

TITLE OF THE DISCLOSURE

EXATECAN-DERIVED ADC LINKER-PAYLOADS, PHARMACEUTICAL COMPOSITIONS, AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/419,150, filed October 25, 2022, the disclosure of which is incorporated herein by its entirety.

BACKGROUND OF THE DISCLOSURE

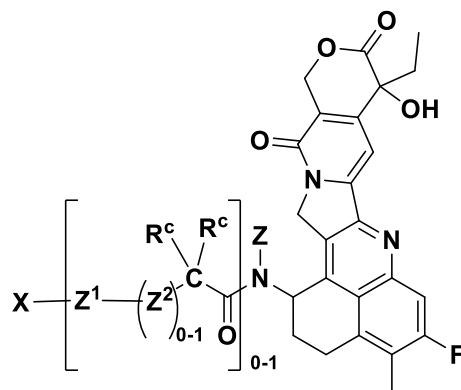
[0002] This disclosure represents a class of linker exatecan (camptothecin)-derived linker-payloads with utility for conjugation to antibodies or other targeting moieties to generate antibody-drug conjugates (ADCs), or other targeting ligand conjugates, for oncology indications. The compounds comprise topoisomerase-1 inhibitors derived from the exatecan scaffold connected to novel linker structures, which, when conjugated to a targeting moiety, are cytotoxic. Documents reporting the use of the camptothecin derivative, exatecan (chemical name: (1S, 9S)-1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':6,7]imidazo[1,2-b]quinoline-10,13(9H,15H)-dione) are disclosed in WO2014057687, US11103593, US9808537, US7091186, US 2010/0062008, WO2015057699, Clinical Cancer Research (2016) 22 (20): 5097-5108, and *Cancer Sci* (2016) 107: 1039-1046. See also WO2022068878, WO2017062271, CN113816969, CN112125915, and US20210353764.

SUMMARY

[0003] Disclosed is a class of linker camptothecin-derived -payload compounds, wherein the linker structures contain a maleimide attached to a peptide linker, with variation on the amino acid sequence, optional incorporation of PEG units, and terminating with a hemiaminal or p-aminobenzyl carbamate (PABC) connection to a camptothecin-derived payload. Utility of these linker camptothecin-derived payload compounds is demonstrated by conjugation to cysteine residues in various targeting moieties, such as antibodies, to yield antibody drug conjugates (ADCs), which show favorable physical-chemical properties and high target-mediated potency. Thus, another example of the disclosure is realized by ADCs disclosed herein. The linker-

payloads of the present disclosure provide for potent and novel ADCs active across multiple cancer cell lines, and thereby demonstrate broad utility to be conjugated to several antibodies or other targeting moieties while still retaining favorable properties and efficacy. Exemplary ADCs from the linker-payloads described herein are also detailed.

[0003a] In a first aspect of the present disclosure, there is provided a compound having a structural Formula I, or salt thereof:



I

wherein:

Z is selected from hydrogen and $-\text{CH}_2\text{C}(\text{R}^x)(\text{R}^y)\text{CHF}_2$;

Z^1 is selected from $-\text{NH}-$ and $-\text{O}-$;

Z^2 is absent or selected from $-\text{CR}^b\text{R}^b-$, $-\text{CH}_2\text{CR}^b\text{R}^b-$, and $-\text{CR}^b\text{R}^b\text{CH}_2-$;

each R^b is independently selected from hydrogen, $-\text{C}_{1-6}$ alkyl, and hydroxyl;

or two adjacent R^b combine to form spirocycloalkyl;

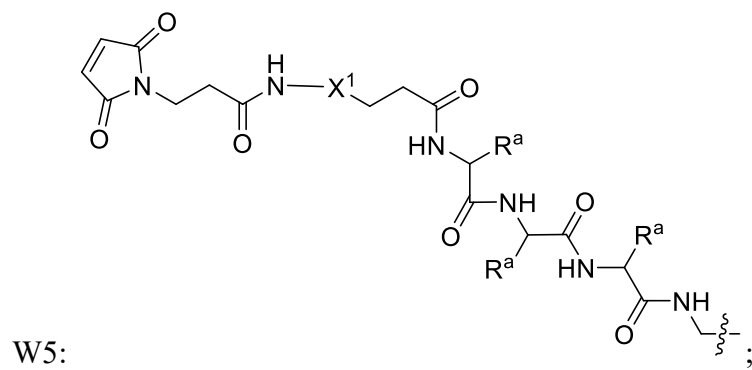
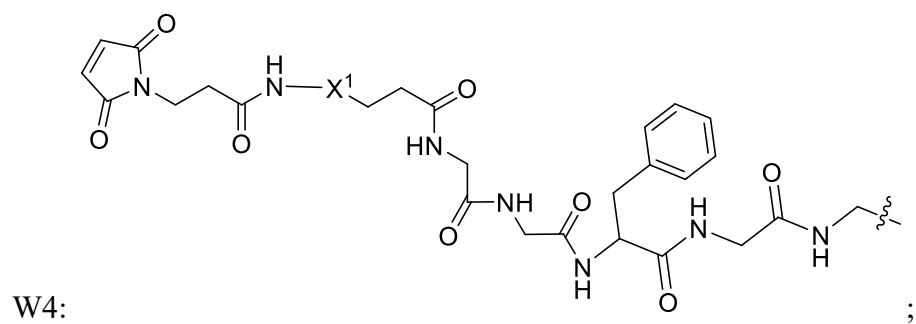
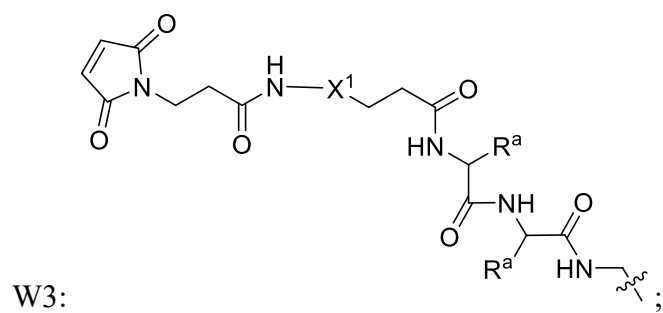
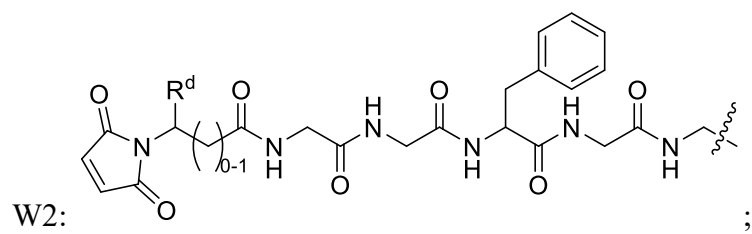
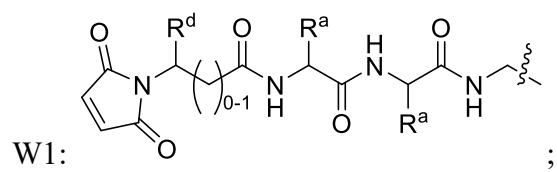
each R^c is independently selected from hydrogen, $-\text{C}_{1-6}$ alkyl, halogen, and hydroxyl;

or two adjacent R^c combine to form spirocycloalkyl;

R^x and R^y are independently selected from hydrogen, C_{1-6} alkyl, C_{1-3} haloalkyl, halogen, hydroxyl, and $-\text{C}_{1-6}$ alkyl-OH;

or R^x and R^y combine to form a C_{3-6} cycloalkyl, or spirocycloalkyl;

X is a linking group selected from:





X¹ is a polyethylene glycol (PEG);

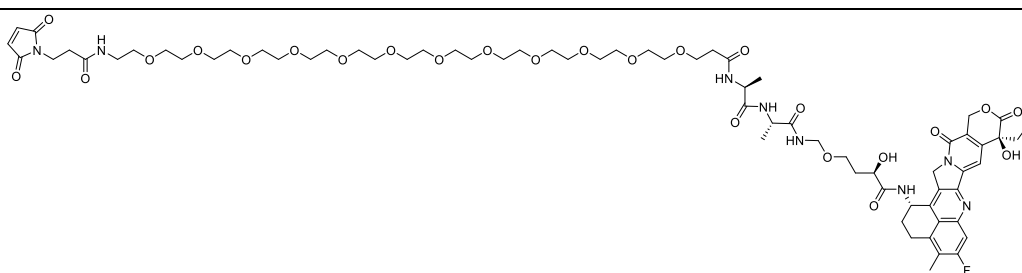
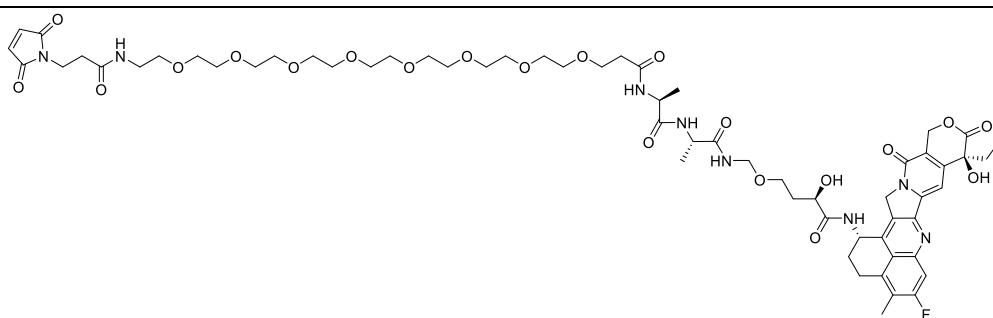
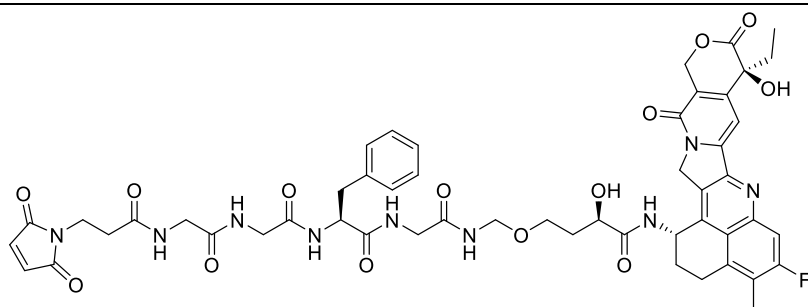
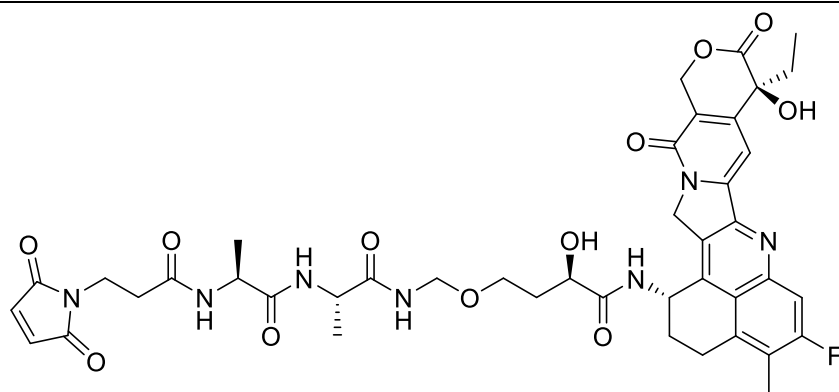
Y^4 is hydrogen or

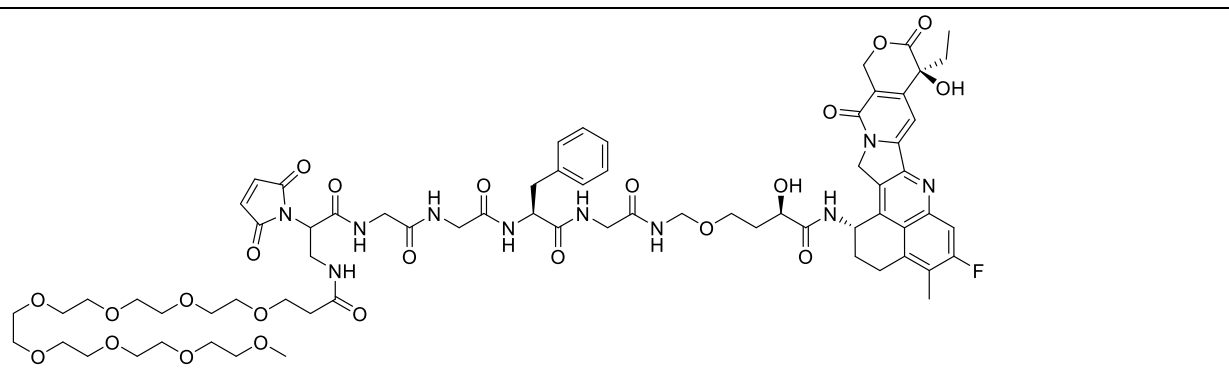
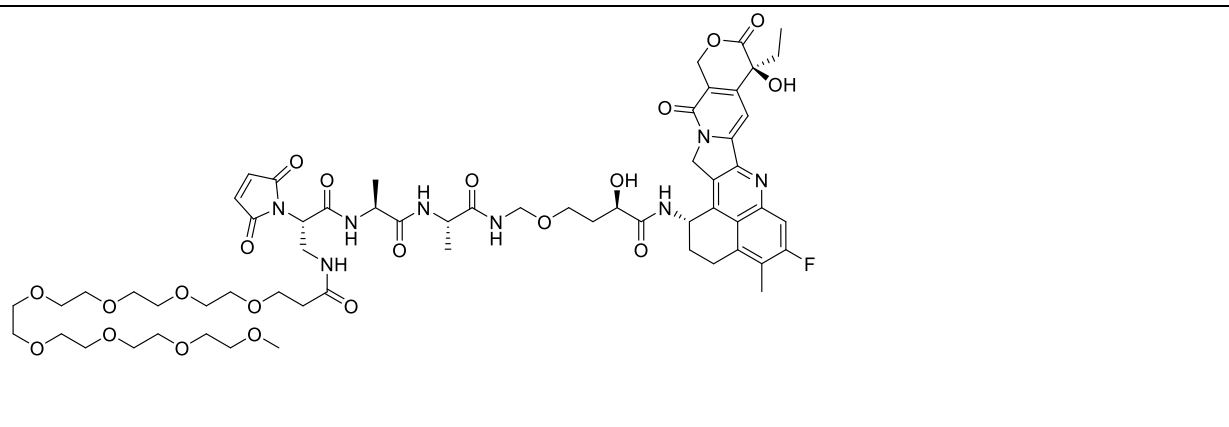
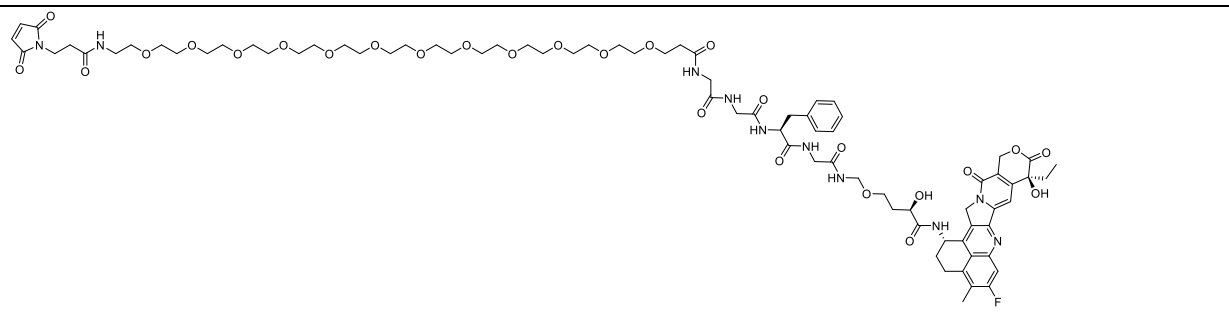
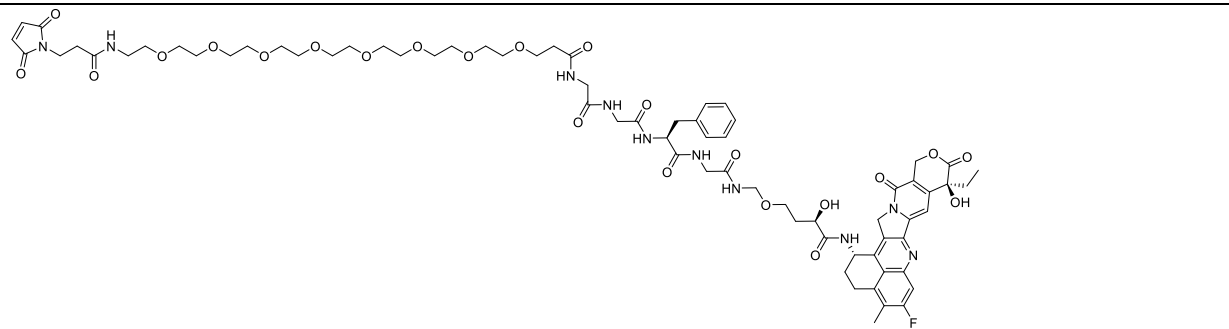


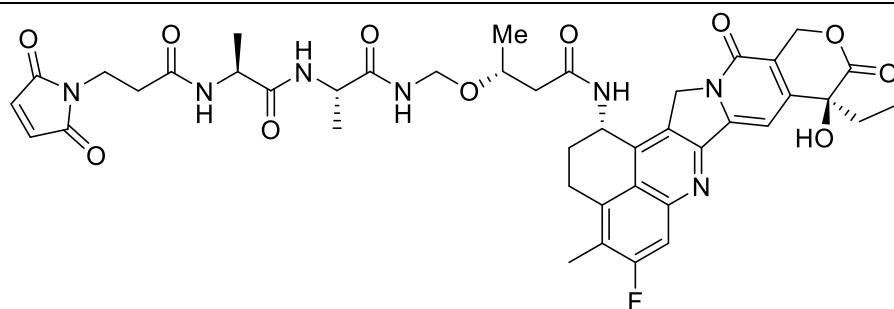
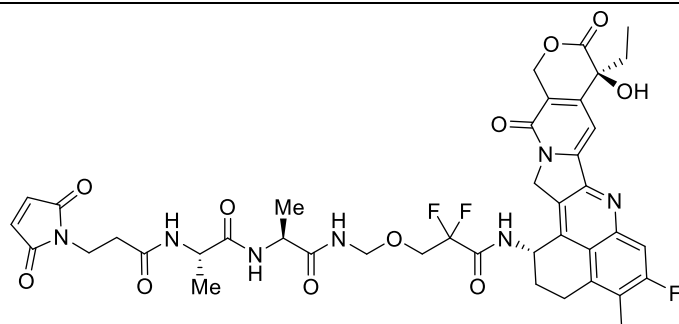
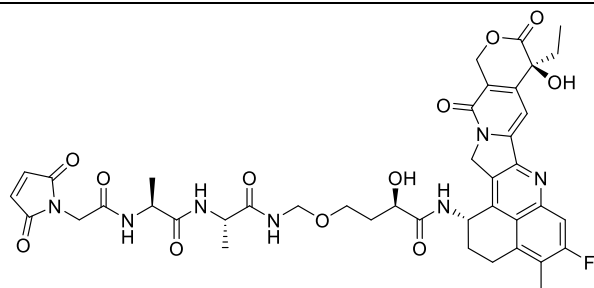
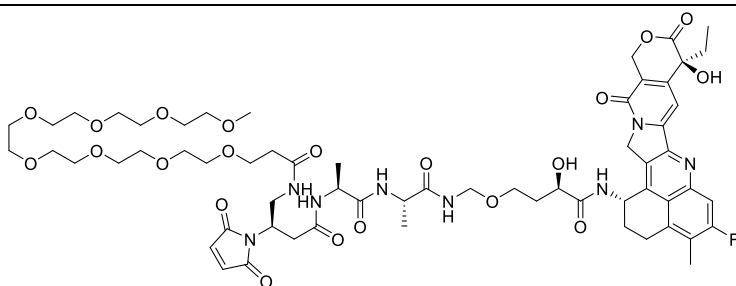
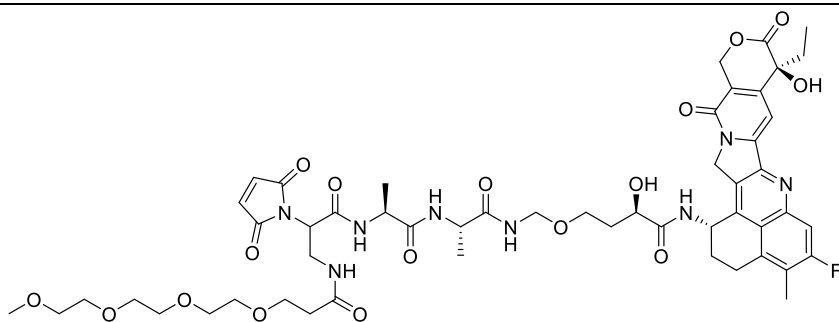
Q is C₁₋₆ alkyl or hydrogen.

