ANTI-CEA IMMUNOCONJUGATES, AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This non-provisional application claims the benefit of priority to U.S. Provisional Application No. 63/124,328, filed 11 December 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 December 3, 2021, is named 17019_010WO1_SL.txt and is 55,248 bytes in size.

FIELD OF THE INVENTION

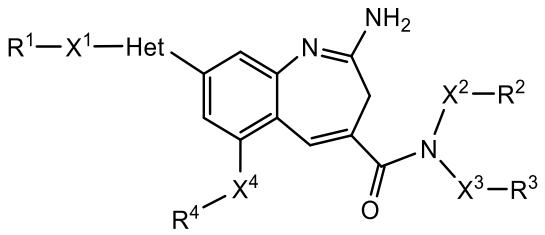
The invention relates generally to an immunoconjugate comprising an anti-Carcinoembryonic Antigen (CEA) antibody conjugated to one or more 8-Het-2-aminobenzazepine molecules.

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 anti-CEA antibody linked by conjugation to one or more 8-Het-2-aminobenzazepine derivatives. The disclosure is further directed to 8-Het-2-aminobenzazepine 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 8-Het-2-aminobenzazepine (HxBz) moiety having the formula:



where Het is selected from heterocyclyldiyl and heteroaryldiyl; and one of R^1, R^2, R^3 and R^4 is attached to L. The R^{1-4} and X^{1-4} substituents are defined herein.

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

In an aspect, there is provided an immunoconjugate comprising an antibody covalently attached to one or more 8-Het-2-aminobenzazepine moieties by a linker, and having Formula I:

$$Ab–[L–HxBz]_p \qquad I$$

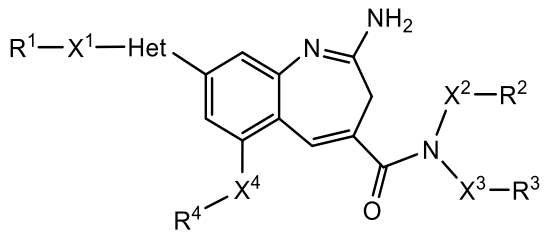
or a pharmaceutically acceptable salt thereof,

wherein:

Ab is an antibody construct that has an antigen binding domain that binds CEA;

p is an integer from 1 to 8;

HxBz is the 8-Het-2-aminobenzazepine moiety having the formula:



Het is selected from heterocyclyldiyl and heteroaryldiyl;

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} heteroaryl)–*;

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

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

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

–(C_1-C_{20} heteroaryl)–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;

–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)–*;

–O–C(=O)N(R^5)$_2$;

–O–C(=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;

X^1, X^2, X^3, and X^4 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^5 is independently selected from the group consisting of H, C$_6$-C$_{20}$ aryl, C$_3$-C$_{12}$ carbocyclyl, 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)–;

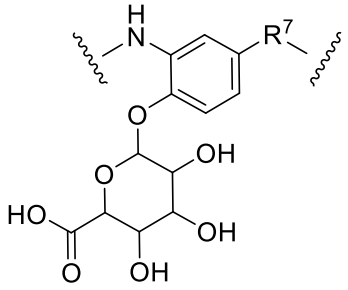
–succinimidyl–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–; and

–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;

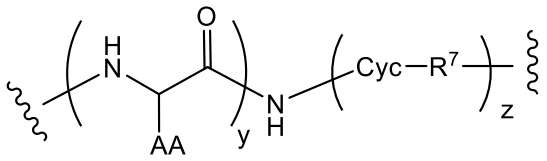
PEG has the formula: $–(CH_2CH_2O)_n–(CH_2)_m–$; m is an integer from 1 to 5, and n is an integer from 2 to 50;

Gluc has the formula:



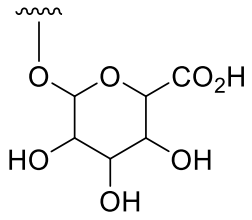
;

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,

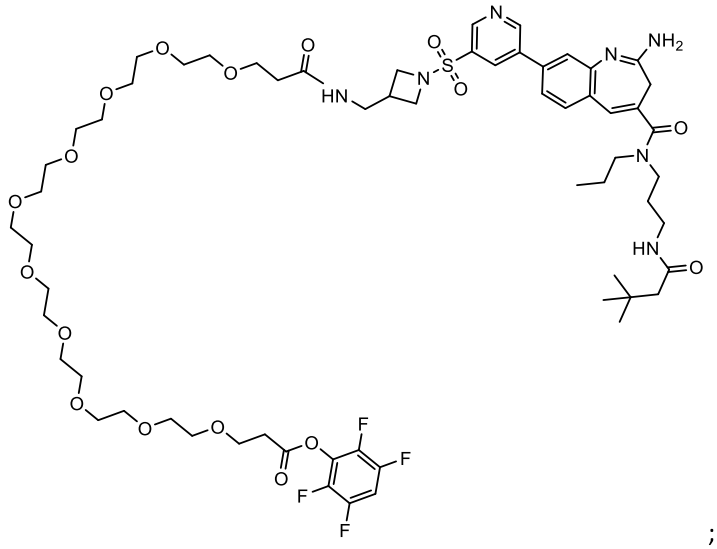
and $-(CH_2CH_2O)_n-(CH_2)_m-OH$, where m is an integer from 1 to 5, and n is an integer from 2 to 50, or two R^9 groups together form a 5- or 6-membered heterocyclyl ring;

y is an integer from 2 to 12;

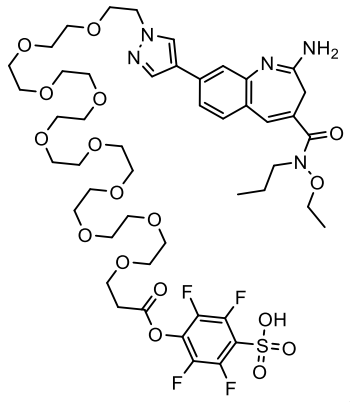
z is 0 or 1; and

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, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH_2N(CH_3)_2$, $-O(CH_2CH_2O)_n-(CH_2)_mCO_2H$, $-O(CH_2CH_2O)_nH$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-OP(O)(OH)_2$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-S(O)_2CH_3$, and $-S(O)_3H$.

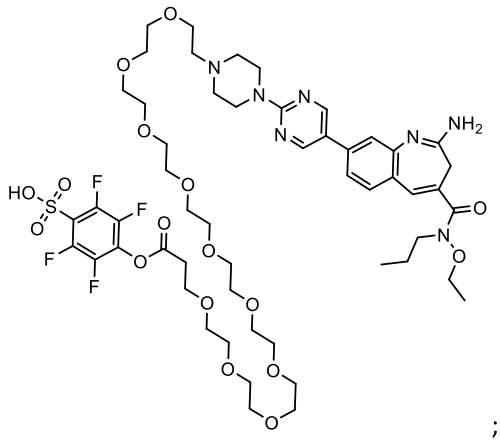
In another aspect, there is provided an 8-Het-2-aminobenzazepine-linker compound selected from the group consisting of:



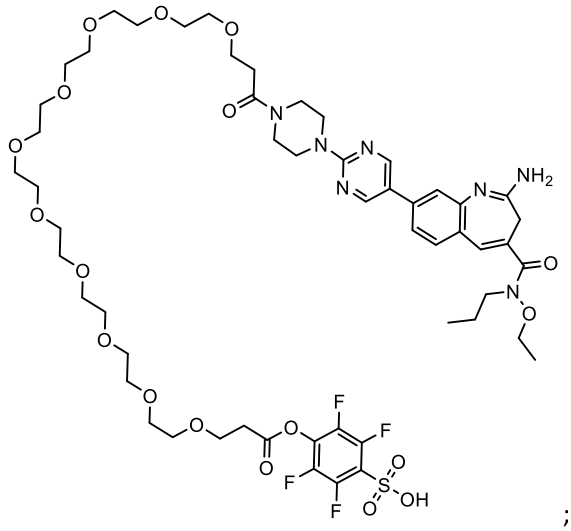
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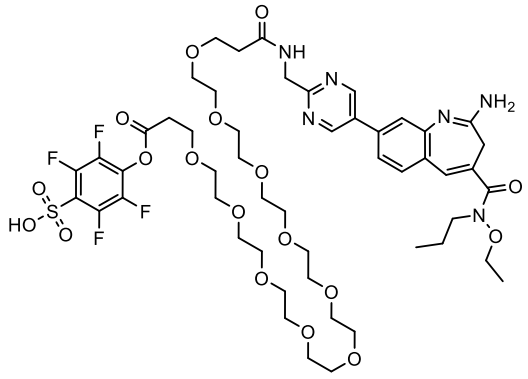
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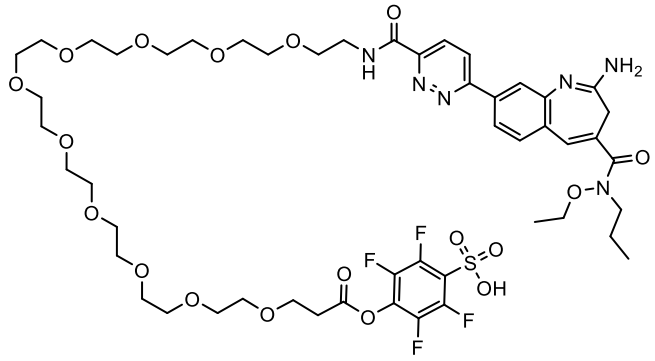
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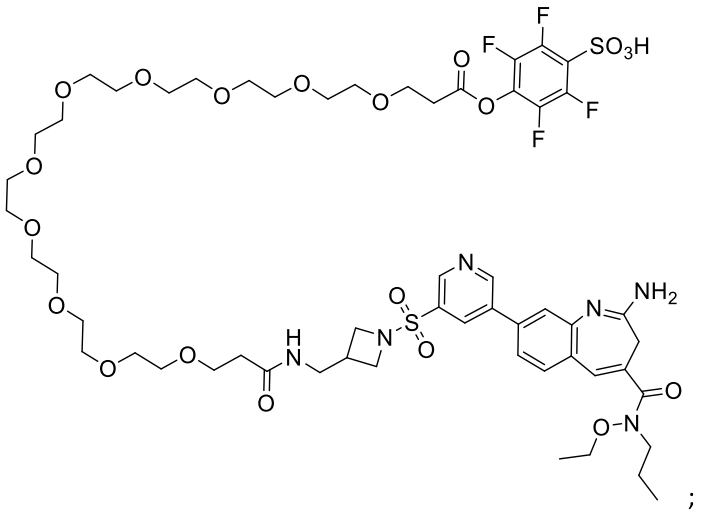
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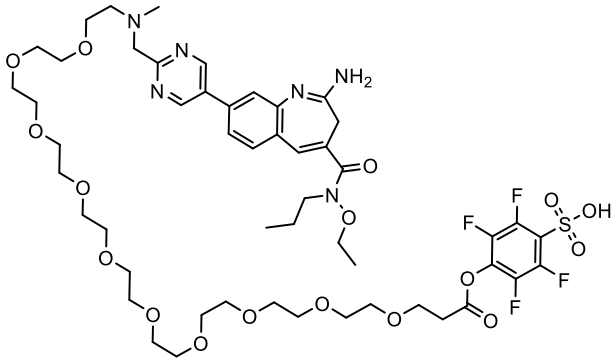
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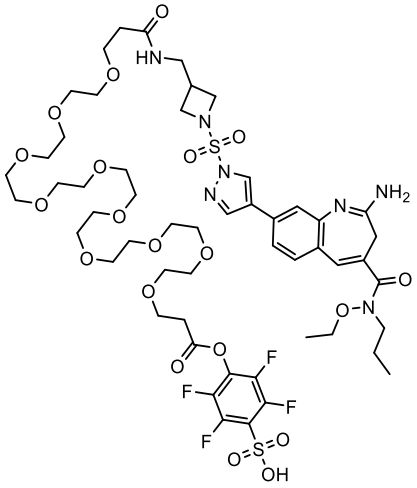
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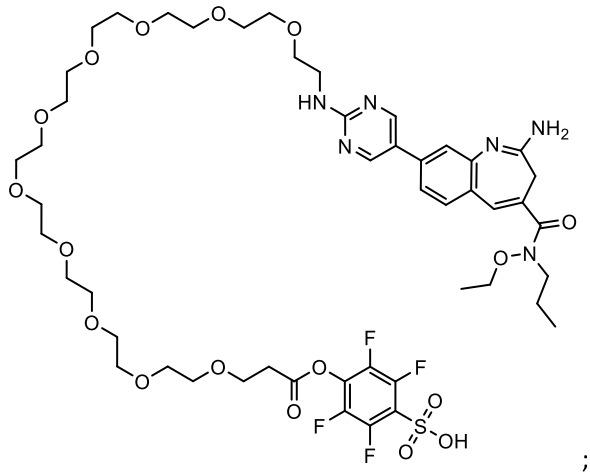
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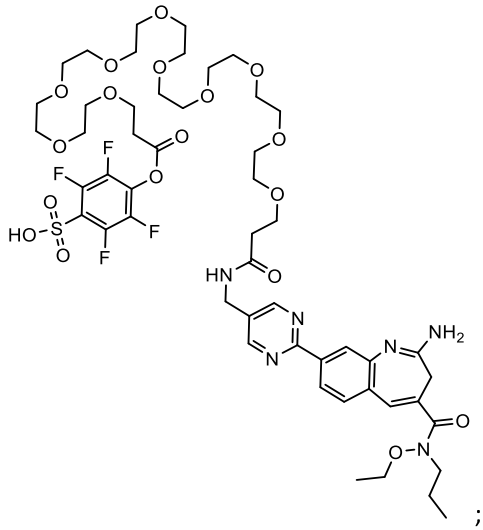
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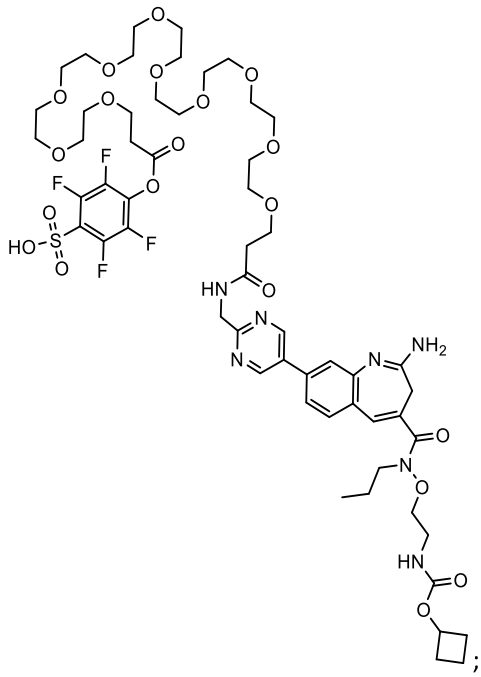
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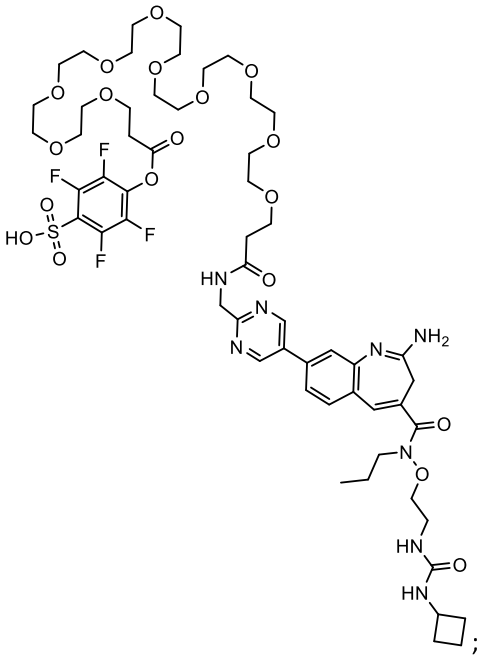
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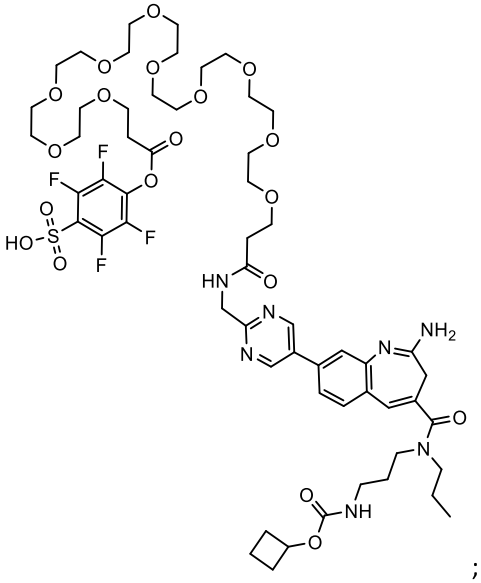


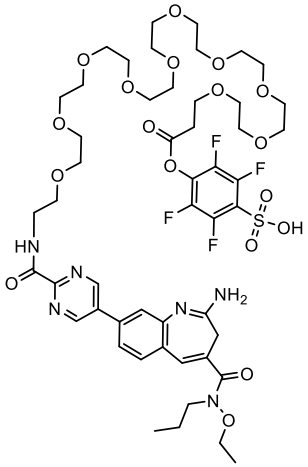
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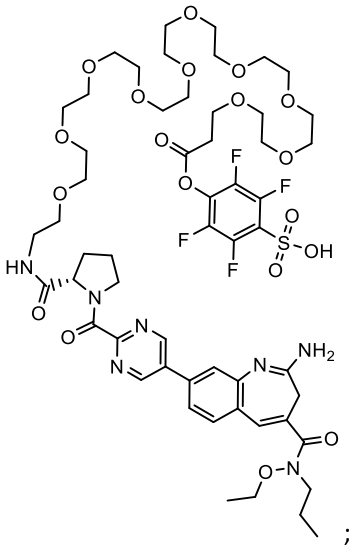


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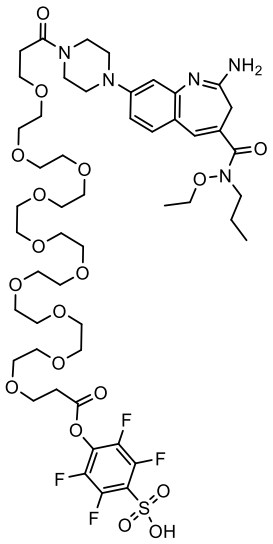

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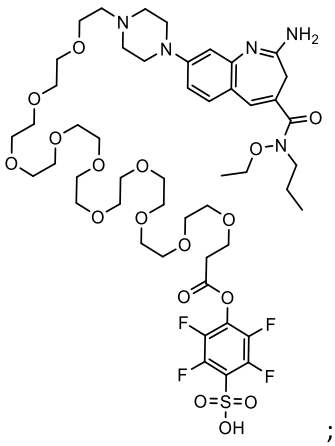

