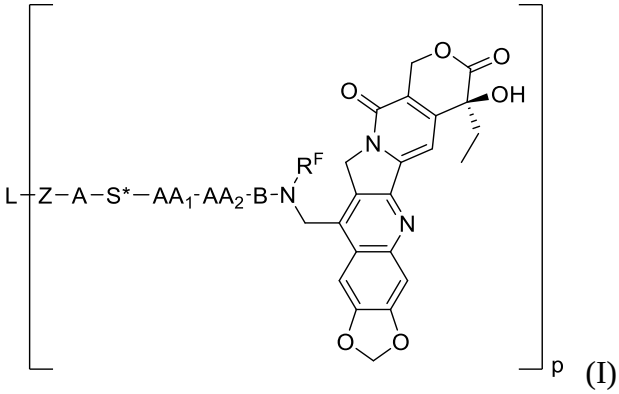
[0006] Therefore**,** a need exists for new linker technologies and conjugates useful for targeted therapy. The present invention addresses those and other needs.

BRIEF SUMMARY

[0007] The present disclosure provides, inter alia, Camptothecin Conjugates, Camptothecin-Linker Compounds and Camptothecin Compounds, methods of preparing and using them, and intermediates useful in the preparation thereof. The Camptothecin Conjugates of the present disclosure are stable in circulation, yet capable of inflicting cell death once free drug is released from a Conjugate in the vicinity or within tumor cells.

[0007a] In an aspect of the present disclosure, there is provided a Camptothecin Conjugate having a formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

Z is a Stretcher Unit;

A is a bond or a Connector Unit;

S* is a bond or a Partitioning Agent;

AA_1 is an amino acid;

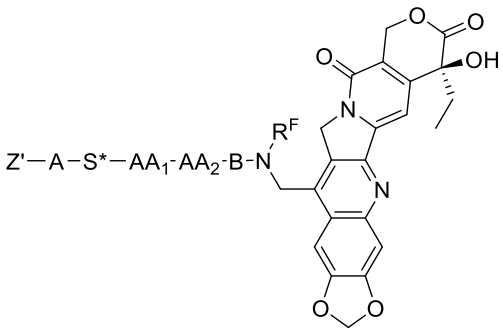
AA_2 is an amino acid;

B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, D-Ala, Aib, and pAbz;

R^F is H or C_1-C_6 alkyl; and

p is from 1 to 16.

[0007b] In another aspect of the present disclosure, there is provided a Camptothecin-Linker Compound having a formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein

Z' is a Stretcher Unit Precursor;

A is a bond or a Connector Unit;

S* is a bond or a Partitioning Agent;

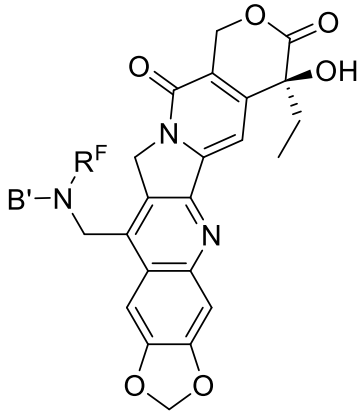
AA_1 is an amino acid;

AA_2 is an amino acid;

B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, D-Ala, Aib, and pAbz; and

R^F is H or C_1-C_6 alkyl.

[0007c] In a further aspect of the present disclosure, there is provided a Camptothecin Compound having a formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

B’ is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, D-Ala, Aib, and pAbz; and

R^F is H or C_1-C_6 alkyl.

[0007d] In another aspect of the present disclosure, there is provided a use of a Camptothecin Conjugate disclosed herein or a pharmaceutically acceptable salt thereof or a Camptothecin Compound disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0007e] In a further aspect of the present disclosure, there is provided a use of a Camptothecin Conjugate disclosed herein or a pharmaceutically acceptable salt thereof or a Camptothecin Compound disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an autoimmune disease in a subject in need thereof.

[0007f] In another aspect of the present disclosure, there is provided a use of a Camptothecin Compound disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer cells are to be contacted with the Camptothecin Compound or a pharmaceutically acceptable salt thereof.

[0007g] In a further aspect of the present disclosure, there is provided a method of preparing a Camptothecin Conjugate disclosed herein or a pharmaceutically acceptable salt thereof, comprising reacting an antibody or antigen-binding fragment thereof with a Camptothecin-Linker Compound disclosed herein or a pharmaceutically acceptable salt thereof.

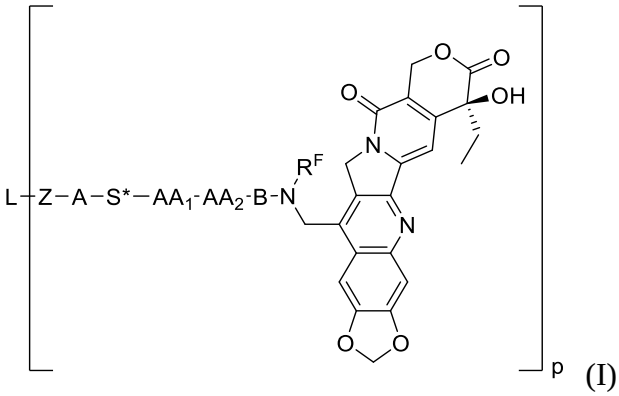
[0007h] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the Camptothecin Conjugate disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0007i] In a further aspect of the present disclosure, there is provided a kit comprising a Camptothecin Conjugate disclosed herein or a pharmaceutically acceptable salt thereof, optionally comprising an additional therapeutic agent.

[0007j] In another aspect of the present disclosure, there is provided a Camptothecin Conjugate disclosed herein or a pharmaceutically acceptable salt thereof or the Camptothecin Compound disclosed herein or a pharmaceutically acceptable salt thereof, for use in treating a disease or disorder.

[0007k] In a further aspect of the present disclosure, there is provided a Camptothecin Conjugate disclosed herein or a pharmaceutically acceptable salt thereof or a Camptothecin Compound disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier, or diluent, for use in treating a disease or disorder.

[0008] In one principal example, a Camptothecin Conjugate is provided having a formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

Z is a Stretcher Unit;

A is a bond or a Connector Unit;

S* is a bond or a Partitioning Agent;

AA_1 is an amino acid;

AA_2 is an amino acid;

B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, D-Ala, Aib, and pAbz;

R^F is H or C_1-C_6 alkyl; and

p is from 1 to 16.

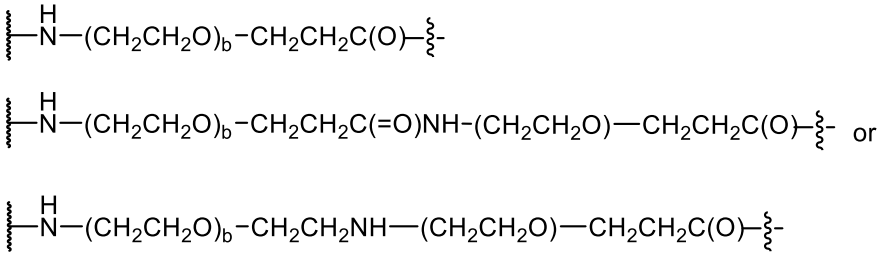
[0009] In some examples of the Camptothecin Conjugate of formula (I), AA_1 is Val. In some examples, AA_1 is Ala or D-Ala.

[0010] In some examples of the Camptothecin Conjugate of formula (I), AA_2 is Lys. In some examples, AA_2 is Ala or D-Ala.

