

ANTI-HER2 ANTIBODY-DRUG CONJUGATES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims benefit of U.S. Provisional Application No. 63/153,530, filed February 25, 2021, which is incorporated by reference in its entirety.

SEQUENCE LISTING

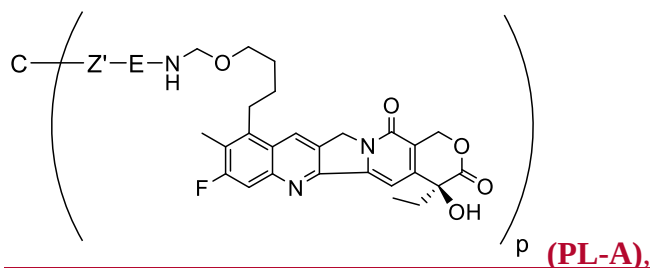
[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on February 17, 2022, is named MDB-002WO_SLtxt and is 10,140 bytes in size.

BACKGROUND OF THE INVENTION

[0003] HER2 (human epidermal growth factor receptor 2) has emerged as an important therapeutic target due its role in the development of cancers such as breast cancer. For example, overexpression of the *HER2* gene is found in up to 25-30% of breast cancer cases, as well as in some gastric and gastroesophageal cancer cases. As the overexpression of HER2 can be associated with a faster rate of growth and a poorer prognosis, there remains a need for new, effective anti-HER2 therapeutic agents.

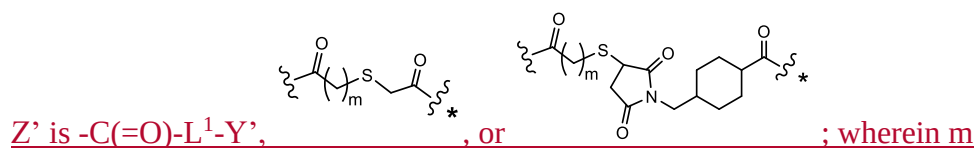
SUMMARY ~~OF INVENTION~~

[003a] In an aspect of the present disclosure, there is provided a compound having the structure of **Formula PL-A**,



or a pharmaceutically acceptable salt thereof, wherein

E is a peptide comprising 2 to 8 amino acids; wherein E is optionally substituted with one or more polyol; and wherein the N terminal of the peptide is covalently attached to Z';



represents an integer of 1-10 and * denotes the site covalently linked to said C;

L¹ is -(C₁-C₁₀ alkylene)-, -CH₂CH₂(OCH₂CH₂)_nN(R₁)C(=O)-L²-, or -CH₂(OCH₂CH₂)_nN(R₁)C(=O)-L²-*; wherein n represents an integer of 1-10; and wherein * denotes the site covalently linked to Y';

L² is -(C₁-C₁₀ alkylene)-; R₁ is -H or -CH₃;

Y' is a group formed by the reaction of an electrophilic group with a reactive nucleophilic group present on cell binding agent C; and

p is the drug to antibody ratio (DAR), which is an average number that is about 2-10; and

C is a binding agent that targets Her2 comprising:

a heavy chain comprising an amino acid sequence having at least about 80% identity to SEQ ID NO:1; and

a light chain comprising an amino acid sequence having at least about 80% identity to SEQ ID NO:2.

[003b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound as disclosed herein, or a pharmaceutically acceptable salt thereof.

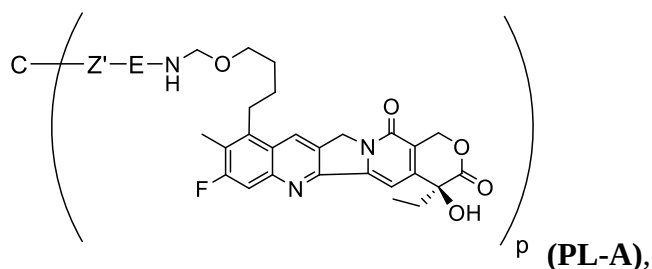
[003c] In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in treating cancer.

[003d] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.

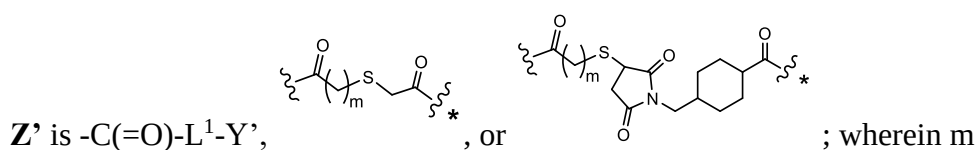
[0004] Antibody Drug Conjugates (ADCs) have attracted significant interest as a new class of therapeutics. For example, ADCs can leverage monoclonal antibodies (mAbs) for the targeted delivery of cytotoxic agents to tumor cells, thereby permitting the use of highly cytotoxic drugs that could not be used using conventional, non-targeted modes. The design of ADCs—which typically feature attachment of a cytotoxic agent to antibody, typically via a

linker—involves consideration of a variety of factors, including the presence of a conjugation handle on the drug for attachment to the linker and linker technology for attaching the drug to an antibody in a conditionally stable manner. Non-optimal design can result in reduced ADC potency, insufficient immunologic specificity of the conjugate and increased toxicity due to non-specific release of the drug from the conjugate.

[0006] In embodimentexamples, the inventiondisclosure features a compound having the structure of **Formula PL-A**,



E is a peptide comprising 2 to 8 amino acids; wherein **E** is optionally substituted with one or more polyol; and wherein the N terminal of the peptide is covalently attached to **Z**';



L¹ is -(C₁-C₁₀ alkylene)-, -CH₂CH₂(OCH₂CH₂)_nN(R₁)C(=O)-L²*, or -CH₂(OCH₂CH₂)_nN(R₁)C(=O)-L²*; wherein n represents an integer of 1-10; and wherein * denotes the site covalently linked to **Y**’;

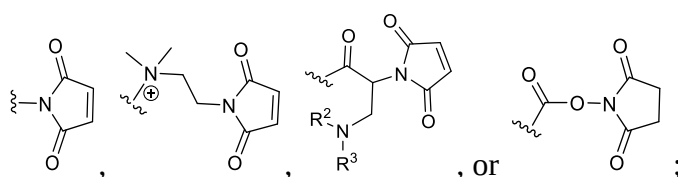
Y' is a group formed by the reaction of an electrophilic group with a reactive nucleophilic group present on cell binding agent **C**; and

p is the drug to antibody ratio (DAR), which is an average number that is about 2-10; and

a heavy chain comprising an amino acid sequence having at least about 80% identity to SEQ ID NO:1; and

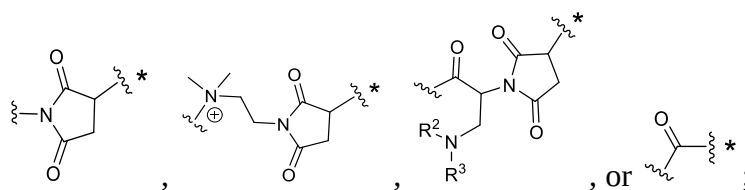
a light chain comprising an amino acid sequence having at least about 80% identity to SEQ ID NO:2.