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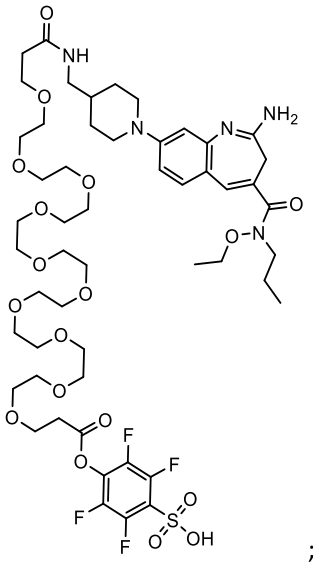
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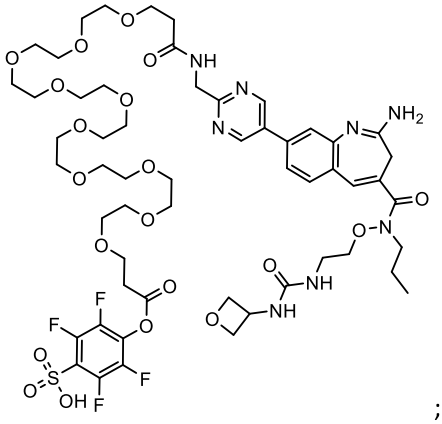
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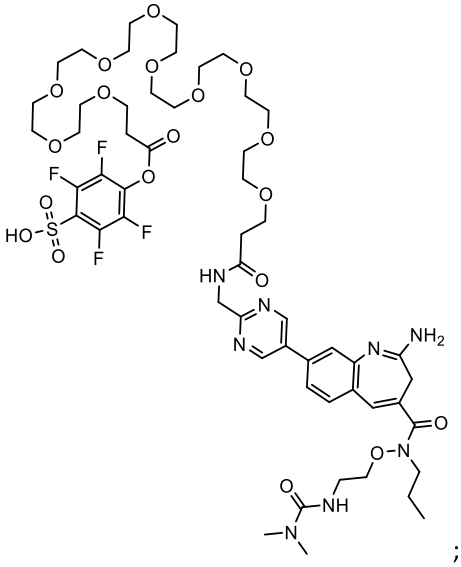
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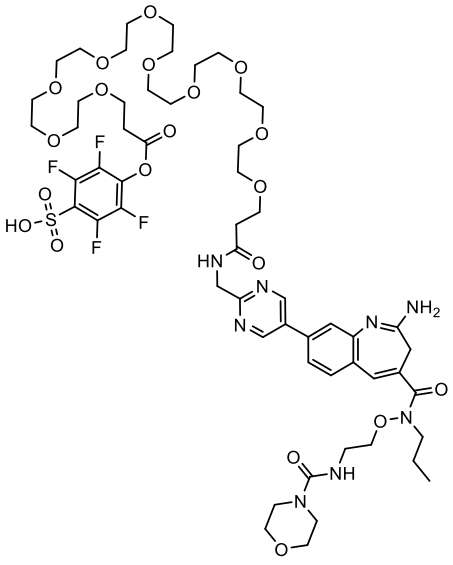
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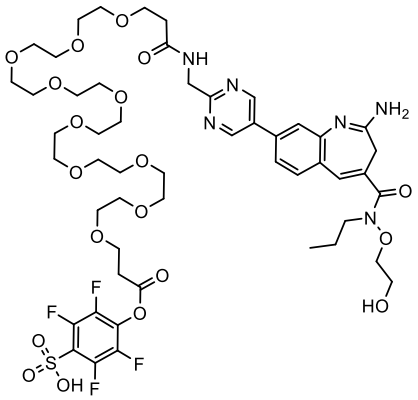
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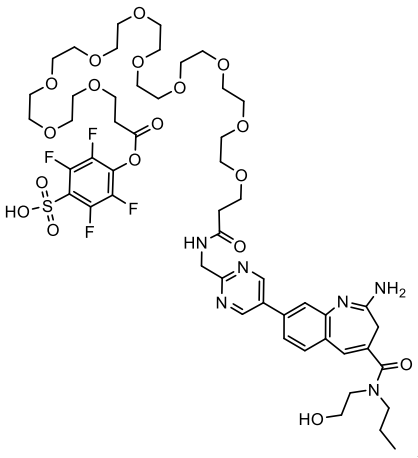
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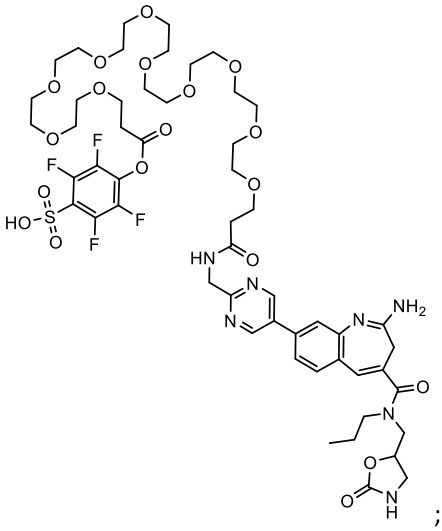
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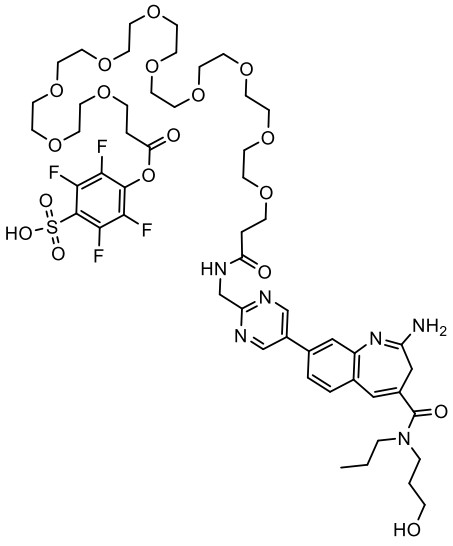
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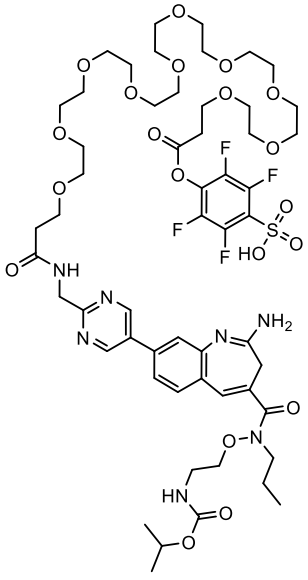
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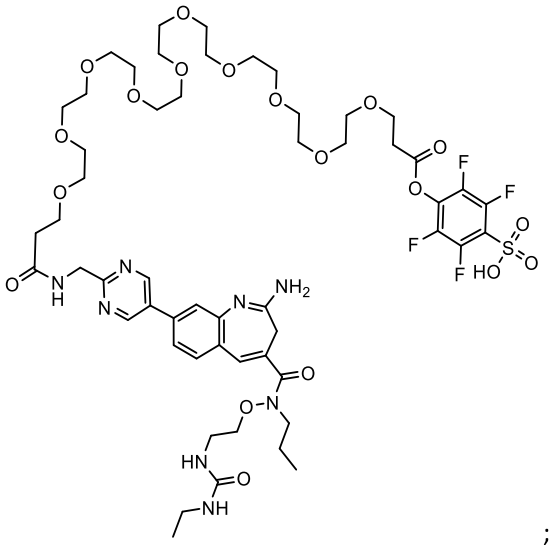
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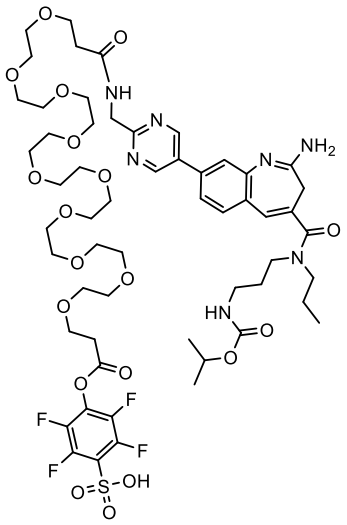
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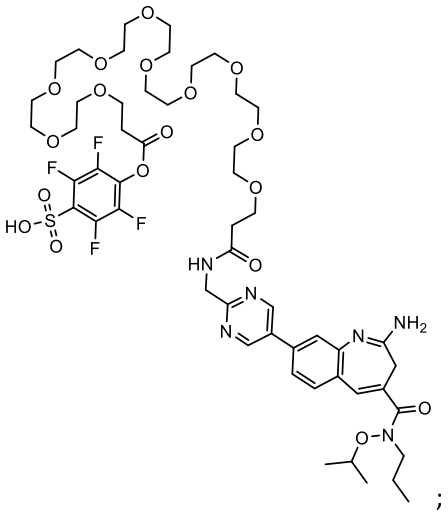
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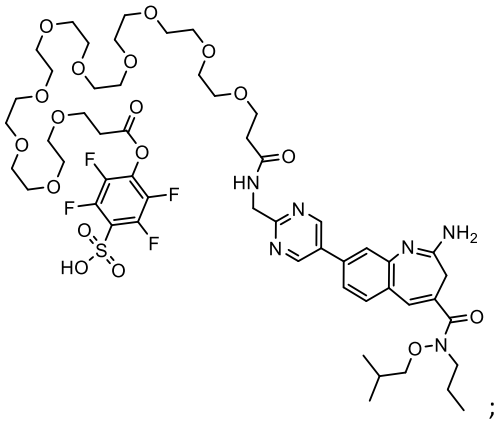
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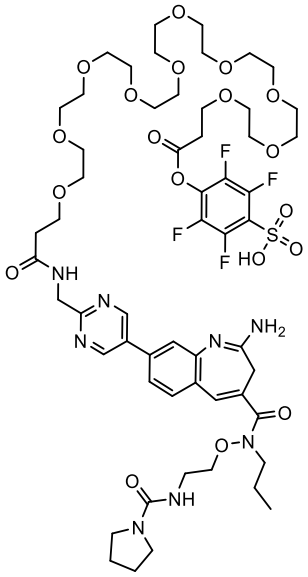
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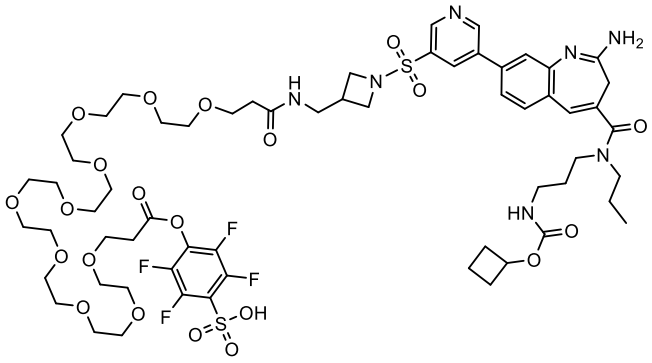
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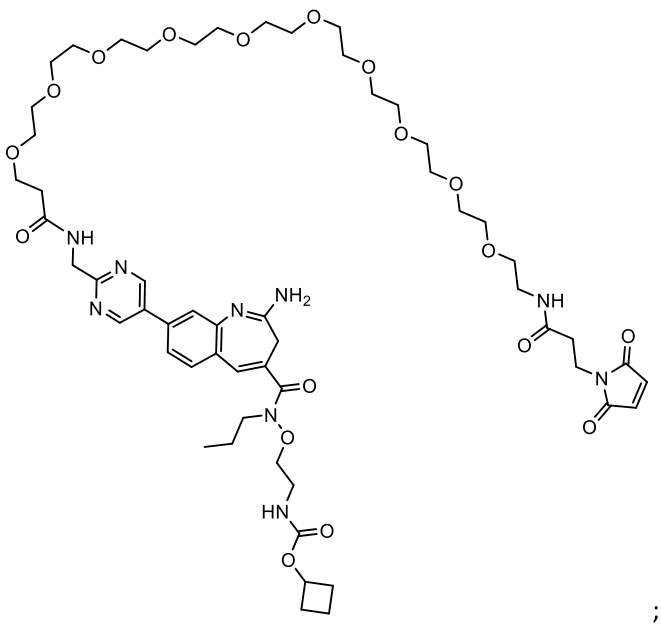
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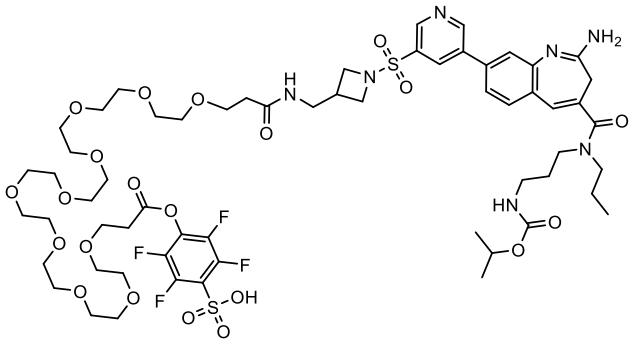
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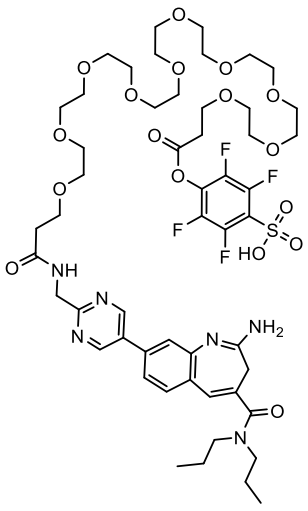
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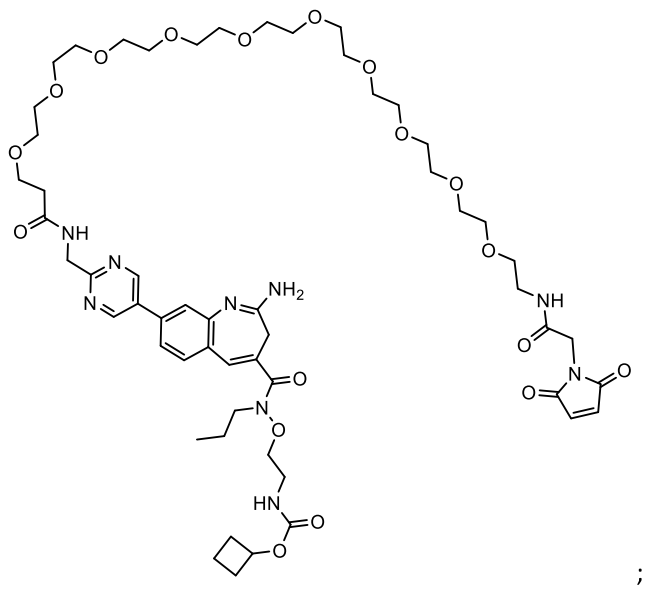
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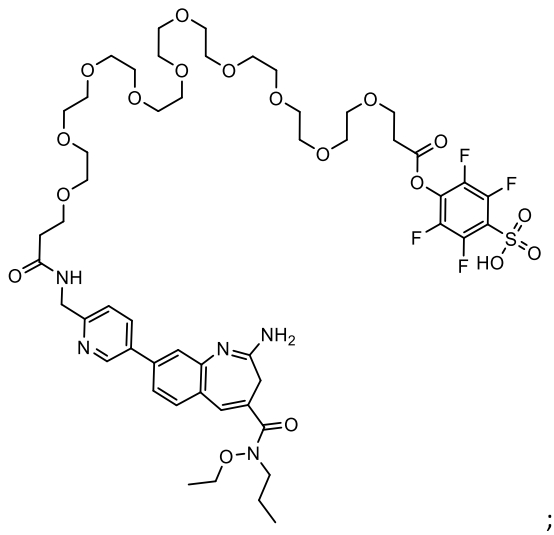
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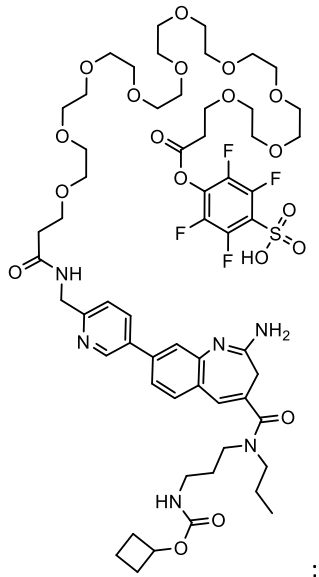
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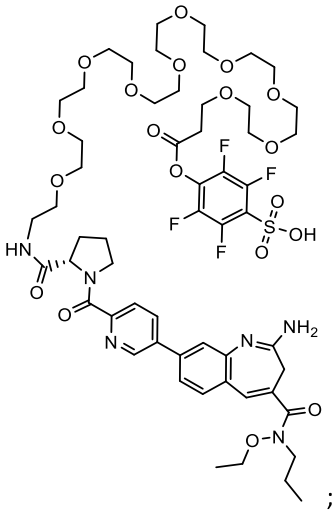
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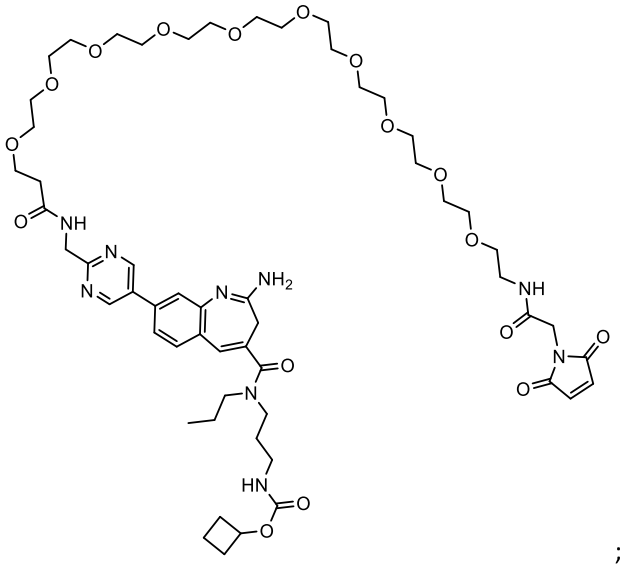
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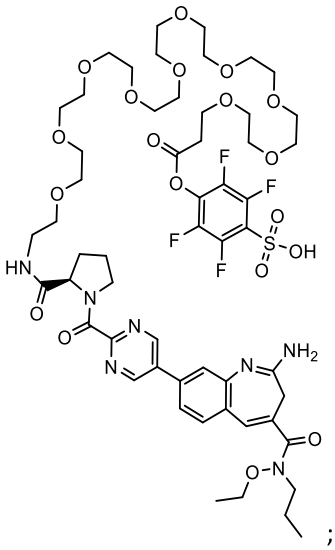
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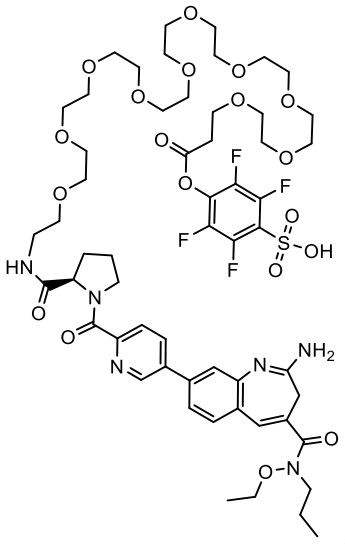
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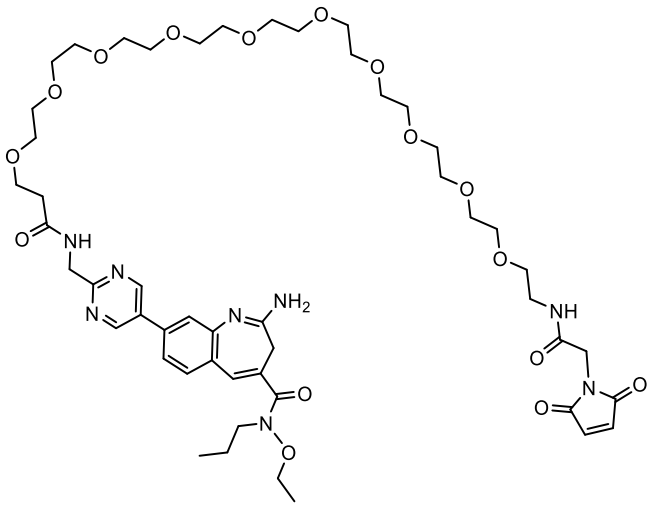
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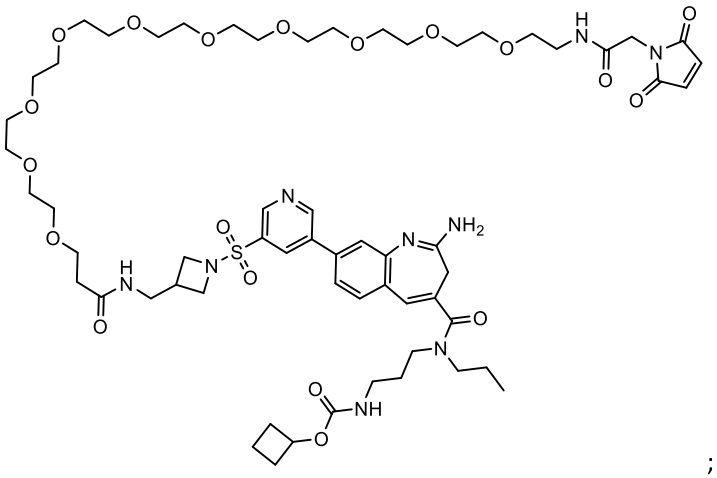
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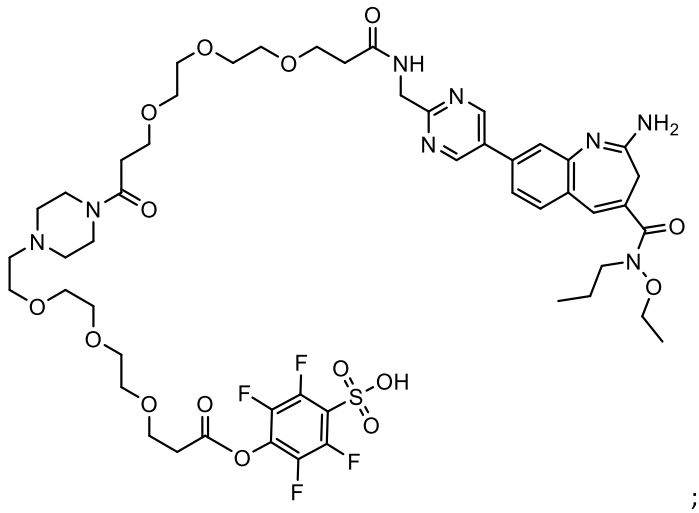
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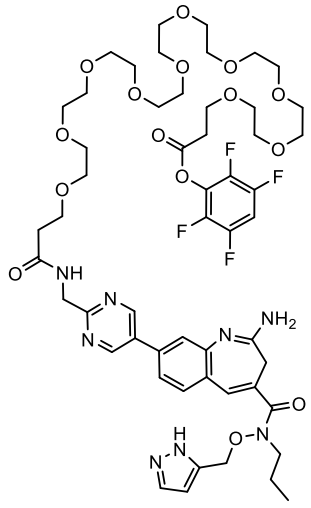
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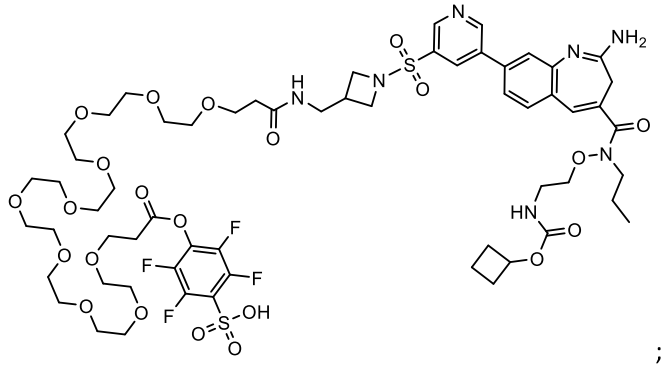
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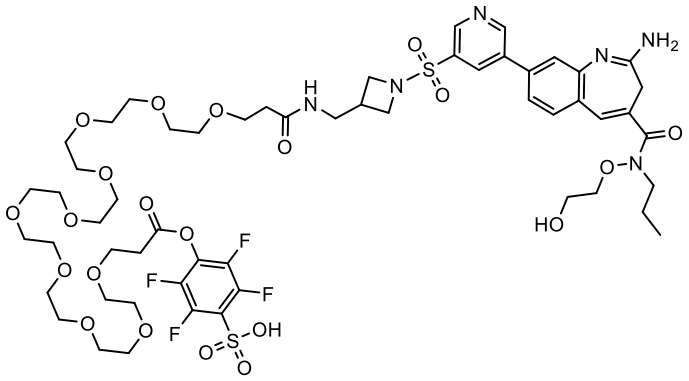
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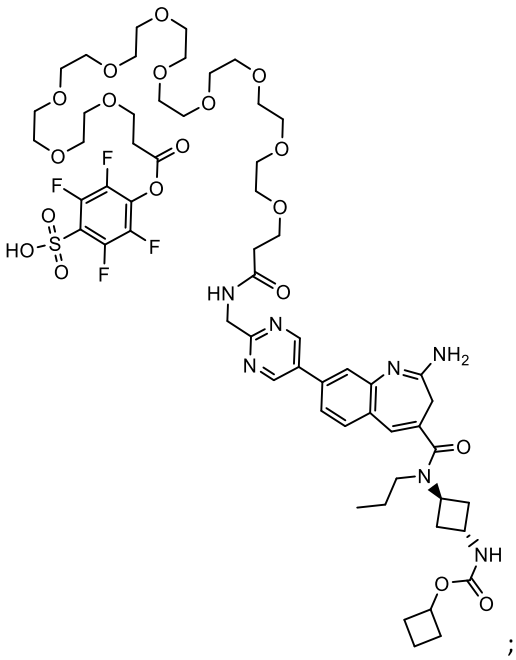
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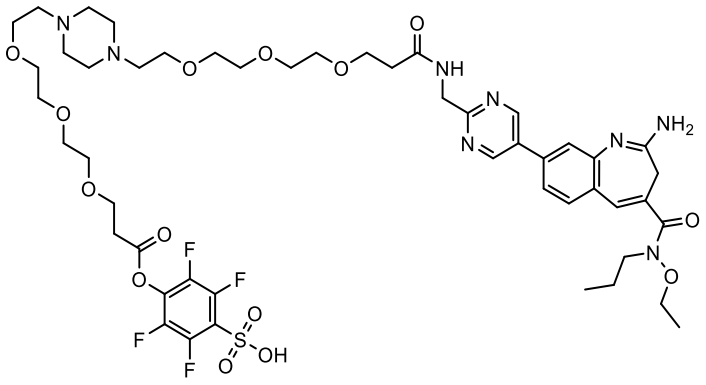
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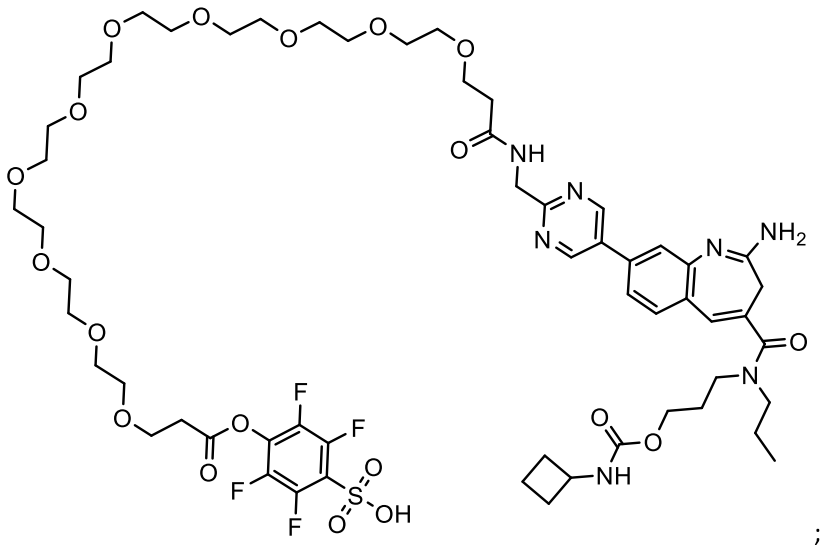
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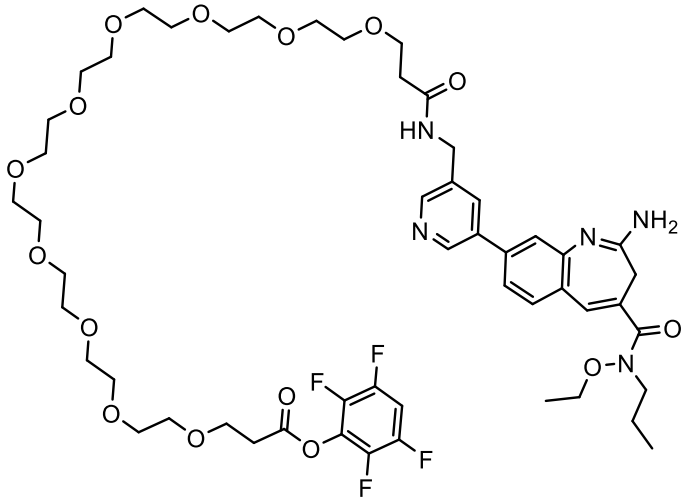