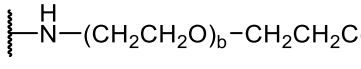
[0011] In some examples of the Camptothecin Conjugate of formula (I), B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, and D-Ala. In some examples, B is D-Ala. In some examples, B is Arg, Lys, His, Asp, or Glu. In some examples, B is Thr or Gln. In some examples, B is Phe, Val, Leu, Met, or Trp.

[0012] In some examples of the Camptothecin Conjugate of formula (I), R^F is H.

[0013] In some examples of the Camptothecin Conjugate of formula (I), S* is a PEG Unit. In some examples, the PEG Unit has the formula:



wherein the wavy line on the left indicates the site of attachment to A, the wavy line on the right indicates the site of attachment to AA_1, and b is an integer from 2 to 20, or is 2, 4, 8, or 12.

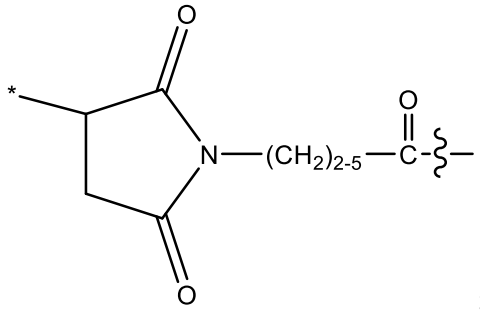
In some examples, the PEG Unit has the formula: ,

wherein the wavy line on the left indicates the site of attachment to A, the wavy line on the right indicates the site of attachment to AA_1, and b is an integer from 2 to 20, or is 2, 4, 8, or 12.

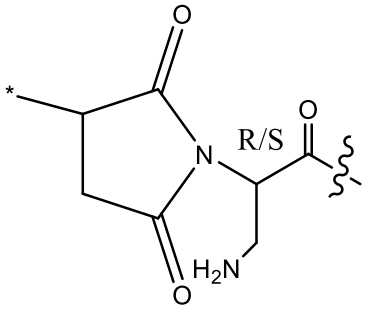
[0014] In some examples of the Camptothecin Conjugate of formula (I), Z has Formula Za:

azetidinyl, pyrrolidinyl or piperidinyl group. In some examples, R^{17} is –(C_1-C_5)alkylene-C(=O)-, wherein the alkylene portion of R^{17} is optionally substituted with the Basic Unit (BU).

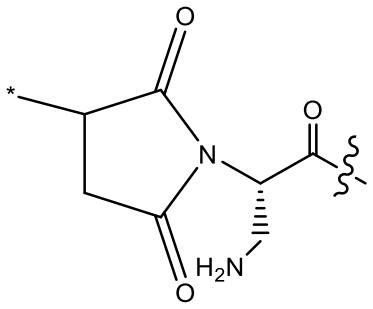
In some examples, Z is:



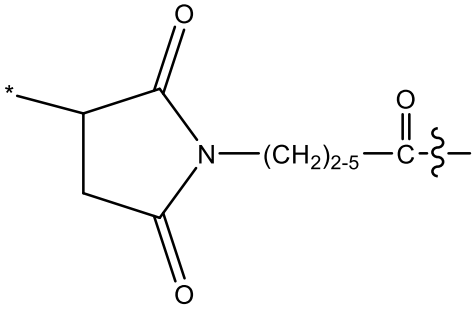
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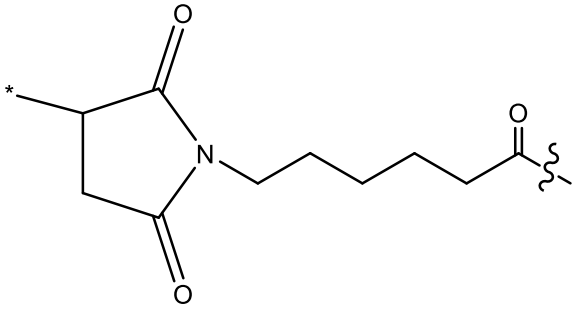
; or



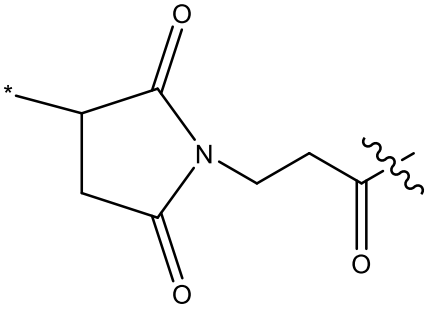
. In some examples, Z is:



.In some examples, Z is:



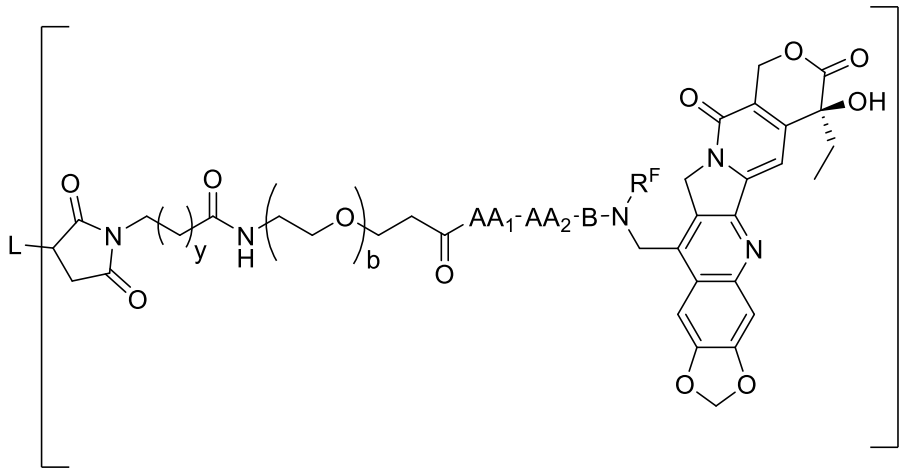
or



.

[0015] In some examples of the Camptothecin Conjugate of formula (I), A is a bond.

[0016] In another example, provided is a Camptothecin Conjugate having a formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

AA_1 is an amino acid;

AA_2 is an amino acid;

B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, D-Ala, Aib, and pAbz;

R^F is hydrogen or C_1-C_6 alkyl;

b is an integer from 2 to 20;

y is an integer from 1 to 8, or 1 to 4; or 1 or 4; and

p is from 1 to 16.

[0017] In some examples of the Camptothecin Conjugate of formula (Ib), y is 1.

[0018] In some examples of the Camptothecin Conjugate of formula (Ib), b is 8.

[0019] In some examples of the Camptothecin Conjugate of formula (Ib), AA_1-AA_2 is Val-Lys.

[0020] In some examples of the Camptothecin Conjugate of formula (Ib), B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, and D-Ala.

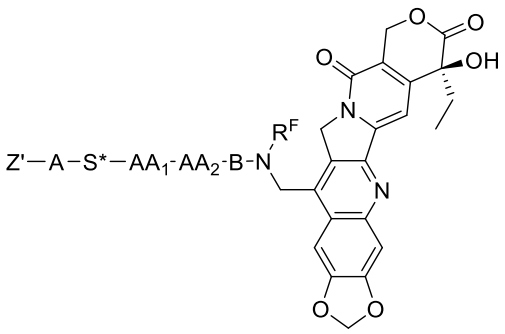
[0021] In some examples of the Camptothecin Conjugate of formula (Ib), AA_1-AA_2-B is Ala-Ala-D-Ala.

[0022] In some examples of the Camptothecin Conjugate of formula (Ib), R^F is H.

[0023] In some examples of the Camptothecin Conjugate of formula (I) or formula (Ib), p is 1 to 16, or is 2 to 8, or is 2, or is 4, or is 8.