- [0007] In embodimentexamples, C is a binding agent comprising
- a heavy chain comprising an amino acid sequence having at least about 85%, 90%, or 95% identity to SEQ ID NO:1; and
- a light chain comprising an amino acid sequence having at least about 85%, 90%, or 95% identity to SEQ ID NO:2.
- [0008] In embodimentexamples, C is a binding agent comprising
- a heavy chain amino acid sequence of SEQ ID NO:1; and
- a light chain amino acid sequence of SEQ ID NO:2.
- [0009] Exemplary compounds according to Formula (PL-A) include **MB-2a** and **MB-3a** (trastuzumab meditecan) as described herein.
- [00010] In embodimentexamples, C is a binding agent that is an antibody or antigen-binding fragment thereof.
- [00011] In embodimentexamples, C is a binding agent that is trastuzumab (Herceptin), trastuzumab-dkst (Ogivri), trastuzumab-pkrb (Herzuma), trastuzumab-dttb (Ontruzant), trastuzumab-qyyp (Trazimera), or trastuzumab-anns (Kanjinti).
- [00012] In embodimentexamples, L¹ is -(C₁-C₁₀ alkylene)-.
- [00013] In embodimentexamples, L¹ is -CH₂CH₂(OCH₂CH₂)_nN(R₁)C(=O)-L²-* or -CH₂(OCH₂CH₂)_nN(R₁)C(=O)-L²-, wherein n represents an integer of 1-10; and wherein * denotes the site covalently linked to Y'.
- [00014] In embodimentexamples, L¹ is -CH₂CH₂CH₂CH₂CH₂-, -CH₂CH₂-, -CH₂-, -CH₂CH₂OCH₂CH₂OCH₂CH₂NHC(=O)CH₂CH₂-* or -CH₂OCH₂CH₂OCH₂CH₂NHC(=O)CH₂CH₂-*; wherein * denotes the site covalently linked to Y'.
- [00015] In embodimentexamples, Y' is formed from a Michael acceptor group, a succinimide, an epoxide, or a halogen.
- [00016] In embodimentexamples, Y' is formed from



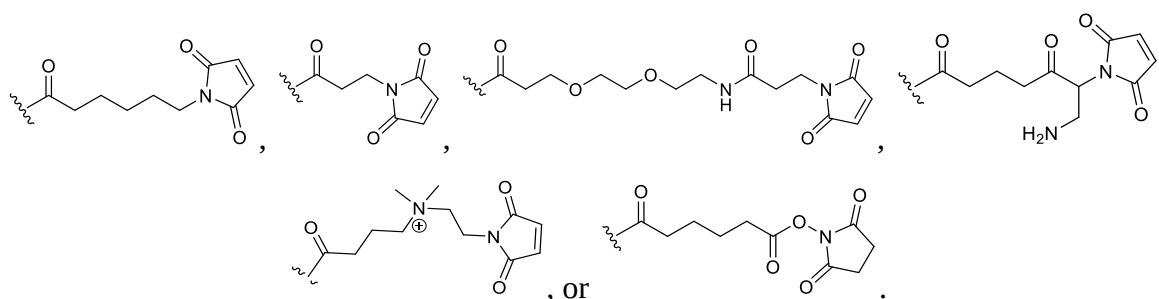
wherein R^2 and R^3 are each independently -H or C₁-C₃ alkyl.

[00017] In embodimentexample, Y' is

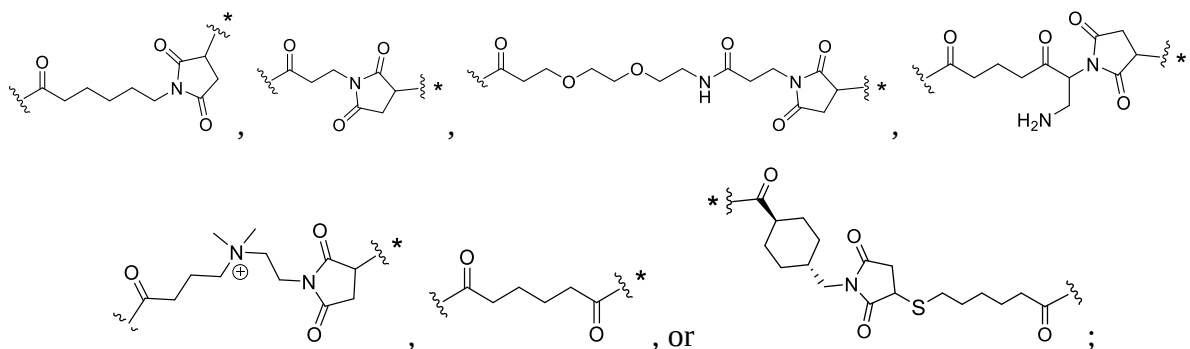


wherein R^2 and R^3 are each independently -H or C₁-C₃ alkyl and * denotes the site covalently linked to said C.

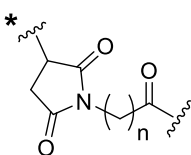
[00018] In embodimentexample, Z' is formed from:

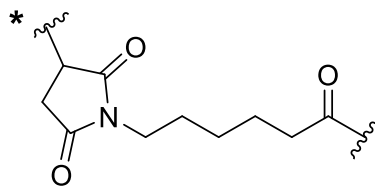


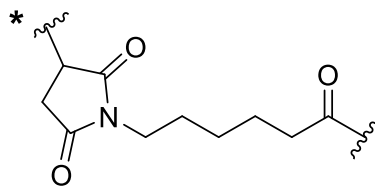
[00019] In embodimentexample, Z' is:

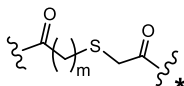


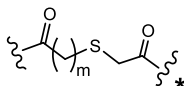
wherein * denotes the site covalently linked to C.

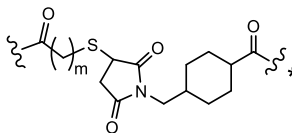
[00020] In embodimentexample, Z' is ; wherein * denotes the covalent attachment to C, and n is an integer of 2-10.

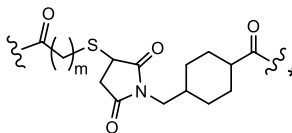


[00021] In embodimentexamples, **Z'** is  ; wherein * denotes the covalent attachment to **C**.



[00022] In embodimentexamples, **Z'** is , wherein * denotes the site covalently linked to said **C**. In embodimentexamples, **m** is 1. In embodimentexamples, **m** is 2. In embodimentexamples, **m** is 3. In embodimentexamples, **m** is 4. In embodimentexamples, **m** is 5. In embodimentexamples, **m** is 6. In embodimentexamples, **m** is 7. In embodimentexamples, **m** is 8. In embodimentexamples, **m** is 9. In embodimentexamples, **m** is 10.



[00023] In embodimentexamples, **Z'** is , wherein * denotes the site covalently linked to said **C**. In embodimentexamples, **m** is 1. In embodimentexamples, **m** is 2. In embodimentexamples, **m** is 3. In embodimentexamples, **m** is 4. In embodimentexamples, **m** is 5. In embodimentexamples, **m** is 6. In embodimentexamples, **m** is 7. In embodimentexamples, **m** is 8. In embodimentexamples, **m** is 9. In embodimentexamples, **m** is 10.

[00024] In embodimentexamples, **E** is a peptide of 2, 3, 4, or 5 amino acids.

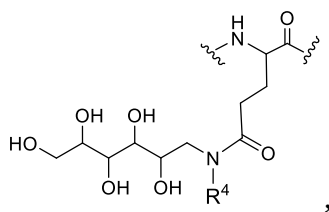
[00025] In embodimentexamples, **E** is a peptide of 2, 3, or 4 amino acids.

[00026] In embodimentexamples, each amino acid in said peptide is an L amino acid, or wherein at least one amino acid in said peptide is a D amino acid.

[00027] In embodimentexamples, **E** comprises one or more amino acids selected from glycine, alanine, valine, glutamine, glutamic acid, phenylalanine, and leucine, and wherein said glutamine or glutamic acid is optionally substituted by a polyol.

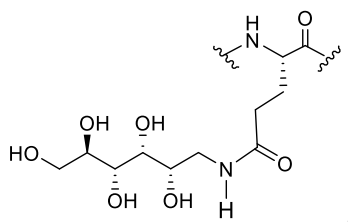
[00028] In embodimentexamples, **E** comprises amino acids selected from glycine, alanine, valine, glutamine, glutamic acid, phenylalanine, and leucine, and wherein said glutamine or glutamic acid is optionally substituted by a polyol.

[00029] In embodimentexamples, **E** comprises an amino acid having the following structure,



wherein **R⁴** is -H or C₁-C₆ alkyl.