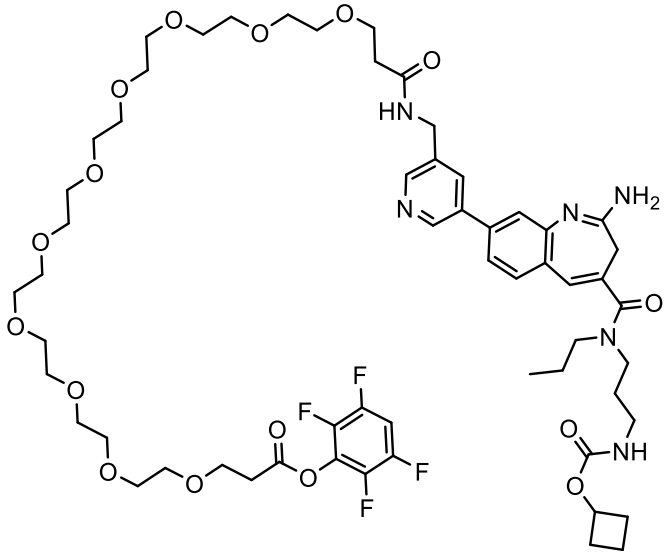
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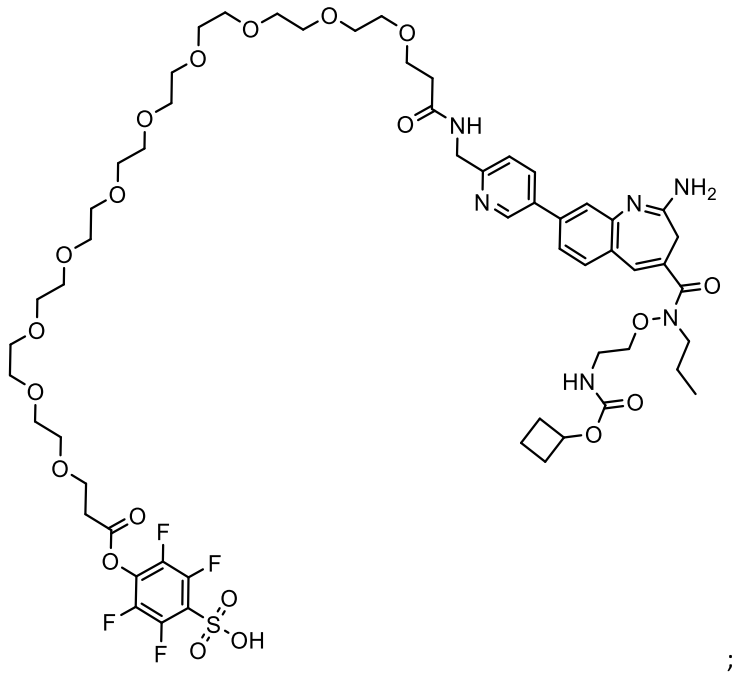


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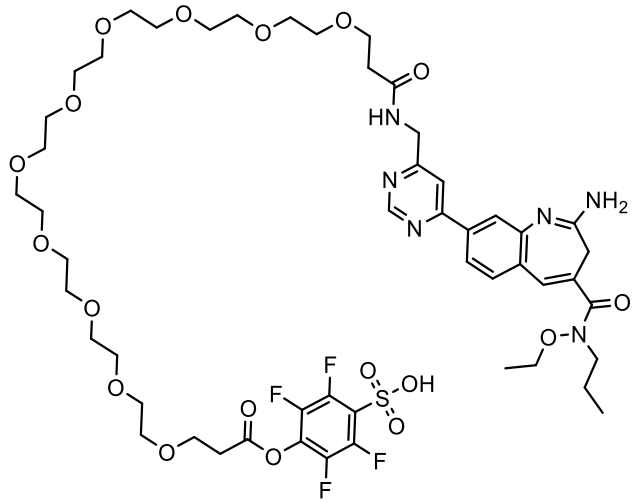

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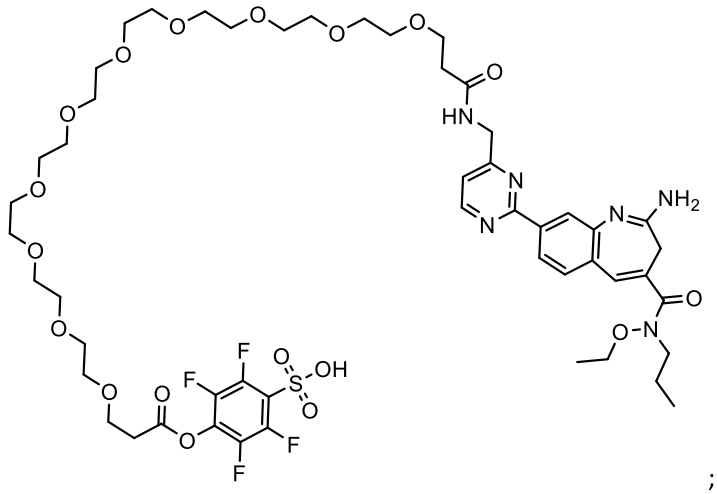

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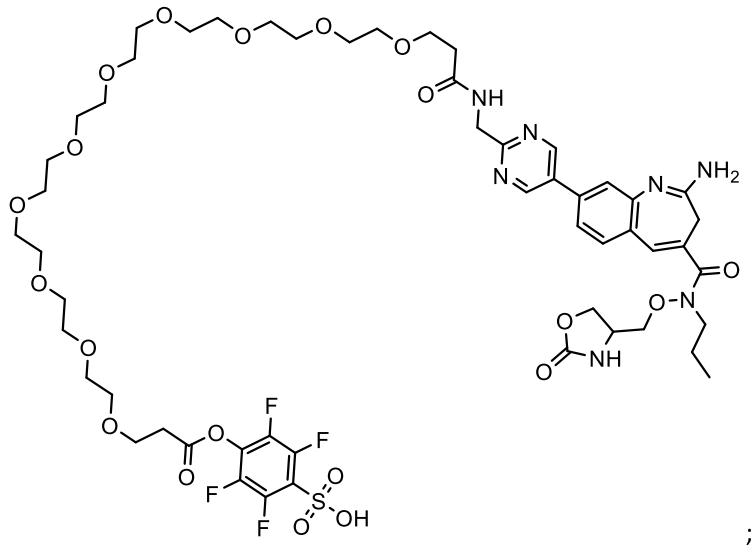
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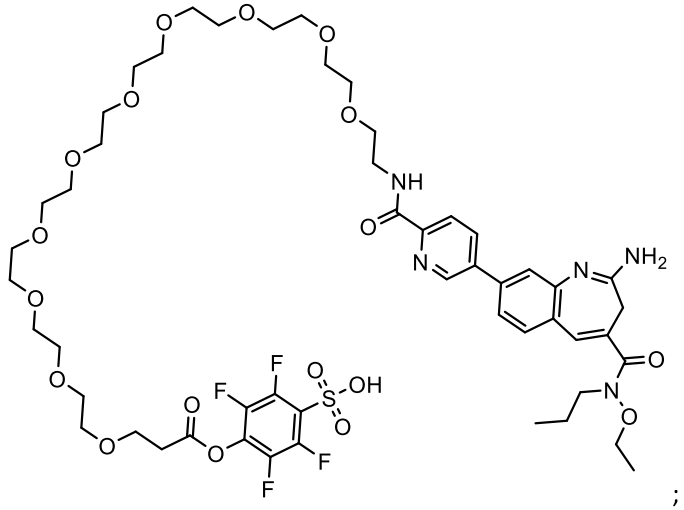
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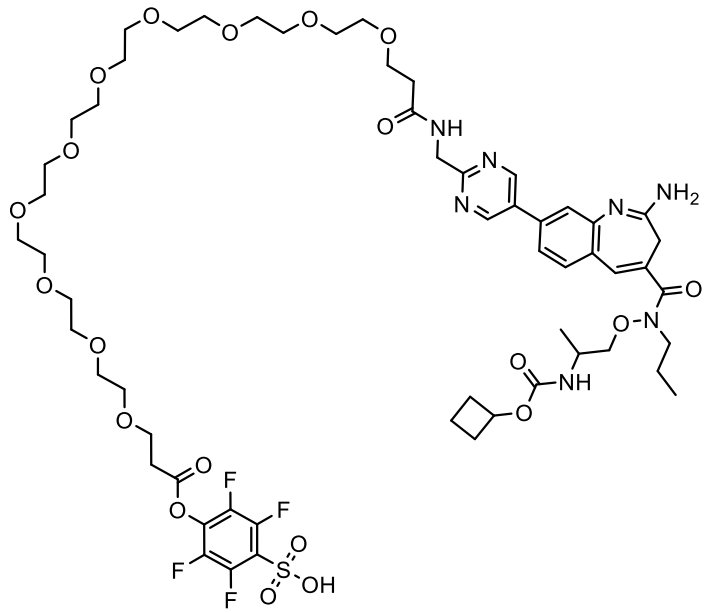
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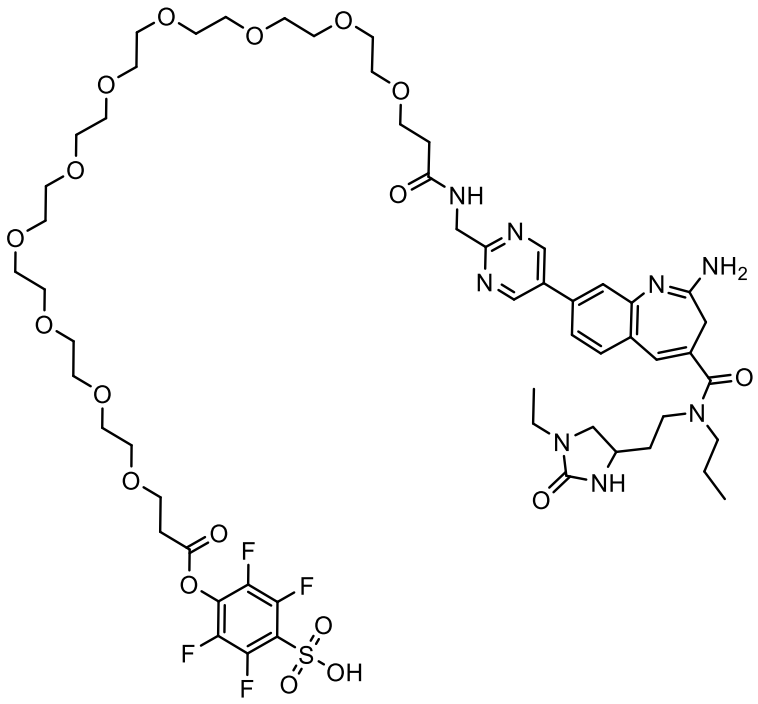
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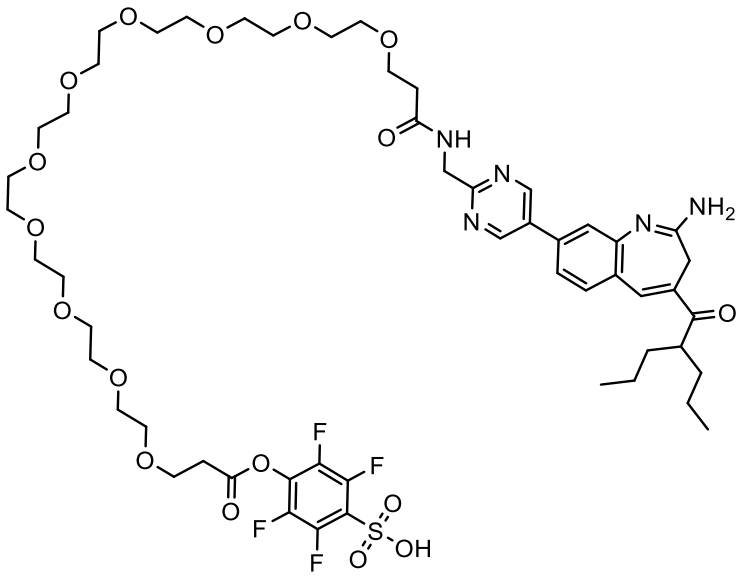
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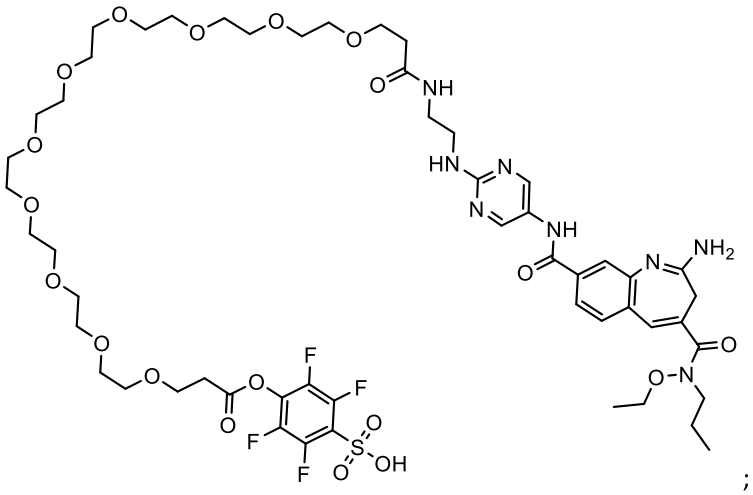
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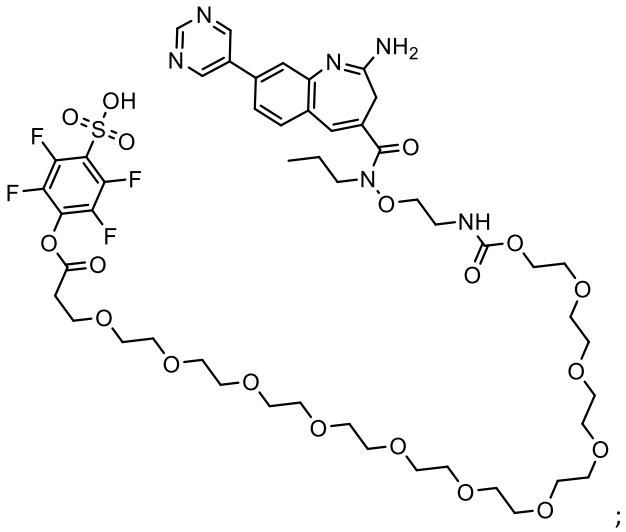
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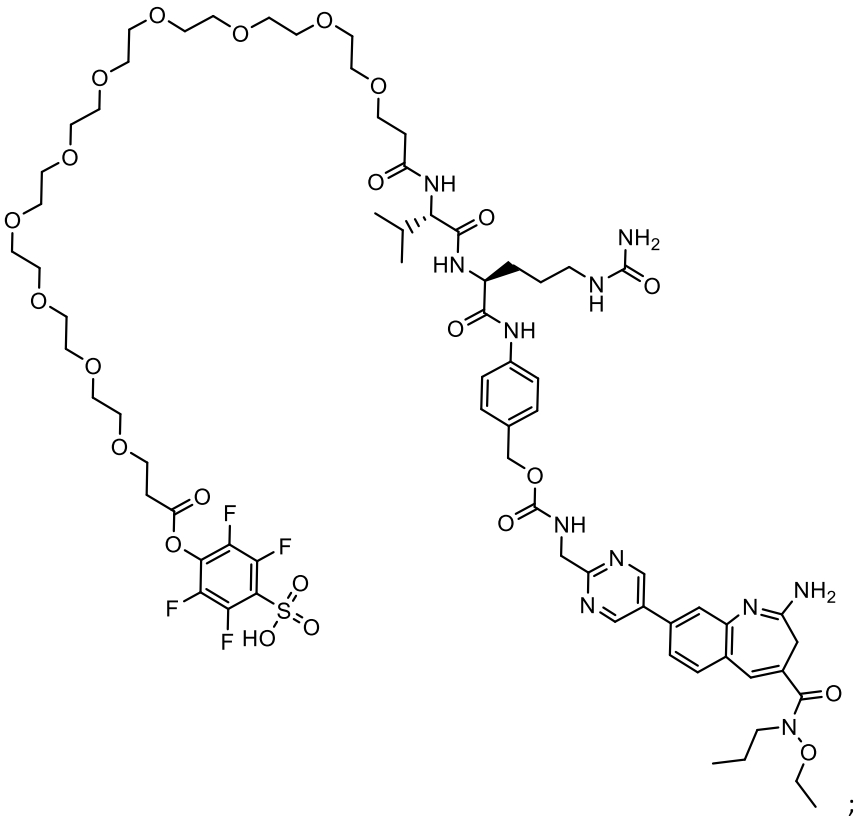
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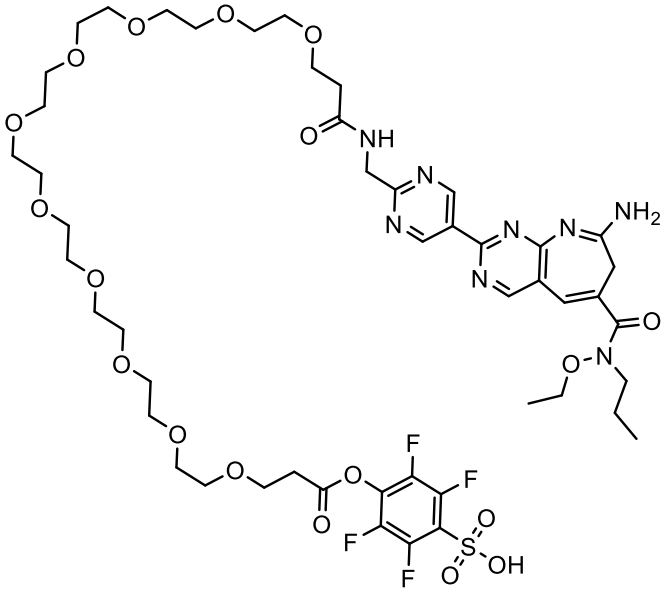
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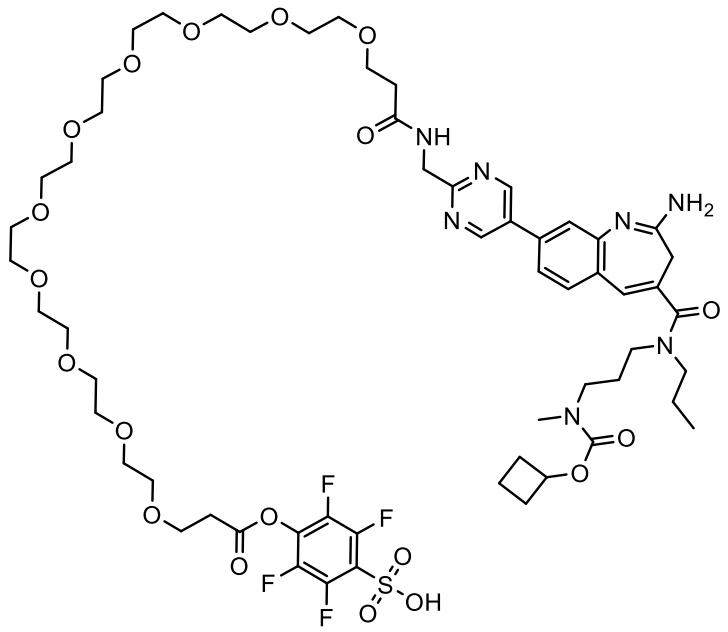
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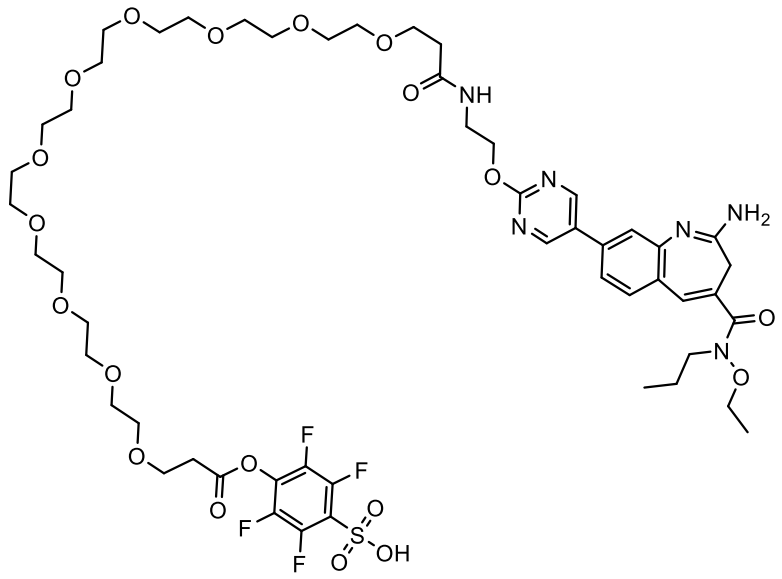
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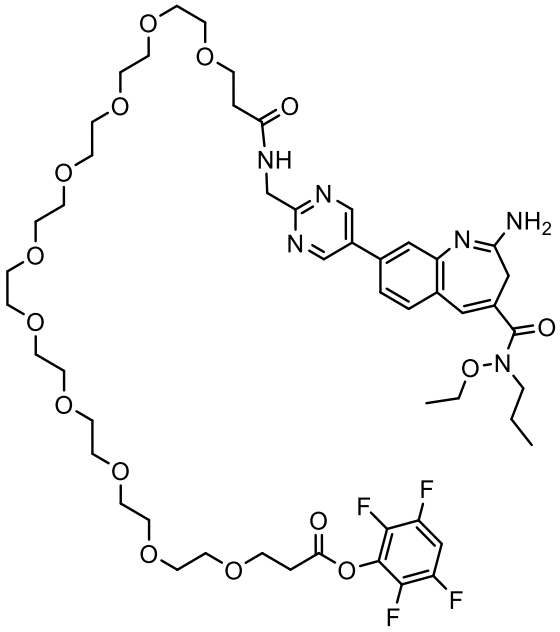
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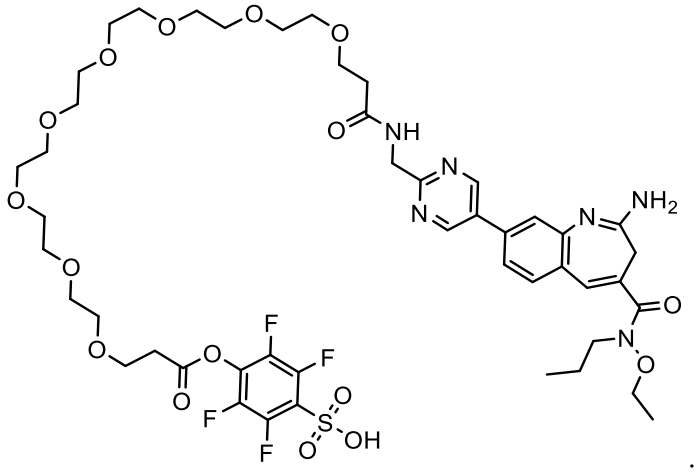
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In another aspect, there is provided an immunoconjugate prepared by conjugation of an anti-CEA antibody with a 8-Het-2-aminobenzazepine-linker compound as defined above.