[0024] In some examples of the Camptothecin Conjugate of formula (I) or formula (Ib), the Ligand Unit is an antibody or an antigen-binding fragment thereof. In some examples, the antibody is a monoclonal antibody or an antigen-binding fragment thereof. In some examples, the antibody is a cAC10 anti-CD30 antibody or an antigen-binding fragment thereof. In some examples, the antibody or antigen-binding fragment thereof comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOs: 1, 2, 3, 4, 5, and 6, respectively. In some examples, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 8. In some examples, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 8. In some examples, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 10 and a light chain comprising the amino acid sequence of SEQ ID NO: 11.

[0025] In another principal example, a Camptothecin-Linker Compound is provided having a formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein

Z' is a Stretcher Unit Precursor;

A is a bond or a Connector Unit;

S* is a bond or a Partitioning Agent;

AA_1 is an amino acid;

AA_2 is an amino acid;

B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, D-Ala, Aib, and pAbz; and

R^F is H or C_1-C_6 alkyl.

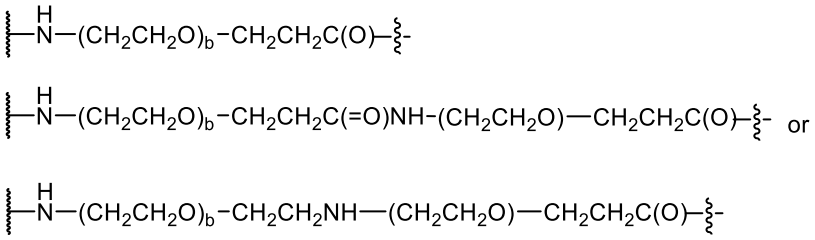
[0026] In some examples of the Camptothecin-Linker Compound of formula (II), AA_1 is Val. In some examples, AA_1 is Ala or D-Ala.

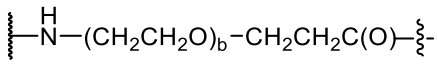
[0027] In some examples of the Camptothecin-Linker Compound of formula (II), AA_2 is Lys. In some examples, AA_2 is Ala or D-Ala.

[0028] In some examples of the Camptothecin-Linker Compound of formula (II), B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, and D-Ala. In some examples, B is D-Ala. In some examples, B is Arg, Lys, His, Asp, or Glu. In some examples, B is Thr or Gln. In some examples, B is Phe, Val, Leu, Met, or Trp.

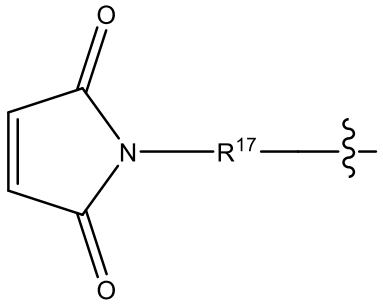
[0029] In some examples of the Camptothecin-Linker Compound of formula (II), R^F is H.

[0030] In some examples of the Camptothecin-Linker Compound of formula (II), S* is a PEG Unit. In some examples, the PEG Unit has the formula:



wherein the wavy line on the left indicates the site of attachment to A, the wavy line on the right indicates the site of attachment to AA_1, and b is an integer from 2 to 20, or is 2, 4, 8, or 12. In some examples, the PEG Unit has the formula: , wherein the wavy line on the left indicates the site of attachment to A, the wavy line on the right indicates the site of attachment to AA_1, and b is an integer from 2 to 20, or is 2, 4, 8, or 12.

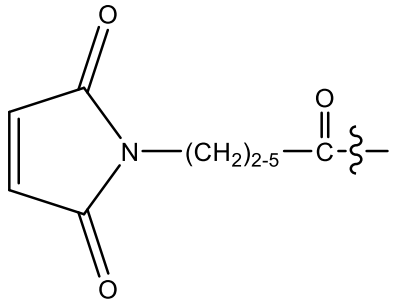
[0031] In some examples of the Camptothecin-Linker Compound of formula (II), Z' has Formula Z'b:



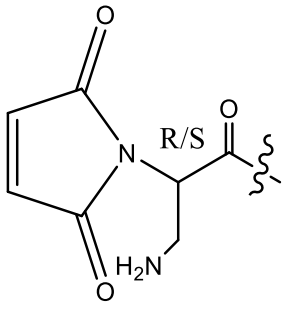
(Z'b**)**

wherein R^{17} is -C_1-C_{10} alkylene-, C_1-C_{10} heteroalkylene-, -C_3-C_8 carbocyclo-, -O-(C_1-C_8 alkylene)-, -arylene-, -C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, -C_3-C_8 heterocyclo-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-C(=O)-, C_1-C_{10} heteroalkylene-C(=O)-, -C_3-C_8 carbocyclo-C(=O)-, -O-(C_1-C_8 alkylene)-C(=O)-, -arylene-C(=O)-, -C_1-C_{10} alkylene-arylene-C(=O)-, -arylene-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-C(=O)-,-(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_3-C_8 heterocyclo-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-C(=O)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-NH-, C_1-C_{10} heteroalkylene-NH-, -C_3-C_8 carbocyclo-NH-, -O-(C_1-C_8 alkylene)-NH-, -arylene-NH-, -C_1-C_{10} alkylene-arylene-NH-, -arylene-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-(C_3-

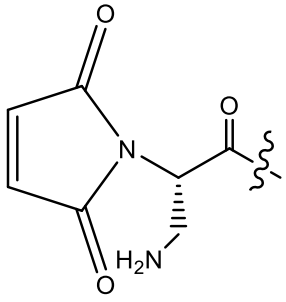
C_8 carbocyclo)-NH-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-NH-, -C_3-C_8 heterocyclo-NH-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-NH-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-S-, C_1-C_{10} heteroalkylene-S-, -C_3-C_8 carbocyclo-S-, -O-(C_1-C_8 alkylene)-S-, -arylene-S-, -C_1-C_{10} alkylene-arylene-S-, -arylene-C_1-C_{10} alkylene-S-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-S-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-S-, -C_3-C_8 heterocyclo-S-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-S-, or -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-S-; wherein R^{17} is optionally substituted with a Basic Unit (BU) that is –$(CH_2)_xNH_2$, –$(CH_2)_xNHR^a$, or–$(CH_2)_xNR^a_2$; wherein x is an integer of from 1-4; and each R^a is independently selected from the group consisting of C_{1-6} alkyl and C_{1-6} haloalkyl, or two R^a groups are combined with the nitrogen to which they are attached to form a 4- to 6-membered heterocycloalkyl ring, or an azetidinyl, pyrrolidinyl or piperidinyl group. In some examples, R^{17} is –(C_1-C_5)alkylene-C(=O)-, wherein the alkylene portion of R^{17} is optionally substituted with the Basic Unit (BU). In some examples, Z' is:



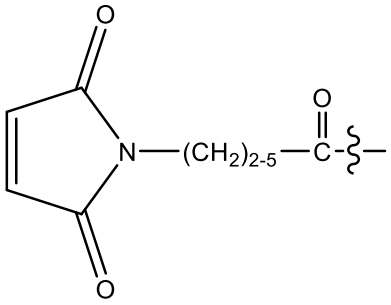
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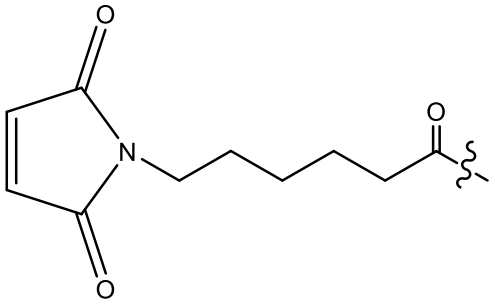
; or