[00030] In embodimentexample, **E** comprises an amino acid having the following structure,

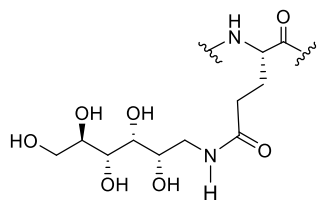


[00031] In embodimentexample, **E** is selected from the group consisting of -Ala-Val-*, -Val-Ala-*, -Gly-Gly-*, -Val-Cit-*, -Cit-Val-*, -Leu-Ala-*, -Ala-Leu-*, -Leu-Cit-*, -Cit-Leu-*, -Leu-Ala-*, -Ala-Leu-*, -Lys-Lys-*, -Ala-Lys-*, -Lys-Ala-*, -Val-Lys-*, -Lys-Val-*, -Tyr-Arg-*, -Arg-Tyr-*, -Arg-Arg-*, -Ala-Ala-*, -Phe-Lys-*, -Lys-Phe-*, -Thr-Thr-*, -Thr-Met-*, -Met-Thr-*, -Met-Tyr-*, -Tyr-Met-*, -Phe-Gln-*, -Gln-Phe-*, -Gly-Ser-*, -Leu-Gln-*, -Gln-Leu-*, -Ser-Ala-*, -Ser-Gly-*, -Val-Thr-*, -Thr-Val-*, -Val-Gln-*, -Ser-Val-*, -Val-Ser-*, -Ala-Met-*, -Met-Ala-*, -Val-Arg-*, -Arg-Val-*, -Phe-Ala-*, -Ala-Phe-*, -Cit-Val-*, -Gln-Val-*, -Phe-Arg-*, -Arg-Phe-*, -Ala-Ala-Ala-*, -Gly-Gly-Gly-*, -Ala-Val-Ala-*, -Gly-Val-Gly-*, -Ala-Val-Gly-*, -Gly-Phe-Lys-*, -Lys-Phe-Gly-*, -Leu-Ala-Leu-*, -Val-Ala-Leu-*, -Leu-Ala-Val-*, -Val-Ala-Val-*, -Ala-Val-Ala-Gly-* (SEQ ID NO: 10), -Gly-Phe-Gly-Gly-* (SEQ ID NO: 11), -Gly-Gly-Phe-Gly-* (SEQ ID NO: 12), -Ala-Val-Gly-Gly-* (SEQ ID NO: 13), -Ala-Ala-Ala-Ala-* (SEQ ID NO: 14), -Ala-Val-Ala-Ala-* (SEQ ID NO: 15), -Ala-Leu-Ala-Leu-* (SEQ ID NO: 16), -Leu-Ala-Leu-Ala-* (SEQ ID NO: 17), -Gly-Phe-Leu-Gly-* (SEQ ID NO: 18) and -Gly-Leu-Phe-Gly-* (SEQ ID NO: 19), and wherein * denotes the N-terminal of the peptides covalently attached to **Z'**.

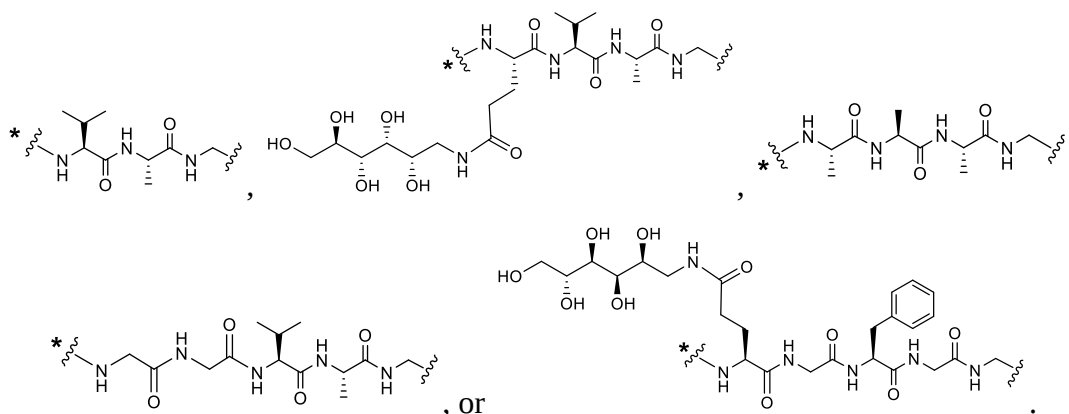
[00032] In embodimentexample, **E** is selected from the group consisting of -L-Ala-D-Val-*, -L-Val-D-Ala-*, -L-Val-D-Lys-*, -L-Val-D-Arg-*, -L-Val-D-Cit-*, -L-Val-D-Arg-*, -L-Val-D-Cit-*, -L-Val-D-Lys-*, -L-Val-D-Arg-*, -L-Arg-D-Arg-*, -L-Ala-D-Ala-*, -L-Ala-D-Lys-*, -L-Ala-D-Arg-*, -L-Ala-D-Ala-L-Ala-*, -L-Ala-D-Val-L-Ala-

, -L-Ala-D-Ala-Gly-, and -L-Ala-D-Val-Gly-*, and wherein * denotes the N-terminal of the peptides covalently attached to **Z'**.

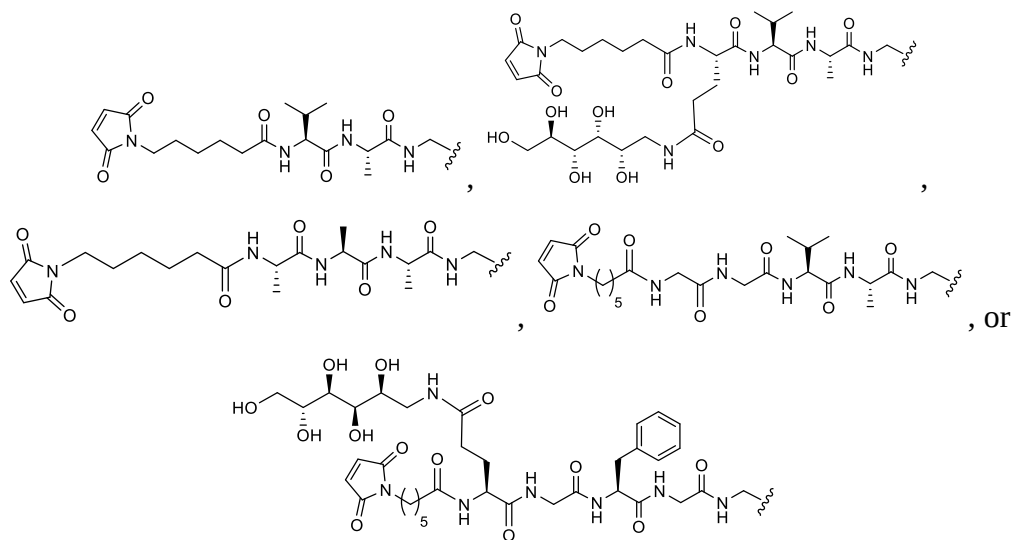
[00033] In embodiment examples, **E** comprises -(L-Val)-(L-Ala)-. In embodiment examples, **E** further comprises an amino acid having the following structure,



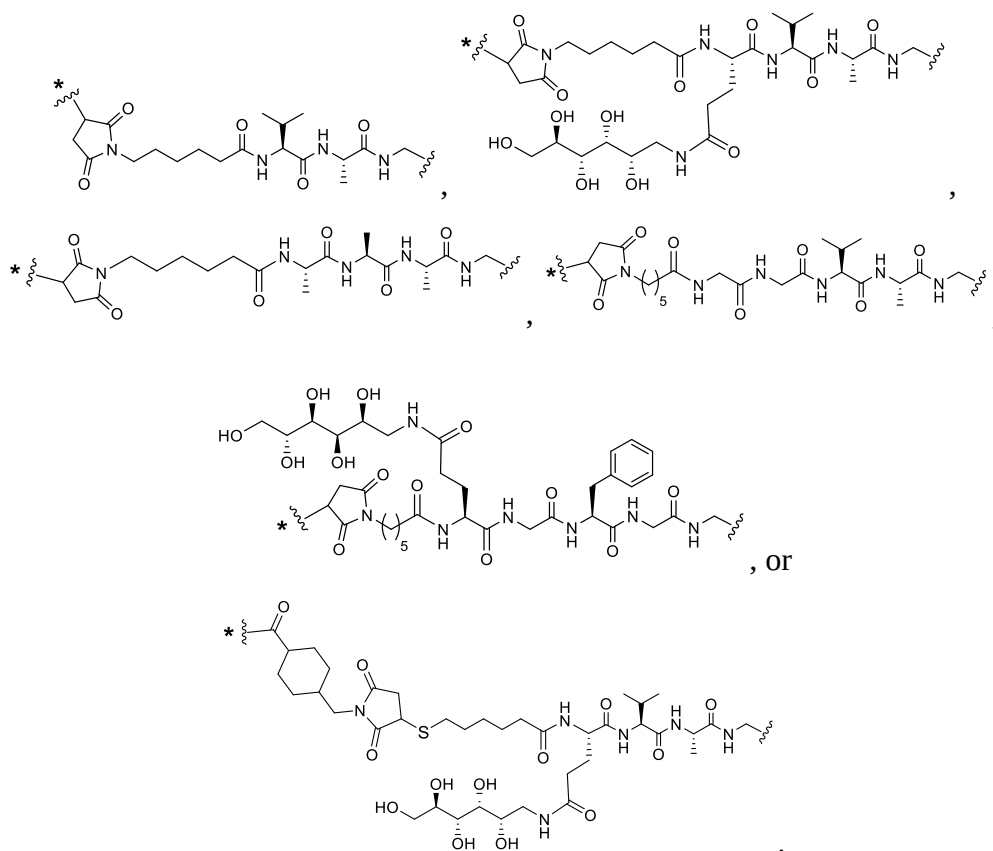
[00034] In embodiment examples, $\text{Z}'\text{-E-NH}$ has one of the following structures, wherein * denotes the N-terminal of the peptides covalently attached to **Z'**:



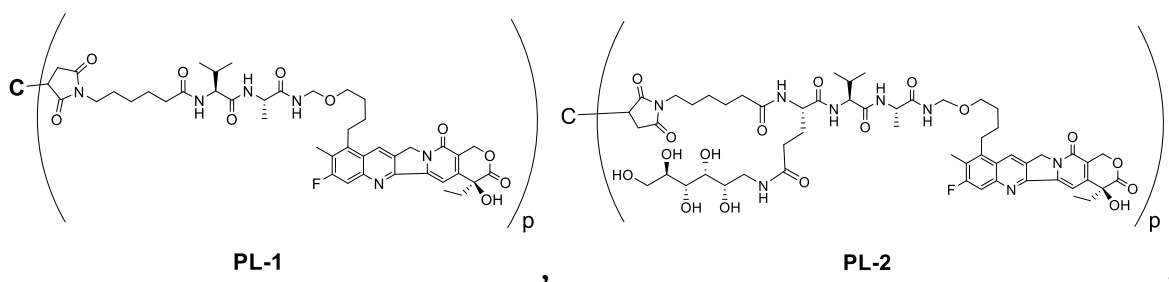
[00035] In embodiment examples, $\text{Z}'\text{-E-NH}$ is formed from one of the following structures:

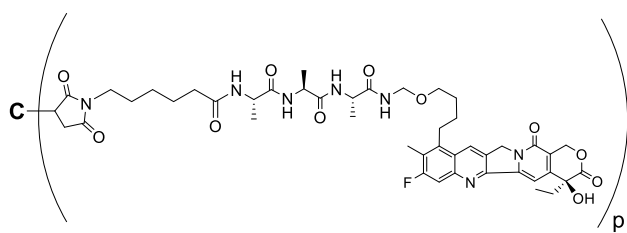


[00036] In embodiment examples,  is one of the following structures, wherein * denotes the point of attachment to the C:



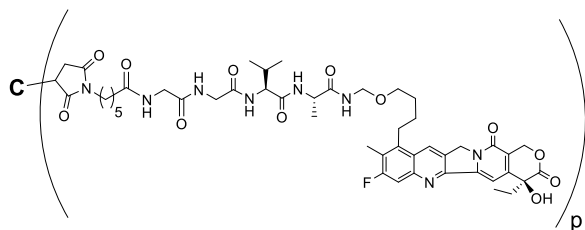
[00037] In embodiment examples, the compound is one of the following structures, or a pharmaceutically acceptable salt thereof:





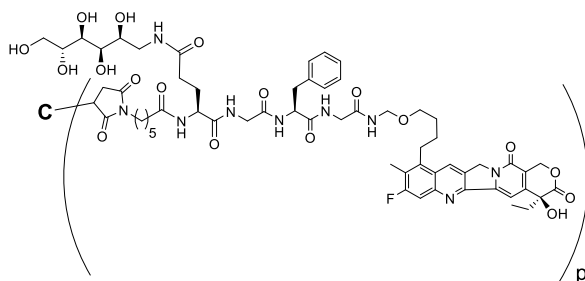
PL-3

,



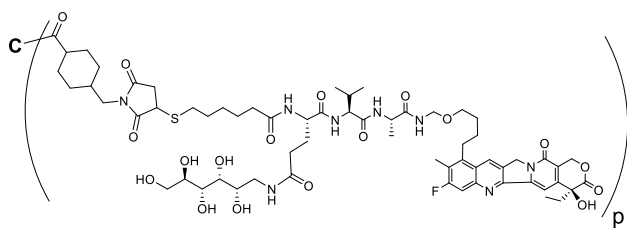
PL-4

,



PL-5

, or

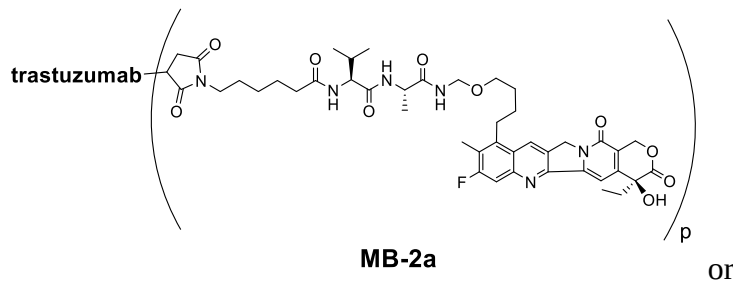


PL-6

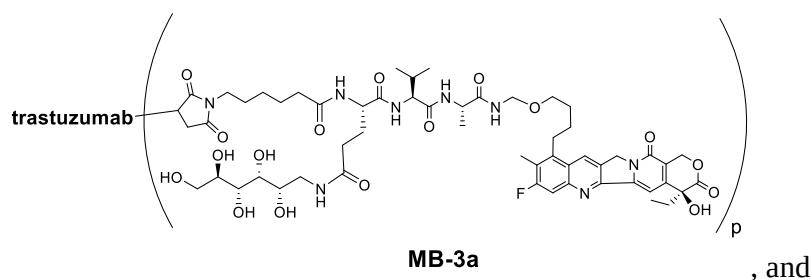
,

and wherein **p** is about 2-10, 4-8, or 7-8.

[00038] In embodiment example, the compound is one of the following structures, or a pharmaceutically acceptable salt thereof:



or



wherein **p** is about 4-8, or 7-8.

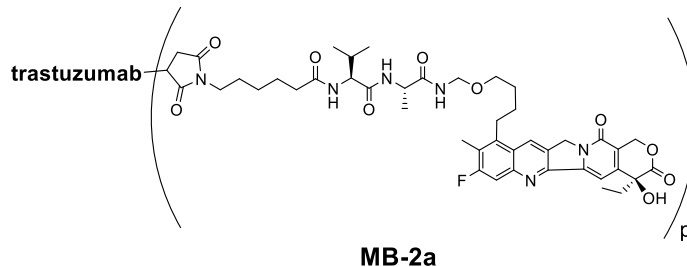
[00039] In embodiment examples, **p** is about 7-8.

[00040] In embodiment examples, **p** is 8.

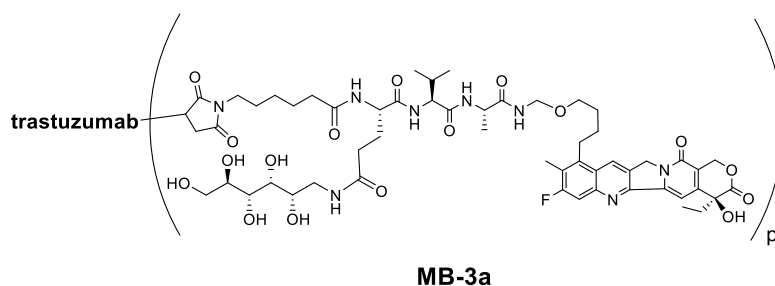
[00041] In another aspect example, the invention disclosure features a pharmaceutical composition comprising any compound described herein, or a pharmaceutically acceptable salt thereof.

