PYRAZOLOAZEPINE IMMUNOCONJUGATES, AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This non-provisional application claims the benefit of priority to U.S. Provisional Application No. 63/065,219, filed 13 August 2020, which is incorporated by reference in its entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on August 5, 2021, is named 17019_009WO1_SL.txt and is 63,469 bytes in size.

FIELD OF THE INVENTION

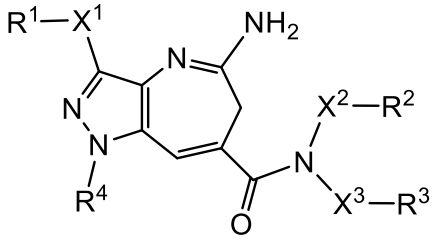
The invention relates generally to an immunoconjugate comprising an antibody conjugated to one or more pyrazoloazepine molecules.

BACKGROUND OF THE INVENTION

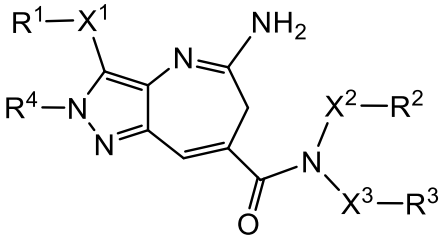
New compositions and methods for the delivery of antibodies and immune adjuvants are needed in order to reach inaccessible tumors and/or to expand treatment options for cancer patients and other subjects. The invention provides such compositions and methods.

SUMMARY

The disclosure is generally directed to immunoconjugates comprising an antibody linked by conjugation to one or more pyrazoloazepine derivatives. The disclosure is further directed to pyrazoloazepine derivative intermediate compositions comprising a reactive functional group. Such intermediate compositions are suitable substrates for formation of immunoconjugates wherein an antibody may be covalently bound by a linker L to a pyrazoloazepine (PAZ) moiety having the formulas:



IIa



IIb;

where one of R^1, R^2, R^3 and R^4 is attached to L. The X^1, X^2, and X^3 and R^1, R^2, R^3 and R^4 substituents are defined herein.

In an aspect, there is provided an immunoconjugate comprising an antibody covalently attached to one or more 5-aminopyrazoloazepine moieties by a linker, and having Formula I:

$$Ab–[L–PAZ]_p \qquad I$$

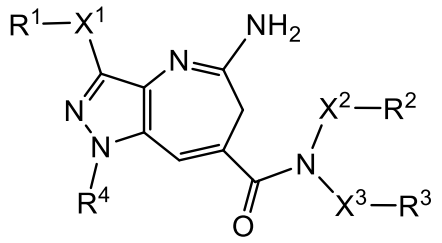
or a pharmaceutically acceptable salt thereof,

wherein:

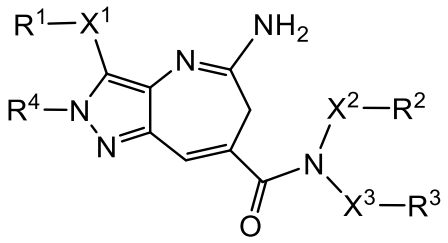
Ab is the antibody;

p is an integer from 1 to 8;

PAZ is the 5-aminopyrazoloazepine moiety selected from formulas IIa and IIb:



IIa



IIb;

X^1, X^2, and X^3 are independently selected from the group consisting of a bond, C(=O), C(=O)N(R^5), O, N(R^5), S, S(O)$_2$, and S(O)$_2$N(R^5);

R^1, R^2, R^3, and R^4 are independently selected from the group consisting of H, C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{12} carbocyclyl, C_6-C_{20} aryl, C_2-C_9 heterocyclyl, and C_1-C_{20} heteroaryl, where alkyl, alkenyl, alkynyl, carbocyclyl, aryl, heterocyclyl, and heteroaryl are independently and optionally substituted with one or more groups selected from:

–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_1-C_{12} alkyldiyl)–OR^5;

–(C_3-C_{12} carbocyclyl);

–(C_3-C_{12} carbocyclyl)–*;

–(C_3-C_{12} carbocyclyl)–(C_1-C_{12} alkyldiyl)–NR^5–*;

–(C_3-C_{12} carbocyclyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_3-C_{12} carbocyclyl)–NR^5–C(=NR^5)NR^5–*;

–(C_6-C_{20} aryl);

–(C_6-C_{20} aryldiyl)–*;

–(C_6-C_{20} aryldiyl)–N(R^5)–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–NR^5–C(=NR^{5a})N(R^5)–*;

–(C_2-C_{20} heterocyclyl);

–(C_2-C_{20} heterocyclyl)–*;

–(C_2-C_9 heterocyclyl)–(C_1-C_{12} alkyldiyl)–NR^5–*;

–(C_2-C_9 heterocyclyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_2-C_9 heterocyclyl)–C(=O)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_2-C_9 heterocyclyl)–NR^5–C(=NR^{5a})NR^5–*;

–(C_2-C_9 heterocyclyl)–NR^5–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_2-C_9 heterocyclyl)–(C_6-C_{20} aryldiyl)–*;

–(C_1-C_{20} heteroaryl);

–(C_1-C_{20} heteroaryldiyl)–*;

–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_1-C_{20} heteroaryldiyl)–NR^5–C(=NR^{5a})N(R^5)–*;

–(C_1-C_{20} heteroaryldiyl)–N(R^5)C(=O)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–C(=O)–*;

–C(=O)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–C(=O)–(C_2-C_{20} heterocyclyldiyl)–*;

–C(=O)N(R^5)$_2$;

–C(=O)N(R^5)–*;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–*;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–C(=O)N(R^5)–*;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)R^5;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)N(R^5)$_2$;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–N(R^5)CO_2R^5;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–N(R^5)C(=NR^{5a})N(R^5)$_2$;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–NR^5C(=NR^{5a})R^5;

–C(=O)NR^5–(C_1-C_8 alkyldiyl)–NR^5(C_2-C_5 heteroaryl);

–C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–N(R^5)–*;

–C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–*;

–C(=O)NR^5–(C$_1$-C$_{20}$ heteroaryldiyl)–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)$_2$;

–C(=O)NR^5–(C$_1$-C$_{20}$ heteroaryldiyl)–(C$_2$-C$_{20}$ heterocyclyldiyl)–C(=O)NR^5–(C$_1$-C$_{12}$ alkyldiyl)–NR^5–*;

–N(R^5)$_2$;

–N(R^5)–*;

–N(R^5)C(=O)R^5;

–N(R^5)C(=O)–*;

–N(R^5)C(=O)N(R^5)$_2$;

–N(R^5)C(=O)N(R^5)–*;

–N(R^5)CO$_2$R^5;

–N(R^5)CO$_2$(R^5)–*;

–NR^{5}C(=NR^{5a})N(R^5)$_2$;

–NR^{5}C(=NR^{5a})N(R^5)–*;

–NR^{5}C(=NR^{5a})R^5;

–N(R^5)C(=O)–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)–*;

–N(R^5)–(C$_2$-C$_5$ heteroaryl);

–N(R^5)–S(=O)$_2$–(C$_1$-C$_{12}$ alkyl);

–O–(C$_1$-C$_{12}$ alkyl);

–O–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)$_2$;

–O–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)–*;

–OC(=O)N(R^5)$_2$;

–OC(=O)N(R^5)–*;

–S(=O)$_2$–(C$_2$-C$_{20}$ heterocyclyldiyl)–*;

–S(=O)$_2$–(C$_2$-C$_{20}$ heterocyclyldiyl)–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)$_2$;

–S(=O)$_2$–(C$_2$-C$_{20}$ heterocyclyldiyl)–(C$_1$-C$_{12}$ alkyldiyl)–NR^5–*; and

–S(=O)$_2$–(C$_2$-C$_{20}$ heterocyclyldiyl)–(C$_1$-C$_{12}$ alkyldiyl)–OH;

or R^2 and R^3 together form a 5- or 6-membered heterocyclyl ring;

R^5 is selected from the group consisting of H, C$_6$-C$_{20}$ aryl, C$_3$-C$_{12}$ carbocyclyl, C$_2$-C$_{20}$ heterocyclyl, C$_6$-C$_{20}$ aryldiyl, C$_1$-C$_{12}$ alkyl, and C$_1$-C$_{12}$ alkyldiyl, or two R^5 groups together form a 5- or 6-membered heterocyclyl ring;

R^{5a} is selected from the group consisting of C$_6$-C$_{20}$ aryl and C$_1$-C$_{20}$ heteroaryl;

where the asterisk * indicates the attachment site of L, and where one of R^1, R^2, R^3 and R^4 is attached to L;

L is the linker selected from the group consisting of:

–C(=O)–PEG–;

–C(=O)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–C(=O)–Gluc–;

–C(=O)–PEG–O–;

–C(=O)–PEG–O–C(=O)–;

–C(=O)–PEG–C(=O)–;

–C(=O)–PEG–C(=O)–PEP–;

–C(=O)–PEG–N(R^6)–;

–C(=O)–PEG–N(R^6)–C(=O)–;

–C(=O)–PEG–N(R^6)–PEG–C(=O)–PEP–;

–C(=O)–PEG–N^+(R^6)$_2$–PEG–C(=O)–PEP–;

–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

–C(=O)–PEG–SS–(C_1-C_{12} alkyldiyl)–OC(=O)–;

–C(=O)–PEG–SS–(C_1-C_{12} alkyldiyl)–C(=O)–;

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–;

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^5)–C(=O);

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–C(=O)–Gluc–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–O–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–O–C(=O)–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–C(=O)–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–N(R^5)–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–N(R^5)–C(=O)–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–C(=O)–PEP–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–SS–(C_1-C_{12} alkyldiyl)–OC(=O)–;

–succinimidyl–(CH_2)$_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

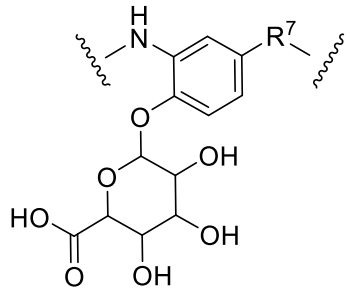
–succinimidyl–(CH_2)$_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–; and

–succinimidyl–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

R^6 is independently H or C_1-C_6 alkyl;

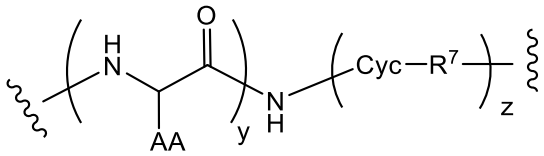
PEG has the formula: –$(CH_2CH_2O)_n$–$(CH_2)_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

Gluc has the formula:



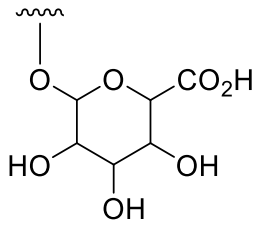
;

PEP has the formula:



where AA is independently selected from a natural or unnatural amino acid side chain, or one or more of AA, and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment;

Cyc is selected from C_6-C_{20} aryldiyl and C_1-C_{20} heteroaryldiyl, optionally substituted with one or more groups selected from F, Cl, NO_2, –OH, $–OCH_3$, and a glucuronic acid having the structure:



;

R^7 is selected from the group consisting of $–CH(R^8)O–$, $–CH_2–$, $–CH_2N(R^8)–$, and $–CH(R^8)O–C(=O)–$, where R^8 is selected from H, C_1-C_6 alkyl, $C(=O)–C_1$-C_6 alkyl, and $–C(=O)N(R^9)_2$, where R^9 is independently selected from the group consisting of H, C_1-C_{12} alkyl, and $–(CH_2CH_2O)_n–(CH_2)_m–OH$, where m is an integer from 1 to 5, and n is an integer from 2 to 50, or two R^9 groups together form a 5- or 6-membered heterocyclyl ring;

y is an integer from 2 to 12;

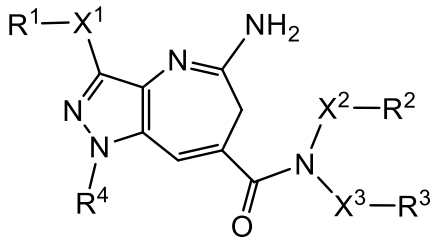
z is 0 or 1; and

alkyl, alkyldiyl, alkenyl, alkenyldiyl, alkynyl, alkynyldiyl, aryl, aryldiyl, carbocyclyl, carbocyclyldiyl, heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl are independently and optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, $–CH_3$, $–CH_2CH_3$, $–CH=CH_2$, $–C\equiv CH$, $–C\equiv CCH_3$, $–CH_2CH_2CH_3$, $–CH(CH_3)_2$, $–CH_2CH(CH_3)_2$, $–CH_2OH$, $–CH_2OCH_3$, $–CH_2CH_2OH$, $–C(CH_3)_2OH$, $–CH(OH)CH(CH_3)_2$, $–C(CH_3)_2CH_2OH$, $–CH_2CH_2SO_2CH_3$, $–CH_2OP(O)(OH)_2$, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CF_3$, $–CH_2CHF_2$, $–CH(CH_3)CN$, $–C(CH_3)_2CN$, $–CH_2CN$, $–CH_2NH_2$, $–CH_2NHSO_2CH_3$, $–CH_2NHCH_3$, $–CH_2N(CH_3)_2$, $–CO_2H$, $–COCH_3$, $–CO_2CH_3$, $–CO_2C(CH_3)_3$, $–COCH(OH)CH_3$, $–CONH_2$, $–CONHCH_3$, $–CON(CH_3)_2$, $–C(CH_3)_2CONH_2$, $–NH_2$, $–NHCH_3$, $–N(CH_3)_2$, $–NHCOCH_3$, $–N(CH_3)COCH_3$, $–NHS(O)_2CH_3$, $–N(CH_3)C(CH_3)_2CONH_2$, $–N(CH_3)CH_2CH_2S(O)_2CH_3$, – NHC(=NH)H, $–NHC(=NH)CH_3$, $–NHC(=NH)NH_2$, $–NHC(=O)NH_2$, $–NO_2$, =O, –OH, $–OCH_3$, $–OCH_2CH_3$, $–OCH_2CH_2OCH_3$, $–OCH_2CH_2OH$, $–OCH_2CH_2N(CH_3)_2$, $–O(CH_2CH_2O)_n–(CH_2)_mCO_2H$, $–O(CH_2CH_2O)_nH$, $–OP(O)(OH)_2$, $–S(O)_2N(CH_3)_2$, $–SCH_3$, $–S(O)_2CH_3$, and $–S(O)_3H$.

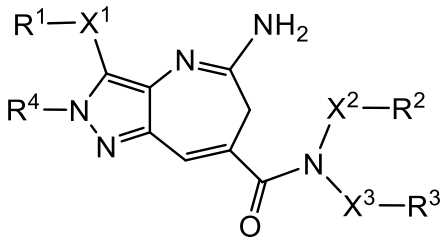
The disclosure is further directed to use of such an immunoconjugates in the treatment of an illness, in particular cancer.

An example of the disclosure is an immunoconjugate comprising an antibody covalently attached to a linker which is covalently attached to one or more pyrazoloazepine moieties.

Another example of the disclosure is a 5-aminopyrazoloazepine-linker compound selected from formulas IIa and IIb:



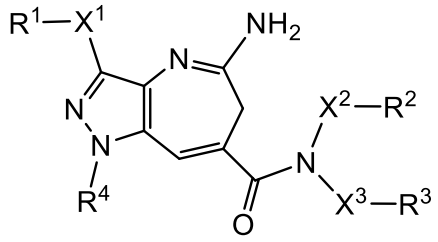
IIa

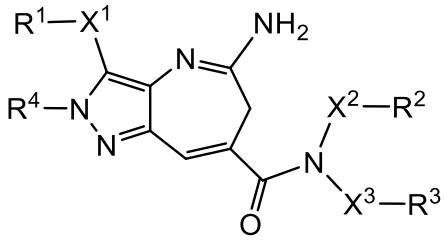


IIb;

where one of R^1, R^2, R^3, and R^4 is attached to L.