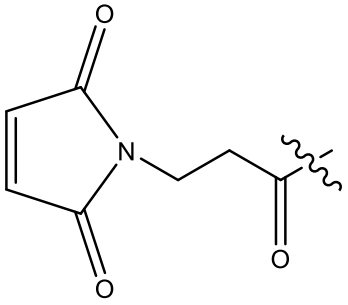


. In some examples, Z' is:



. In some examples, Z' is:

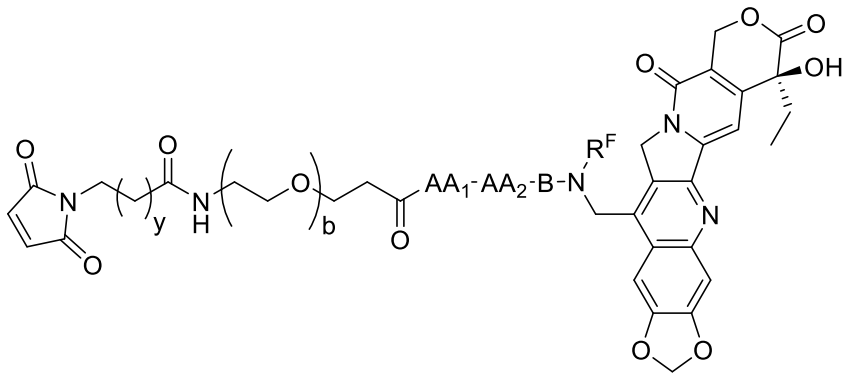




or .

[0032] In some examples of the Camptothecin-Linker Compound of formula (II), A is a bond.

[0033] In another example, provided is a Camptothecin-Linker Compound having a formula (IIb):



(IIb)

or a pharmaceutically acceptable salt thereof, wherein

AA_1 is an amino acid;

AA_2 is an amino acid;

B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, D-Ala, Aib, and pAbz;

R^F is hydrogen or C_1-C_6 alkyl;

b is an integer from 2 to 20; and

y is an integer from 1 to 8, or 1 to 4; or 1 or 4.

[0034] In some examples of the Camptothecin Conjugate of formula (IIb), y is1.

[0035] In some examples of the Camptothecin Conjugate of formula (IIb), b is 8.

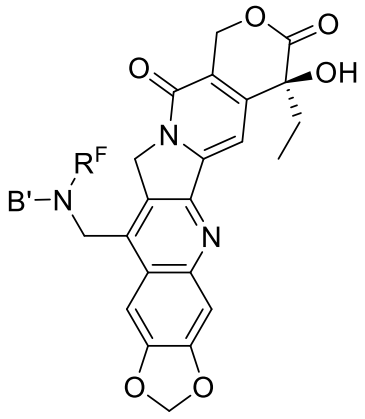
[0036] In some examples of the Camptothecin Conjugate of formula (IIb), AA_1-AA_2 is Val-Lys.

[0037] In some examples of the Camptothecin Conjugate of formula (IIb), B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, and D-Ala.

[0038] In some examples of the Camptothecin Conjugate of formula (IIb), AA_1-AA_2-B is Ala-Ala-D-Ala.

[0039] In some examples of the Camptothecin Conjugate of formula (IIb), R^F is H.

[0040] In another principal example, a Camptothecin Compound is provided having a formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

B’ is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, D-Ala, Aib, and pAbz; and
R^F is H or C_1-C_6 alkyl.

[0041] Provided in some examples is a method of treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of a Camptothecin Conjugate of formula (I) or any variation thereof, or a pharmaceutically acceptable salt thereof or a Camptothecin Compound of formula (III) or a pharmaceutically acceptable salt thereof. In some examples, the cancer is a lymphoma, a leukemia, or a solid tumor. In some examples, the method comprises administering to the subject an effective amount of an additional therapeutic agent, one or more chemotherapeutic agents, or radiation therapy.

[0042] Provided in some examples is a method of treating an autoimmune disease in a subject in need thereof, comprising administering to the subject an effective amount of a Camptothecin Conjugate of formula (I) or any variation thereof, or a pharmaceutically acceptable salt thereof or a Camptothecin Compound of formula (III) or a pharmaceutically acceptable salt thereof. In some examples, the autoimmune disease is a Th2 lymphocyte related disorder, a Th1 lymphocyte-related disorder, or an activated B lymphocyte-related disorder.

[0043] Provided in some examples is a method of treating cancer in a subject in need thereof, comprising contacting the cancer cells with the Camptothecin Compound of formula (III) or a pharmaceutically acceptable salt thereof. In some examples, the cancer is a lymphoma, a leukemia, or a solid tumor.

[0044] Provided in some examples is a method of preparing a Camptothecin Conjugate of formula (I) or any variation thereof, or a pharmaceutically acceptable salt thereof, comprising reacting an antibody or antigen-binding fragment thereof with a Camptothecin-Linker Compound of formula (II) or any variation thereof, or a pharmaceutically acceptable salt thereof.

[0045] Provided in some examples is a pharmaceutical composition comprising the Camptothecin Conjugate of formula (I) or any variation thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0046] Provided in some examples is a kit comprising a Camptothecin Conjugate of formula (I) or any variation thereof, or a pharmaceutically acceptable salt thereof, optionally comprising an additional therapeutic agent.

[0047] Provided in some examples is use of the Camptothecin Conjugate of formula (I) or any variation thereof, or a pharmaceutically acceptable salt thereof or the Camptothecin Compound of formula (III) or a pharmaceutically acceptable salt thereof, for treating a disease or disorder.

[0048] Provided in some examples is use of the Camptothecin Conjugate of formula (I) or any variation thereof, or a pharmaceutically acceptable salt thereof or a Camptothecin Compound of formula (III) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier, or diluent, in preparation of a medicament for treating a disease or disorder.

[0049] Other principal examples as noted above, are Camptothecin-Linker Compounds useful as intermediates for preparing Camptothecin Conjugates, wherein the Camptothecin-Linker Compound is comprised of a Camptothecin Stretcher Unit precursor (Z') capable of forming a covalent bond to a targeting ligand that provides for a Ligand Unit, and a Releasable Linker (RL) (i.e., -AA_1-AA_2-B-).

[0050] Other principal examples as noted above, are Camptothecin-Linker Compounds useful as intermediates for preparing Camptothecin Conjugates, wherein the Camptothecin-Linker Compound is comprised of a Camptothecin and a Linker Unit Precursor (Q'), wherein the Linker Unit Precursor is comprised of a Stretcher Unit precursor (Z') capable of forming a covalent bond to a targeting ligand that provides for a Ligand Unit, and a Releasable Linker (RL) (i.e., -AA_1-AA_2-B-).

[0051] In another example, provided herein are methods of treating cancer comprising administering to a subject in need thereof a Camptothecin Conjugate described herein.

[0052] In another example, provided herein are methods of treating cancer using Camptothecin-Linker Compounds or Camptothecins described herein.

[0053] In another example, provided herein are kits comprising a Camptothecin Conjugate described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0054] Figure 1. In vitro drug release from Ag1-8 ADC (DAR 8), Ag1-8k ADC (DAR8) and Ag1-8o ADC (DAR 8) in Karpas 299 and L540cy cells at 24h.

DETAILED DESCRIPTION

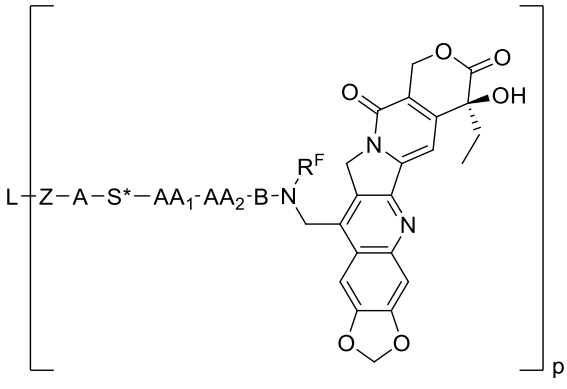
[0055] Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings. When trade names are used herein, the trade name includes the product formulation, the generic drug, and the active pharmaceutical ingredient(s) of the trade name product, unless otherwise indicated by context.

