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of Inventions related to Genetic Resources
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Patentability of Sample Case

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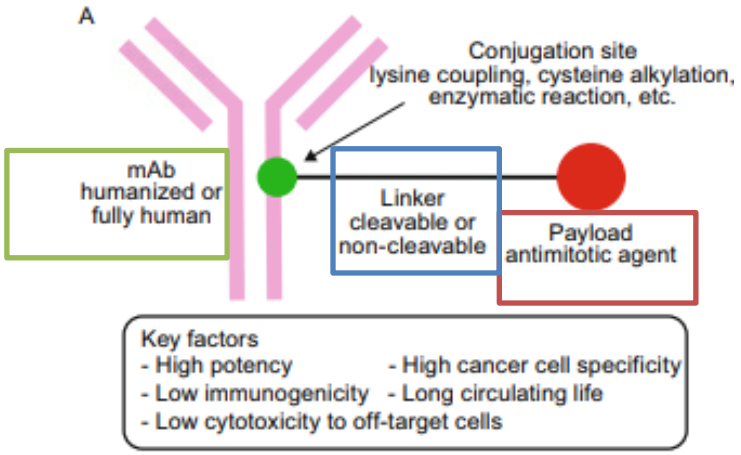
Patent Examiner
Korean Intellectual Property Office

CASE STUDY:
WO 2014/011520 A1

Priority: 9 July 2012
Published: 16 January 2014

WHAT IS CLAIMED IS:

1. An immunoconjugate comprising an antibody that binds CD22 covalently attached to a cytotoxic agent, wherein the antibody binds an epitope within amino acids 20 to 240 of SEQ ID NO: 28, and wherein the cytotoxic agent is a nemorubicin derivative.



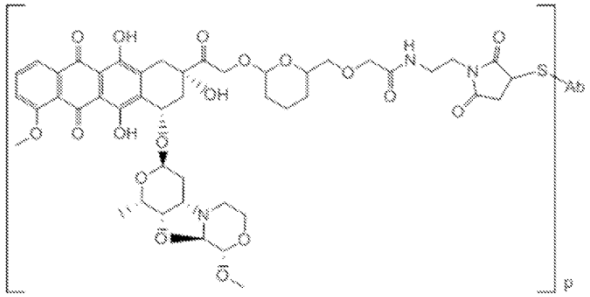
Antibody-drug conjugate (ADC)

Figure from Protein Cell 2018, 9(1): 33-46

Thio Hu anti-CD22 10F4v3 HC A118C-MC-acetal-PNU-159682 ("10F4v3-PNU-2")

[0281] Prior to conjugation, the antibody was reduced with dithiothreitol (DTT) to remove blocking groups (e.g. cysteine) from the engineered cysteines of the thio-antibody. This process also reduces the interchain disulfide bonds of the antibody. The reduced antibody was purified to remove the released blocking groups and the interchain disulfides were

A ThioHuanti-CD2210F4v3HCA118C-MC-acetal-PNU-159682 ("10F4v3-PNU-2")



B ThioHuanti-CD2210F4v3HCA118C-MC-val-cit-PAB-PNU-159682 ("10F4v3-PNU-1")

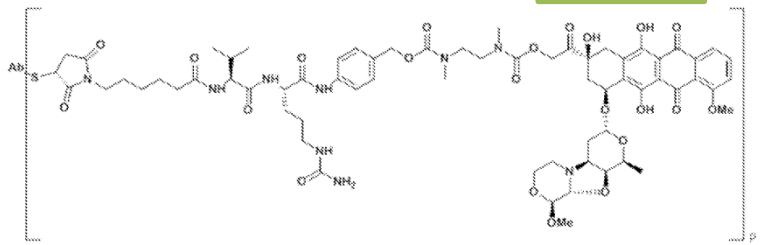


FIG.4

was purified to remove the released blocking groups and the interchain disulfides were reoxidized using dehydro-ascorbic acid (dhAA). The intact antibody was then combined with the drug-linker moiety MC-val-cit-PAB-MMAE ("val-cit" may also be referred to herein as "vc") to allow conjugation of the drug-linker moiety to the engineered cysteine residues of the antibody. The conjugation reaction was quenched by adding excess N-acetyl-cysteine to react with any free linker-drug moiety, and the ADC was purified. The drug load (average number of drug moieties per antibody) for the ADC was determined to be about 2, as indicated in the examples below. Thio Hu anti-CD22 10F4v3 HC A118C-MC-val-cit-PAB-MMAE is described, e.g., in US 2008/0050310.

Table 2: Anti-CD22 ADC administration to mice with WSU-DLCL2 xenografts

Antibody administered (Treatment)	TI	PR	CR	Drug Dose (μg//kg)	Ab Dose (mg/kg)	Drug Load (Drug /Ab)
Vehicle*	9/9	0	0	n/a	n/a	n/a
10F4v3-PNU-1	9/9	2	0	15.40	2	1.8
Control ADC-A118C-MC-val-cit-PAB-PNU-159682 ("Control-PNU-1")	9/9	0	0	15.83	2	1.85
10F4v3-PNU-2	9/9	1	0	61.60	8	1.8
Control ADC-A118C-MC-acetal-PNU-159682 ("Control-PNU-2")	9/9	0	0	61.60	8	1.8
Thio Hu anti-CD22 10F4v3 HC A118C-MC-vc-PAB-MMAE ("10F4v3-MMAE")	7/9	6	3	76.59	8	2

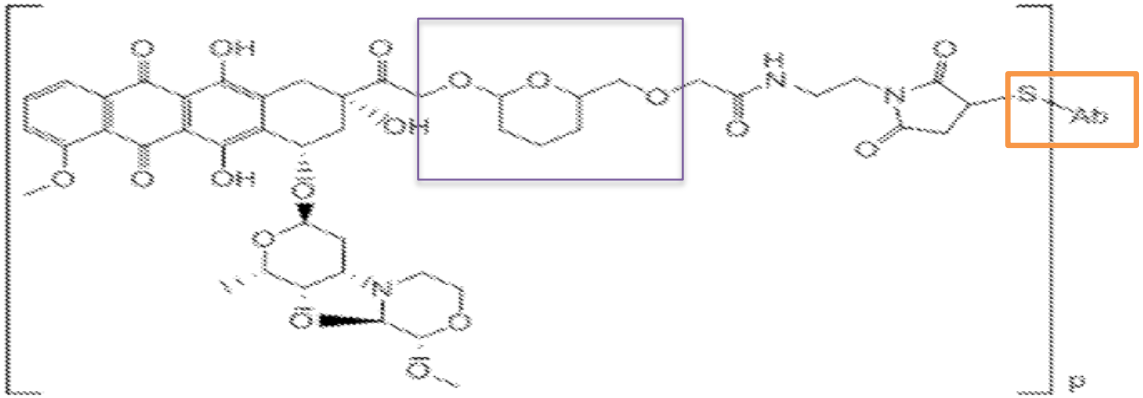
*Vehicle = 20 mM histidine acetate, pH 5.5, 240 mM sucrose, 0.02% PS20; n/a = not applicable.

[0288] In a 35 day time course with drug conjugates and doses as shown in Table 2, 10F4v3 ADC conjugated through a protease cleavable linker with PNU-159682 ("10F4v3-PNU-1") showed inhibition of tumor growth in SCID mice with WSU-DLCL2 tumors compared to the vehicle and the control ADC ("Control-PNU-1"). *See* Figure 5. Thio Hu anti-CD22 conjugated through an acid-labile linker with PNU-159682 ("10F4v3-PNU-2") also showed inhibition of tumor growth in SCID mice with WSU-DLCL2 tumors compared to the vehicle and the control ADC ("Control-PNU-2").

[0289] In this study, the percent body weight change was determined in each dosage group. The results indicated that administration of the 10F4v3 ADCs did not cause a significant decrease in body weight during the study.

