the differential properties of the linker between the plasma and some cytoplasmic compartment. Linkers are relative stable in the blood's neutral pH environment but can get cleaved once the ADC enters the lower pH environment inside the cell. An *in vivo* trial demonstrated that chemically-labile linkers often suffer from limited plasma stability.

[0006] Enzyme-labile linkers take an alternative approach-the differential activities of proteases inside and outside of the cells-to achieve control of the drug release. Proteases normally are not active outside cells due to the unfavorable pH conditions and the presence of serum protease inhibitors. A drug can be conjugated to antibody via peptide bond. The drug can be specifically cleaved from the antibody by the action of lysosomal proteases present inside the cells, and at elevated levels in certain tumor types (Koblinsk et al). Compared to ADC with chemically-labile linker, enzyme-labile linkers can achieve better control of the drug release. However, the increased associated hydrophobicity of some enzyme-labile linkers can lead to aggregation of ADC, particularly with strongly hydrophobic drugs.

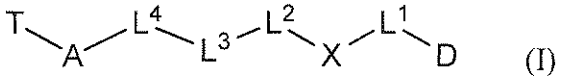
[0007] A third class of linkers is non-cleavable linkers. The release of the drug is believed to occur via the internalization of the ADC followed by the degradation of the antibody component in the lysosome, resulting in the release of the drug which is still attached to the linker. These non-cleavable linkers are stable in serum, but compared to enzyme-labile linkers, no bystander effect can result due to the fact that the released drugs are charged and are not able to diffuse into neighboring cells. Also, since internalization of the ADC is a factor for the release of the drug, the efficacy is antigen-(and thus antibody-) dependent.

[0008] Linker technology affects ADC potency, specificity, and safety. There is a need for linkers for ADCs which can provide serum stability as well as increased solubility, allowing efficient conjugation and intracellular delivery of hydrophobic drugs.

SUMMARY

[0009] The compounds of the present disclosure comprise a drug moiety, a targeting moiety capable of targeting a selected cell population, and a linker which contains an acyl unit, an optional spacer unit for providing distance between the drug moiety and the targeting moiety, a peptide linker which can be cleavable under appropriate conditions, a hydrophilic self-immolative linker, and an optional second self-immolative spacer or cyclization self-elimination linker.

[0010] ~~The present disclosure~~In one aspect, there is provided~~s~~ a compound of the ~~F~~formula (I):



(I)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

T is a targeting moiety;

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;

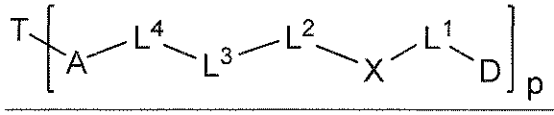
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit.

[0010a] In one aspect, there is provided 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;

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;

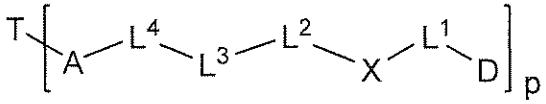
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit.

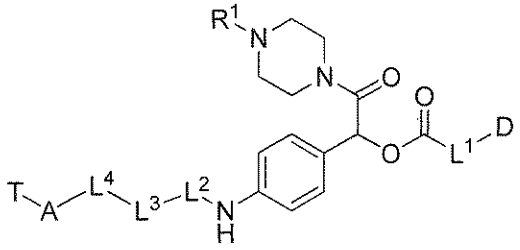
[0011] In some embodiments, provided is a compound of Formula (Ia):



(Ia)

or a salt or solvate or stereoisomer thereof; wherein D, T, X, L^1, L^2, L^3, L^4 and A are as defined for Formula (I), and p is 1 to 20. In some embodiments, p is 1 to 8. In some embodiments, p is 1 to 6. In some embodiments, p is 1 to 4. In some embodiments, p is 2 to 4. In some embodiments, p is 1, 2, 3 or 4.

[0012] ~~The present disclosure also~~In one aspect, there is provideds a compound of the ~~F~~formula (II):



(II)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

T is a targeting moiety;

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, 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;

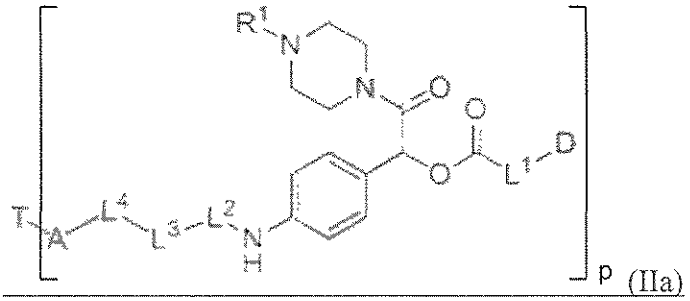
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit.