In another aspect, there is provided a 5-aminopyrazoloazepine-linker compound selected from formulas IIa and IIb:


IIa


IIb;

wherein X^1, X^2, and X^3 are independently selected from the group consisting of a bond, C(=O), C(=O)N(R^5), O, N(R^5), S, S(O)$_2$, and S(O)$_2$N(R^5);

R^1, R^2, R^3, and R^4 are independently selected from the group consisting of H, C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{12} carbocyclyl, C_6-C_{20} aryl, C_2-C_9 heterocyclyl, and C_1-C_{20} heteroaryl, where alkyl, alkenyl, alkynyl, carbocyclyl, aryl, heterocyclyl, and heteroaryl are independently and optionally substituted with one or more groups selected from:

–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_1-C_{12} alkyldiyl)–OR^5;

–(C_3-C_{12} carbocyclyl);

–(C_3-C_{12} carbocyclyl)–*;

–(C_3-C_{12} carbocyclyl)–(C_1-C_{12} alkyldiyl)–NR^5–*;

–(C_3-C_{12} carbocyclyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_3-C_{12} carbocyclyl)–NR^5–C(=NR^5)NR^5–*;

–(C_6-C_{20} aryl);

–(C_6-C_{20} aryldiyl)–*;

–(C_6-C_{20} aryldiyl)–N(R^5)–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–NR^5–C(=NR^{5a})N(R^5)–*;

–(C_2-C_{20} heterocyclyl);

–(C_2-C_{20} heterocyclyl)–*;

–(C_2-C_9 heterocyclyl)–(C_1-C_{12} alkyldiyl)–NR^5–*;

–(C_2-C_9 heterocyclyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_2-C_9 heterocyclyl)–C(=O)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_2-C_9 heterocyclyl)–NR^5–C(=NR^{5a})NR^5–*;

–(C_2-C_9 heterocyclyl)–NR^5–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–(C_2-C_9 heterocyclyl)–(C_6-C_{20} aryldiyl)–*;

–(C_1-C_{20} heteroaryl);

–(C_1-C_{20} heteroaryldiyl)–*;

–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)_2$;

–(C_1-C_{20} heteroaryldiyl)–NR^5–$C(=NR^{5a})N(R^5)$–*;

–(C_1-C_{20} heteroaryldiyl)–$N(R^5)C(=O)$–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–C(=O)–*;

–C(=O)–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–C(=O)–(C_2-C_{20} heterocyclyldiyl)–*;

–$C(=O)N(R^5)_2$;

–$C(=O)N(R^5)$–*;

–$C(=O)N(R^5)$–(C_1-C_{12} alkyldiyl)–*;

–$C(=O)N(R^5)$–(C_1-C_{12} alkyldiyl)–$C(=O)N(R^5)$–*;

–$C(=O)N(R^5)$–(C_1-C_{12} alkyldiyl)–$N(R^5)C(=O)R^5$;

–$C(=O)N(R^5)$–(C_1-C_{12} alkyldiyl)–$N(R^5)C(=O)N(R^5)_2$;

–$C(=O)NR^5$–(C_1-C_{12} alkyldiyl)–$N(R^5)CO_2R^5$;

–$C(=O)NR^5$–(C_1-C_{12} alkyldiyl)–$N(R^5)C(=NR^{5a})N(R^5)_2$;

–$C(=O)NR^5$–(C_1-C_{12} alkyldiyl)–$NR^5C(=NR^{5a})R^5$;

–$C(=O)NR^5$–(C_1-C_8 alkyldiyl)–NR^5(C_2-C_5 heteroaryl);

–$C(=O)NR^5$–(C_1-C_{20} heteroaryldiyl)–$N(R^5)$–*;

–$C(=O)NR^5$–(C_1-C_{20} heteroaryldiyl)–*;

–$C(=O)NR^5$–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)_2$;

–$C(=O)NR^5$–(C_1-C_{20} heteroaryldiyl)–(C_2-C_{20} heterocyclyldiyl)–$C(=O)NR^5$–(C_1-C_{12} alkyldiyl)–NR^5–*;

–$N(R^5)_2$;

–$N(R^5)$–*;

–$N(R^5)C(=O)R^5$;

–$N(R^5)C(=O)$–*;

–$N(R^5)C(=O)N(R^5)_2$;

–$N(R^5)C(=O)N(R^5)$–*;

–$N(R^5)CO_2R^5$;

–$N(R^5)CO_2(R^5)$–*;

–$NR^5C(=NR^{5a})N(R^5)_2$;

–$NR^5C(=NR^{5a})N(R^5)$–*;

–$NR^5C(=NR^{5a})R^5$;

–$N(R^5)C(=O)$–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–$N(R^5)$–(C_2-C_5 heteroaryl);

–$N(R^5)$–$S(=O)_2$–(C_1-C_{12} alkyl);

–O–(C_1-C_{12} alkyl);

–O–(C_1-C_{12} alkyldiyl)–$N(R^5)_2$;

–O–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–$OC(=O)N(R^5)_2$;

–$OC(=O)N(R^5)$–*;

–$S(=O)_2$–(C_2-C_{20} heterocyclyldiyl)–*;

–$S(=O)_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)_2$;

–$S(=O)_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–NR^5–*; and

–$S(=O)_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–OH;

or R^2 and R^3 together form a 5- or 6-membered heterocyclyl ring;

R^5 is selected from the group consisting of H, C_6-C_{20} aryl, C_3-C_{12} carbocyclyl, C_2-C_{20} heterocyclyl, C_6-C_{20} aryldiyl, C_1-C_{12} alkyl, and C_1-C_{12} alkyldiyl, or two R^5 groups together form a 5- or 6-membered heterocyclyl ring;

R^{5a} is selected from the group consisting of C_6-C_{20} aryl and C_1-C_{20} heteroaryl;

where the asterisk * indicates the attachment site of L, and where one of R^1, R^2, R^3 and R^4 is attached to L;

L is the linker selected from the group consisting of:

Q–C(=O)–PEG–;

Q–C(=O)–PEG–$C(=O)N(R^6)$–(C_1-C_{12} alkyldiyl)–C(=O)–Gluc–;

Q–C(=O)–PEG–O–;

Q–C(=O)–PEG–O–C(=O)–;

Q–C(=O)–PEG–C(=O)–;

Q–C(=O)–PEG–C(=O)–PEP–;

Q–C(=O)–PEG–$N(R^6)$–;

Q–C(=O)–PEG–$N(R^6)$–C(=O)–;

Q–C(=O)–PEG–$N(R^6)$–PEG–C(=O)–PEP–;

Q–C(=O)–PEG–$N^+(R^6)_2$–PEG–C(=O)–PEP–;

Q–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

Q–C(=O)–PEG–SS–(C_1-C_{12} alkyldiyl)–OC(=O)–;

Q–C(=O)–PEG–SS–(C_1-C_{12} alkyldiyl)–C(=O)–;

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–;

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^5)–C(=O);

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–C(=O)–Gluc–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–O–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–O–C(=O)–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–C(=O)–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–N(R^5)–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–N(R^5)–C(=O)–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–C(=O)–PEP–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–SS–(C_1-C_{12} alkyldiyl)–OC(=O)–;

Q–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

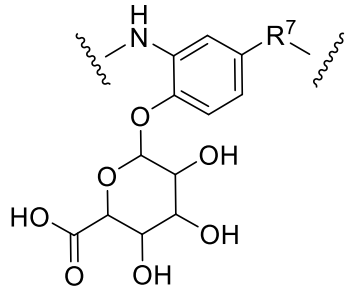
Q–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–; and

Q–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

R^6 is independently H or C_1-C_6 alkyl;

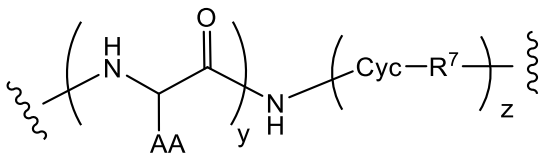
PEG has the formula: –$(CH_2CH_2O)_n$–$(CH_2)_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

Gluc has the formula:



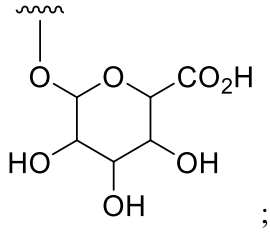
;

PEP has the formula:



where AA is independently selected from a natural or unnatural amino acid side chain, or one or more of AA, and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment;

Cyc is selected from C_6-C_{20} aryldiyl and C_1-C_{20} heteroaryldiyl, optionally substituted with one or more groups selected from F, Cl, NO_2, –OH, $–OCH_3$, and a glucuronic acid having the structure:



;

R^7 is selected from the group consisting of $–CH(R^8)O–$, $–CH_2–$, $–CH_2N(R^8)–$, and $–CH(R^8)O–C(=O)–$, where R^8 is selected from H, C_1-C_6 alkyl, $C(=O)–C_1$-C_6 alkyl, and $–C(=O)N(R^9)_2$, where R^9 is independently selected from the group consisting of H, C_1-C_{12} alkyl, and $–(CH_2CH_2O)_n–(CH_2)_m–OH$, where m is an integer from 1 to 5, and n is an integer from 2 to 50, or two R^9 groups together form a 5- or 6-membered heterocyclyl ring;

y is an integer from 2 to 12;

z is 0 or 1; and

Q is selected from the group consisting of N-hydroxysuccinimidyl, N-hydroxysulfosuccinimidyl, maleimide, and phenoxy substituted with one or more groups independently selected from F, Cl, NO_2, and SO_3^-;

where alkyl, alkyldiyl, alkenyl, alkenyldiyl, alkynyl, alkynyldiyl, aryl, aryldiyl carbocyclyl, carbocyclyldiyl, heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl are optionally

substituted with one or more groups independently selected from F, Cl, Br, I, –CN, –CH_3, –CH_2CH_3, –CH=CH_2, –C≡CH, –C≡CCH_3, –$CH_2CH_2CH_3$, –$CH(CH_3)_2$, –$CH_2CH(CH_3)_2$, –CH_2OH, –CH_2OCH_3, –CH_2CH_2OH, –$C(CH_3)_2OH$, –$CH(OH)CH(CH_3)_2$, –$C(CH_3)_2CH_2OH$, –$CH_2CH_2SO_2CH_3$, –$CH_2OP(O)(OH)_2$, –CH_2F, –CHF_2, –CF_3, –CH_2CF_3, –CH_2CHF_2, –$CH(CH_3)CN$, –$C(CH_3)_2CN$, –CH_2CN, –CH_2NH_2, –$CH_2NHSO_2CH_3$, –CH_2NHCH_3, –$CH_2N(CH_3)_2$, –CO_2H, –$COCH_3$, –CO_2CH_3, –$CO_2C(CH_3)_3$, –$COCH(OH)CH_3$, –$CONH_2$, –$CONHCH_3$, –$CON(CH_3)_2$, –$C(CH_3)_2CONH_2$, –NH_2, –$NHCH_3$, –$N(CH_3)_2$, –$NHCOCH_3$, –$N(CH_3)COCH_3$, –$NHS(O)_2CH_3$, –$N(CH_3)C(CH_3)_2CONH_2$, –$N(CH_3)CH_2CH_2S(O)_2CH_3$, – NHC(=NH)H, –NHC(=NH)$CH_3$, –NHC(=NH)$NH_2$, –NHC(=O)$NH_2$, –$NO_2$, =O, –OH, –$OCH_3$, –$OCH_2CH_3$, –$OCH_2CH_2OCH_3$, –$OCH_2CH_2OH$, –$OCH_2CH_2N(CH_3)_2$, –$O(CH_2CH_2O)_n$–$(CH_2)_mCO_2H$, –$O(CH_2CH_2O)_nH$, –$OP(O)(OH)_2$, –$S(O)_2N(CH_3)_2$, –$SCH_3$, –$S(O)_2CH_3$, and –$S(O)_3H$.

Another example of the disclosure is a method for treating cancer comprising administering a therapeutically effective amount of an immunoconjugate comprising an antibody linked by conjugation to one or more pyrazoloazepine moieties.

Another example of the disclosure is a use of an immunoconjugate comprising an antibody linked by conjugation to one or more pyrazoloazepine moieties for treating cancer.

Another example of the disclosure is a method of preparing an immunoconjugate by conjugation of one or more pyrazoloazepine moieties with an antibody.

In another aspect, there is provided an immunoconjugate prepared by conjugation of an antibody with a 5-amino-pyrazoloazepine-linker compound as defined above.

In another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of an immunoconjugate as defined above and one or more pharmaceutically acceptable diluent, vehicle, carrier, or excipient.

In another aspect, there is provided the use of an immunoconjugate as defined above for treating cancer.

In another aspect, there is provided a method of preparing an immunoconjugate of Formula I as defined above wherein a 5-amino-pyrazoloazepine-linker compound of Formula II as defined above is conjugated with the antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a graph of HEK human TLR7 activity at 24 hours of pyrazoloazepine compounds PAZ-2, PAZ-4 and PAZ-11, versus comparator adjuvant compounds C-1 and C-2.

Figure 2 shows a graph of HEK human TLR8 activity at 24 hours of pyrazoloazepine compounds PAZ-2, PAZ-4 and PAZ-11, versus comparator adjuvant compounds C-1 and C-2.

DETAILED DESCRIPTION OF THE INVENTION

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the invention as defined by the claims.

CLAIMS:

1. An immunoconjugate comprising an antibody covalently attached to one or more 5-aminopyrazoloazepine moieties by a linker, and having Formula I:

$$Ab–[L–PAZ]_p \qquad I$$

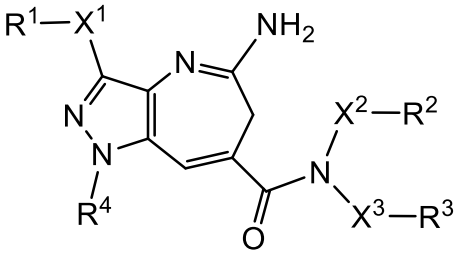
or a pharmaceutically acceptable salt thereof,

wherein:

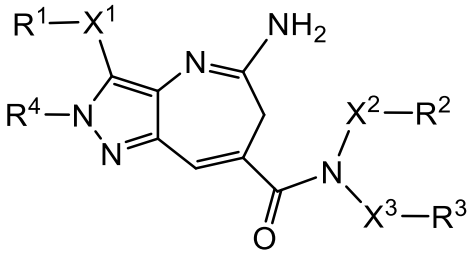
Ab is the antibody;

p is an integer from 1 to 8;

PAZ is the 5-aminopyrazoloazepine moiety selected from formulas IIa and IIb:



IIa



IIb;

X^1, X^2, and X^3 are independently selected from the group consisting of a bond, C(=O), $C(=O)N(R^5)$, O, $N(R^5)$, S, $S(O)_2$, and $S(O)_2N(R^5)$;

R^1, R^2, R^3, and R^4 are independently selected from the group consisting of H, C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{12} carbocyclyl, C_6-C_{20} aryl, C_2-C_9 heterocyclyl, and C_1-C_{20} heteroaryl, where alkyl, alkenyl, alkynyl, carbocyclyl, aryl, heterocyclyl, and heteroaryl are independently and optionally substituted with one or more groups selected from:

–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–(C_1-C_{12} alkyldiyl)–$N(R^5)_2$;

–(C_1-C_{12} alkyldiyl)–OR^5;

–(C_3-C_{12} carbocyclyl);

–(C_3-C_{12} carbocyclyl)–*;

–(C_3-C_{12} carbocyclyl)–(C_1-C_{12} alkyldiyl)–NR^5–*;

–(C_3-C_{12} carbocyclyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)_2$;

–(C_3-C_{12} carbocyclyl)–NR^5–$C(=NR^5)NR^5$–*;

–(C_6-C_{20} aryl);

–(C_6-C_{20} aryldiyl)–*;

–(C_6-C_{20} aryldiyl)–$N(R^5)$–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–NR^5–C(=NR^{5a})N(R^5)–*;

–(C_2-C_{20} heterocyclyl);

–(C_2-C_{20} heterocyclyl)–*;

–(C_2-C_9 heterocyclyl)–(C_1-C_{12} alkyldiyl)–NR^5–*;

–(C_2-C_9 heterocyclyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_2-C_9 heterocyclyl)–C(=O)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_2-C_9 heterocyclyl)–NR^5–C(=NR^{5a})NR^5–*;

–(C_2-C_9 heterocyclyl)–NR^5–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_2-C_9 heterocyclyl)–(C_6-C_{20} aryldiyl)–*;

–(C_1-C_{20} heteroaryl);

–(C_1-C_{20} heteroaryldiyl)–*;

–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_1-C_{20} heteroaryldiyl)–NR^5–C(=NR^{5a})N(R^5)–*;