Description

A ThioHuanti-CD2210F4v3HCA118C-MC-acetal-PNU-159682("10F4v3-PNU-2")



B ThioHuanti-CD2210F4v3HCA118C-MC-val-cit-PAB-PNU-159682("10F4v3-PNU-1")

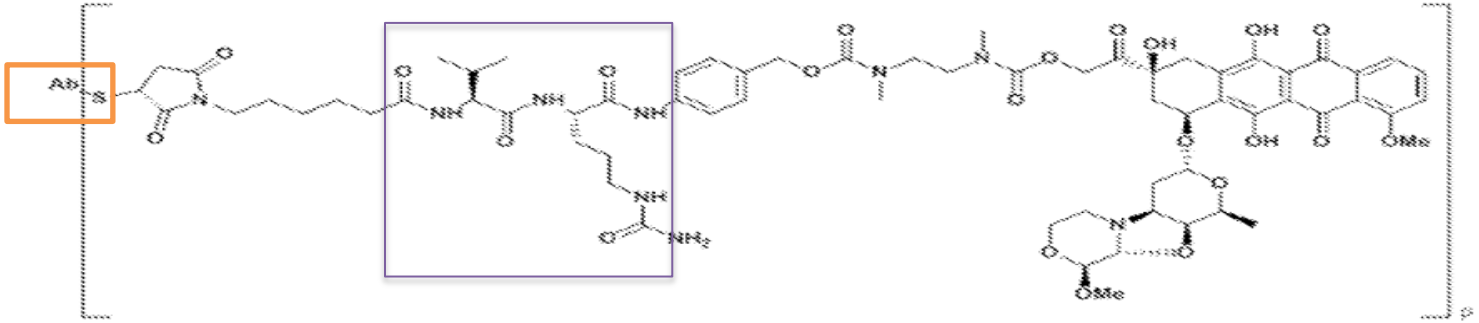
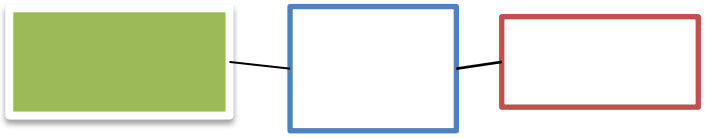


FIG.4

WHAT IS CLAIMED IS:

1. An immunoconjugate comprising an antibody that binds CD22 covalently attached to a cytotoxic agent, wherein the antibody binds an epitope within amino acids 20 to 240 of SEQ ID NO: 28, and wherein the cytotoxic agent is a nemorubicin derivative.

Antibody



Antibody-drug conjugate (ADC)

STN Results

```
=> D L1 CN SQL SEQ 28-31


L1    ANSWER 28 OF 31  REGISTRY  COPYRIGHT 2019 ACS on STN
CN    Immunoglobulin, chimeric, anti-(Human CD22 (antigen)) (synthetic Mus
      musculus clone ch10F4 heavy chain V region)  (CA INDEX NAME)
OTHER NAMES:
CN    45: PN: WO2007140371 SEQID: 34 claimed protein
SQL   120

SEQ      1 QVQLQQSGPE LVKPGASVKI SCKASGYEFS RSWMNWVKQR PGQGREWIGR
                                   ===== ========== ==========
        51 IYPGDGDTNY SGKFKGKATL TADSSSSTAY MQLSSLTSVD SAVYFCARDG
           ========== ========== ========== ========== ==========
       101 SSWDWYFDVW GAGTTVTVSS
           =========
HITS AT:    26-109
```

HVR H1 : GYEFSRSWMN
HVR H2 : GRIYPGDGDTNYSGKFKG
HVR H3 : DGSSWDWYFDV

Data obtained using STN

Prior Art Document 1:
WO 2007/140371 (6 December 2007)

WHAT IS CLAIMED IS:

1. An antibody that binds to CD22, wherein the antibody comprises (a) an HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs:9, 10, 19-23, 32 and 33, and (b) at least one, two, three, four, or five HVRs selected from:
   (1) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:2;
   (2) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:4;
   (3) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:6;
   (4) an HVR-L2 comprising the amino acid sequence of SEQ ID NO: 12; and
   (5) an HVR-L3 comprising an amino acid sequence of SEQ ID NO: 14.
2. The antibody of claim 1, comprising an HVR-L1 comprising an amino acid sequence that conforms to the consensus sequence of SEQ ID NO: 10.
3. The antibody of claim 2, further comprising an HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; an HVR-H2 comprising the amino acid sequence of SEQ ID NO:4; and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:6.
4. The antibody of claim 1, wherein the HVR-L1 comprises SEQ ID NO:9, and the antibody further comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; an HVR-H2 comprising the amino acid sequence of SEQ ID NO:4; and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:6.
5. The antibody of claim 1, wherein the HVR-L1 comprises SEQ ID NO: 19, and the antibody further comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; an HVR-H2 comprising the amino acid sequence of SEQ ID NO:4; and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:6.
6. The antibody of claim 1, wherein the HVR-L1 comprises SEQ ID NO:20, and the antibody further comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; an HVR-H2 comprising the amino acid sequence of SEQ ID NO:4; and an HVR-H3 comprising the amino acid sequence of SEEQ ID NO:6.
7. The antibody of claim 1, wherein the HVR-L1 comprises SEQ ID NO:21, and the antibody further comprises an HVR-H1 comprising the amino acid sequence of SEQ ID NO:2; an HVR-H2 comprising the amino acid sequence of SEQ ID NO:4; and an HVR-H3 comprising the amino acid sequence of SEQ ID NO:6.

WO 2007/140371 PCT/US2007/069889

76. An immunoconjugate comprising an antibody of claim 1 covalently attached to a cytotoxic agent.
77. An immunoconjugate comprising an antibody of claim 23 covalently attached to a cytotoxic agent.
78. The immunoconjugate of claim 76, wherein the cytotoxic agent is selected from a toxin, a chemotherapeutic agent, a drug moiety, an antibiotic, a radioactive isotope, and a nucleolytic enzyme.
79. The immunoconjugate of claim 78, the immunoconjugate having the formula Ab-(L-D)p, wherein:
   (a) Ab is the antibody of claim 1;
   (b) L is a linker;
   (c) D is a drug moiety.

46. A method of making an anti-CD22 antibody, wherein the method comprises a) culturing the host cell of claim 38 under conditions suitable for expression of the polynucleotide encoding the antibody, and b) isolating the antibody.
47. A method of making an anti-CD22 antibody, wherein the method comprises a) culturing the host cell of claim 39 under conditions suitable for expression of the polynucleotide encoding the antibody, and b) isolating the antibody.
48. The antibody of claim 28, wherein the CD22 is expressed on the surface of a cell.
49. The antibody of claim 48, wherein the cell is a B cell.
50. The antibody of claim 29, wherein the CD22 is expressed on the surface of a cell.
51. The antibody of claim 50, wherein the CD22 is a B cell.
52. The antibody of claim 1, wherein the antibody binds to an epitope within a region of CD22 from amino acid 22-240 of SEQ ID NO:27.
53. The antibody of claim 23, wherein the antibody binds to an epitope within a region of CD22 from amino acid 22-240 of SEQ ID NO:27.
54. The antibody of claim 49, wherein the B cell is associated with a B cell proliferative disorder.
55. The antibody of claim 54, wherein the B cell proliferative disorder is a cancer.
56. The antibody of claim 54, wherein the B cell proliferative disorder is selected from -lymphoma, non-Hogkins lymphoma (NHL), aggressive NHL, relapsed aggressive NHL, relapsed indolent NHL, refractory NHL, refractory indolent NHL, chronic lymphocytic

2. The immunoconjugate of claim 1, wherein the antibody comprises (i) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 11, (ii) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 14, and (iii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 10.

3. The immunoconjugate of claim 1 or claim 2, wherein the antibody comprises (i) HVR-Hl comprising the amino acid sequence of SEQ ID NO: 9, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 10, and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 11.

HVR-Hl (GIy Tyr GIu Phe Ser Arg Ser Trp Met Asn, SEQ ID NO:2)

HVR-H2 (GIy Arg He Tyr Pro GIy Asp GIy Asp Thr Asn Tyr Ser GIy Lys Phe Lys GIy, SEQ ID NO:4)

HVR-H3 (Asp GIy Ser Ser Trp Asp Try Tyr Phe Asp Tyr, SEQ ID NO:6)

HVR-L3 (Phe GIn GIy Ser GIn Phe Pro Tyr Thr, SEQ ID NO: 14).