[0012a] In one 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;

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;

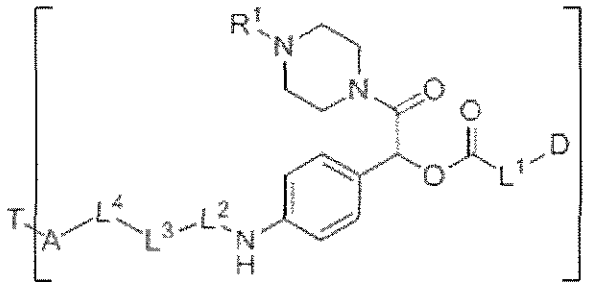
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit.

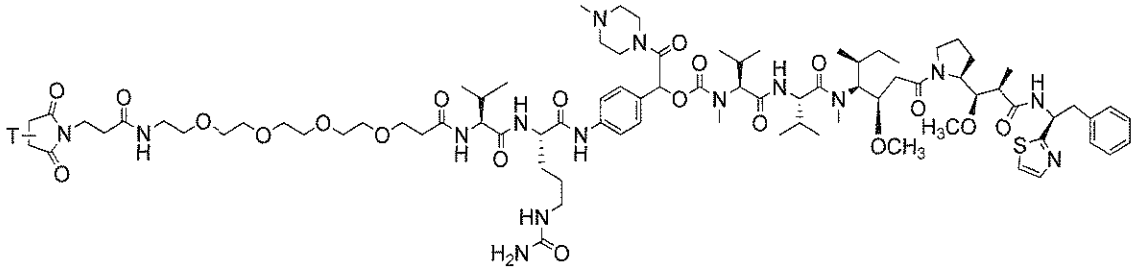
[0013] In some embodiments, provided is a compound of Formula (IIa):



(IIa)

or a salt or solvate or stereoisomer thereof; wherein D, T, L^1, L^2, L^3, L^4 and A are as defined for Formula (II), and p is 1 to 20. In some embodiments, p is 1 to 8. In some embodiments, p is 1 to 6. In some embodiments, p is 1 to 4. In some embodiments, p is 2 to 4. In some embodiments, p is 1, 2, 3 or 4.

[0014] The present disclosure also provides a compound of Formula (III):

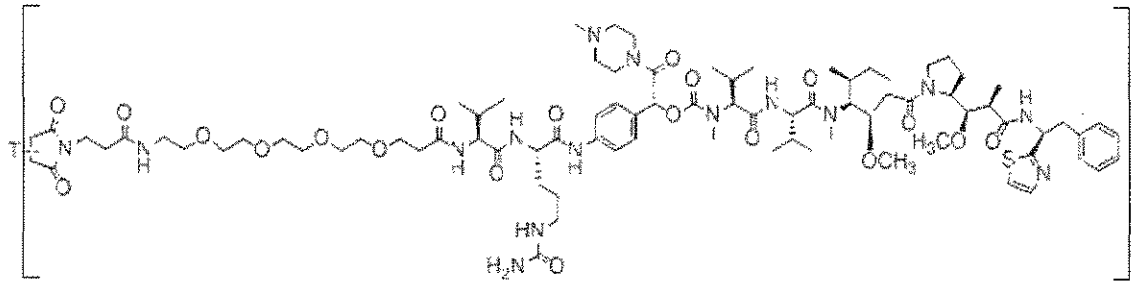


(III),

or a salt or solvate or stereoisomer thereof;

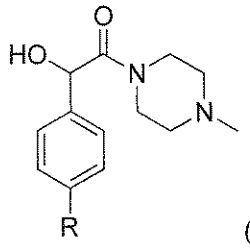
wherein T is a targeting moiety.

[0015] In some embodiments, provided is a compound of Formula (IIIa):



(IIIa)

[0023] ~~The present disclosure~~In one aspect, there is provided~~s~~ a compound of Formula (XII):



(XII)

or a salt or solvate or stereoisomer thereof; wherein R is NO_2 or NH_2.

[0024] In certain embodiments, the compound of Formulae (I)-(XII) is a compound selected from those species described or exemplified in the detailed description herein.

[0025] In certain embodiments of the compound of Formulae (I)-(V) or (Ia)-(Va), T is an antibody targeting molecule. In some embodiments, T is antibody h5F1Ca.1 or c5D7. In further embodiments, one or more amino acid residues of the heavy chain and/or the light chain of the antibody are replaced with cysteine residues (*e.g.*, engineered to comprise cysteine residue at a position not present in the parent antibody). In some embodiments, one or more amino acid residues of the Fc region of the antibody are replaced with a cysteine residue. In some embodiments, one or more amino acid residues of the Fc region of the antibody are at positions 157, 169 and/or 442 using EU numbering. In some embodiments of the compound of Formulae (I)-(V) or (Ia)-(Va), D is linked to T by way of the added (e.g. engineered) cysteine residue.

[0025a] In one aspect, there is provided a pharmaceutical composition comprising a compound as described herein, or a salt or solvate or stereoisomer thereof; and a pharmaceutically acceptable carrier

[0026] In a further ~~aspect~~embodiment, the present disclosure provides a pharmaceutical composition comprising at least one compound of Formulae (I)-(V) or (Ia)-(Va) or a pharmaceutically acceptable salt thereof. Pharmaceutical compositions according to the embodiments may further comprise a pharmaceutically acceptable excipient. The present disclosure also provides a compound of Formulae (I)-(V) or (Ia)-(Va) or a pharmaceutically acceptable salt thereof for use as a medicament.