[00042] In another aspect example, the invention disclosure features method of treating cancer comprising administering to a subject in need thereof any compound described herein, or a pharmaceutically acceptable salt thereof.

[00043] In embodiment examples, said compound is



or



or a pharmaceutically acceptable salt thereof.

[00044] In embodiment examples, **p** is about 4-8, or 7-8.

[00045] In embodiment examples, **p** is about 7-8.

[00046] In embodiment examples, **p** is 8.

- [00047] In [embodimentexamples](#), the cancer is lung cancer, urothelial cancer, colorectal cancer, prostate cancer, ovarian cancer, pancreatic cancer, breast cancer, bladder cancer, gastric cancer, gastrointestinal stromal tumor, uterine cervix cancer, esophageal cancer, squamous cell carcinoma, peritoneal cancer, liver cancer, hepatocellular cancer, colon cancer, rectal cancer, colorectal cancer, endometrial cancer, uterine cancer, salivary gland cancer, kidney cancer, vulval cancer, thyroid cancer, penis cancer, leukemia, malignant lymphoma, plasmacytoma, myeloma, or sarcoma.
- [00048] In [embodimentexamples](#), the cancer is breast cancer.
- [00049] In [embodimentexamples](#), the cancer is gastric cancer.
- [00050] In [embodimentexamples](#), the cancer is lung cancer (e.g., non-small cell lung cancer)
- [00051] In [embodimentexamples](#), the cancer is ovarian cancer.
- [00052] In [embodimentexamples](#), the cancer is metastatic.
- [00053] In [embodimentexamples](#), the cancer is characterized by low Her2-expression.
- [00054] In [embodimentexamples](#), the cancer is characterized by moderate Her2-expression.
- [00055] In [embodimentexamples](#), the cancer is characterized by high Her2-expression.
- [00056] In [embodimentexamples](#), the cancer is trastuzumab resistant.

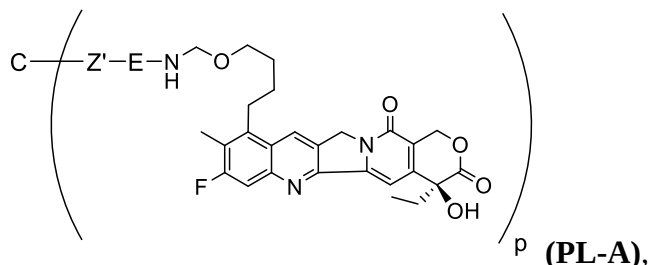
BRIEF DESCRIPTION OF DRAWINGS

- [00057] **FIGS. 1A-1F** show exemplary results of *in vitro* cell growth inhibitory activity of the ADC metabolites in NCI-N87 cell line (**FIG. 1A**); JIMT-1 cell line (**FIG. 1B**); MDA-MB-468 cell line (**FIG. 1C**); SK-OV-3 cell line (**FIG. 1D**); SK-Br-3 cell line (**FIG. 1E**); and MCF-7 cell line (**FIG. 1F**). DXd is the metabolite of DS-8201a (Enhertu) in cells, and **MB-1** is the metabolite of certain ADCs described herein.
- [00058] **FIGS. 2A-2C** depicts HIC-HPLC of the ADCs MB-2a (**FIG. 2A**); MB-3a (**FIG. 2B**) and DS-8201a (Enhertu) (**FIG. 2C**).
- [00059] **FIG. 3A-3D** show exemplary results of *in vitro* cell growth inhibitory activity of ADCs in Her2 high expression cell line NCI-N87 (**FIG. 3A**); NCI-N87 with trastuzumab blocking (**FIG. 3B**); JIMT-1 which has a moderate Her2-expression and is a trastuzumab-resistant cell line (**FIG. 3C**); and Her2 negative cell line MDA-MB-468 (**FIG. 3D**).

CLAIMS

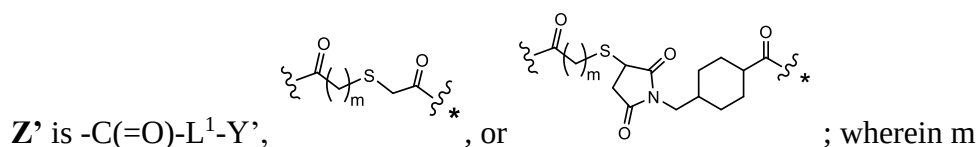
What is claimed is:

1. A compound having the structure of **Formula PL-A**,



or a pharmaceutically acceptable salt thereof, wherein

E is a peptide comprising 2 to 8 amino acids; wherein **E** is optionally substituted with one or more polyol; and wherein the N terminal of the peptide is covalently attached to **Z'**;



represents an integer of 1-10 and * denotes the site covalently linked to said **C**;

L¹ is $-(\text{C}_1\text{-C}_{10} \text{ alkylene})-$, $-\text{CH}_2\text{CH}_2(\text{OCH}_2\text{CH}_2)_n\text{N}(\text{R}_1)\text{C}(=\text{O})-\text{L}^2-*$, or $-\text{CH}_2(\text{OCH}_2\text{CH}_2)_n\text{N}(\text{R}_1)\text{C}(=\text{O})-\text{L}^2-*$; wherein n represents an integer of 1-10; and wherein * denotes the site covalently linked to **Y'**;

L² is $-(\text{C}_1\text{-C}_{10} \text{ alkylene})-$; **R**₁ is -H or -CH₃;

Y' is a group formed by the reaction of an electrophilic group with a reactive nucleophilic group present on cell binding agent **C**; and

p is the drug to antibody ratio (DAR), which is an average number that is about 2-10; and

C is a binding agent that targets Her2 comprising:

a heavy chain comprising an amino acid sequence having at least about 80% identity to SEQ ID NO:1; and

a light chain comprising an amino acid sequence having at least about 80% identity to SEQ ID NO:2.

2. The compound of claim 1, wherein
- a. C is a binding agent comprising
- a heavy chain comprising an amino acid sequence having at least about 85%, 90%, or 95% identity to SEQ ID NO:1; and
- a light chain comprising an amino acid sequence having at least about 85%, 90%, or 95% identity to SEQ ID NO:2;

optionally-

- ~~3. The compound of claim 1 or 2, wherein C is a binding agent comprising~~
- ~~a heavy chain amino acid sequence of SEQ ID NO:1; and~~
- ~~a light chain amino acid sequence of SEQ ID NO:2;~~

and/or

- ~~4. The compound of any of claims 1-3, wherein~~

b. C is a binding agent that is an antibody or antigen-binding fragment thereof; and/or

- ~~5. The compound of any one of claims 1-4, wherein~~

c. C is a binding agent that is trastuzumab (Herceptin), trastuzumab-dkst (Ogivri), trastuzumab-pkrb (Herzuma), trastuzumab-dttb (Ontruzant), trastuzumab-qyyp (Trazimera), or trastuzumab-anns (Kanjinti).

36. The compound of ~~any one of claims 1 or 2-5~~, wherein

a. L¹ is

i. -(C₁-C₁₀ alkylene)-; or-

- ~~7. The compound of any one of claims 1-5, wherein L¹ is~~

ii. -CH₂CH₂(OCH₂CH₂)_nN(R₁)C(=O)-L²-* or -CH₂(OCH₂CH₂)_nN(R¹)C(=O)-L²-*; wherein n represents an integer of 1-10; and wherein * denotes the site covalently linked to Y'; and/or-

- ~~8. The compound of any one of claims 1-7, wherein~~

b. L^1 is $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NHC}(=\text{O})\text{CH}_2\text{CH}_2-$ or $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NHC}(=\text{O})\text{CH}_2\text{CH}_2-$; wherein * denotes the site covalently linked to Y' .

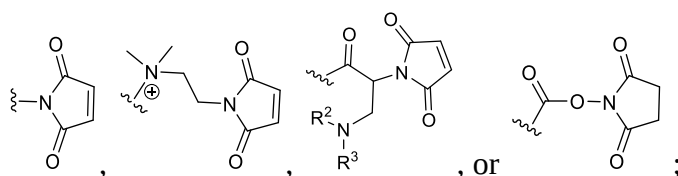
49. The compound of any one of claims 1-~~83~~, wherein

a. Y' is formed from a Michael acceptor group, a succinimide, an epoxide, or a halogen; and/or-

~~10. The compound of any one of claims 1-9, wherein~~

b.