Table of Sequences

SEQ ID NO	Description	Sequence
1	humIII variable region sequence	EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVSV ISGDGGSTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGF DYWGQGTLVT VSS
2	humκ1 variable region sequence	DIQMTQSPSS LSASVGDRVT ITCRASQSIS NYLAWYQQKP GKAPKLLIYA ASSLESGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNSLPWTFGQ GTKVEIK
3	mu10F4 heavy chain variable region	QVQLQQSGPE LVKPGASVKI SCKASGYEFS RSWMNWVKQR PGQGREWIGR IYPGDGDTNY SGKFKGKATL TADKSSSTAY MQLSSLTSVD SAVYFCARDG SSWDWYFDVW GAGTTVTVSS
4	mu10F4 light chain variable region	DILMTQTPLS LPVSLGDQAS ISCRSSQSIV HSNGNTFLEW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YYCFQGSQFP YTFGGGTKVE IK
5	hu10F4v1 heavy chain variable region	EVQLVESGGG LVQPGGSLRL SCAASGYEFS RSWMNWVRQA PGKGLEWVGR IYPGDGDTNY SGKFKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCARDG SSWDWYFDVW GQGTLVTVSS
6	hu10F4v1 light chain variable region	DIQMTQSPSS LSASVGDRVT ITCRSSQSIV HSNGNTFLEW YQQKPGKAPK LLIYKVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCFQGSQFP YTFGQGTKVE IK
7	hu10F4v3 heavy chain variable region	EVQLVESGGG LVQPGGSLRL SCAASGYEFS RSWMNWVRQA PGKGLEWVGR IYPGDGDTNY SGKFKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCARDG SSWDWYFDVW GQGTLVTVSS
8	hu10F4v3 light chain variable region	DIQMTQSPSS LSASVGDRVT ITCRSSQSIV HSVGNTFLEW YQQKPGKAPK LLIYKVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCFQGSQFP YTFGQGTKVE IK
9	10F4 HVR H1	GYEFSRSWMN
10	10F4 HVR H2	GRIYPGDGDTNYSGKFKG
11	10F4 HVR H3	DGSSWDWYFDV
12	10F4 HVR L1	RSSQSIVHSNGNTFLE
13	10F4 HVR L2	KVSNRFS
14	10F4 HVR L3	FQGSQFPYT
15	10F4 HVR L1 N28V (10F4v3 HVR L1)	RSSQSIVHSVGNTFLE
16	10F4 HVR L1 N28A	RSSQSIVHSAGNTFLE
17	10F4 HVR L1 N28Q	RSSQSIVHSQGNTFLE
18	10F4 HVR L1 N28S	RSSQSIVHSSGNTFLE
19	10F4 HVR L1 N28D	RSSQSIVHSDGNTFLE
20	10F4 HVR L1 N28I	RSSQSIVHSIGNTFLE
21	10F4 HVR L1 N30A	RSSQSIVHSNGITFLE
22	10F4 HVR L1 N30Q	RSSQSIVHSNGQTFLE
45	hu10F4v3 heavy chain (HC) framework (FR) 1	EVQLVESGGG LVQPGGSLRL SCAAS
46	hu10F4v3 HC FR2	WVRQA PGKGLEWV
47	hu10F4v3 HC FR3	RFTI SADTSKNTAY LQMNSLRAED TAVYYCAR
48	hu10F4v3 HC FR4	W GQGTLVTVSS

4. The immunoconjugate of claim 1, wherein the antibody comprises:

a) (i) HVR-Hl comprising the amino acid sequence of SEQ ID NO: 9, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 10, (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 11, (iv) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 12 and 15 to 22, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 13, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 14; or

b) (i) HVR-Hl comprising the amino acid sequence of SEQ ID NO: 9, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 10, (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 11, (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 15, (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 13, and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 14.

HVR-Hl (GIy Tyr GIu Phe Ser Arg Ser Trp Met Asn, SEQ ID NO:2)

HVR-H2 (GIy Arg He Tyr Pro GIy Asp GIy Asp Thr Asn Tyr Ser GIy Lys Phe Lys GIy, SEQ ID NO:4)

HVR-H3 (Asp GIy Ser Ser Trp Asp Try Tyr Phe Asp Tyr, SEQ ID NO:6)

HVR-Ll (Arg Ser Ser GIn Ser He VaI His Ser Asn GIy Asn Thr Phe Leu GIu, SEQ ID N0:9)

HVR-L2 (Lys VaI Ser Asn Arg Phe Ser, SEQ ID NO: 12)

HVR-L3 (Phe GIn GIy Ser GIn Phe Pro Tyr Thr, SEQ ID NO: 14).

HVR-Ll (Arg Ser Ser GIn Ser He VaI His Ser VaI GIy Asn Thr Phe Leu GIu, SEQ ID NO: 10)

HVR-Ll (Arg Ser Ser GIn Ser He VaI His Ser Ala GIy Asn Thr Phe Leu GIu, SEQ ID NO: 19)

HVR-Ll (Arg Ser Ser GIn Ser He VaI His Ser GIn GIy Asn Thr Phe Leu GIu, SEQ ID NO:20)

HVR-Ll (Arg Ser Ser GIn Ser He VaI His Ser Ser GIy Asn Thr Phe Leu GIu, SEQ E >N0:21)

HVR-Ll (Arg Ser Ser GIn Ser He VaI His Ser Asp GIy Asn Thr Phe Leu GIu, SEQ ID NO:22)

HVR-Ll (Arg Ser Ser GIn Ser He VaI His Ser He GIy Asn Thr Phe Leu GIu, SEQ ID NO:23)

HVR-Ll (Arg Ser Ser GIn Ser He VaI His Ser He GIy Ala Thr Phe Leu GIu, SEQ ID NO:32)

HVR-Ll (Arg Ser Ser GIn Ser He VaI His Ser He GIy GIn Thr Phe Leu GIu, SEQ ID NO:33)

Table of Sequences

SEQ ID NO	Description	Sequence
1	humIII variable region sequence	EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVSV ISGDGGSTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGF DYWGQGTLVT VSS
2	humκ1 variable region sequence	DIQMTQSPSS LSASVGDRVT ITCRASQSIS NYLAWYQQKP GKAPKLLIYA ASSLESGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNSLPWTFGQ GTKVEIK
3	mu10F4 heavy chain variable region	QVQLQQSGPE LVKPGASVKI SCKASGYEFS RSWMNWVKQR PGQGREWIGR IYPGDGDTNY SGKFKGKATL TADKSSSTAY MQLSSLTSVD SAVYFCARDG SSWDWYFDVW GAGTTVTVSS
4	mu10F4 light chain variable region	DILMTQTPLS LPVSLGDQAS ISCRSSQSIV HSNGNTFLEW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YYCFQGSQFP YTFGGGTKVE IK
5	hu10F4v1 heavy chain variable region	EVQLVESGGG LVQPGGSLRL SCAASGYEFS RSWMNWVRQA PGKGLEWVGR IYPGDGDTNY SGKFKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCARDG SSWDWYFDVW GQGTLVTVSS
6	hu10F4v1 light chain variable region	DIQMTQSPSS LSASVGDRVT ITCRSSQSIV HSNGNTFLEW YQQKPGKAPK LLIYKVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCFQGSQFP YTFGQGTKVE IK
7	hu10F4v3 heavy chain variable region	EVQLVESGGG LVQPGGSLRL SCAASGYEFS RSWMNWVRQA PGKGLEWVGR IYPGDGDTNY SGKFKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCARDG SSWDWYFDVW GQGTLVTVSS
8	hu10F4v3 light chain variable region	DIQMTQSPSS LSASVGDRVT ITCRSSQSIV HSVGNTFLEW YQQKPGKAPK LLIYKVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCFQGSQFP YTFGQGTKVE IK
9	10F4 HVR H1	GYEFSRSWMN
10	10F4 HVR H2	GRIYPGDGDTNYSGKFKG
11	10F4 HVR H3	DGSSWDWYFDV
12	10F4 HVR L1	RSSQSIVHSNGNTFLE
13	10F4 HVR L2	KVSNRFS
14	10F4 HVR L3	FQGSQFPYT
15	10F4 HVR L1 N28V (10F4v3 HVR L1)	RSSQSIVHSVGNTFLE
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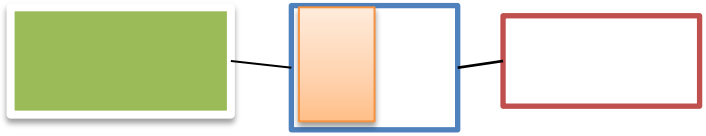
22	10F4 HVR L1 N30Q	RSSQSIVHSNGQTFLE