–(C_1-C_{20} heteroaryldiyl)–N(R^5)C(=O)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–C(=O)–*;

–C(=O)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–C(=O)–(C_2-C_{20} heterocyclyldiyl)–*;

–C(=O)N(R^5)$_2$;

–C(=O)N(R^5)–*;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–*;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–C(=O)N(R^5)–*;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)R^5;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)N(R^5)$_2$;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–N(R^5)CO_2R^5;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–N(R^5)C(=NR^{5a})N(R^5)$_2$;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–NR^5C(=NR^{5a})R^5;

–C(=O)NR^5–(C_1-C_8 alkyldiyl)–NR^5(C_2-C_5 heteroaryl);

–C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–N(R^5)–*;

–C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–*;

–C(=O)NR^5–(C$_1$-C$_{20}$ heteroaryldiyl)–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)$_2$;

–C(=O)NR^5–(C$_1$-C$_{20}$ heteroaryldiyl)–(C$_2$-C$_{20}$ heterocyclyldiyl)–C(=O)NR^5–(C$_1$-C$_{12}$ alkyldiyl)–NR^5–*;

–N(R^5)$_2$;

–N(R^5)–*;

–N(R^5)C(=O)R^5;

–N(R^5)C(=O)–*;

–N(R^5)C(=O)N(R^5)$_2$;

–N(R^5)C(=O)N(R^5)–*;

–N(R^5)CO$_2$R^5;

–N(R^5)CO$_2$(R^5)–*;

–NR^{5}C(=NR^{5a})N(R^5)$_2$;

–NR^{5}C(=NR^{5a})N(R^5)–*;

–NR^{5}C(=NR^{5a})R^5;

–N(R^5)C(=O)–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)–*;

–N(R^5)–(C$_2$-C$_5$ heteroaryl);

–N(R^5)–S(=O)$_2$–(C$_1$-C$_{12}$ alkyl);

–O–(C$_1$-C$_{12}$ alkyl);

–O–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)$_2$;

–O–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)–*;

–OC(=O)N(R^5)$_2$;

–OC(=O)N(R^5)–*;

–S(=O)$_2$–(C$_2$-C$_{20}$ heterocyclyldiyl)–*;

–S(=O)$_2$–(C$_2$-C$_{20}$ heterocyclyldiyl)–(C$_1$-C$_{12}$ alkyldiyl)–N(R^5)$_2$;

–S(=O)$_2$–(C$_2$-C$_{20}$ heterocyclyldiyl)–(C$_1$-C$_{12}$ alkyldiyl)–NR^5–*; and

–S(=O)$_2$–(C$_2$-C$_{20}$ heterocyclyldiyl)–(C$_1$-C$_{12}$ alkyldiyl)–OH;

or R^2 and R^3 together form a 5- or 6-membered heterocyclyl ring;

R^5 is selected from the group consisting of H, C$_6$-C$_{20}$ aryl, C$_3$-C$_{12}$ carbocyclyl, C$_2$-C$_{20}$ heterocyclyl, C$_6$-C$_{20}$ aryldiyl, C$_1$-C$_{12}$ alkyl, and C$_1$-C$_{12}$ alkyldiyl, or two R^5 groups together form a 5- or 6-membered heterocyclyl ring;

R^{5a} is selected from the group consisting of C$_6$-C$_{20}$ aryl and C$_1$-C$_{20}$ heteroaryl;

where the asterisk * indicates the attachment site of L, and where one of R^1, R^2, R^3 and R^4 is attached to L;

L is the linker selected from the group consisting of:

–C(=O)–PEG–;

–C(=O)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–C(=O)–Gluc–;

–C(=O)–PEG–O–;

–C(=O)–PEG–O–C(=O)–;

–C(=O)–PEG–C(=O)–;

–C(=O)–PEG–C(=O)–PEP–;

–C(=O)–PEG–N(R^6)–;

–C(=O)–PEG–N(R^6)–C(=O)–;

–C(=O)–PEG–N(R^6)–PEG–C(=O)–PEP–;

–C(=O)–PEG–N^+(R^6)$_2$–PEG–C(=O)–PEP–;

–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

–C(=O)–PEG–SS–(C_1-C_{12} alkyldiyl)–OC(=O)–;

–C(=O)–PEG–SS–(C_1-C_{12} alkyldiyl)–C(=O)–;

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–;

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^5)–C(=O);

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–C(=O)–Gluc–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–O–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–O–C(=O)–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–C(=O)–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–N(R^5)–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–N(R^5)–C(=O)–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–C(=O)–PEP–;

–succinimidyl–(CH_2)$_m$–C(=O)N(R^6)–PEG–SS–(C_1-C_{12} alkyldiyl)–OC(=O)–;

–succinimidyl–(CH_2)$_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

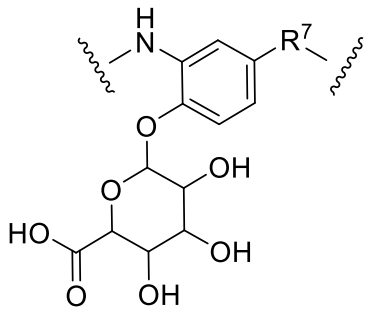
–succinimidyl–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–; and

–succinimidyl–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

R^6 is independently H or C_1-C_6 alkyl;

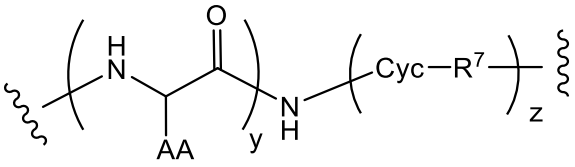
PEG has the formula: –$(CH_2CH_2O)_n$–$(CH_2)_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

Gluc has the formula:



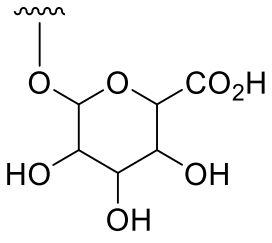
;

PEP has the formula:



where AA is independently selected from a natural or unnatural amino acid side chain, or one or more of AA, and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment;

Cyc is selected from C_6-C_{20} aryldiyl and C_1-C_{20} heteroaryldiyl, optionally substituted with one or more groups selected from F, Cl, NO_2, –OH, $–OCH_3$, and a glucuronic acid having the structure:



;

R^7 is selected from the group consisting of –CH(R^8)O–, $–CH_2–$, $–CH_2N(R^8)–$, and –CH(R^8)O–C(=O)–, where R^8 is selected from H, C_1-C_6 alkyl, C(=O)–C_1-C_6 alkyl, and –C(=O)N(R^9)$_2$, where R^9 is independently selected from the group consisting of H, C_1-C_{12} alkyl, and –$(CH_2CH_2O)_n$–$(CH_2)_m$–OH, where m is an integer from 1 to 5, and n is an integer from 2 to 50, or two R^9 groups together form a 5- or 6-membered heterocyclyl ring;

y is an integer from 2 to 12;

z is 0 or 1; and

alkyl, alkyldiyl, alkenyl, alkenyldiyl, alkynyl, alkynyldiyl, aryl, aryldiyl, carbocyclyl, carbocyclyldiyl, heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl are independently and optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, $–CH_3$, $–CH_2CH_3$, $–CH=CH_2$, $–C≡CH$, $–C≡CCH_3$, $–CH_2CH_2CH_3$, $–CH(CH_3)_2$, $–CH_2CH(CH_3)_2$, $–CH_2OH$, $–CH_2OCH_3$, $–CH_2CH_2OH$, $–C(CH_3)_2OH$, $–CH(OH)CH(CH_3)_2$, $–C(CH_3)_2CH_2OH$, $–CH_2CH_2SO_2CH_3$, $–CH_2OP(O)(OH)_2$, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CF_3$, $–CH_2CHF_2$, $–CH(CH_3)CN$, $–C(CH_3)_2CN$, $–CH_2CN$, $–CH_2NH_2$, $–CH_2NHSO_2CH_3$, $–CH_2NHCH_3$, $–CH_2N(CH_3)_2$, $–CO_2H$, $–COCH_3$, $–CO_2CH_3$, $–CO_2C(CH_3)_3$, $–COCH(OH)CH_3$, $–CONH_2$, $–CONHCH_3$, $–CON(CH_3)_2$, $–C(CH_3)_2CONH_2$, $–NH_2$, $–NHCH_3$, $–N(CH_3)_2$, $–NHCOCH_3$, $–N(CH_3)COCH_3$, $–NHS(O)_2CH_3$, $–N(CH_3)C(CH_3)_2CONH_2$, $–N(CH_3)CH_2CH_2S(O)_2CH_3$, –NHC(=NH)H, $–NHC(=NH)CH_3$, $–NHC(=NH)NH_2$, $–NHC(=O)NH_2$, $–NO_2$, =O, –OH, $–OCH_3$, $–OCH_2CH_3$, $–OCH_2CH_2OCH_3$, $–OCH_2CH_2OH$, $–OCH_2CH_2N(CH_3)_2$, $–O(CH_2CH_2O)_n–(CH_2)_mCO_2H$, $–O(CH_2CH_2O)_nH$, $–OP(O)(OH)_2$, $–S(O)_2N(CH_3)_2$, $–SCH_3$, $–S(O)_2CH_3$, and $–S(O)_3H$.

2. The immunoconjugate of claim 1 wherein the antibody is an antibody construct that has an antigen binding domain that binds to a target selected from PD-L1, HER2, CEA, and TROP2.

3. The immunoconjugate of claim 2 wherein the antibody is selected from the group consisting of atezolizumab, durvalumab, avelumab, trastuzumab, pertuzumab, labetuzumab, and sacituzumab or a biosimilar or a biobetter thereof.

4. The immunoconjugate of any one of claims 1 to 3 wherein X^1 is a bond, and R^1 is H.

5. The immunoconjugate of any one of claims 1 to 3 wherein X^2 is a bond, and R^2 is C_1-C_8 alkyl.

6. The immunoconjugate of any one of claims 1 to 3 wherein X^2 and X^3 are each a bond, and R^2 and R^3 are independently selected from C_1-C_8 alkyl, $–O–(C_1$-C_{12} alkyl), $–(C_1$-C_{12} alkyldiyl)$–OR^5$, $–(C_1$-C_8 alkyldiyl)$–N(R^5)CO_2R^5$, $–(C_1$-C_{12} alkyl)$–OC(O)N(R^5)_2$, $–O–(C_1$-C_{12} alkyl)$–N(R^5)CO_2R^5$, and $–O–(C_1$-C_{12} alkyl)$–OC(O)N(R^5)_2$.

7. The immunoconjugate of claim 6 wherein R^2 is C_1-C_8 alkyl and R^3 is $–(C_1$-C_8 alkyldiyl)$–N(R^5)CO_2R^4$.

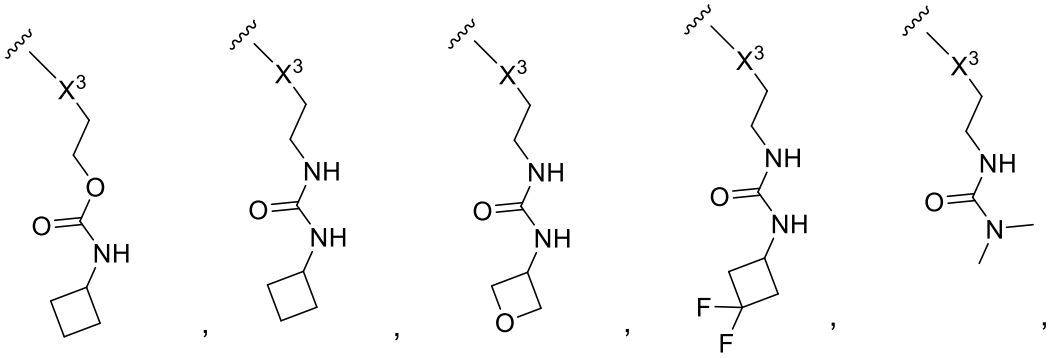
8. The immunoconjugate of claim 6 wherein R^2 is $-CH_2CH_2CH_3$ and R^3 is selected from $-CH_2CH_2CH_2NHCO_2$(t-Bu), $-OCH_2CH_2NHCO_2$(cyclobutyl), and $-CH_2CH_2CH_2NHCO_2$(cyclobutyl).

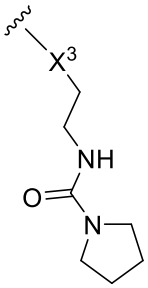
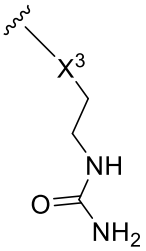
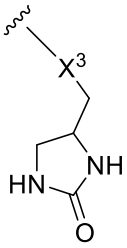
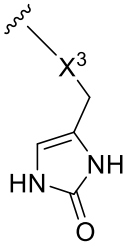
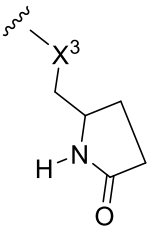
9. The immunoconjugate of claim 6 wherein R^2 and R^3 are each independently selected from $-CH_2CH_2CH_3$, $-OCH_2CH_3$, $-OCH_2CF_3$, $-CH_2CH_2CF_3$, $-OCH_2CH_2OH$, and $-CH_2CH_2CH_2OH$.

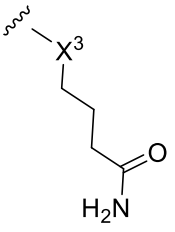
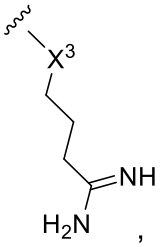
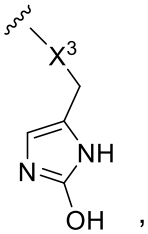
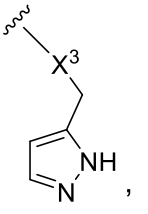
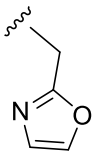
10. The immunoconjugate of claim 6 wherein R^2 and R^3 are each $-CH_2CH_2CH_3$.

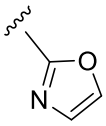
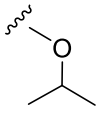
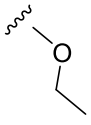
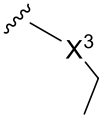
11. The immunoconjugate of claim 6 wherein R^2 is $-CH_2CH_2CH_3$ and R^3 is $-OCH_2CH_3$.

12. The immunoconjugate of any one of claims 1 to 3 wherein X^3-R^3 is selected from the group consisting of:


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,
,
,

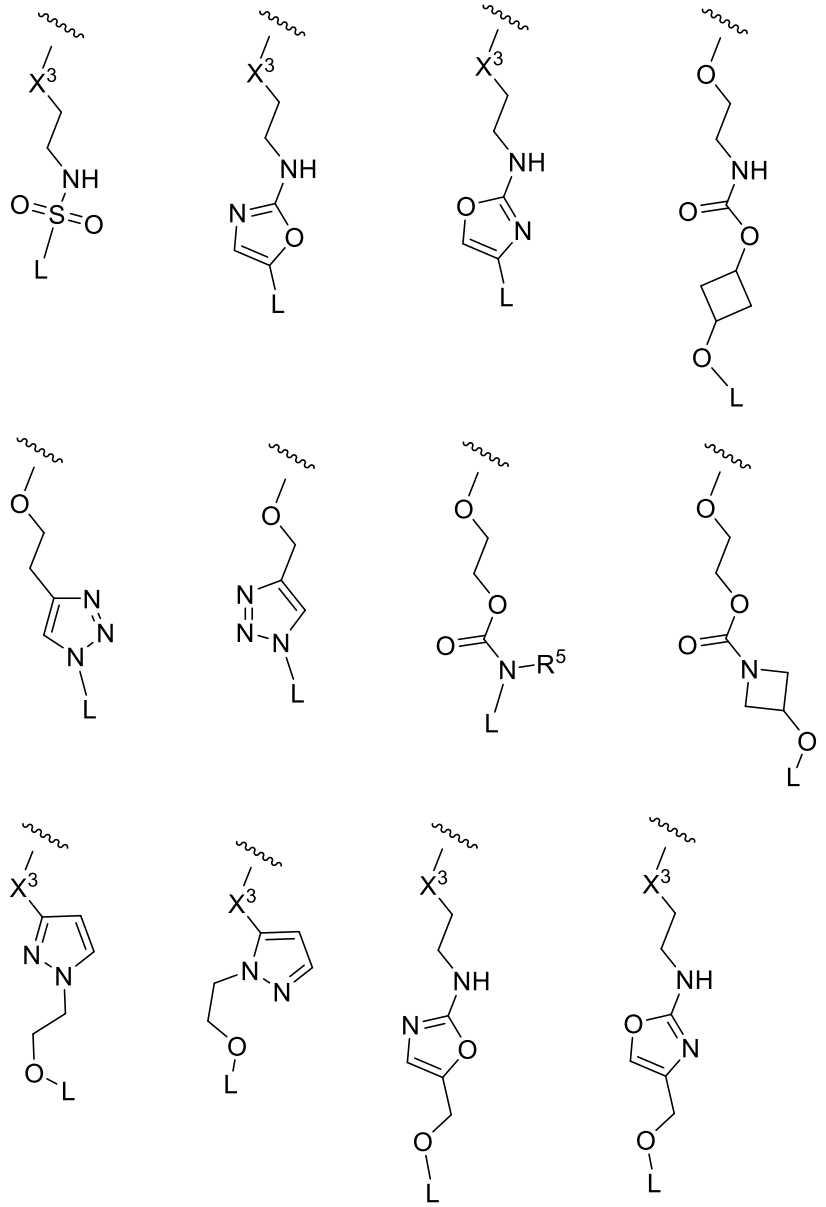

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, and 
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13. The immunoconjugate of any one of claims 1 to 3 where R^2 or R^3 is attached to L.

