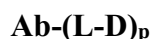


[0006] Central among such immunostimulatory compounds, toll-like receptors (TLRs) play an important role in activating the immune system against invading pathogens and against damaged cells with the potential to become tumorigenic (*see* Kaczanowska, et al., *J. Leukoc. Biol.* 2013; 93(6): 847-863). TLRs are a family of membrane bound proteins that, when activated, recruit adaptor proteins to propagate antigen-induced signals to modify cellular phenotype and activity. As immunostimulatory compounds, TLR agonists have been developed as vaccine adjuvants, to boost production of immune cells that target the desired viral or bacterial antigen in the vaccine. TLRs also recognize endogenous markers of tumorigenesis such as cell death and chronic inflammation and activate an innate immune response to these cells. (*see*, e.g., Ellerman, et al., *Clin. Cancer Res.* 2007; 13: 2836-2848; Hernandez, et al., *Oncogene* 2016; 35: 5931-5941; and Urban-Wojciuk, et al., *Front. Immunol.*, Vol. 10, pp. 2388-2398 (2019). However, due to their immunostimulatory properties, systemic use of TLR agonists may be restricted by dose-limiting toxicities resulting from systemic cytokine induction. *See* Adams, S., *Immunotherapy* 2009; 1(6): 949-964. Thus, there remains a need for targeted immunostimulatory compounds to localize the immune response to the desired cells while minimizing off-target effects.

SUMMARY

[0006a] In an aspect, there is provided an antibody drug conjugate (ADC) having the structure:

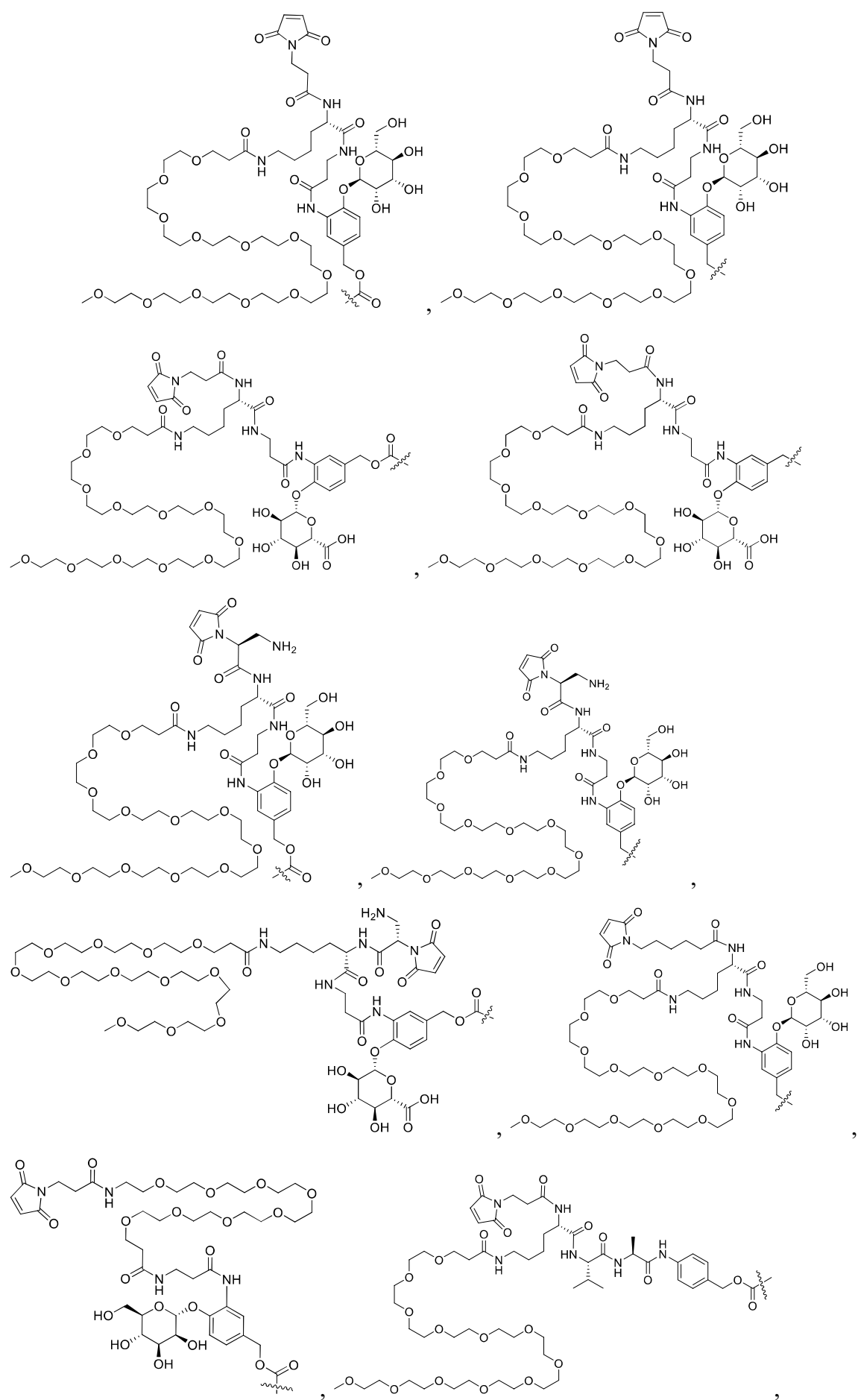


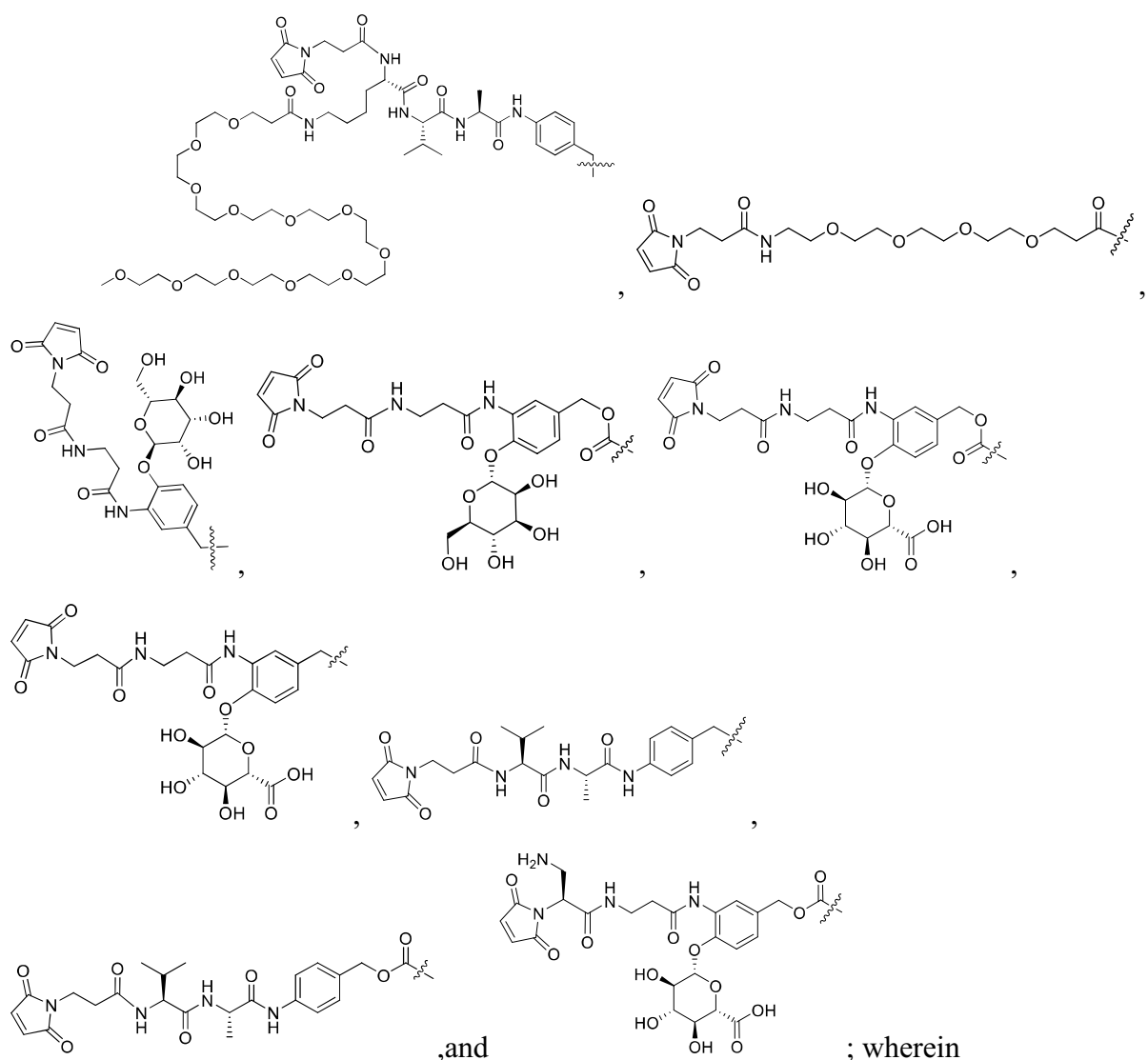
or a pharmaceutically acceptable salt thereof;

wherein:

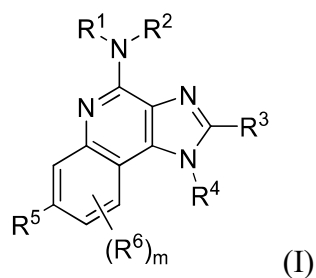
Ab is an antibody;

each L is a linker ; selected from the group consisting of:





$\sim$ represents covalent attachment of L to D;
 wherein each D is conjugated to a linker;
 wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;
 subscript p is an integer from 1 to 16;
 each D has the structure of Formula (I):



or a pharmaceutically acceptable salt thereof;

wherein:

R¹ is (a) the point of covalent attachment to L; or hydrogen;

R^2 is the point of covalent attachment to L; or hydrogen; or

R^3 is selected from the group consisting of C_1 - C_6 alkyl; wherein the C_1 - C_6 alkyl is optionally substituted with C_1 - C_6 alkoxy;

R^4 is the point of covalent attachment to L; hydrogen; or $-C_1$ - C_6 alkyl optionally substituted with:

(ii) $-OR^C$;

(iv) $-NH-S(O_2)R^C$;

(ix) $-NR^D R^E$;

(x) $-[N(C_1-C_6 \text{ alkyl})R^D R^E]^+$;

(xi) $-(\text{phenyl})C_1-C_6 \text{ alkyl}$, wherein the C_1 - C_6 alkyl of the $-(\text{phenyl})C_1-C_6 \text{ alkyl}$ is substituted with 5-10 membered heteroaryl, $-NR^D R^E$, $-[N(C_1-C_6 \text{ alkyl})R^D R^E]^+$;

(xii) phenyl substituted with $-NR^D R^E$;

wherein when R^4 is C_1 - C_6 alkyl, the C_1 - C_6 alkyl or a substituent thereof is optionally further substituted with the point of covalent attachment to L;

R^5 is $-C(=O)OR^F$;

m is 0;

each instance of R^C is hydrogen, or phenyl;

each instance of R^D and R^E is independently selected from the group consisting of: (a) the point of covalent attachment to L; (b) the group consisting of hydrogen and C_1 - C_6 alkyl; and (c) R^D and R^E , together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl;

each instance of R^F is independently selected from the group consisting of hydrogen or C_1 - C_6 alkyl;

wherein each D has only one point of covalent attachment to L; and

wherein Ab comprises an Anti-PD-L1 antibody.