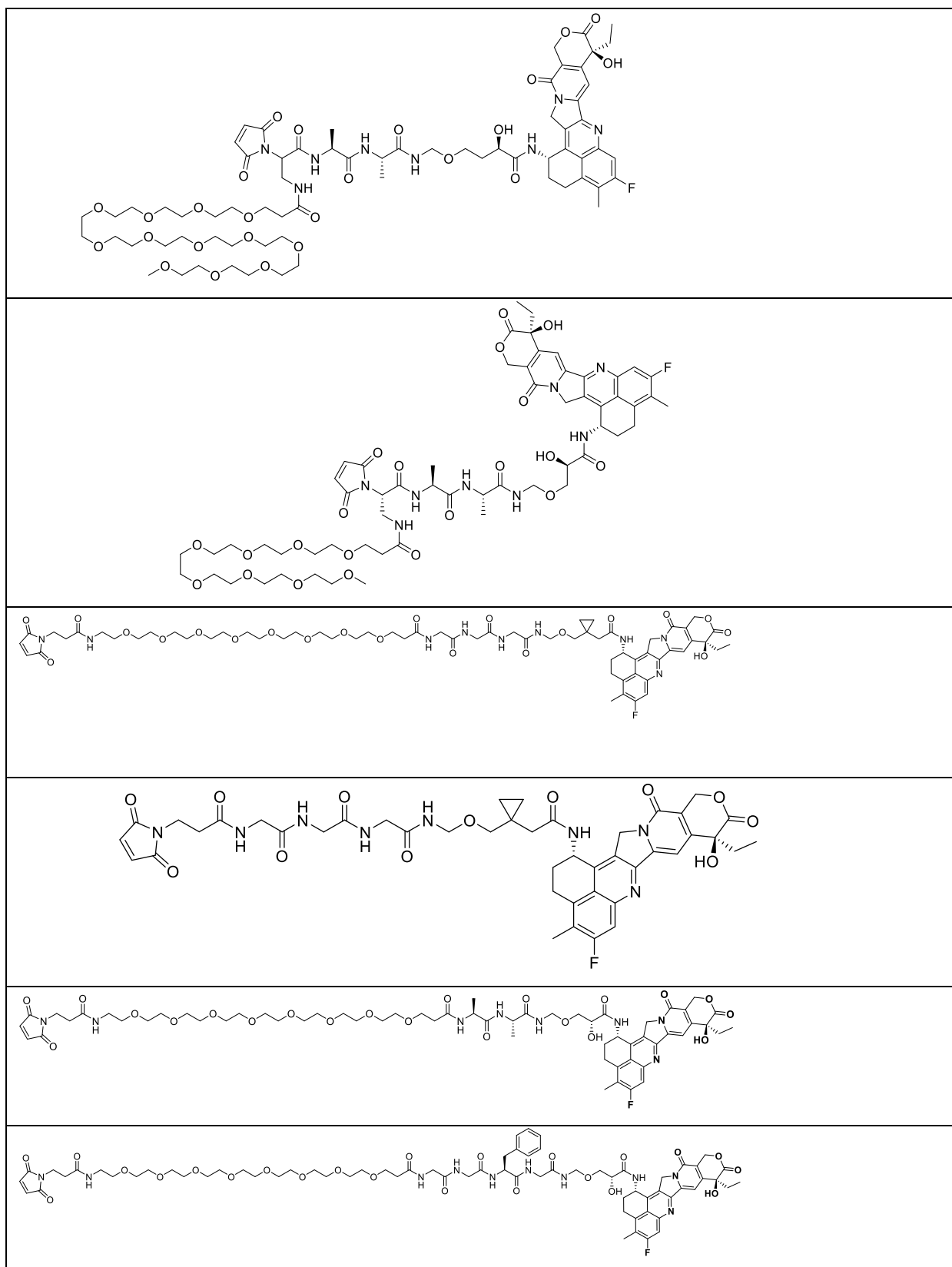
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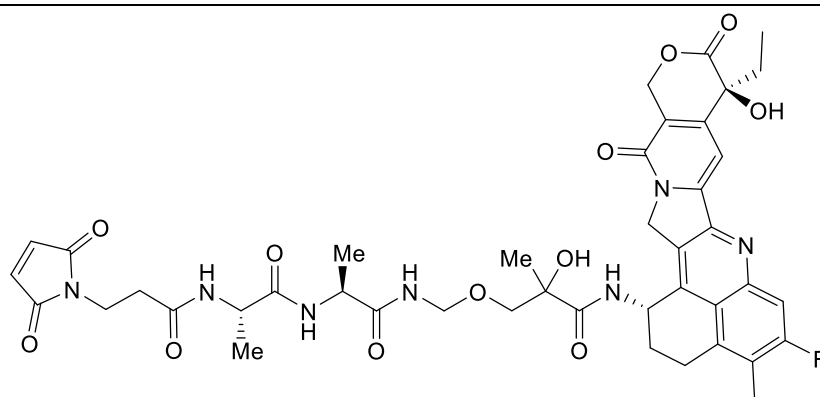
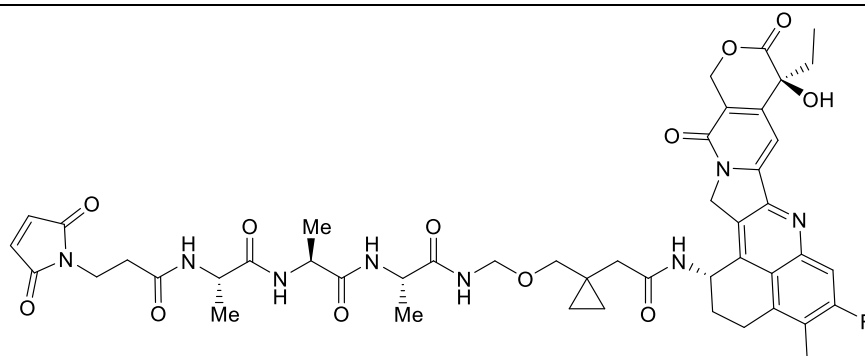
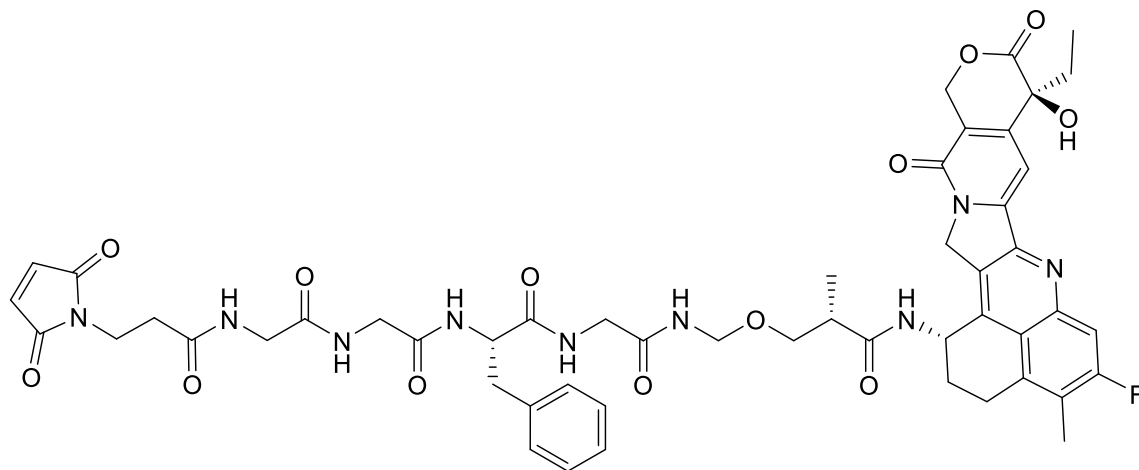
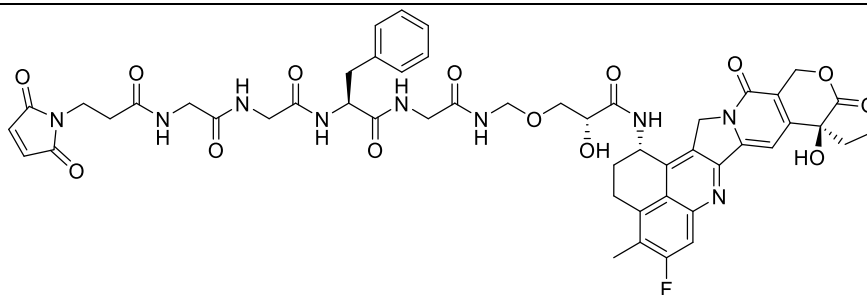
Structure

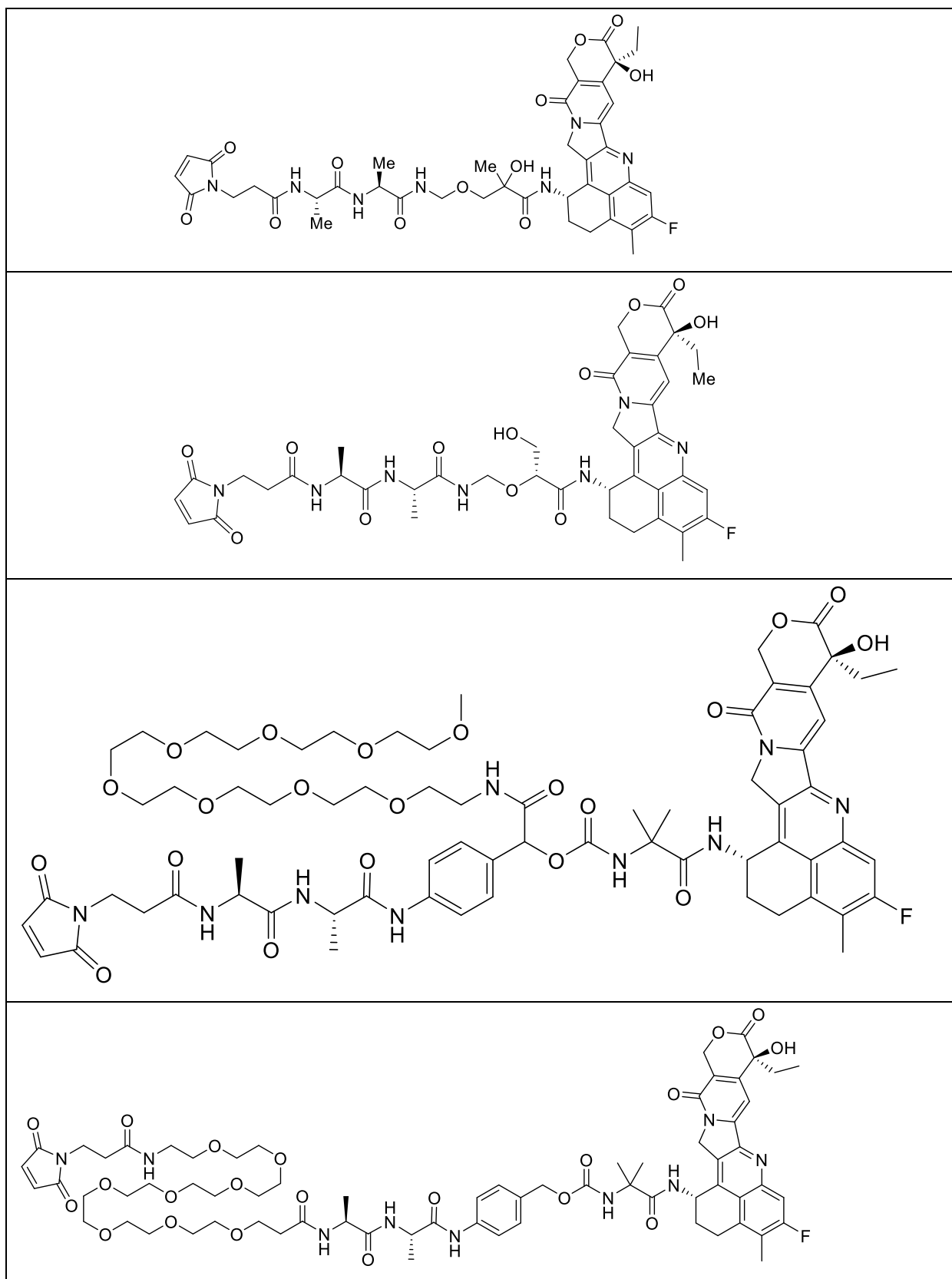


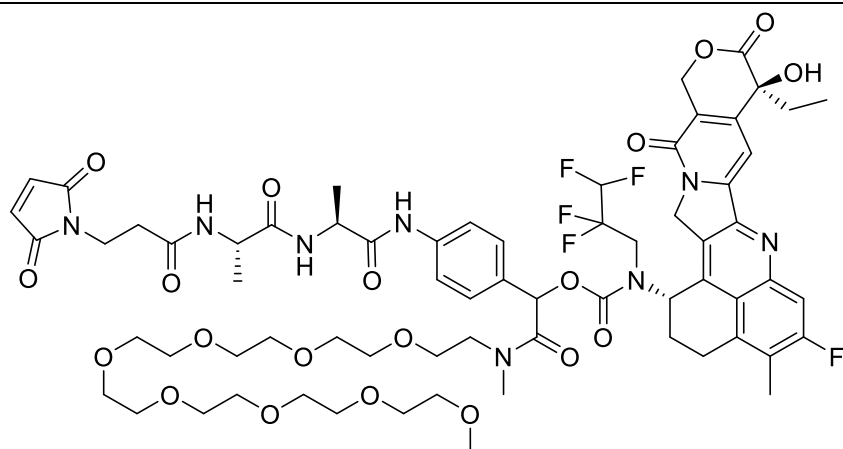
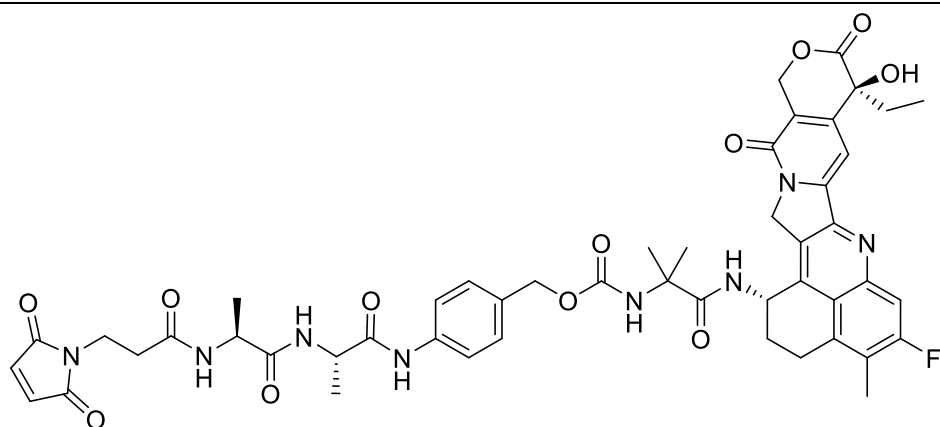
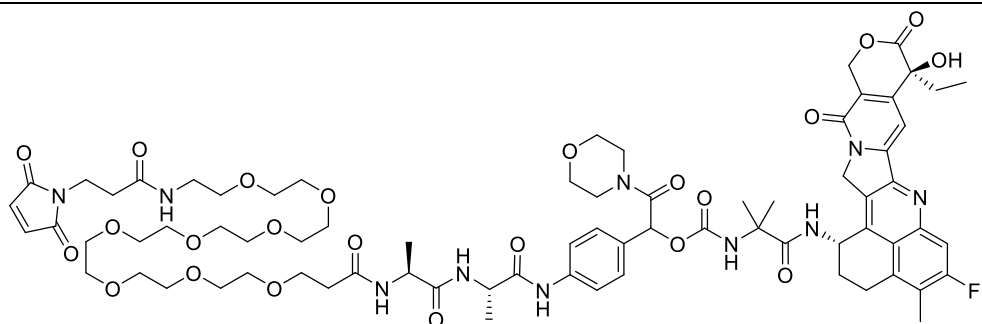




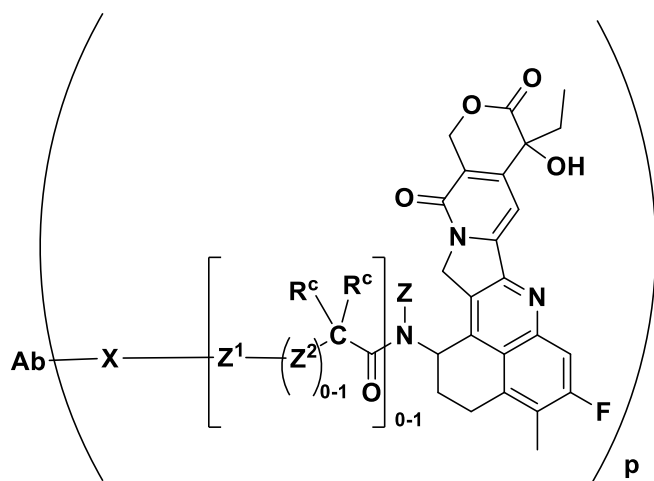








[0003c] In yet another aspect of the present disclosure, there is provided a compound of structural Formula IV, or a pharmaceutically acceptable salt thereof:



IV

wherein Ab is an antibody;

p is an integer from 1 to 24;

Z is selected from hydrogen and $-\text{CH}_2\text{C}(\text{R}^x)(\text{R}^y)\text{CHF}_2$;

Z^1 is selected from $-\text{NH}-$ and $-\text{O}-$;

Z^2 is absent or selected from $-\text{CR}^b\text{R}^b-$, $-\text{CH}_2\text{CR}^b\text{R}^b-$, and $-\text{CR}^b\text{R}^b\text{CH}_2-$;

each R^b is independently selected from hydrogen, $-\text{C}_{1-6}$ alkyl, and hydroxyl;

or two adjacent R^b combine to form a spirocycloalkyl;