14. The immunoconjugate of claim 13 wherein X^3–R^3–L is selected from the group consisting of:



where the wavy line indicates the point of attachment to N.

15. The immunoconjugate of any one of claims 1 to 3 wherein R^4 is C_1-C_{12} alkyl.

16. The immunoconjugate of any one of claims 1 to 3 wherein R^4 is –(C_1-C_{12} alkyldiyl)–N(R^5)–*; where the asterisk * indicates the attachment site of L.

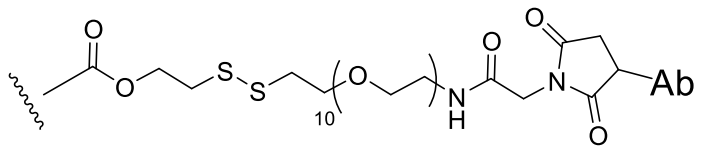
17. The immunoconjugate of any one of claims 1 to 3 wherein L is –C(=O)–PEG– or –C(=O)–PEG–C(=O)–.

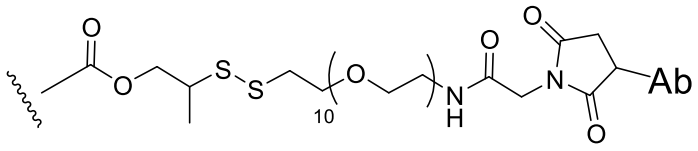
18. The immunoconjugate of any one of claims 1 to 3 wherein L is attached to a cysteine thiol of the antibody.

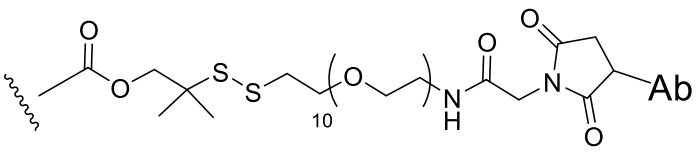
19. The immunoconjugate of any one of claims 1 to 3 wherein for the PEG, m is 1 or 2, and n is an integer from 2 to 10.

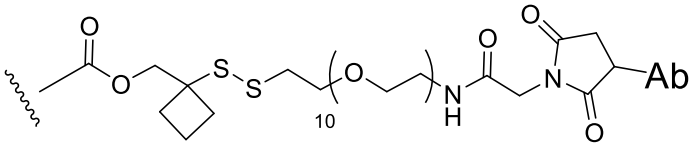
20. The immunoconjugate of claim 19 wherein n is 10.

21. The immunoconjugate of any one of claims 1 to 3 wherein L is selected from the structures:



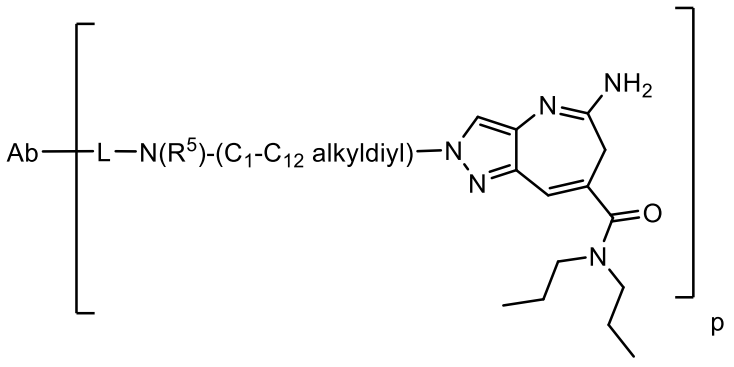




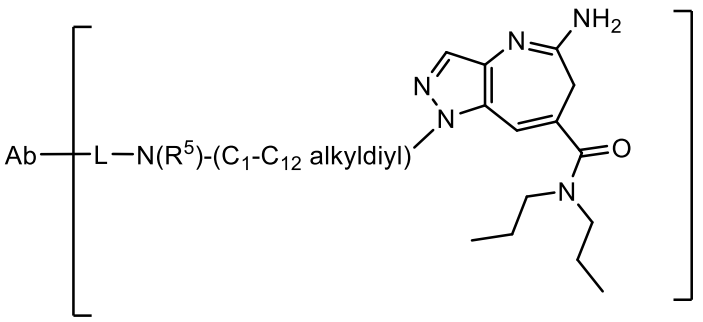


where the wavy line indicates the attachment to R^5.

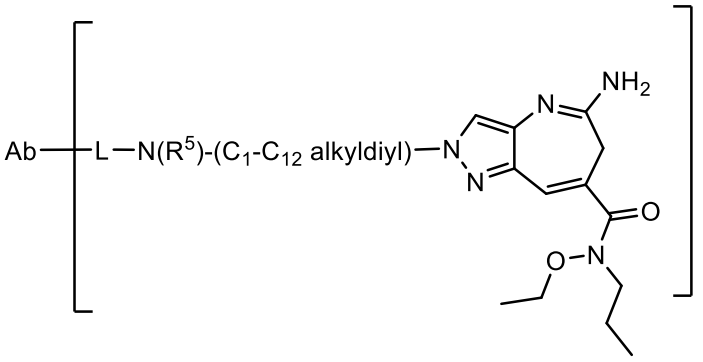
22. The immunoconjugate of any one of claims 1 to 3 selected from Formulae Ia-Id:



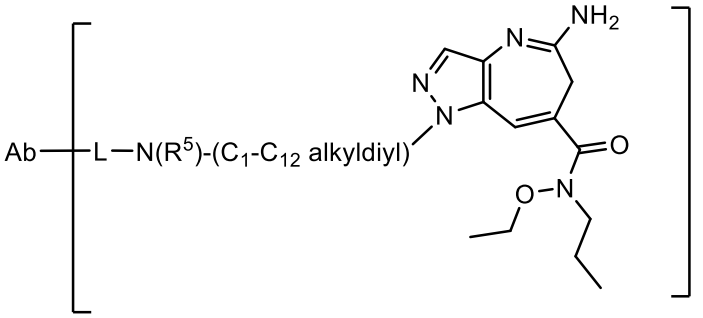
Ia;



Ib;

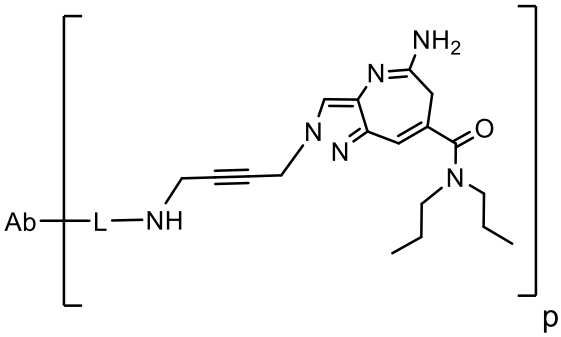


Ic; and

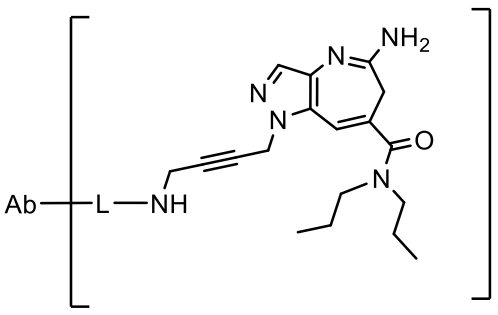


Id.

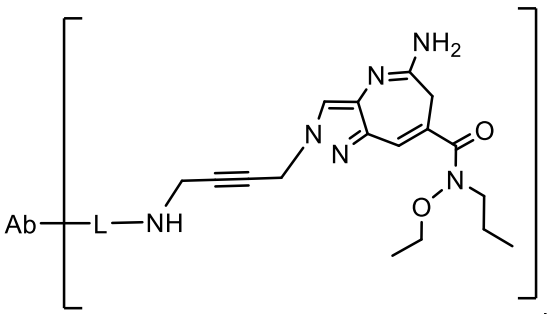
23. The immunoconjugate of any one of claims 1 to 3 selected from Formulae Ie-Il:



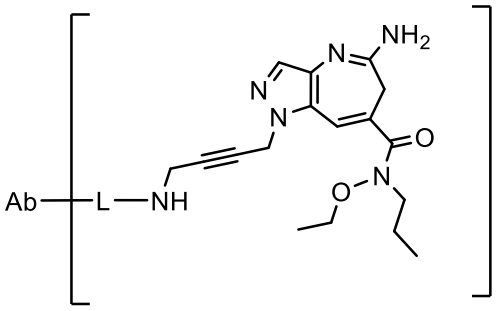
Ie;



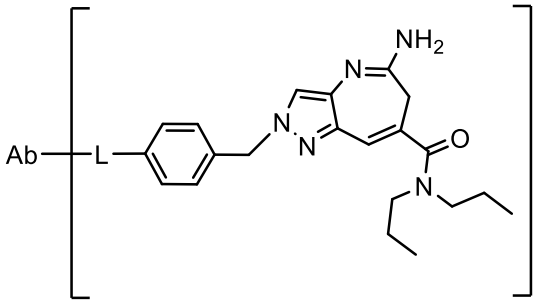
If;



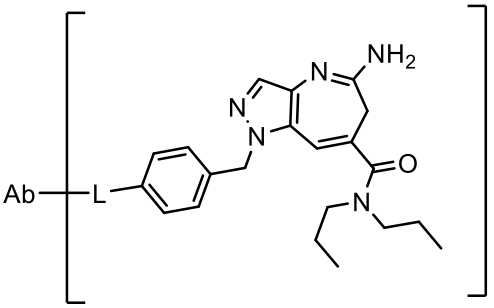
Ig;



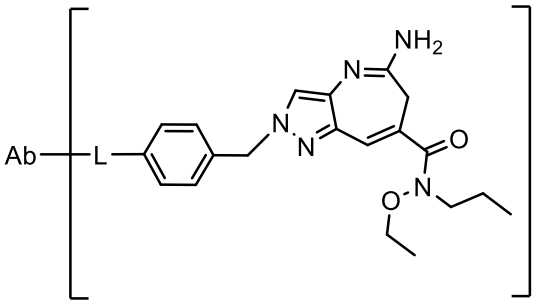
Ih;



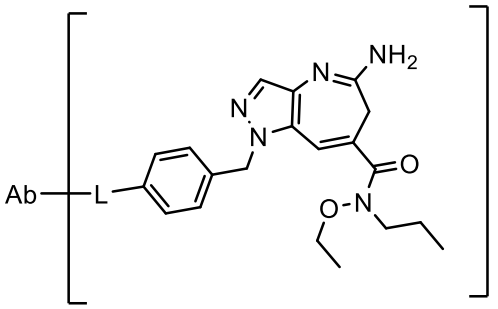
Ii;



Ij;

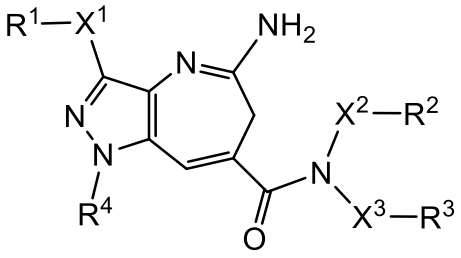


Ik; and

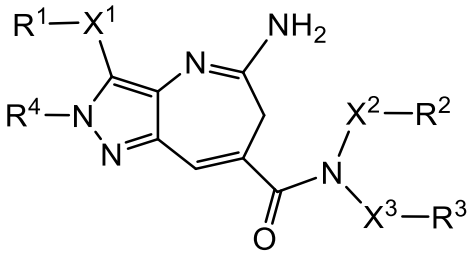


Il.

24. A 5-aminopyrazoloazepine-linker compound selected from formulas IIa and IIb:



IIa



IIb;

wherein X^1, X^2, and X^3 are independently selected from the group consisting of a bond, C(=O), C(=O)N(R^5), O, N(R^5), S, S(O)$_2$, and S(O)$_2$N(R^5);

R^1, R^2, R^3, and R^4 are independently selected from the group consisting of H, C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{12} carbocyclyl, C_6-C_{20} aryl, C_2-C_9 heterocyclyl, and C_1-C_{20} heteroaryl, where alkyl, alkenyl, alkynyl, carbocyclyl, aryl, heterocyclyl, and heteroaryl are independently and optionally substituted with one or more groups selected from:

–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–(C_1-C_{12} alkyldiyl)–OR^5;

–(C_3-C_{12} carbocyclyl);

–(C_3-C_{12} carbocyclyl)–*;

–(C_3-C_{12} carbocyclyl)–(C_1-C_{12} alkyldiyl)–NR^5–*;

–(C_3-C_{12} carbocyclyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)_2$;

–(C_3-C_{12} carbocyclyl)–NR^5–$C(=NR^5)NR^5$–*;

–(C_6-C_{20} aryl);

–(C_6-C_{20} aryldiyl)–*;

–(C_6-C_{20} aryldiyl)–$N(R^5)$–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–*;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)_2$;

–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–NR^5–$C(=NR^{5a})N(R^5)$–*;

–(C_2-C_{20} heterocyclyl);

–(C_2-C_{20} heterocyclyl)–*;

–(C_2-C_9 heterocyclyl)–(C_1-C_{12} alkyldiyl)–NR^5–*;

–(C_2-C_9 heterocyclyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)_2$;

–(C_2-C_9 heterocyclyl)–C(=O)–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–(C_2-C_9 heterocyclyl)–NR^5–$C(=NR^{5a})NR^5$–*;

–(C_2-C_9 heterocyclyl)–NR^5–(C_6-C_{20} aryldiyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–(C_2-C_9 heterocyclyl)–(C_6-C_{20} aryldiyl)–*;

–(C_1-C_{20} heteroaryl);

–(C_1-C_{20} heteroaryldiyl)–*;

–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–$N(R^5)_2$;

–(C_1-C_{20} heteroaryldiyl)–NR^5–$C(=NR^{5a})N(R^5)$–*;

–(C_1-C_{20} heteroaryldiyl)–$N(R^5)C(=O)$–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–C(=O)–*;

–C(=O)–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–C(=O)–(C_2-C_{20} heterocyclyldiyl)–*;

–$C(=O)N(R^5)_2$;

–C(=O)$N(R^5)$–*;

–C(=O)$N(R^5)$–(C_1-C_{12} alkyldiyl)–*;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–C(=O)N(R^5)–*;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)R^5;

–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)N(R^5)$_2$;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–N(R^5)CO_2R^5;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–N(R^5)C(=NR^{5a})N(R^5)$_2$;

–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–NR^5C(=NR^{5a})R^5;

–C(=O)NR^5–(C_1-C_8 alkyldiyl)–NR^5(C_2-C_5 heteroaryl);

–C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–N(R^5)–*;

–C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–*;

–C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–C(=O)NR^5–(C_1-C_{20} heteroaryldiyl)–(C_2-C_{20} heterocyclyldiyl)–C(=O)NR^5–(C_1-C_{12} alkyldiyl)–NR^5–*;

–N(R^5)$_2$;

–N(R^5)–*;

–N(R^5)C(=O)R^5;

–N(R^5)C(=O)–*;