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 in the manufacture of a medicament for treating cancer, wherein the cancer is selected from cervical cancer, endometrial cancer, ovarian cancer, prostate cancer, pancreatic cancer, esophageal cancer, bladder cancer, urinary tract cancer, urothelial carcinoma, lung cancer, non-small cell lung cancer, Merkel cell carcinoma, colon cancer, colorectal cancer, gastric cancer, and breast cancer.

In another aspect, there is provided a method of preparing an immunoconjugate of Formula I as defined above wherein the 8-Het-2-amino-thienoazepine-linker compound as defined above is conjugated with the anti-CEA antibody.

An example of the disclosure is an immunoconjugate comprising an anti-CEA antibody covalently attached to a linker which is covalently attached to one or more 8-Het-2-aminobenzazepine moieties.

Another example of the disclosure is a 8-Het-2-aminobenzazepine-linker compound.

Another example of the disclosure is a method for treating cancer comprising administering a therapeutically effective amount of an immunoconjugate comprising an anti-CEA antibody linked by conjugation to one or more 8-Het-2-aminobenzazepine moieties.

Another example of the disclosure is a use of an immunoconjugate comprising an anti-CEA antibody linked by conjugation to one or more 8-Het-2-aminobenzazepine moieties for treating cancer.

Another example of the disclosure is a method of preparing an immunoconjugate by conjugation of one or more 8-Het-2-aminobenzazepine moieties with an anti-CEA antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a graph of an *in vivo* xenograft tumor model in mice. Tumor volume over time after treatment was measured to compare the efficacy of immunoconjugate IC-2 with an isotype immunoconjugate (ISAC) and naked antibody CEA.9-G1fhL2 in tumor inhibition of mice bearing CEA-high human pancreatic HPAF-II tumors.

Figure 2a shows a graph of cytokine IL-12p70 induction in a co-culture of CEA-high MKN-45 cells with a Human conventional dendritic cells (cDC)-enriched primary cell isolate by immunoconjugates IC-2, IC-3, IC-4, IC-6, IC-14 (Table 3a), and naked antibody CEA.9-G1fhL2.

Figure 2b shows a graph of cytokine TNFα (Tumor Necrosis Factor alpha) induction in a co-culture of CEA-high MKN-45 cells with a cDC-enriched primary cell isolate by immunoconjugates IC-2, IC-3, IC-4, IC-6, IC-14, and naked antibody CEA.9-G1fhL2.

Figure 2c shows a graph of IL-6 (Interleukin-6) induction in a co-culture of CEA-high MKN-45 cells with a cDC-enriched primary cell isolate by immunoconjugates IC-2, IC-3, IC-4, IC-6, IC-14, and naked antibody CEA.9-G1fhL2.

Figure 2d shows a graph of cytokine IFNγ (Interferon gamma) induction in a co-culture of CEA-high MKN-45 cells with a cDC-enriched primary cell isolate by immunoconjugates IC-2, IC-3, IC-4, IC-6, IC-14, and naked antibody CEA.9-G1fhL2.

CLAIMS:

1. An immunoconjugate comprising an antibody covalently attached to one or more 8-Het-2-aminobenzazepine moieties by a linker, and having Formula I:

$$Ab–[L–HxBz]_p \qquad I$$

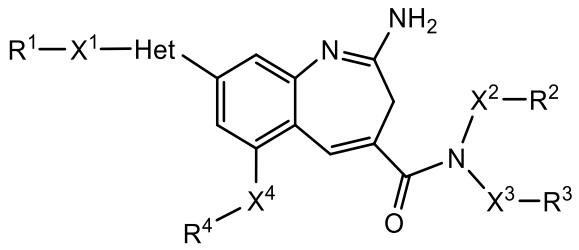
or a pharmaceutically acceptable salt thereof,

wherein:

Ab is an antibody construct that has an antigen binding domain that binds CEA;

p is an integer from 1 to 8;

HxBz is the 8-Het-2-aminobenzazepine moiety having the formula:



Het is selected from heterocyclyldiyl and heteroaryldiyl;

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} heteroaryl)–*;

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

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

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

–(C_1-C_{20} heteroaryl)–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;

–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)–*;

–O–C(=O)N(R^5)$_2$;

–O–C(=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;

X^1, X^2, X^3, and X^4 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^5 is independently selected from the group consisting of H, C$_6$-C$_{20}$ aryl, C$_3$-C$_{12}$ carbocyclyl, 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)–;

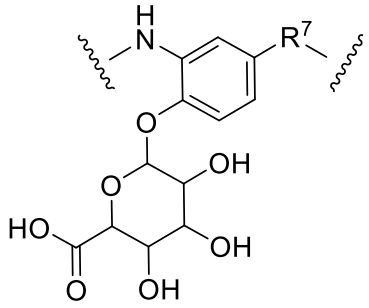
–succinimidyl–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–; and

–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;

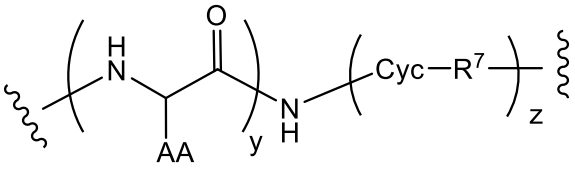
PEG has the formula: $–(CH_2CH_2O)_n–(CH_2)_m–$; m is an integer from 1 to 5, and n is an integer from 2 to 50;

Gluc has the formula:



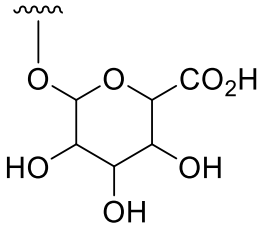
;

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, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH_2N(CH_3)_2$, $-O(CH_2CH_2O)_n-(CH_2)_mCO_2H$, $-O(CH_2CH_2O)_nH$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-OP(O)(OH)_2$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-S(O)_2CH_3$, and $-S(O)_3H$.

2. The immunoconjugate of claim 1 wherein the antibody is selected from labetuzumab and arcitumomab.

3. The immunoconjugate of claim 1 wherein the antibody construct comprises:

a) CDR-L1 comprising an amino acid sequence of SEQ ID NO:3, CDR-L2 comprising an amino acid sequence of SEQ ID NO:5, CDR-L3 comprising an amino acid sequence of SEQ ID NO:7, CDR-H1 comprising an amino acid sequence of SEQ ID NO:11, CDR-H2 comprising an amino acid sequence of SEQ ID NO:13, and CDR-H3 comprising an amino acid sequence of SEQ ID NO:15;

b) CDR-L1 comprising an amino acid sequence of SEQ ID NO:19, CDR-L2 comprising an amino acid sequence of SEQ ID NO:21, CDR-L3 comprising an amino acid sequence of SEQ ID NO:23, CDR-H1 comprising an amino acid sequence of SEQ ID NO:26, CDR-H2 comprising an amino acid sequence of SEQ ID NO:28, and CDR-H3 comprising an amino acid sequence of SEQ ID NO:30;

c) CDR-L1 comprising an amino acid sequence of SEQ ID NO:35, CDR-L2 comprising an amino acid sequence of SEQ ID NO:37, CDR-L3 comprising an amino acid sequence of SEQ ID NO:39, CDR-H1 comprising an amino acid sequence of SEQ ID NO:44,

CDR-H2 comprising an amino acid sequence of SEQ ID NO:46, and CDR-H3 comprising an amino acid sequence of SEQ ID NO:48;

d) CDR-L1 comprising an amino acid sequence of SEQ ID NO:53, CDR-L2 comprising an amino acid sequence of SEQ ID NO:55, CDR-L3 comprising an amino acid sequence of SEQ ID NO:39, CDR-H1 comprising an amino acid sequence of SEQ ID NO:44, CDR-H2 comprising an amino acid sequence of SEQ ID NO:46, and CDR-H3 comprising an amino acid sequence of SEQ ID NO:48;

e) CDR-L1 comprising an amino acid sequence of SEQ ID NO:59, CDR-L2 comprising an amino acid sequence of SEQ ID NO:61, CDR-L3 comprising an amino acid sequence of SEQ ID NO:63, CDR-H1 comprising an amino acid sequence of SEQ ID NO:67, CDR-H2 comprising an amino acid sequence of SEQ ID NO:69, and CDR-H3 comprising an amino acid sequence of SEQ ID NO:71;

f) CDR-L1 comprising an amino acid sequence of SEQ ID NO:75, CDR-L2 comprising an amino acid sequence of SEQ ID NO:77, CDR-L3 comprising an amino acid sequence of SEQ ID NO:79, CDR-H1 comprising an amino acid sequence of SEQ ID NO:83, CDR-H2 comprising an amino acid sequence of SEQ ID NO:85, and CDR-H3 comprising an amino acid sequence of SEQ ID NO:87;

g) CDR-L1 comprising an amino acid sequence of SEQ ID NO:91, CDR-L2 comprising an amino acid sequence of SEQ ID NO:93, CDR-L3 comprising an amino acid sequence of SEQ ID NO:95, CDR-H1 comprising an amino acid sequence of SEQ ID NO:99, CDR-H2 comprising an amino acid sequence of SEQ ID NO:101, and CDR-H3 comprising an amino acid sequence of SEQ ID NO:103;

h) CDR-L1 comprising an amino acid sequence of SEQ ID NO:107, CDR-L2 comprising an amino acid sequence of SEQ ID NO:109, CDR-L3 comprising an amino acid sequence of SEQ ID NO:111, CDR-H1 comprising an amino acid sequence of SEQ ID NO:115, CDR-H2 comprising an amino acid sequence of SEQ ID NO:117 or 118, and CDR-H3 comprising an amino acid sequence of SEQ ID NO:120; or

i) CDR-L1 comprising an amino acid sequence of SEQ ID NO:107, CDR-L2 comprising an amino acid sequence of SEQ ID NO:109, CDR-L3 comprising an amino acid sequence of SEQ ID NO:111, CDR-H1 comprising an amino acid sequence of SEQ ID NO:124, CDR-H2 comprising an amino acid sequence of SEQ ID NO:126, and CDR-H3 comprising an amino acid sequence of SEQ ID NO:128.

4. The immunoconjugate of claim 1 wherein the antibody construct comprises a variable light chain comprising an amino acid sequence that is at least 95% identical to an amino acid sequence selected from SEQ ID NOs: 1, 17, 32, 50, 57, 73, 89, and 105; and a

variable heavy chain comprising an amino acid sequence that is at least 95% identical to an amino acid sequence selected from SEQ ID NO: 9, 41, 65, 81, 97, 113, 122, and 130.

5. The immunoconjugate of claim 1 wherein the antibody construct comprises a variable light chain comprising an amino acid sequence selected from SEQ ID NOs: 1, 17, 32, 50, 57, 73, 89, and 105; and a variable heavy chain comprising an amino acid sequence selected from SEQ ID NO: 9, 41, 65, 81, 97, 113, 122, and 130.

6. The immunoconjugate of claim 5 wherein the antibody construct comprises a variable light chain comprising the amino acid sequence from SEQ ID NO: 105; and the heavy chain CDR (complementarity determining region) CDR-H2 comprising the amino acid sequence from SEQ ID NO: 118.

7. The immunoconjugate of claim 6 wherein the antibody construct comprises a variable light chain comprising the amino acid sequence from SEQ ID NO: 105; and a variable heavy chain comprising the amino acid sequence from SEQ ID NO: 113.

8. The immunoconjugate of any one of claims 1 to 7 wherein Het is selected from the group consisting of pyridyldiyl, pyrimidyldiyl, pyrazolyldiyl, piperazinyldiyl, piperidinyldiyl, and pyrazinyldiyl.

9. The immunoconjugate of any one of claims 1 to 7 wherein X^1 is a bond, and R^1 is H.

10. The immunoconjugate of any one of claims 1 to 7 wherein X^2 is a bond, and R^2 is C_1-C_8 alkyl.

11. The immunoconjugate of any one of claims 1 to 7 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)–$OC(O)N(R^5)_2$.

12. The immunoconjugate of claim 11 wherein R^2 is C_1-C_8 alkyl and R^3 is –(C_1-C_8 alkyldiyl)–$N(R^5)CO_2R^5$.

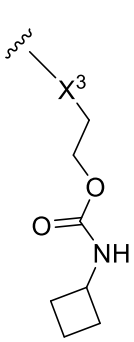
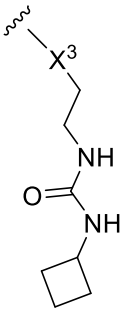
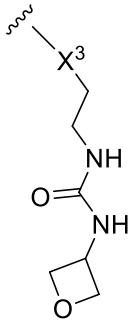
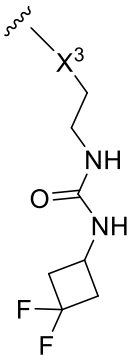
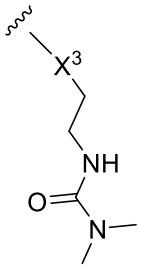
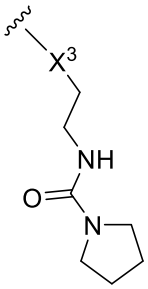
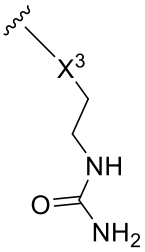
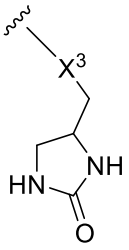
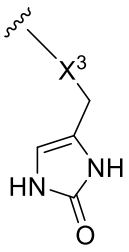
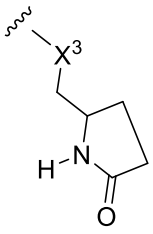
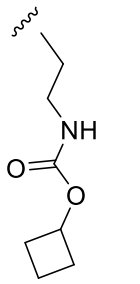
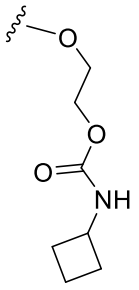
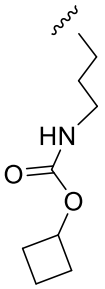
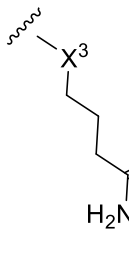
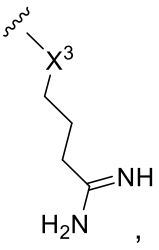
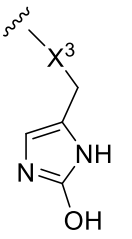
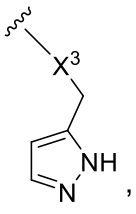
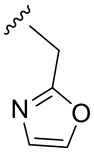
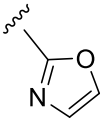
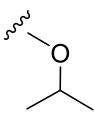
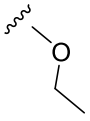
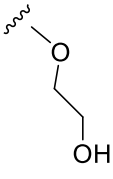
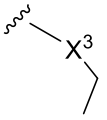
13. The immunoconjugate of claim 12 wherein R^2 is $–CH_2CH_2CH_3$ and R^3 is selected from $–CH_2CH_2CH_2NHCO_2$(t-Bu), $–OCH_2CH_2NHCO_2$(cyclobutyl), and $–CH_2CH_2CH_2NHCO_2$(cyclobutyl).

14. The immunoconjugate of claim 12 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 $–CH_2CH_2CH_2OH$.

15. The immunoconjugate of claim 12 wherein R^2 and R^3 are each $–CH_2CH_2CH_3$.

16. The immunoconjugate of claim 12 wherein R^2 is $–CH_2CH_2CH_3$ and R^3 is $–OCH_2CH_3$.

17. The immunoconjugate of any one of claims 1 to 7 wherein X^3-R^3 is selected from the group consisting of:

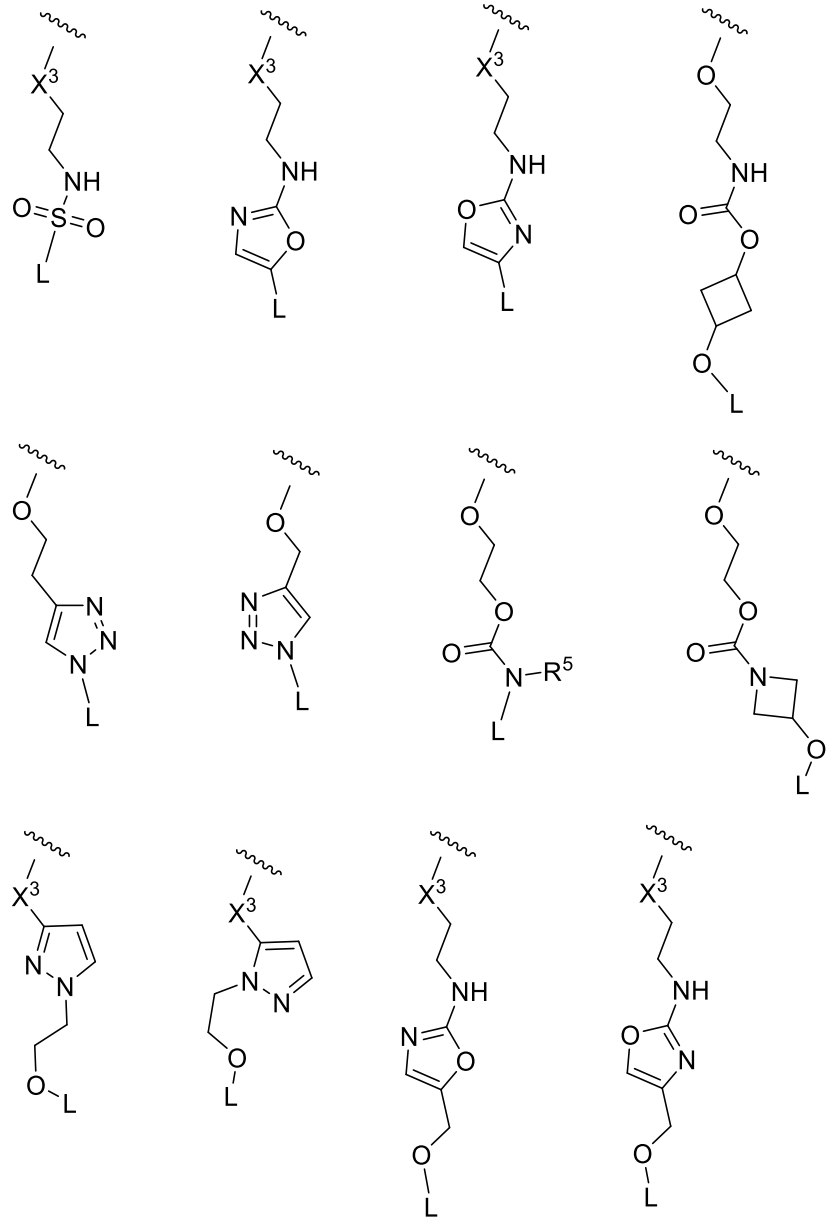






















and


18. The immunoconjugate of any one of claims 1 to 7 wherein X^4 is a bond, and R^4 is H.

19. The immunoconjugate of any one of claims 1 to 7 where R^1 is attached to L.

20. The immunoconjugate of any one of claims 1 to 7 where R^2 or R^3 is attached to L.

21. The immunoconjugate of claim 20 wherein X^3–R^3–L is selected from the group consisting of:



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

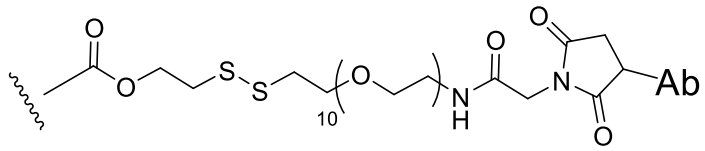
22. The immunoconjugate of any one of claims 1 to 7 wherein L is –C(=O)–PEG– or –C(=O)–PEG–C(=O)–.