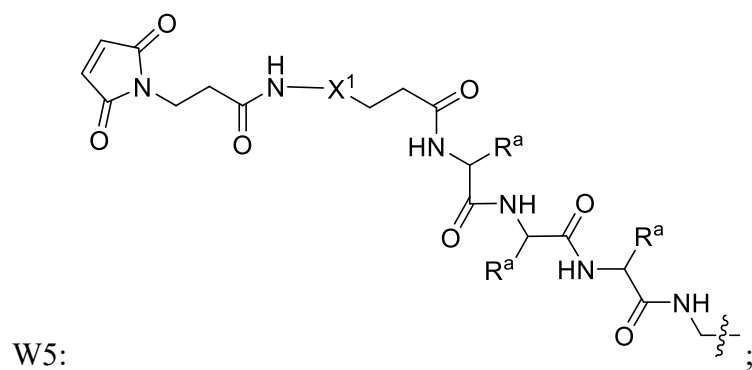
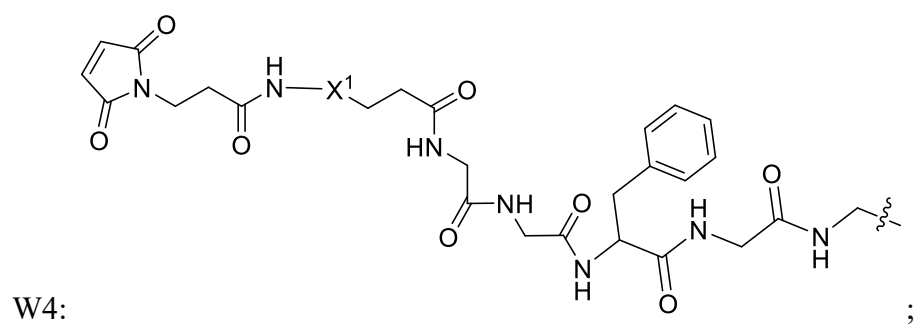
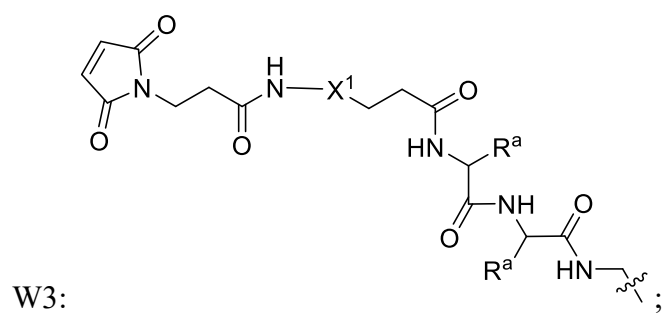
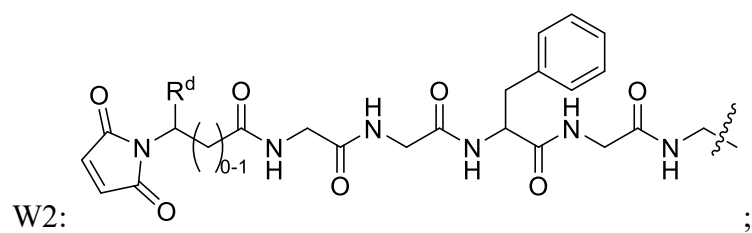
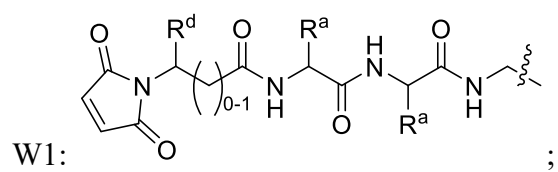
each R^c is independently selected from hydrogen, $-\text{C}_{1-6}$ alkyl, halogen, and hydroxyl;

or two adjacent R^c combine to form a spirocycloalkyl;

R^x and R^y are independently selected from hydrogen, C_{1-6} alkyl, C_{1-3} haloalkyl, halogen, hydroxyl, and $-\text{C}_{1-6}$ alkyl-OH;

or R^x and R^y combine to form a C_{3-6} cycloalkyl, or spirocycloalkyl;

X is a linking group selected from:

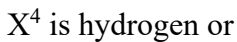




X¹ is a polyethylene glycol (PEG);



X^3 is hydrogen or $-C(O)X^2$,

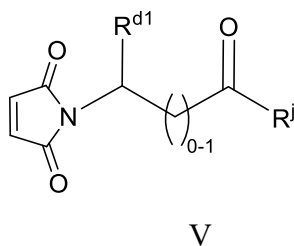


R^a is selected from hydrogen and C₁₋₆ alkyl; and

R^d is hydrogen or -CH₂NHC(O)X¹Q,

or a pharmaceutically acceptable salt thereof.

[0003d] In a further aspect of the present disclosure, there is provided a compound of structural formula V:



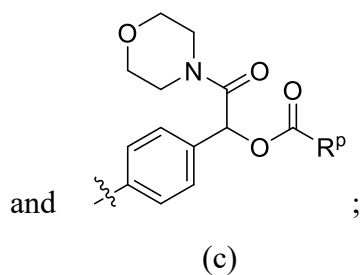
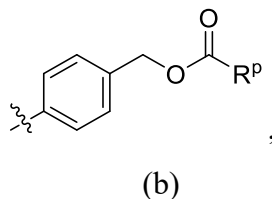
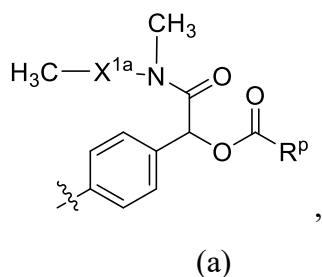
wherein:

R^j is selected from OH, $-NH_2$, $-NHR^kR^g$, $-NHR^kNH(CH_2)_nOR^q$, $-NHR^kNH(CH_2)_nOC(O)CH_3$, $-NHX^{1a}(CH_2)_nC(O)R^kNHCH_2OC(O)CH_3$, $-NHR^kNHR^L$, $-NHX^{1a}R^kNHR^L$, and $-NHCH_2O(CH_2)_nCH(OH)C(O)OH$;

R^g is COOH or CONH₂;

R^k is an amino acid residue of up to 10 amino acids;

R^L is selected from :



R^p is selected from NH₂ and ;

R^q is hydrogen or C₁₋₆ alkyl;

X^{1a} is a PEG of 1 to 24 $-\text{CH}_2\text{CH}_2\text{O}-$ subunits;

R^{d1} is hydrogen, $-\text{CH}_2\text{NHC}(\text{O})X^{1a}\text{Q}$ or $-\text{CH}_2\text{NHC}(\text{O})X^{21}\text{Q}$;

Q is C_{1-6} alkyl or H;

X^{21} is selected from a PEG of 1 to 24 $-\text{CH}_2\text{CH}_2\text{O}-$ subunits, PEG-amino sugar, and p-aminobenzylcarbonyl and

n is 1, 2, 3, or 4.

[0003e] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0004] The instant compounds are cytotoxic and can be applied as chemotherapeutic drugs in oncologic settings, for example as an anti-tumor agent. The compounds are potent, novel in structure, and active across multiple cancer cell lines.

[0004a] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment or prevention of cancers or tumors.

[0004b] In another aspect of the present disclosure, there is provided the compound or pharmaceutical composition comprising the compound as disclosed herein, or a pharmaceutically acceptable salt thereof for use in therapy.

DETAILED DESCRIPTION OF THE DISCLOSURE

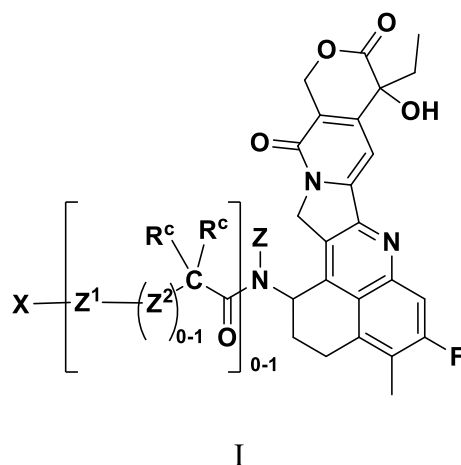
[0005] For each of the following embodiments, any variable not explicitly defined in the embodiment is as defined in Formula (I). In each of the embodiments described herein, each variable is selected independently of the other unless otherwise noted.

[0006] This disclosure is directed to a class of linker camptothecin-derived payload compounds, wherein the linker structures contain a maleimide attached to a peptide linker, with variation on the amino acid sequence and the optional incorporation of PEG units and terminating with a hemiaminal connection to a camptothecin-derived payload. An embodiment of the disclosure relates to a class of linker camptothecin-derived -payload compounds, wherein the linker structures contain a maleimide attached to a peptide linker, with variation on the amino acid sequence and the optional incorporation of PEG units and terminating with a PABC connection to a camptothecin-derived payload. Another embodiment of the disclosure relates to compounds where the linker camptothecin-derived payload compounds is conjugated to a targeting moiety that has a free cysteine group, including antibodies, proteins, peptides, polypeptides, and engineered antibodies. Still another embodiment of the disclosure relates to the maleimide-containing linker group.

[0007] In another embodiment, the present disclosure provides linker camptothecin-derived -payload compounds (also referred to as linker-payload(s)), and pharmaceutically acceptable salts, solvates, or stereoisomer thereof, comprising a structure of formula I:

WHAT IS CLAIMED:

1. A compound having a structural Formula I, or salt thereof:



wherein:

Z is selected from hydrogen and $-\text{CH}_2\text{C}(\text{R}^x)(\text{R}^y)\text{CHF}_2$;

Z^1 is selected from $-\text{NH}-$ and $-\text{O}-$;

Z^2 is absent or selected from $-\text{CR}^b\text{R}^b-$, $-\text{CH}_2\text{CR}^b\text{R}^b-$, and $-\text{CR}^b\text{R}^b\text{CH}_2-$;

each R^b is independently selected from hydrogen, $-\text{C}_{1-6}$ alkyl, and hydroxyl;

or two adjacent R^b combine to form spirocycloalkyl;

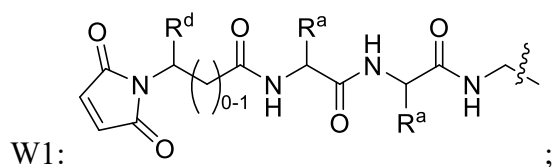
each R^c is independently selected from hydrogen, $-\text{C}_{1-6}$ alkyl, halogen, and hydroxyl;

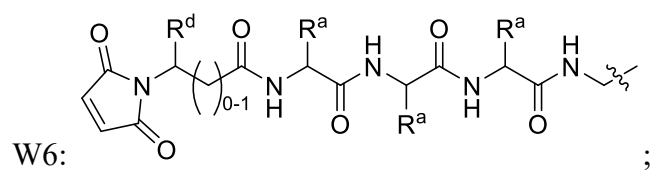
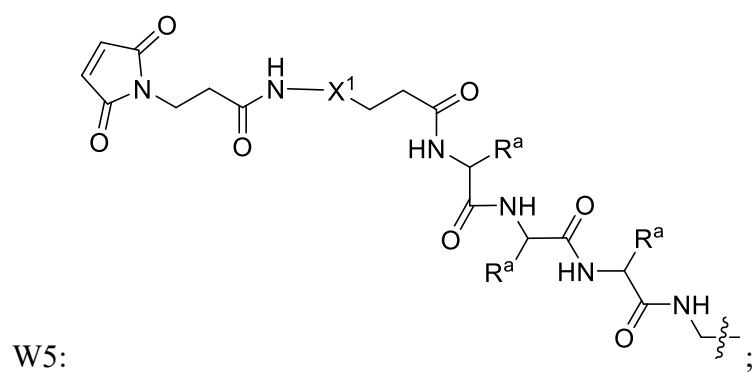
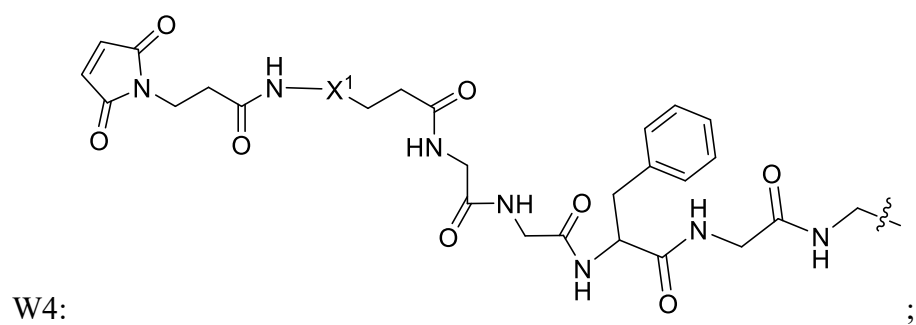
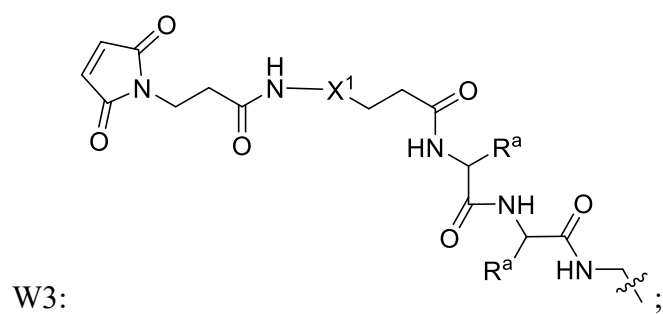
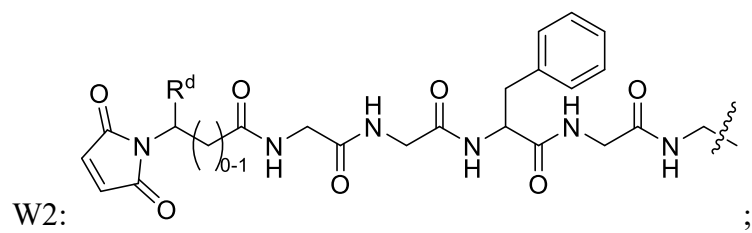
or two adjacent R^c combine to form spirocycloalkyl;

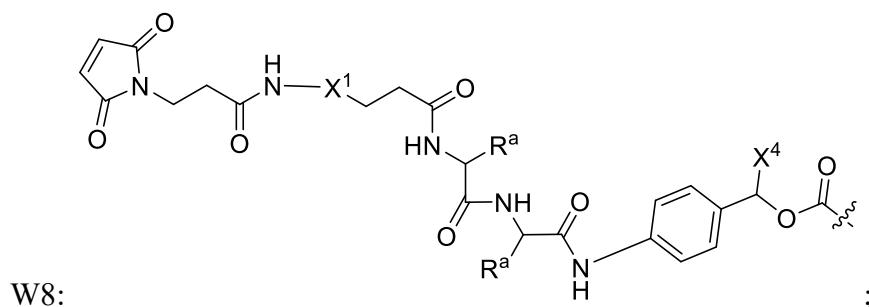
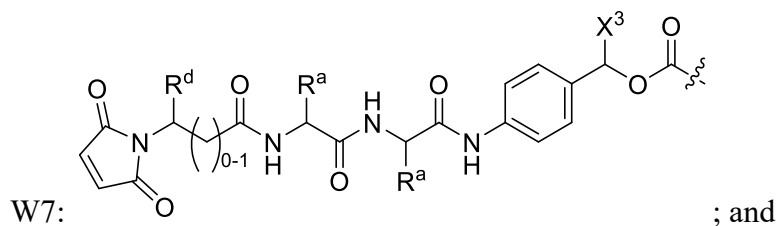
R^x and R^y are independently selected from hydrogen, C_{1-6} alkyl, C_{1-3} haloalkyl, halogen, hydroxyl, and $-\text{C}_{1-6}$ alkyl-OH;

or R^x and R^y combine to form a C_{3-6} cycloalkyl, or spirocycloalkyl;

X is a linking group selected from:



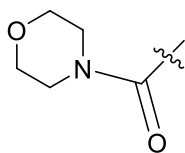




~ represents point of attachment to structural Formula I;

X¹ is a polyethylene glycol (PEG);

X³ is hydrogen or -C(O)NR^aR^z,



X⁴ is hydrogen or

R^a are R^z are independently selected from hydrogen, C₁₋₆ alkyl, and X¹, or R^a and R^z combine to form a C₃₋₁₀ cycloalkyl, or a 3 to 10 membered heterocyclyl;

R^d is hydrogen, -CH₂NHC(O)X¹ or -CH₂NHC(O)X¹Q; and

Q is C₁₋₆ alkyl or hydrogen.

2. The compound according to claim 1 where in Z¹ is -O-, or a salt thereof.
3. The compound according to claim 1 wherein Z¹ is -NH-, or a salt thereof.
4. The compound according to any one of claims 1-3 wherein R^d is hydrogen, or a salt thereof.

5. The compound according to any one of claims 1-3 wherein R^d is -
 $\text{CH}_2\text{NHC}(\text{O})\text{X}^1\text{Q}$, or a salt thereof

6. The compound according to any one of claims 1-5 wherein each R^a is
independently selected from hydrogen and methyl,
or a salt thereof.

7. The compound according to any one of claims 1-6 wherein each R^c is
independently selected from hydrogen, hydroxyl, methyl, fluorine, and CHF_2 , or two adjacent R^c
combine to form spirocyclopropyl, or a salt thereof.

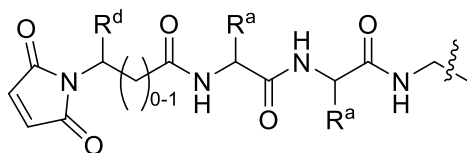
8. The compound according to any one of claims 1-7 wherein Z is hydrogen, or a
salt thereof.

9. The compound according to any one of claims 1-7 wherein Z is $-\text{CH}_2\text{C}(\text{F}_2)\text{CHF}_2$,
or a salt thereof.

10. The compound according to any one of claims 1-9 wherein Z^2 is selected from -
 CH_2CH_2 -, $-\text{CH}_2$ -, $-\text{CH}(\text{CH}_3)$ -, $-\text{CH}_2\text{CH}(\text{CH}_3)$ - spirocyclopropyl $(\text{CH}_2)_2$ -, and -
 $(\text{CH}_2)_2$ spirocyclopropyl-, or salt thereof.

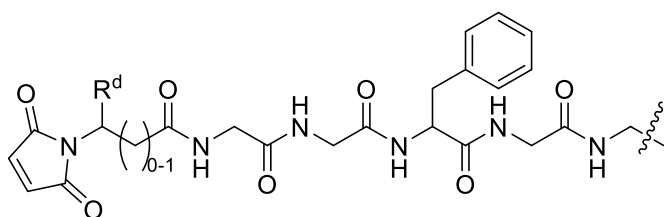
11. The compound according to any one of claims 1-9 wherein Z^2 is absent, or a salt
thereof.

12. The compound according to any one of claims 1-11 wherein X is W1:



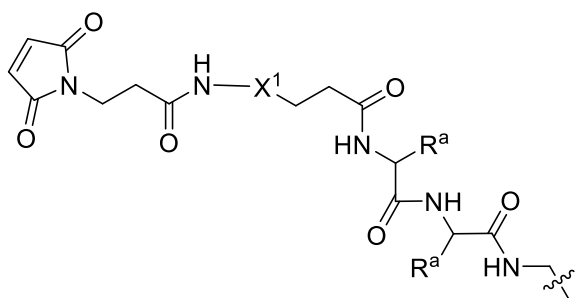
, or a salt thereof.

13. The compound according to any one of claims 1-11 wherein X is W2:



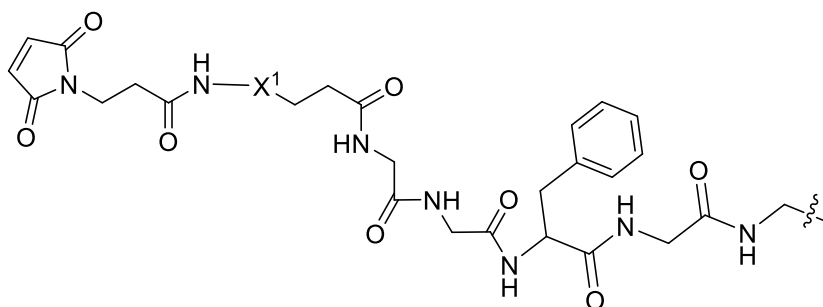
or a salt thereof.

14. The compound according to any one of claims 1-11 wherein X is W3:



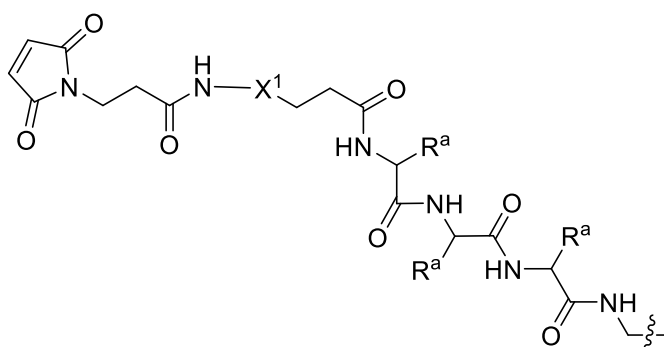
or a salt thereof.

15. The compound according to any one of claims 1-11 wherein X is W4:



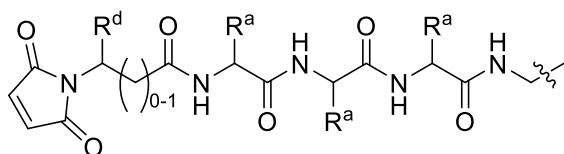
or a salt thereof.