–N(R^5)C(=O)N(R^5)$_2$;

–N(R^5)C(=O)N(R^5)–*;

–N(R^5)CO_2R^5;

–N(R^5)CO_2(R^5)–*;

–NR^5C(=NR^{5a})N(R^5)$_2$;

–NR^5C(=NR^{5a})N(R^5)–*;

–NR^5C(=NR^{5a})R^5;

–N(R^5)C(=O)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–N(R^5)–(C_2-C_5 heteroaryl);

–N(R^5)–S(=O)$_2$–(C_1-C_{12} alkyl);

–O–(C_1-C_{12} alkyl);

–O–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–O–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–OC(=O)N(R^5)$_2$;

–OC(=O)N(R^5)–*;

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–*;

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$;

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–NR^5–*; and

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–OH;

or R^2 and R^3 together form a 5- or 6-membered heterocyclyl ring;

R^5 is selected from the group consisting of H, C_6-C_{20} aryl, C_3-C_{12} carbocyclyl, C_2-C_{20} heterocyclyl, C_6-C_{20} aryldiyl, C_1-C_{12} alkyl, and C_1-C_{12} alkyldiyl, or two R^5 groups together form a 5- or 6-membered heterocyclyl ring;

R^{5a} is selected from the group consisting of C_6-C_{20} aryl and C_1-C_{20} heteroaryl;

where the asterisk * indicates the attachment site of L, and where one of R^1, R^2, R^3 and R^4 is attached to L;

L is the linker selected from the group consisting of:

Q–C(=O)–PEG–;

Q–C(=O)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–C(=O)–Gluc–;

Q–C(=O)–PEG–O–;

Q–C(=O)–PEG–O–C(=O)–;

Q–C(=O)–PEG–C(=O)–;

Q–C(=O)–PEG–C(=O)–PEP–;

Q–C(=O)–PEG–N(R^6)–;

Q–C(=O)–PEG–N(R^6)–C(=O)–;

Q–C(=O)–PEG–N(R^6)–PEG–C(=O)–PEP–;

Q–C(=O)–PEG–N^+(R^6)$_2$–PEG–C(=O)–PEP–;

Q–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

Q–C(=O)–PEG–SS–(C_1-C_{12} alkyldiyl)–OC(=O)–;

Q–C(=O)–PEG–SS–(C_1-C_{12} alkyldiyl)–C(=O)–;

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–;

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^5)–C(=O);

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

Q–(CH_2)$_m$–C(=O)N(R^6)–PEG–;

Q–(CH_2)$_m$–C(=O)N(R^6)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–C(=O)–Gluc–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–O–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–O–C(=O)–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–C(=O)–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–N(R^5)–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–N(R^5)–C(=O)–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–C(=O)–PEP–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–SS–(C_1-C_{12} alkyldiyl)–OC(=O)–;

Q–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

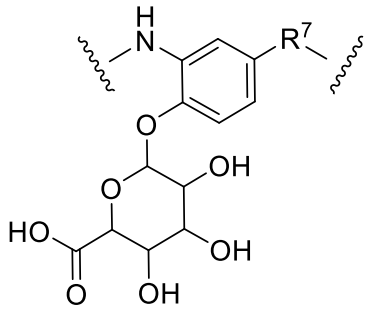
Q–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–; and

Q–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

R^6 is independently H or C_1-C_6 alkyl;

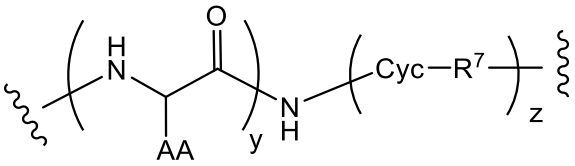
PEG has the formula: –$(CH_2CH_2O)_n$–$(CH_2)_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

Gluc has the formula:



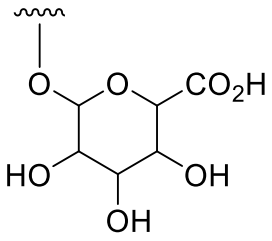
;

PEP has the formula:



where AA is independently selected from a natural or unnatural amino acid side chain, or one or more of AA, and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment;

Cyc is selected from C_6-C_{20} aryldiyl and C_1-C_{20} heteroaryldiyl, optionally substituted with one or more groups selected from F, Cl, NO_2, –OH, $–OCH_3$, and a glucuronic acid having the structure:



;

R^7 is selected from the group consisting of $–CH(R^8)O–$, $–CH_2–$, $–CH_2N(R^8)–$, and $–CH(R^8)O–C(=O)–$, where R^8 is selected from H, C_1-C_6 alkyl, $C(=O)–C_1$-C_6 alkyl, and $–C(=O)N(R^9)_2$, where R^9 is independently selected from the group consisting of H, C_1-C_{12} alkyl, and $–(CH_2CH_2O)_n–(CH_2)_m–OH$, where m is an integer from 1 to 5, and n is an integer from 2 to 50, or two R^9 groups together form a 5- or 6-membered heterocyclyl ring;

y is an integer from 2 to 12;

z is 0 or 1; and

Q is selected from the group consisting of N-hydroxysuccinimidyl, N-hydroxysulfosuccinimidyl, maleimide, and phenoxy substituted with one or more groups independently selected from F, Cl, NO_2, and SO_3^-;

where alkyl, alkyldiyl, alkenyl, alkenyldiyl, alkynyl, alkynyldiyl, aryl, aryldiyl carbocyclyl, carbocyclyldiyl, heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, $–CH_3$, $–CH_2CH_3$, $–CH=CH_2$, $–C≡CH$, $–C≡CCH_3$, $–CH_2CH_2CH_3$, $–CH(CH_3)_2$, $–CH_2CH(CH_3)_2$, $–CH_2OH$, $–CH_2OCH_3$, $–CH_2CH_2OH$, $–C(CH_3)_2OH$, $–CH(OH)CH(CH_3)_2$, $–C(CH_3)_2CH_2OH$, $–CH_2CH_2SO_2CH_3$, $–CH_2OP(O)(OH)_2$, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CF_3$, $–CH_2CHF_2$, $–CH(CH_3)CN$, $–C(CH_3)_2CN$, $–CH_2CN$, $–CH_2NH_2$, $–CH_2NHSO_2CH_3$, $–CH_2NHCH_3$, $–CH_2N(CH_3)_2$, $–CO_2H$, $–COCH_3$, $–CO_2CH_3$, $–CO_2C(CH_3)_3$, $–COCH(OH)CH_3$, $–CONH_2$, $–CONHCH_3$, $–CON(CH_3)_2$, $–C(CH_3)_2CONH_2$, $–NH_2$, $–NHCH_3$, $–N(CH_3)_2$, $–NHCOCH_3$, $–N(CH_3)COCH_3$, $–NHS(O)_2CH_3$, $–N(CH_3)C(CH_3)_2CONH_2$, $–N(CH_3)CH_2CH_2S(O)_2CH_3$, $–NHC(=NH)H$, $–NHC(=NH)CH_3$, $–NHC(=NH)NH_2$, $–NHC(=O)NH_2$, $–NO_2$, =O, –OH, $–OCH_3$, $–OCH_2CH_3$, $–OCH_2CH_2OCH_3$, $–OCH_2CH_2OH$, $–OCH_2CH_2N(CH_3)_2$, $–O(CH_2CH_2O)_n–(CH_2)_mCO_2H$, $–O(CH_2CH_2O)_nH$, $–OP(O)(OH)_2$, $–S(O)_2N(CH_3)_2$, $–SCH_3$, $–S(O)_2CH_3$, and $–S(O)_3H$.

25. The 5-amino-pyrazoloazepine-linker compound of claim 24 wherein X^1 is a bond, and R^1 is H.

26. The 5-amino-pyrazoloazepine-linker compound of claim 24 wherein X^2 is a bond, and R^2 is C_1-C_8 alkyl.

27. The 5-amino-pyrazoloazepine-linker compound of claim 24 wherein X^2 and X^3 are each a bond, and R^2 and R^3 are independently selected from C_1-C_8 alkyl, –O–(C_1-C_{12} alkyl), –(C_1-C_{12} alkyldiyl)–OR^5, –(C_1-C_8 alkyldiyl)–$N(R^5)CO_2R^5$, –(C_1-C_{12} alkyl)–$OC(O)N(R^5)_2$, –O–(C_1-C_{12} alkyl)–$N(R^5)CO_2R^5$, and –O–(C_1-C_{12} alkyl)–$OC(O)N(R^5)_2$.

28. The 5-amino-pyrazoloazepine-linker compound of claim 27 wherein R^2 is C_1-C_8 alkyl and R^3 is –(C_1-C_8 alkyldiyl)–$N(R^5)CO_2R^4$.

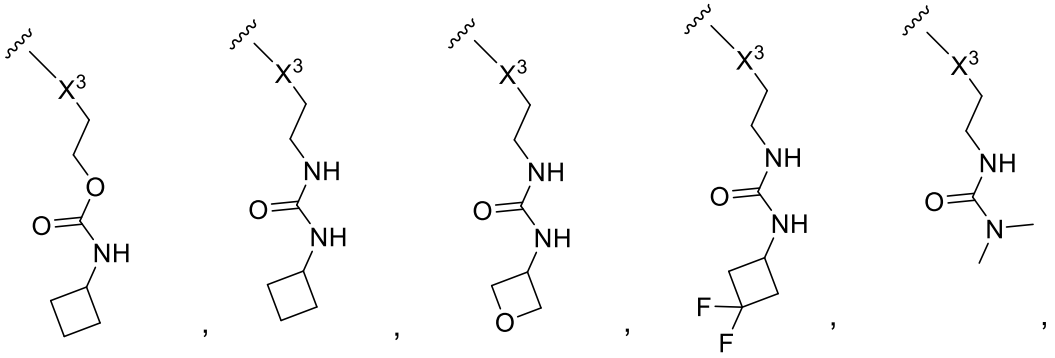
29. The 5-amino-pyrazoloazepine-linker compound of claim 27 wherein R^2 is –$CH_2CH_2CH_3$ and R^3 is selected from –$CH_2CH_2CH_2NHCO_2$(t-Bu), –$OCH_2CH_2NHCO_2$(cyclobutyl), and –$CH_2CH_2CH_2NHCO_2$(cyclobutyl).

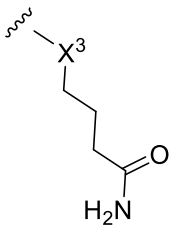
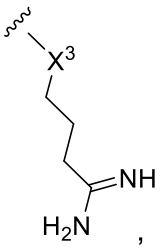
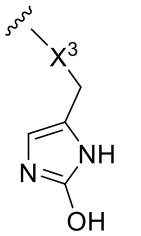
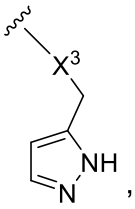
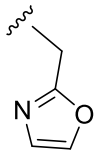
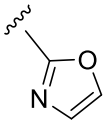
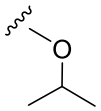
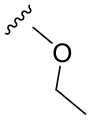
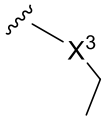
30. The 5-amino-pyrazoloazepine-linker compound of claim 27 wherein R^2 and R^3 are each independently selected from –$CH_2CH_2CH_3$, –OCH_2CH_3, –OCH_2CF_3, –$CH_2CH_2CF_3$, –OCH_2CH_2OH, and –$CH_2CH_2CH_2OH$.

31. The 5-amino-pyrazoloazepine-linker compound of claim 27 wherein R^2 and R^3 are each –$CH_2CH_2CH_3$.

32. The 5-amino-pyrazoloazepine-linker compound of claim 27 wherein R^2 is –$CH_2CH_2CH_3$ and R^3 is –OCH_2CH_3.

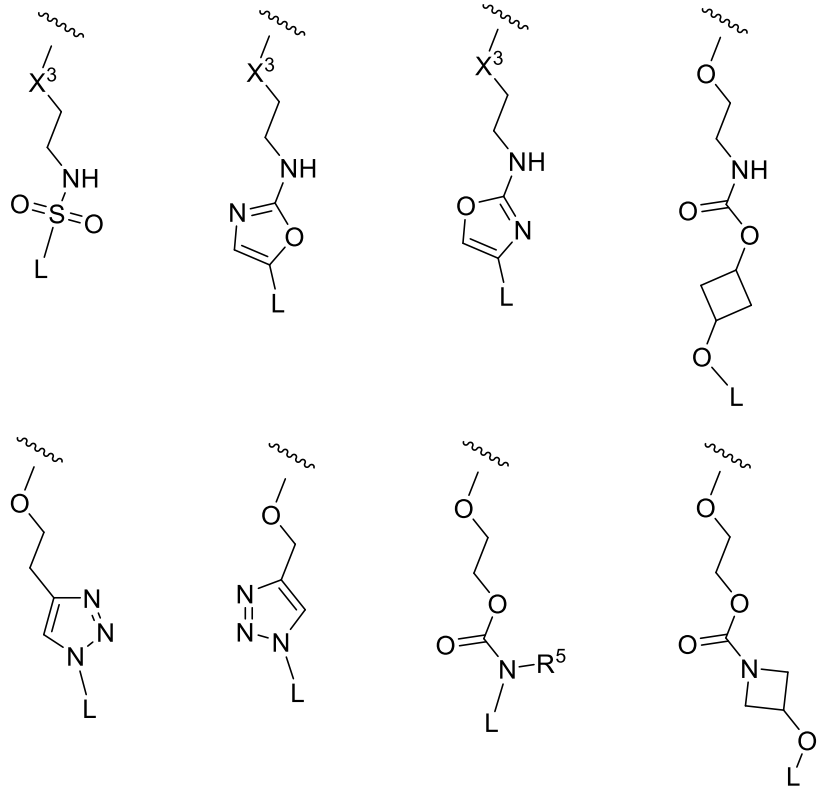
33. The 5-amino-pyrazoloazepine-linker compound of claim 24 wherein X^3-R^3 is selected from the group consisting of:

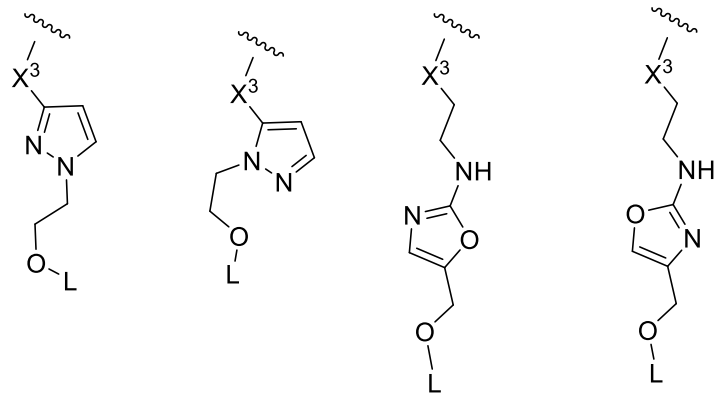



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34. The 5-amino-pyrazoloazepine-linker compound of claim 24 where R^2 or R^3 is attached to L.

35. The 5-amino-pyrazoloazepine-linker compound of claim 24 wherein X^3–R^3–L is selected from the group consisting of:





where the wavy line indicates the point of attachment to N.

36. The 5-amino-pyrazoloazepine-linker compound of claim 24 wherein R^4 is C_1-C_{12} alkyl.

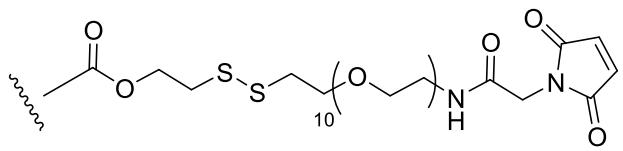
37. The 5-amino-pyrazoloazepine-linker compound of claim 24 wherein R^4 is –(C_1-C_{12} alkyldiyl)–N(R^5)–*; where the asterisk * indicates the attachment site of L.

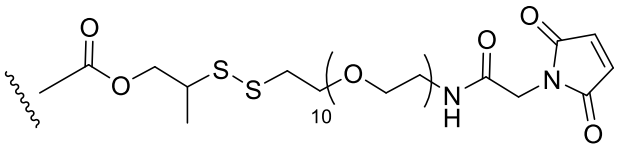
38. The 5-amino-pyrazoloazepine-linker compound of claim 24 wherein L is –C(=O)–PEG– or –C(=O)–PEG–C(=O)–.

