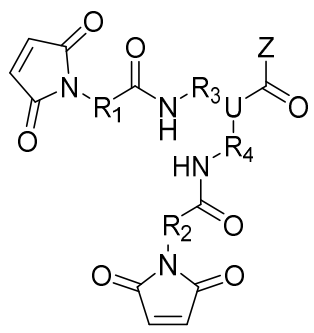


[0006] The identity of the linker can influence the reaction conditions that the therapeutic must experience during production of the ADC. Accordingly, there is also a need for improved linkers that can incorporate unprotected/unmodified peptide therapeutics with or without non-native amino acids.

SUMMARY

[0006a] In an aspect, there is provided a compound of the formula:



wherein:

R₁ and R₂ are independently C₁ to C₅ alkyl, optionally substituted with one or more of -NH₂, -CH₂NH₂, and -CH₂CH₂NH₂;

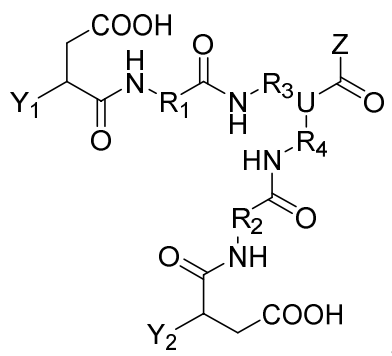
R₃ and R₄ are independently C₁ to C₅ alkyl or absent;

U is tertiary amine or 1,3,5-substituted phenyl;

Z comprises a therapeutic; and

pharmaceutically acceptable salts thereof.

[0006b] In another aspect, there is provided a compound of the formula:



wherein:

R₁ and R₂ are independently C₁ to C₅ alkyl, optionally substituted with one or more of NH₂, CH₂NH₂, and CH₂CH₂NH₂;

R₃ and R₄ are independently C₁ to C₅ alkyl or absent;

U is tertiary amine or 1,3,5-substituted phenyl;

Y₁ and Y₂ independently comprise an amide, amine, imine, sulfonamide, thiourea, urea, or thioether;

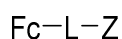
Z comprises a therapeutic; and
pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION

[0007] The present invention relates to novel linkers, including novel conjugates comprising the novel linkers, for the delivery of a therapeutic to an animal. The novel conjugates can also include an Fc region and a therapeutic, such as a peptide therapeutic.

[0008] It has been surprisingly found that by attaching a therapeutic to one of the disclosed novel linkers and another moiety, such as an Fc region of an antibody, the duration of action of the therapeutic can be improved and/or lengthened. While not wishing to be bound by theory, it is believed that the attachment of the therapeutic to the linker and Fc region can increase the duration of action of the therapeutic by enlarging the overall moiety and preventing the breakdown of the therapeutic. The reaction conditions for the conjugation reaction between the novel linkers and the Fc region are relatively mild, so the payload or therapeutic does not need to be modified to be protected during the reaction.

[0009] It has also been surprisingly found that the disclosed novel linkers can produce an ADC that can incorporate unprotected/unmodified peptide therapeutics with or without non-native amino acids.



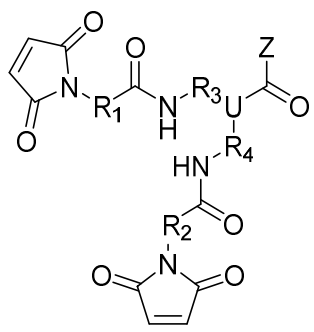
Formula I-A.

[00010] Disclosed herein are novel conjugate compounds of Formula I-A, wherein Fc comprises an Fc region, such as an Fc region of an antibody, L comprises a linker, and Z comprises a therapeutic, a functional group suitable for the later attachment of a therapeutic, or a functional group suitable for the conjugate compound to exist without attaching a therapeutic.