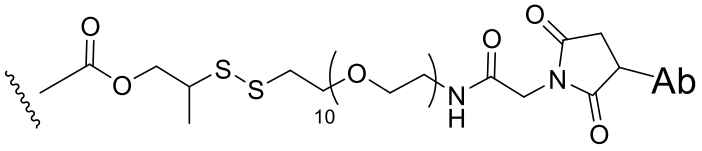
23. The immunoconjugate of any one of claims 1 to 7 wherein L is attached to a cysteine thiol of the antibody.

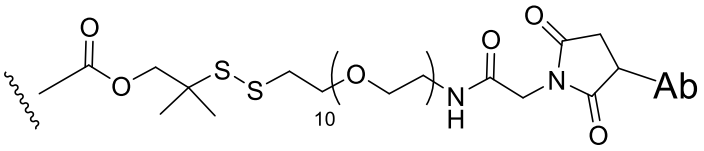
24. The immunoconjugate of any one of claims 1 to 7 wherein for the PEG, m is 1 or 2, and n is an integer from 2 to 10.

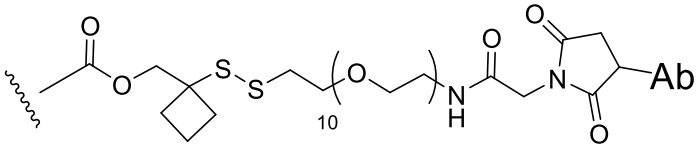
25. The immunoconjugate of claim 24 wherein n is 10.

26. The immunoconjugate of any one of claims 1 to 7 wherein L is selected from the structures:



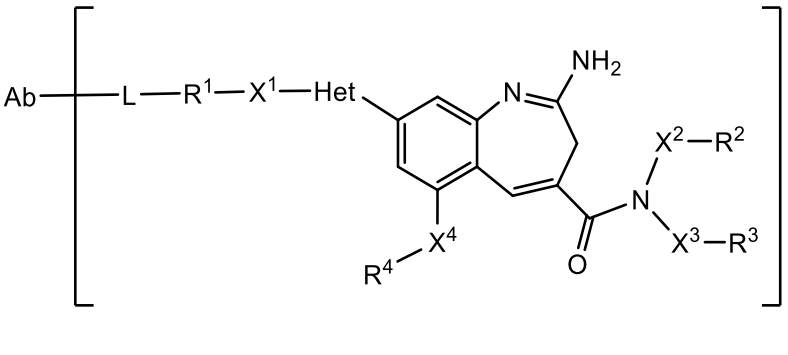






where the wavy line indicates the attachment to R^5.

27. The immunoconjugate of any one of claims 1 to 7 having Formula Ia:



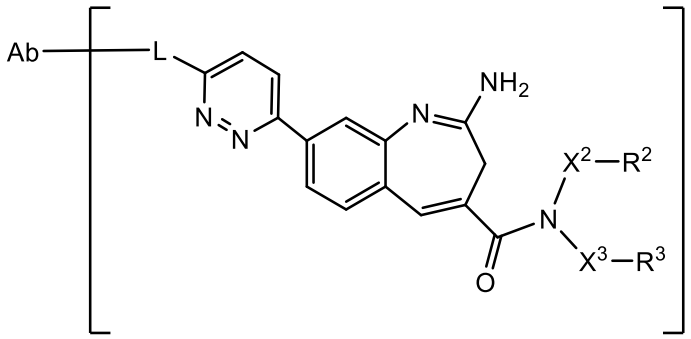
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28. The immunoconjugate of claim 27 wherein X^4 is a bond and R^4 is H.

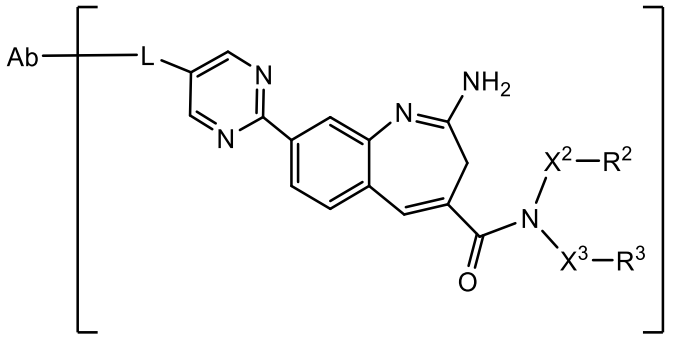
29. The immunoconjugate of claim 27 wherein X^2 and X^3 are each a bond, and R^2 and R^3 are independently selected from C_1-C_8 alkyl, –O–(C_1-C_{12} alkyl), –(C_1-C_{12} alkyldiyl)–OR^5, –(C_1-C_8 alkyldiyl)–$N(R^5)CO_2R^5$, –(C_1-C_{12} alkyl)–$OC(O)N(R^5)_2$, –O–(C_1-C_{12} alkyl)–$N(R^5)CO_2R^5$,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

30. The immunoconjugate of claim 27 wherein X^2 is O.

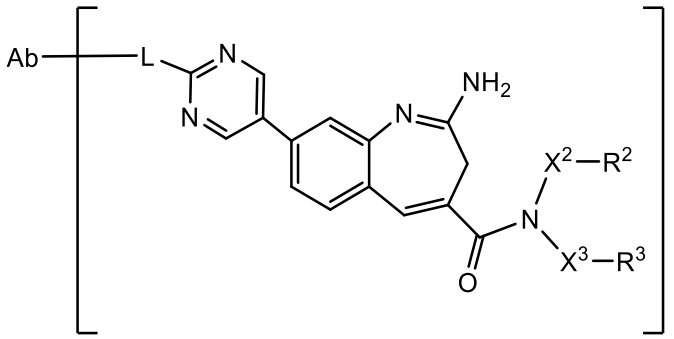
31. The immunoconjugate of claim 27 selected from Formulae Ib-Ii:



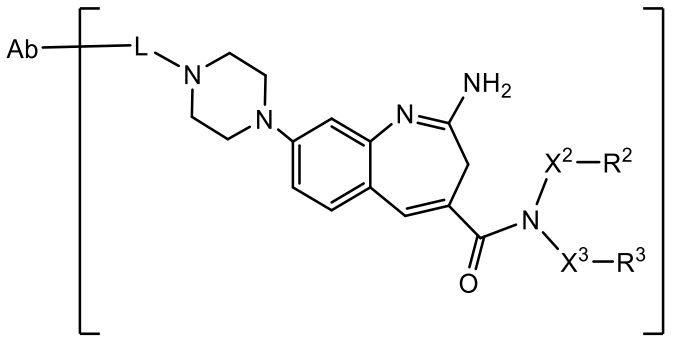
Ib;



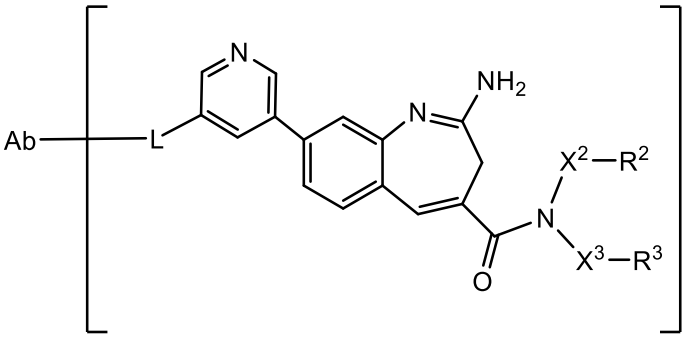
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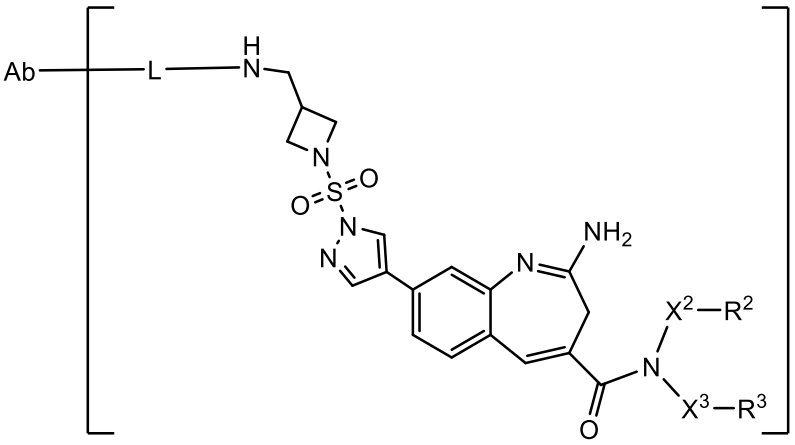
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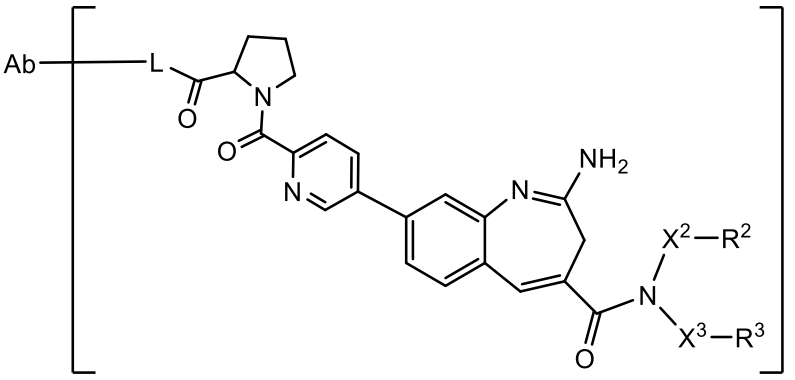
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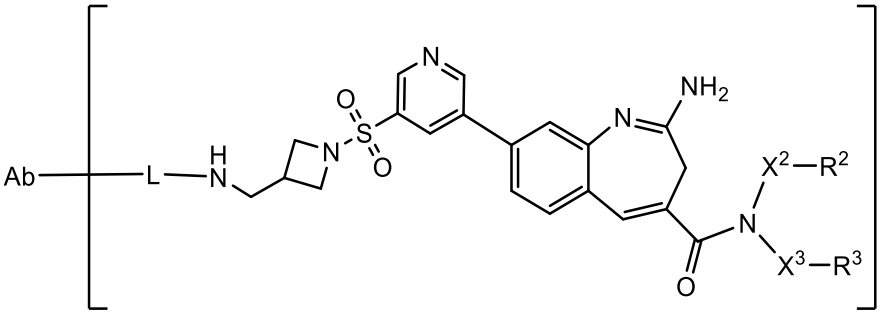
p If;



p Ig;



p Ih; and

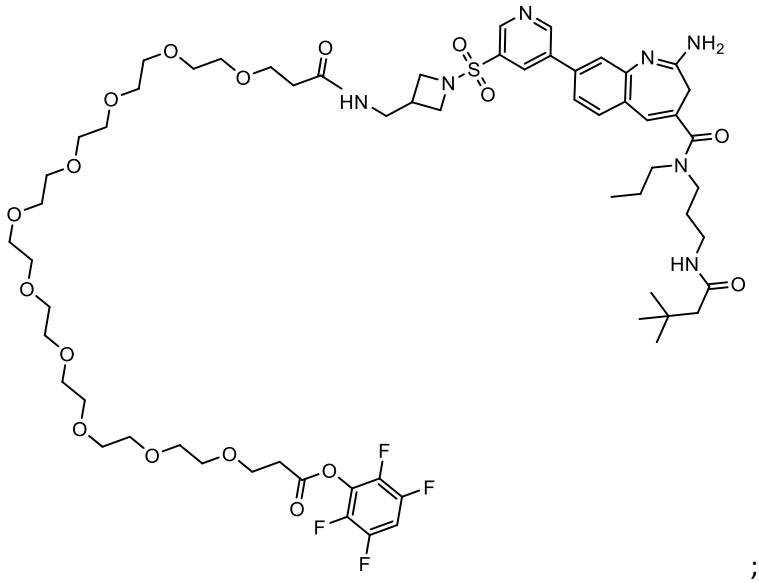


p Ii .

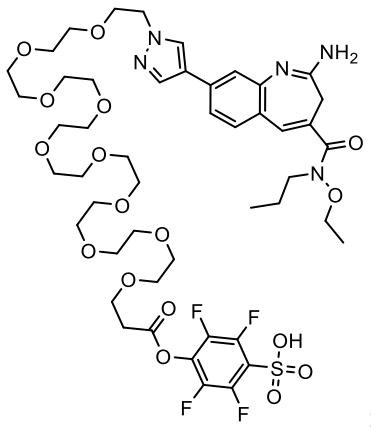
32. The immunoconjugate of claim 31 wherein X^2 and X^3 are each a bond, and R^2 and R^3 are independently selected from C_1-C_8 alkyl, –O–(C_1-C_{12} alkyl), –(C_1-C_{12} alkyldiyl)–OR^5, –(C_1-C_8 alkyldiyl)–$N(R^5)CO_2R^5$, and –O–(C_1-C_{12} alkyl)–$N(R^5)CO_2R^5$.

33. The immunoconjugate of claim 31 wherein X^2 and X^3 are each a bond, R^2 is C_1-C_8 alkyl, and R^3 is selected from –O–(C_1-C_{12} alkyl) and –O–(C_1-C_{12} alkyl)–N(R^5)CO_2R^5.

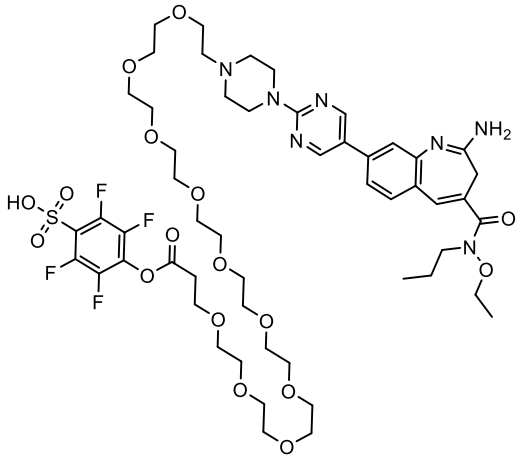
34. An 8-Het-2-aminobenzazepine-linker compound selected from the group consisting of:



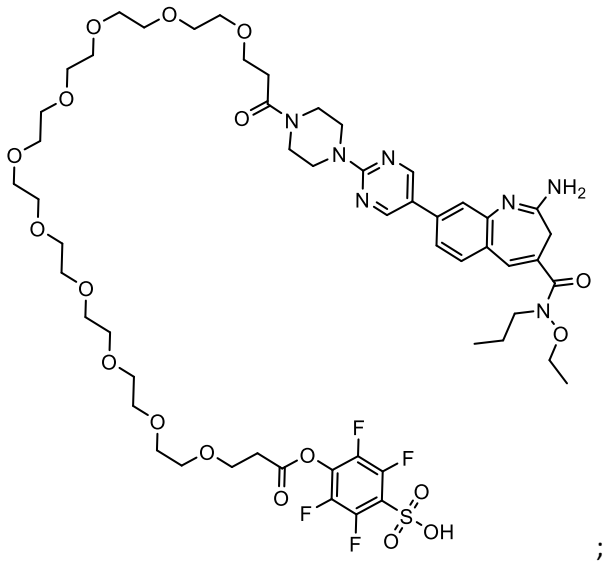
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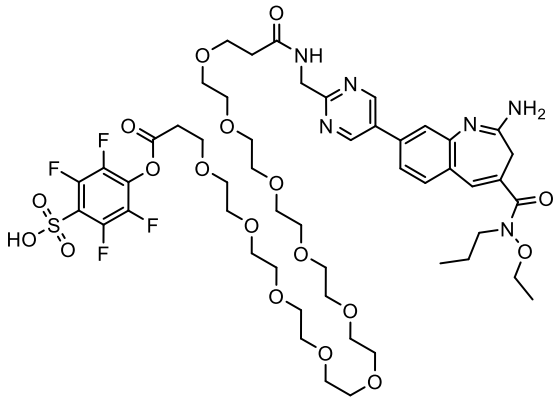
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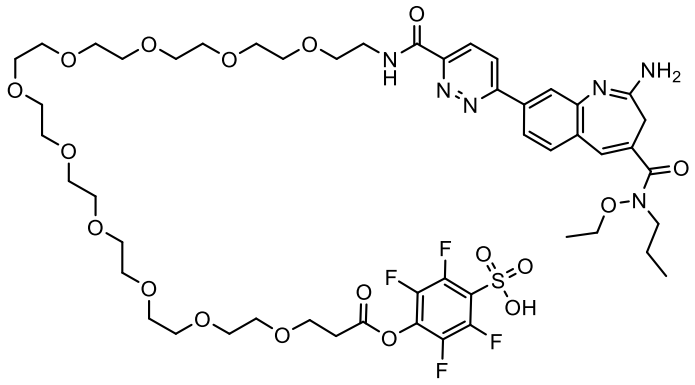
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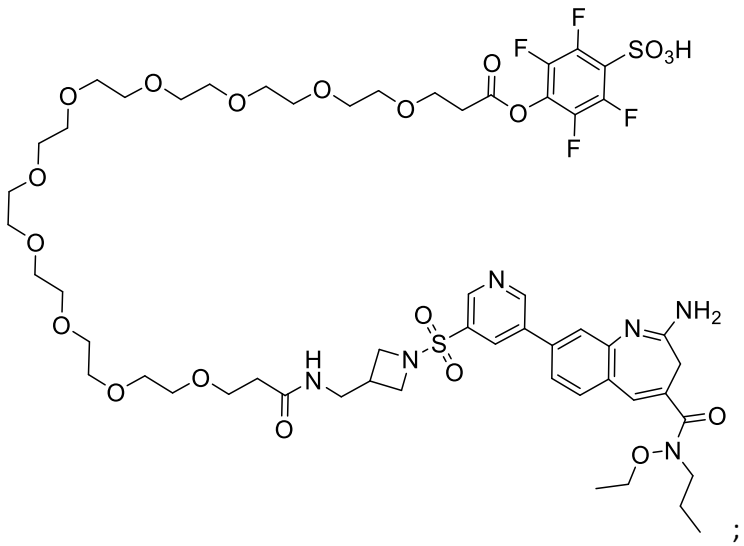
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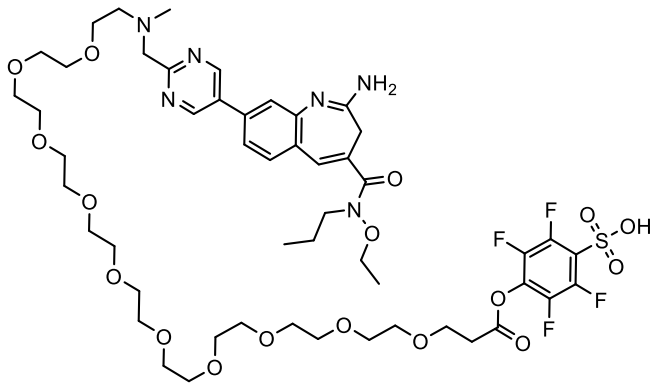
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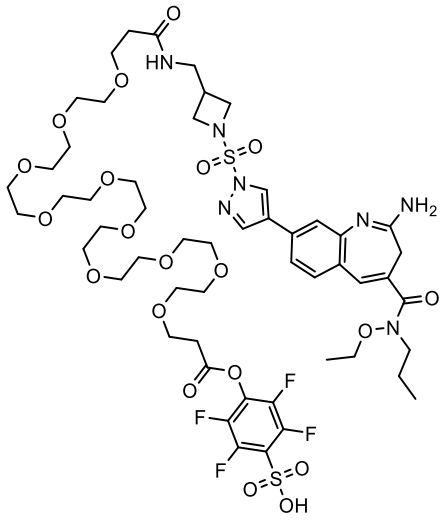
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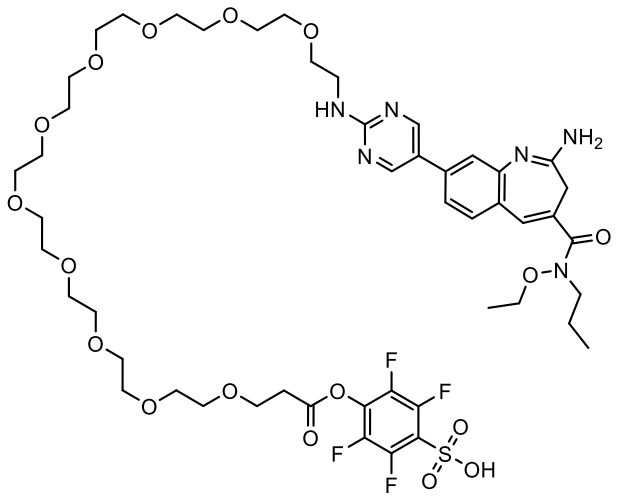
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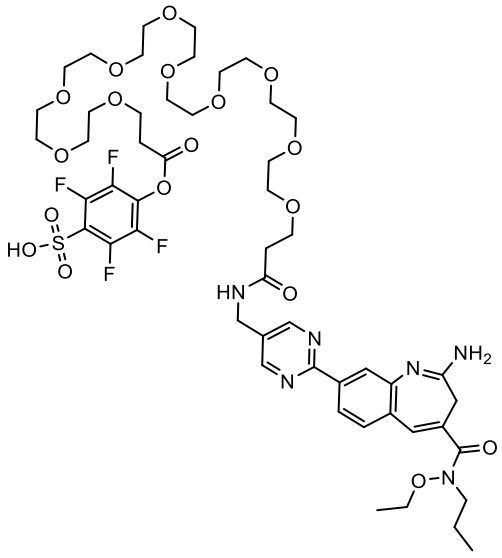
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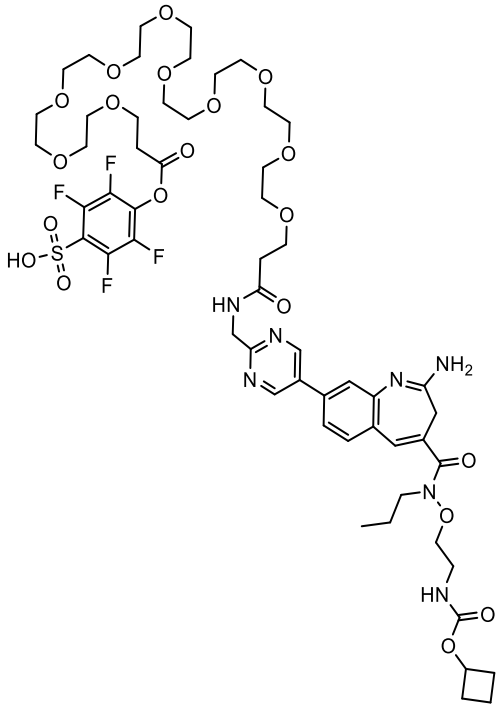
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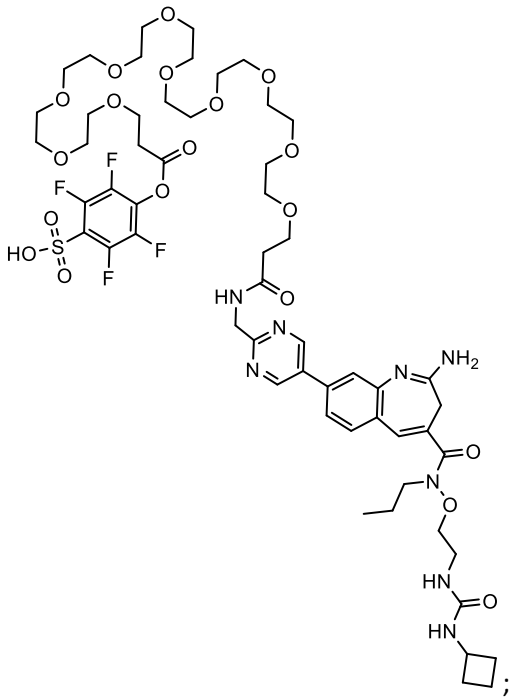
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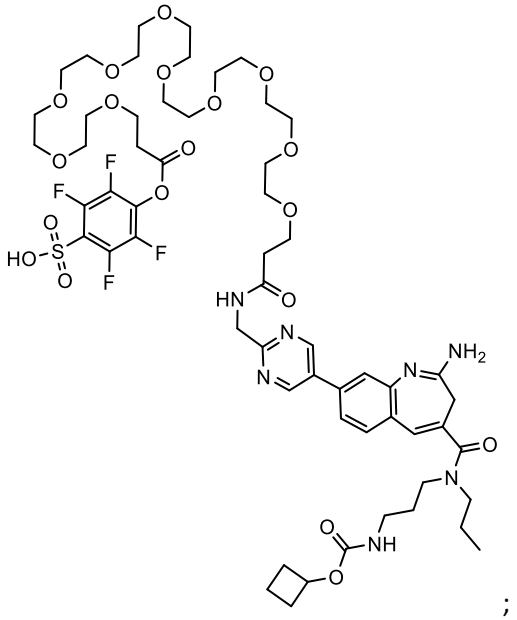
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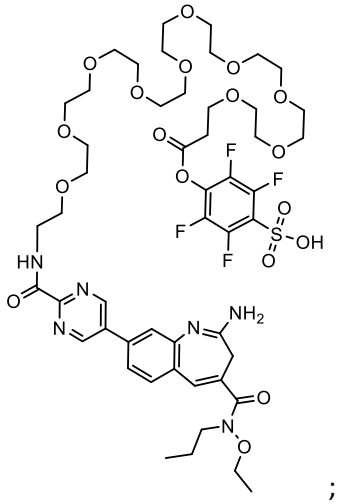
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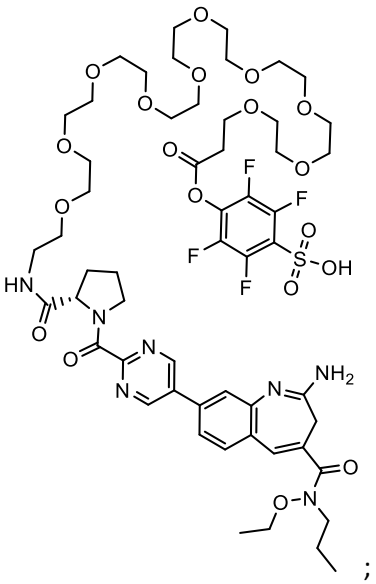
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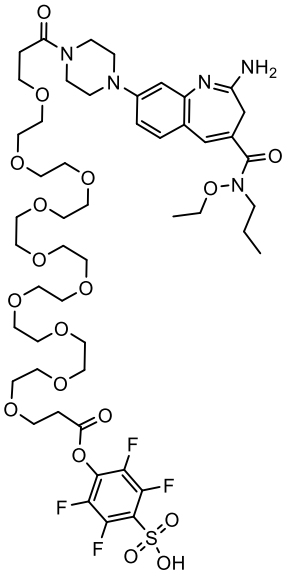
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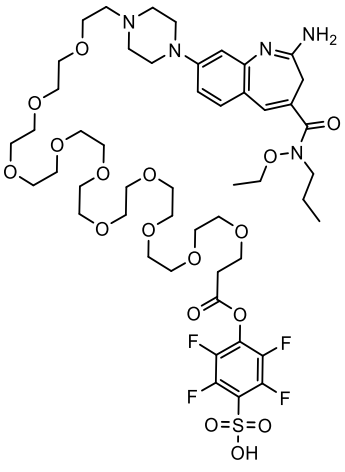
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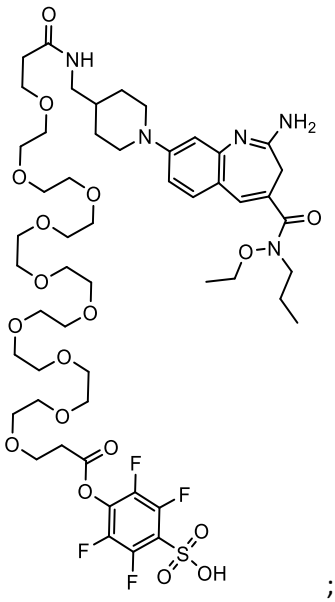
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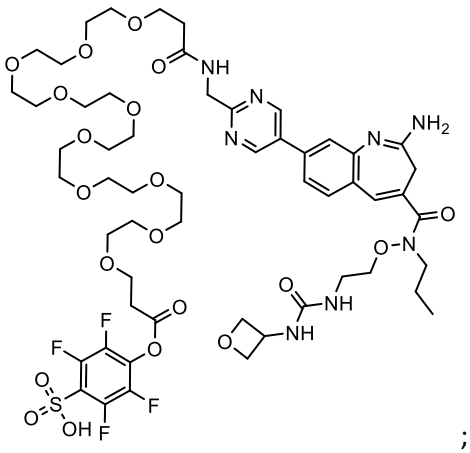
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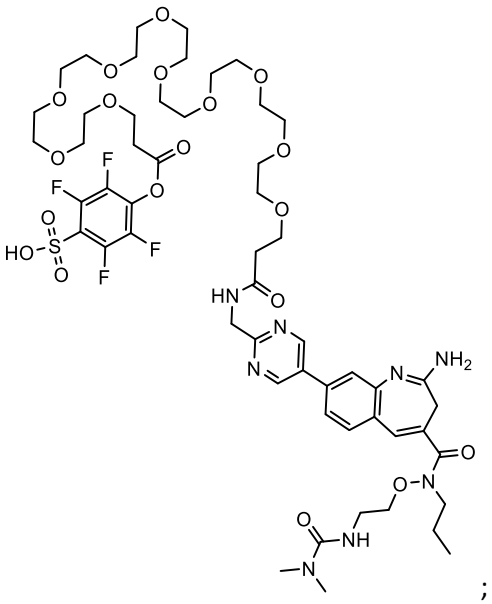
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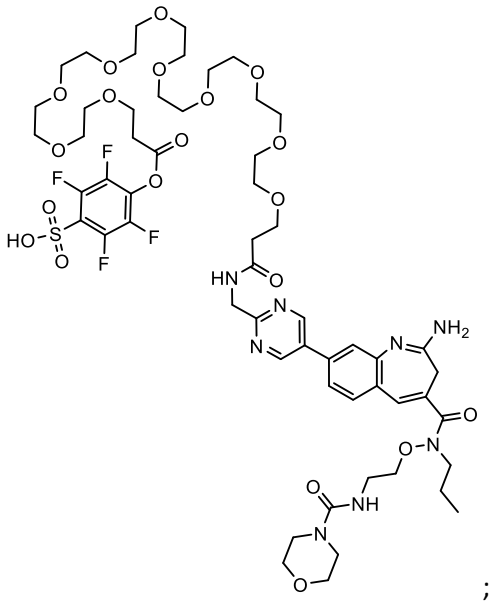
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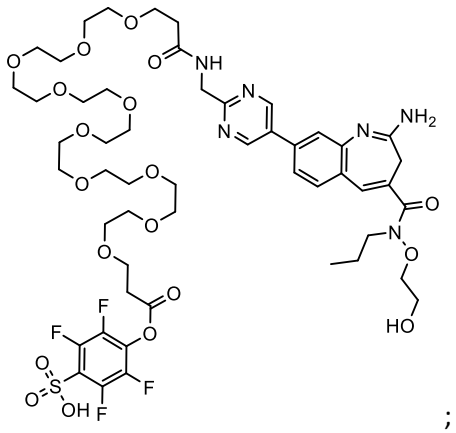
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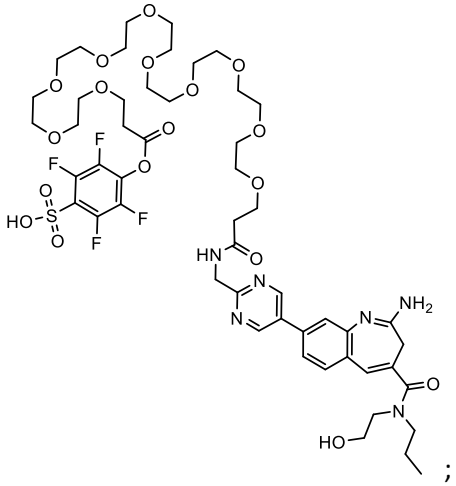
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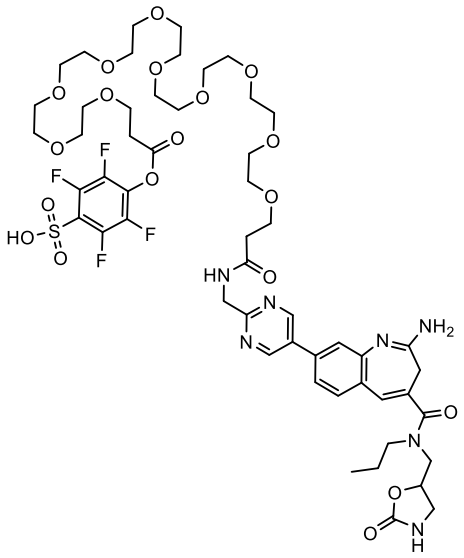
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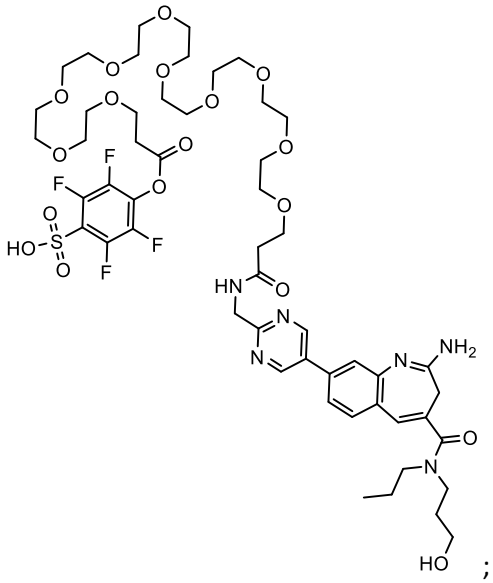
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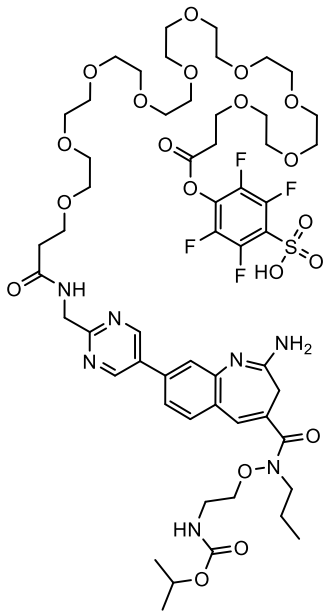
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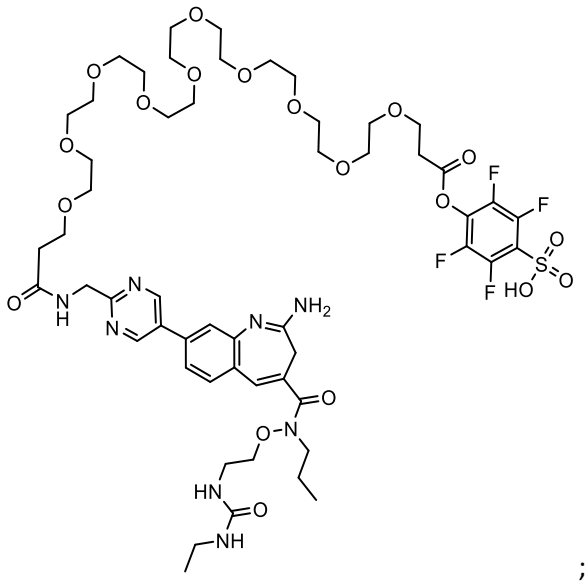
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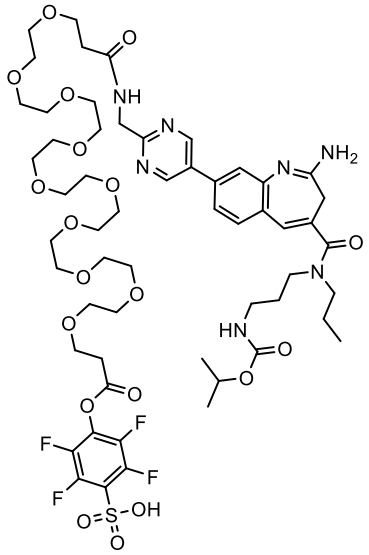