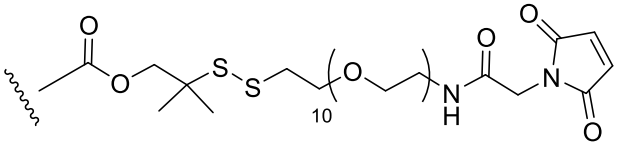
39. The 5-amino-pyrazoloazepine-linker compound of claim 24 wherein for the PEG, m is 1 or 2, and n is an integer from 2 to 10.

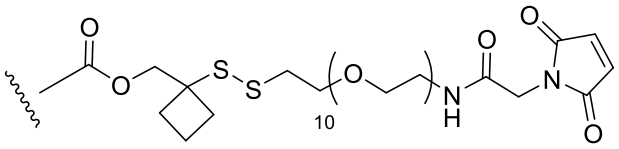
40. The 5-amino-pyrazoloazepine-linker compound of claim 39 wherein n is 10.

41. The 5-amino-pyrazoloazepine-linker compound of claim 24 wherein L is selected from the structures:



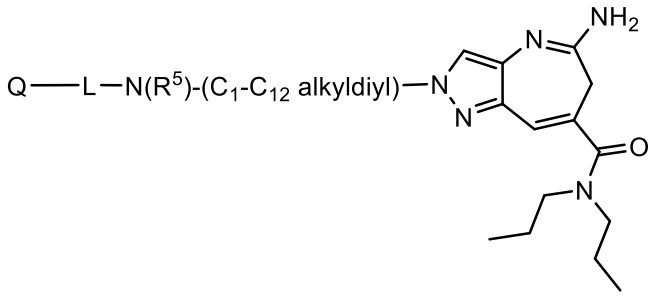




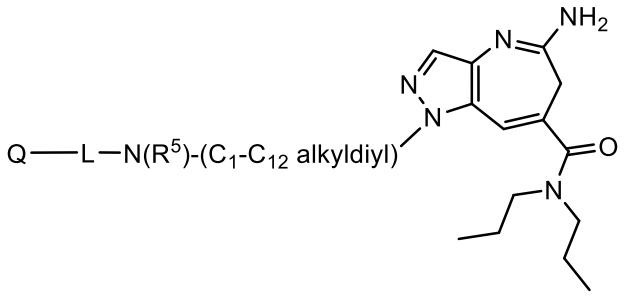


where the wavy line indicates the attachment to one of R^1, R^2, R^3 and R^4.

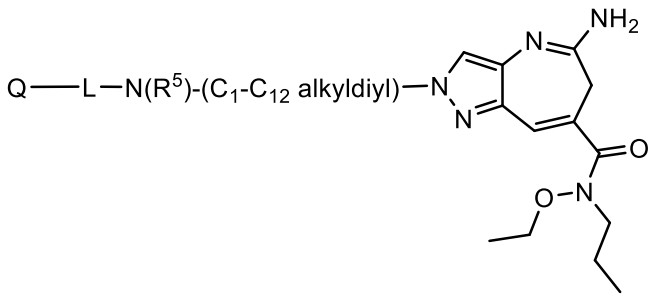
42. The 5-amino-pyrazoloazepine-linker compound of claim 24 selected from Formulae IIa-IId:



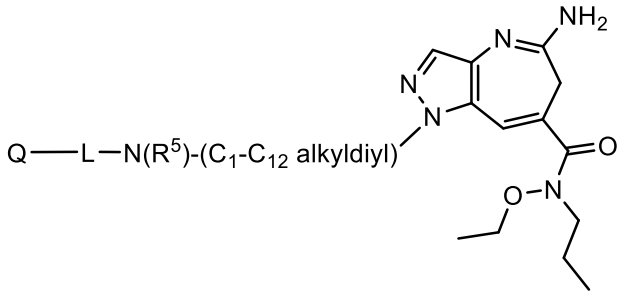
IIa;



IIb;

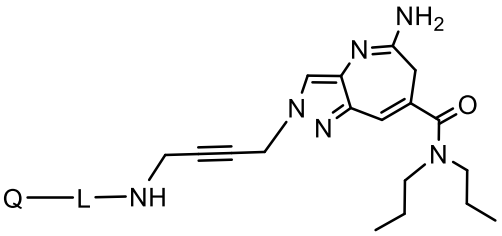


IIc; and

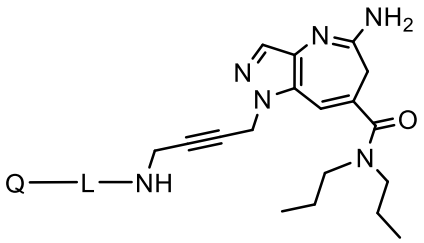


IId.

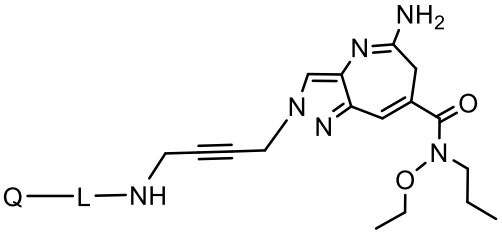
43. The 5-amino-pyrazoloazepine-linker compound of claim 24 selected from Formulae IIe-IIl:



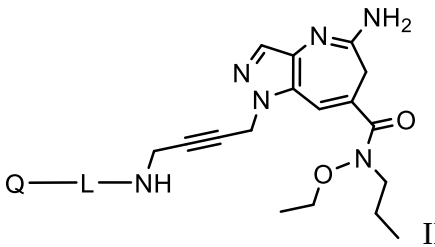
IIe;



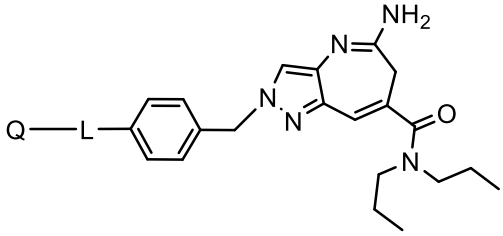
IIf;



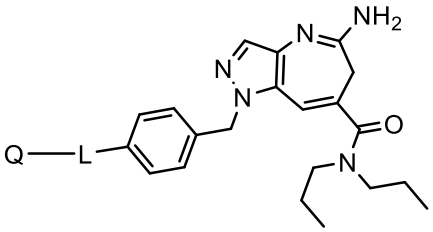
IIg;



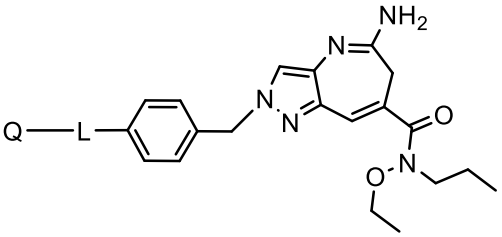
IIh;



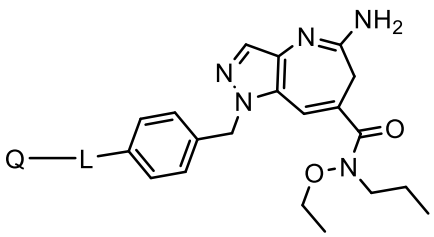
IIi;



IIj;

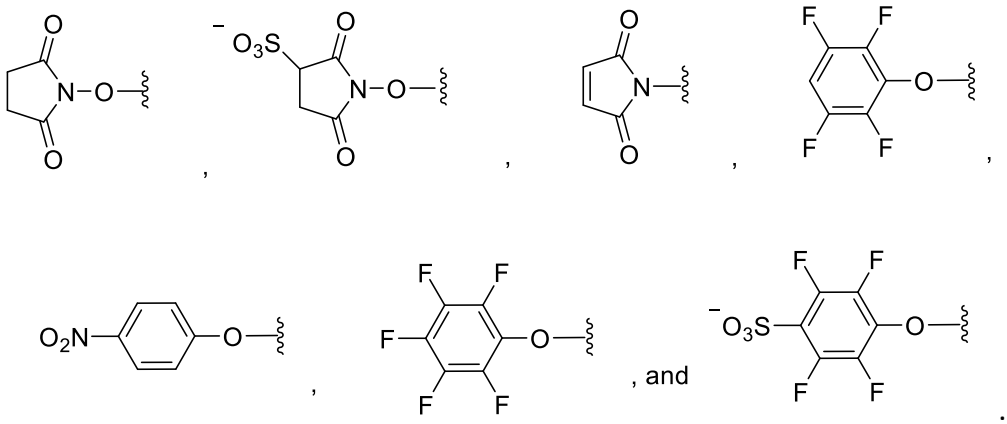


Ik; and



Il.

44. The 5-amino-pyrazoloazepine-linker compound of claim 24 wherein Q is selected from:

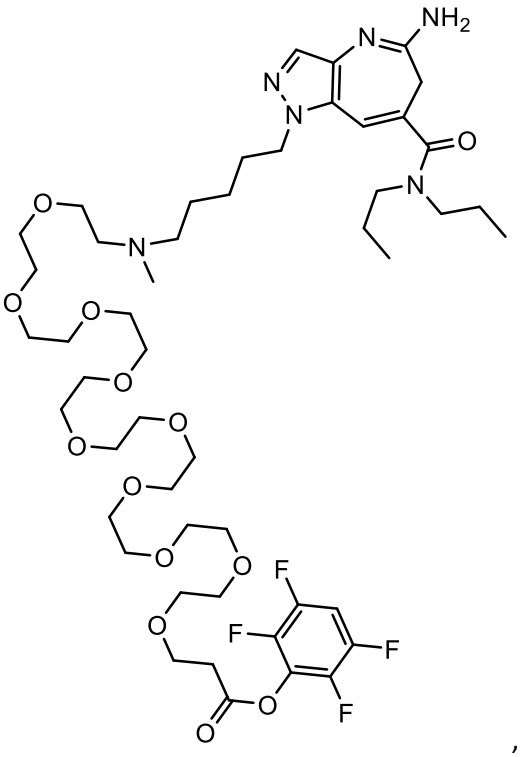


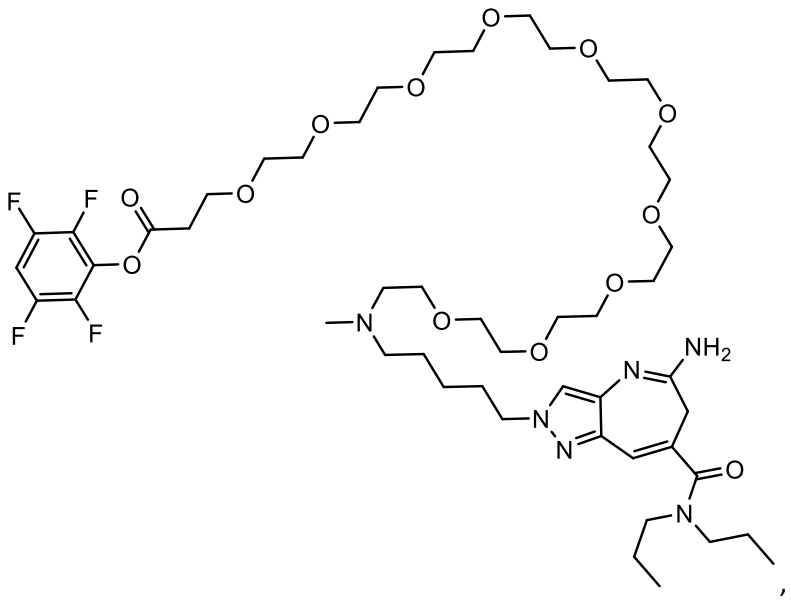
45. The 5-amino-pyrazoloazepine-linker compound of claim 44 wherein Q is phenoxy substituted with one or more F.

46. The 5-amino-pyrazoloazepine-linker compound of claim 45 wherein Q is 2,3,5,6-tetrafluorophenoxy.

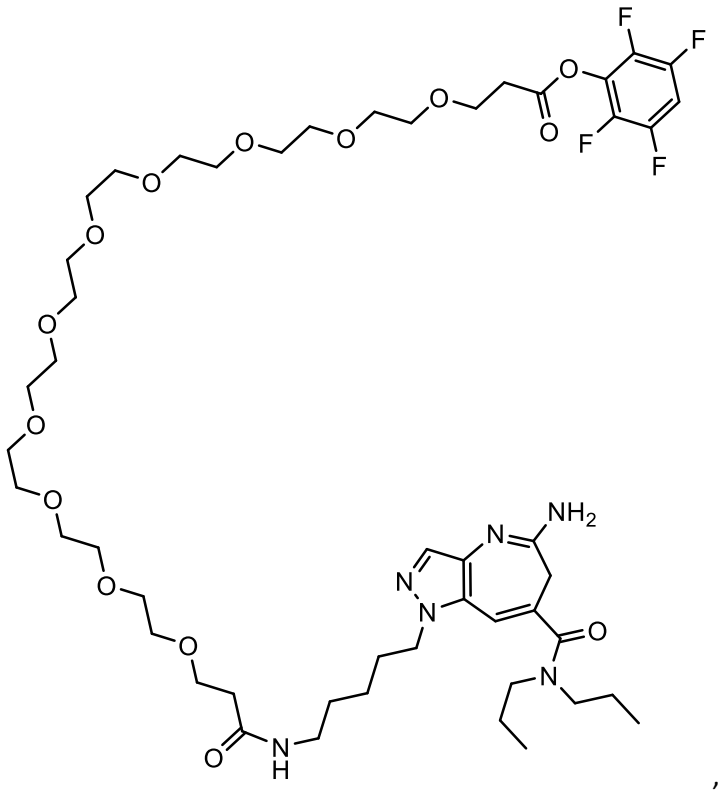
47. The 5-amino-pyrazoloazepine-linker compound of claim 44 wherein Q is maleimide.

