ANTI-PD-L1 IMMUNOCONJUGATES, AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This non-provisional application claims the benefit of priority to U.S. Provisional Application No. 63/124,396, 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 6, 2021, is named 17019 013WO1_SL.txt and is 244,809 bytes in size.

FIELD OF THE INVENTION

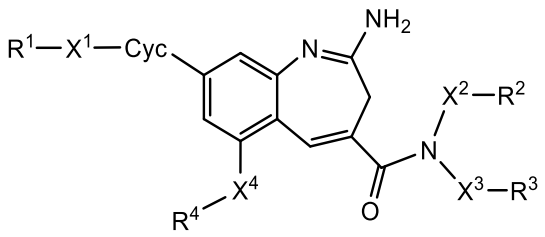
The invention relates generally to an immunoconjugate comprising an anti-PD-L1 antibody conjugated to one or more 8-cyclyl-2-aminobenzazepine molecules.

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-PD-L1 antibody linked by conjugation to one or more 8-cycyl-2-aminobenzazepine derivatives. The disclosure is further directed to 8-cyclyl-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-Cyc-2-aminobenzazepine (CycBz) moiety having the formula:



where Cyc is selected from phenyldiyl, 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-Cyc-2-aminobenzazepine moieties by a linker, and having Formula I:

$$Ab–[L–CycBz]_p \qquad I$$

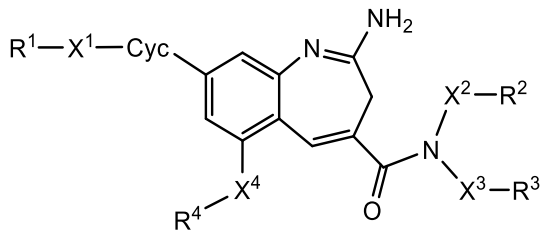
or a pharmaceutically acceptable salt thereof,

wherein:

Ab is an antibody construct that has an antigen binding domain that binds PD-L1;

p is an integer from 1 to 8;

CycBz is the 8-Cyc-2-aminobenzazepine moiety having the formula:



Cyc is selected from the group consisting of phenyldiyl, 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)–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)–;

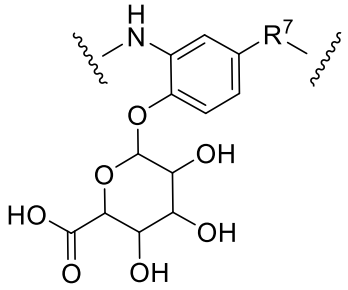
–succinimidyl–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–; and

–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;

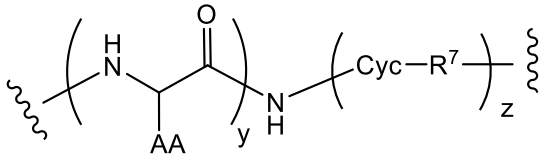
PEG has the formula: $–(CH_2CH_2O)_n–(CH_2)_m–$; m is an integer from 1 to 5, and n is an integer from 2 to 50;

Gluc has the formula:



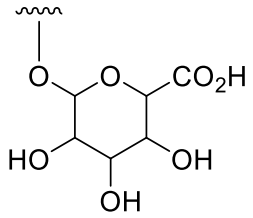
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PEP has the formula:



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,

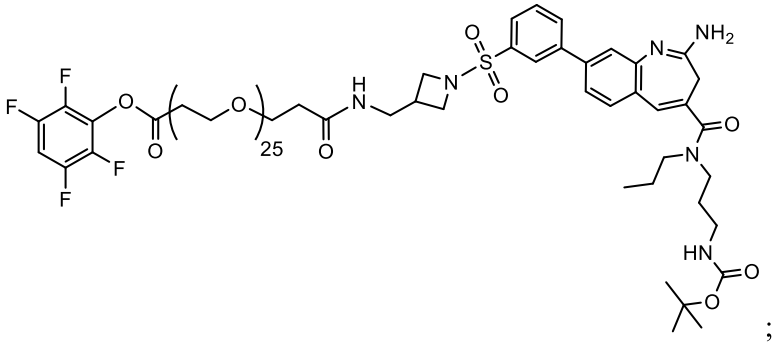
and $-(CH_2CH_2O)_n-(CH_2)_m-OH$, where m is an integer from 1 to 5, and n is an integer from 2 to 50, or two R^9 groups together form a 5- or 6-membered heterocyclyl ring;

y is an integer from 2 to 12;