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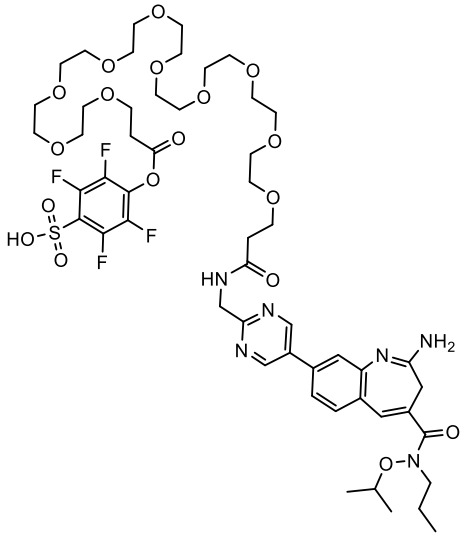
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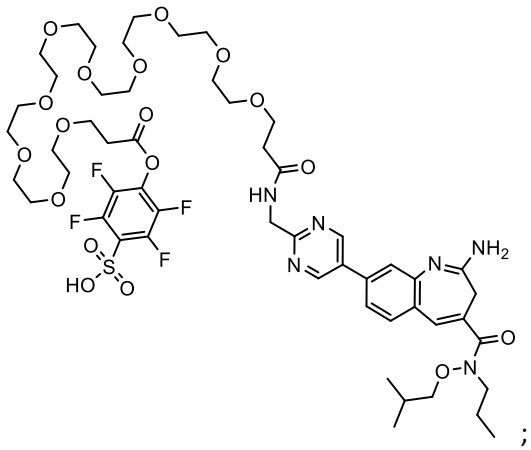
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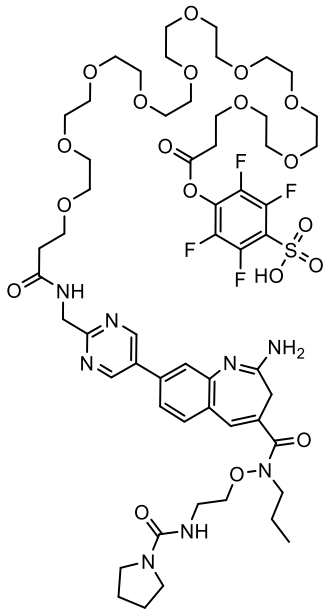
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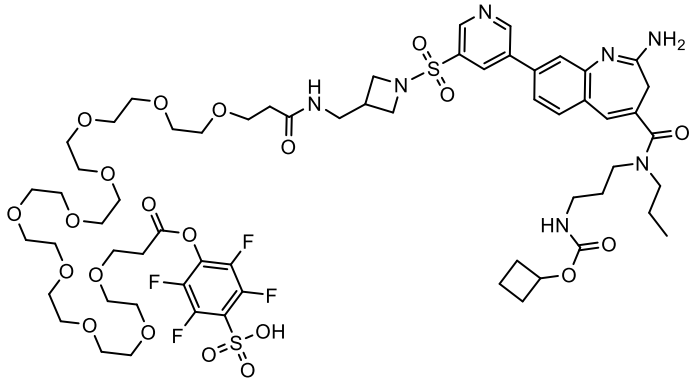
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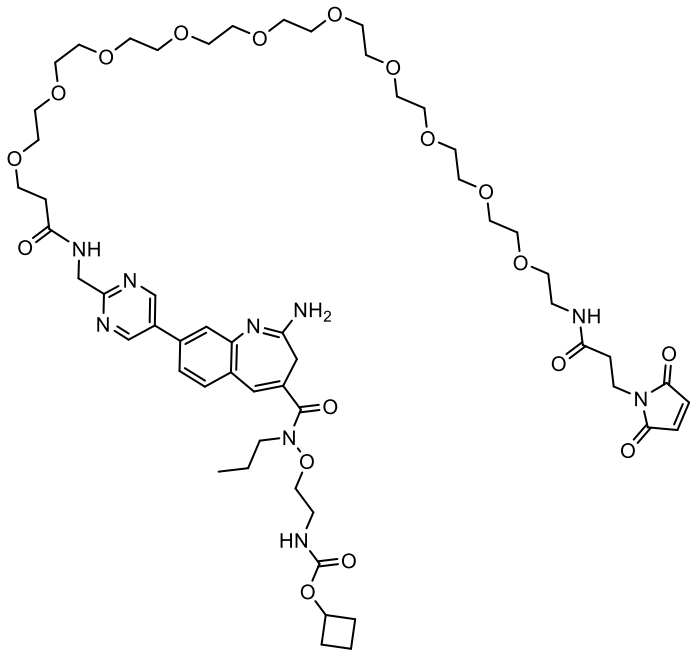
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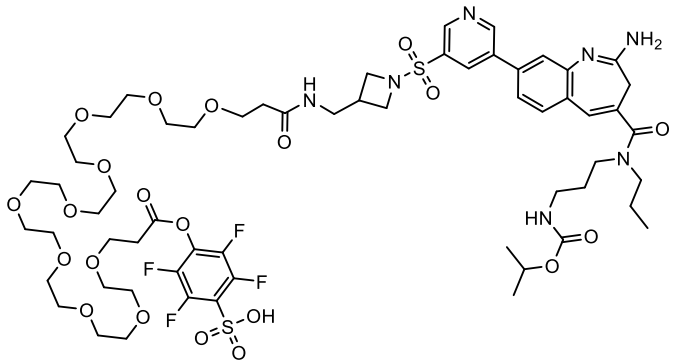
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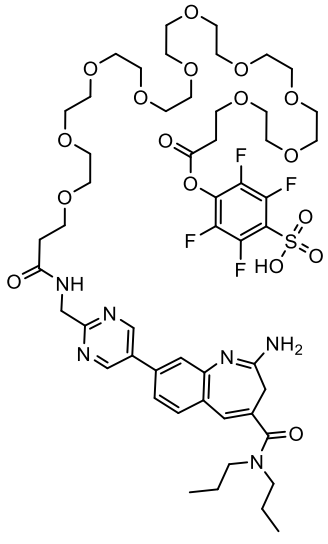
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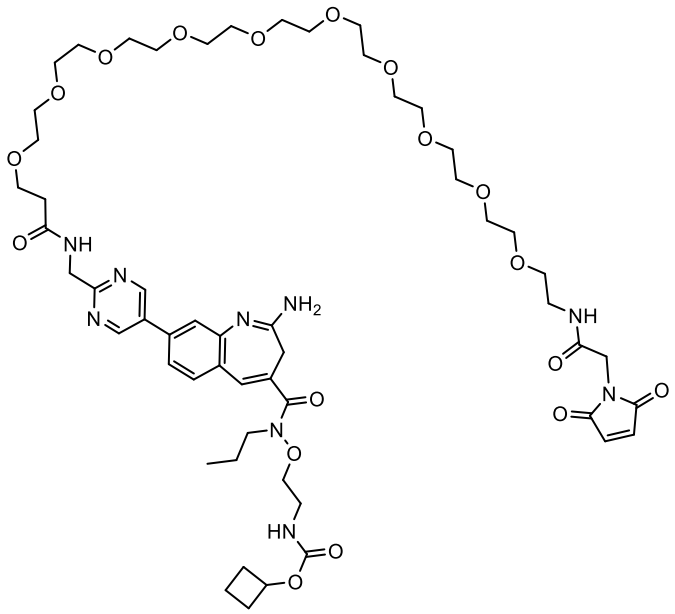
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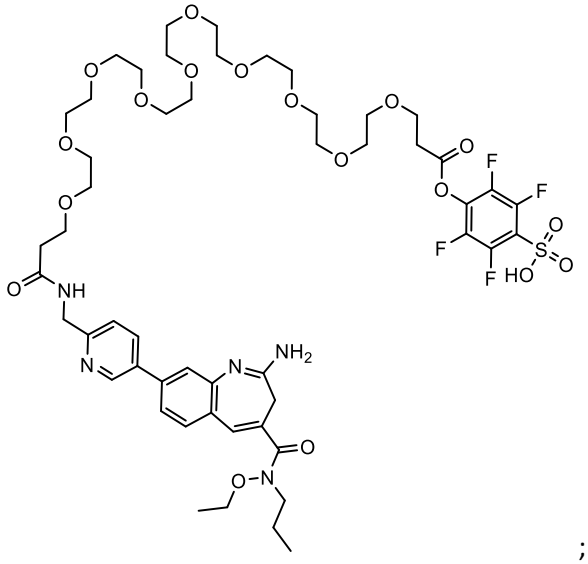
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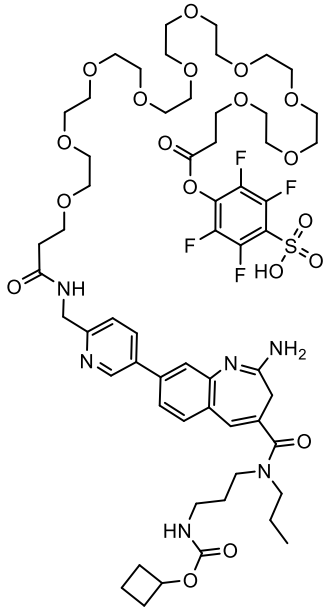
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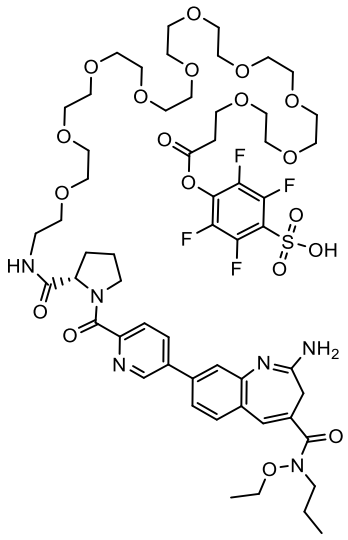
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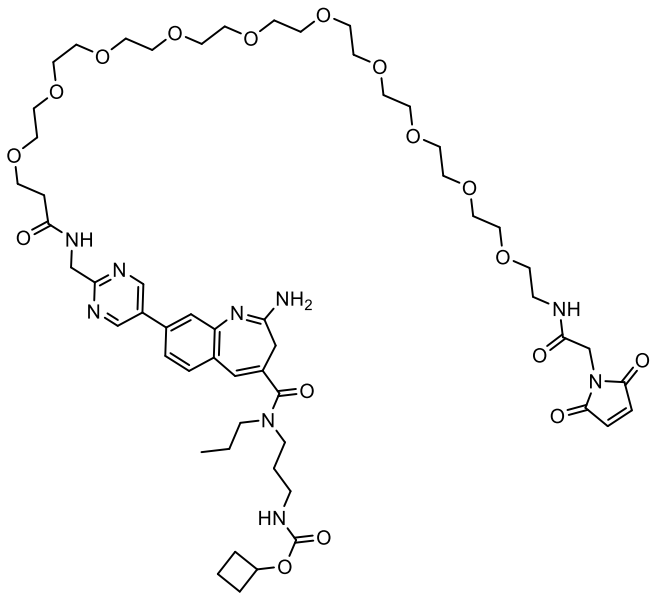
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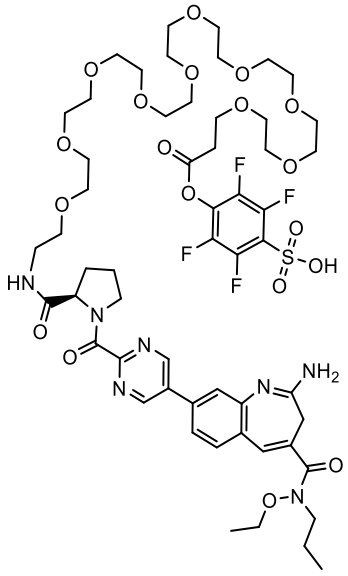
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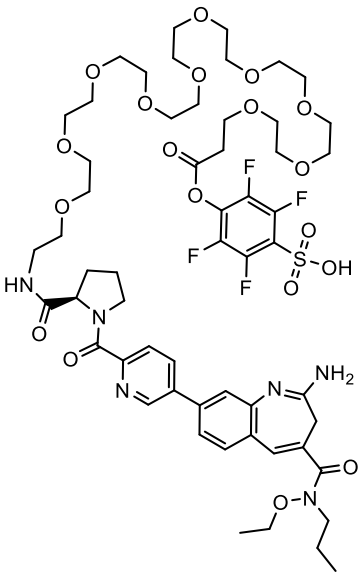
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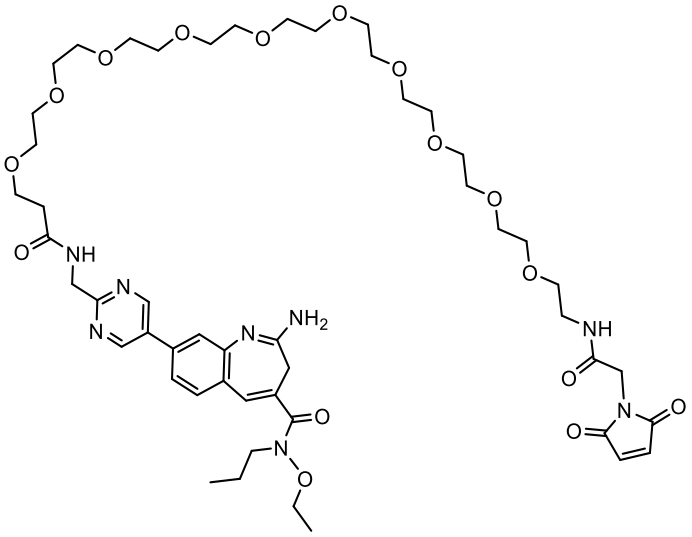
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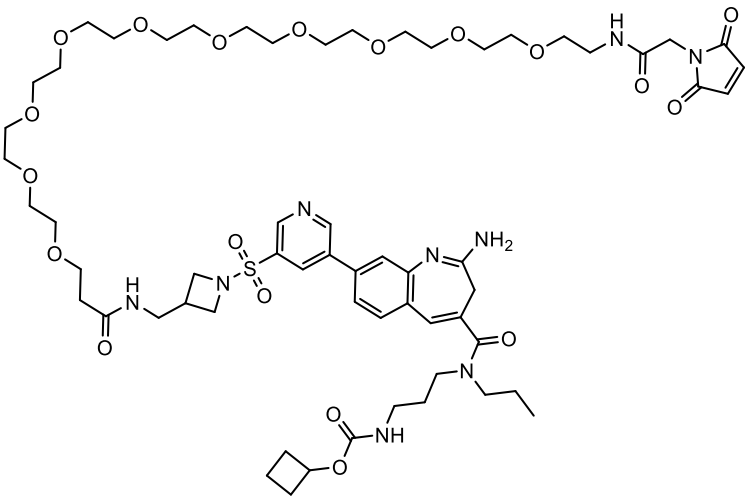
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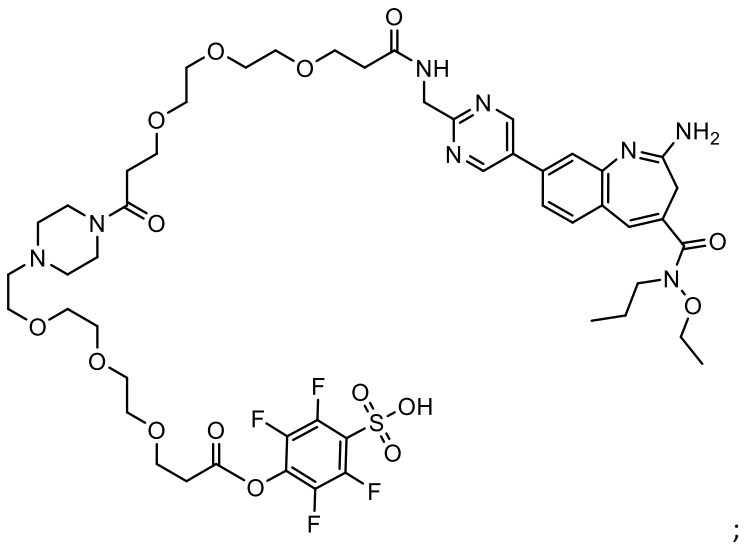
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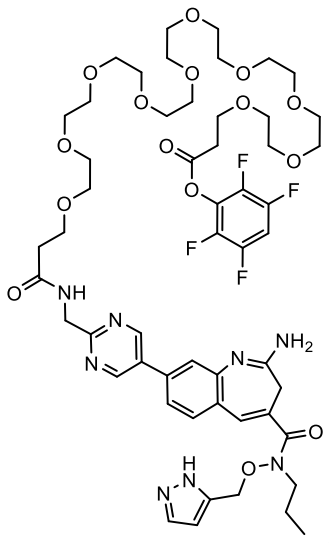
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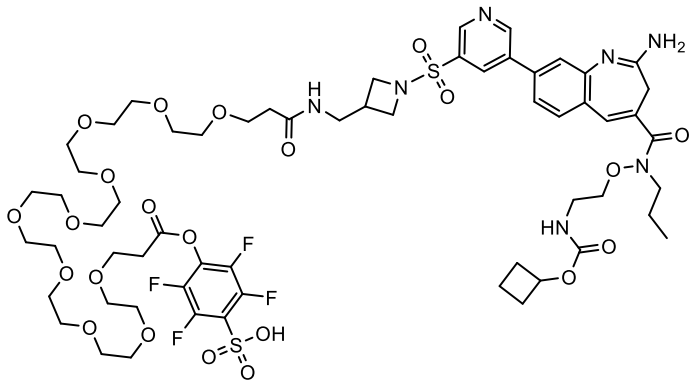
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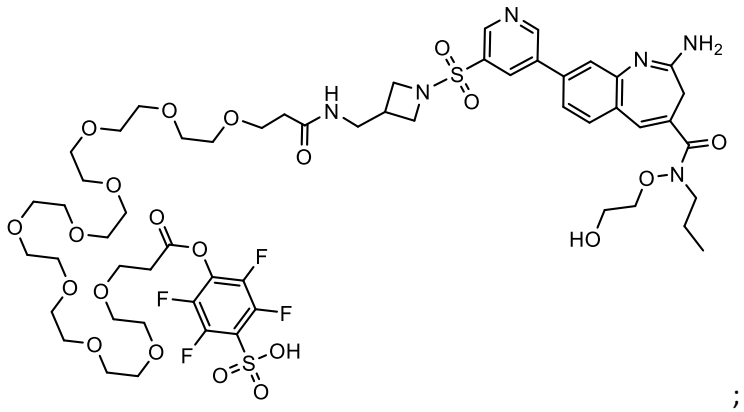
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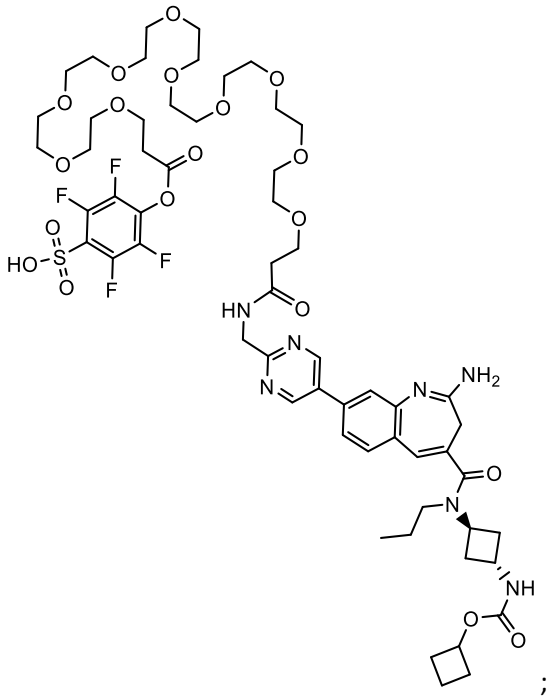
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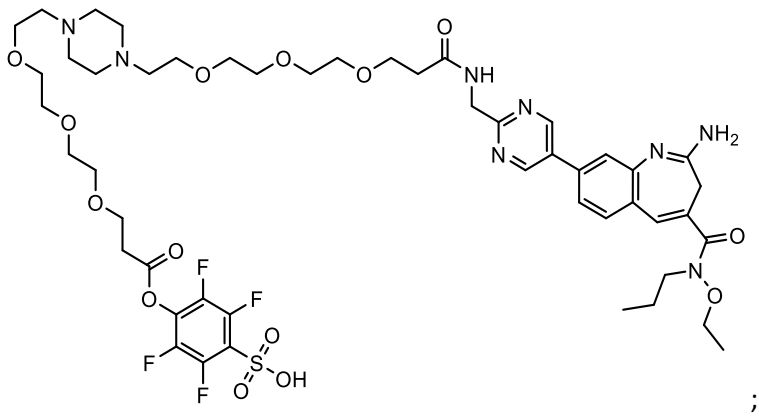
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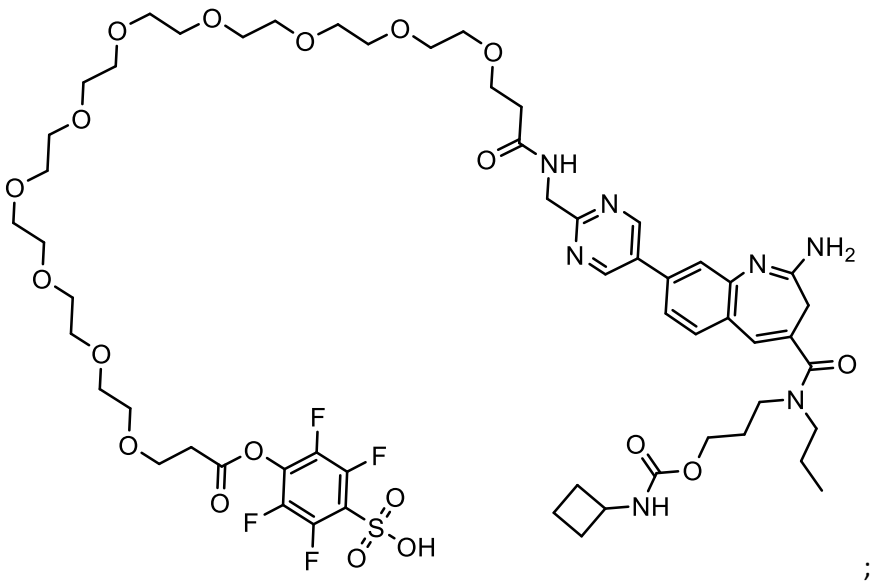
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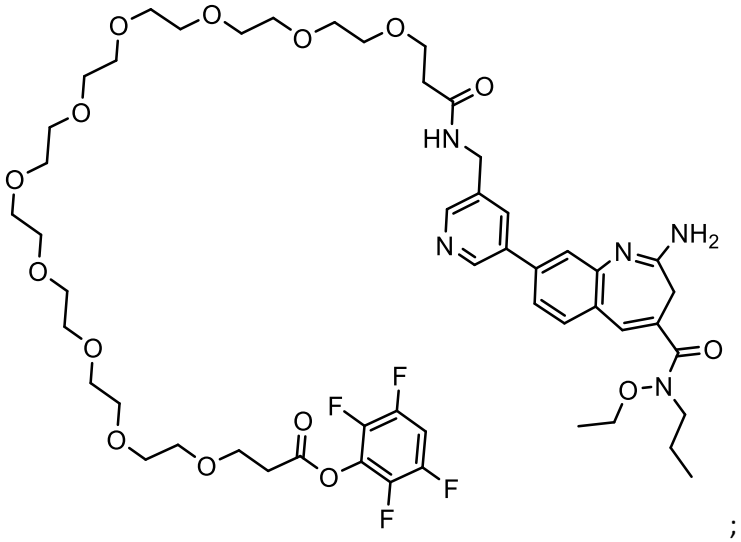
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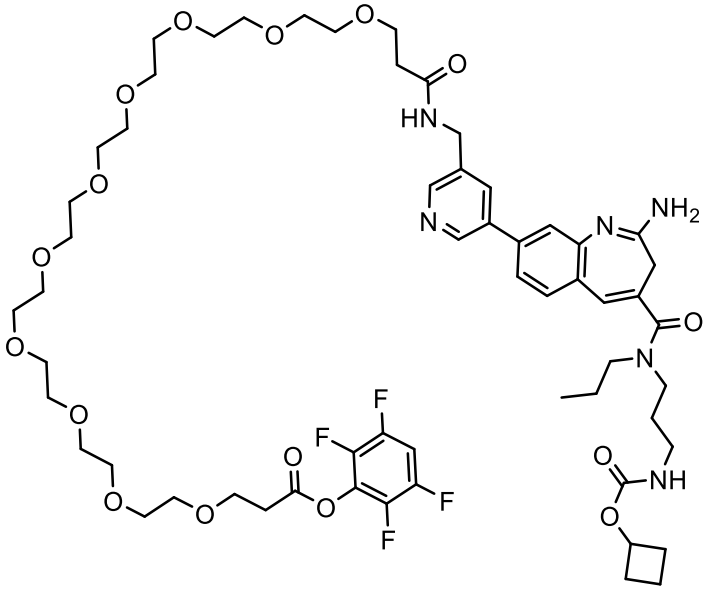
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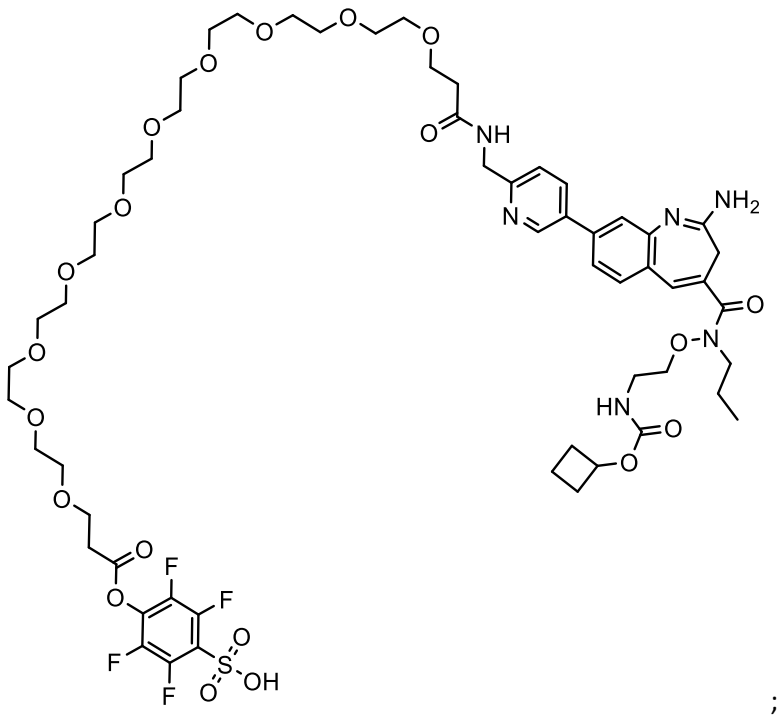