[0006b] In another aspect, there is provided a pharmaceutical composition comprising an ADC as defined above, and a pharmaceutically acceptable excipient.

[0006c] In another aspect, there is provided the use of an antibody drug conjugate (ADC) as defined above, or a pharmaceutically acceptable salt thereof, or a composition as defined above, in the manufacture of a medicament for the treatment of cancer.

[0006d] In another aspect, there is provided an antibody drug conjugate (ADC) as defined above, or a composition as defined above for use in therapy.

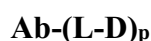
[0007] The present disclosure provides compounds and biomolecular complexes (e.g., antibody-drug conjugates) which elicit cell- and tissue-specific immune responses. As cancer immunosuppression is often localized within microenvironments proximal to the cancerous cells,

targeting payloads to these cancer sites can be essential for affecting immune reactivation. To achieve this end, in certain examples, the present disclosure provides antibody-drug conjugates (ADCs) configured to selectively activate immune responses within tumor microenvironments. In addition to delivering payloads to targeted cancer sites, ADCs of the present disclosure can be configured to release their payloads (e.g., TLR agonists) upon uptake by the cancer or cancer-associated cells, thereby targeting immune activation to cancer sites, and preventing off-target immune activation.

[0008] The ADCs described herein, as well as pharmaceutically acceptable salts thereof, can be configured for uptake by a target cell or tissue. In some examples, an ADC is configured to endocytose upon binding to a membrane bound and/or surface displayed antigen. In such cases, the ADC may target intracellular receptors such as TLR7 or TLR8, which are often primarily localized within endosomes. Endocytosis can be aided by lipophilic groups appended to the ADC, such as PEGylated or neutral and nonpolar peptidic linkers.

[0009] In addition to targeting, release of an ADC drug unit can be controlled such that the release occurs at a designated site (e.g., within a cell targeted by the antibody). As a linker (L) cleavable group can be configured for cleavage within particular physiological conditions or by specific enzymes, release of the Drug Unit can be limited primarily to the target site. Accordingly, the biological effects of the Drug Unit (such as immunostimulatory effects) can be localized to a target site. Alternatively, the Drug Unit can be configured to remain attached to the antibody, or a portion of the antibody and/or linker and induce its biological effect while coupled to the antibody.

[0010] Examples of the present disclosure provide an antibody drug conjugate (ADC) having the structure:



or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

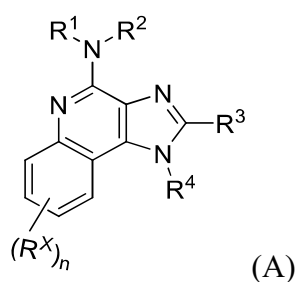
each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

subscript p is an integer from 1 to 16;

each D has the structure of Formula (A):



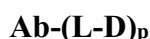
or a pharmaceutically acceptable salt thereof;

wherein:

R¹ is (a) the point of covalent attachment to L; or (b) selected from the group consisting of hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkanoyl, C₁-C₆ alkoxycarbonyl, C₁-C₆ alkoxythiocarbonyl, C₁-C₆ carbamoyl, C₁-C₆ amidine, C₁-C₆ sulfone, C₁-C₆ thione, C₃-C₆ cycloalkyl, phenyl, and 5-10 membered heteroaryl; wherein each C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkanoyl, C₁-C₆ alkoxycarbonyl, C₁-C₆ alkoxythiocarbonyl, C₁-C₆ carbamoyl, C₁-C₆ amidine, C₁-C₆ sulfone, C₁-C₆ thione, C₃-C₆ cycloalkyl, phenyl, and 5-10 membered

second sequence is SEQ ID NO: 234; the first sequence is SEQ ID NO: 241 and the second sequence is SEQ ID NO: 242; the first sequence is SEQ ID NO: 249 and the second sequence is SEQ ID NO: 250; the first sequence is SEQ ID NO: 629 and the second sequence is SEQ ID NO: 630; the first sequence is SEQ ID NO: 637 and the second sequence is SEQ ID NO: 638; the first sequence is SEQ ID NO: 645 and the second sequence is SEQ ID NO: 646; the first sequence is SEQ ID NO: 653 and the second sequence is SEQ ID NO: 654; the first sequence is SEQ ID NO: 661 and the second sequence is SEQ ID NO: 662; the first sequence is SEQ ID NO: 669 and the second sequence is SEQ ID NO: 670; the first sequence is SEQ ID NO: 677 and the second sequence is SEQ ID NO: 678; the first sequence is SEQ ID NO: 685 and the second sequence is SEQ ID NO: 686; the first sequence is SEQ ID NO: 693 and the second sequence is SEQ ID NO: 694; the first sequence is SEQ ID NO: 701 and the second sequence is SEQ ID NO: 702; the first sequence is SEQ ID NO: 703 and the second sequence is SEQ ID NO: 704; the first sequence is SEQ ID NO: 711 and the second sequence is SEQ ID NO: 712; the first sequence is SEQ ID NO: 713 and the second sequence is SEQ ID NO: 714; the first sequence is SEQ ID NO: 715 and the second sequence is SEQ ID NO: 716; or the first sequence is SEQ ID NO: 1027 and the second sequence is SEQ ID NO: 1028. In some cases, the first sequence is SEQ ID NO: 19 and the second sequence is SEQ ID NO: 20. In some cases, the heavy chain variable region has at least 90% sequence identity to the first sequence and the light chain variable region has at least 90% sequence identity to the second sequence. In some cases, the heavy chain variable region has at least 98% sequence identity to the first sequence and the light chain variable region has at least 98% sequence identity to the second sequence

[0011] Certain examples of the present disclosure provide an antibody drug conjugate (ADC) having the structure:



or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

each L is a linker;

wherein each D is conjugated to a linker;

wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

subscript p is an integer from 1 to 16;

each D has the structure of Formula (A):

alkanoyl, C₁-C₆ alkoxy carbonyl, C₁-C₆ alkanoyloxy, C₃-C₆ cycloalkyl, phenyl, 5-10 membered heteroaryl, and 3-12 membered heterocycle is optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halogen, sulfhydryl, cyano, oxo, oxiranyl, C₃-C₈ cycloalkyl, phenyl, 5-10 membered heteroaryl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, and -NR^AR^B;

R⁴ is selected from the group consisting of: the point of covalent attachment to L; hydrogen; -OR^C; -S(=O)₂R^C; -C(=O)NR^DR^E; -C(=O)OR^C; -C(=O)SR^C; -C(=S)R^C; -PO₃R^C; and -C₁-C₆ alkyl optionally substituted with:

- (i) 1-3 independently selected halogen;
- (ii) -OR^C;
- (iii) -SR^C;
- (iv) -NH-S(O₂)R^C;
- (v) -OC(=O)R^C;
- (vi) -CO₂H;
- (vii) C₁-C₆ alkoxy carbonyl;
- (viii) -C(=O)NR^DR^E;
- (ix) -NR^DR^E;
- (x) -[N(C₁-C₆ alkyl)R^DR^E]⁺;
- (xi) -(phenyl)C₁-C₆ alkyl, wherein the C₁-C₆ alkyl of the -(phenyl)C₁-C₆ alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, -NR^DR^E, -[N(C₁-C₆ alkyl)R^DR^E]⁺, or 1-3 independently selected halogen;
- (xii) phenyl substituted with halogen, hydroxyl, C₁-C₆ alkoxy, -NR^DR^E, -C(=O)NR^DR^E or -CO₂H;
- (xiii) -(5-10 membered heteroaryl)C₁-C₆ alkyl, wherein the C₁-C₆ alkyl of the -(5-10 membered heteroaryl)C₁-C₆ alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, -[N(C₁-C₆ alkyl)R^DR^E]⁺, or 1-3 independently selected halogen; or
- (xiv) 5-10 membered heteroaryl optionally substituted with halogen, -NR^DR^E, C₁-C₆ alkoxy, -C(=O)NR^DR^E, -SR^C, (C₁-C₆)alkoxy carbonyl, or -CO₂H;

wherein when R⁴ is C₁-C₆ alkyl, the C₁-C₆ alkyl or a substituent thereof is optionally further substituted with the point of covalent attachment to L;

each R^X is independently selected from the group consisting of (a) the point of covalent attachment to L; and (b) the group consisting of hydrogen, -C(=O)OR^F, -C(=O)NR^GR^H, -S(O₂)NR^GR^H, -N(R^I)-C(=O)R^J, -N(R^I)-S(O₂)R^K, halogen, hydroxyl, nitro, cyano, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkanoyl, C₁-C₆ alkanoyloxy, C₁-C₆

(xi) -(phenyl)C₁-C₆ alkyl, wherein the C₁-C₆ alkyl of the -(phenyl)C₁-C₆ alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, $-\text{[N(C}_1\text{-C}_6\text{ alkyl)R}^{\text{D}}\text{R}^{\text{E}}]^+$.