[0056] The term "antibody" as used herein is used in the broadest sense and specifically covers intact monoclonal antibodies, polyclonal antibodies, monospecific antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), and antibody fragments that exhibit the desired biological activity. The native form of an antibody is a tetramer and consists of two identical pairs of immunoglobulin chains, each pair having one light chain and one heavy chain. In each pair, the light and heavy chain variable regions (VL and VH) are together primarily responsible for binding to an antigen. The light chain and heavy chain variable domains consist of a framework region interrupted by three hypervariable regions, also called "complementarity determining regions" or "CDRs." The constant regions may be recognized by and interact with the immune system. (*see, e.g.*, Janeway *et al.*, 2001, *Immunol. Biology, 5th Ed.*, Garland Publishing, New York). An antibody can be of any type (*e.g.*, IgG, IgE, IgM, IgD, and IgA), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass. The antibody can be derived from any suitable species. In some embodiments, the antibody is of human or murine origin. An antibody can be, for example, human, humanized or chimeric.

[0057] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the

WHAT IS CLAIMED IS:

1. A Camptothecin Conjugate having a formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

Z is a Stretcher Unit;

A is a bond or a Connector Unit;

S* is a bond or a Partitioning Agent;

AA_1 is an amino acid;

AA_2 is an amino acid;

B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, D-Ala, Aib, and pAbz;

R^F is H or C_1-C_6 alkyl; and

p is from 1 to 16.

2. The Camptothecin Conjugate of claim 1, or a pharmaceutically acceptable salt thereof, wherein AA_1 is Val.

3. The Camptothecin Conjugate of claim 1, or a pharmaceutically acceptable salt thereof, wherein AA_1 is Ala or D-Ala.

4. The Camptothecin Conjugate of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein AA_2 is Lys.

5. The Camptothecin Conjugate of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein AA_2 is Ala or D-Ala.

6. The Camptothecin Conjugate of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, and D-Ala.

7. The Camptothecin Conjugate of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein B is D-Ala.

8. The Camptothecin Conjugate of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein B is Arg, Lys, His, Asp, or Glu.

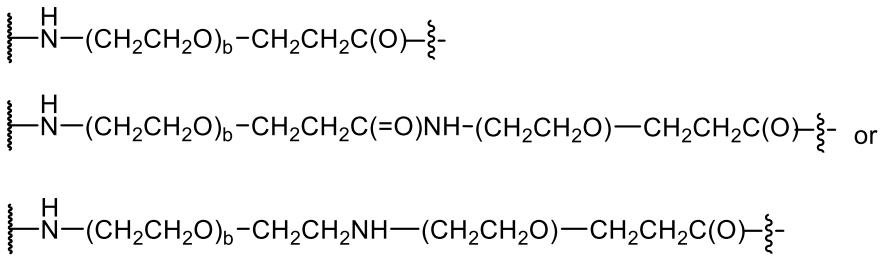
9. The Camptothecin Conjugate of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein B is Thr or Gln.

10. The Camptothecin Conjugate of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein B is Phe, Val, Leu, Met, or Trp.

11. The Camptothecin Conjugate of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^F is H.

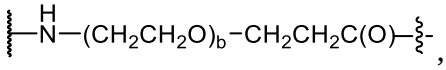
12. The Camptothecin Conjugate of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein S* is a PEG Unit.

13. The Camptothecin Conjugate of claim 12, or a pharmaceutically acceptable salt thereof, wherein the PEG Unit has the formula:



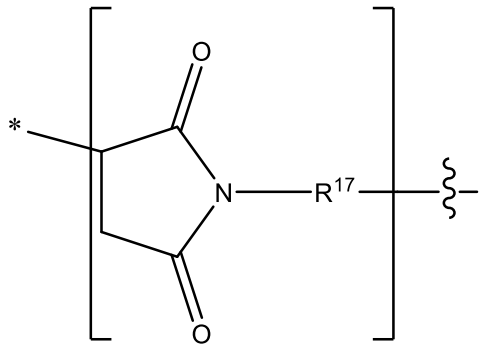
wherein the wavy line on the left indicates the site of attachment to A, the wavy line on the right indicates the site of attachment to AA_1, and b is an integer from 2 to 20, or is 2, 4, 8, or 12.

14. The Camptothecin Conjugate of claim 13, or a pharmaceutically acceptable salt thereof, wherein the PEG Unit has the formula:



wherein the wavy line on the left indicates the site of attachment to A, the wavy line on the right indicates the site of attachment to AA_1, and b is an integer from 2 to 20, or is 2, 4, 8, or 12.

15. The Camptothecin Conjugate of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein Z has Formula Za:



(Za)

wherein the asterisk indicates the position of attachment to the Ligand Unit (L);
the wavy line indicates the position of attachment to the Connector Unit (A); and
R^{17} is -C_1-C_{10} alkylene-, C_1-C_{10} heteroalkylene-, -C_3-C_8 carbocyclo-, -O-(C_1-C_8 alkylene)-, -arylene-, -C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8

carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, -C_3-C_8 heterocyclo-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-C(=O)-, C_1-C_{10} heteroalkylene-C(=O)-, -C_3-C_8 carbocyclo-C(=O)-, -O-(C_1-C_8 alkylene)-C(=O)-, -arylene-C(=O)-, -C_1-C_{10} alkylene-arylene-C(=O)-, -arylene-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-C(=O)-,-(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_3-C_8 heterocyclo-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-C(=O)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-NH-, C_1-C_{10} heteroalkylene-NH-, -C_3-C_8 carbocyclo-NH-, -O-(C_1-C_8 alkylene)-NH-, -arylene-NH-, -C_1-C_{10} alkylene-arylene-NH-, -arylene-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-NH-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-NH-, -C_3-C_8 heterocyclo-NH-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-NH-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-S-, C_1-C_{10} heteroalkylene-S-, -C_3-C_8 carbocyclo-S-, -O-(C_1-C_8 alkylene)-S-, -arylene-S-, -C_1-C_{10} alkylene-arylene-S-, -arylene-C_1-C_{10} alkylene-S-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-S-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-S-, -C_3-C_8 heterocyclo-S-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-S-, or -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-S-;

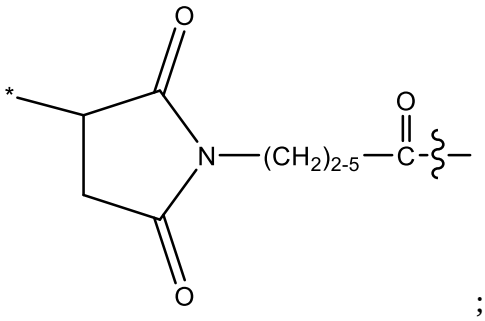
wherein R^{17} is optionally substituted with a Basic Unit (BU) that is $–(CH_2)_xNH_2$, $–(CH_2)_xNHR^a$, or $–(CH_2)_xNR^a{}_2$;

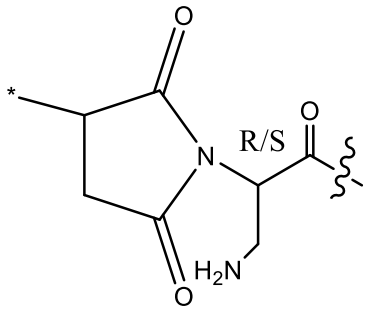
wherein x is an integer of from 1-4; and

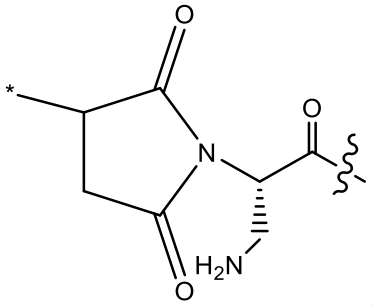
each R^a is independently selected from the group consisting of C_{1-6} alkyl and C_{1-6} haloalkyl, or two R^a groups are combined with the nitrogen to which they are attached to form a 4- to 6-membered heterocycloalkyl ring, or an azetidinyl, pyrrolidinyl or piperidinyl group.