[0026a] In one aspect, there is provided an in vitro method of killing a cell, comprising administering to the cell an amount of the compound as described herein, or a salt or solvate or stereoisomer thereof, sufficient to kill the cell.

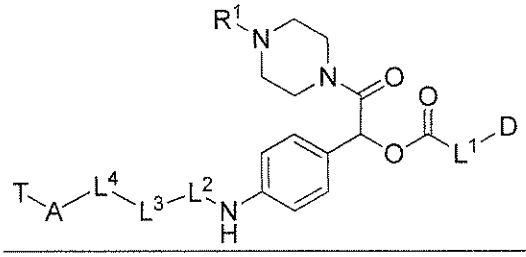
[0027] In another embodiment~~aspect~~, the present disclosure provides a method of killing a cell, comprising administering to the cell an amount of the compound of Formulae (I)-(V) or (Ia)-(Va) sufficient to kill the cell.

[0027a] In one aspect, there is provided use of an effective amount of a compound as described herein, or a salt or solvate or stereoisomer thereof, in the manufacture of a medicament for treating cancer in an individual in need thereof.

[0028] In another embodiment~~aspect~~, the present disclosure provides a method of treating cancer in an individual in need thereof comprising administering to the individual an effective amount of a compound of Formulae (I)-(V) or (Ia)-(Va).

[0028a] In one aspect, there is provided a kit comprising a compound as described herein, or a salt or solvate or stereoisomer thereof.

[0028b] In one aspect, there is provided a process for making a compound of formula (II):



(II)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

T is an antibody;

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;

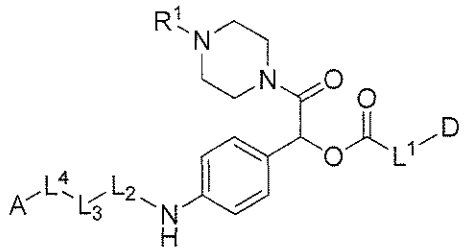
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit;

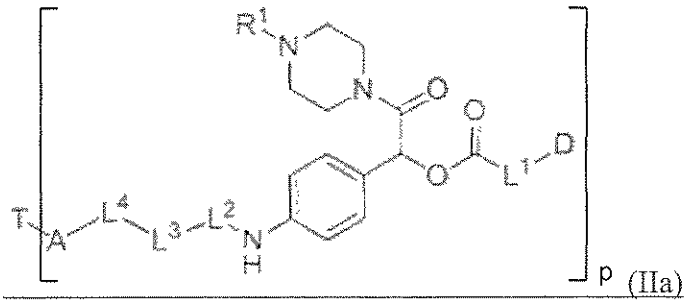
comprising reacting an antibody with Compound Z:



(Compound Z).

or a salt or solvate or stereoisomer thereof.

[0028c] In one aspect, there is provided a process for making a compound of formula (IIa):



(IIa)

or a salt or solvate or stereoisomer thereof;

wherein:

p is 1 to 20;

D is a drug moiety;

T is an antibody;

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;

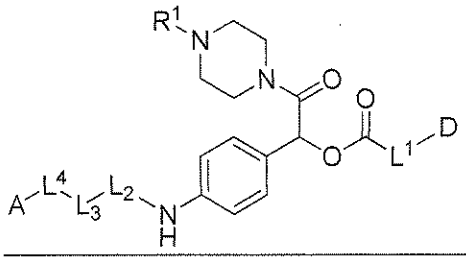
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit;

comprising reacting an antibody with Compound Z:

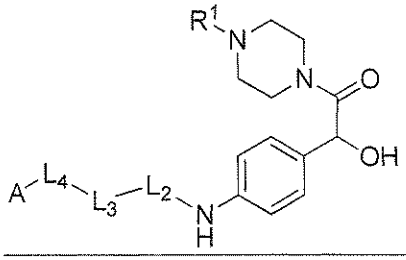


(Compound Z),

or a salt or solvate or stereoisomer thereof.

[0028d] In one aspect, there is provided a compound, or a salt or solvate or stereoisomer thereof, wherein the compound is prepared by a process as described herein, wherein the antibody comprises one or more sulfhydryl groups.

[0028e] In one aspect, there is provided a method of preparing Compound X:



(Compound X)

or a salt or solvate or stereoisomer thereof;

wherein:

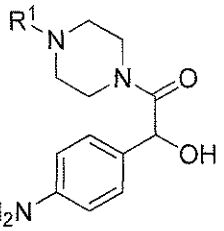
L^2 is a bond or a second self-immolative linker;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit; and

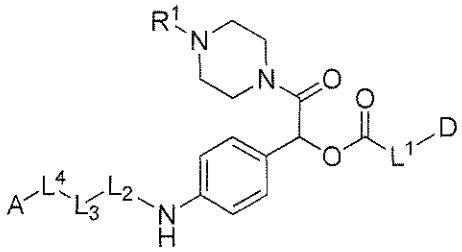
R^1 is hydrogen, unsubstituted or substituted C_{1-3} alkyl, or unsubstituted or substituted heterocyclyl;



comprising reacting Compound W: A-L^4-L^3-L^2; and Compound I:

.