[0179] In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R⁴ is C₁-C₆ alkyl optionally substituted with: (i) 1-3 independently selected halogen; (ii) -O(C₁-C₆ alkyl); (ix) -NR^DR^E, wherein the R^D of -NR^DR^E is C₁-C₆ alkyl; (x) $-\text{[N(C}_1\text{-C}_6\text{ alkyl)R}^{\text{D}}\text{R}^{\text{E}}]^+$; (xi) -(phenyl)C₁-C₆ alkyl, wherein the C₁-C₆ alkyl of the -(phenyl)C₁-C₆ alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, $-\text{[N(C}_1\text{-C}_6\text{ alkyl)R}^{\text{D}}\text{R}^{\text{E}}]^+$; or (xii) phenyl substituted with halogen, hydroxyl, C₁-C₆ alkoxy, -NR^DR^E, -C(=O)NR^DR^E or -CO₂H. In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R⁴ is C₁-C₆ alkyl substituted with: (ii) -O(C₁-C₆ alkyl); (ix) -NR^DR^E, wherein the R^D of -NR^DR^E is C₁-C₆ alkyl; (x) $-\text{[N(C}_1\text{-C}_6\text{ alkyl)R}^{\text{D}}\text{R}^{\text{E}}]^+$; (xi) -(phenyl)C₁-C₆ alkyl, wherein the C₁-C₆ alkyl of the -(phenyl)C₁-C₆ alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, $-\text{[N(C}_1\text{-C}_6\text{ alkyl)R}^{\text{D}}\text{R}^{\text{E}}]^+$; or (xii) phenyl substituted with halogen, hydroxyl, C₁-C₆ alkoxy, -NR^DR^E, -C(=O)NR^DR^E or -CO₂H. In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R⁴ is C₁-C₆ alkyl substituted with: (ix) -NR^DR^E, wherein the R^D of -NR^DR^E is C₁-C₆ alkyl; or (xi) -(phenyl)C₁-C₆ alkyl, wherein the C₁-C₆ alkyl of the -(phenyl)C₁-C₆ alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, $-\text{[N(C}_1\text{-C}_6\text{ alkyl)R}^{\text{D}}\text{R}^{\text{E}}]^+$.

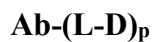
[0180] In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R⁴ is -C(=O)NR^DR^E; -C(=O)OR^C; -C(=O)SR^C; -C(=S)R^C; or C₁-C₆ alkyl optionally substituted with: (i) 1-3 independently selected halogen; (ii) -OR^C; (iii) -SR^C; (iv) -NH-S(O₂)R^C; (v) -OC(=O)R^C; (vi) -CO₂H; (vii) -C₁-C₆ alkoxycarbonyl; (viii) -C(=O)NR^DR^E; (ix) -NR^DR^E; (x) $-\text{[N(C}_1\text{-C}_6\text{ alkyl)R}^{\text{D}}\text{R}^{\text{E}}]^+$; (xi) -(phenyl)C₁-C₆ alkyl, wherein its C₁-C₆ alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, -NR^DR^E, $-\text{[N(C}_1\text{-C}_6\text{ alkyl)R}^{\text{D}}\text{R}^{\text{E}}]^+$, or 1-3 independently selected halogen; (xii) phenyl substituted with halogen, hydroxyl, C₁-C₆ alkoxy, -NR^DR^E, -C(=O)NR^DR^E or -CO₂H; (xiii) -(5-10 membered heteroaryl)C₁-C₆ alkyl, wherein the C₁-C₆ alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, $-\text{[N(C}_1\text{-C}_6\text{ alkyl)R}^{\text{D}}\text{R}^{\text{E}}]^+$, or 1-3 independently selected halogen; or (xiv) 5-10 membered heteroaryl optionally substituted with halogen, -NR^DR^E, C₁-C₆ alkoxy, -C(=O)NR^DR^E, -SR^C, (C₁-C₆)alkoxycarbonyl, or -CO₂H; wherein when R⁴ is C₁-C₆ alkyl, the C₁-C₆ alkyl or a substituent thereof is optionally further substituted with the point of covalent attachment to L.

[0181] In some cases of Formulae (A), (I), (II), (IIa), (IV), (V), (VI), (VII), and (VIII), R⁴ is C₁-C₆ alkyl optionally substituted with: (ii) -OR^C; (iii) -SR^C; (iv) -NH-S(O₂)R^C; (ix) -NR^DR^E; (xi) -(phenyl)C₁-C₆ alkyl, wherein its C₁-C₆ alkyl is substituted with 5-10 membered heteroaryl, 5-10 membered heterocycle, -NR^DR^E, or $-\text{[N(C}_1\text{-C}_6\text{ alkyl)R}^{\text{D}}\text{R}^{\text{E}}]^+$; or (xii) phenyl substituted with halogen, hydroxyl, C₁-C₆ alkoxy, -NR^DR^E, -C(=O)NR^DR^E or -CO₂H.

CLAIMS

WHAT IS CLAIMED IS:

1. An antibody drug conjugate (ADC) having the structure:

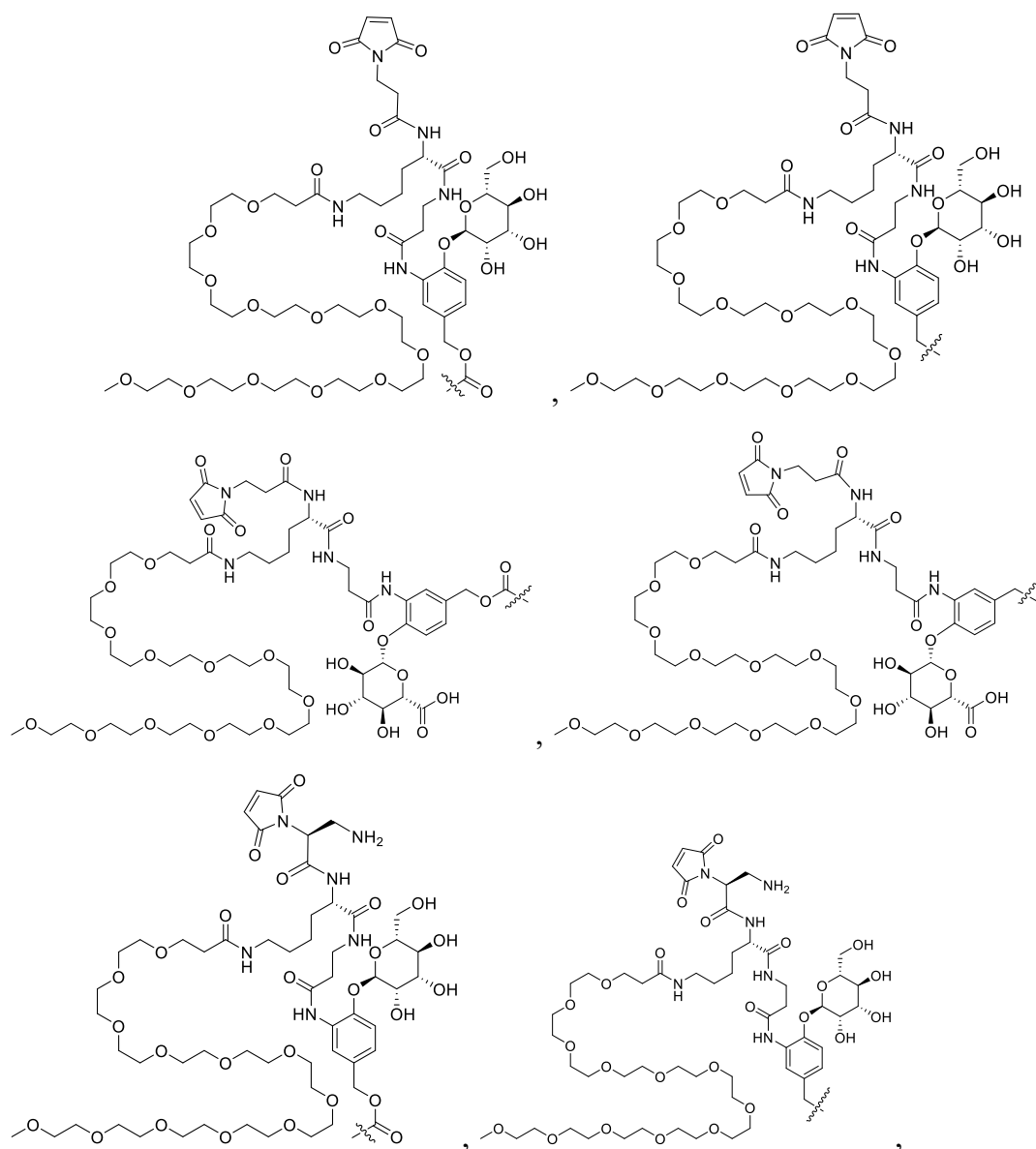


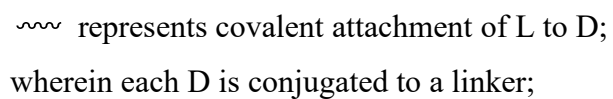
or a pharmaceutically acceptable salt thereof;

wherein:

Ab is an antibody;

each L is a linker ; selected from the group consisting of:

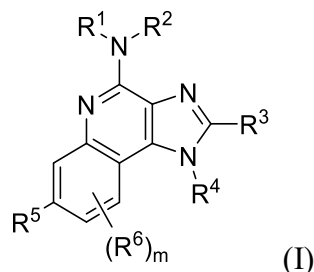




wherein each L is covalently attached to an amino acid, N-terminal tag, C-terminal tag, or post-translational modification of Ab;

subscript p is an integer from 1 to 16;

each D has the structure of Formula (I):



or a pharmaceutically acceptable salt thereof;

wherein:

R¹ is (a) the point of covalent attachment to L; or hydrogen;

R² is the point of covalent attachment to L; or hydrogen; or

R³ is selected from the group consisting of C₁-C₆ alkyl; wherein the C₁-C₆ alkyl is optionally substituted with C₁-C₆ alkoxy;

R⁴ is the point of covalent attachment to L; hydrogen; or -C₁-C₆ alkyl optionally substituted with:

(ii) -OR^C;

(iv) -NH-S(O₂)R^C;

(ix) -NR^DR^E;

(x) -[N(C₁-C₆ alkyl)R^DR^E]⁺;

(xi) -(phenyl)C₁-C₆ alkyl, wherein the C₁-C₆ alkyl of the -(phenyl)C₁-C₆ alkyl is substituted with 5-10 membered heteroaryl, -NR^DR^E, -[N(C₁-C₆ alkyl)R^DR^E]⁺;

(xii) phenyl substituted with -NR^DR^E;

wherein when R⁴ is C₁-C₆ alkyl, the C₁-C₆ alkyl or a substituent thereof is optionally further substituted with the point of covalent attachment to L;

R⁵ is -C(=O)OR^F;

m is 0;

each instance of R^C is hydrogen, or phenyl;

each instance of R^D and R^E is independently selected from the group consisting of: (a) the point of covalent attachment to L; (b) the group consisting of hydrogen and C₁-C₆ alkyl; and (c) R^D and R^E, together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl;

each instance of R^F is independently selected from the group consisting of hydrogen or C₁-C₆ alkyl;

wherein each D has only one point of covalent attachment to L; and

wherein Ab comprises an Anti-PD-L1 antibody.