Antibody Linker



Claim 18

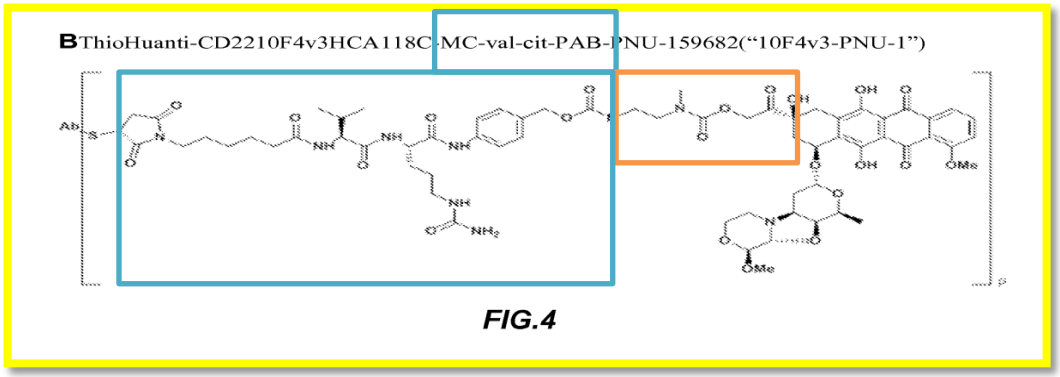


FIG.4

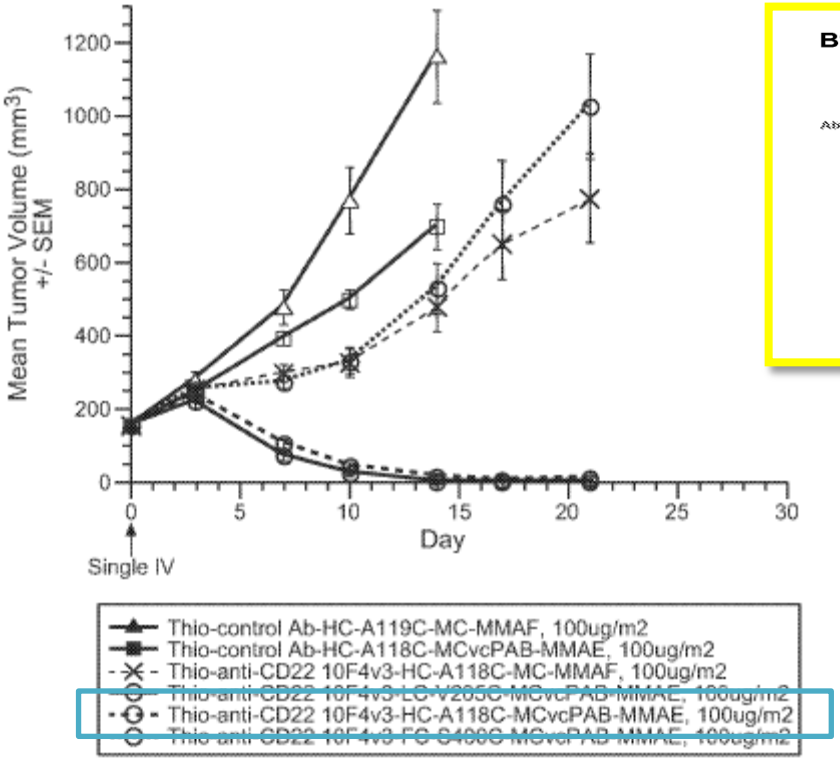
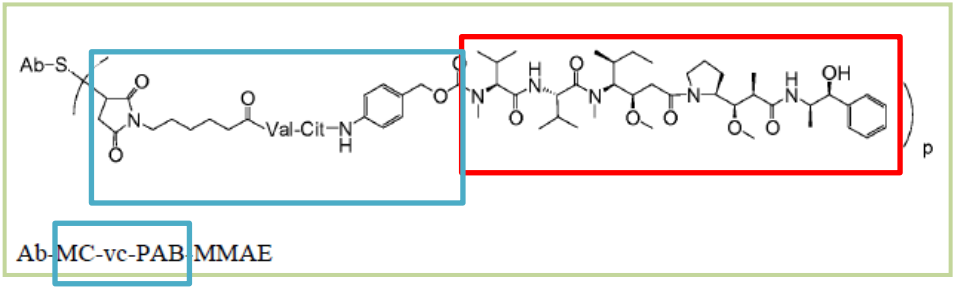


FIG. 19



MMAE: monomethylauristatin

Claims:

11. An immunoconjugate of any one of claims 1 to 10, wherein the immunoconjugate has the formula Ab-(L-D)p, wherein:

(a) Ab is the antibody;

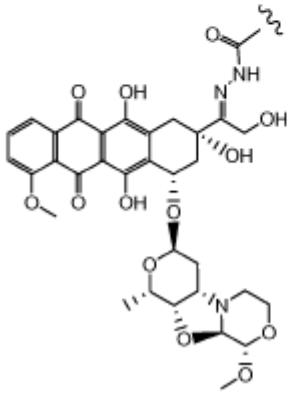
(b) L is a linker;

(c) D is the cytotoxic agent; and

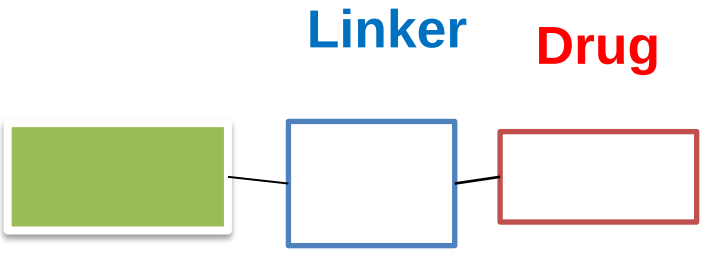
(d) p ranges from 1-8.

12. The immunoconjugate of claim 11, wherein D is a nemorubicin derivative.

13. The immunoconjugate of claim 12, wherein D has a structure selected from:



; and



Antibody-drug conjugate (ADC)

전체 이미지 동영상 지도 뉴스 더보기 설정 도구

검색결과 약 5,070개 (0.34초)

CONJUGATES OF PNU-159682 and NEMORUBICIN | Biodiscovery
https://biodiscovery.eu/.../adc.../conjugates-of-pnu-159682-and-n... ▾ 이 페이지 번역하기
Conjugates with cleavable and non-cleavable linkers Hydrazide linkers (e.g. maleimidocaprohydrazide) DEA-PABC-Val-Cit-MC linker Spacers can be included.

Antibody-drug conjugates: Design and development for therapy and ...
https://www.tandfonline.com/doi/full/.../19420862.2017.1412130 - 이 페이지 번역하기
C Martin 저술 - 2018 - 8회 인용 - 관련 학술자료
The focus was on antibody-drug-conjugates (**ADCs**), new entities which realize ..... The new anthracyclin PNU-159682, an in vivo metabolite of **nemorubicin** with ...

Third-generation antibody drug conjugates for cancer therapy – a ...
https://www.future-science.com/doi/full/10.4155/tde-2016-0002 ▾ 이 페이지 번역하기
M Vankemmelbeke 저술 - 2016 - 13회 인용 - 관련 학술자료
2016. 2. 19. - **ADC** linkers are broadly classified into cleavable: through disulfide .... the duocarmycins [17,18] and anthracyclines (**nemorubicin** and its more ...

AACR 2018 Proceedings: Abstracts 1-3027 - Google 도서 검색결과
https://books.google.co.kr/books?isbn=1370257430 - 이 페이지 번역하기
American Association for Cancer Research - 2018
Background: Antibody Drug Conjugates (**ADCs**) target highly potent small molecule ... DNA damaging anthracycline toxin, based on the **nemorubicin** derivative ...

Antibody-Drug Conjugates: Fundamentals, Drug Development, and ...
https://books.google.co.kr/books?isbn=1119060842 - 이 페이지 번역하기
Kenneth J. Olivier, Jr., Sara A. Hurvitz - 2016 - Medical
... NO NO Doxorubicin OH **Nemorubicin** O PNU-159682 O O O O =NMS249 OH ... profile of anthracyline-based **ADCs** in solid and hematological malignancies.

WO 2009/099741

US8742076B2 - Nemorubicin metabolite and analog reagents ...
https://patents.google.com/patent/US8742076B2/en ▾ 이 페이지 번역하기
The present invention provides **nemorubicin** metabolite and analog drug moiety reagents for the preparation of therapeutic antibody-drug conjugate (**ADC**) ...

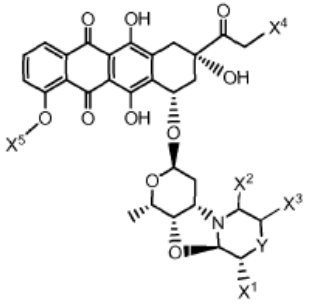
Prior Art Document 2:
WO 2009/099741 (13 August 2009)

[00251] comprising an antibody covalently attached by a linker to one or more nemorubicin metabolite or analog drug moieties, or a pharmaceutically acceptable salt thereof, wherein:

[00252] Ab is an antibody;

[00253] L is a linker; and

[00254] D is a nemorubicin metabolite or analog drug moiety having the structure:



[00255] wherein:

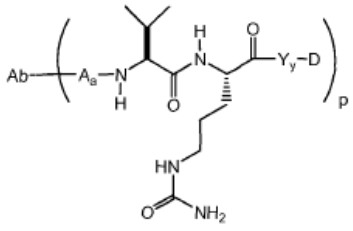
[00256] Y is N-X^6 or O;

[00257] L is attached at one of X^1, X^2, X^3, X^4, X^5, or X^6; and

[00258] p is 1, 2, 3, 4, 5, 6, 7, or 8.