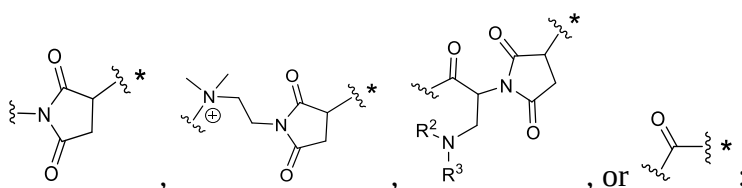
i. Y' is formed from



wherein R^2 and R^3 are each independently $-\text{H}$ or $\text{C}_1\text{-C}_3$ alkyl; or-

~~11. The compound of any one of claims 1-9, wherein~~

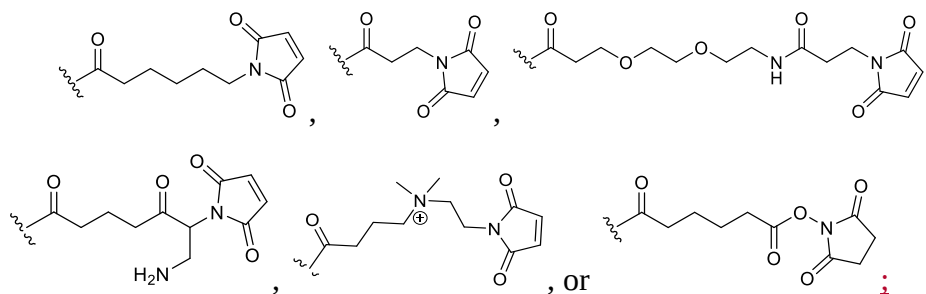
ii. Y' is



wherein R^2 and R^3 are each independently $-\text{H}$ or $\text{C}_1\text{-C}_3$ alkyl and * denotes the site covalently linked to said C.

125. The compound of any one of claims 1-114, wherein

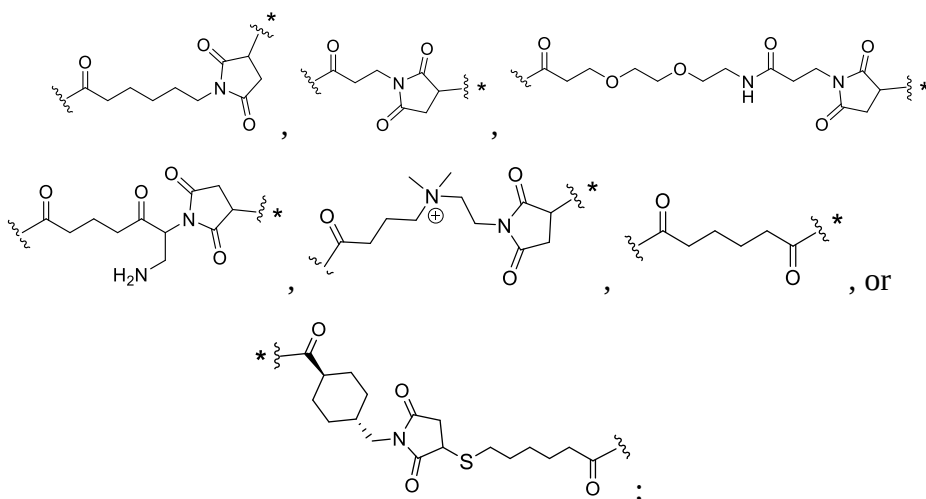
a. $\mathbf{Z}'$ is formed from:



and/or-

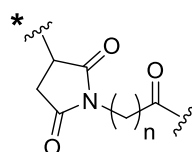
~~13. The compound of any one of claims 1-12, wherein~~

b. $\mathbf{Z}'$ is:



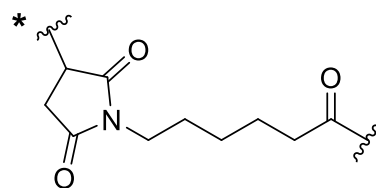
wherein * denotes the site covalently linked to C.

~~146.~~ The compound of claim 1, wherein **Z'** is



The compound of claim 1, wherein **Z'** is ; wherein * denotes the covalent attachment to **C**, and **n** is an integer of 2-10, optionally:

~~15. The compound of claim 14, wherein Z' is~~



~~The compound of claim 14, wherein **Z'** is~~  ~~; wherein *~~
denotes the covalent attachment to **C**.

a. **E** is a peptide of 2, 3, 4, or 5 amino acids, optionally:

i. wherein **E** is a peptide of 2, 3, or 4 amino acids; and/or:

ii. wherein each amino acid in said peptide is an L amino acid, or wherein at least one amino acid in said peptide is a D amino acid;

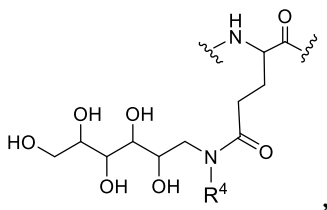
~~19. The compound of any one of claims 1-18, wherein~~

b. E comprises one or more amino acids selected from glycine, alanine, valine, glutamine, glutamic acid, phenylalanine, and leucine, and wherein said glutamine or glutamic acid is optionally substituted by a polyol; **optionally**

~~20. The compound of claim 19, wherein E comprises amino acids selected from glycine, alanine, valine, glutamine, glutamic acid, phenylalanine, and leucine, and wherein said glutamine or glutamic acid is optionally substituted by a polyol; and/or-~~

~~21. The compound of any one of claims 1-20, wherein~~

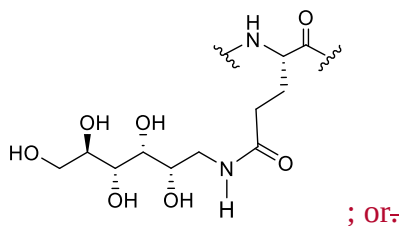
i. E comprises an amino acid having the following structure,



wherein **R**⁴ is -H or C₁-C₆ alkyl;

optionally

~~22. The compound of claim 21,~~ wherein **E** comprises an amino acid having the following structure,