2. The antibody drug conjugate of claim 1 wherein the Ab comprises a heavy chain variable region having at least 80% sequence identity to a first sequence and a light chain variable region having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 3 and the second sequence is SEQ ID NO: 5.

3. The ADC of claim 2 wherein the heavy chain variable region has at least 90% sequence identity to the first sequence and the light chain variable region has at least 90% sequence identity to the second sequence.

4. The ADC of claim 2 or claim 3, wherein the heavy chain variable region has at least 98% sequence identity to the first sequence and the light chain variable region has at least 98% sequence identity to the second sequence.

5. The antibody drug conjugate of claim 1 or a pharmaceutically acceptable salt thereof; wherein the Ab comprises a heavy chain having at least 80% sequence identity to a first sequence and a light chain having at least 80% sequence identity to a second sequence, wherein: the first sequence is SEQ ID NO: 19 and the second sequence is SEQ ID NO: 20.

6. The ADC of claim 5, wherein the heavy chain has at least 90% sequence identity to the first sequence and the light chain has at least 90% sequence identity to the second sequence.

7. The ADC of claim 5 or claim 6, wherein the heavy chain has at least 98% sequence identity to the first sequence and the light chain has at least 98% sequence identity to the second sequence.

8. The antibody drug conjugate of claim 1 or a pharmaceutically acceptable salt thereof; wherein the Ab comprises a CDR-H1 comprising at least 80% sequence identity to a first sequence, a CDR-H2 comprising at least 80% sequence identity to a second sequence, a CDR-H3 comprising at least 80% sequence identity to a third sequence, a CDR-L1 comprising at least 80% sequence identity to a fourth sequence, a CDR-L2 comprising at least 80% sequence identity to a fifth sequence, and a CDR-L3 comprising at least 80% sequence identity to a sixth sequence, wherein the first, second, third, fourth, fifth, and sixth sequences are: SEQ ID NO: 13, 14, 15, 16, 17, and 18, respectively.

9. The ADC of claim 8, wherein the CDR-H1 comprises at most one mutation relative to the first sequence, the CDR-H2 comprises at most one mutation relative to the second sequence, the

CDR-H3 comprises at most one mutation relative to the third sequence, the CDR-L1 comprises at most one mutation relative to the fourth sequence, the CDR-L2 comprises at most one mutation relative to the fifth sequence, and the CDR-L3 comprises at most one mutation relative to the sixth sequence.

10. The ADC of claim 8 or claim 9, wherein the first, second, third, fourth, fifth, and sixth sequences are: SEQ ID NO: 13, 14, 15, 16, 17, and 18, respectively.

11. The ADC of any one of claims 1-10, wherein Ab comprises an effector function-diminishing mutation.

12. The ADC of claim 11, wherein the effector function diminishing mutation is selected from the group consisting of L234A/L235A, D265A/N297A, D270A, K322A, P329A, P329G, and combinations thereof.

13. The ADC of claim 11 or 12, wherein the effector function diminishing mutation is L234A/L235A.

14. The ADC of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein

R³ is C₁-C₆ alkyl;

R⁴ is (a) the point of covalent attachment to L; or C₁-C₆ alkyl optionally substituted with:

(ii) -OR^C;

(ix) -NR^DR^E;

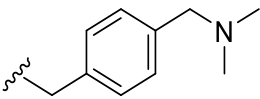
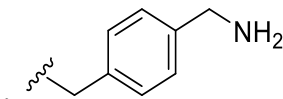
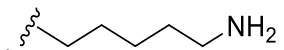
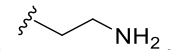
(xi) -(phenyl)C₁-C₆ alkyl, wherein C₁-C₆ alkyl of the -(phenyl)C₁-C₆ alkyl is substituted with -NR^DR^E;

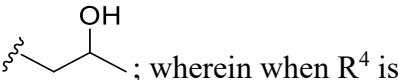
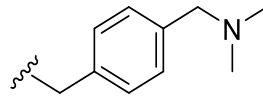
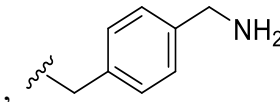
wherein when R⁴ is C₁-C₆ alkyl, the C₁-C₆ alkyl, or a substituent thereof, may be further substituted with the point of covalent attachment to L; and

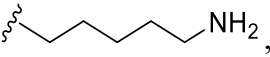
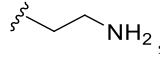
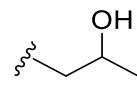
R^C is hydrogen.

15. The ADC of any one of claims 1-13, or a pharmaceutically acceptable salt thereof; wherein

L is selected from the group consisting of:

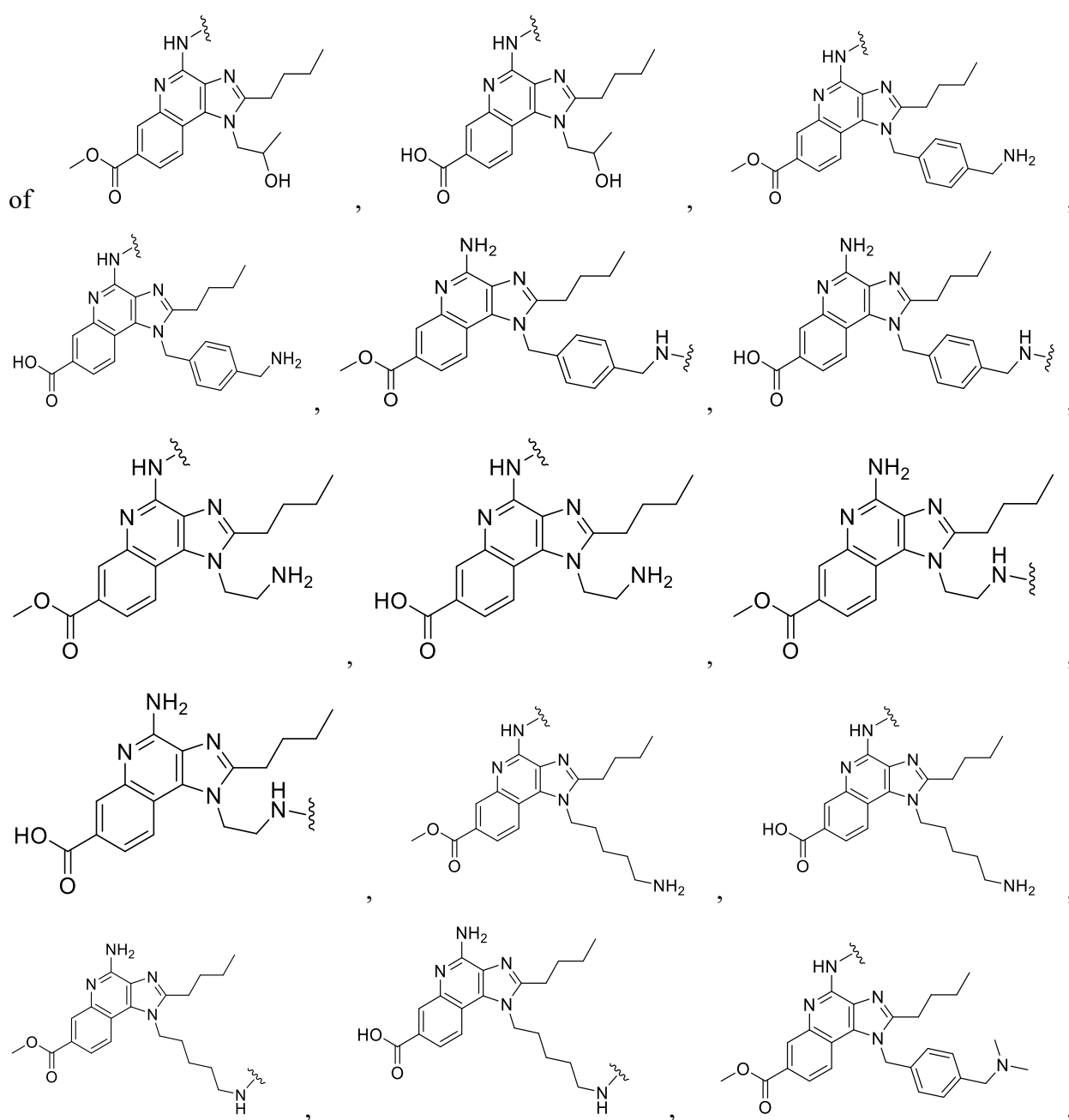





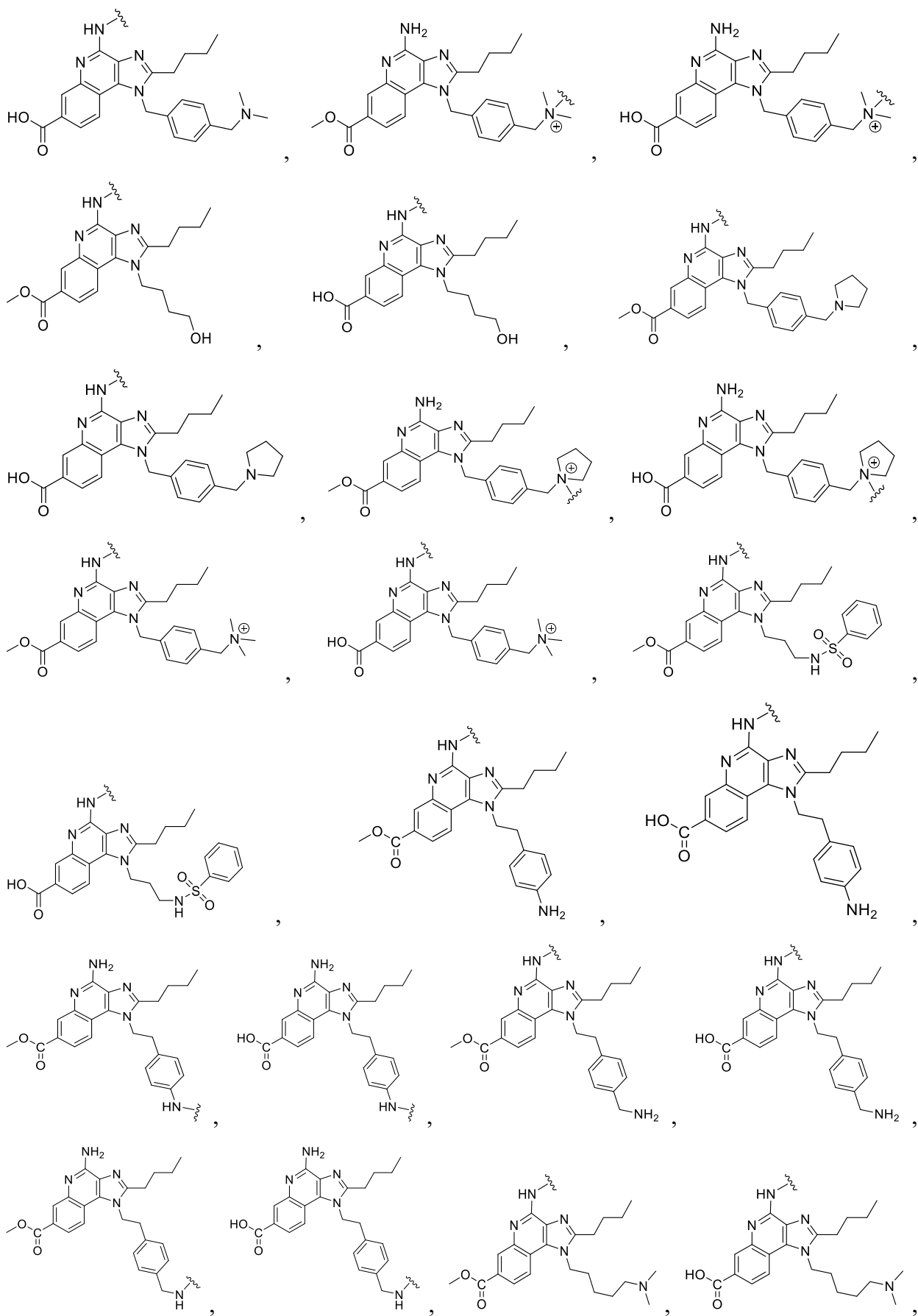

 ; wherein when R⁴ is 

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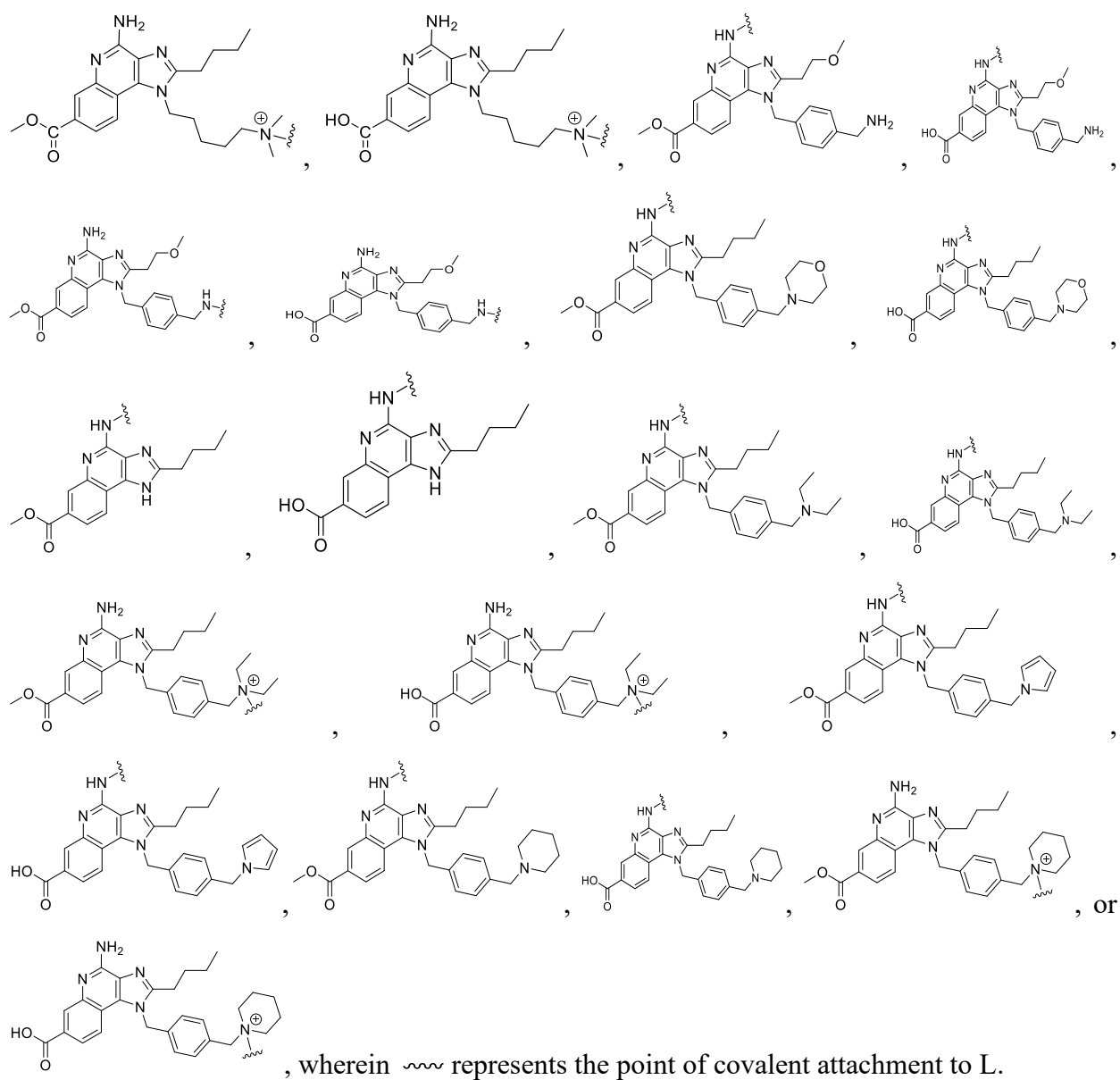



 , the alkyl or a substituent thereof is optionally further substituted with the point of covalent attachment to L; and

 R^F is selected from the group consisting of hydrogen, and methyl.

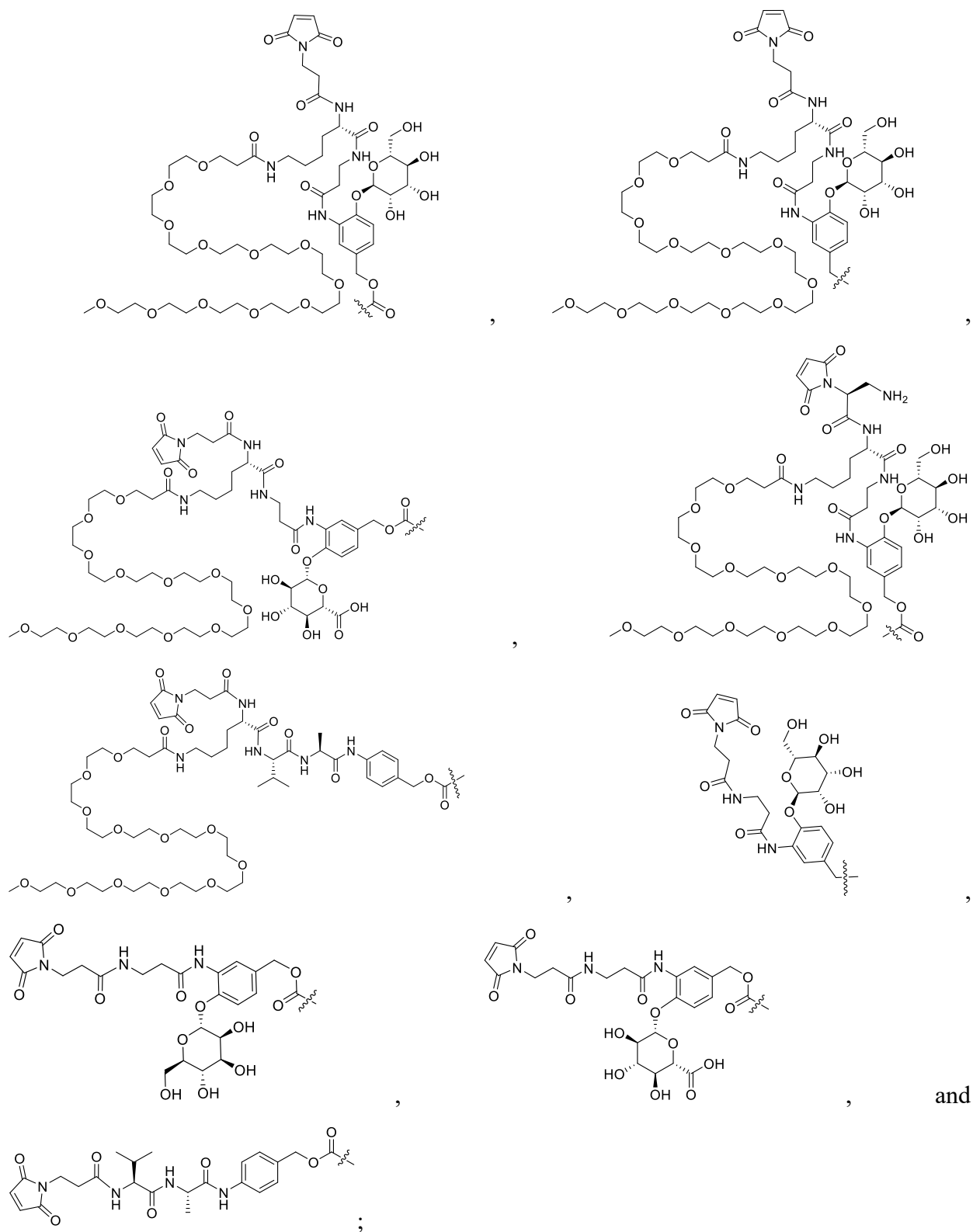
16. The ADC of any one of claims 1-13, wherein each D is selected from the group consisting





