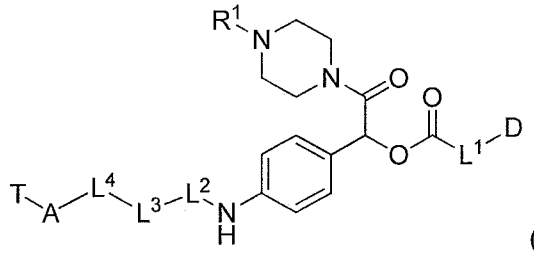
A is an acyl unit.

[0010a] In a first aspect, there is provided a compound of the formula (II):



(II)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

T is a targeting moiety which is an antibody that specifically binds to a human folate receptor alpha (FRA);

R^1 is hydrogen, unsubstituted or substituted C_{1-3} alkyl, or unsubstituted or substituted heterocyclyl;

L^1 is a bond, a second self-immolative linker, or a cyclization self-elimination linker;

L^2 is a bond or a second self-immolative linker;

wherein if L^1 is a second self-immolative linker or a cyclization self-elimination linker, then L^2 is a bond;

wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit;

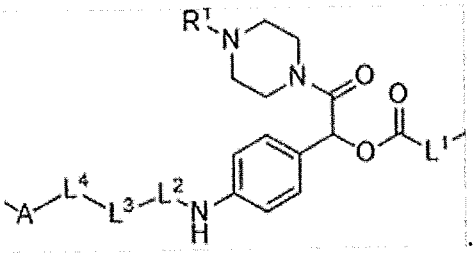
wherein:

(i) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 1, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, wherein an amino acid residue at position 201 in the light chain constant region is replaced with a cysteine residue; or

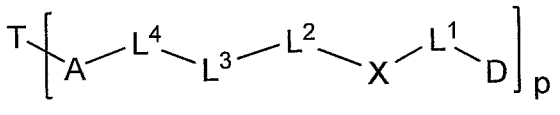
(ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 2, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, wherein an amino acid residue at position 199 in the heavy chain constant region is replaced with a cysteine residue, and/or wherein an amino acid residue at position 201 in the light chain constant region is replaced with a cysteine residue;

wherein the numbering is according to the EU index of Kabat; and

wherein D is linked to T via a cysteine residue connected through the linker moiety



[0011] The present disclosure provides a compound of the formula (Ia):



(Ia)

or a salt or solvate or stereoisomer thereof;

wherein:

p is 1 to 20;

D is a drug moiety;

T is a targeting moiety which is an antibody that specifically binds to a folate receptor alpha (FRA) (e.g., a human FRA);

X is a hydrophilic self-immolative linker;

L^1 is a bond, a second self-immolative linker, or a cyclization self-elimination linker;

L^2 is a bond or a second self-immolative linker;

wherein if L^1 is a second self-immolative linker or a cyclization self-elimination linker, then L^2 is a bond;

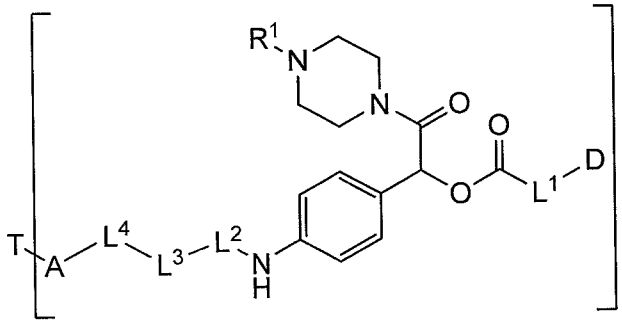
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit.

[0012] The present disclosure provides a compound of the formula (IIa):



(IIa)

or a salt or solvate or stereoisomer thereof;

wherein:

p is 1 to 20;

D is a drug moiety;

T is a targeting moiety which is an antibody that specifically binds to a folate receptor alpha (FRA) (e.g., a human FRA);

R^1 is hydrogen, unsubstituted or substituted C_{1-3} alkyl, or unsubstituted or substituted heterocyclyl;

L^1 is a bond, a second self-immolative linker, or a cyclization self-elimination linker;

L^2 is a bond or a second self-immolative linker;

wherein if L^1 is a second self-immolative linker or a cyclization self-elimination linker, then L^2 is a bond;

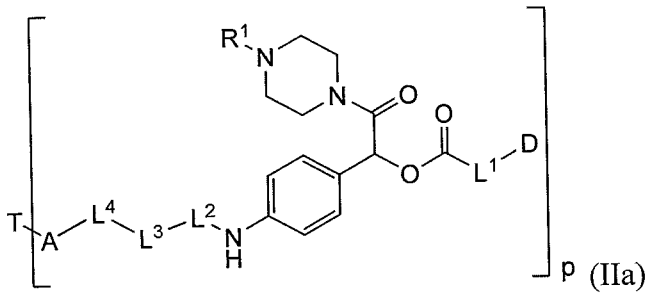
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit.