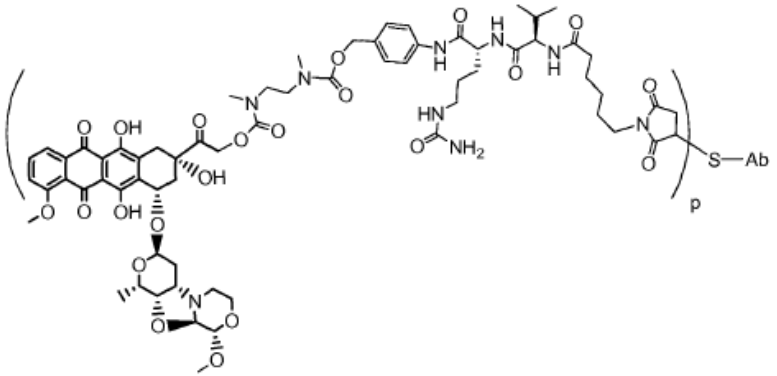
[00259] The drug to antibody ratio or drug loading is represented by p for Formula I compounds. The drug loading value p is 1 to 8. Formula I compounds include all mixtures of variously loaded and attached antibody-drug conjugates where 1, 2, 3, 4, 5, 6, 7, and 8 drug moieties are covalently attached to the antibody.

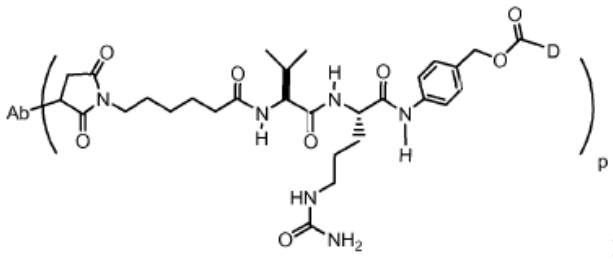
[00260] Embodiments of antibody-drug conjugates include:



valine-citrulline (val-cit or vc)

[00296] Embodiments of antibody-drug conjugates include:

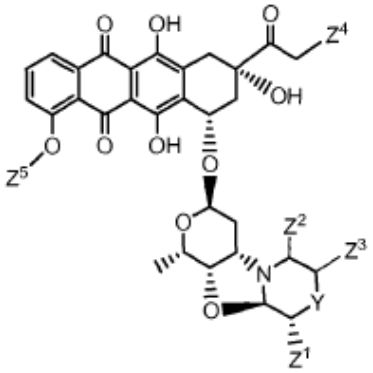




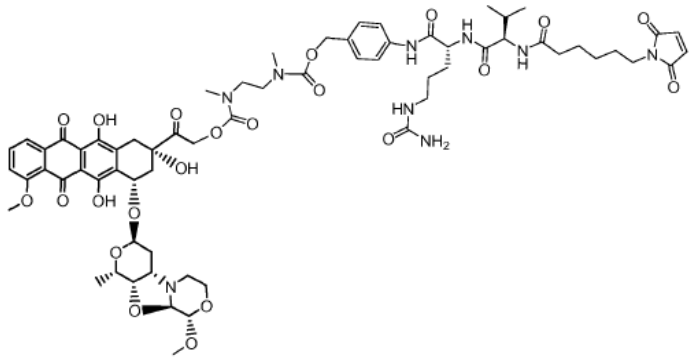
MC-val-cit-PAB

CLAIMS

1. A drug moiety reagent having a structure:



10. The drug-linker reagent of claim 9 selected from the structures:



18. An antibody-drug conjugate compound comprising an antibody covalently attached by a linker to one or more nemorubicin metabolite or analog drug moieties, the compound having Formula I:

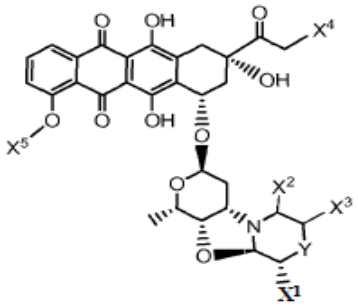
$$Ab–(L–D)_p \qquad I$$

or a pharmaceutically acceptable salt thereof, wherein:

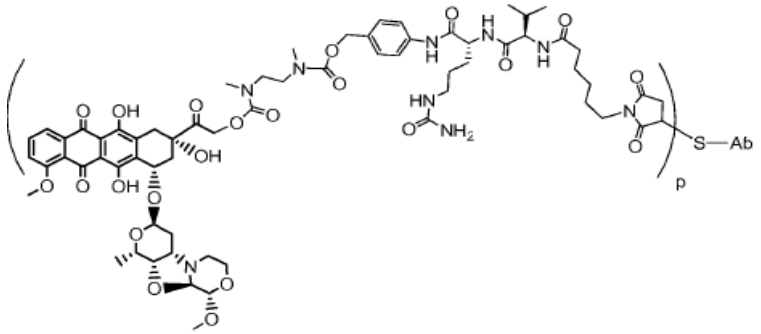
Ab is an antibody;

L is a linker; and

D is a nemorubicin metabolite or analog drug moiety having the structure:



38. The antibody-drug conjugate compound of claim 37 selected from the structures:



29. The antibody-drug conjugate compound of claim 18 wherein Ab is an antibody which binds to one or more tumor-associated antigens or cell-surface receptors selected from (1)-(36):

(1) BMPR1B (bone morphogenetic protein receptor-type IB);

(2) E16 (LAT1, SLC7A5);

(3) STEAP1 (six transmembrane epithelial antigen of prostate);

(4) 0772P (CA125, MUC16);

(5) MPF (MPF, MSLN, SMR, megakaryocyte potentiating factor, mesothelin);

(6) Napi3b (NAPI-3B, NPTIIb, SLC34A2, solute carrier family 34 (sodium phosphate), member 2, type II sodium-dependent phosphate transporter 3b);

(7) Sema 5b (FLJ10372, KIAA1445, Mm.42015, SEMA5B, SEMAG, Semaphorin 5b Hlog, sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B);

(8) PSCA hlg (2700050C12Rik, C530008O16Rik, RIKEN cDNA 2700050C12, RIKEN cDNA 2700050C12 gene);

(9) ETBR (Endothelin type B receptor);

(10) MSG783 (RNF124, hypothetical protein FLJ20315);

(11) STEAP2 (HGNC_8639, IPCA-1, PCANAP1, STAMP1, STEAP2, STMP, prostate cancer associated gene 1, prostate cancer associated protein 1, six transmembrane epithelial antigen of prostate 2, six transmembrane prostate protein);

(12) TrpM4 (BR22450, FLJ20041, TRPM4, TRPM4B, transient receptor potential cation channel, subfamily M, member 4);

(13) CRIPTO (CR, CR1, CRGF, CRIPTO, TDGF1, teratocarcinoma-derived growth factor);

(14) CD21 (CR2 (Complement receptor 2) or C3DR (C3d/Epstein Barr virus receptor) or Hs 73792);

(15) CD79b (CD79B, CD79β, IGb (immunoglobulin-associated beta), B29);

(16) FcRH2 (IFGP4, IRTA4, SPAP1A (SH2 domain containing phosphatase anchor protein Ia), SPAP1B, SPAP1C);

(17) HER2;

(18) NCA;

(19) MDP;

(20) IL20Rα;

(21) Brevican;

(22) EphB2R;

(23) ASLG659;

(24) PSCA;

(25) GEDA;

(26) BAFF-R (B cell -activating factor receptor, BLyS receptor 3, BR3);

(27) CD22 (B-cell receptor CD22-B isoform);

(28) CD79a (CD79A, CD79α, immunoglobulin-associated alpha);

(29) CXCR5 (Burkitt's lymphoma receptor 1);

(30) HLA-DOB (Beta subunit of MHC class II molecule (Ia antigen));

(31) P2X5 (Purinergic receptor P2X ligand-gated ion channel 5);

(32) CD72 (B-cell differentiation antigen CD72, Lyb-2);