16. The compound according to any one of claims 1-11 wherein X is W5:



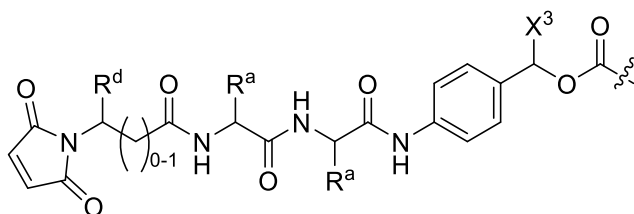
or a salt thereof.

17. The compound according to any one of claims 1-11 wherein X is W6:



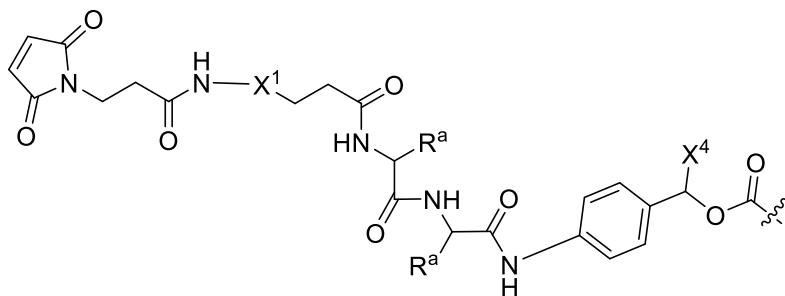
or a salt thereof.

18. The compound according to any one of claims 1-11 wherein X is W7:



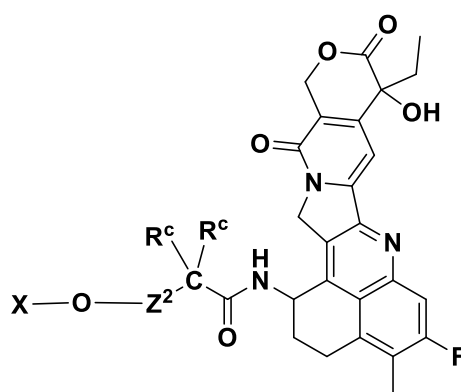
or a salt thereof.

19. The compound according to any one of claims 1-11 wherein X is W8:



or a salt thereof.

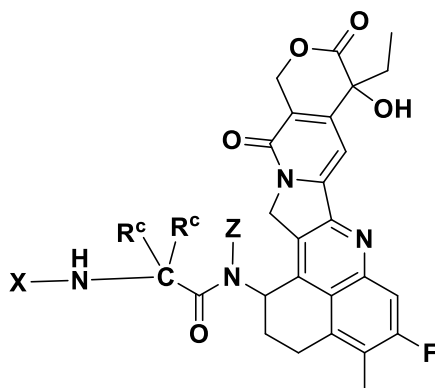
20. The compound according to any one of claims 1, 4-7 and 10-18 represented by structural Formula II:



II

or a salt thereof.

21. The compound according to any one of claims 1, 4-7 and 10-18 represented by structural Formula III:

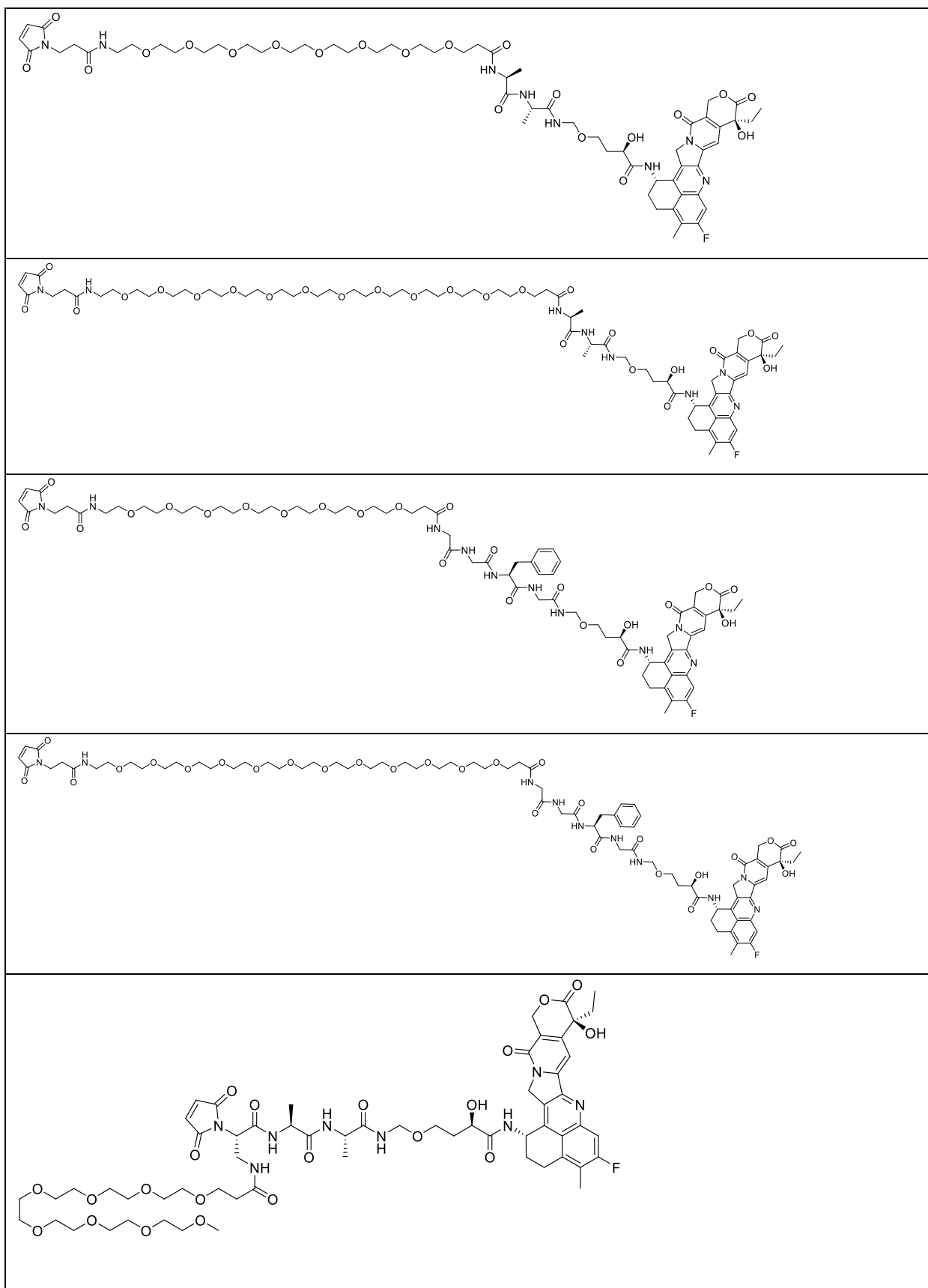


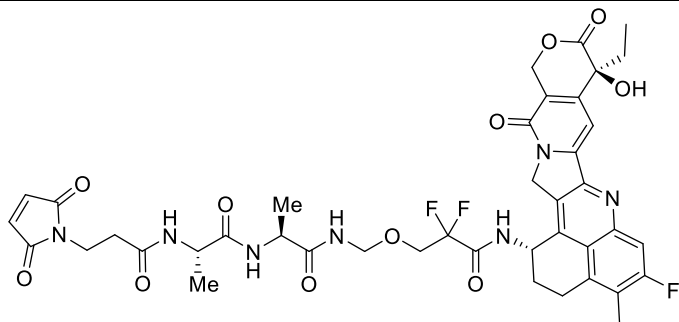
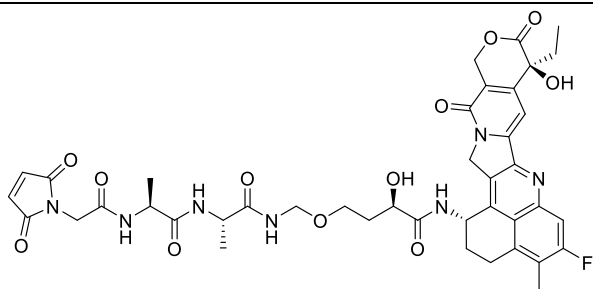
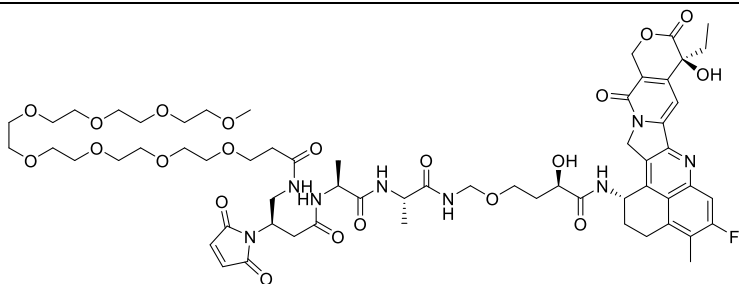
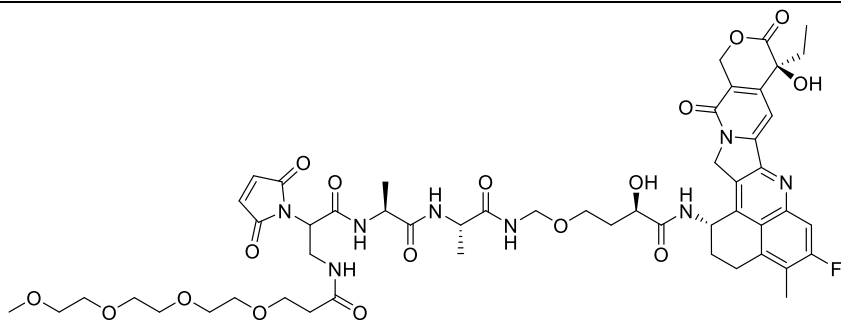
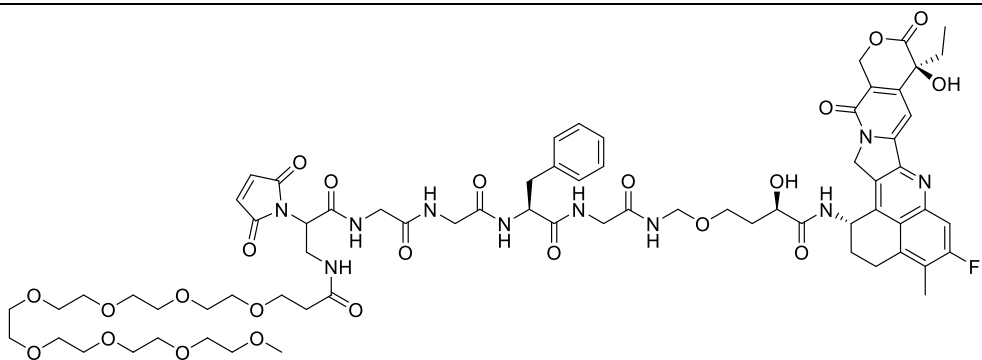
III

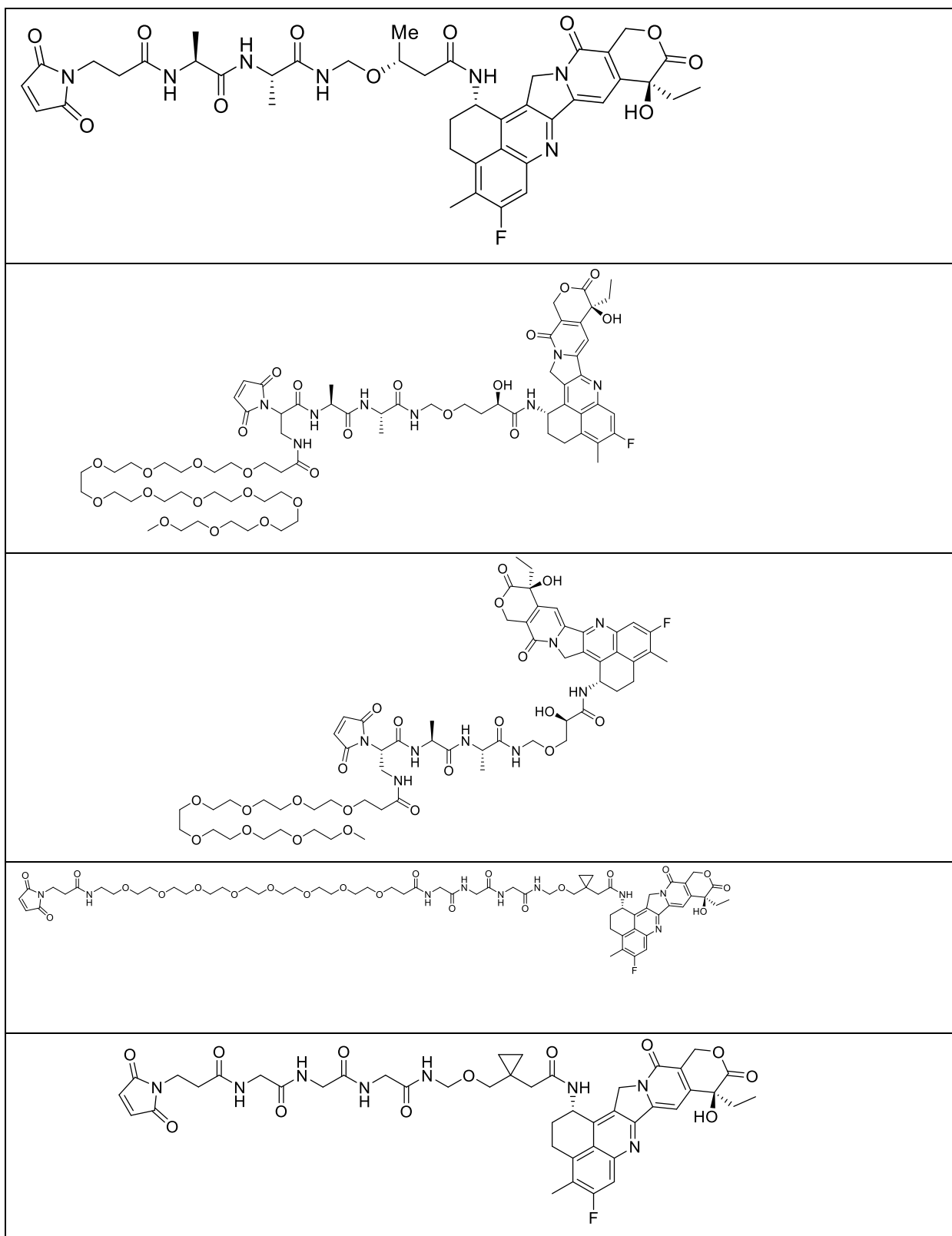
or a salt thereof.

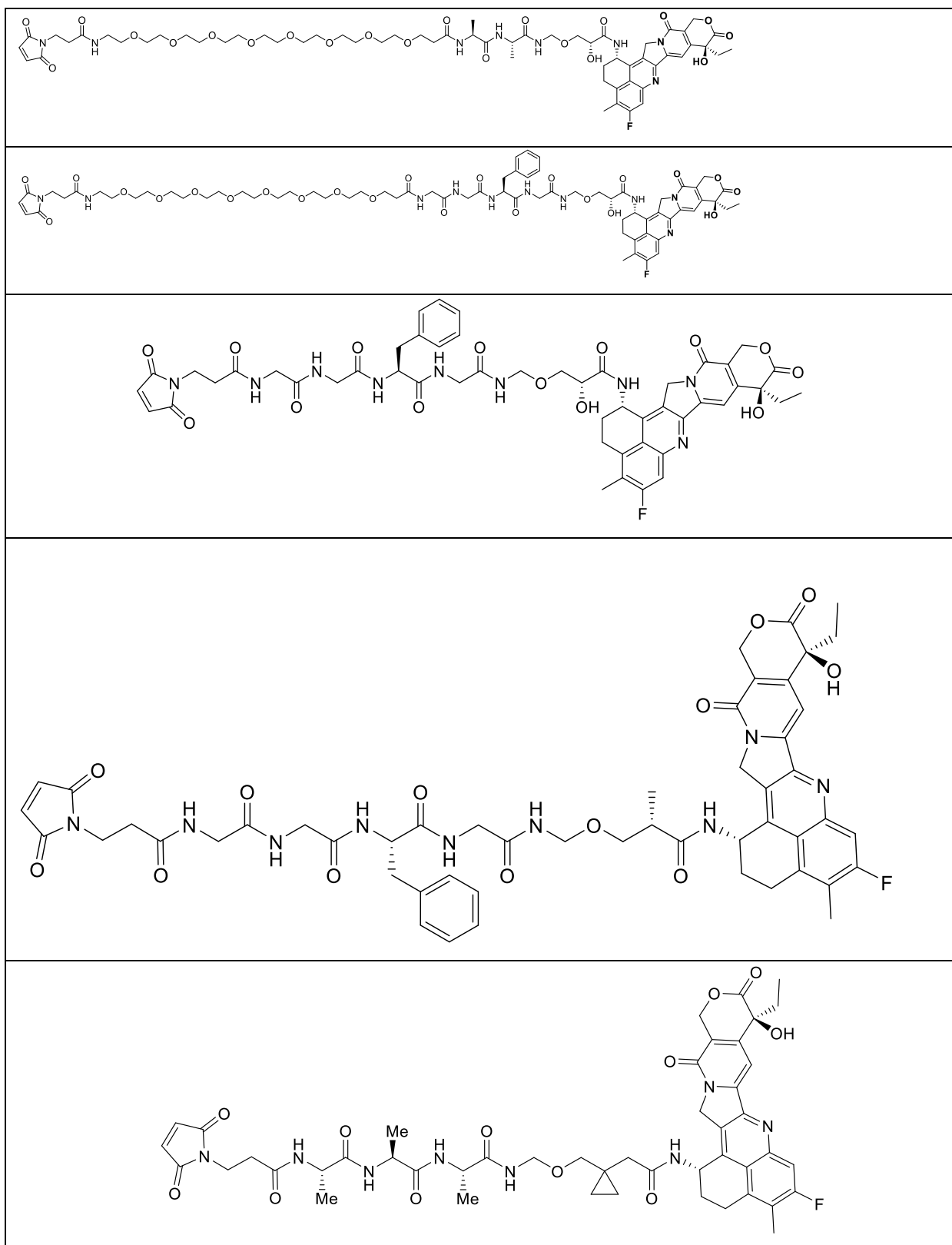
22. A linker-drug compound, or a salt thereof selected from:

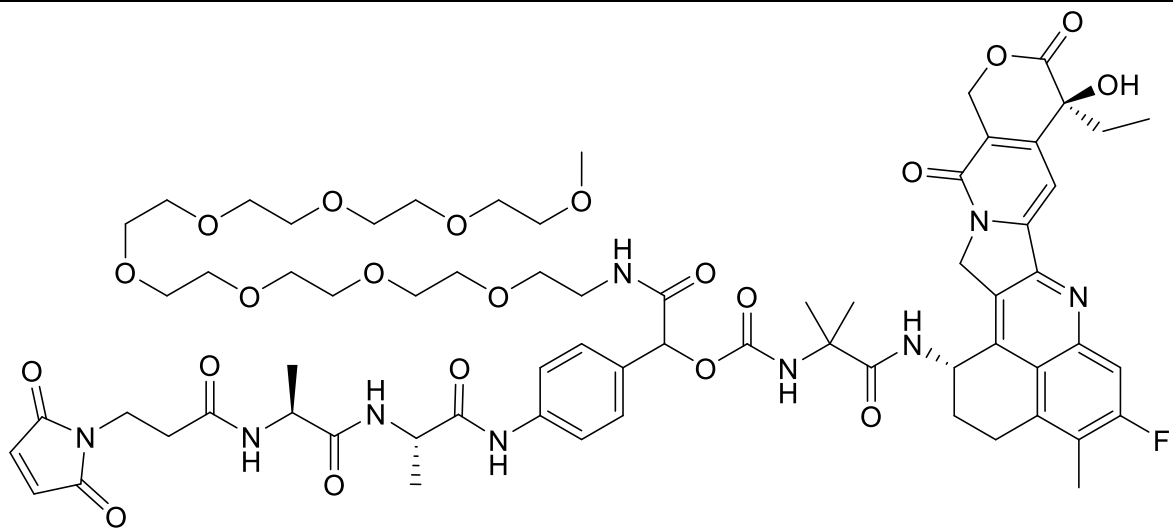
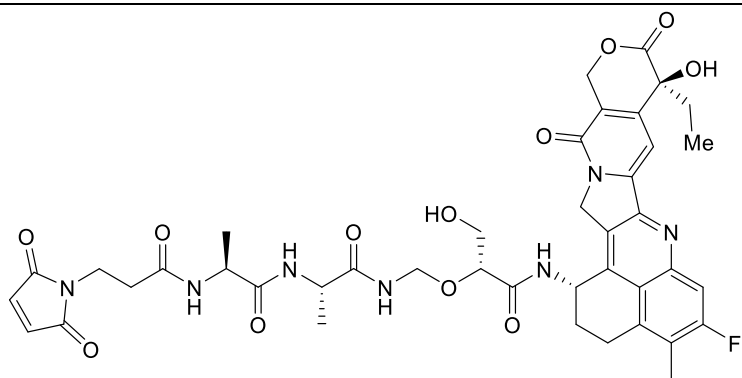
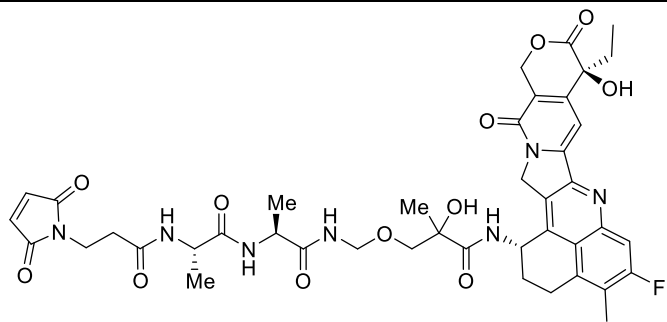
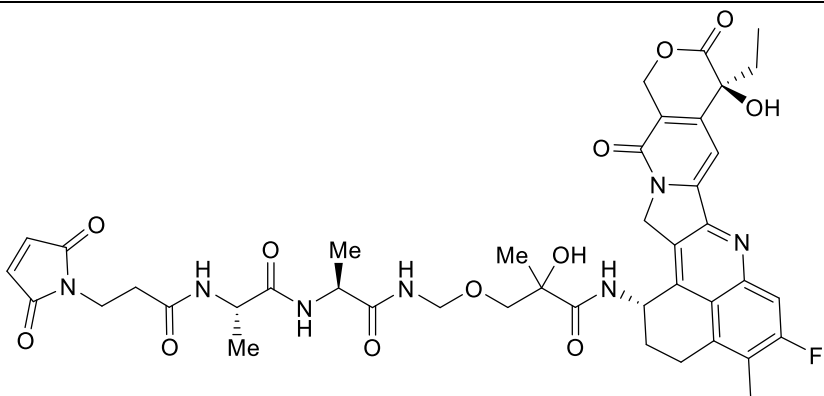
Structure

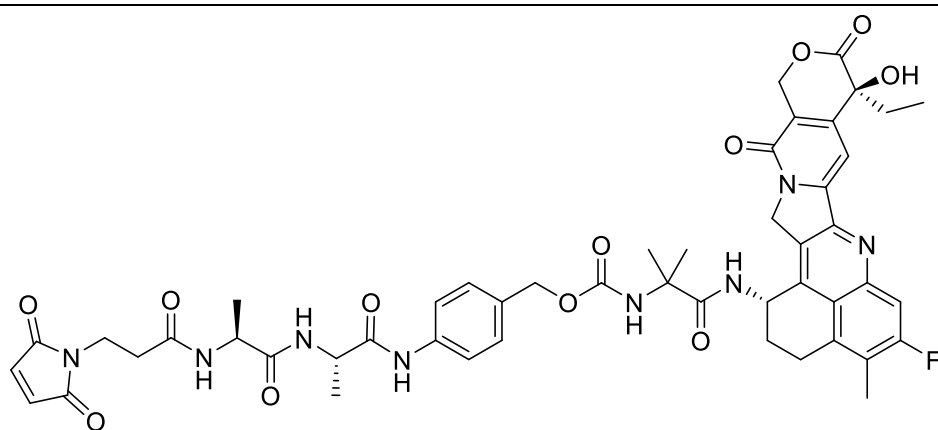
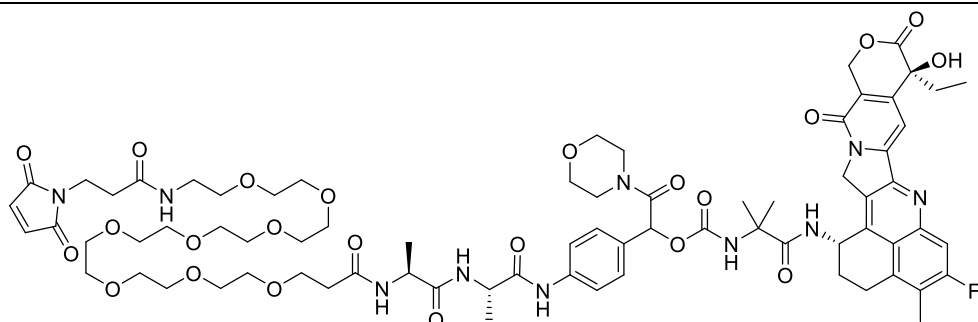
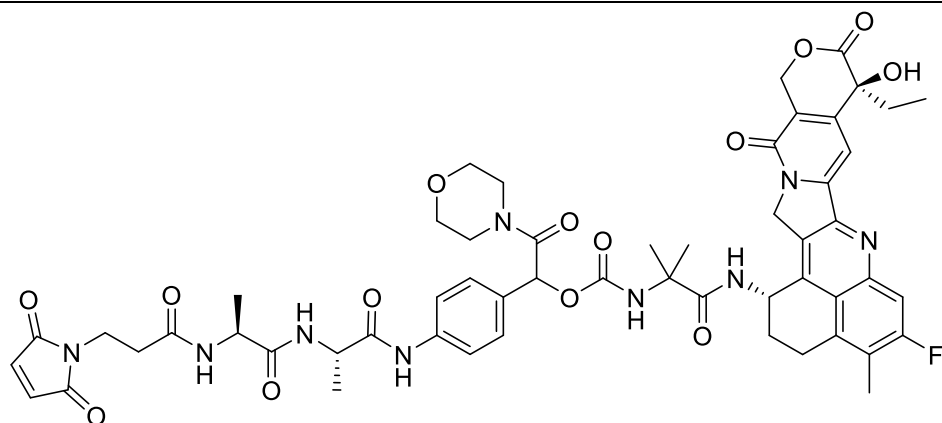
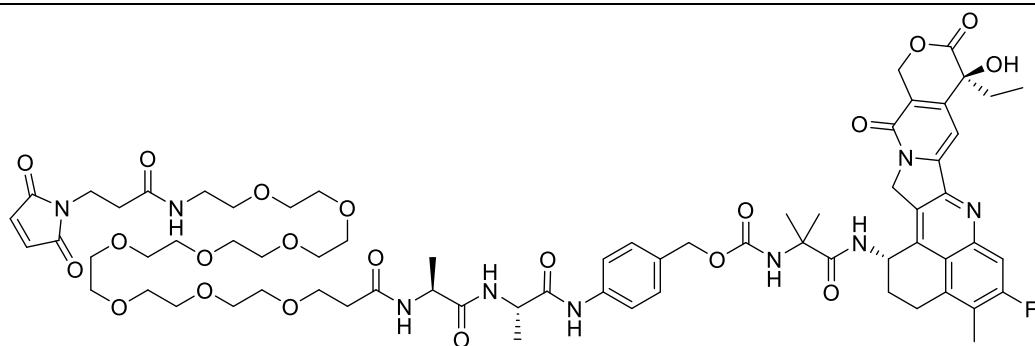


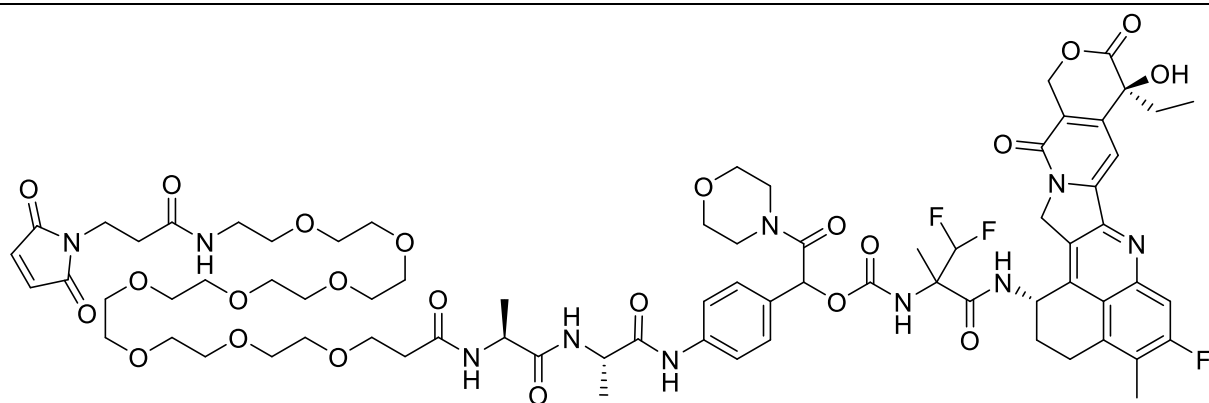
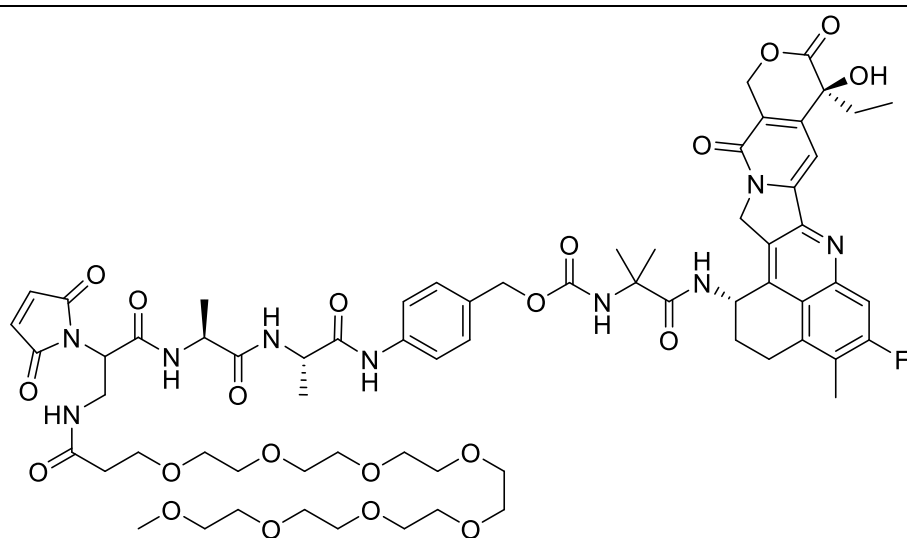
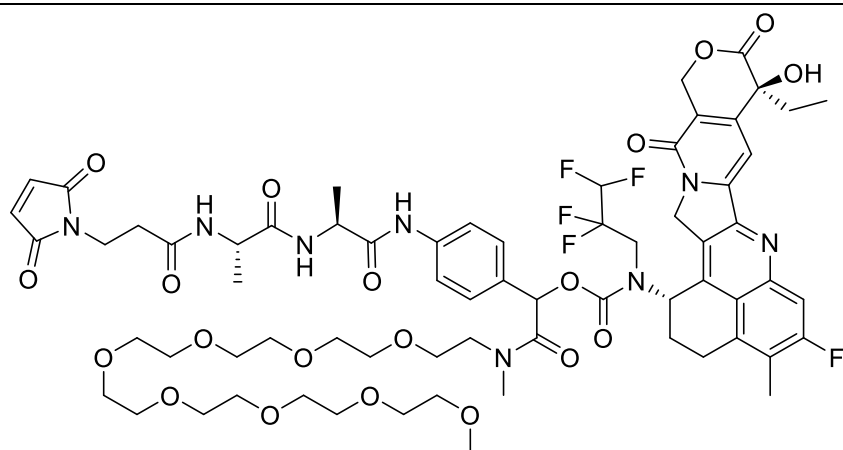


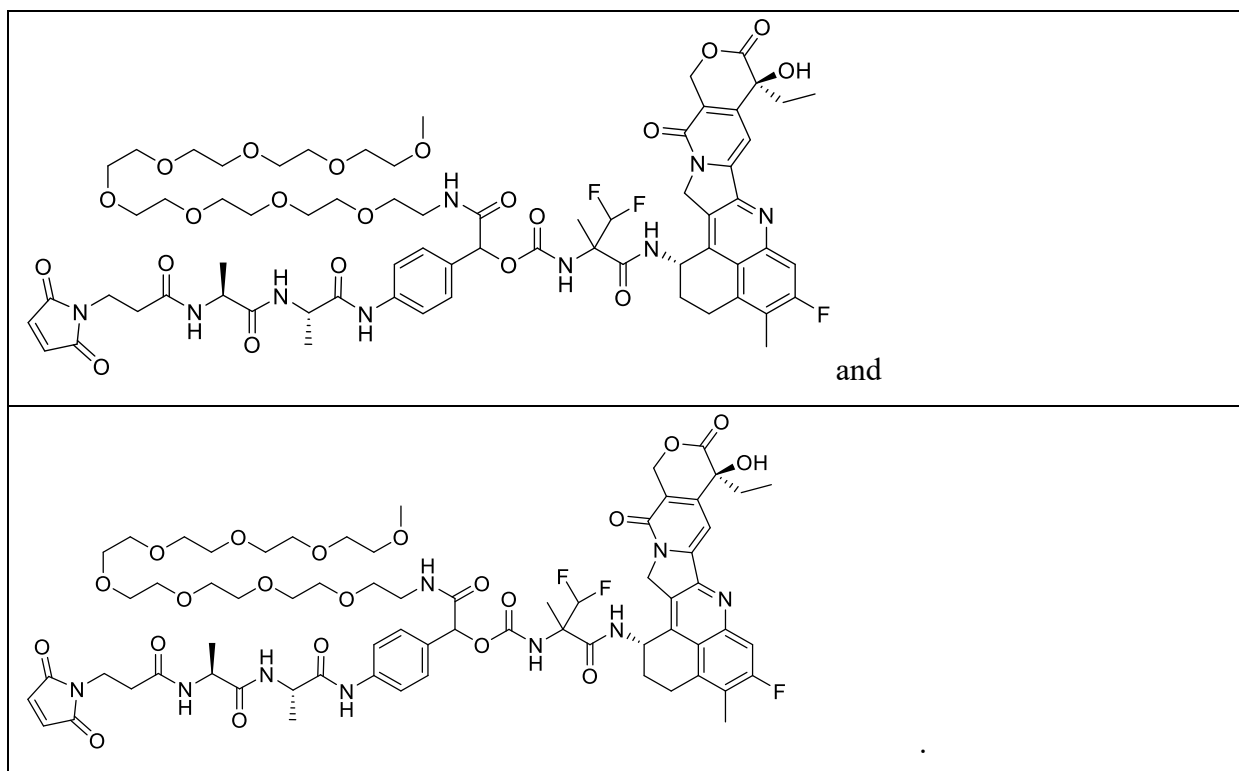




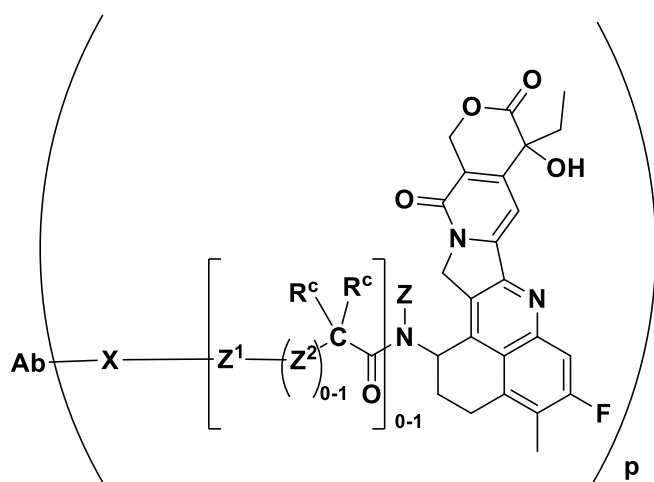








23. A compound of structural Formula IV, or a pharmaceutically acceptable salt thereof:



wherein Ab is an antibody;

p is an integer from 1 to 24;

Z is selected from hydrogen and $-\text{CH}_2\text{C}(\text{R}^x)(\text{R}^y)\text{CHF}_2$;

Z^1 is selected from $-\text{NH}-$ and $-\text{O}-$;

Z^2 is absent or selected from $-\text{CR}^b\text{R}^b-$, $-\text{CH}_2\text{CR}^b\text{R}^b-$, and $-\text{CR}^b\text{R}^b\text{CH}_2-$;

each R^b is independently selected from hydrogen, $-C_{1-6}$ alkyl, and hydroxyl;

or two adjacent R^b combine to form a spirocycloalkyl;

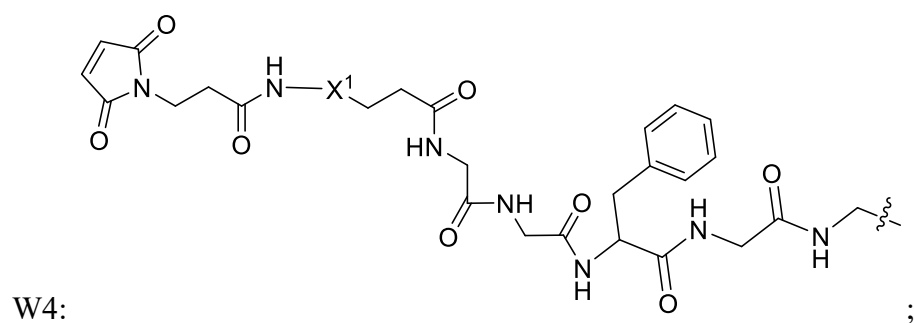
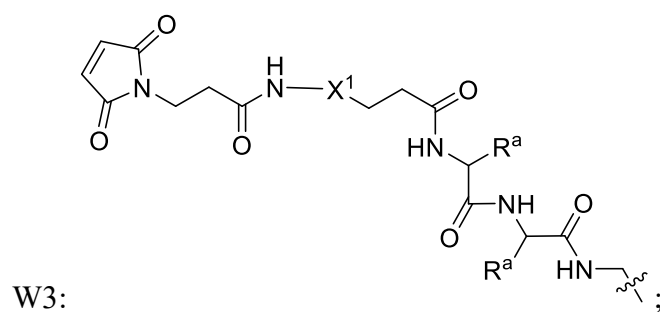
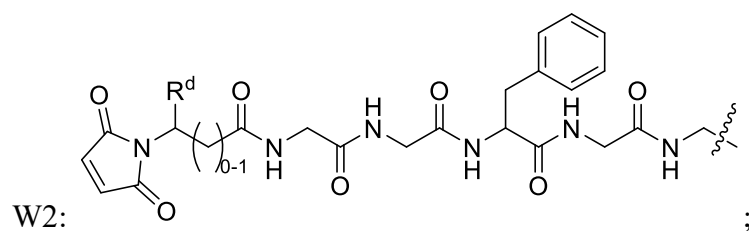
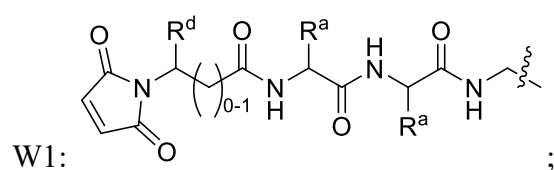
each R^c is independently selected from hydrogen, $-C_{1-6}$ alkyl, halogen, and hydroxyl;