[0012a] In a second aspect, there is provided a compound of the formula (IIa):



(IIa)

or a salt or solvate or stereoisomer thereof;

wherein:

p is 1 to 20;

D is a drug moiety;

T is a targeting moiety which is an antibody that specifically binds to a human folate receptor alpha (FRA);

R^1 is hydrogen, unsubstituted or substituted C_{1-3} alkyl, or unsubstituted or substituted heterocyclyl;

L^1 is a bond, a second self-immolative linker, or a cyclization self-elimination linker;

L^2 is a bond or a second self-immolative linker;

wherein if L^1 is a second self-immolative linker or a cyclization self-elimination linker, then L^2 is a bond;

wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit;

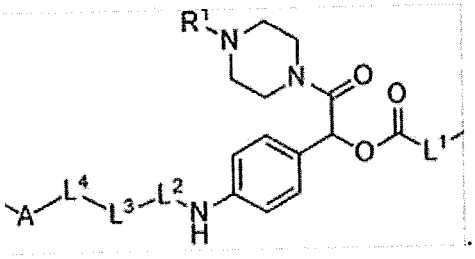
wherein:

(i) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 1, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, wherein an amino acid residue at position 201 in the light chain constant region is replaced with a cysteine residue; or

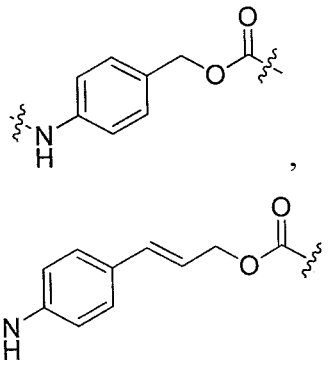
(ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 2, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, wherein an amino acid residue at position 199 in the heavy chain constant region is replaced with a cysteine residue, and/or wherein an amino acid residue at position 201 in the light chain constant region is replaced with a cysteine residue;

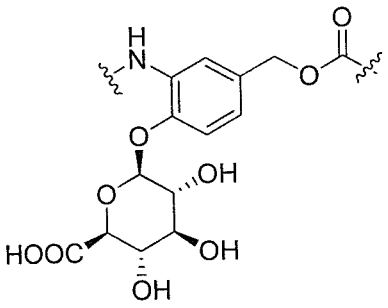
wherein the numbering is according to the EU index of Kabat; and

wherein D is linked to T via a cysteine residue connected through the linker moiety



[0013] In certain embodiments of the compounds above, p is 1 to 4. In certain embodiments, L^1 is a bond. In certain embodiments, L^1 is a second self-immolative linker or a cyclization self-elimination linker. In certain embodiments, L^1 is an aminobenzyloxycarbonyl linker. In certain embodiments, L^1 is selected from the group consisting of





, and

amino acid residues selected from L201 and T206 in the light chain constant region is replaced with a cysteine residue. In certain embodiments, the antibody is an antigen-binding fragment selected from the group consisting of Fab, Fab', $F(ab')_2$, Fv, and ScFv.

[0027] The present disclosure provides a pharmaceutical composition comprising a compound described above and herein, or a salt or solvate or stereoisomer thereof; and a pharmaceutically acceptable carrier.

[0027a] In a third aspect, there is provided a pharmaceutical composition comprising a compound of the second aspect, or a salt or solvate or stereoisomer thereof; and a pharmaceutically acceptable carrier.

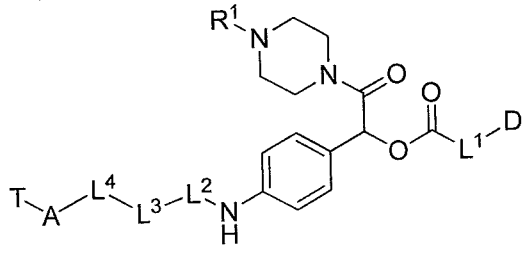
[0028] The present disclosure provides a method of killing a cell that expresses a human folate receptor alpha (FRA), comprising administering to the cell an amount of a compound described herein, or a salt or solvate or stereoisomer thereof, sufficient to kill the cell. In certain embodiments, the cell is a cancer cell. In certain embodiments, the cancer cell in is an individual (e.g., a human). In certain embodiments, the cancer cell is a lymphoma or leukemia cell. In certain embodiments, the cancer cell is a folate receptor alpha (FRA)-positive lymphoma or folate receptor alpha (FRA)-positive leukemia cell.

[0029] The present disclosure provides a method of treating cancer in an individual comprising administering to the individual an effective amount of a compound described herein, or a salt or solvate or stereoisomer thereof. In certain embodiments, the individual has cancer or has been diagnosed with cancer. In certain embodiments, the cancer is ovarian cancer, lung cancer, uterine cancer, testicular choriocarcinoma, ependymoma, mesothelioma, breast cancer, colon cancer, or renal cell carcinoma. In some embodiments, the cancer is a folate receptor alpha (FRA)-positive cancer. In certain embodiments, the individual is a human.