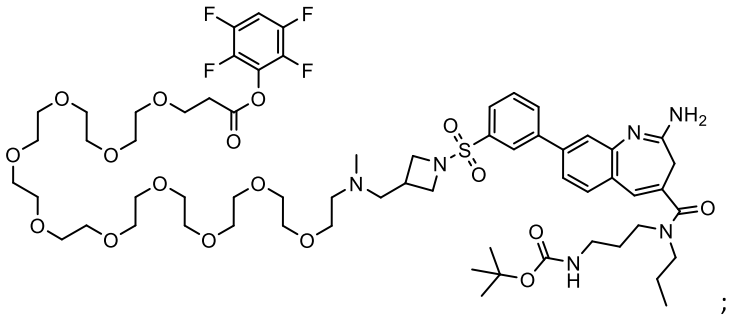
z is 0 or 1; and

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 $-S(O)_3H$.

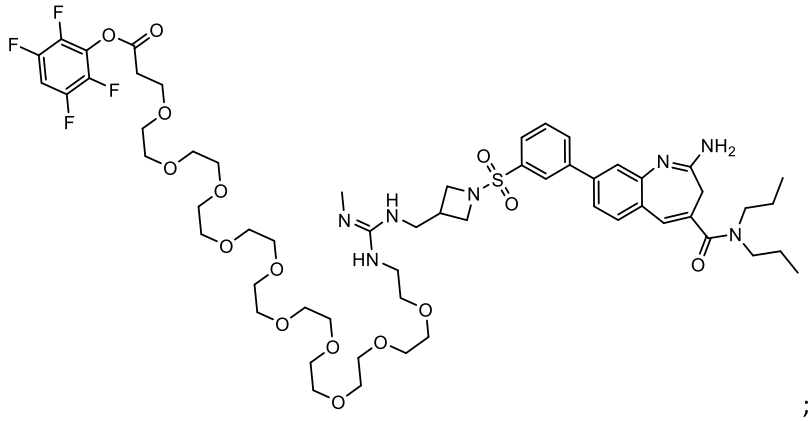
In another aspect, there is provided A 8-Cyc-2-aminobenzazepine-linker compound selected from the group consisting of:



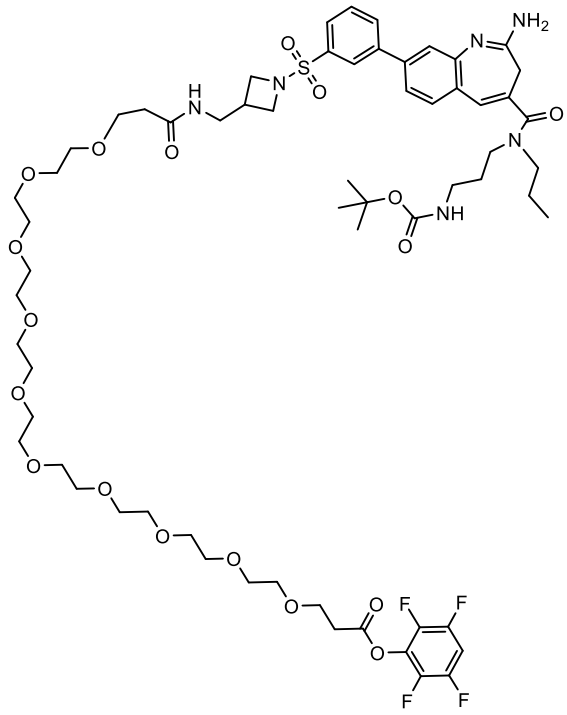
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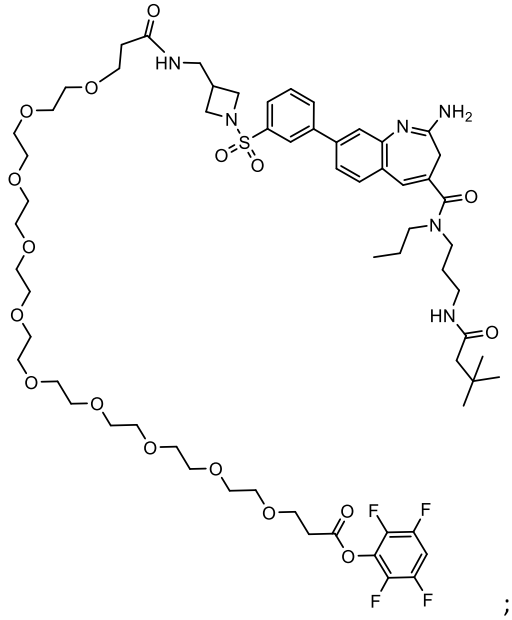
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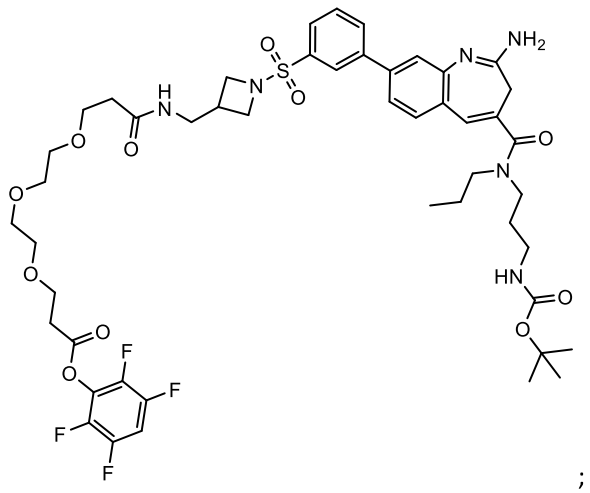
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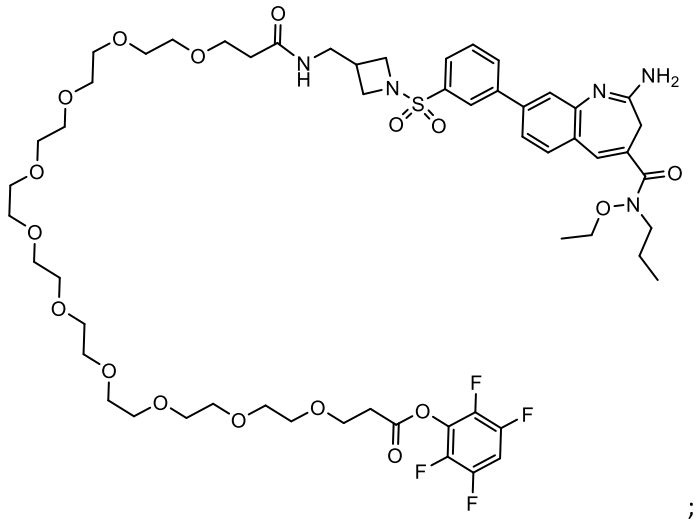
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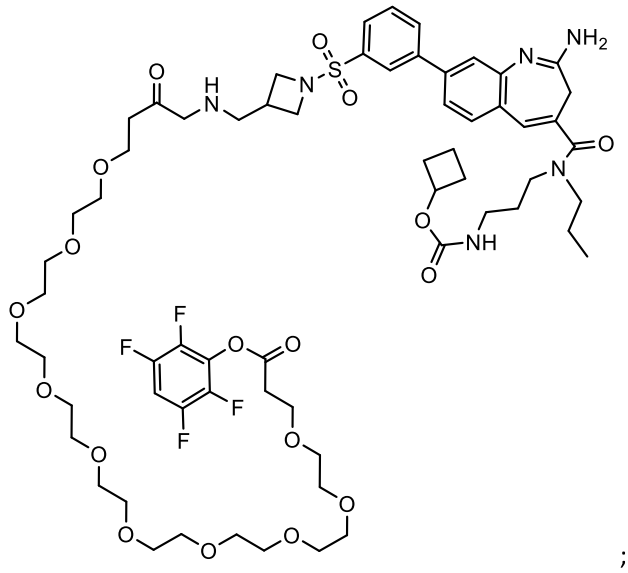
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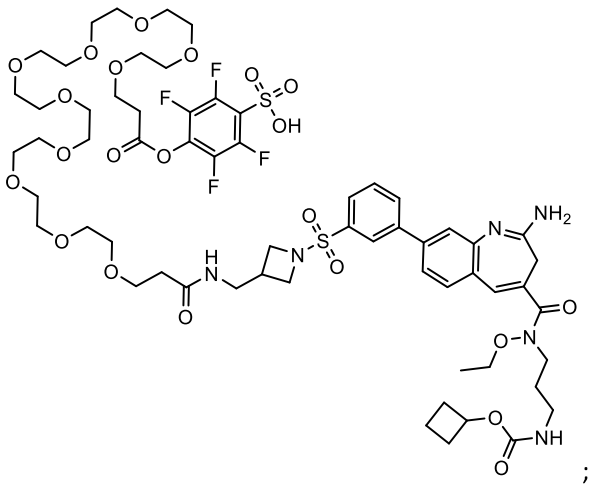
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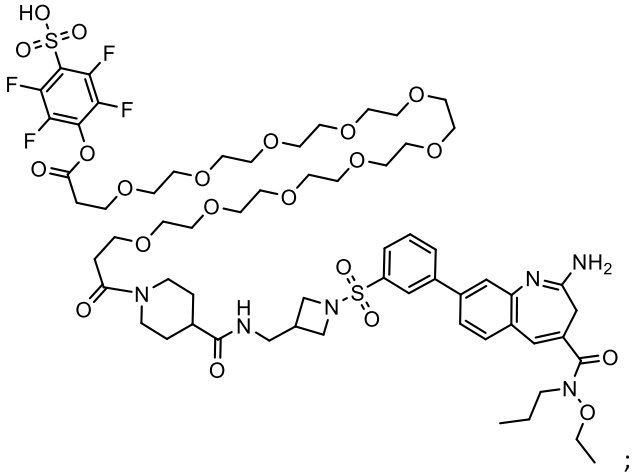