[0028f] In one aspect, there is provided a method of preparing Compound Z:



(Compound Z)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

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;

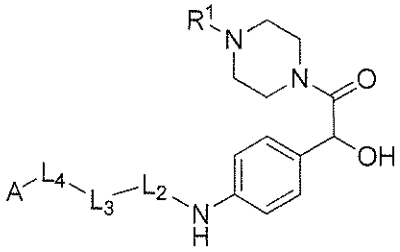
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

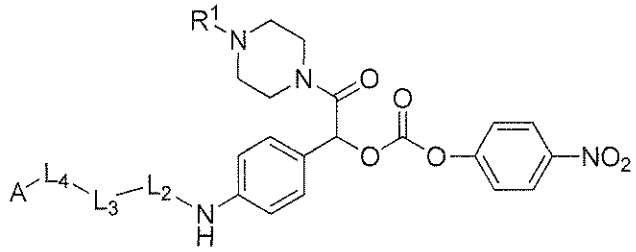
L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit

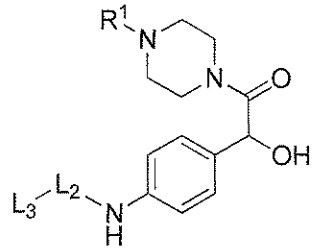
R^1 is hydrogen, unsubstituted or substituted C_{1-3} alkyl, or unsubstituted or substituted heterocyclyl;

comprising: reacting Compound X:  and p-nitrophenylchloroformate to form Compound Y:

 ;

reacting Compound Y with a compound comprising L^1-D.

[0028g] In one aspect, there is provided a method of preparing Compound X^1:

 (Compound X^1)

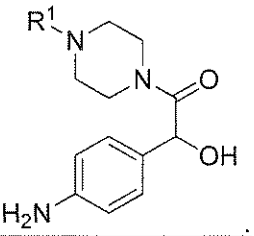
or a salt or solvate or stereoisomer thereof;

wherein:

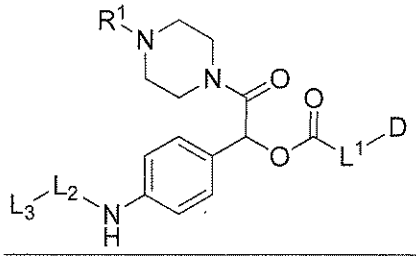
L^2 is a bond or a second self-immolative linker;

L^3 is a peptide linker; and

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

comprising: reacting Compound W^1: L^3-L^2; and Compound I:  .

[0028h] In one aspect, there is provided a method of preparing Compound Y^1:


(Compound Y^1)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

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

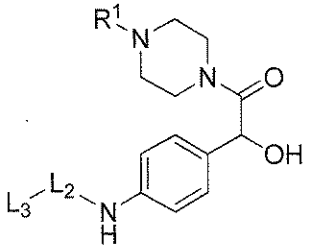
L^2 is a bond or a second self-immolative linker;

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

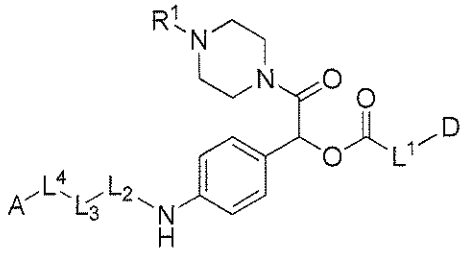
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker; and

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

comprising: reacting Compound X^1:  ; and a compound comprising L^1-D.

[0028i] In one aspect, there is provided a method of preparing Compound Z:



(Compound Z)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

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;

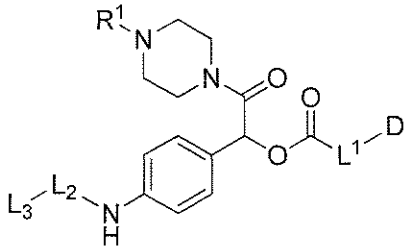
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

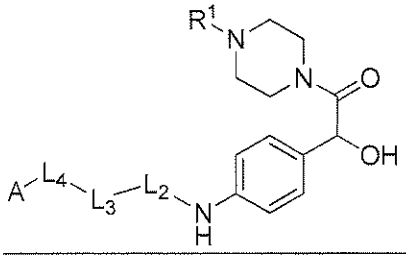
L^4 is a bond or a spacer;

A is an acyl unit; and

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

comprising: reacting Compound Y^1:  , and a compound comprising A-L^4.

