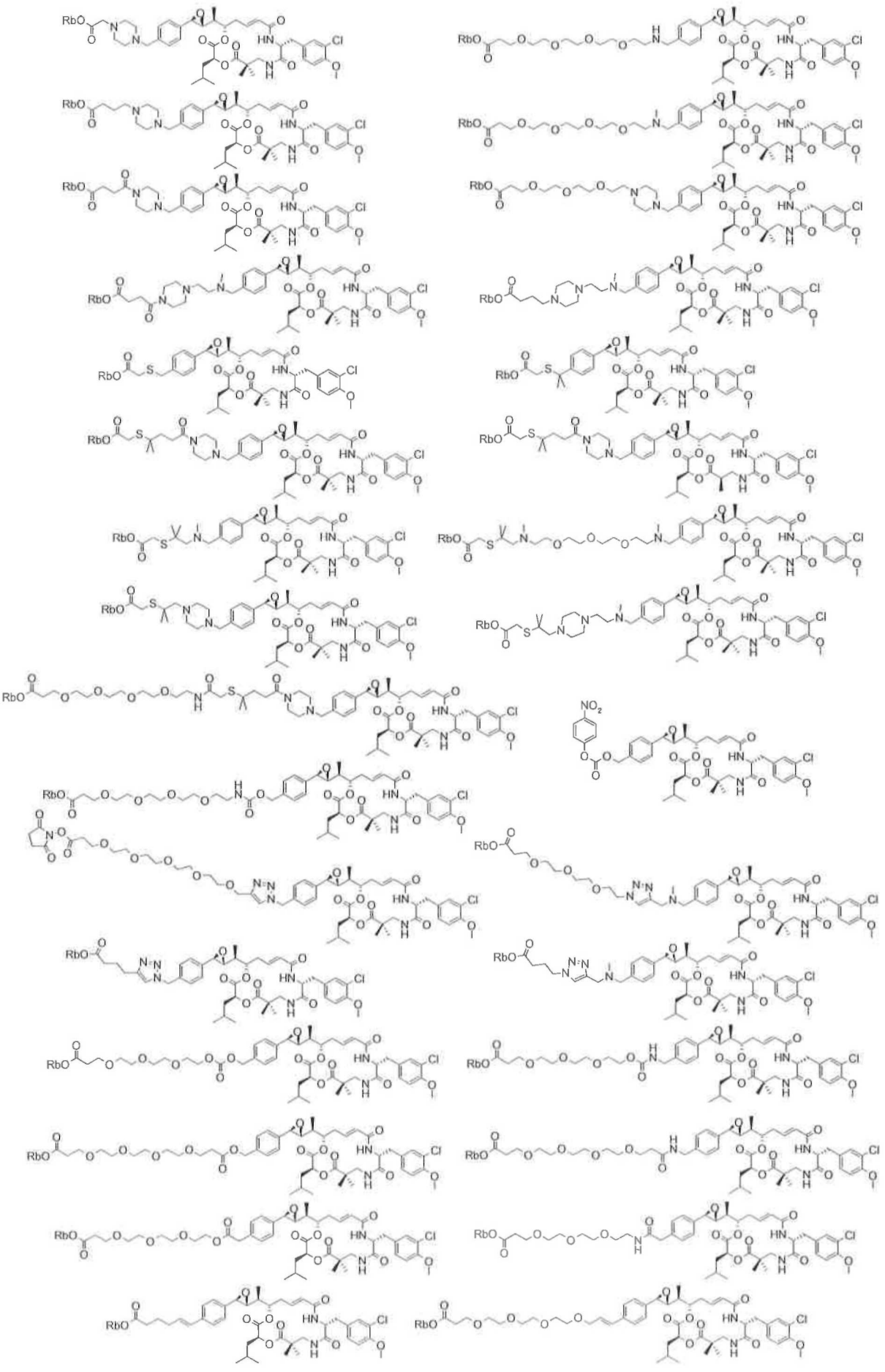


the groups $\mathbf{R_1}$ to $\mathbf{R_{11}}$ having the same meaning as in Claim 1, 6 or 7 and n being an integer ranging from 1 to 6,

for the preparation of a binding agent to which is attached at least one of the said cryptophycin derivatives.

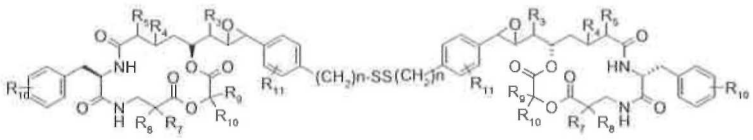
21. Use of a cryptophycin derivative chosen from one of the following:





Z_a, Z_b and R_b being as defined in Claim 1 or 5, for the preparation of a binding agent to which is attached at least one cryptophycin derivative.

22. Cryptophycin derivative of formula:



the groups $\mathbf{R_1}$ to $\mathbf{R_{11}}$ having the same meanings as in Claim 1, 6 or 7 and n being an integer ranging from 1 to 6.

23. Cryptophycin derivative according to one of Claims 1 to 12, for use as an anticancer agent.

24. Conjugate derivative in conjugation with a binding agent according to Claims 15 to 17, for use as an anticancer agent.

25. Conjugate solution according to Claim 18, for use as an anticancer agent.

26. Use of a cryptophycin derivative according to one of Claims 1 to 12, for the preparation of an anticancer medicament.

27. Use of a conjugate derivative in conjugation with a binding agent according to Claims 15 to 17, for the preparation of an anticancer medicament.

28. Use of a conjugate solution according to Claim 18, for the preparation of an anticancer medicament.