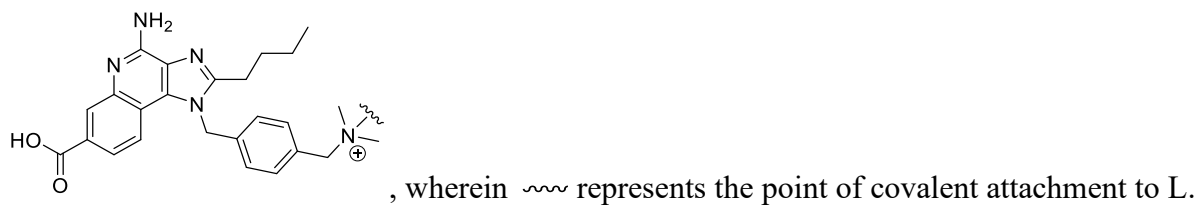


17. The ADC of claim 16, wherein and L is selected from the group consisting of;

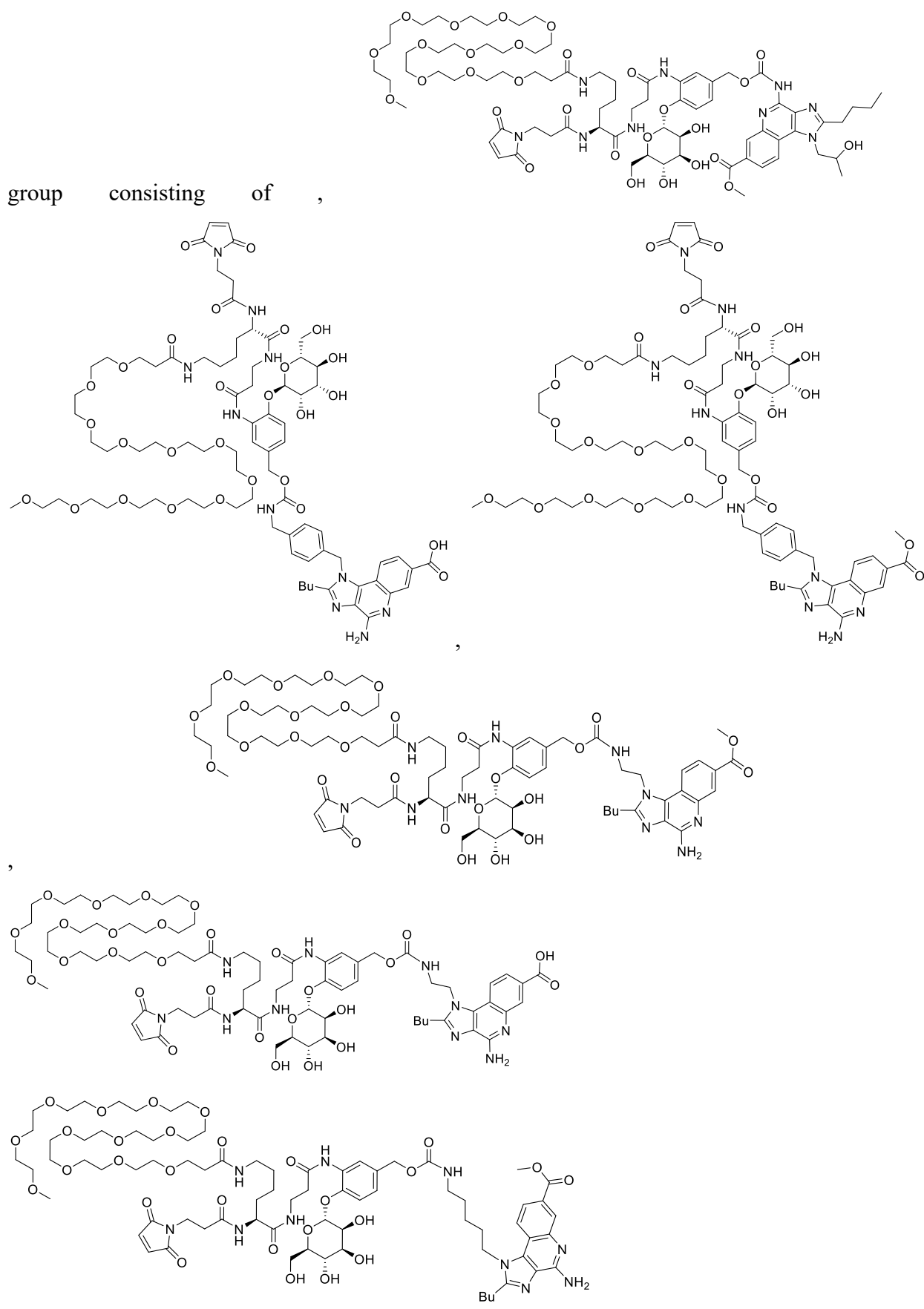


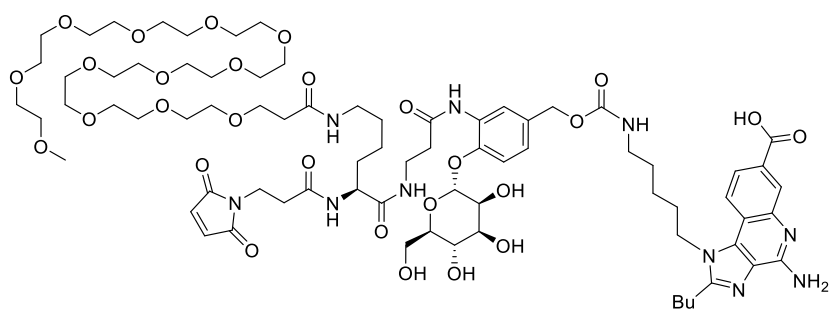
CCCC1=NN(C(C)CO)C2=C1C(=C3C=CC(=C2)C(=O)OC)N=C3NCCCC1=CN2C(=N1)c3cc(N)nc3c2c4ccc(cc4)C(=O)OC5=CC=C(C=C5)CN(C)C[N+](C)(C)C