[0028j] In one aspect, there is provided a compound of formula:



(Compound X)

or a salt or solvate or stereoisomer thereof;

wherein:

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

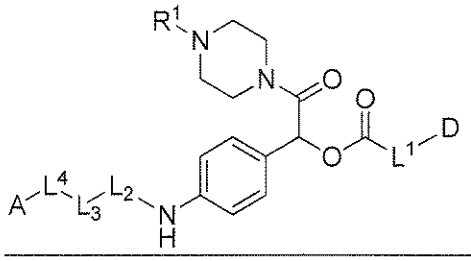
L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit; and

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

[0028k] In one aspect, there is provided a compound of formula:



(Compound Z)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

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;

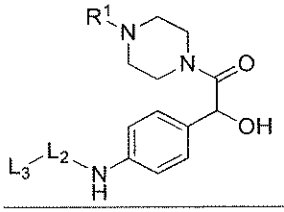
L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit; and

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

[0028l] In one aspect, there is provided a compound of formula:



(Compound X^1)

or a salt or solvate or stereoisomer thereof;

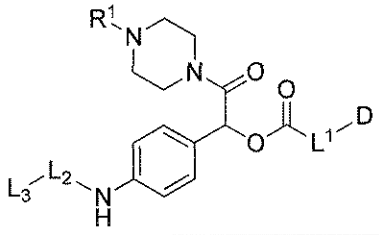
wherein:

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

L^3 is a peptide linker; and

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

[0028m] In one aspect, there is provided a compound of formula:



(Compound Y^1)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

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; and

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

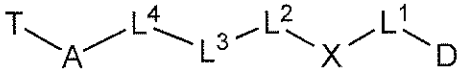
In one aspect, there is provided use of the compound as described herein, or a salt or solvate or stereoisomer thereof, in the manufacture of a medicament for killing a cell, wherein the medicament is to be administered to the cell in an amount sufficient to kill the cell.

[0029] Additional embodiments, features, and advantages of the ~~invention~~ disclosure will be apparent from the following detailed description and through practice of the ~~invention~~disclosure.

CLAIMS

What is claimed is:

1. A compound of the formula (I):



(I)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

T is a targeting moiety;

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;

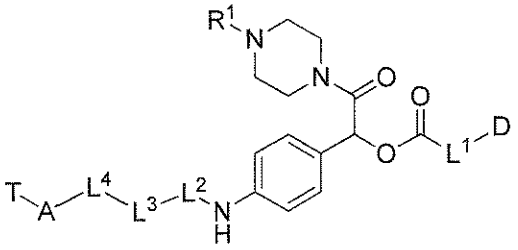
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit.

2. 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;

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;

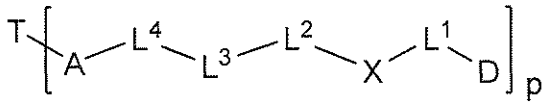
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit.

3. 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;

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;

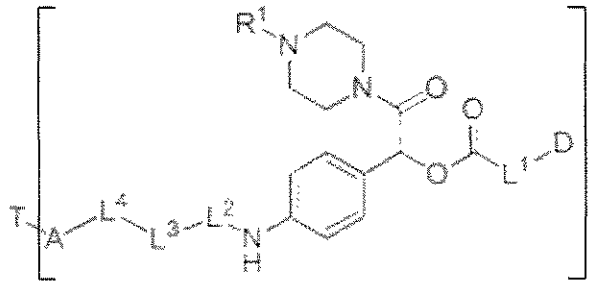
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit.

4. 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;

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.

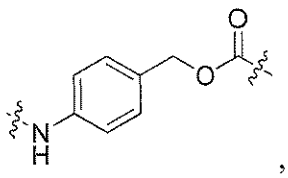
5. The compound of claim 3 or 4, wherein p is 1 to 4.

6. The compound of any one of claims 1 to 5, wherein L^1 is a bond.

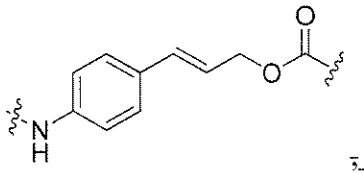
7. The compound of any one of claims 1 to 5, wherein L^1 is a second self-immolative linker or a cyclization self-elimination linker.

8. The compound of claim 7, wherein L^1 is an aminobenzyloxycarbonyl linker.

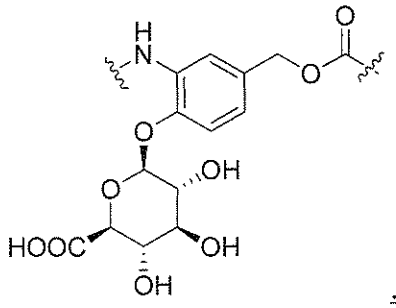
9. The compound of claim 7, wherein L^1 is selected from the group consisting of



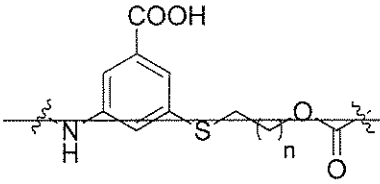
,



; and

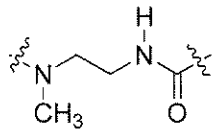


~~., and~~

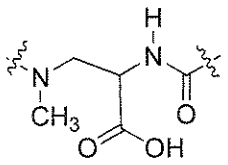


~~, wherein n is 1 or 2.~~

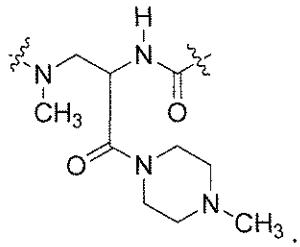
10. The compound of claim 7, wherein L^1 is selected from the group consisting of



,



, and



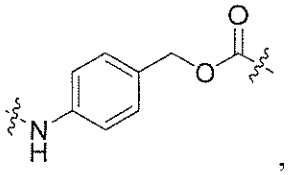
.