16. The Camptothecin Conjugate of claim 15, or a pharmaceutically acceptable salt thereof, wherein R^{17} is $–(C_1$-$C_5)$alkylene-C(=O)-, wherein the alkylene portion of R^{17} is optionally substituted with the Basic Unit (BU).

17. The Camptothecin Conjugate of claim 15 or claim 16, or a pharmaceutically acceptable salt thereof, wherein Z is:

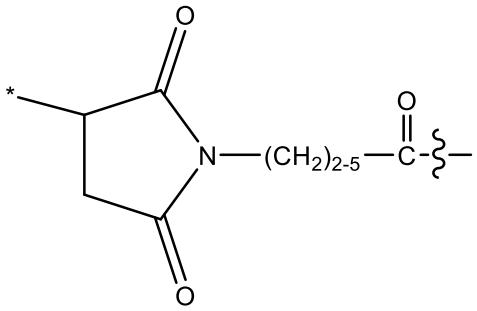


;


; or


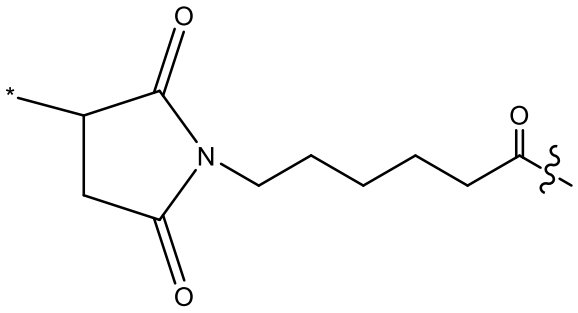
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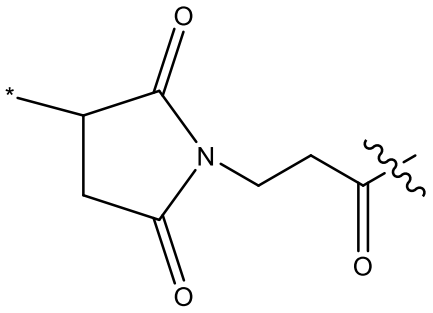
18. The Camptothecin Conjugate of claim 17, or a pharmaceutically acceptable salt thereof, wherein Z is:



.

19. The Camptothecin Conjugate of claim 17, or a pharmaceutically acceptable salt thereof, wherein Z is:

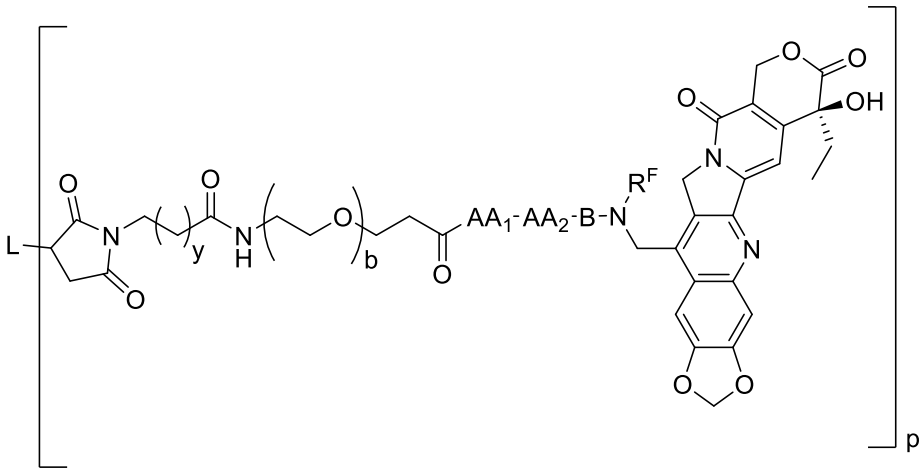


or


.

20. The Camptothecin Conjugate of any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, wherein A is a bond.

21. The Camptothecin Conjugate of claim 1 having a formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof, wherein

L is a Ligand Unit;

AA_1 is an amino acid;

AA_2 is an amino acid;

B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, D-Ala, Aib, and pAbz;

R^F is hydrogen or C_1-C_6 alkyl;

b is an integer from 2 to 20;

y is an integer from 1 to 8, or 1 to 4; or 1 or 4; and

p is from 1 to 16.

22. The Camptothecin Conjugate of claim 21, or a pharmaceutically acceptable salt thereof, wherein y is 1.

23. The Camptothecin Conjugate of claim 21 or 22, or a pharmaceutically acceptable salt thereof, wherein b is 8.

24. The Camptothecin Conjugate of any one of claims 21-23, or a pharmaceutically acceptable salt thereof, wherein AA_1-AA_2 is Val-Lys.

25. The Camptothecin Conjugate of any one of claims 21-24, or a pharmaceutically acceptable salt thereof, wherein B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, and D-Ala.

26. The Camptothecin Conjugate of any one of claims 21-23, or a pharmaceutically acceptable salt thereof, wherein AA_1-AA_2-B is Ala-Ala-D-Ala.

27. The Camptothecin Conjugate of any one of claims 21-26, or a pharmaceutically acceptable salt thereof, wherein R^F is H.

28. The Camptothecin Conjugate of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein p is 1 to 16, or is 2 to 8, or is 2, or is 4, or is 8.

29. The Camptothecin Conjugate of any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, wherein the Ligand Unit is an antibody or an antigen-binding fragment thereof.

30. The Camptothecin Conjugate of claim 29, or a pharmaceutically acceptable salt thereof, wherein the antibody is a monoclonal antibody or an antigen-binding fragment thereof.

31. The Camptothecin Conjugate of claim 29 or claim 30, or a pharmaceutically acceptable salt thereof, wherein the antibody is a cAC10 anti-CD30 antibody or an antigen-binding fragment thereof.

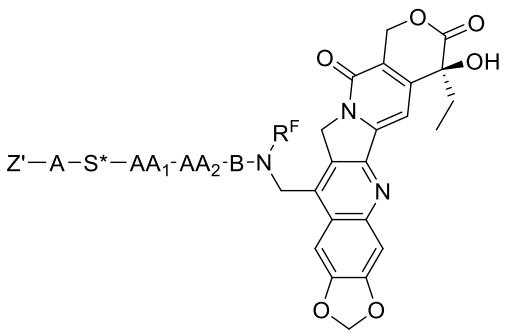
32. The Camptothecin Conjugate of any one of claims 29-31, or a pharmaceutically acceptable salt thereof, wherein the antibody or antigen-binding fragment thereof comprises CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 comprising the amino acid sequences of SEQ ID NOs: 1, 2, 3, 4, 5, and 6, respectively.

33. The Camptothecin Conjugate of claim 31, or a pharmaceutically acceptable salt thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 8.

34. The Camptothecin Conjugate of claim 31, or a pharmaceutically acceptable salt thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 8.

35. The Camptothecin Conjugate of claim 31, or a pharmaceutically acceptable salt thereof, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 10 and a light chain comprising the amino acid sequence of SEQ ID NO: 11.