CLAIMS

What is claimed is:

1. A compound of the formula:



wherein:

R₁ and R₂ are independently C₁ to C₅ alkyl, optionally substituted with one or more of -NH₂, -CH₂NH₂, and -CH₂CH₂NH₂;

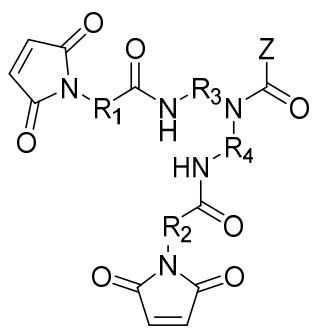
R₃ and R₄ are independently C₁ to C₅ alkyl or absent;

U is tertiary amine or 1,3,5-substituted phenyl;

Z comprises a therapeutic; and

pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein the compound is of the formula:

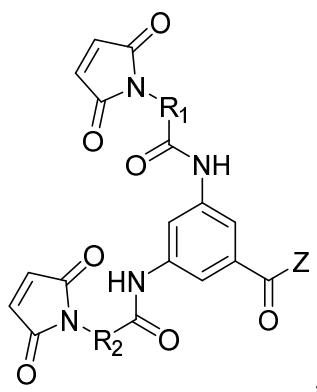


wherein:

R₁ and R₂ are independently C₁ to C₅ alkyl, optionally substituted with one or more of -NH₂, -CH₂NH₂, or -CH₂CH₂NH₂;

R₃ and R₄ are C₁ to C₅ alkyl;
Z comprises a therapeutic; and
pharmaceutically acceptable salts thereof.

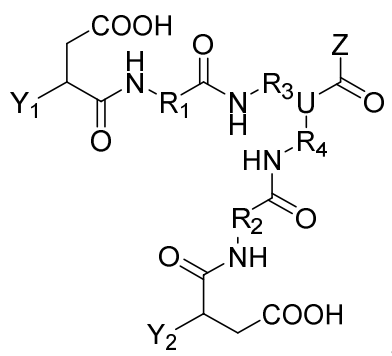
3. The compound of claim 1, wherein the compound is of the formula:



wherein:

R₁ and R₂ are independently C₁ to C₅ linear alkyl, optionally substituted with one or more of -NH₂, -CH₂NH₂, or -CH₂CH₂NH₂;
Z comprises a therapeutic; and
pharmaceutically acceptable salts thereof.

4. A compound of the formula:



wherein:

R₁ and R₂ are independently C₁ to C₅ alkyl, optionally substituted with one or more of NH₂, CH₂NH₂, and CH₂CH₂NH₂;
R₃ and R₄ are independently C₁ to C₅ alkyl or absent;

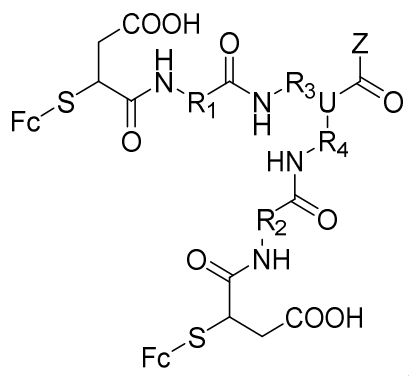
U is tertiary amine or 1,3,5-substituted phenyl;

Y₁ and Y₂ independently comprise an amide, amine, imine, sulfonamide, thiourea, urea, or thioether;

Z comprises a therapeutic; and

pharmaceutically acceptable salts thereof.

5. The compound of claim 4, wherein the compound is of the formula:



wherein:

R₁ and R₂ are independently C₂ linear alkyl, optionally substituted with one or more of NH₂, CH₂NH₂, and CH₂CH₂NH₂;

R₃ and R₄ are independently C₁ to C₅ linear alkyl or absent;

U is tertiary amine or 1,3,5-substituted phenyl;

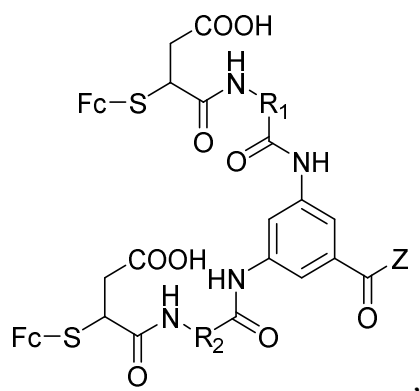
Z comprises a therapeutic;

Fc comprises an Fc region;

S is a sulfur atom from the Fc region; and

pharmaceutically acceptable salts thereof.