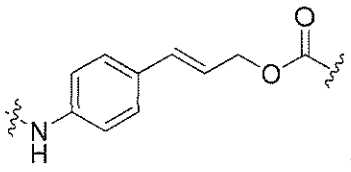
11. The compound of any one of claims 1 to 10, wherein L^2 is a bond.

12. The compound of claim 6, wherein L^2 is a second self-immolative linker.

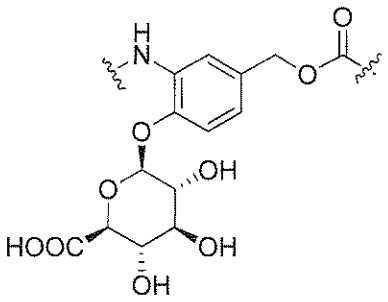
13. The compound of claim 12, wherein L^2 is an aminobenzyloxycarbonyl linker.

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

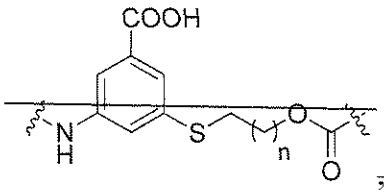




; and



~~; and~~



~~; wherein n is 1 or 2.~~

15. The compound of any one of claims 1 to 14, wherein L^3 is a peptide linker of 1 to 10 amino acid residues.

16. The compound of claim 15, wherein L^3 is a peptide linker of 2 to 4 amino acid residues.

17. The compound of any one of claims 1 to 5, wherein L^3 is a peptide linker comprising at least one lysine or arginine residue.

18. The compound of any one of claims 1 to 16, wherein L^3 is a peptide linker comprising an amino acid residue selected from lysine, D-lysine, citrulline, arginine, proline, histidine, ornithine and glutamine.

19. The compound of any of claims 1 to 16, 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.

50. A pharmaceutical composition comprising a compound of any one of claims 1 to 49, or a salt or solvate or stereoisomer thereof; and a pharmaceutically acceptable carrier.

51. An in vitro method of killing a cell, comprising administering to the cell an amount of the compound of any one of claims 1 to 49, or a salt or solvate or stereoisomer thereof, sufficient to kill the cell.

52. The method of claim 51, wherein the cell is a cancer cell.

53. The method of claim 52, wherein the cancer cell is a gastric cancer cell, pancreatic cancer cell, colorectal cancer cell, lung cancer cell, lymphoma cell, breast cancer cell, cervical cancer cell or ovarian cancer cell.

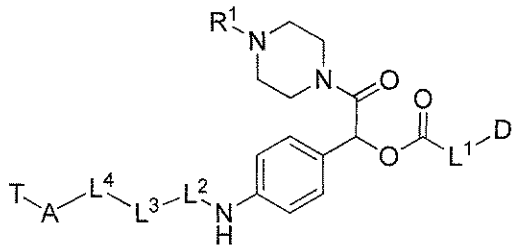
54. ~~A method of treating cancer in an individual in need thereof comprising administering to the individual~~ Use of an effective amount of a compound of any one of claims 1 to 49, or a salt or solvate or stereoisomer thereof, in the manufacture of a medicament for treating cancer in an individual in need thereof.

55. The ~~method~~ use of claim 54, wherein the cancer is gastric cancer, pancreatic cancer, colorectal cancer, lung cancer, lymphoma, breast cancer, cervical cancer or ovarian cancer.

56. A kit comprising a compound of any one of claims 1 to 49, or a salt or solvate or stereoisomer thereof.

57. The kit of claim 56, further comprising instructions for use in the treatment of cancer.

58. A process for making a compound of formula (II):



(II)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

T is an antibody;

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;

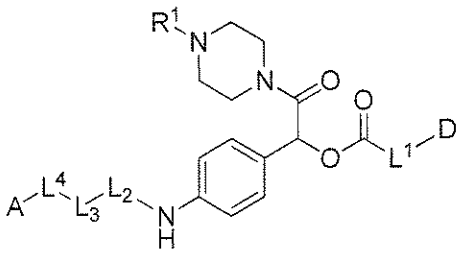
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit;

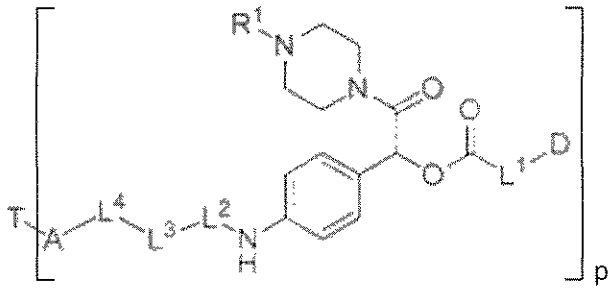
comprising reacting an antibody with Compound Z:



(Compound Z),

or a salt or solvate or stereoisomer thereof.