36. A Camptothecin-Linker Compound having a formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein

Z' is a Stretcher Unit Precursor;

A is a bond or a Connector Unit;

S* is a bond or a Partitioning Agent;

AA_1 is an amino acid;

AA_2 is an amino acid;

B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, D-Ala, Aib, and pAbz; and

R^F is H or C_1-C_6 alkyl.

37. The Camptothecin-Linker Compound of claim 36, or a pharmaceutically acceptable salt thereof, wherein AA_1 is Val.

38. The Camptothecin-Linker Compound of claim 36, or a pharmaceutically acceptable salt thereof, wherein AA_1 is Ala or D-Ala.

39. The Camptothecin-Linker Compound of any one of claims 36-38, or a pharmaceutically acceptable salt thereof, wherein AA_2 is Lys.

40. The Camptothecin-Linker Compound of any one of claims 36-38, or a pharmaceutically acceptable salt thereof, wherein AA_2 is Ala or D-Ala.

41. The Camptothecin-Linker Compound of any one of claims 36-40, or a pharmaceutically acceptable salt thereof, wherein B is an amino acid selected from the

group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, and D-Ala.

42. The Camptothecin-Linker Compound of any one of claims 36-41, or a pharmaceutically acceptable salt thereof, wherein B is D-Ala.

43. The Camptothecin-Linker Compound of any one of claims 36-41, or a pharmaceutically acceptable salt thereof, wherein B is Arg, Lys, His, Asp, or Glu.

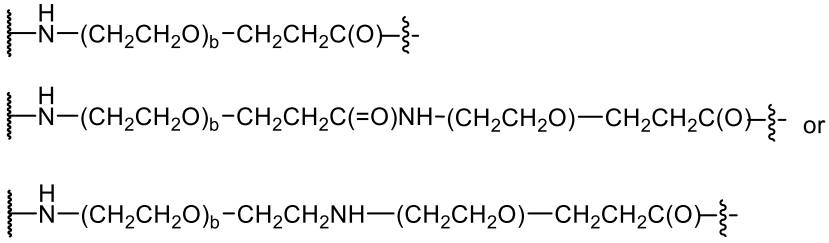
44. The Camptothecin-Linker Compound of any one of claims 36-41, or a pharmaceutically acceptable salt thereof, wherein B is Thr or Gln.

45. The Camptothecin-Linker Compound of any one of claims 36-41, or a pharmaceutically acceptable salt thereof, wherein B is Phe, Val, Leu, Met, or Trp.

46. The Camptothecin-Linker Compound of any one of claims 36-45, or a pharmaceutically acceptable salt thereof, wherein R^F is H.

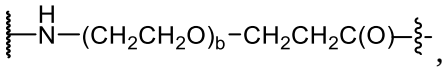
47. The Camptothecin-Linker Compound of any one of claims 36-46, or a pharmaceutically acceptable salt thereof, wherein S* is a PEG Unit.

48. The Camptothecin-Linker Compound of claim 47, or a pharmaceutically acceptable salt thereof, wherein the PEG Unit has the formula:



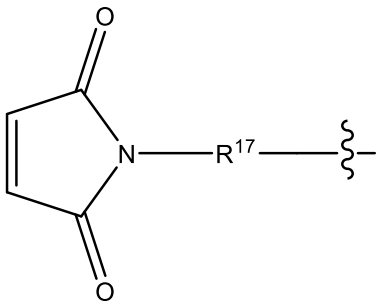
wherein the wavy line on the left indicates the site of attachment to A, the wavy line on the right indicates the site of attachment to AA_1, and b is an integer from 2 to 20, or is 2, 4, 8, or 12.

49. The Camptothecin-Linker Compound of claim 48, or a pharmaceutically acceptable salt thereof, wherein the PEG Unit has the formula:



wherein the wavy line on the left indicates the site of attachment to A, the wavy line on the right indicates the site of attachment to AA_1, and b is an integer from 2 to 20, or is 2, 4, 8, or 12.

50. The Camptothecin-Linker Compound of any one of claims 36 to 49, or a pharmaceutically acceptable salt thereof, wherein Z' has Formula Z'b:



(Z'b)

wherein

R^{17} is -C_1-C_{10} alkylene-, C_1-C_{10} heteroalkylene-, -C_3-C_8 carbocyclo-, -O-(C_1-C_8 alkylene)-, -arylene-, -C_1-C_{10} alkylene-arylene-, -arylene-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-, -C_3-C_8 heterocyclo-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-, -C_1-C_{10} alkylene-C(=O)-, C_1-C_{10} heteroalkylene-C(=O)-, -C_3-C_8 carbocyclo-C(=O)-, -O-(C_1-C_8 alkylene)-C(=O)-, -arylene-C(=O)-, -C_1-C_{10} alkylene-arylene-C(=O)-, -arylene-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-C(=O)-,-(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_3-C_8 heterocyclo-C(=O)-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-C(=O)-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-C(=O)-, -C_1-C_{10} alkylene-NH-, C_1-C_{10}

heteroalkylene-NH-, -C_3-C_8 carbocyclo-NH-, -O-(C_1-C_8 alkylene)-NH-, -arylene-NH-, -C_1-C_{10} alkylene-arylene-NH-, -arylene-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-NH-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-NH-, -C_3-C_8 heterocyclo-NH-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-NH-, -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-NH-, -C_1-C_{10} alkylene-S-, C_1-C_{10} heteroalkylene-S-, -C_3-C_8 carbocyclo-S-, -O-(C_1-C_8 alkylene)-S-, -arylene-S-, -C_1-C_{10} alkylene-arylene-S-, -arylene-C_1-C_{10} alkylene-S-, -C_1-C_{10} alkylene-(C_3-C_8 carbocyclo)-S-, -(C_3-C_8 carbocyclo)-C_1-C_{10} alkylene-S-, -C_3-C_8 heterocyclo-S-, -C_1-C_{10} alkylene-(C_3-C_8 heterocyclo)-S-, or -(C_3-C_8 heterocyclo)-C_1-C_{10} alkylene-S-;

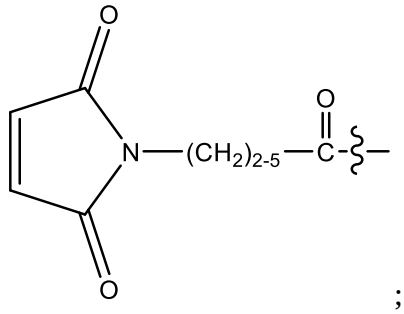
wherein R^{17} is optionally substituted with a Basic Unit (BU) that is $–(CH_2)_xNH_2$, $–(CH_2)_xNHR^a$, or $–(CH_2)_xNR^a{}_2$;

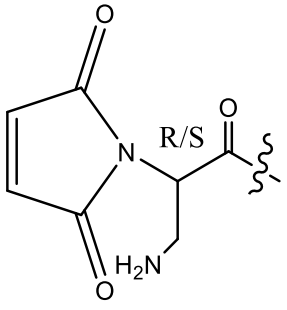
wherein x is an integer of from 1-4; and

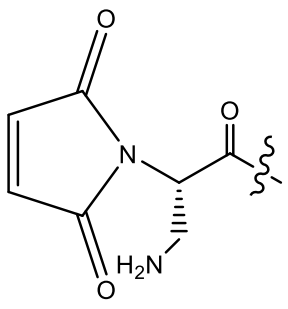
each R^a is independently selected from the group consisting of C_{1-6} alkyl and C_{1-6} haloalkyl, or two R^a groups are combined with the nitrogen to which they are attached to form a 4- to 6-membered heterocycloalkyl ring, or an azetidinyl, pyrrolidinyl or piperidinyl group.