6. The compound of claim 4, wherein the compound is of the formula:



wherein:

R₁ and R₂ are independently C₁ to C₅ linear alkyl, optionally substituted with one or more of -NH₂, -CH₂NH₂, and -CH₂CH₂NH₂;

Z comprises a therapeutic;

Fc comprises an Fc region;

S is a sulfur atom from the Fc region; and

pharmaceutically acceptable salts thereof.

7. The compound of any one of claims 1 to 6, wherein R₁ and R₂ are independently C₂ alkyl, optionally substituted with one or more of -NH₂, -CH₂NH₂, or -CH₂CH₂NH₂, or pharmaceutically acceptable salts thereof.

8. The compound of any one of claims 1 to 7, wherein R₁ and R₂ are identical, or pharmaceutically acceptable salts thereof.

9. The compound of any one of claims 1, 2, 4, 5, 7 or 8, wherein R₃ and R₄ are identical, or pharmaceutically acceptable salts thereof.

10. The compound of any one of claims 1, 2, 4, 5, or 7 to 9, wherein R₃ and R₄ are C₂ alkyl, or pharmaceutically acceptable salts thereof.

11. The compound of any one of claims 1 to 10, wherein Z comprises NH, C₁ to C₃₀ alkyl, (OCH₂CH₂)_m, or combinations thereof, and a therapeutic, or pharmaceutically acceptable salts thereof, and wherein m is a whole number integer from 1 to 30.
12. The compound of claim 11, wherein the therapeutic comprises an amino acid or a peptide, or pharmaceutically acceptable salts thereof.
13. The compound of claim 12, wherein the peptide comprises from 2 to 100 amino acids, or pharmaceutically acceptable salts thereof.
14. The compound of claim 12 or 13, wherein the therapeutic comprises adrenocorticotrophic hormone (ACTH), adropin, amylin, angiotensin, atrial natriuretic peptide (ANP), calcitonin, cholecystokinin (CCK), gastrin, ghrelin, glucagon, growth hormone, follicle-stimulating hormone (FSH), insulin, leptin, luteinizing hormone (LH), melanocyte-stimulating hormone (MSH), natriuretic peptide, oxyntomodulin, oxytocin, parathyroid hormone (PTH), prolactin, renin, somatostatin, thyroid-stimulating hormone (TSH), thyrotropin-releasing hormone (TRH), vasopressin, also called arginine vasopressin (AVP) or anti-diuretic hormone (ADH), vasoactive intestinal peptide (VIP), analogs thereof, or combinations thereof, or pharmaceutically acceptable salts thereof.
15. The compound of any one of claims 12 to 14, wherein the therapeutic comprises oxyntomodulin, natriuretic peptide, analogs thereof, or combinations thereof, or pharmaceutically acceptable salts thereof.
16. The compound of any one of claims 12 to 14 wherein the therapeutic comprises SEQ ID NO 11 or SEQ ID NO 12, or pharmaceutically acceptable salts thereof.
17. The compound of claim 12, wherein the therapeutic comprises a monoclonal antibody, an interleukin, an interferon, a protein kinase inhibitor, a hematopoietic growth factor, a protein, a fused protein, oligonucleotide, or combinations thereof, or pharmaceutically acceptable salts thereof.

18. The compound of claim 4, wherein Y_1 and Y_2 comprise an Fc region.
19. The compound of any one of claims 5 to 18, wherein the compound is connected to a single Fc region, or pharmaceutically acceptable salts thereof.
20. The compound of any one of claims 5 to 19, wherein the Fc region comprises an Fc region of a monoclonal antibody, or pharmaceutically acceptable salts thereof.
21. The compound of any one of claims 5 to 20, wherein the Fc region comprises at least a portion of IgA, IgD, IgE, IgG, IgM, or combinations thereof, or pharmaceutically acceptable salts thereof.
22. The compound of any one of claims 5 to 21, wherein the Fc region comprises SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, or SEQ ID NO 6, or pharmaceutically acceptable salts thereof.
23. The compound of claim 22, wherein the Fc region comprises SEQ ID NO 6.
24. The compound of claim 23, wherein Z comprises SEQ ID NO 11 or SEQ ID NO 12.