59. A process for making a compound of formula (IIa):



(IIa)

or a salt or solvate or stereoisomer thereof;

wherein:

p is 1 to 20;

D is a drug moiety;

T is an antibody;

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;

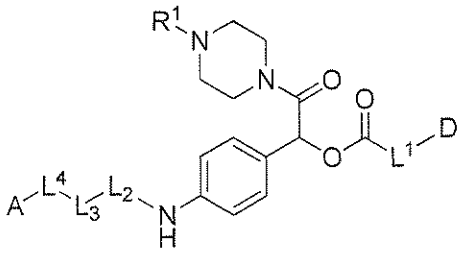
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit;

comprising reacting an antibody with Compound Z:



(Compound Z),

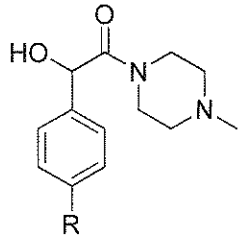
or a salt or solvate or stereoisomer thereof.

60. The process of claim 59, wherein the antibody comprises one or more sulfhydryl groups.

61. A compound, or a salt or solvate or stereoisomer thereof, wherein the compound is prepared by a process according to any one of claims 58 to 60, wherein the antibody comprises one or more sulfhydryl groups.

62. A pharmaceutical composition comprising the compound of claim 61, or a salt or solvate or stereoisomer thereof, and a pharmaceutically acceptable carrier.

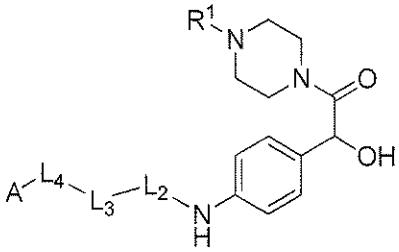
63. A compound of Formula (XII)



(XII)

or a salt or solvate or stereoisomer thereof; wherein R is NO_2 or NH_2.

64. A method of preparing Compound X:



(Compound X)

or a salt or solvate or stereoisomer thereof;

wherein:

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;~~

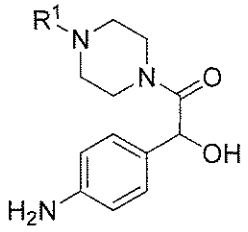
~~wherein if L^2 is a second self-immolative linker, then L^1 is a bond;~~

L^3 is a peptide linker;

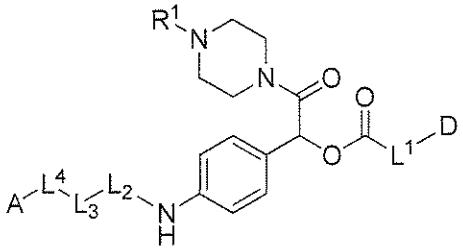
L^4 is a bond or a spacer; and

A is an acyl unit; and

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

comprising reacting Compound W: A-L^4-L^3-L^2; and Compound I:  .

65. A method of preparing Compound Z:



(Compound Z)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

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;

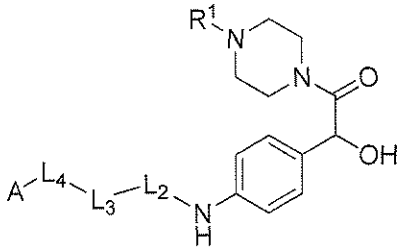
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

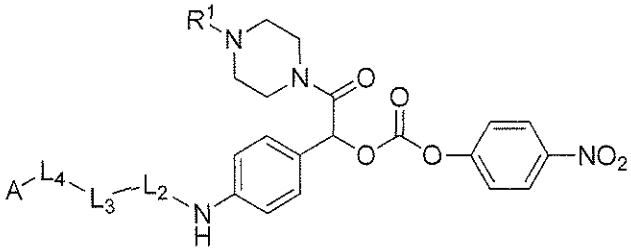
L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit

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

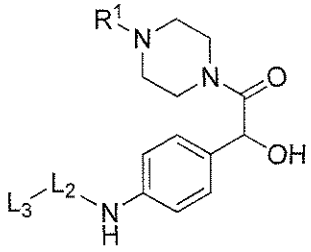
comprising: reacting Compound X:  and p-nitrophenylchloroformate to form Compound Y:



;

reacting Compound Y with a compound comprising L^1-D.