51. The Camptothecin-Linker Compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein R^{17} is $–(C_1$-$C_5)$alkylene-C(=O)-, wherein the alkylene portion of R^{17} is optionally substituted with the Basic Unit (BU).

52. The Camptothecin-Linker Compound of claim 50 or claim 51, or a pharmaceutically acceptable salt thereof, wherein Z' is:

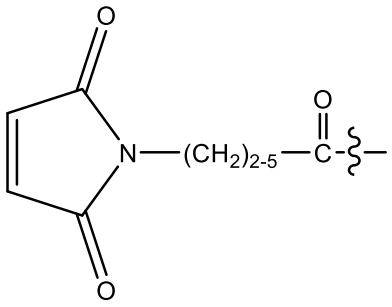


;


; or


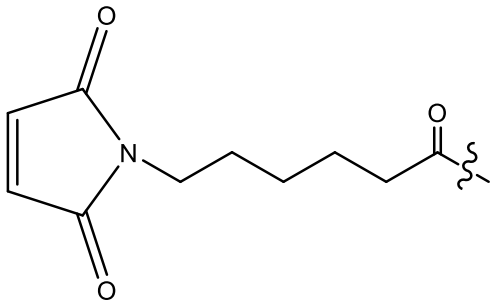
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53. The Camptothecin-Linker Compound of claim 52, or a pharmaceutically acceptable salt thereof, wherein Z' is:

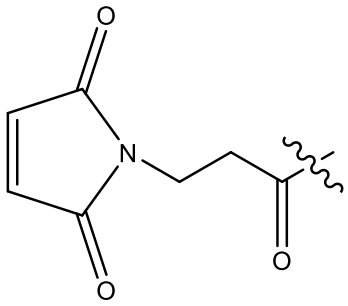


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54. The Camptothecin-Linker Compound of claim 52, or a pharmaceutically acceptable salt thereof, wherein Z' is:



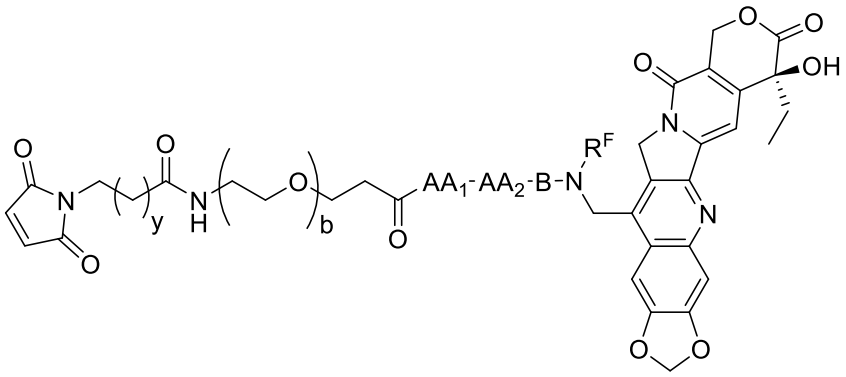
or



.

55. The Camptothecin-Linker Compound of any one of claims 36 to 54, or a pharmaceutically acceptable salt thereof, wherein A is a bond.

56. The Camptothecin-Linker Compound of claim 36, having a formula (IIb):



(IIb)

or a pharmaceutically acceptable salt thereof, wherein

AA_1 is an amino acid;

AA_2 is an amino acid;

B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, D-Ala, Aib, and pAbz;

R^F is hydrogen or C_1-C_6 alkyl;

b is an integer from 2 to 20; and

y is an integer from 1 to 8, or 1 to 4; or 1 or 4.

57. The Camptothecin-Linker Compound of claim 56, or a pharmaceutically acceptable salt thereof, wherein y is 1.

58. The Camptothecin-Linker Compound of claim 56 or 57, or a pharmaceutically acceptable salt thereof, wherein b is 8.

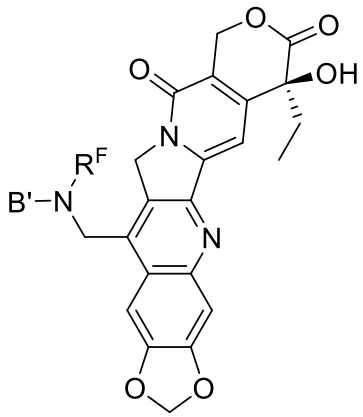
59. The Camptothecin-Linker Compound of any one of claims 56-58, or a pharmaceutically acceptable salt thereof, wherein AA_1-AA_2 is Val-Lys.

60. The Camptothecin-Linker Compound of any one of claims 56-59, or a pharmaceutically acceptable salt thereof, wherein B is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, and D-Ala.

61. The Camptothecin-Linker Compound of any one of claims 56-58, or a pharmaceutically acceptable salt thereof, wherein AA_1-AA_2-B is Ala-Ala-D-Ala.

62. The Camptothecin-Linker Compound of any one of claims 56-61, or a pharmaceutically acceptable salt thereof, wherein R^F is H.

63. A Camptothecin Compound having a formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein

B’ is an amino acid selected from the group consisting of Arg, Lys, His, Asp, Glu, Thr, Gln, Ala, Phe, Val, Leu, Met, Trp, D-Ala, Aib, and pAbz; and

R^F is H or C_1-C_6 alkyl.

64. Use of a Camptothecin Conjugate of any one of claims 1 to 35 or a pharmaceutically acceptable salt thereof or a Camptothecin Compound of claim 63 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a subject in need thereof.

65. The use of claim 64, wherein the cancer is a lymphoma, a leukemia, or a solid tumor.

66. The use of claim 64 or claim 65, wherein an effective amount of the Camptothecin Conjugate or a pharmaceutically acceptable salt thereof, or a Camptothecin Compound or a pharmaceutically acceptable salt thereof is to be administered to the subject, and wherein an effective amount of a therapeutic agent, one or more chemotherapeutic agents, or radiation therapy is to be additionally administered.

67. Use of a Camptothecin Conjugate of any one of claims 1 to 35 or a pharmaceutically acceptable salt thereof or a Camptothecin Compound of claim 63 or a

pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an autoimmune disease in a subject in need thereof.

68. The use of claim 67, wherein the autoimmune disease is a Th2 lymphocyte related disorder, a Th1 lymphocyte-related disorder, or an activated B lymphocyte-related disorder.

69. Use of a Camptothecin Compound of claim 63 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer cells are to be contacted with the Camptothecin Compound or a pharmaceutically acceptable salt thereof.

70. The use of claim 69, wherein the cancer is a lymphoma, a leukemia, or a solid tumor.

71. A method of preparing a Camptothecin Conjugate of any one of claims 1 to 35 or a pharmaceutically acceptable salt thereof, comprising reacting an antibody or antigen-binding fragment thereof with a Camptothecin-Linker Compound of any one of claims 36 to 62 or a pharmaceutically acceptable salt thereof.

72. A pharmaceutical composition comprising the Camptothecin Conjugate of any one of claims 1 to 35 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

73. A kit comprising a Camptothecin Conjugate of any one of claims 1 to 35 or a pharmaceutically acceptable salt thereof, optionally comprising an additional therapeutic agent.

74. A Camptothecin Conjugate of any one of claims 1 to 35 or a pharmaceutically acceptable salt thereof or the Camptothecin Compound of claim 63 or a pharmaceutically acceptable salt thereof, for use in treating a disease or disorder.

75. A Camptothecin Conjugate of any one of claims 1 to 35 or a pharmaceutically acceptable salt thereof or a Camptothecin Compound of claim 63 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, carrier, or diluent, for use in treating a disease or disorder.