~~23. The compound of any one of claims 1-20, wherein~~

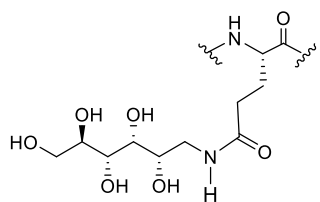
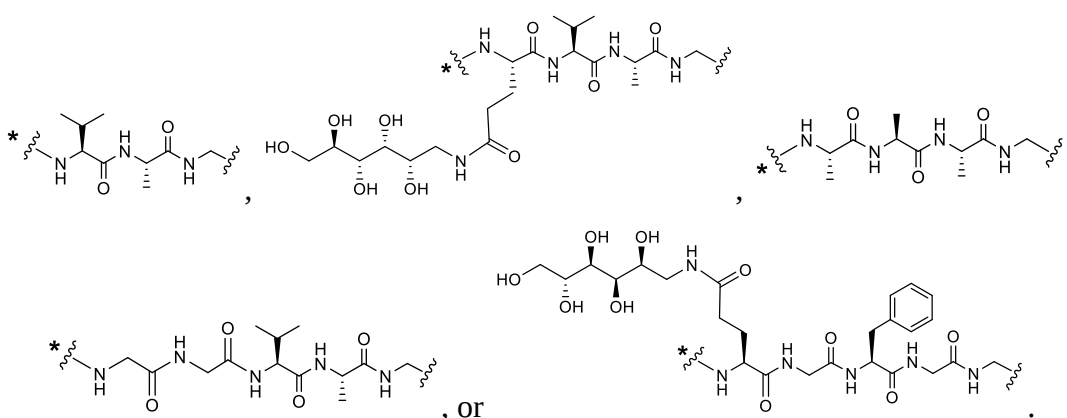
ii. **E** is selected from the group consisting of -Ala-Val-*, -Val-Ala-*, -Gly-Gly-*, -Val-Cit-*, -Cit-Val-*, -Leu-Ala-*, -Ala-Leu-*, -Leu-Cit-*, -Cit-Leu-*, -Leu-Ala-*, -Ala-Leu-*, -Lys-Lys-*, -Ala-Lys-*, -Lys-Ala-*, -Val-Lys-*, -Lys-Val-*, -Tyr-Arg-*, -Arg-Tyr-*, -Arg-Arg-*, -Ala-Ala-*, -Phe-Lys-*, -Lys-Phe-*, -Thr-Thr-*, -Thr-Met-*, -Met-Thr-*, -Met-Tyr-*, -Tyr-Met-*, -Phe-Gln-*, -Gln-Phe-*, -Gly-Ser-*, -Leu-Gln-*, -Gln-Leu-*, -Ser-Ala-*, -Ser-Gly-*, -Val-Thr-*, -Thr-Val-*, -Val-Gln-*, -Ser-Val-*, -Val-Ser-*, -Ala-Met-*, -Met-Ala-*, -Val-Arg-*, -Arg-Val-*, -Phe-Ala-*, -Ala-Phe-*, -Cit-Val-*, -Gln-Val-*, -Phe-Arg-*, -Arg-Phe-*, -Ala-Ala-Ala-*, -Gly-Gly-Gly-*, -Ala-Val-Ala-*, -Gly-Val-Gly-*, -Ala-Val-Gly-*, -Gly-Phe-Lys-*, -Lys-Phe-Gly-*, -Leu-Ala-Leu-*, -Val-Ala-Leu-*, -Leu-Ala-Val-*, -Val-Ala-Val-*, -Ala-Val-Ala-Gly-* (SEQ ID NO: 10), -Gly-Phe-Gly-Gly-* (SEQ ID NO: 11), -Gly-Gly-Phe-Gly-* (SEQ ID NO: 12), -Ala-Val-Gly-Gly-* (SEQ ID NO: 13), -Ala-Ala-Ala-Ala-* (SEQ ID NO: 14), -Ala-Val-Ala-Ala-* (SEQ ID NO: 15), -Ala-Leu-Ala-Leu-* (SEQ ID NO: 16), -Leu-Ala-Leu-Ala-* (SEQ ID NO: 17), -Gly-Phe-Leu-Gly-* (SEQ ID NO: 18) and -Gly-Leu-Phe-Gly-* (SEQ ID NO: 19); ~~and wherein * denotes the N terminal of the peptides covalently attached to Z'.~~ optionally

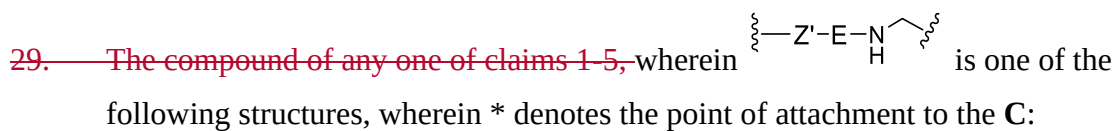
~~24. The compound of claim 23,~~

wherein * denotes the N-terminal of the peptides covalently attached to **Z'**; or:

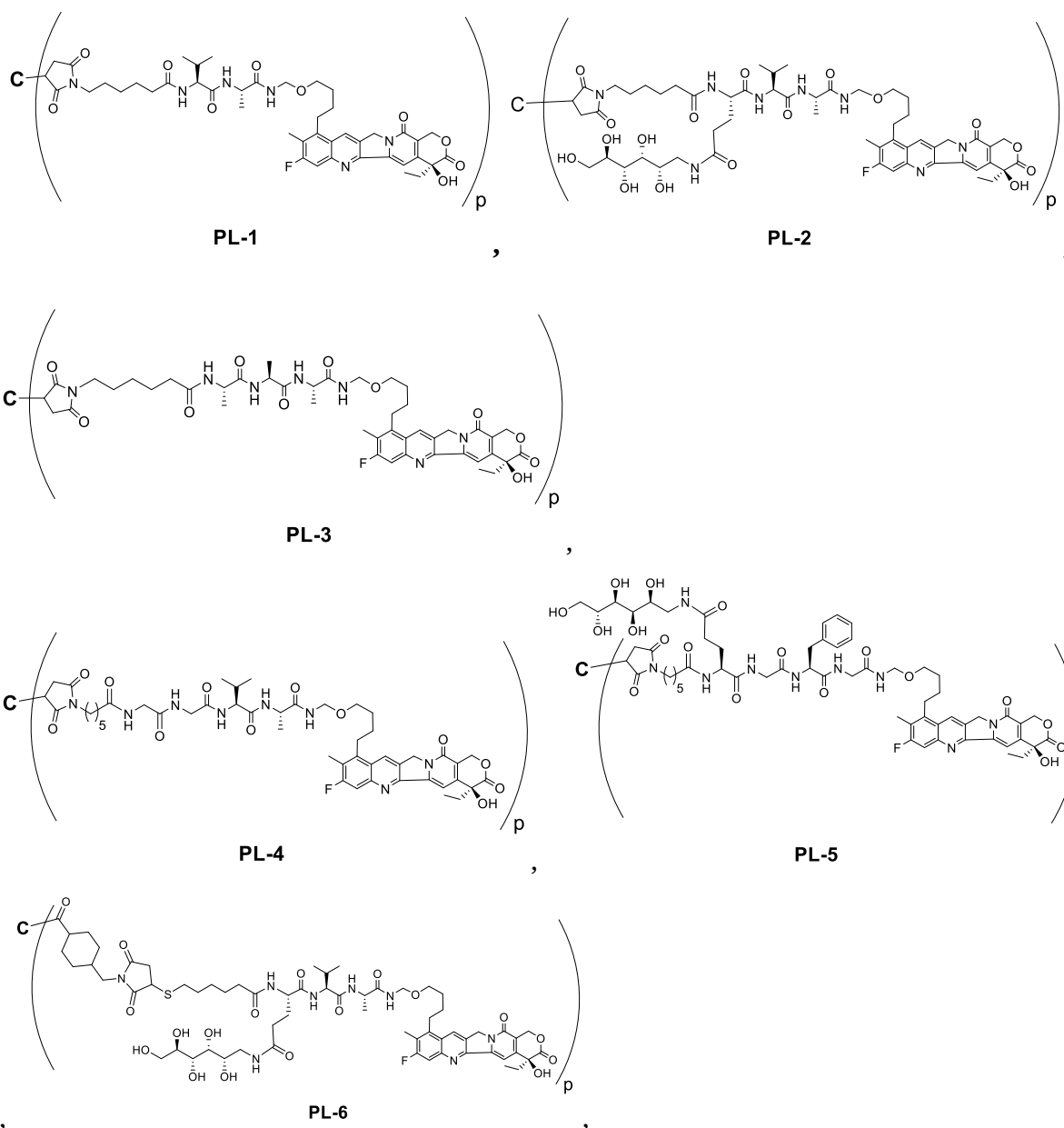
iii. E comprises -(L-Val)-(L-Ala)-, optionally