[0030] The present disclosure provides a kit comprising a compound described herein, or a salt or solvate or stereoisomer thereof. In certain embodiments, the kit further comprises instructions for use in the treatment of cancer.

[0030a] In a fourth aspect, there is provided a kit comprising a compound of the second aspect, or a salt or solvate or stereoisomer thereof.

[0031] Provided herein is a process for making a compound of formula (II):



(II)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

SEQ ID NO: 32 or 33 and/or the light chain comprises a variable region comprising the amino acid sequence of SEQ ID NO: 11 and a constant region comprising the amino acid sequence of SEQ ID NO: 34; or

(4) the heavy chain comprises the amino acid sequence of SEQ ID NO: 6 and/or the light chain comprises the amino acid sequence of SEQ ID NO: 7.

[0040] In certain embodiments of the methods and processes herein, the antibody comprises a heavy chain constant region comprising the amino acid sequence of SEQ ID NO:32 or SEQ ID NO:33 and a human kappa light chain constant region comprising the amino acid sequence of SEQ ID NO:34, wherein one or more amino acid residues selected from T155, S157, S165, T169, T197, T199, and S442 in the heavy chain constant region, and/or one or more amino acid residues selected from L201 and T206 in the kappa light chain constant region are replaced with a cysteine residue, and wherein the numbering is according to the EU index of Kabat. In some of these embodiments, at least one (e.g., one) amino acid residue selected from T155, S157, S165, T169, T197, T199, and S442 in the heavy chain constant region, and/or at least one (e.g., one) amino acid residue selected from L201 and T206 in the light chain constant region is replaced with a cysteine residue.

[0041] The present disclosure provides a compound, or a salt or solvate or stereoisomer thereof, wherein the compound is prepared by a method or process described herein, wherein the antibody comprises one or more sulfhydryl groups.

[0042] The present disclosure provides a pharmaceutical composition comprising a compound, or a salt or solvate or stereoisomer thereof, wherein the compound is prepared by a process described herein, wherein the antibody comprises one or more sulfhydryl groups, and a pharmaceutically acceptable carrier.

[0043] It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present disclosure. These and other aspects of the disclosure will become apparent to one of skill in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

[0044] **FIG. 1** shows an NMR spectrum of Tap-18H.

[0045] **FIG. 2** shows an NMR spectrum of Tap-18Hr1.

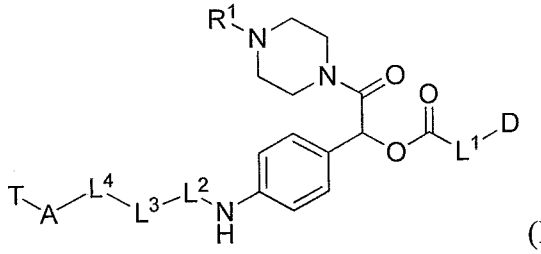
[0046] **FIG. 3** shows an NMR spectrum of Tap-18Hr2.

[0047] **FIG. 4** shows *in vivo* anti-tumor activity of hLK26-IgG1-Tap18Hr1 against xenograft derived from ovarian cancer cell line SK-OV-3.

CLAIMS

What is claimed is:

1. A compound of the formula (II):



(II)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

T is a targeting moiety which is an antibody that specifically binds to a human folate receptor alpha (FRA);

R^1 is hydrogen, unsubstituted or substituted C_{1-3} alkyl, or unsubstituted or substituted heterocyclyl;

L^1 is a bond, a second self-immolative linker, or a cyclization self-elimination linker;

L^2 is a bond or a second self-immolative linker;

wherein if L^1 is a second self-immolative linker or a cyclization self-elimination linker, then L^2 is a bond;

wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit;

wherein:

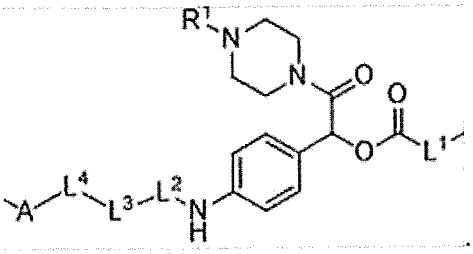
(i) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 1, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, wherein an amino acid residue at position 201 in the light chain constant region is replaced with a cysteine residue; or

(ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 2, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, wherein an amino acid residue at position 199 in the heavy chain constant region is replaced with a cysteine

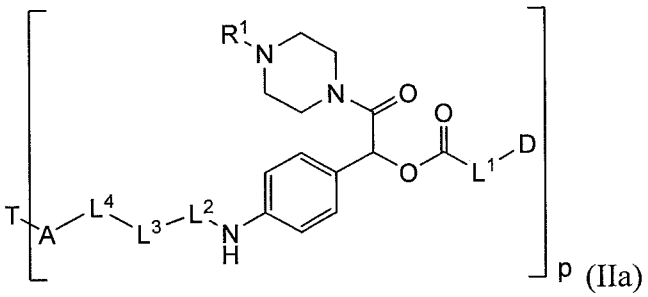
residue, and/or wherein an amino acid residue at position 201 in the light chain constant region is replaced with a cysteine residue;

wherein the numbering is according to the EU index of Kabat; and

wherein D is linked to T via a cysteine residue connected through the linker moiety