48. The 5-amino-pyrazoloazepine-linker compound of claim 24 selected from

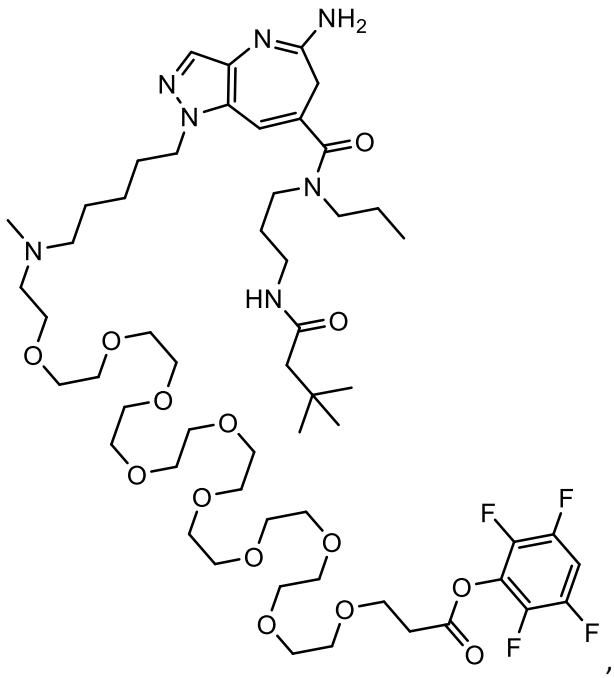




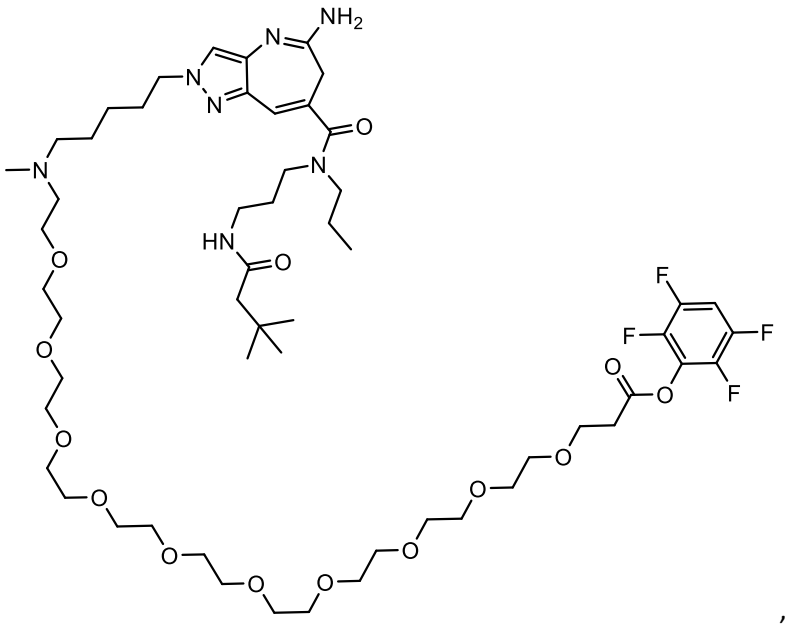
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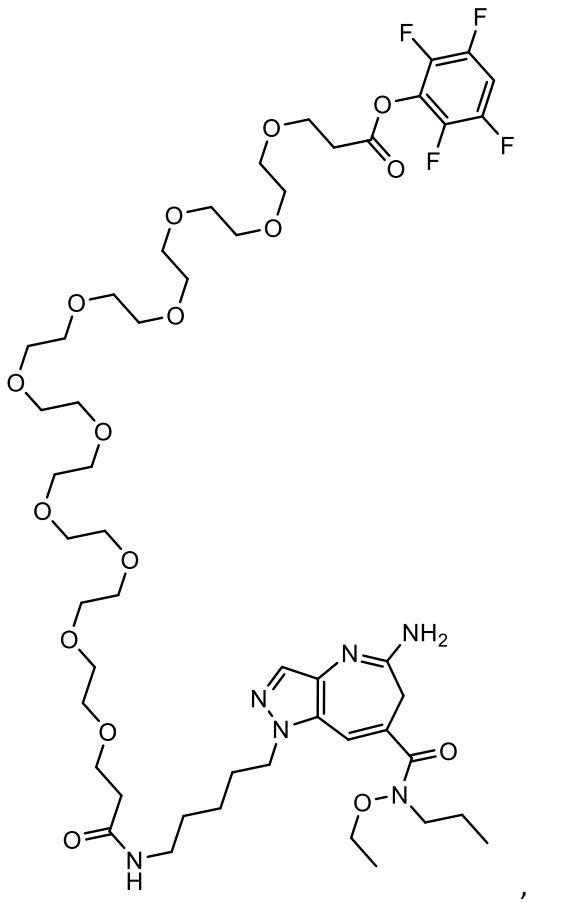
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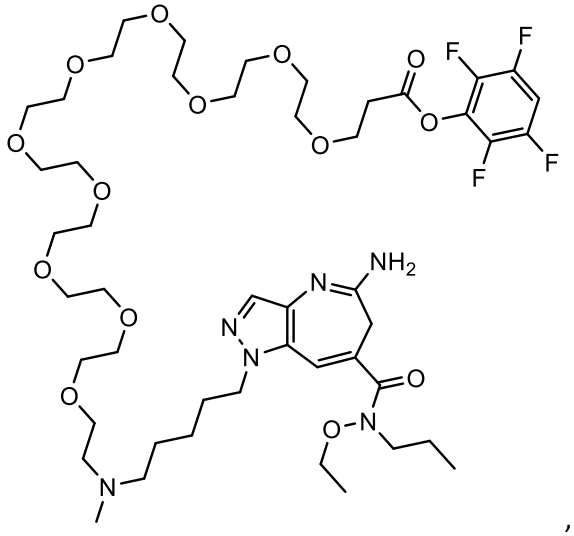
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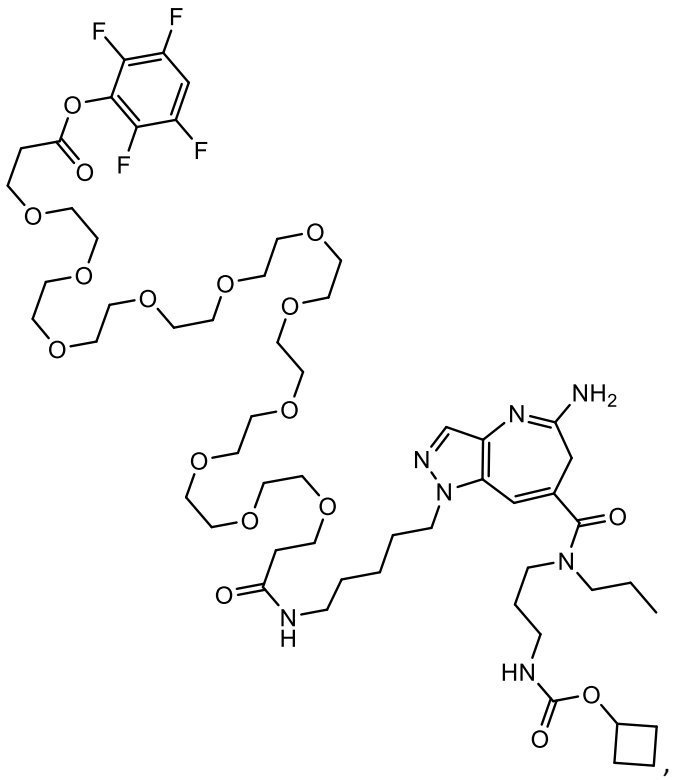
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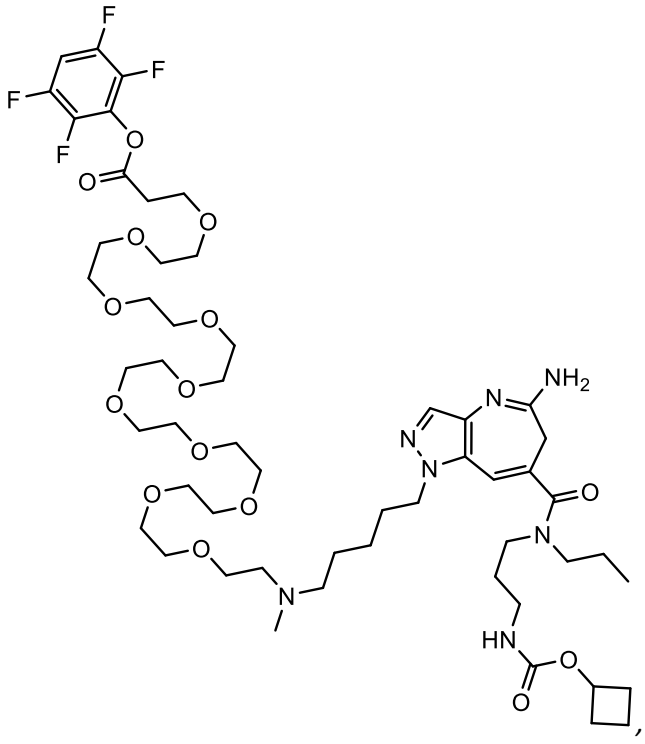


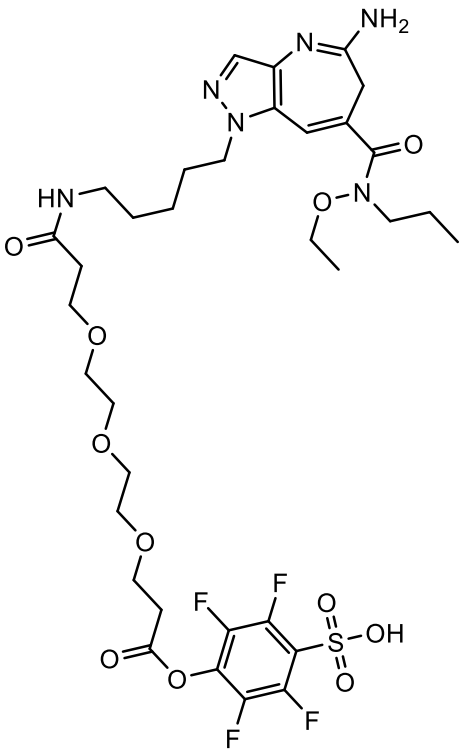
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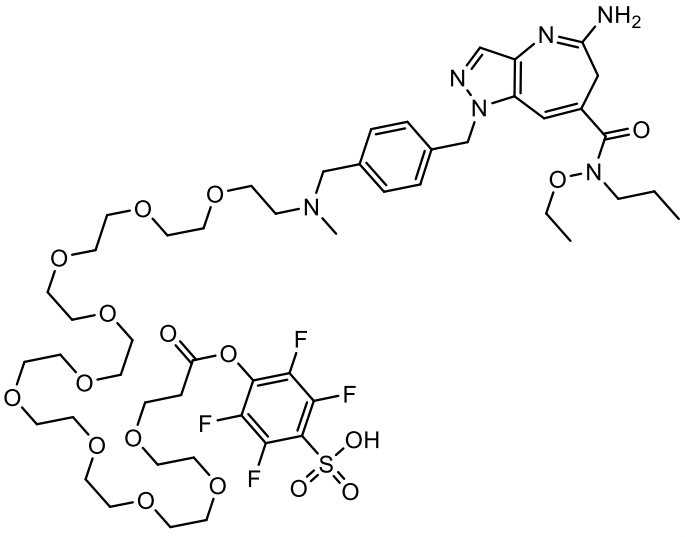
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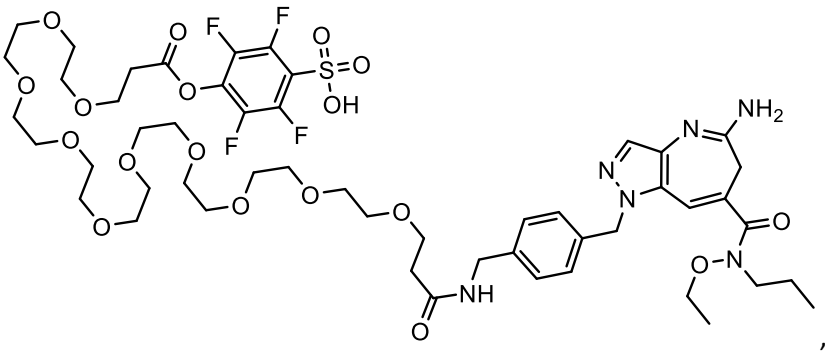