wherein **E** further comprises an amino acid having the following structure,


$$\sim \text{E}-\underset{\text{H}}{\text{N}}-\sim$$

$$Z'-E-N \begin{array}{c} \diagup \\ H \end{array}$$

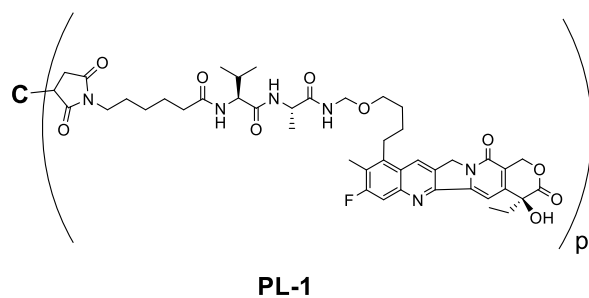


124



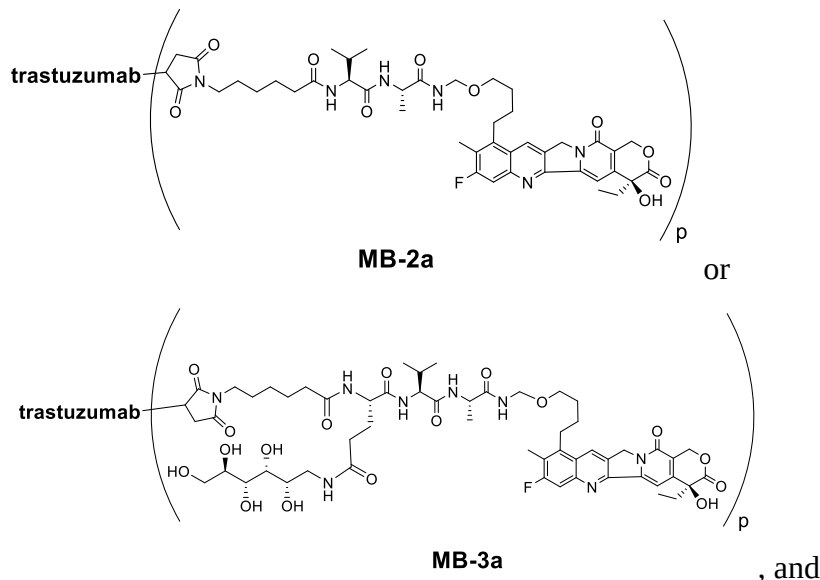
and wherein **p** is about 2-10, 4-8, or 7-8, optionally -

~~31.~~ — ~~The compound of claim 30,~~ wherein the compound is one of the following structures, or a pharmaceutically acceptable salt thereof,



~~32. The compound of any of claims 1 and 30-31,~~

b. wherein the compound is one of the following structures, or a pharmaceutically acceptable salt thereof:



wherein **p** is about 4-8, or 7-8;

optionally

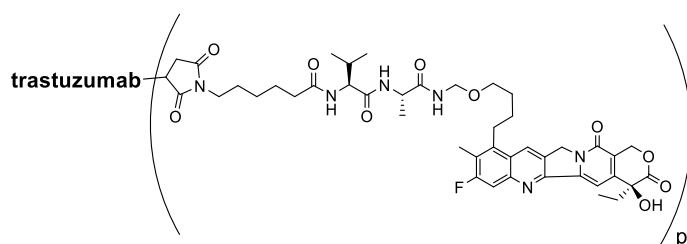
~~33. The compound of any one of claims 30-32,~~ wherein **p** is about 7-8, optionally;

~~34. The compound of any one of claims 30-33,~~ wherein **p** is 8.

~~3511.~~ A pharmaceutical composition comprising the compound of any one of claims 1-~~3410~~, or a pharmaceutically acceptable salt thereof.

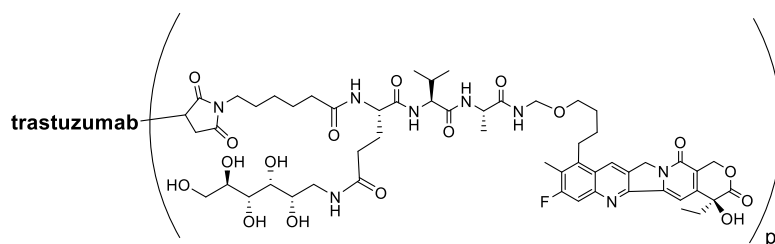
~~3612.~~ A ~~method of treating cancer comprising administering to a subject in need thereof the~~ compound of any one of claims 1-~~3410~~, or a pharmaceutically acceptable salt thereof, for use in treating cancer.

~~3713.~~ The ~~method of claim 36~~compound or salt for use according to claim 12, wherein said compound is



MB-2a

or



MB-3a

or a pharmaceutically acceptable salt thereof;

optionally.

~~38. The method of claim 37, wherein **p** is about 4-8, or 7-8, optionally;~~

~~39. The method of claim 38, wherein **p** is about 7-8, optionally;~~

~~40. The method of claim 39, wherein **p** is 8.~~

~~4114. The method compound or salt for use according to of any one of claims 36-40 12 or 13, wherein the cancer is lung cancer, urothelial cancer, colorectal cancer, prostate cancer, ovarian cancer, pancreatic cancer, breast cancer, bladder cancer, gastric cancer, gastrointestinal stromal tumor, uterine cervix cancer, esophageal cancer, squamous cell carcinoma, peritoneal cancer, liver cancer, hepatocellular cancer, colon cancer, rectal cancer, colorectal cancer, endometrial cancer, uterine cancer, salivary gland cancer, kidney cancer, vulval cancer, thyroid cancer, penis cancer, leukemia, malignant lymphoma, plasmacytoma, myeloma, or sarcoma;~~

optionally

~~42. The method of any one of claims 36-41, wherein the cancer is~~

a. breast cancer; or-

~~43. The method of any one of claims 36-41, wherein the cancer is a~~

b. gastric cancer; or-

~~44. The method of any one of claims 36-41, wherein the cancer is a~~

c. lung cancer; optionally

~~45. The method of claim 44, wherein the lung cancer is non-small cell lung cancer; or-~~

~~46. The method of any one of claims 36-41, wherein the cancer is~~

d. ovarian cancer.

~~47~~15. The ~~method~~compound or salt for use according to ~~of~~ any one of claims ~~36-46~~12-14, wherein the cancer is

a. metastatic; or-

~~48. The method of any one of claims 36-46, wherein the cancer is~~

b. characterized by

i. low Her2-expression; or-

~~49. The method of any one of claims 36-46, wherein the cancer is characterized by~~

ii. moderate Her2-expression; or

~~50. The method of any one of claims 36-46, wherein the cancer is characterized by~~

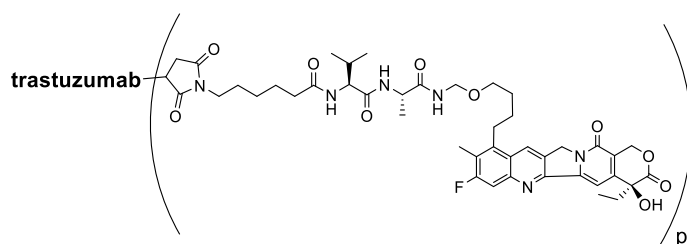
iii. high Her2-expression; and/or -

~~51. The method of any one of claims 36-50, wherein the cancer is~~

c. trastuzumab resistant.

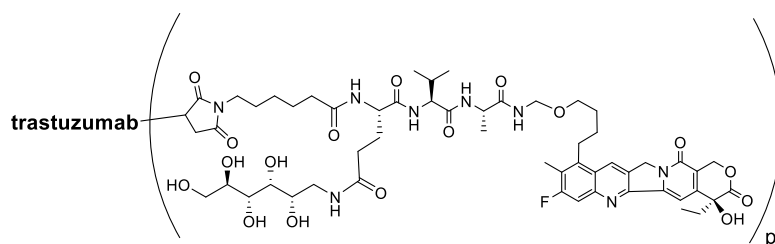
16. Use of a compound of any of claims 1-10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.

17. The use of claim 16, wherein said compound is



MB-2a

or



MB-3a

or a pharmaceutically acceptable salt thereof;

optionally

wherein p is about 4-8, or 7-8, optionally

wherein p is about 7-8, optionally

wherein p is 8.

18. The use of claim 16 or 17, wherein the cancer is lung cancer, urothelial cancer, colorectal cancer, prostate cancer, ovarian cancer, pancreatic cancer, breast cancer, bladder cancer, gastric cancer, gastrointestinal stromal tumor, uterine cervix cancer, esophageal cancer, squamous cell carcinoma, peritoneal cancer, liver cancer, hepatocellular cancer, colon cancer, rectal cancer, colorectal cancer, endometrial cancer, uterine cancer, salivary gland cancer, kidney cancer, vulval cancer, thyroid

cancer, penis cancer, leukemia, malignant lymphoma, plasmacytoma, myeloma, or sarcoma;

optionally

wherein the cancer is

a. breast cancer; or

b. gastric cancer; or

c. lung cancer, optionally

wherein the lung cancer is non-small cell lung cancer; or

d. ovarian cancer.

19. The use of any one of claims 16-18, wherein the cancer is

a. metastatic; or

b. characterized by

i. low Her2-expression; or

ii. moderate Her2-expression; or

iii. high Her2-expression; and/or

c. trastuzumab resistant.