2. A compound of the formula (IIa):



(IIa)

or a salt or solvate or stereoisomer thereof;

wherein:

p is 1 to 20;

D is a drug moiety;

T is a targeting moiety which is an antibody that specifically binds to a human folate receptor alpha (FRA);

R^1 is hydrogen, unsubstituted or substituted C_{1-3} alkyl, or unsubstituted or substituted heterocyclyl;

L^1 is a bond, a second self-immolative linker, or a cyclization self-elimination linker;

L^2 is a bond or a second self-immolative linker;

wherein if L^1 is a second self-immolative linker or a cyclization self-elimination linker, then L^2 is a bond;

wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit;

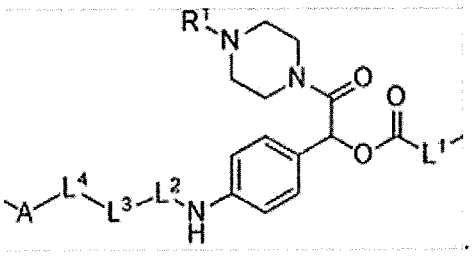
wherein:

(i) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 1, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, wherein an amino acid residue at position 201 in the light chain constant region is replaced with a cysteine residue; or

(ii) the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 2, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, wherein an amino acid residue at position 199 in the heavy chain constant region is replaced with a cysteine residue, and/or wherein an amino acid residue at position 201 in the light chain constant region is replaced with a cysteine residue;

wherein the numbering is according to the EU index of Kabat; and

wherein D is linked to T via a cysteine residue connected through the linker moiety



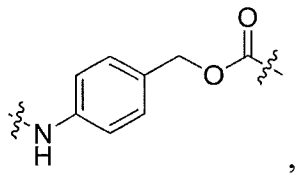
3. The compound of claim 2, wherein p is 1 to 4.

4. The compound of claim 2, wherein L^1 is a bond.

5. The compound of claim 2, wherein L^1 is a second self-immolative linker or a cyclization self-elimination linker.

6. The compound of claim 5, wherein L^1 is an aminobenzyloxycarbonyl linker.

7. The compound of claim 5, wherein L^1 is selected from the group consisting of



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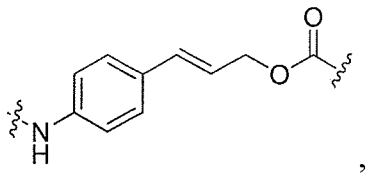
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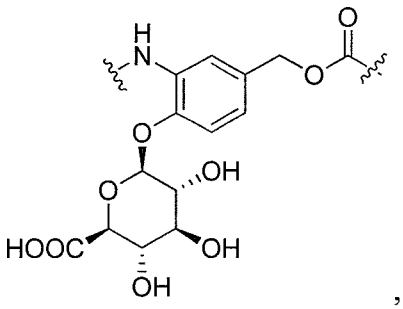
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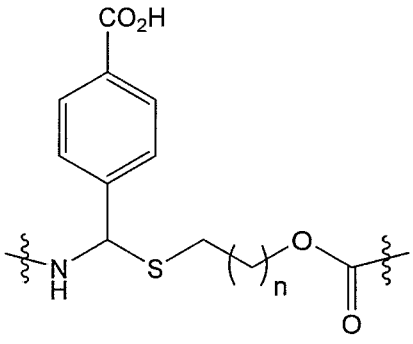
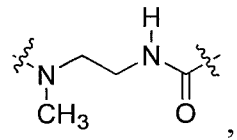

, wherein n is 1 or 2.

8. The compound of claim 5, wherein L^1 is selected from the group consisting of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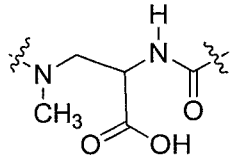
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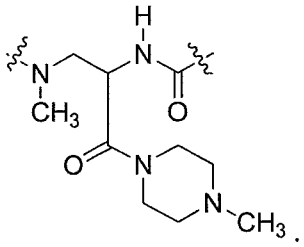
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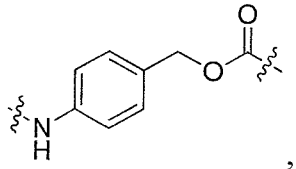
9. The compound of claim 2, wherein L^2 is a bond.