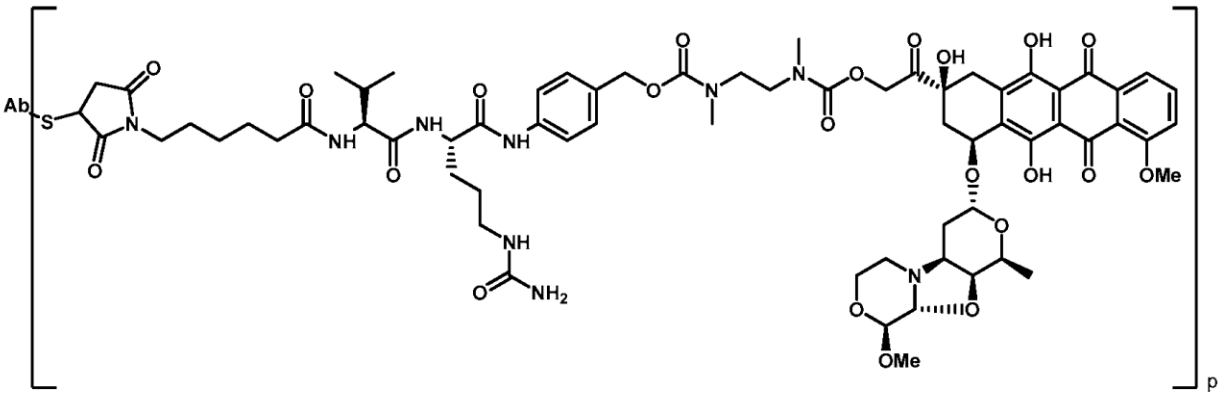
(33) LY64 (Lymphocyte antigen 64 (RP105), type I membrane protein of the leucine rich repeat (LRR) family);

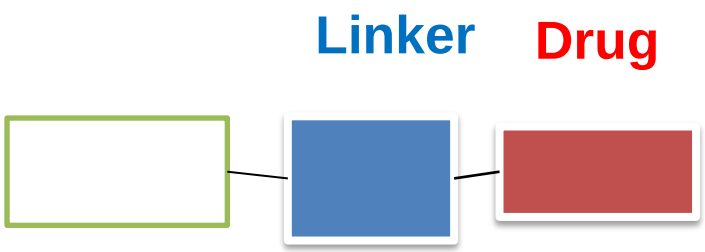
(34) FcRH1 (Fc receptor-like protein 1);

(35) IRTA2 (Immunoglobulin superfamily receptor translocation associated 2); and

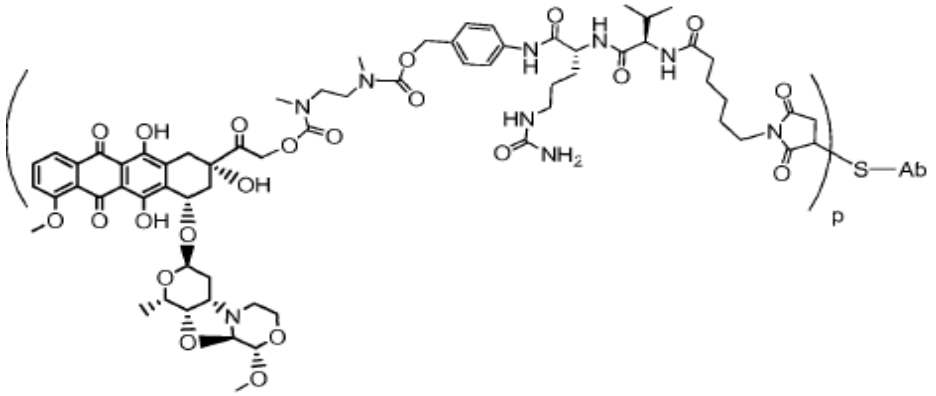
(36) TENB2 (putative transmembrane proteoglycan).

18. The immunoconjugate of claim 12 having a formula selected from:

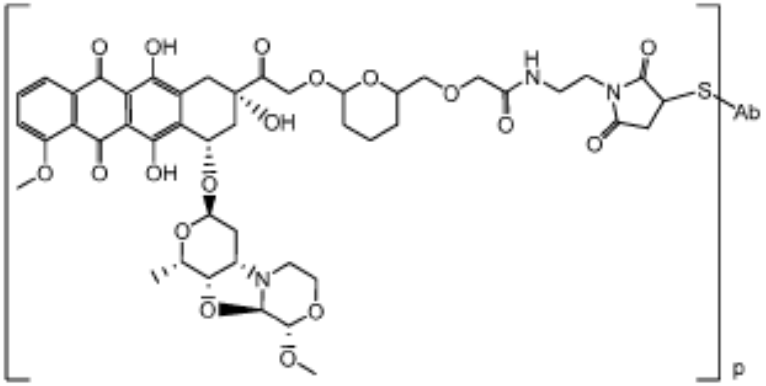


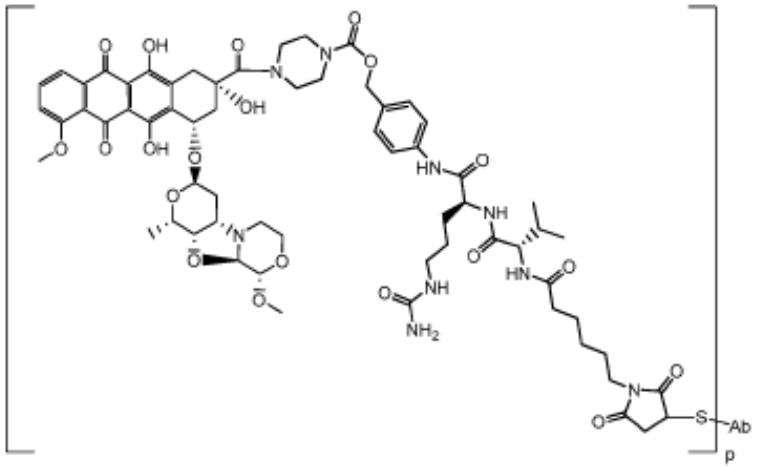


38. The antibody-drug conjugate compound of claim 37 selected from the structures:



18. The immunoconjugate of claim 12 having a formula selected from:





-acetal-

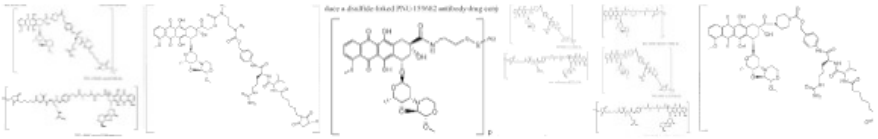
-piperazine-

Google acetal-pnu159682

전체 이미지 동영상 쇼핑 지도 더보기 설정 도구

검색결과 약 328개 (0.28초)

acetal-pnu159682 관련 이미지



acetal-pnu159682에 대한 이미지 더보기 이미지 신고

Targeting LGR5+ cells with an antibody-drug conjugate for the ...
https://stm.sciencemag.org/content/7/314/314ra186 - 이 페이지 번역하기
MR Junttila 저술 - 2015 - 69회 인용 - 관련 학술자료
2B), which contains an acetal component connected to the C-14 hydroxyl of the ... cells, PNU159682 was 10-fold more potent on dividing normal keratinocytes.

EP2879711A1 - Anti-etbr antibodies and immunoconjugates - Google ...
https://www.google.com/patents/EP2879711A1 - 이 페이지 번역하기
[027] Figure 7 shows the structures of various antibody-drug conjugates, including (A) Ab-MC-val-cit-PAB-MMAE; (B) Ab-MC-acetal-PNU- 159682; (C) ...

thioMAbs | English to Russian | Medical (general) - ProZ.com
https://www.proz.com/kudoz/english-to.../5705753-thiomabs.html - 이 페이지 번역하기
2014. 11. 10. - Что делать с thio и acetal и anti-в названии антител. ... a thio huMA79bv28 HC A118C-MC-val-cit-PAB-PNU-159682, a Thio huMA79bv28 ...

US20150196660A1 - Anti-etbr antibodies and immunoconjugates ...
https://patents.google.com/patent/US20150196660A1/en ▾ 이 페이지 번역하기
... structures of various antibody-drug conjugates, including (A) Ab-MC-val-cit-PAB-MMAE; (B) Ab-MC-acetal-PNU-159682; (C) Ab-MC-val-cit-PAB-PNU-159682; ...