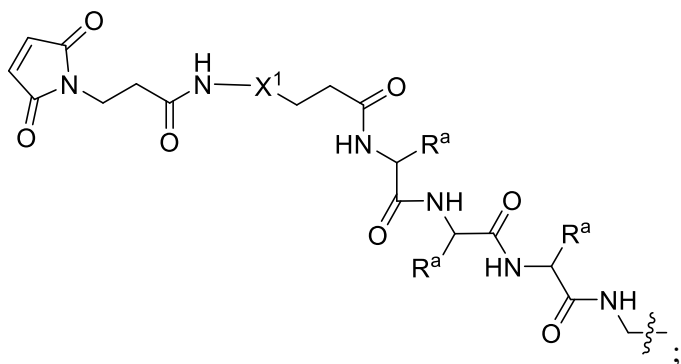
or two adjacent R^c combine to form a spirocycloalkyl;

R^x and R^y are independently selected from hydrogen, C_{1-6} alkyl, C_{1-3} haloalkyl, halogen, hydroxyl, and $-C_{1-6}$ alkyl-OH;

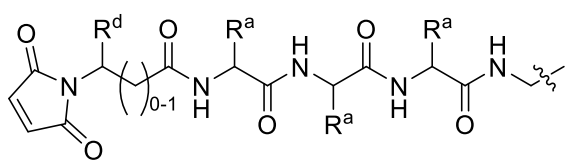
or R^x and R^y combine to form a C_{3-6} cycloalkyl, or spirocycloalkyl;

X is a linking group selected from:

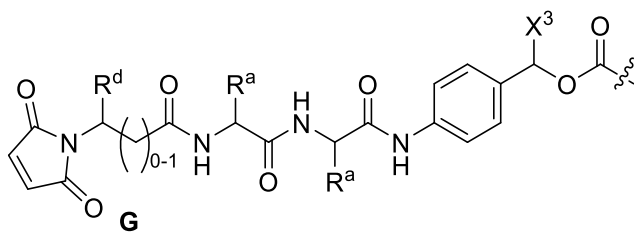




W5:

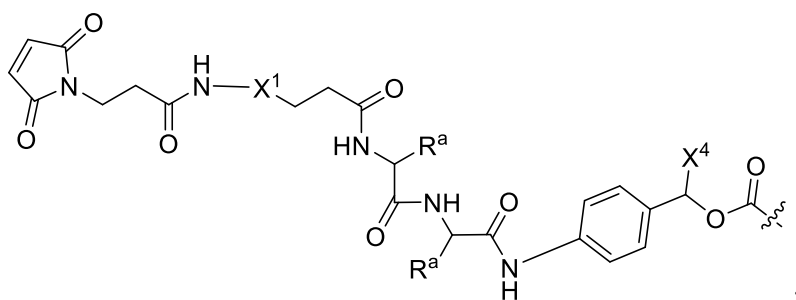


W6:



W7:

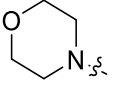
; and



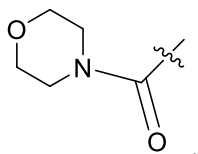
W8:

~ represents point of attachment to structural Formula I;

X^1 is a polyethylene glycol (PEG);

X^2 is $-NR^aX^1-$, or ,

X^3 is hydrogen or $-C(O)X^2$,



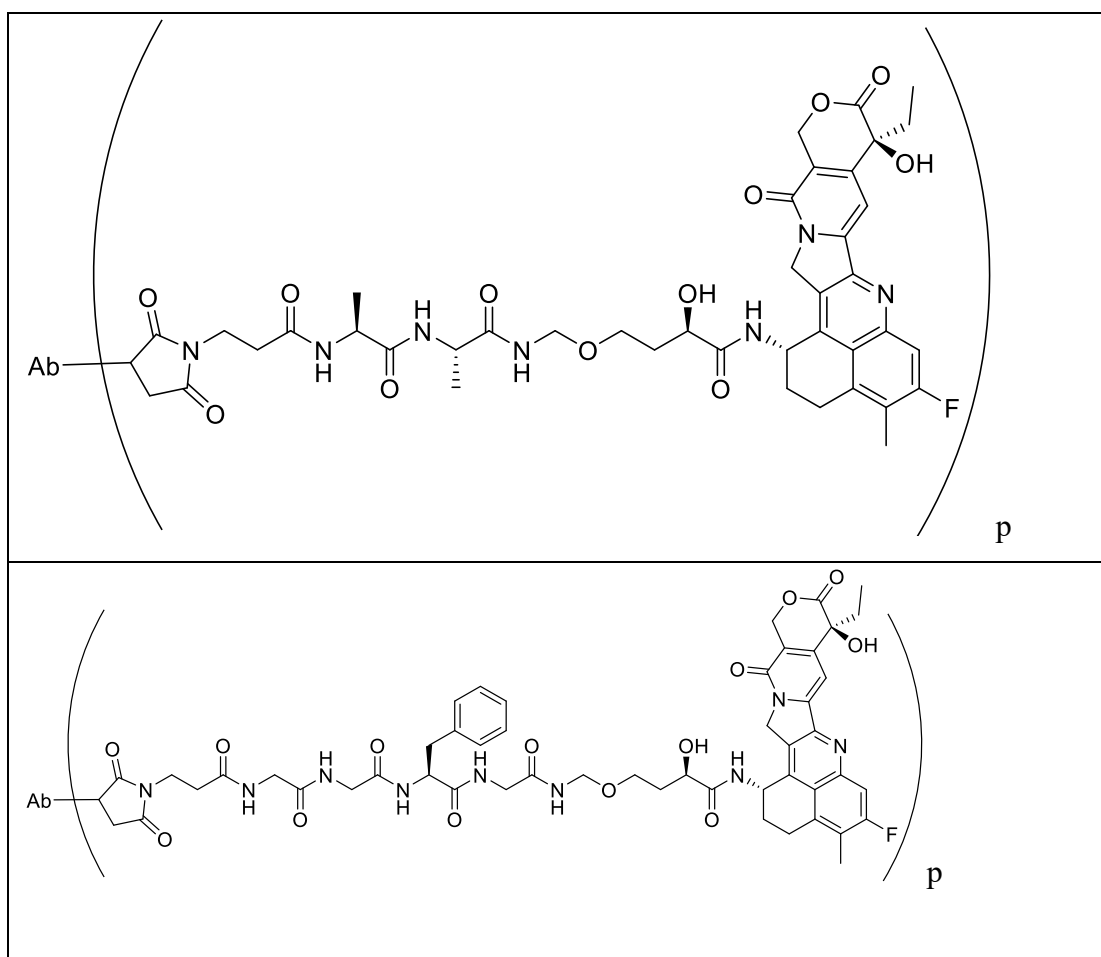
X^4 is hydrogen or

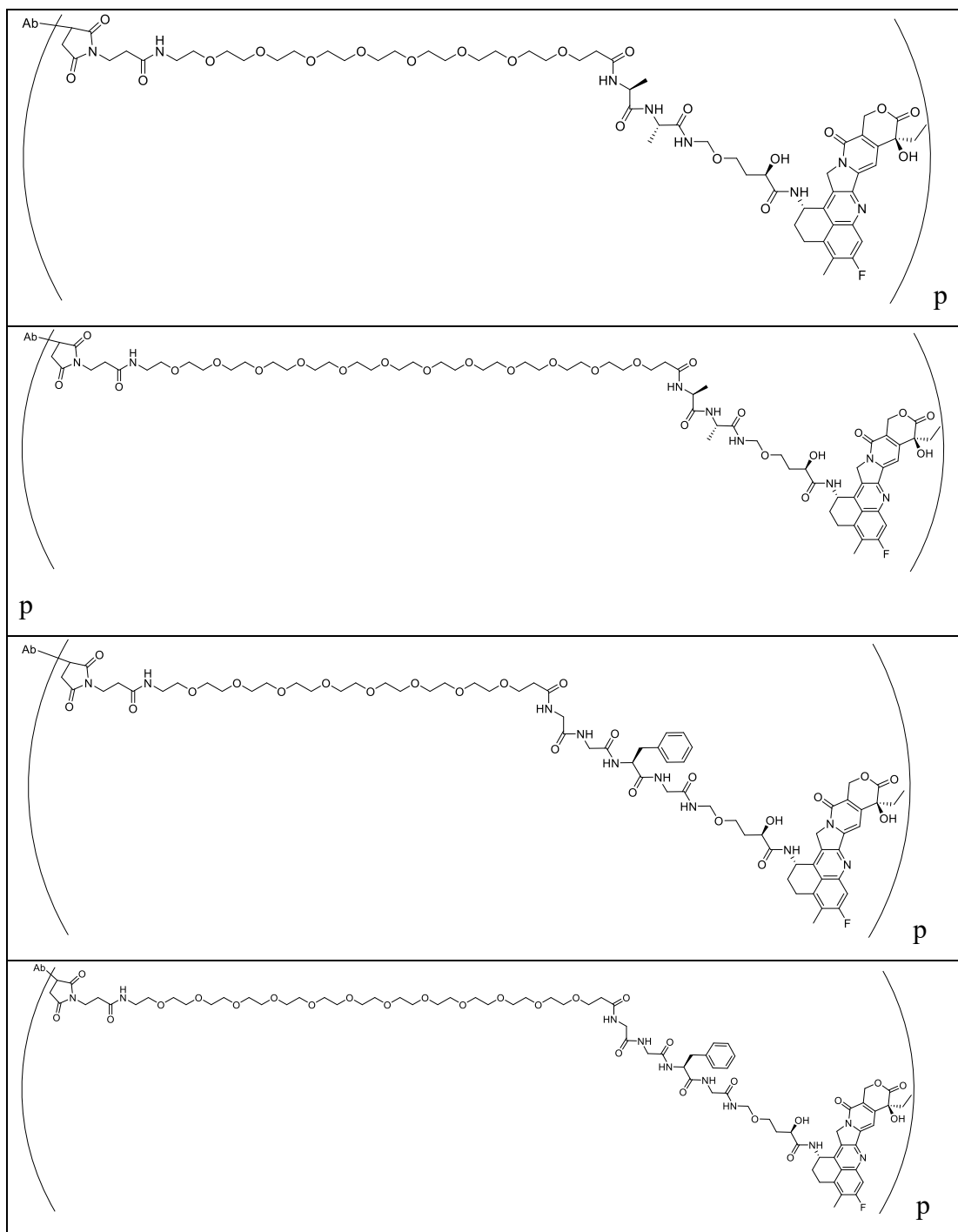
R^a is selected from hydrogen and C_{1-6} alkyl; and

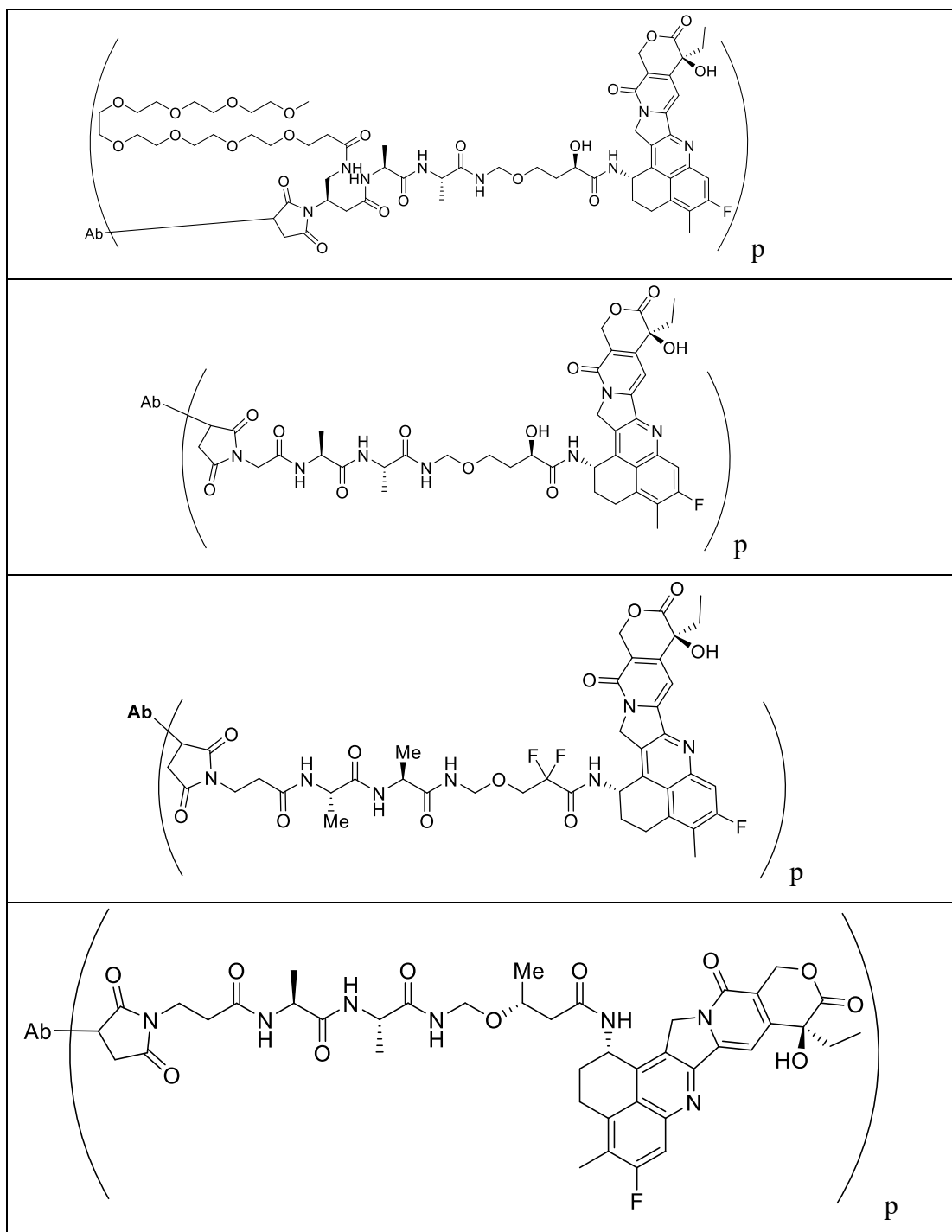
R^d is hydrogen or $-CH_2NHC(O)X^1Q$,

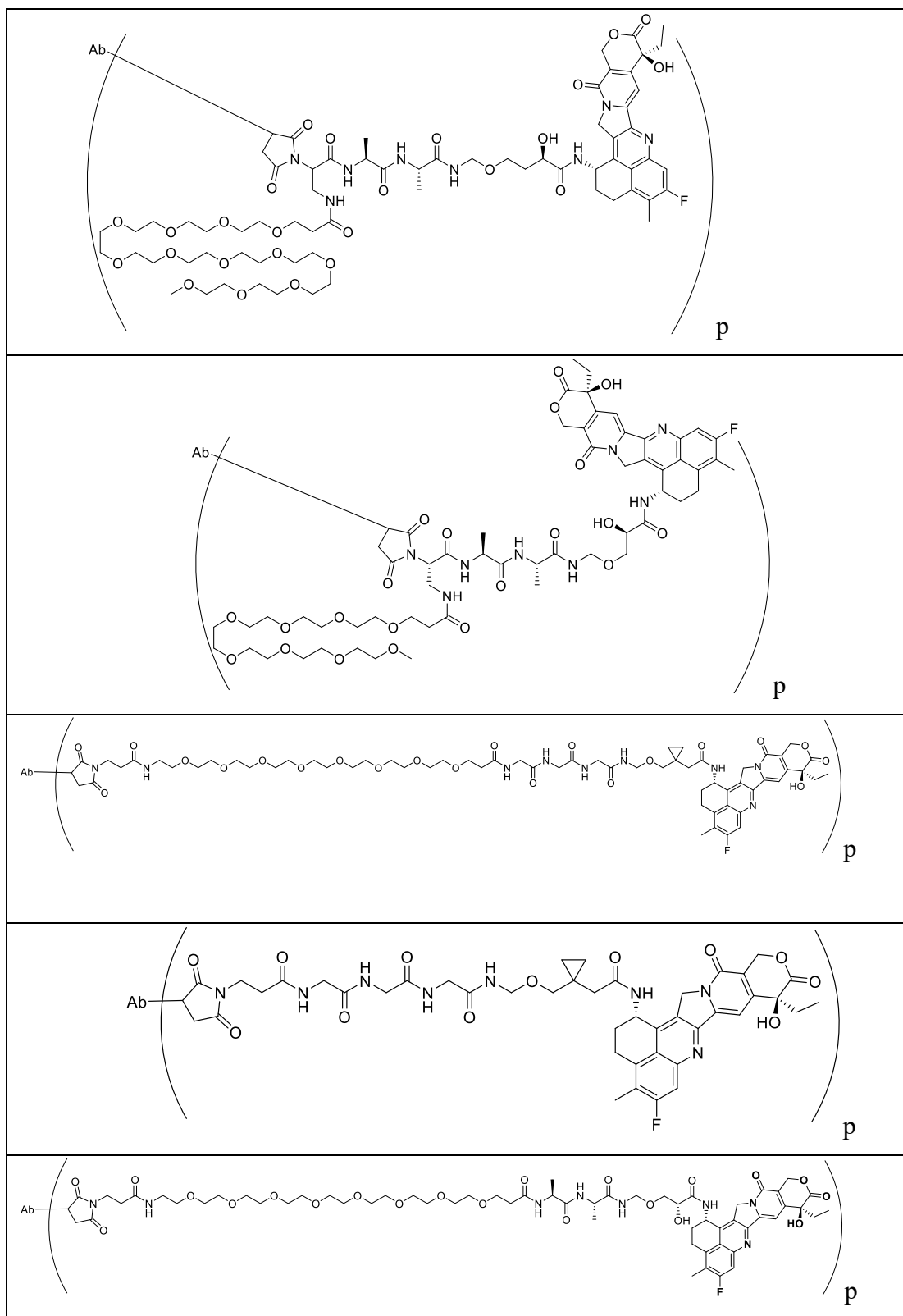
or a pharmaceutically acceptable salt thereof.