66. A method of preparing Compound X^1:



(Compound X^1)

or a salt or solvate or stereoisomer thereof;

wherein:

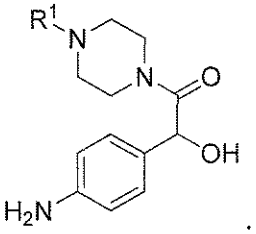
L^2 is a bond or a second self-immolative linker;

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

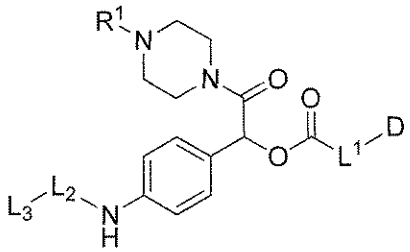
~~wherein if L^2 is a second self-immolative linker, then L^1 is a bond;~~

L^3 is a peptide linker; and

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

comprising: reacting Compound W^1: L^3-L^2; and Compound I:  .

67. A method of preparing Compound Y^1:



(Compound Y^1)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

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

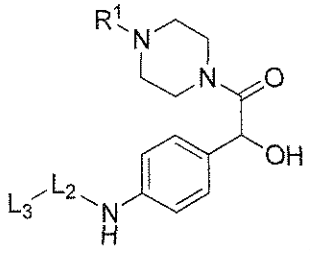
L^2 is a bond or a second self-immolative linker;

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

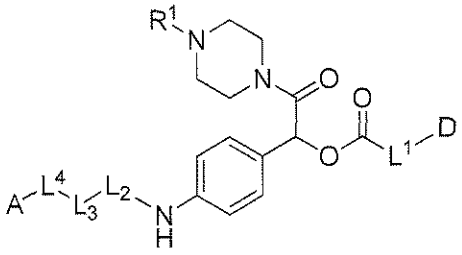
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker; and

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

comprising: reacting Compound X^1:  ; and a compound comprising L^1-D.

68. A method of preparing Compound Z:



(Compound Z)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

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;

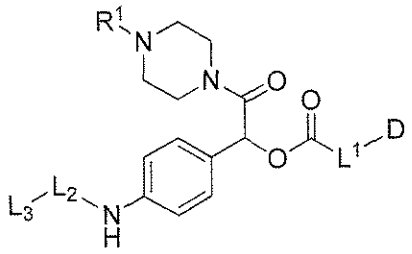
wherein if L^2 is a second self-immolative linker, then L^1 is a bond;

L^3 is a peptide linker;

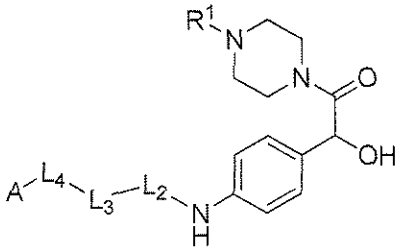
L^4 is a bond or a spacer;

A is an acyl unit; and

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

comprising: reacting Compound Y^1:  , and a compound comprising A-L^4.

69. A compound of formula:



(Compound X)

or a salt or solvate or stereoisomer thereof;

wherein:

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;~~

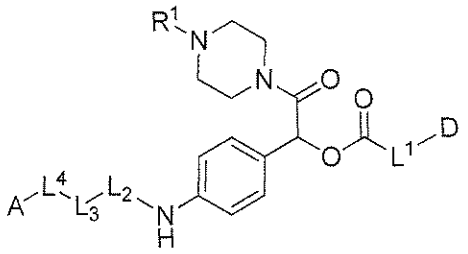
L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit; and

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

70. A compound of formula:



(Compound Z)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

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;

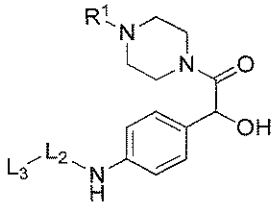
L^3 is a peptide linker;

L^4 is a bond or a spacer; and

A is an acyl unit; and

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

71. A compound of formula:



(Compound X^1)

or a salt or solvate or stereoisomer thereof;

wherein:

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

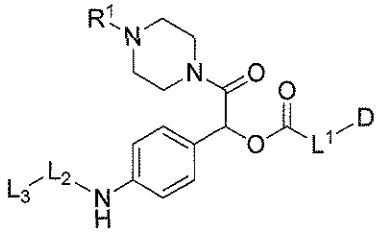
~~wherein if L^1 is a second self-immolative linker or a cyclization self-elimination linker, then L^2 is a bond;~~

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

L^3 is a peptide linker; and

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

72. A compound of formula:



(Compound Y^1)

or a salt or solvate or stereoisomer thereof;

wherein:

D is a drug moiety;

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; and

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

73. Use of the compound of any one of claims 1 to 49, or a salt or solvate or stereoisomer thereof, in the manufacture of a medicament for killing a cell, wherein the medicament is to be administered to the cell in an amount sufficient to kill the cell.

74. The use of claim 73, wherein the cell is a cancer cell.

75. The use of claim 74, wherein the cancer cell is a gastric cancer cell, pancreatic cancer cell, colorectal cancer cell, lung cancer cell, lymphoma cell, breast cancer cell, cervical cancer cell or ovarian cancer cell.