WO 2010/009124

US8389697B2 - Anthracycline derivative conjugates, process for their ...
https://patents.google.com/patent/US8389697B2/en ▾

Prior Art Document 3:
WO 2010/009124 (21 January 2010)

CLAIMS

1. An anthracycline derivative conjugate of formula (I) or formula (I')

$$[\text{Ant-L-Z-}]_m\text{-T} \quad \text{(I)}$$

$$\text{Ant-L-Z-}Q \quad \text{(I')}$$

or a pharmaceutical acceptable salt thereof, wherein

Ant is an anthracycline derivative residue,

L is a linker,

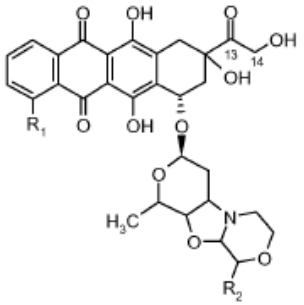
Z is a spacer,

m is an integer of from 1 to 30,

T is a carrier selected from protein, peptide, monoclonal or polyclonal antibody or a chemically modified derivative thereof suitable to be attached to the [Ant-L-Z-] moiety or moieties, or a polymeric carrier, and

Q is a hydrogen atom, C_1-Ce alkyl, C3-C6 cycloalkyl, phenyl or benzyl group;

and the Ant can be released to give an anthracycline derivative of formula (II)



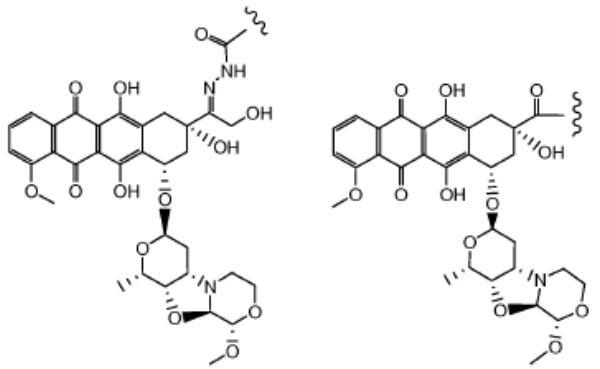
(II)

wherein Ri is a hydroxy or methoxy group and R_2 is a C_1-Cs alkoxy group, or a pharmaceutically acceptable salt thereof.

21. An anthracycline derivative of formula (lie)

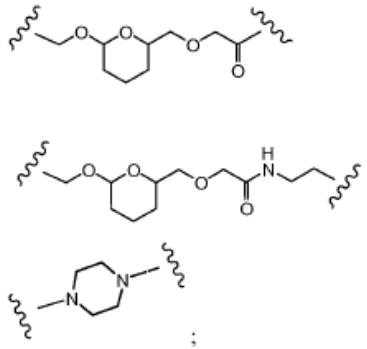
$$\text{Ant-L-(Z)}_m\text{-X} \quad \text{(lie)}$$

wherein Ant is selected from the structures:



where the wavy line indicates the attachment to L;

L is a linker selected from -N(R)-, -N(R) $_n$(C_1-Ci_2 alkylene)-, -N(R) $_n$(C_2- C_8 alkenylene)-, -N(R) $_n$(C_2- C_8 alkynylene)-, -N(R) $_n$($CH_2CH_2O)_n$- , and the structures:



;

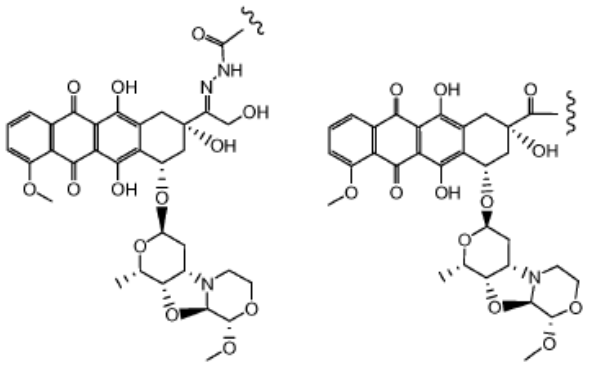
36. An antibody-drug conjugate compound comprising an antibody covalently attached by a linker L and an optional spacer Z to one or more anthracycline derivative drug moieties D, the compound having formula (Ic)

$$\mathbf{Ab\text{-}(L\text{-}Z_m\text{-}D)_p} \qquad \mathbf{Ic}$$

or a pharmaceutically acceptable salt thereof, wherein:

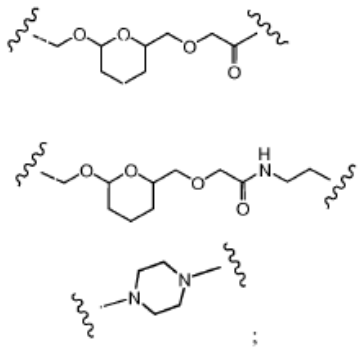
Ab is an antibody;

D is an anthracycline derivative selected from the structures:



where the wavy line indicates the attachment to L;

L is a linker selected from -N(R)-, -N(R)$_n$(C_1-Ci_2 alkylene)-, -N(R)$_n$(C_2- C_8 alkenylene)-, -N(R)$_n$(C_2- C_8 alkynylene)-, -N(R)$_n$$(CH_2CH_2O)_n$- , and the structures:



;

(9) ETBR (Endothelin type B receptor);

(10) MSG783 (RNF124, hypothetical protein FLJ20315);

(11) STEAP2 (HGNC_8639, IPCA-I, PCANAP1, STAMP1, STEAP2, STMP, prostate cancer associated gene 1, prostate cancer associated protein 1, six transmembrane epithelial antigen of prostate 2, six transmembrane prostate protein);

(12) TrpM4 (BR22450, FLJ20041, TRPM4, TRPM4B, transient receptor potential cation channel, subfamily M, member 4);

(13) CRIPTO (CR, CR1, CRGF, CRIPTO, TDGF1, teratocarcinoma-derived growth factor);

(14) CD21 (CR2 (Complement receptor 2) or C3DR (C3d/Epstein Barr virus receptor) or Hs 73792);

(15) CD79b (CD79B, CD79β, IGb (immunoglobulin-associated beta), B29);

(16) FcRH2 (IFGP4, IRTA4, SPAP1A (SH2 domain containing phosphatase anchor protein Ia), SPAP1B, SPAP1C);

(17) HER2;

(18) NCA;

(19) MDP;

(20) IL20Rα;

(21) Brevican;

(22) EphB2R;

(23) ASLG659;

(24) PSCA;

(25) GEDA;

(26) BAFF-R (B cell -activating factor receptor, BLyS receptor 3, BR3);

(27) CD22 (B-cell receptor CD22-B isoform);

(28) CD79a (CD79A, CD79α, immunoglobulin-associated alpha);

(29) CXCR5 (Burkitt's lymphoma receptor 1);

(30) HLA-DOB (Beta subunit of MHC class II molecule (Ia antigen));

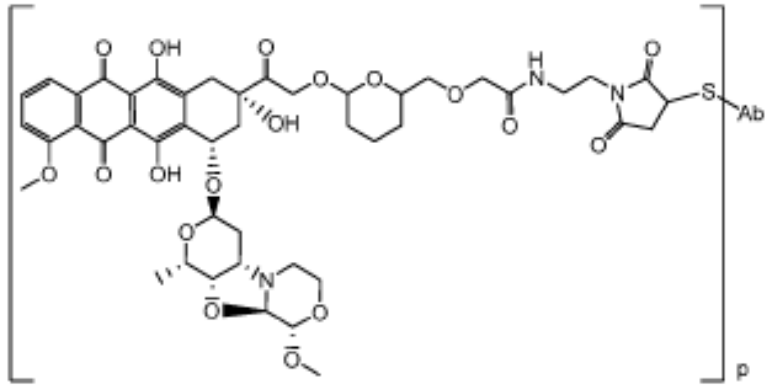
(31) P2X5 (Purinergic receptor P2X ligand-gated ion channel 5);

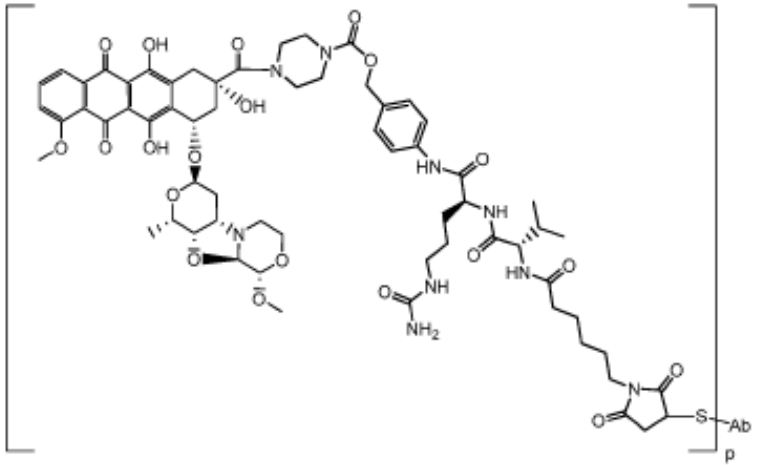
(32) CD72 (B-cell differentiation antigen CD72, Lyb-2);

(33) LY64 (Lymphocyte antigen 64 (RP105), type I membrane protein of the leucine rich repeat (LRR) family);

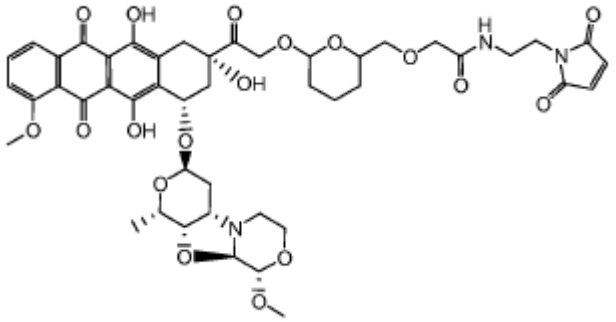
(34) FcRH1 (Fc receptor-like protein 1);