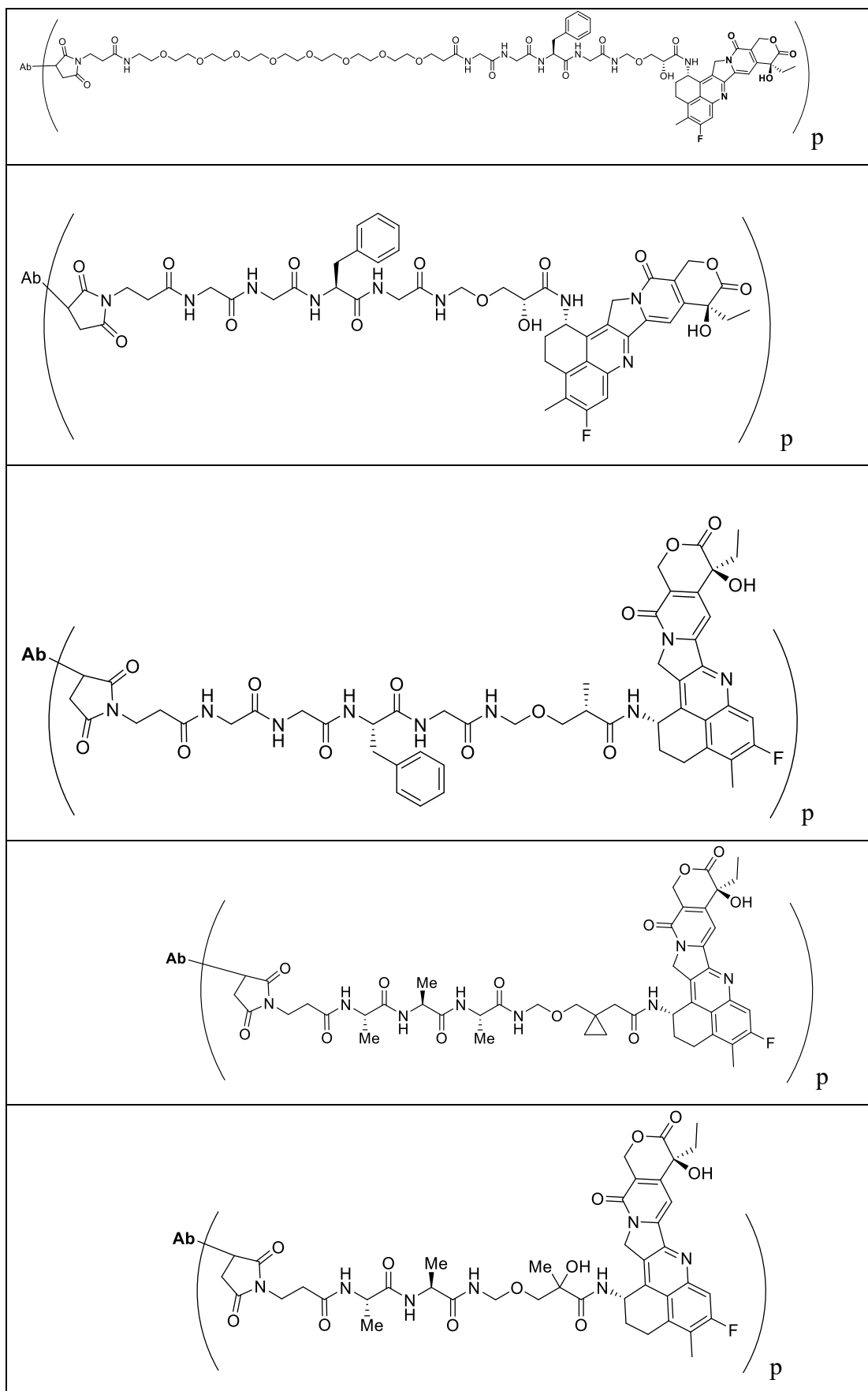
24. The compound according to claim 23, or a pharmaceutically acceptable salt thereof which is:

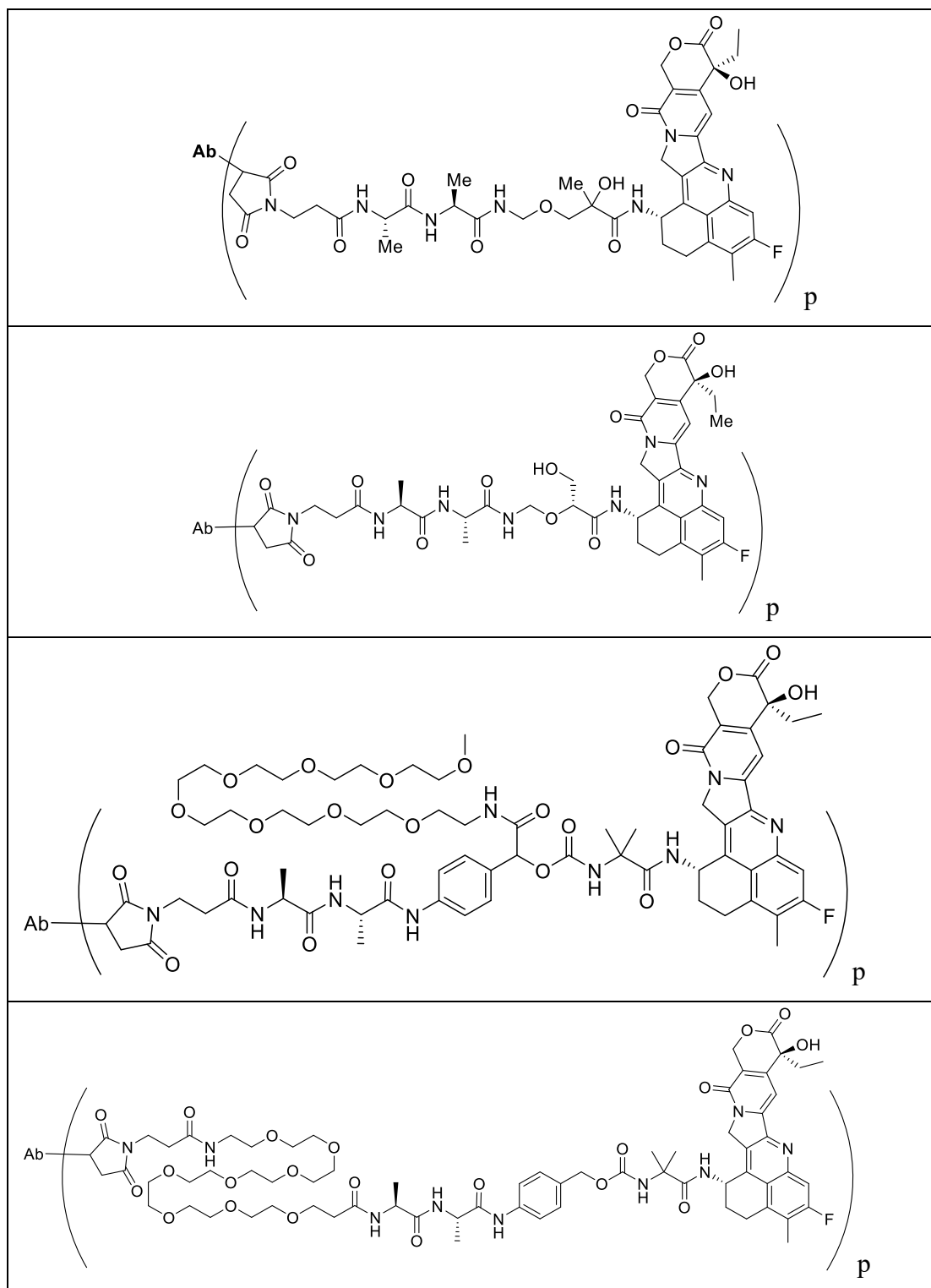


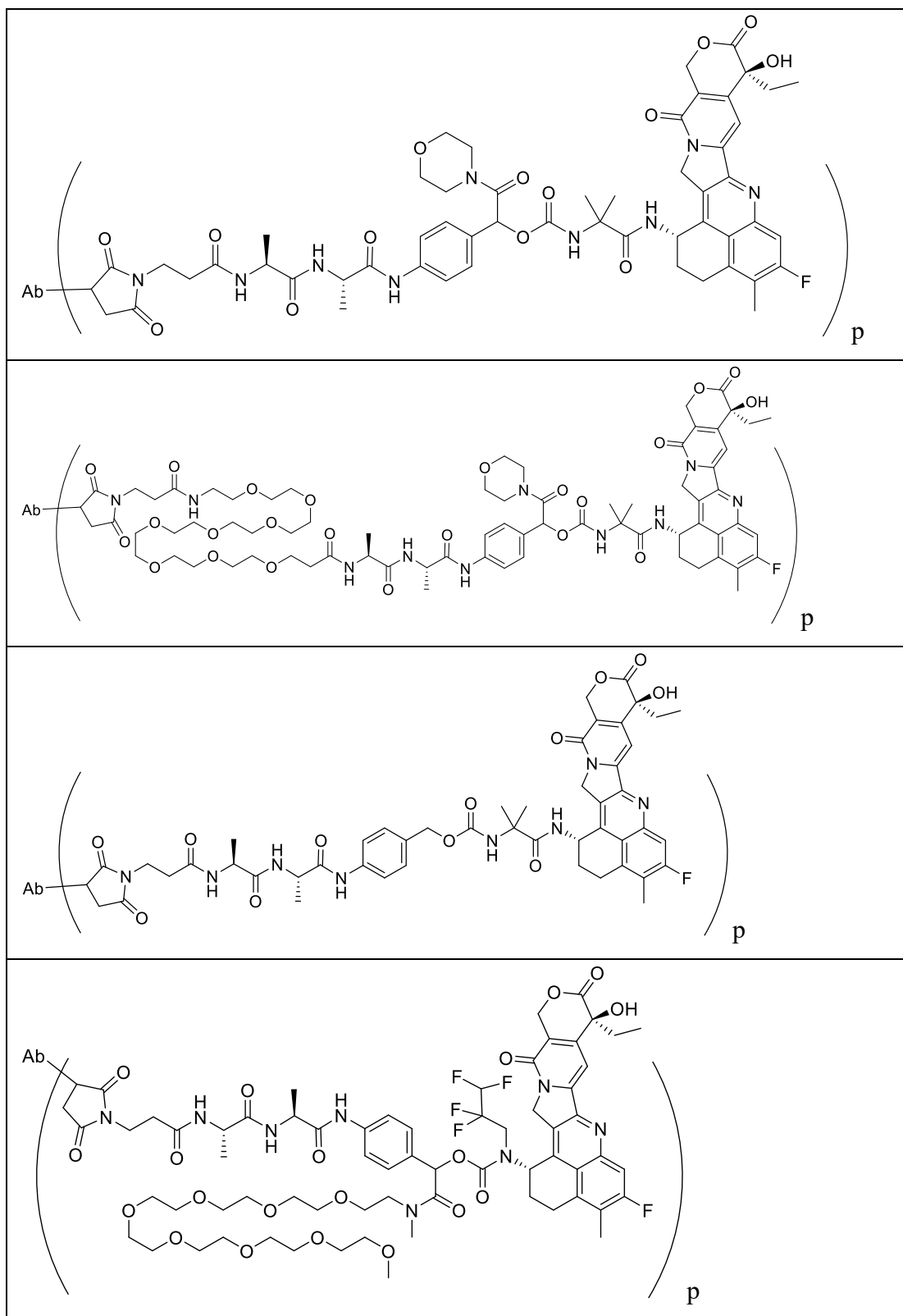


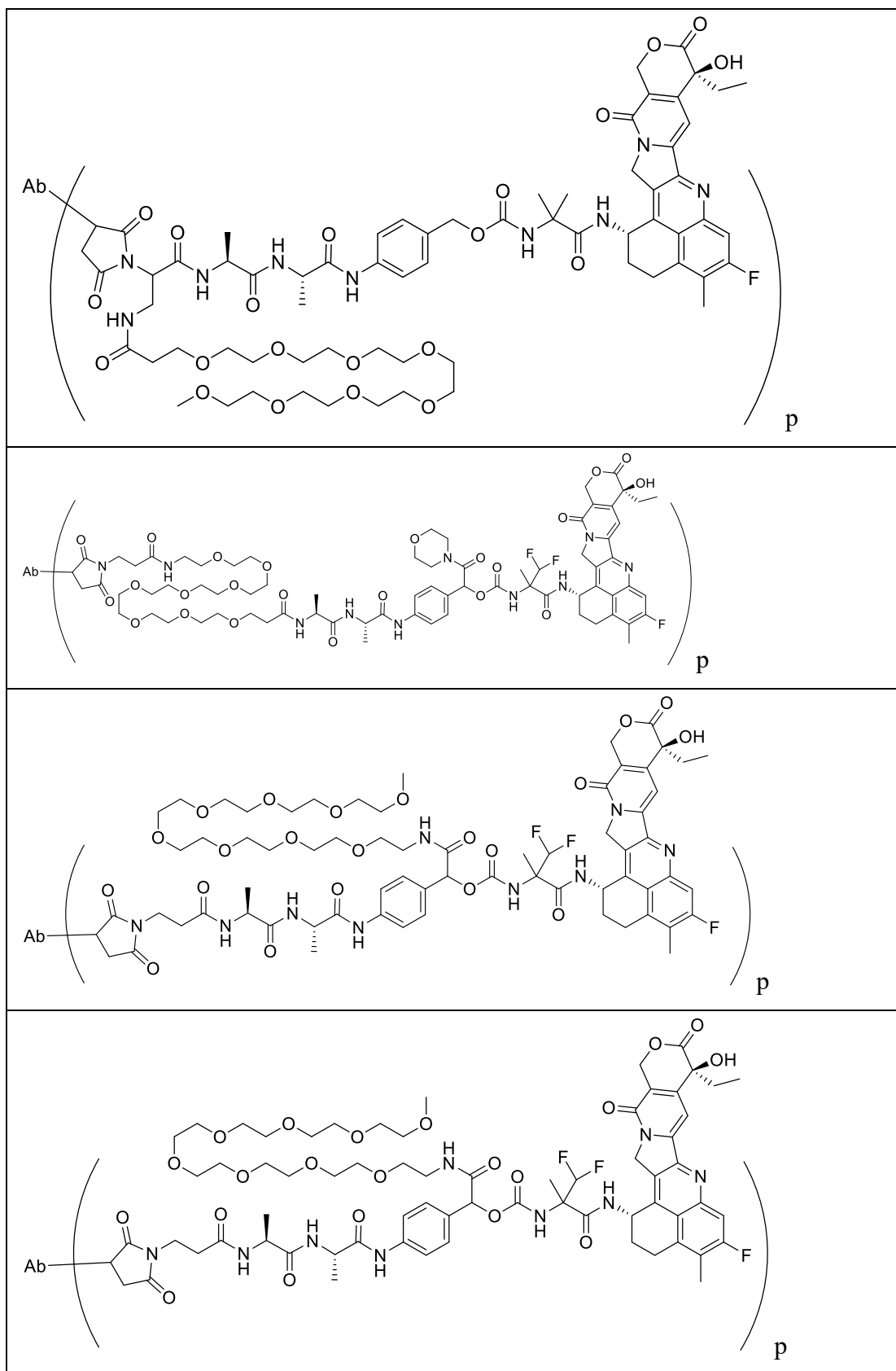






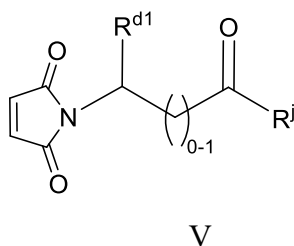






wherein Ab is an antibody and p is an integer 1 to 12.

25. A compound of structural formula V:



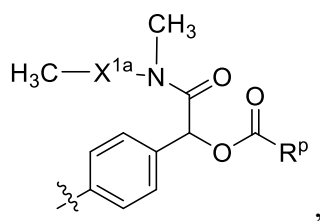
wherein:

R^j is selected from OH, $-NH_2$, $-NHR^kR^g$, $-NHR^kNH(CH_2)_nOR^q$, $-NHR^kNH(CH_2)_nOC(O)CH_3$, $-NHX^{1a}(CH_2)_nC(O)R^kNHCH_2OC(O)CH_3$, $-NHR^kNHR^L$, $-NHX^{1a}R^kNHR^L$, and $-NHCH_2O(CH_2)_nCH(OH)C(O)OH$;

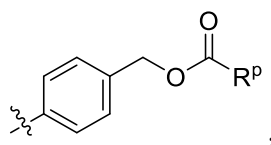
R^g is COOH or CONH₂;

R^k is an amino acid residue of up to 10 amino acids;

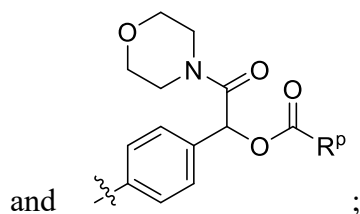
R^L is selected from :



(a)

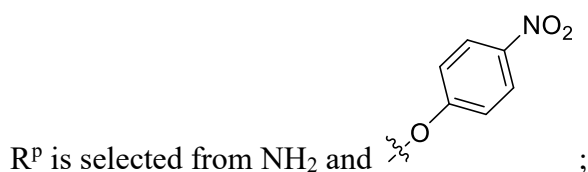


(b)



(c)

and



R^p is selected from NH₂ and ;

R^q is hydrogen or C₁₋₆ alkyl;

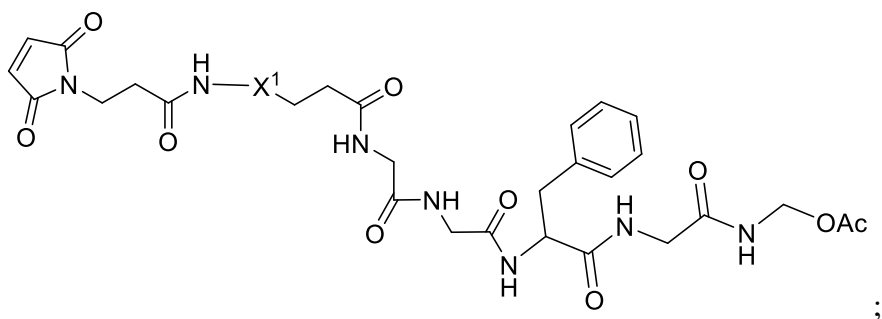
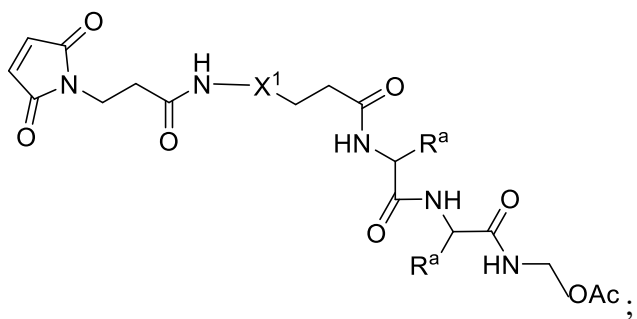
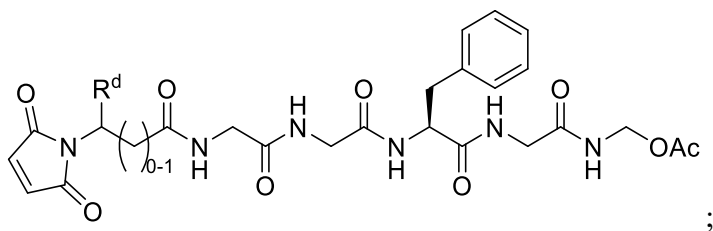
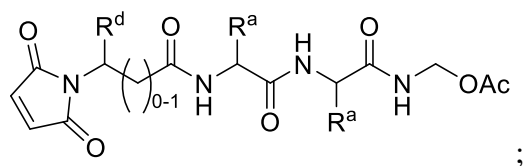
X^{1a} is a PEG of 1 to 24 $-CH_2CH_2O-$ subunits;

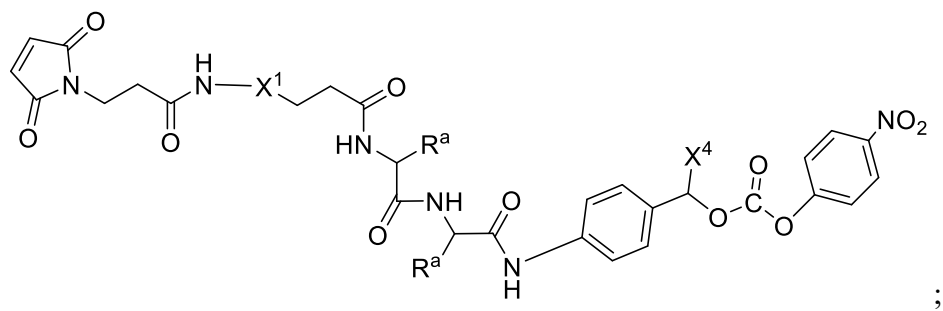
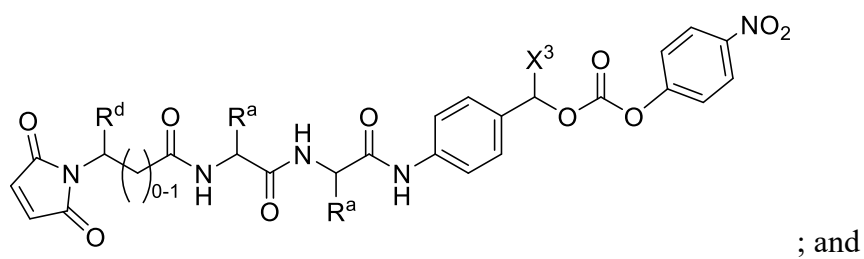
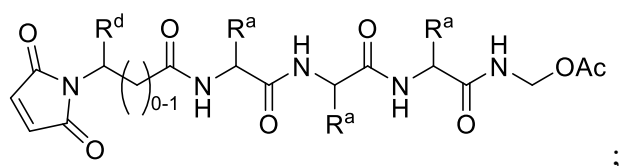
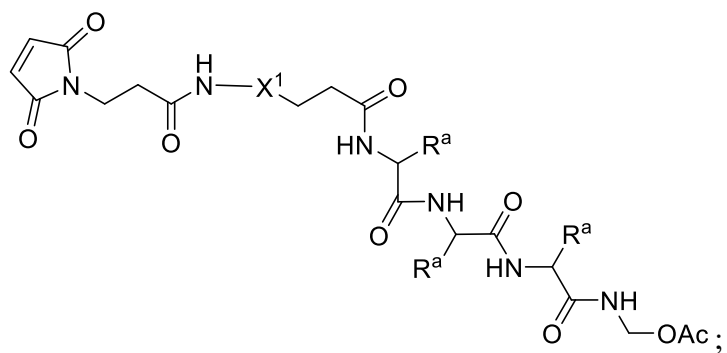
R^{d1} is hydrogen, $-CH_2NHC(O)X^{1a}Q$ or $-CH_2NHC(O)X^{21}Q$;

Q is C₁₋₆ alkyl or H;

X^{21} is selected from a PEG of 1 to 24 $-\text{CH}_2\text{CH}_2\text{O}-$ subunits, PEG-amino sugar, and p-aminobenzylcarbonyl and
 n is 1, 2, 3, or 4.