or

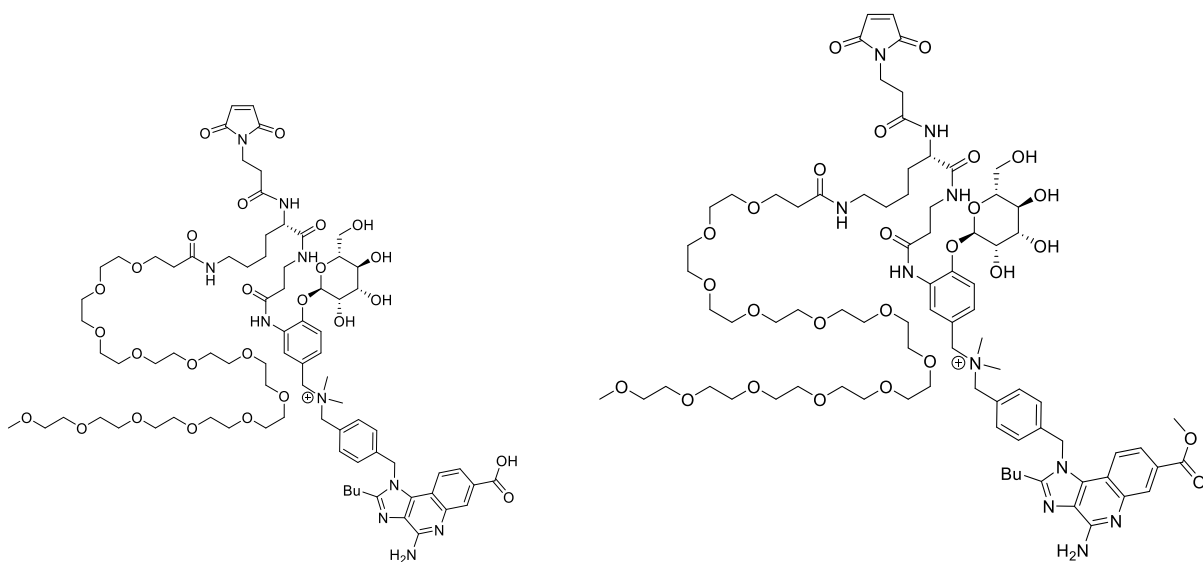


19. The ADC of any one of claims 1-13, wherein each L-D of the Ab-(L-D)_p is selected from the

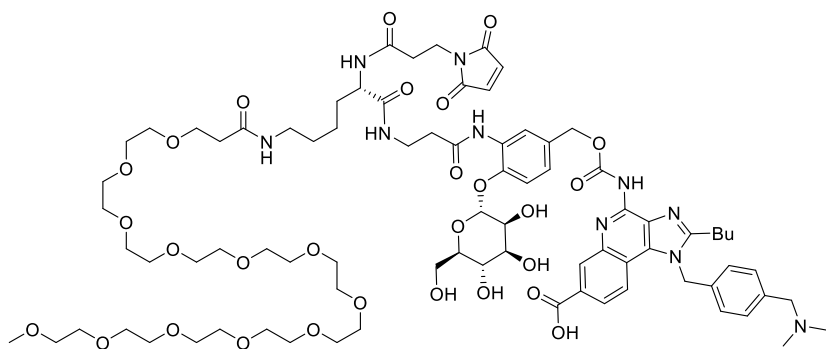




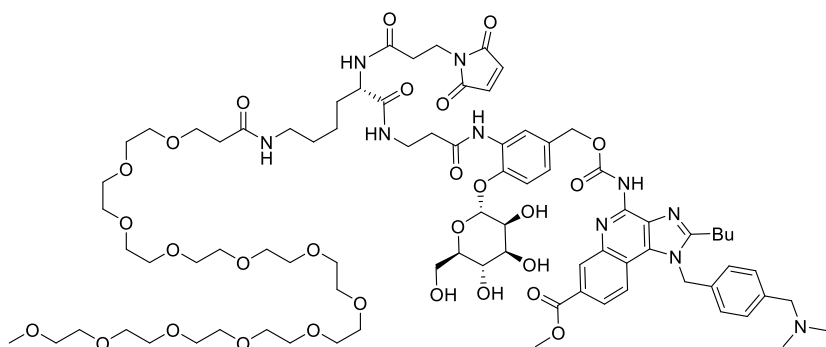
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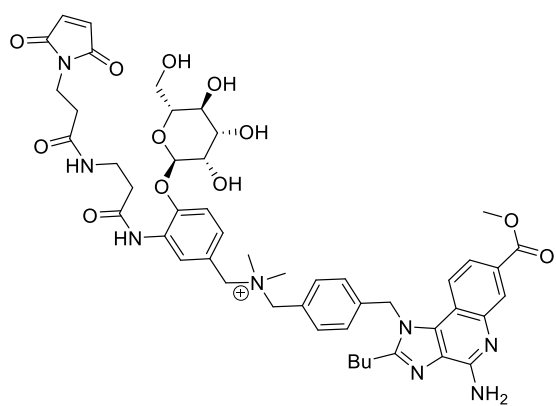
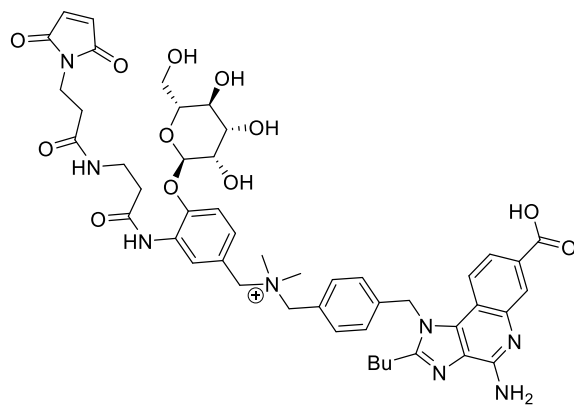
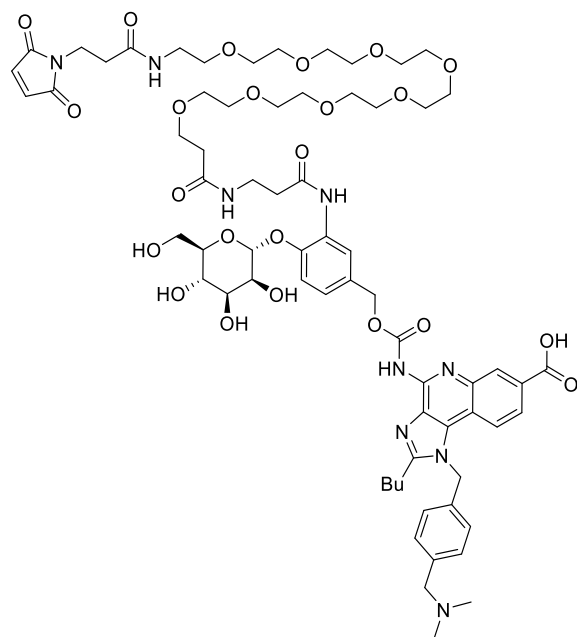
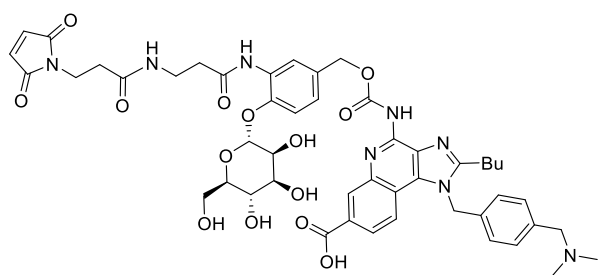
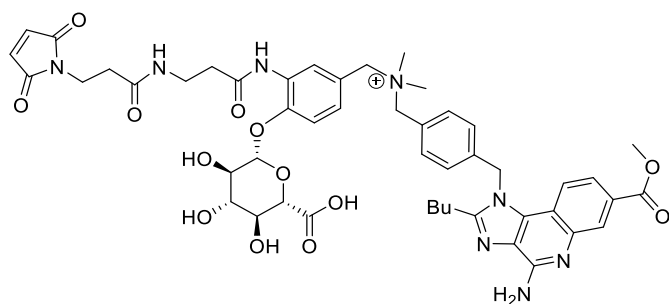
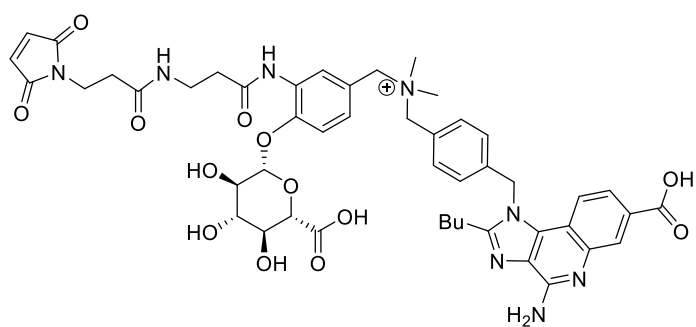
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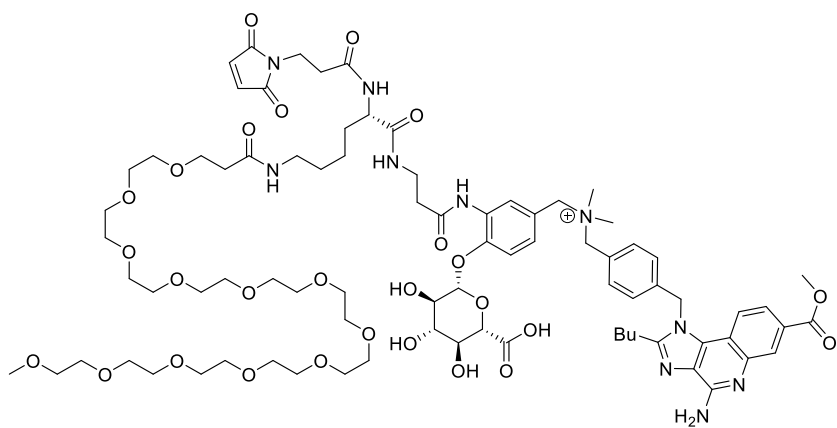


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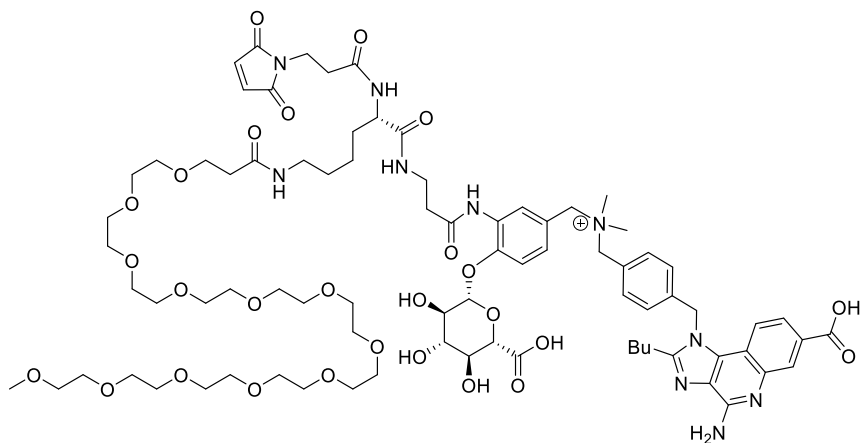


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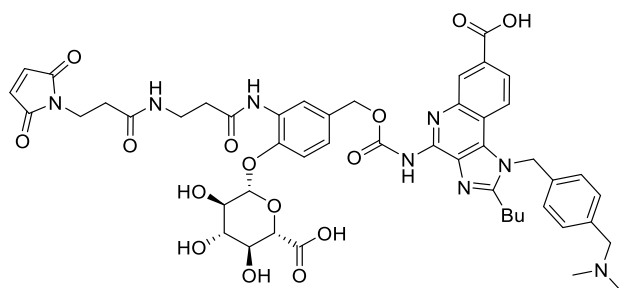