18. The immunoconjugate of claim 12 having a formula selected from:

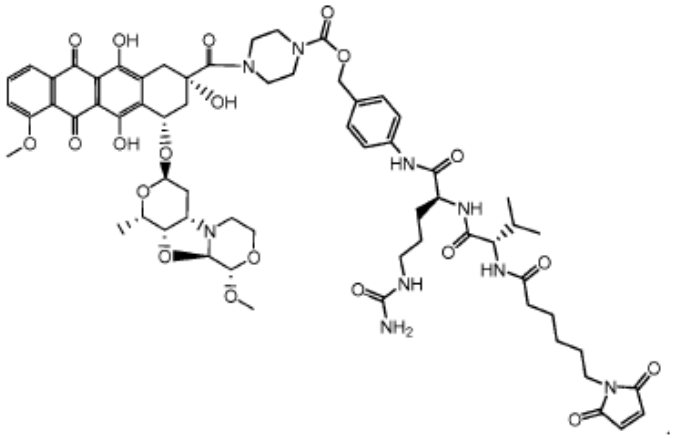


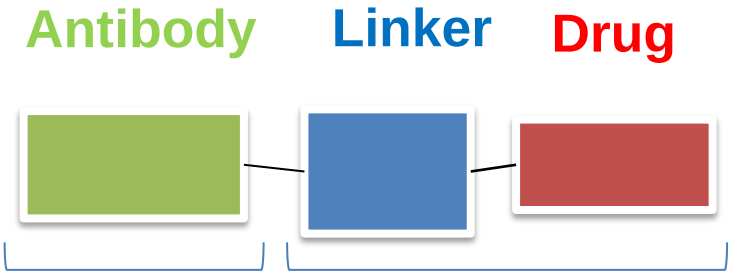


24. The anthracycline derivative of claim 22 having the structure:

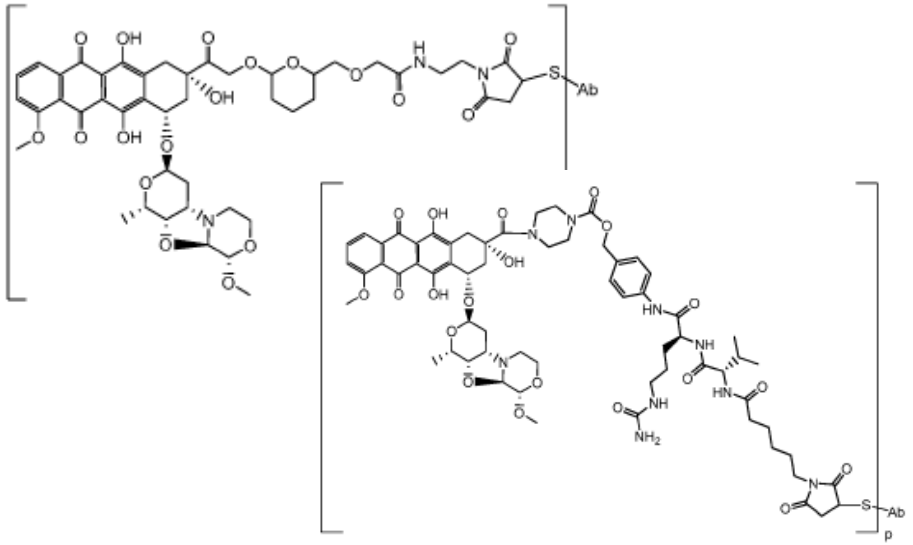


31. The anthracycline derivative of claim 29 having the structure:





18. The immunoconjugate of claim 12 having a formula selected from:



HVR-H1 (Gly Tyr Glu Phe Ser Arg Ser Trp Met Asn, SEQ ID NO:2)

HVR-H2 (Gly Arg He Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Ser Gly Lys Phe Lys Gly, SEQ ID NO:4)

HVR-H3 (Asp Gly Ser Ser Trp Asp Try Tyr Phe Asp Tyr, SEQ ID NO:6)

HVR-L1 (Arg Ser Ser Gln Ser He Val His Ser Asn Gly Asn Thr Phe Leu Glu, SEQ ID N0:9)

HVR-L2 (Lys Val Ser Asn Arg Phe Ser, SEQ ID NO: 12)

HVR-L3 (Phe Gln Gly Ser Gln Phe Pro Tyr Thr, SEQ ID NO: 14).

HVR-L1 (Arg Ser Ser Gln Ser He Val His Ser Val Gly Asn Thr Phe Leu Glu, SEQ ID NO: 10)

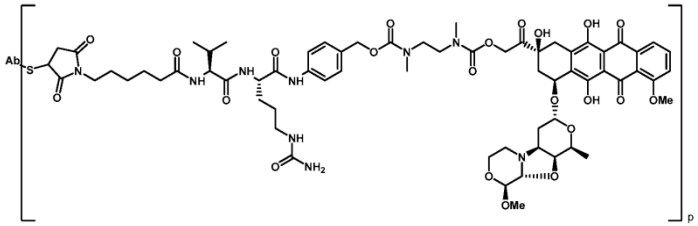
HVR-L1 (Arg Ser Ser Gln Ser He Val His Ser Ala Gly Asn Thr Phe Leu Glu, SEQ ID NO: 19)

HVR-L1 (Arg Ser Ser Gln Ser He Val His Ser Gln Gly Asn Thr Phe Leu Glu, SEQ ID NO:20)

HVR-L1 (Arg Ser Ser Gln Ser He Val His Ser Ser Gly Asn Thr Phe Leu Glu, SEQ ID NO:21)

HVR-L1 (Arg Ser Ser Gln Ser He Val His Ser Asp Gly Asn Thr Phe Leu Glu, SEQ ID NO:22)

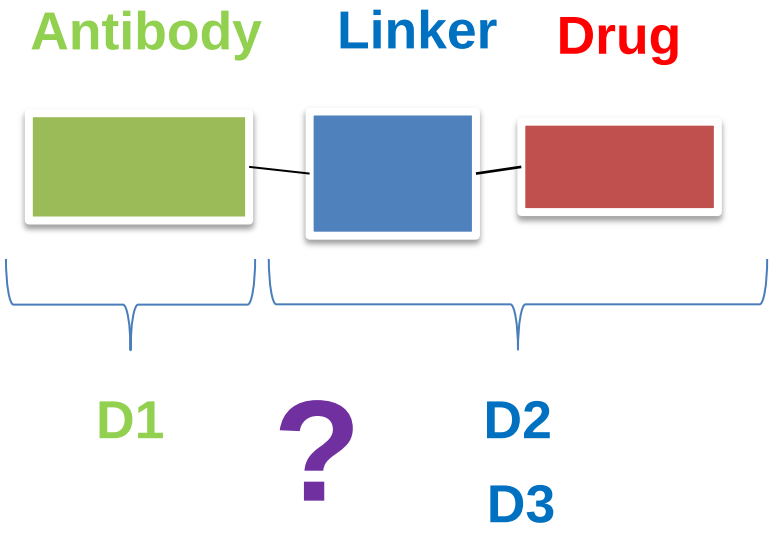
HVR-L1 (Arg Ser Ser Gln Ser He Val His Ser He Gly Asn Thr Phe Leu Glu, SEQ ID NO:23)



9	10F4 HVR H1	
10	10F4 HVR H2	
11	10F4 HVR H3	
12	10F4 HVR L1	
13	10F4 HVR L2	
14	10F4 HVR L3	
15	10F4 HVR L1 N28V (10F4v3 HVR L1)	
16	10F4 HVR L1 N28A	RSSQSIVHSAGNTFLE
17	10F4 HVR L1 N28Q	RSSQSIVHSQGNTFLE
18	10F4 HVR L1 N28S	RSSQSIVHSSGNTFLE
19	10F4 HVR L1 N28D	RSSQSIVHSDGNTFLE
20	10F4 HVR L1 N28I	RSSQSIVHSIGNTFLE
21	10F4 HVR L1 N30A	RSSQSIVHSNGITFLE
22	10F4 HVR L1 N30Q	RSSQSIVHSNGQTFLE

HVR-L1 (Arg Ser Ser Gln Ser He Val His Ser He Gly Ala Thr Phe Leu Glu, SEQ ID NO:32)

HVR-L1 (Arg Ser Ser Gln Ser He Val His Ser He Gly Gln Thr Phe Leu Glu, SEQ ID NO:33)


Antibody
Linker
Drug
D1
?
D2
D3

Thank You !