10. The compound of claim 4, wherein L^2 is a second self-immolative linker.

11. The compound of claim 10, wherein L^2 is an aminobenzyloxycarbonyl linker.

12. The compound of claim 10, wherein L^2 is selected from



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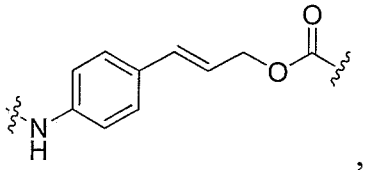

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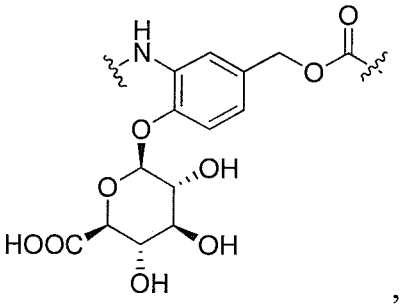

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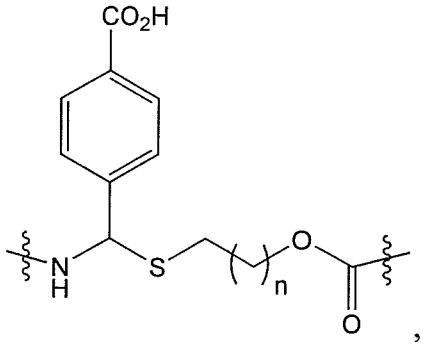


, wherein n is 1 or 2.

13. The compound of claim 2, wherein L^3 is a peptide linker of 1 to 10 amino acid residues.

14. The compound of claim 13, wherein L^3 is a peptide linker of 2 to 4 amino acid residues.

15. The compound of claim 2, wherein L^3 is a peptide linker comprising at least one lysine or arginine residue.

16. The compound of claim 2, wherein L^3 is a peptide linker comprising an amino acid residue selected from lysine, D-lysine, citrulline, arginine, proline, histidine, ornithine and glutamine.

17. The compound of claim 2, wherein L^3 is a peptide linker comprising an amino acid residue selected from valine, isoleucine, phenylalanine, methionine, asparagine, proline, alanine, leucine, tryptophan, and tyrosine.

18. The compound of claim 13, wherein L^3 is a dipeptide unit selected from valine-citrulline, proline-lysine, methionine-D-lysine, asparagine-D-lysine, isoleucine-proline, phenylalanine- lysine, and valine-lysine.

19. The compound of claim 18, wherein L^3 is valine-citrulline.

20. The compound of claim 2, wherein L^4 is a bond.

21. The compound of claim 2, wherein L^4 is a spacer.

22. The compound of claim 21, wherein the spacer is polyalkylene glycol, alkylene, alkenylene, alkynylene, or polyamine.

23. The compound of claim 21, wherein L^4 is L^{4a}-C(O), L^{4a}-C(O)-NH, L^{4a}-$S(O)_2$, or L^{4a}-$S(O)_2$-NH, wherein each L^{4a} is independently polyalkylene glycol, alkylene, alkenylene, alkynylene, or polyamine.

24. The compound of claim 21, wherein L^4 is L^{4a}-C(O), wherein L^{4a} is polyalkylene glycol, alkylene, alkenylene, alkynylene, or polyamine.

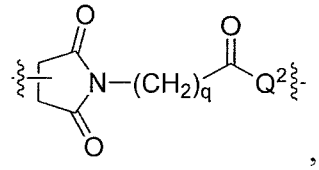
25. The compound of claim 21, wherein L^4 is L^{4a}-C(O), wherein L^{4a} is a polyalkylene glycol.

26. The compound of claim 21, wherein L^4 is L^{4a}-C(O), wherein L^{4a} is a polyethylene glycol.

27. The compound of claim 21, wherein the spacer is of the formula $-CH_2-(CH_2-O-CH_2)_m-CH_2-C(O)-$, wherein m is an integer from 0 to 30.

28. The compound of claim 21, wherein L^4 is L^{4a}-C(O), wherein L^{4a} is alkylene.

29. The compound of claim 2, wherein A is selected from the group consisting of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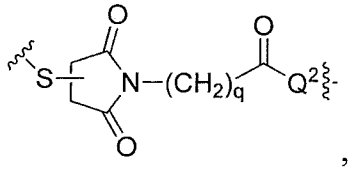
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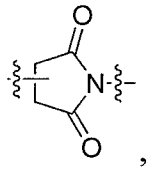
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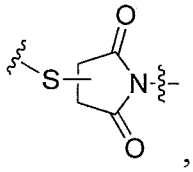
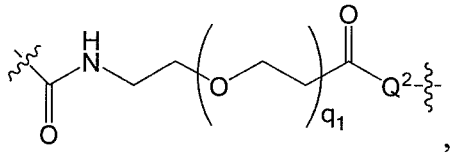