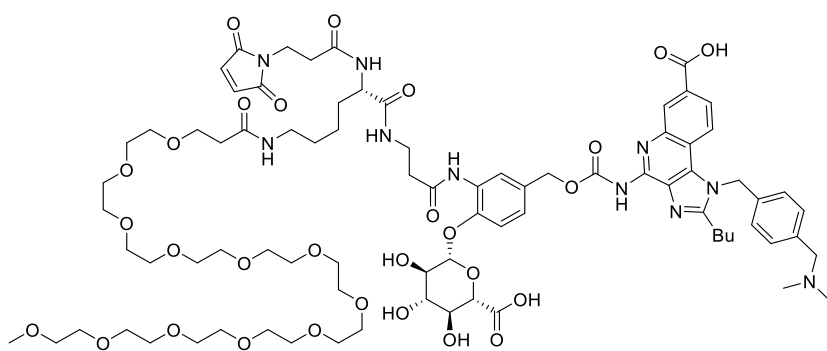
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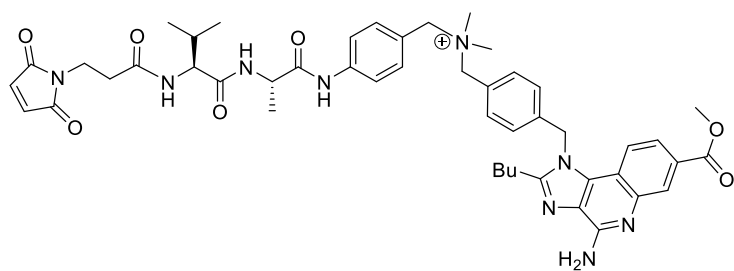
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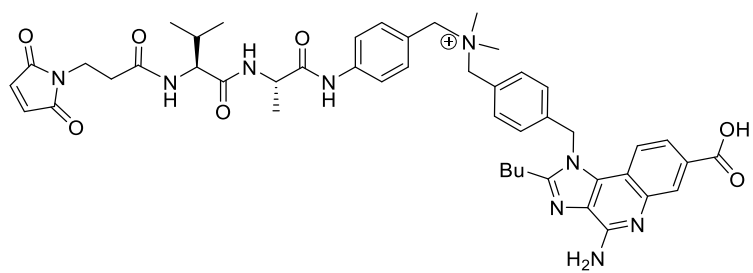
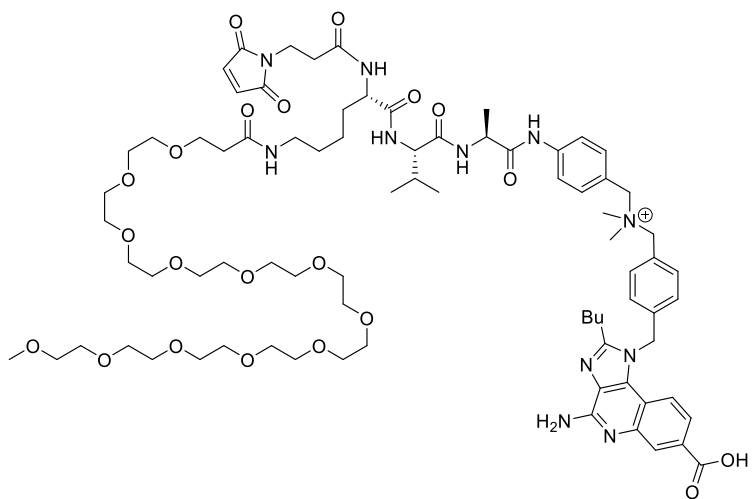
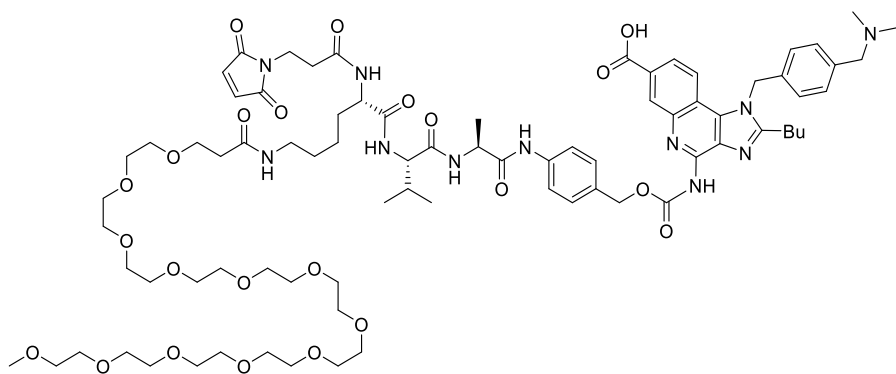
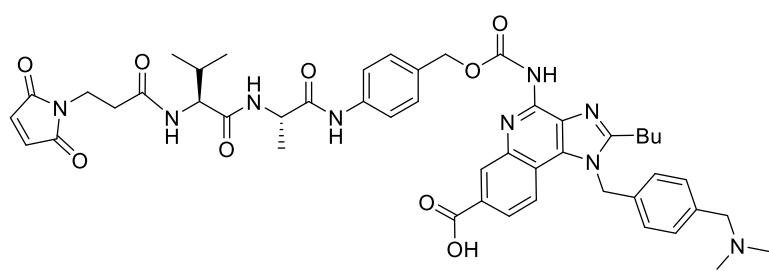
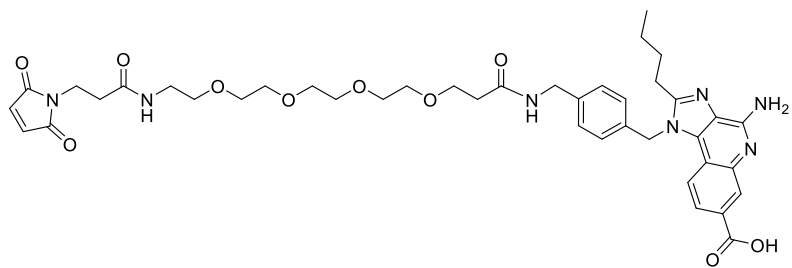
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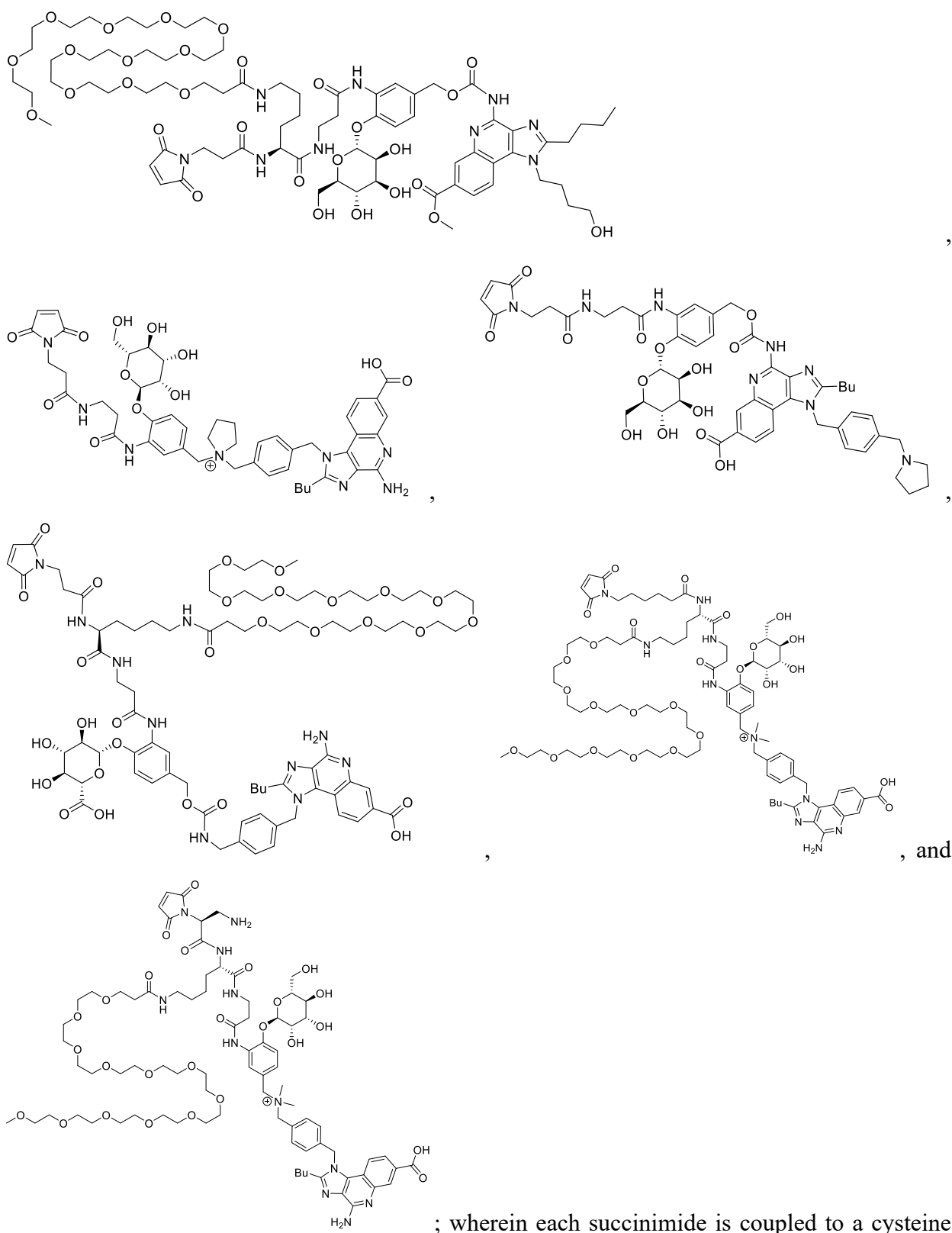


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; wherein each succinimide is coupled to a cysteine of the Ab.

20. The ADC of any one of claims 16-19, wherein Ab comprises a heavy chain with at least 80% sequence identity to SEQ ID NO: 3 and a light chain with at least 80% sequence identity to SEQ ID NO: 5.

21. A pharmaceutical composition comprising an ADC according to any one of claims 1-21, and a pharmaceutically acceptable excipient.
22. Use of an antibody drug conjugate (ADC) according to any one of claims 1-20, or a pharmaceutically acceptable salt thereof, or a composition according to claim 21, in the manufacture of a medicament for the treatment of cancer.
23. The use of claim 22, wherein the ADC is configured to internalize within a cell.
24. The use of claim 23, wherein the ADC targets a cancer-associated antigen.
25. The use of claim 24, wherein the cell expresses the cancer-associated antigen.
26. The use of claim 24, wherein the cell does not express the cancer-associated antigen.
27. The use of any one of claims 23-26, wherein the cell is an immune cell.
28. The use of claim 27, wherein the immune cell is a CD8⁺ T-cell, a CD4⁺ T-Cell, a T-regulatory cell, a macrophage, or a natural killer cell.
29. The use of claim 27 or 28, wherein the immune cell is a macrophage.
30. The use of any one of claims 27-29, wherein the immune cell expresses TLR7, TLR8, or TLR7 and TLR8.
31. The use of claim 27-30, wherein the cancer does not express TLR7 or TLR8.
32. The use of any one of claims 27-31, wherein the immune cell expresses a surface protein which binds to the cancer-associated antigen.
33. The use of any one of claims 23-32, wherein the internalizing comprises endocytosis or micropinocytosis.
34. The use of claim 22-33, wherein the D of the ADC is configured to bind to toll-like receptor 7, toll-like receptor 8, or toll-like receptor 7 and toll-like receptor 8.
35. The use of any one of claims 22-34, wherein the linker (L) of the ADC is configured to undergo cleavage subsequent to internalizing within the immune cell.
36. The use of any one of claims 22-35, wherein the cancer does not express CD4, CD8, an immune checkpoint, or a combination thereof.
37. The use of claim 36, wherein less than about 10%, less than about 7.5%, 5%, less than about 4.5%, less than about 4%, less than about 3.5%, less than about 3%, less than about 2.5%, less than about 2%, less than about 1.5%, less than about 1%, or less than about 0.5% of cancer

cells of the cancer express the CD4, the CD8, the immune checkpoint, or the combination thereof.

38. The use of claim 36 or 37, wherein the CD4 expression, the CD8 expression, the immune checkpoint expression, or the combination thereof is membrane expression.

39. The use of any one of claims 36-38, wherein the immune checkpoint is PDL1, PD1, CTLA-4, B7H4, B7H3, TIGIT, TIM-3, VISTA, GITR/GITRL, CD80/CD86, CD155, PDL1, PDL2, galectin 9, CD40, OX40L, 4-1BB/4-1BBL, ICOS/ICOSL, CD70, or a combination thereof.

40. The use of any one of claims 36-39, wherein the immune checkpoint is PDL1.

41. The use of any one of claims 36-40, wherein the expression is in cancer cells derived from a tumor.

42. The use of claim 41, wherein the cancer cells derived from the tumor do not comprise tumor-associated immune cells.

43. The use of claim 41 or claim 42, wherein the cancer cells derived from the tumor comprise stromal cells from the tumor.

44. The use of any one of claims 36-43, wherein the determining comprises flow cytometry, immunohistochemistry, immunocytochemistry, immunofluorescence, immunoprecipitation, western blotting, ELISA, or mRNA analysis.

45. The use of claim 44, wherein the mRNA analysis comprises quantitative polymerase chain reaction (qPCR), reverse transcription qPCR (RT-qPCR), RNA sequencing, microarray analysis, in situ hybridization, or sequential gene expression analysis.

46. An antibody drug conjugate (ADC) according to any one of claims 1-20, or a composition according to claim 21 for use in therapy.