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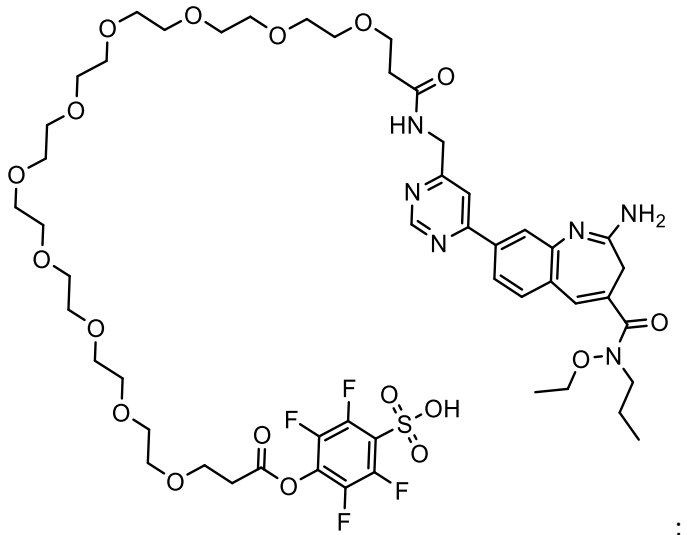
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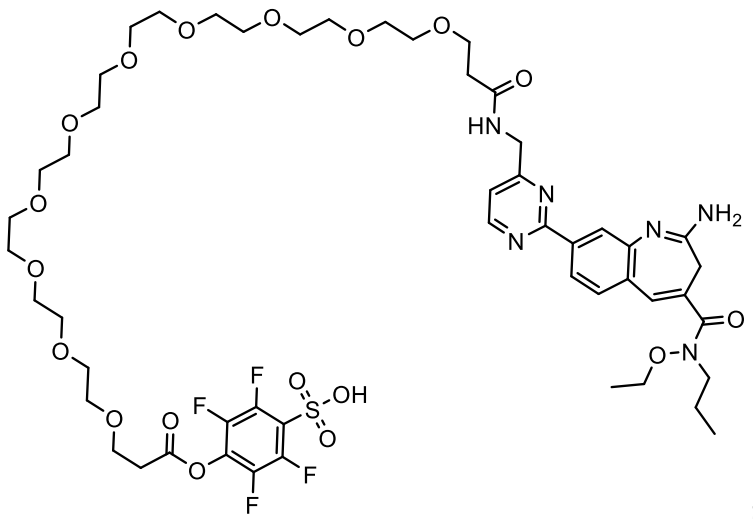
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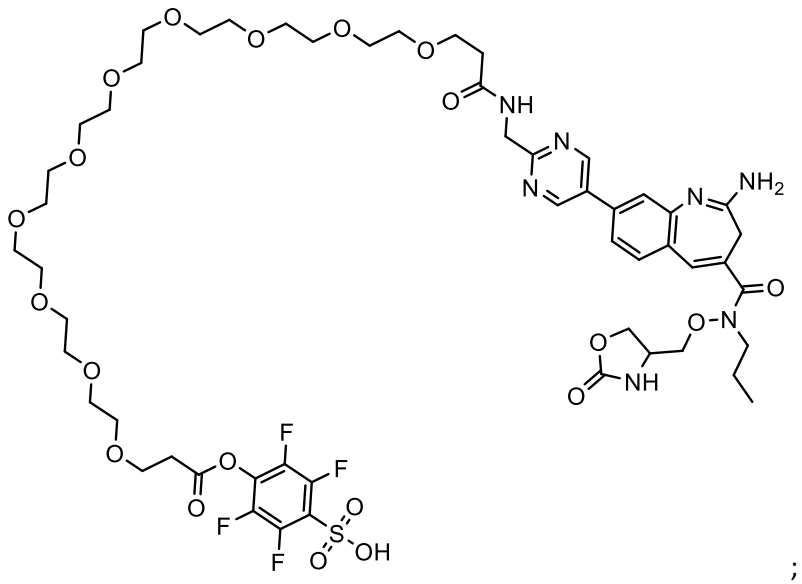
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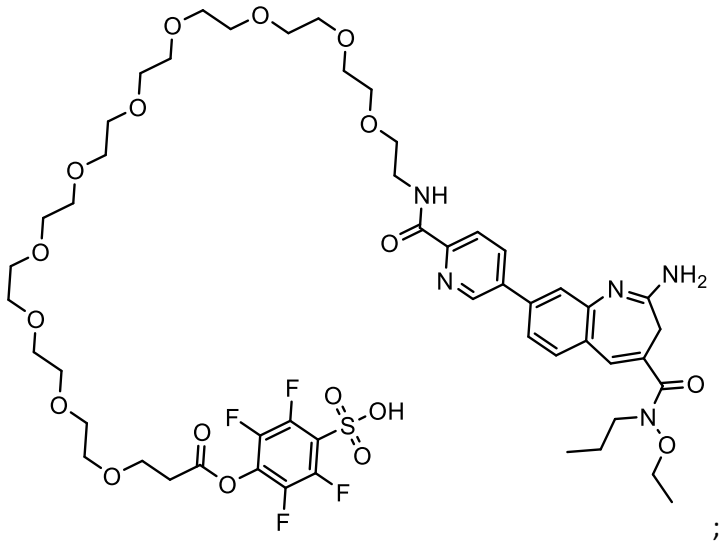
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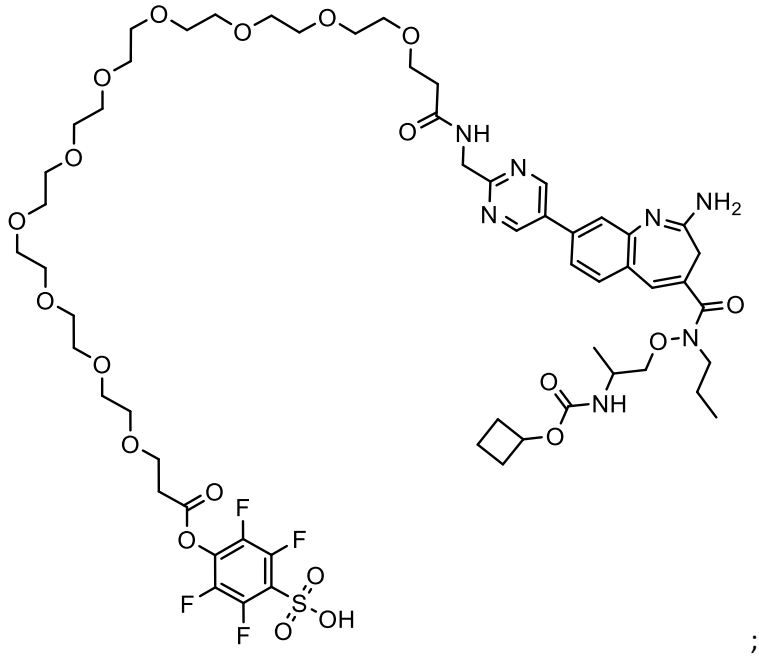
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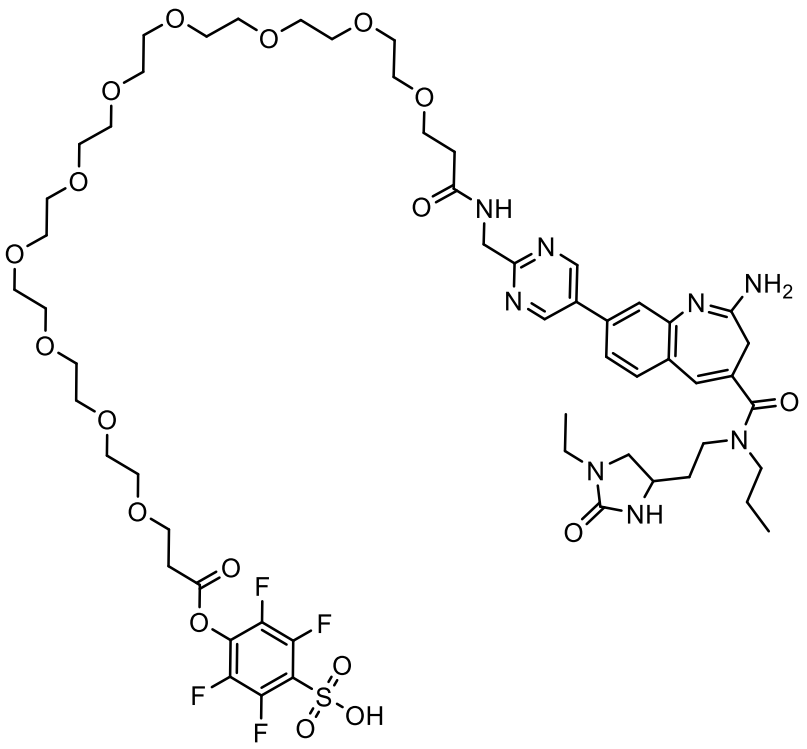
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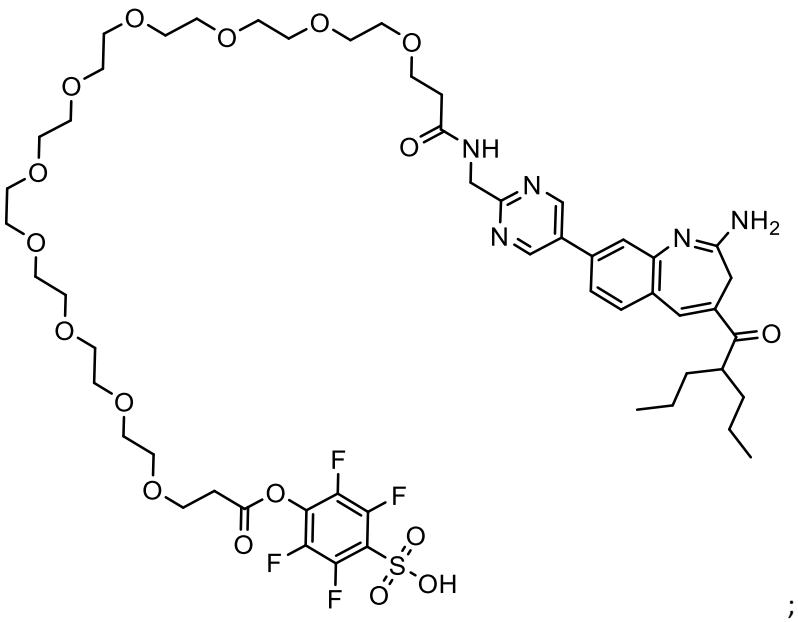
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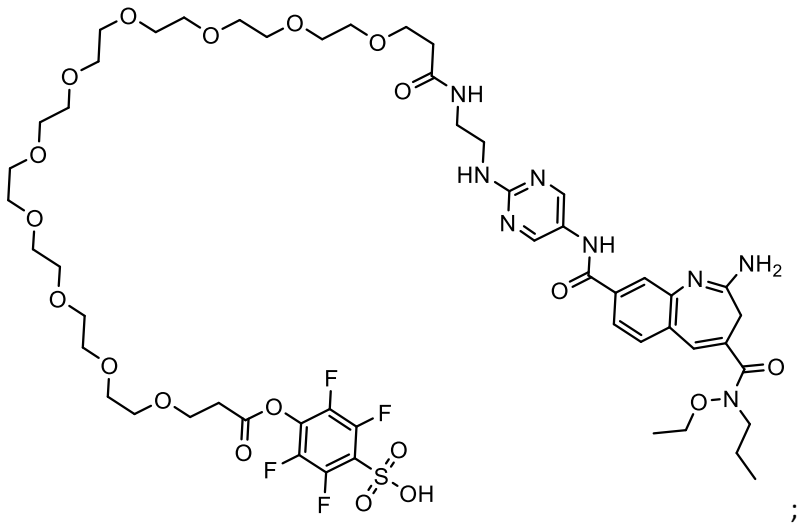
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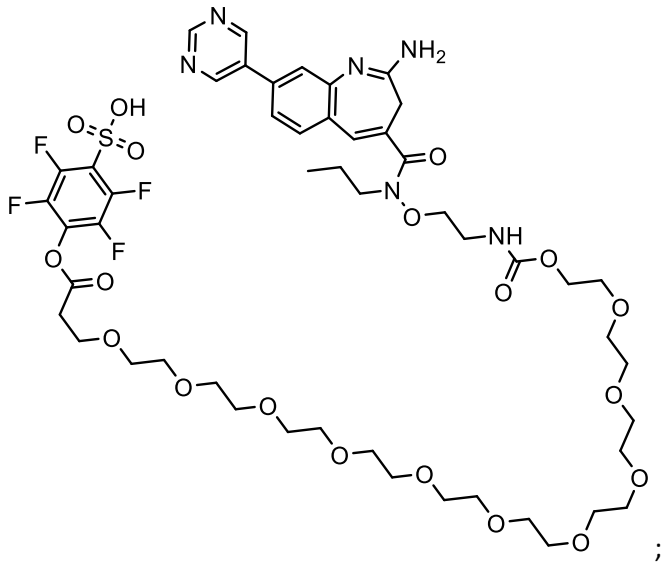
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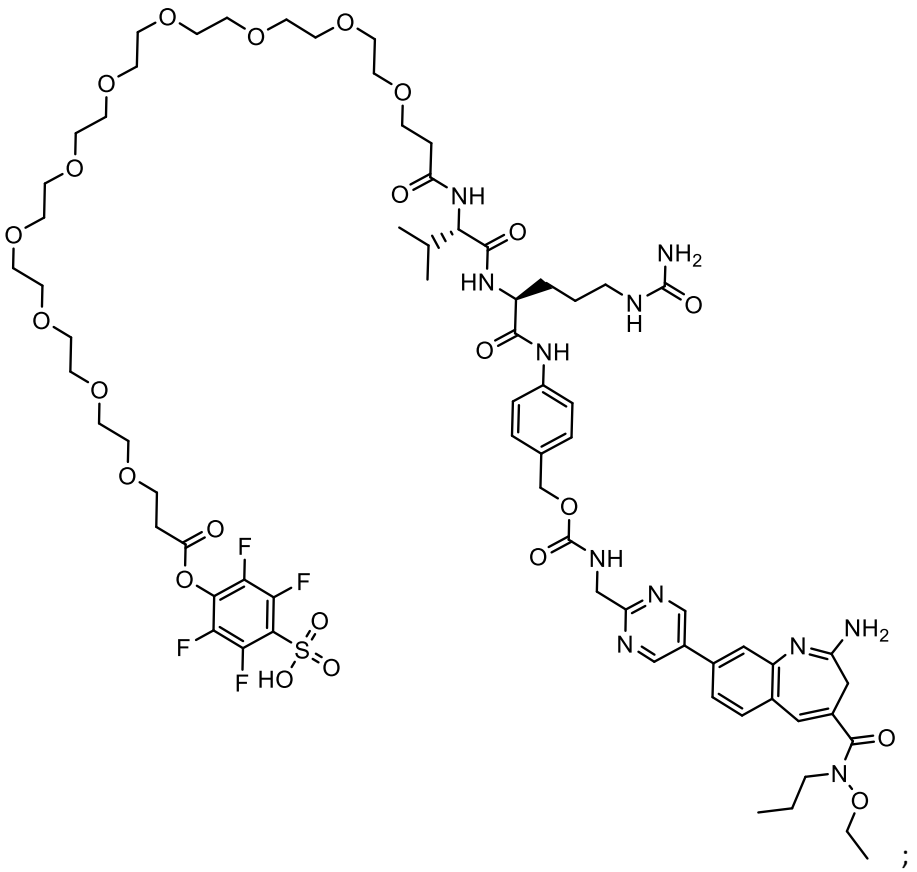
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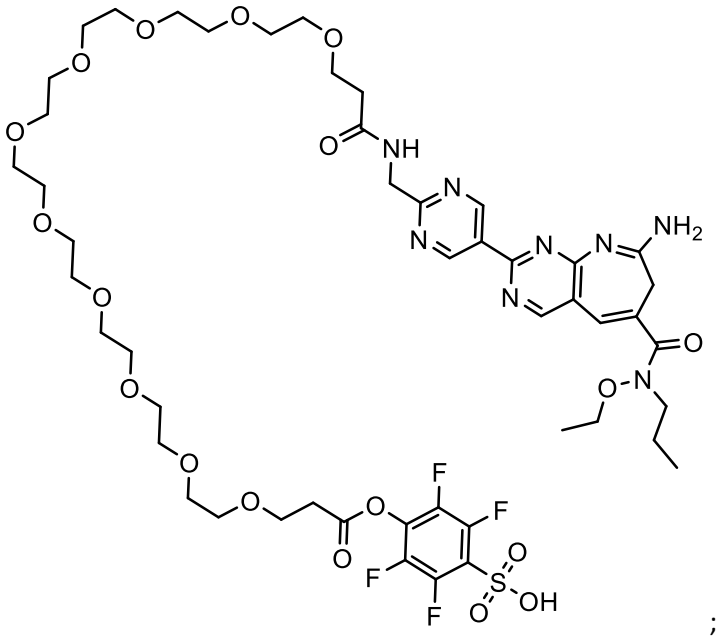
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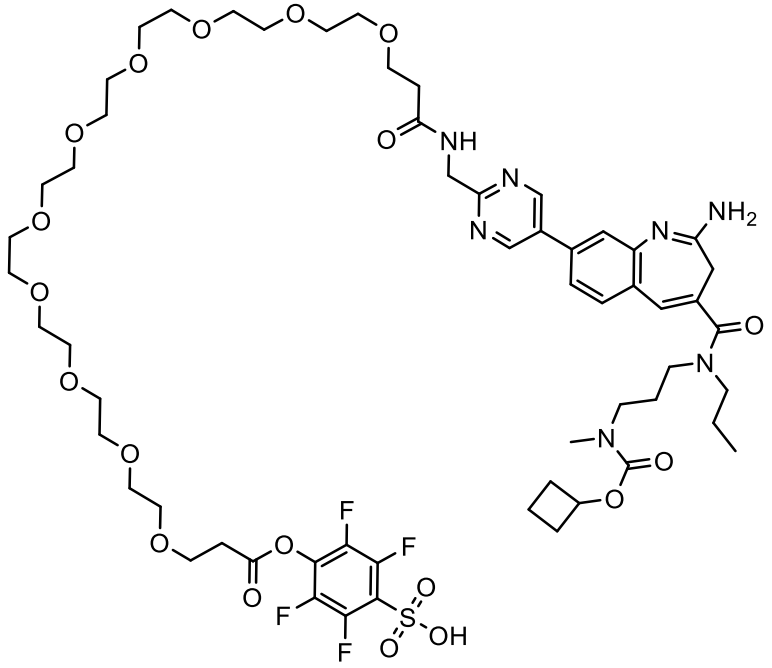
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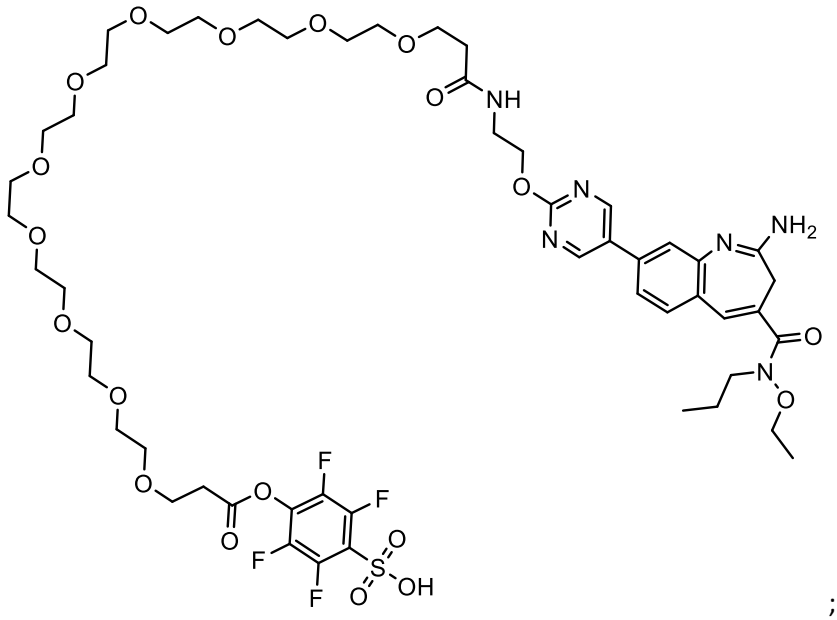
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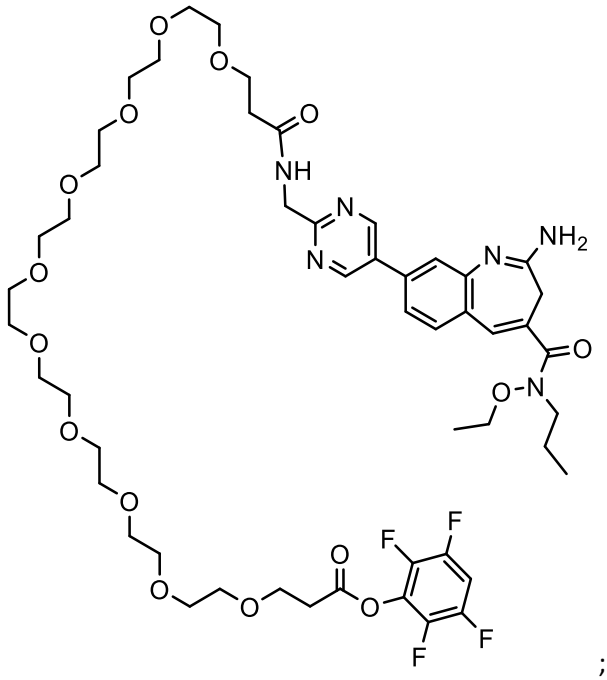
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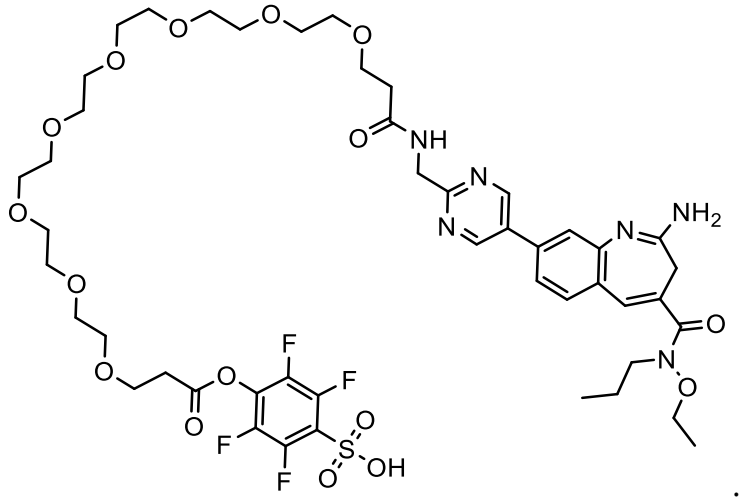
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35. An immunoconjugate prepared by conjugation of an anti-CEA antibody with a 8-Het-2-aminobenzazepine-linker compound selected from claim 34.

36. A pharmaceutical composition comprising a therapeutically effective amount of an immunoconjugate according to any one of claims 1 to 7, and one or more pharmaceutically acceptable diluent, vehicle, carrier or excipient.

37. Use of an immunoconjugate according to any one of claims 1 to 35 in the manufacture of a medicament for treating cancer, wherein the cancer is selected from cervical cancer, endometrial cancer, ovarian cancer, prostate cancer, pancreatic cancer, esophageal cancer, bladder cancer, urinary tract cancer, urothelial carcinoma, lung cancer, non-small cell lung cancer, Merkel cell carcinoma, colon cancer, colorectal cancer, gastric cancer, and breast cancer.

38. A method of preparing an immunoconjugate of Formula I of claim 1 wherein the 8-Het-2-amino-thienoazepine-linker compound of claim 34 is conjugated with the anti-CEA antibody.