,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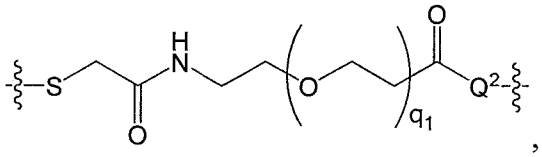
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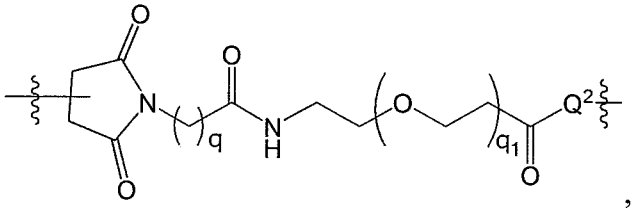
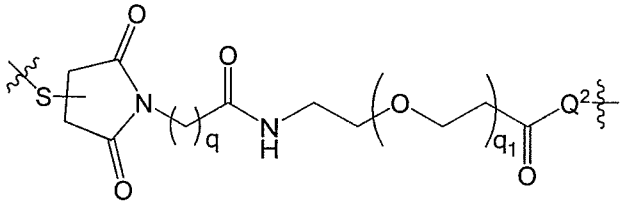
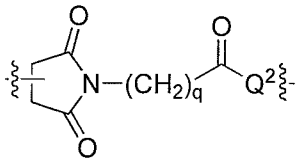
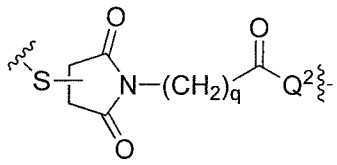

, and


;

wherein each Q^2 is NH or O, each q is independently an integer from 1 to 10, and each q_1 is independently an integer from 1 to 10.

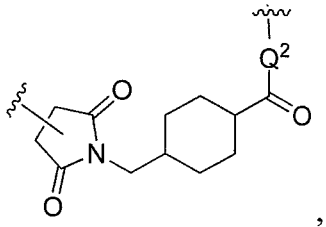
30. The compound of claim 29, wherein A is selected from the group consisting of


and

;

wherein each Q^2 is independently NH or O and each q is independently an integer from 1 to 10.

31. The compound of claim 30, wherein q is 2, 3, 4, or 5.

32. The compound of claim 2, wherein A is selected from the group consisting of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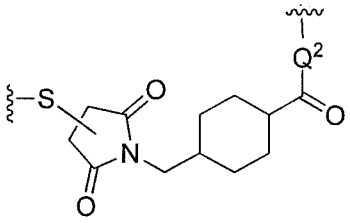
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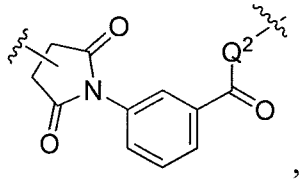
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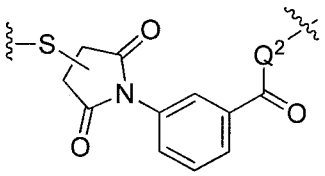
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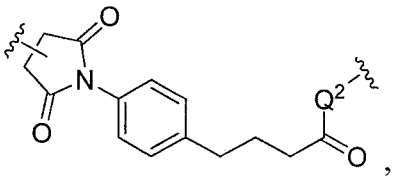
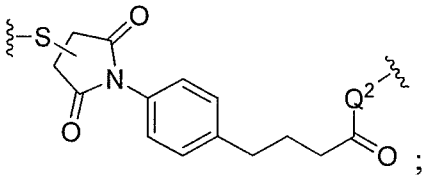
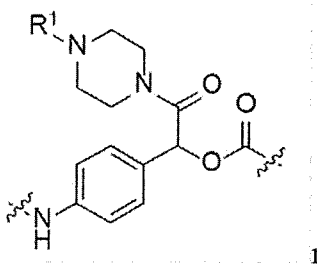
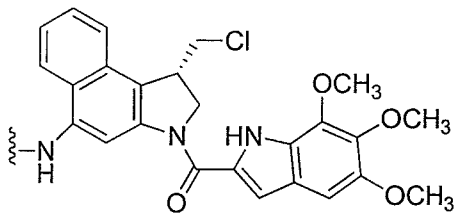
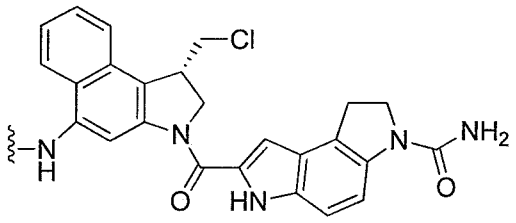

, and

;

wherein each Q^2 is independently NH or O.

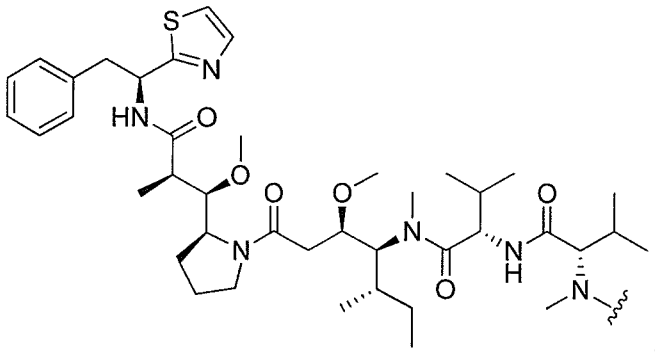
33. The compound of claim 2, wherein D is an amino-containing drug moiety, wherein the drug is connected to L^1 or the  moiety through the amino group.