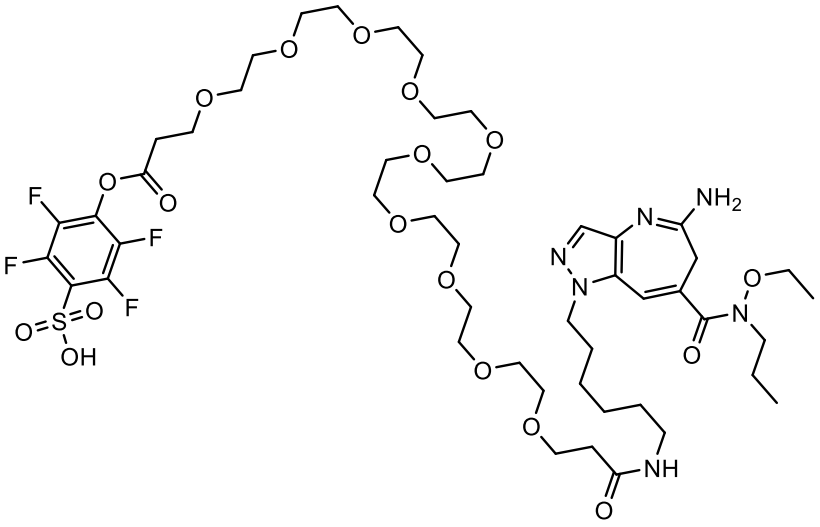
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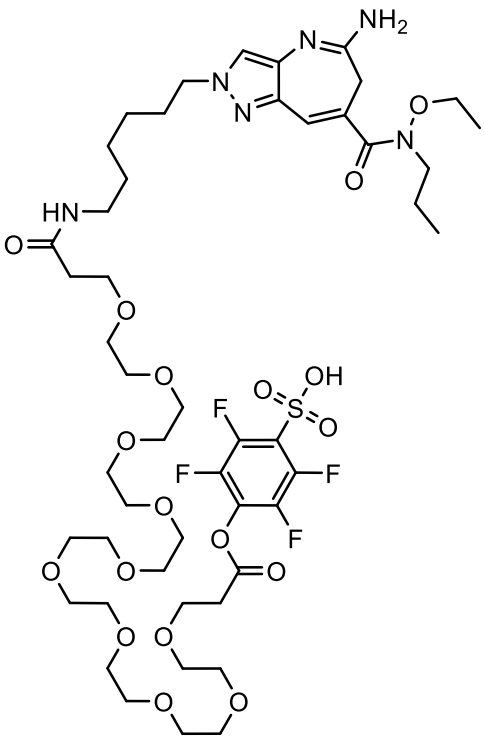
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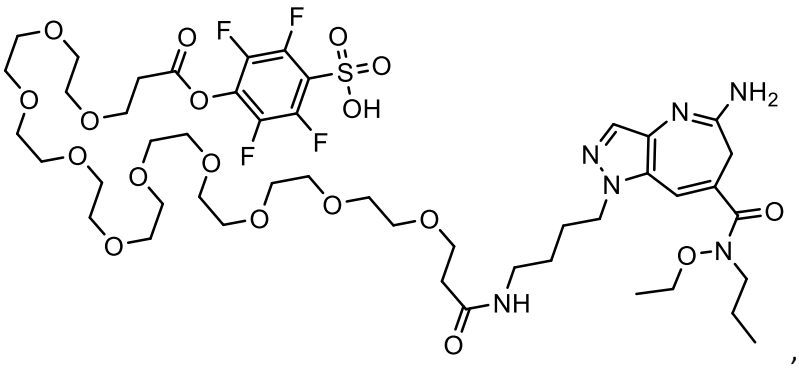
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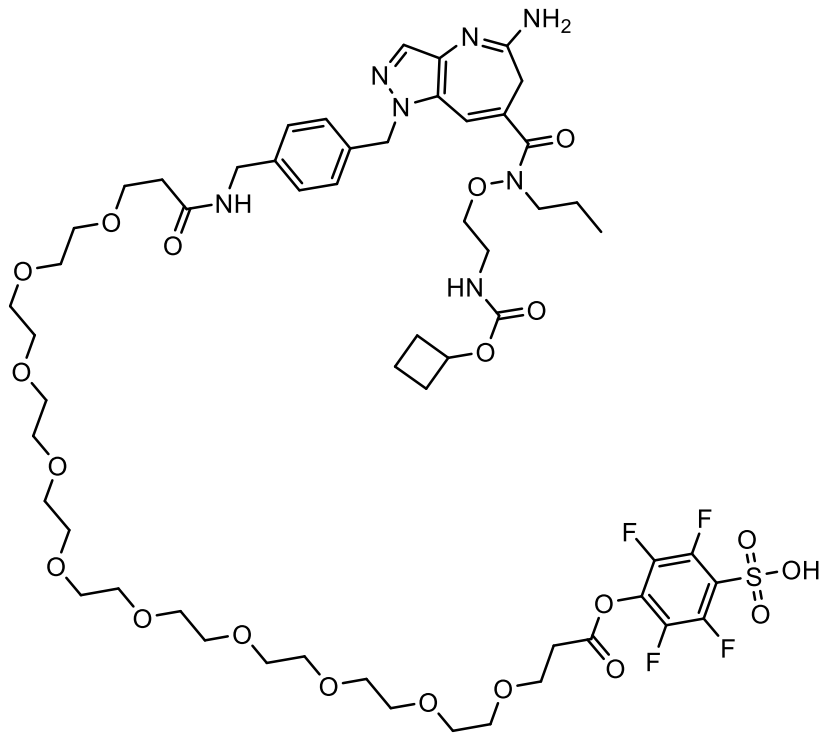
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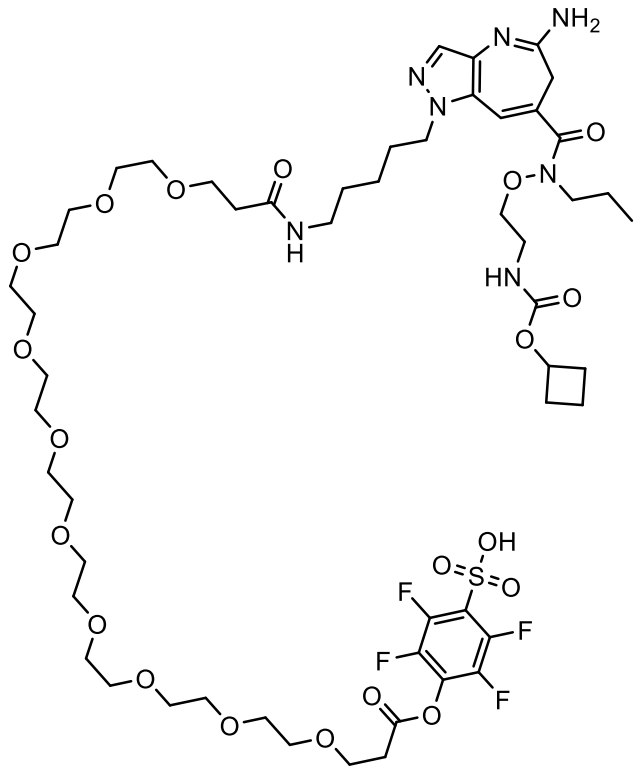
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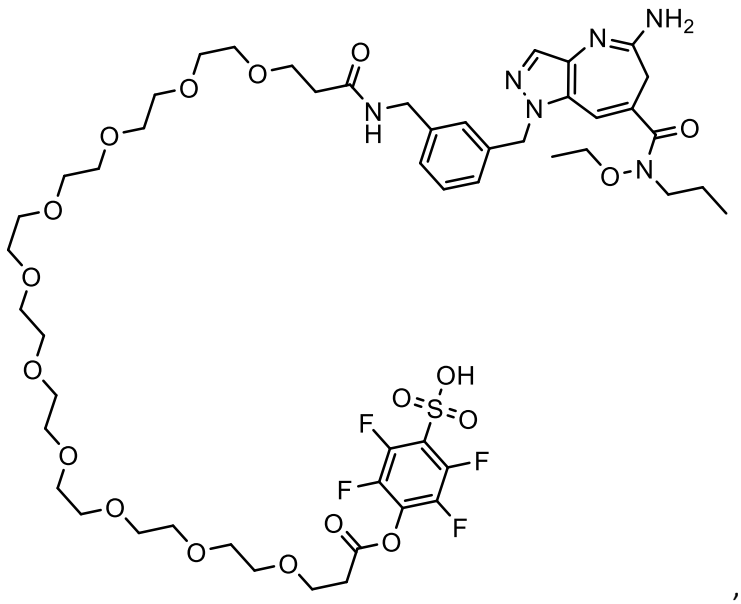
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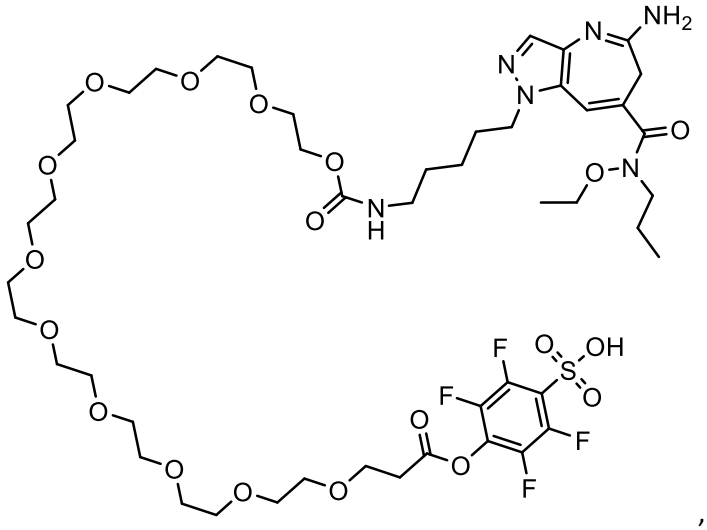
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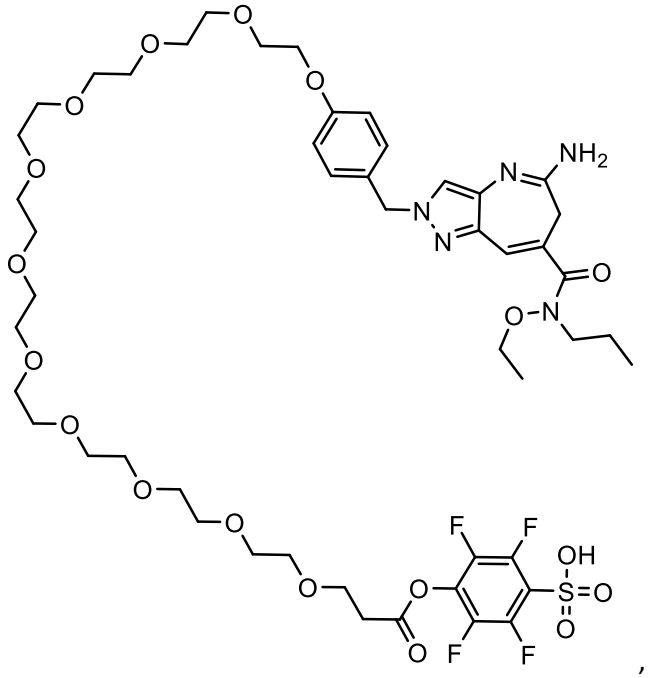
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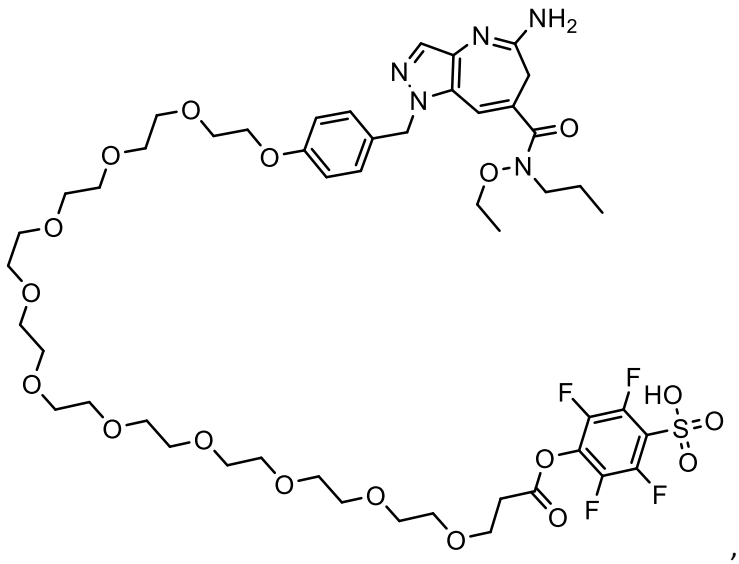
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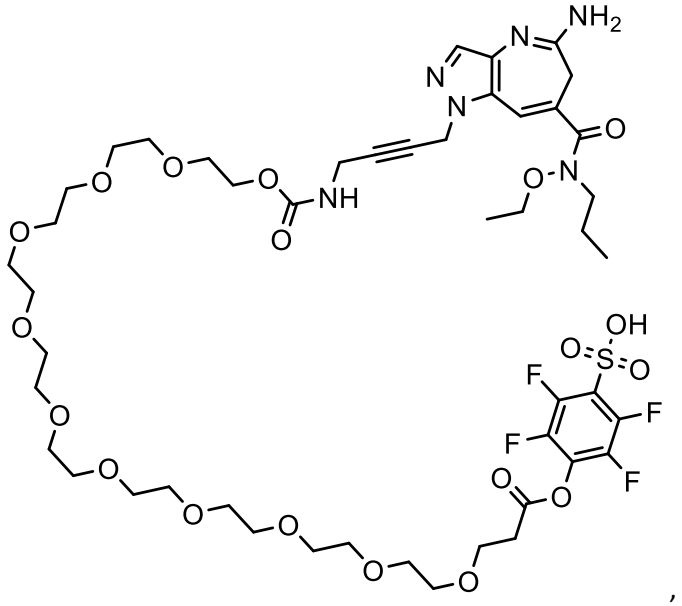
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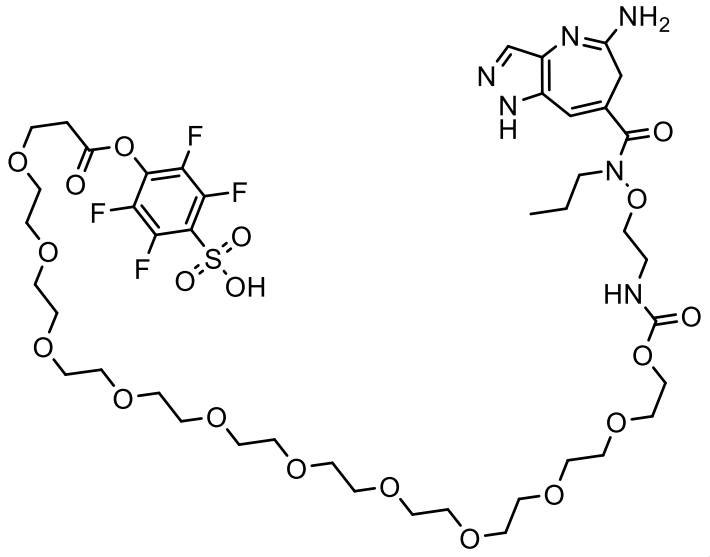
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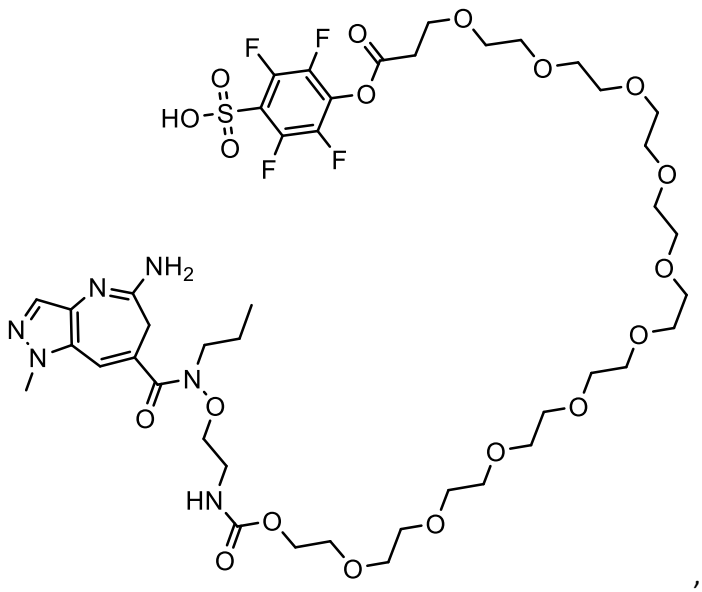
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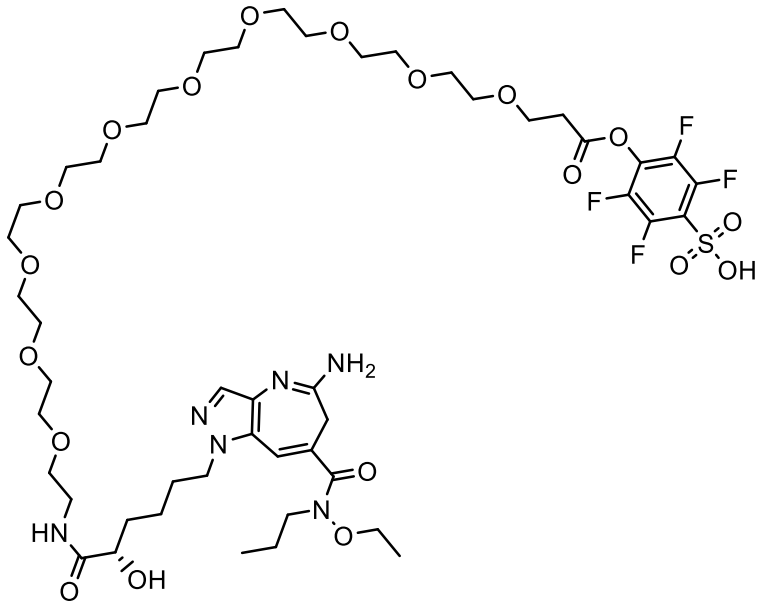
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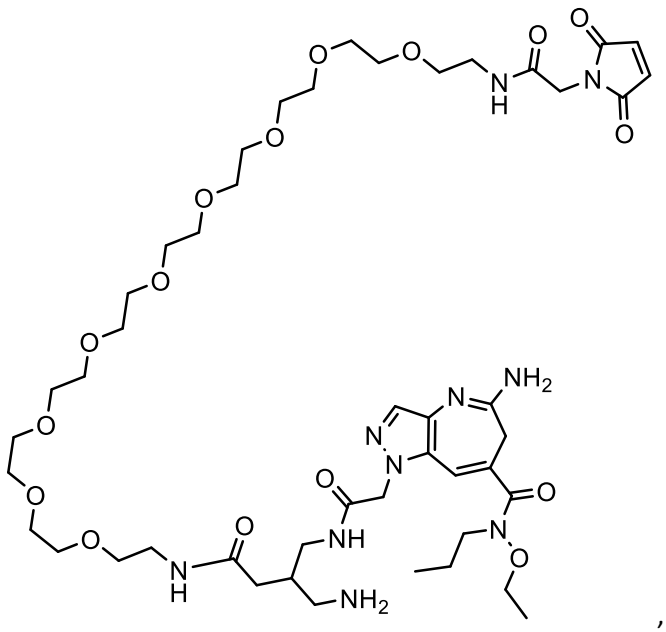
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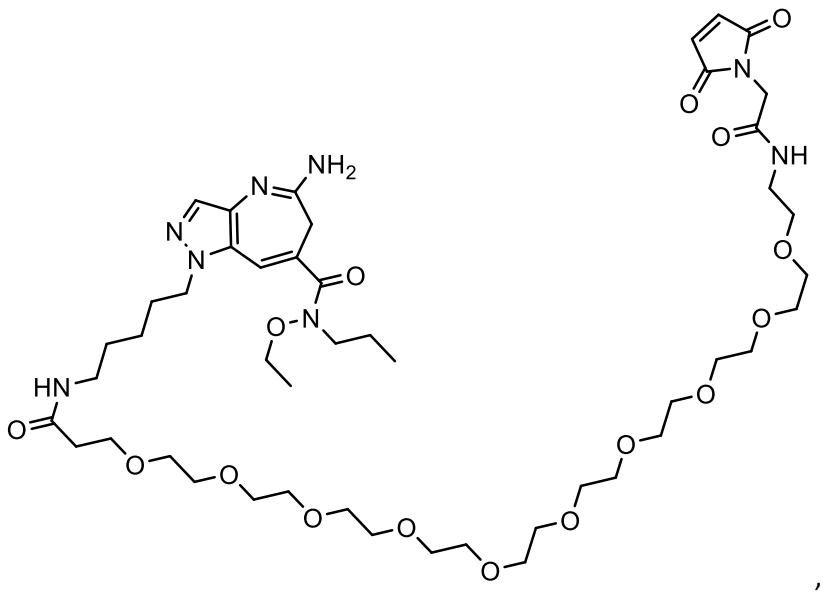
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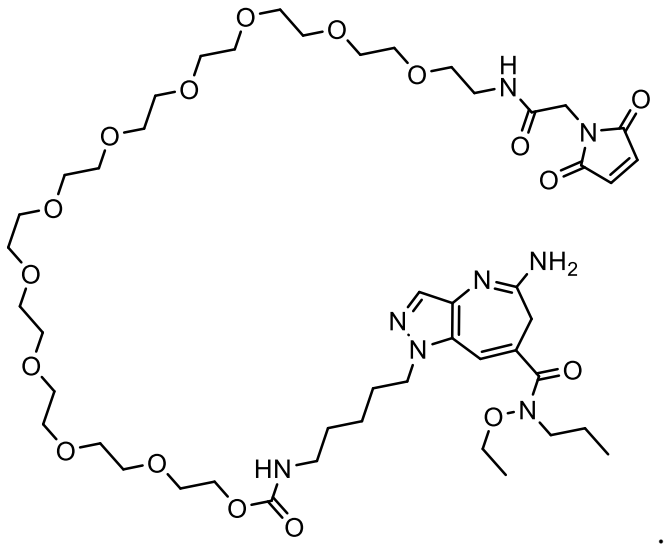
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49. An immunoconjugate prepared by conjugation of an antibody with a 5-amino-pyrazoloazepine-linker compound of claim 24.

50. A pharmaceutical composition comprising a therapeutically effective amount of an immunoconjugate according to any one of claims 1-23 and one or more pharmaceutically acceptable diluent, vehicle, carrier, or excipient.

51. Use of an immunoconjugate according to any one of claims 1 to 20 for treating cancer.

52. A method of preparing an immunoconjugate of Formula I of claim 1 wherein a 5-amino-pyrazoloazepine-linker compound of Formula II of claim 24 is conjugated with the antibody