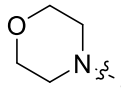
26. A compound of claim 25, selected from:



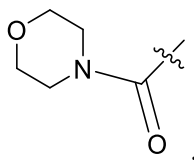


or a pharmaceutically acceptable salt or solvate thereof, wherein

X^1 is a Polyethylene Glycol (PEG);

X^2 is $-NR^aX^1-$, or ,

X^3 is hydrogen or $-C(O)X^2$,

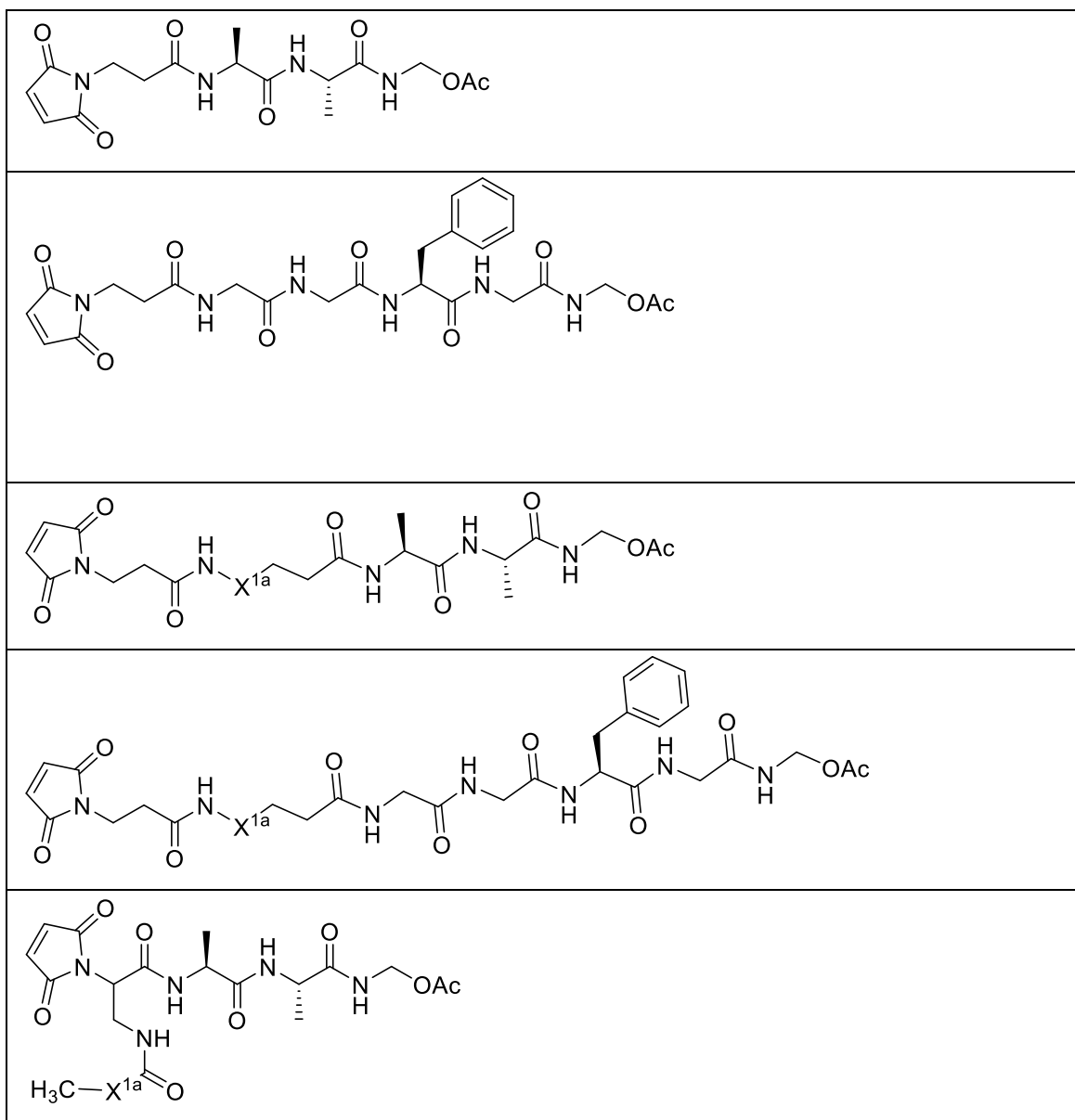


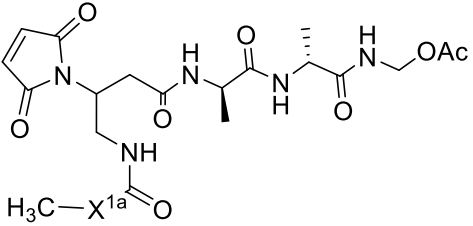
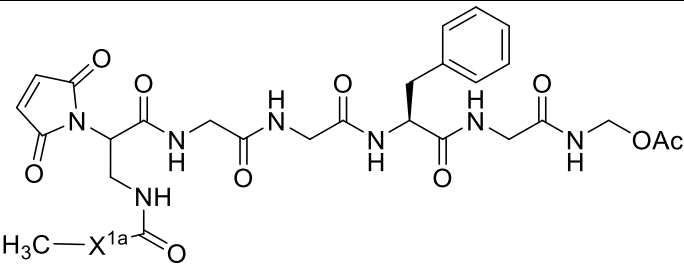
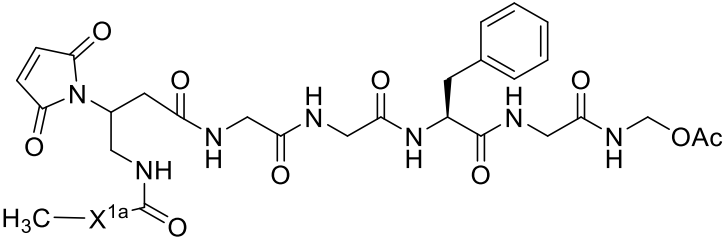
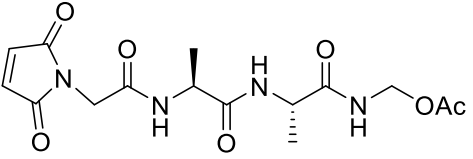
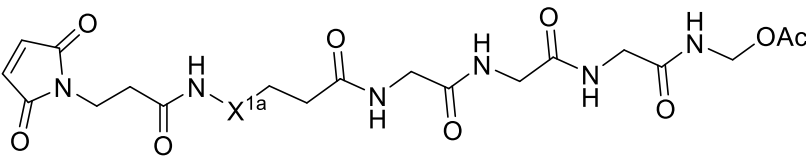
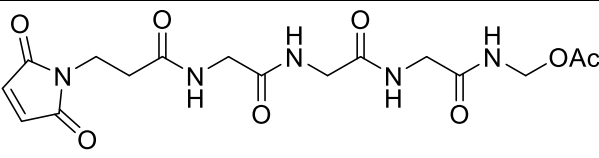
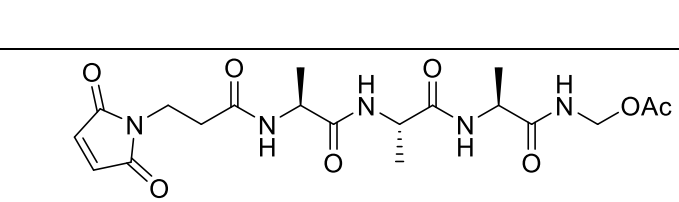
X^4 is hydrogen or

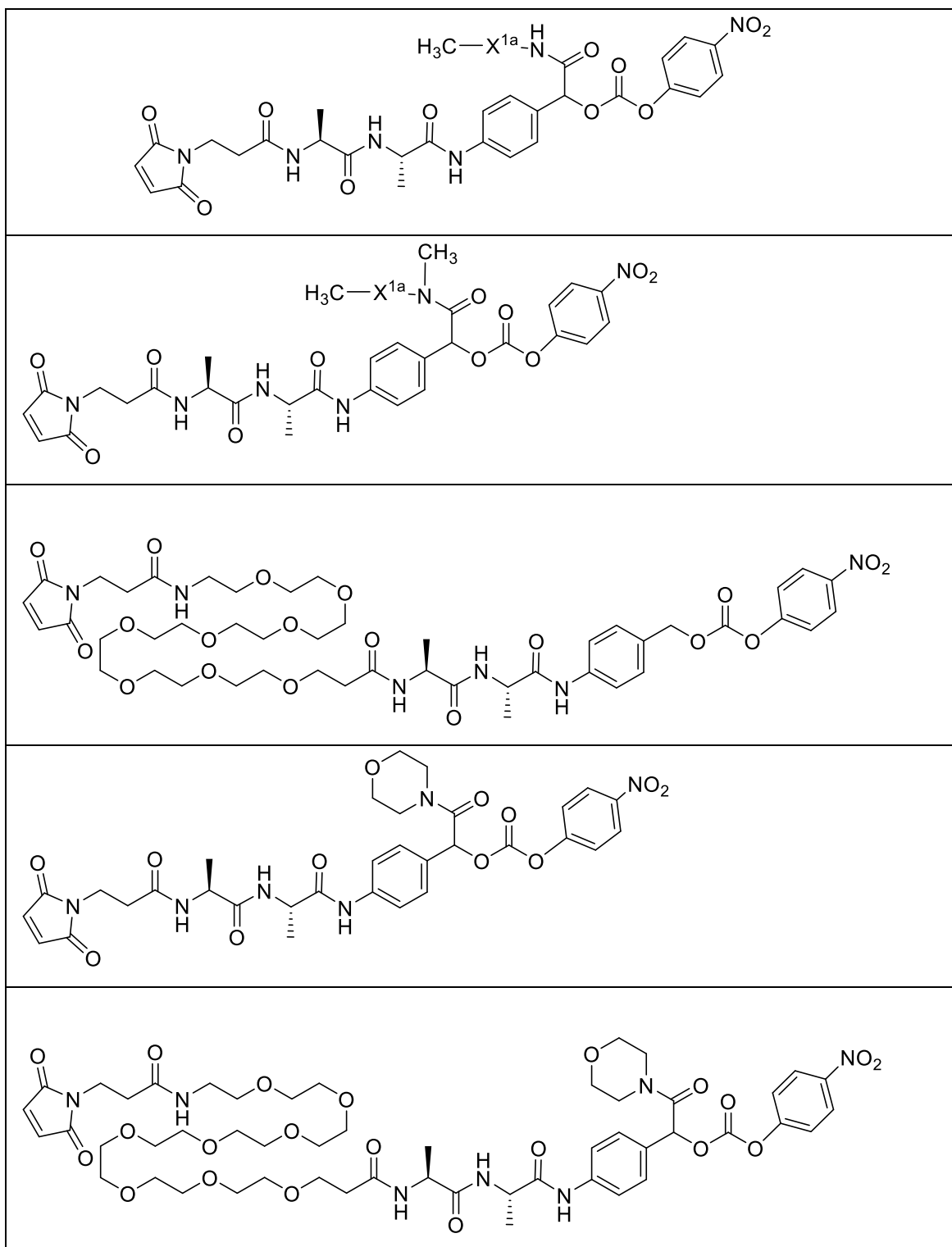
R^a is selected from hydrogen and C_{1-6} alkyl; and

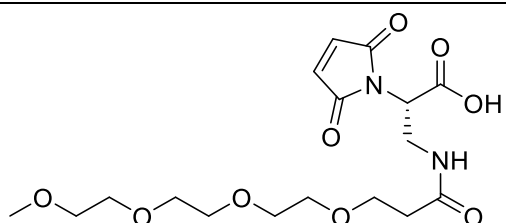
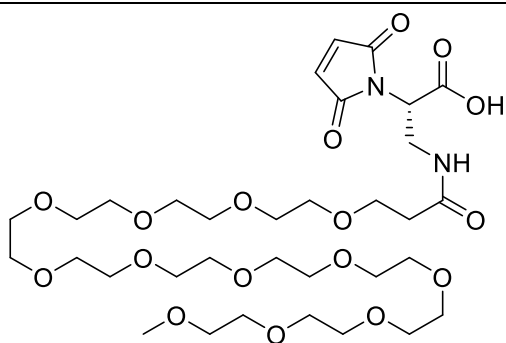
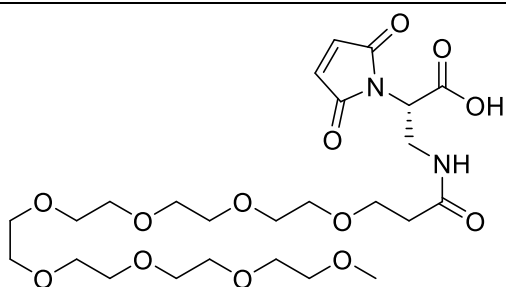
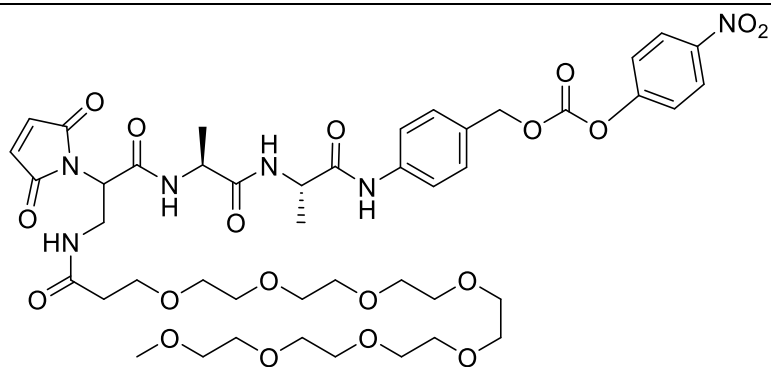
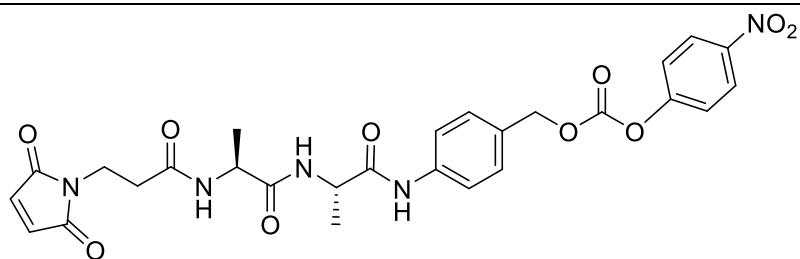
R^d is hydrogen or $-CH_2NHC(O)X^1Q$.

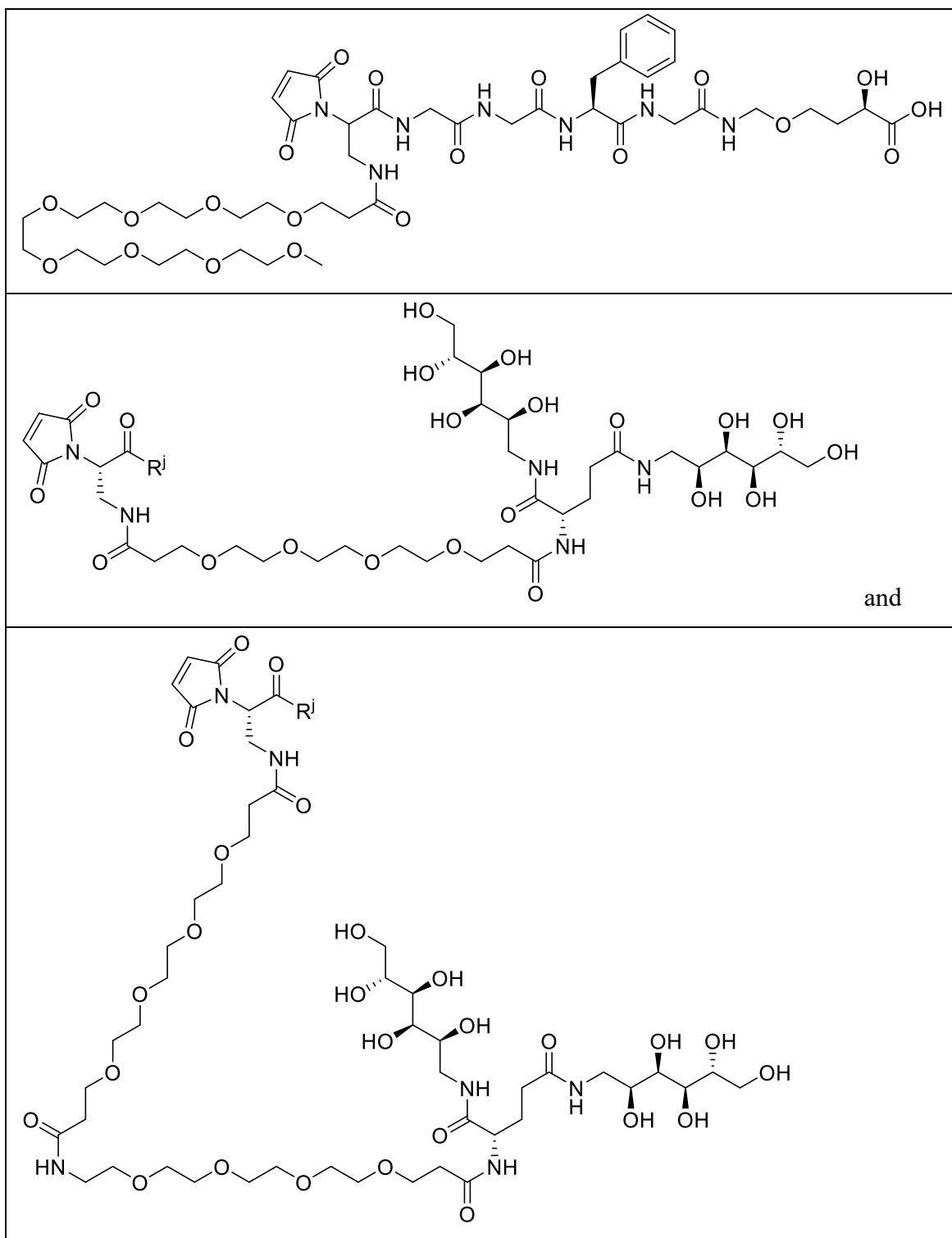
27. The compound according to any of claims 25 -26, selected from:









wherein X^{1a} is a PEG of 1 to 24 $\text{-CH}_2\text{CH}_2\text{O-}$ subunits,

or a salt thereof.

28. A pharmaceutical composition comprising a compound of any of claims 1 to 27, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

29. Use of a compound of any of Claims 1 to 27, or a pharmaceutically acceptable salt thereof, or of the pharmaceutical composition of claim 28, in the manufacture of a medicament for the treatment or prevention of cancers or tumors.

30. The use of claim 29, wherein the cancer is selected from breast cancer, ovarian cancer, cervical cancer, uterine cancer, prostate cancer, kidney cancer, urethral cancer, bladder cancer, liver cancer, stomach cancer, endometrial cancer, salivary gland cancer, esophageal cancer, melanoma, glioma, neuroblastoma, sarcoma, lung cancer, colon cancer, rectal cancer, colorectal cancer, leukemia, bone cancer, skin cancer, thyroid cancer, pancreatic cancer, and lymphoma.

31. The compound or pharmaceutical composition comprising the compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof for use in therapy.