34. The compound of claim 33, wherein D is duocarmycin, dolastatin, tubulysin, doxorubicin (DOX), paclitaxel, or mitomycin C (MMC), or an amino derivative thereof.

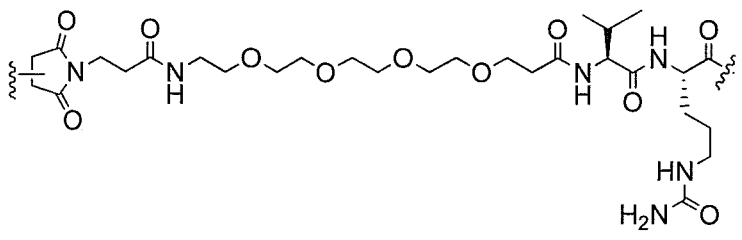
35. The compound of claim 33, wherein D is selected from the group consisting of

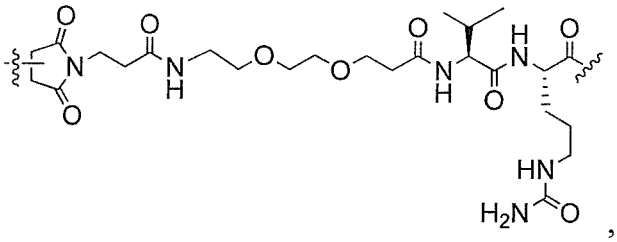
 and .

36. The compound of claim 33, wherein D is:

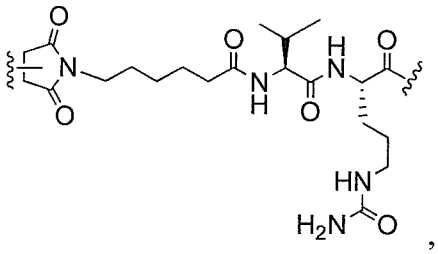
.

37. The compound of claim 2, wherein -A-L^4-L^3-L^2- is

,



,



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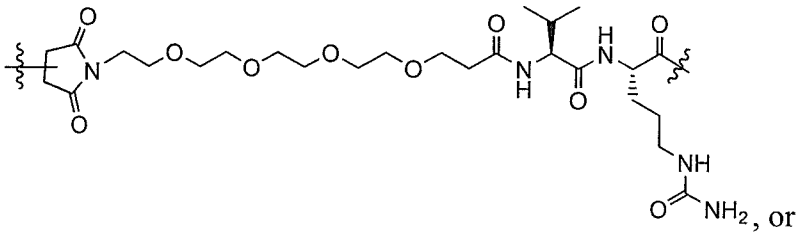
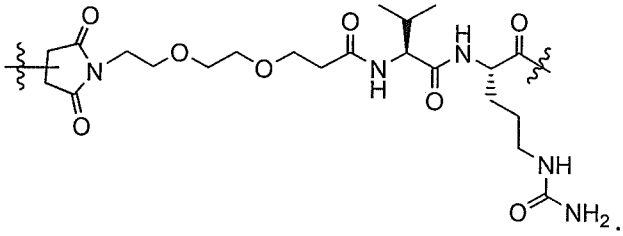


, or



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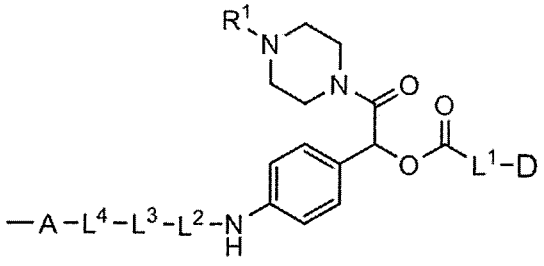
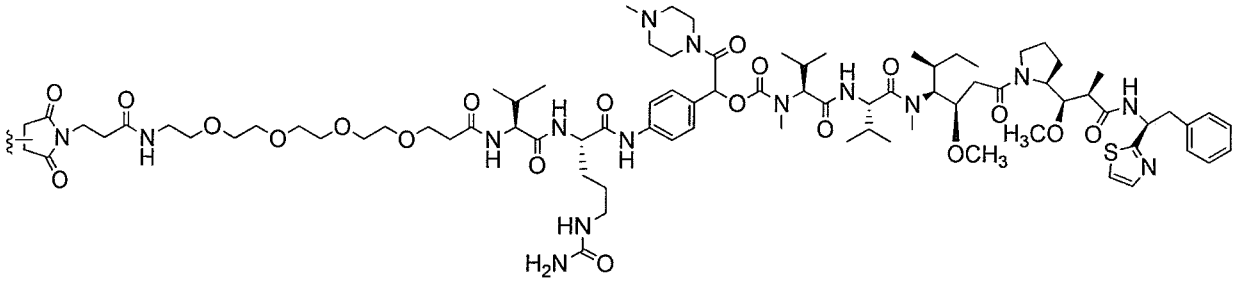
38. The compound of claim 2, wherein the  moiety is:



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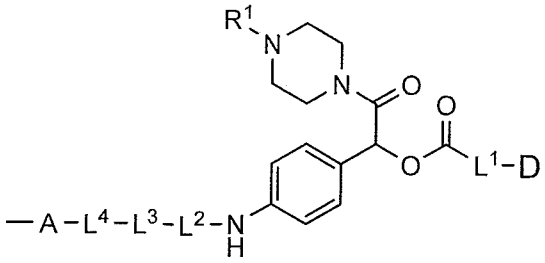
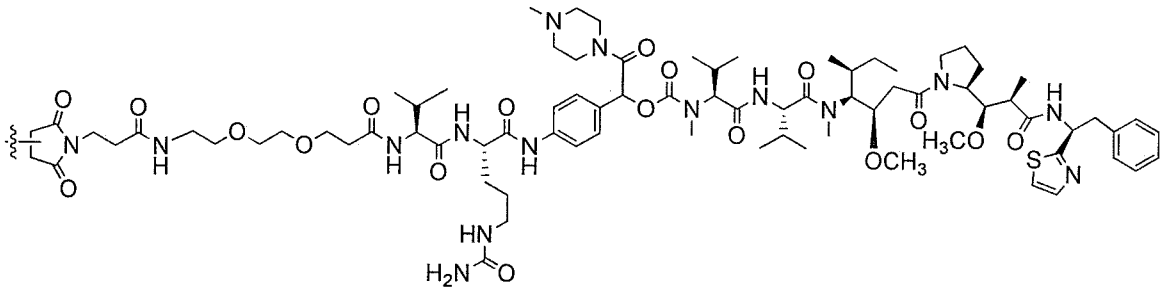
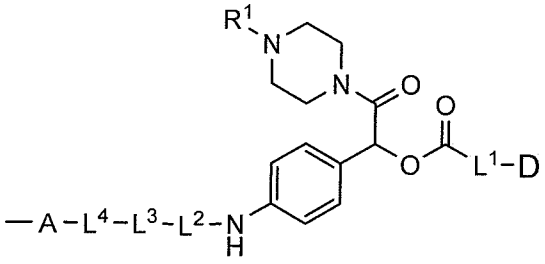
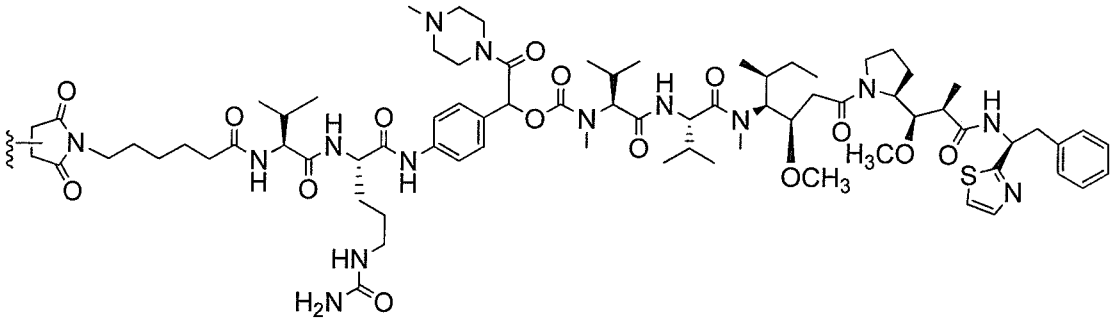
39. The compound of claim 2, wherein the  moiety is:



40. The compound of claim 2, wherein the  moiety is:



41. The compound of claim 2, wherein the anti-folate receptor alpha (FRA) antibody is a humanized antibody, a chimeric antibody or a human antibody.

42. A pharmaceutical composition comprising a compound of claim 2, or a salt or solvate or stereoisomer thereof; and a pharmaceutically acceptable carrier.

43. A kit comprising a compound of claim 2, or a salt or solvate or stereoisomer thereof.

44. The compound of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 2, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, and wherein an amino acid residue at position 199 in the heavy chain constant region is replaced with a cysteine residue.

45. The compound of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 2, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, and wherein an amino acid residue at position 201 in the light chain constant region is replaced with a cysteine residue.

46. The compound of claim 1, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 2, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, wherein an amino acid residue at position 199 in the heavy chain constant region is replaced with a cysteine residue, and wherein an amino acid residue at position 201 in the light chain constant region is replaced with a cysteine residue.

47. The compound of claim 2, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 2, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, and wherein an amino acid residue at position 199 in the heavy chain constant region is replaced with a cysteine residue.

48. The compound of claim 2, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 2, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, and wherein an amino acid residue at position 201 in the light chain constant region is replaced with a cysteine residue.

49. The compound of claim 2, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 2, and a light chain comprising the amino acid sequence of SEQ ID NO: 3, wherein an amino acid residue at position 199 in the heavy chain constant region is replaced with a cysteine residue, and wherein an amino acid residue at position 201 in the light chain constant region is replaced with a cysteine residue.