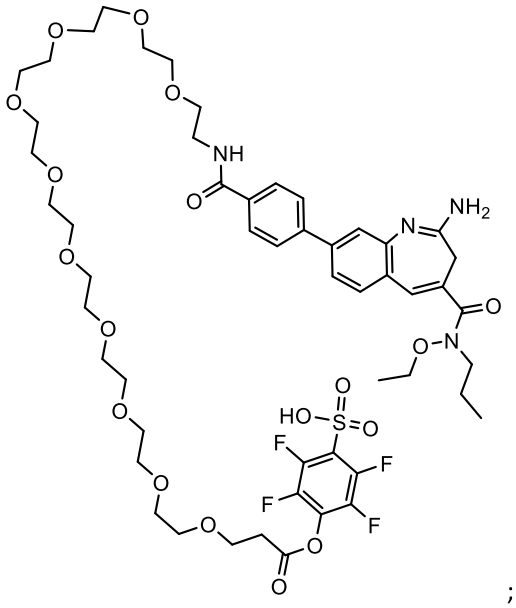
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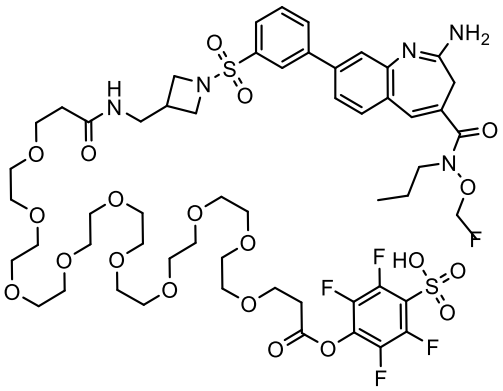


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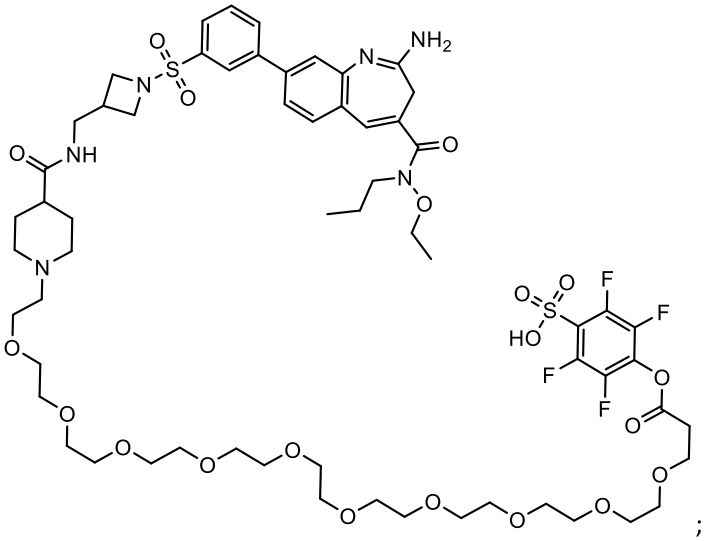

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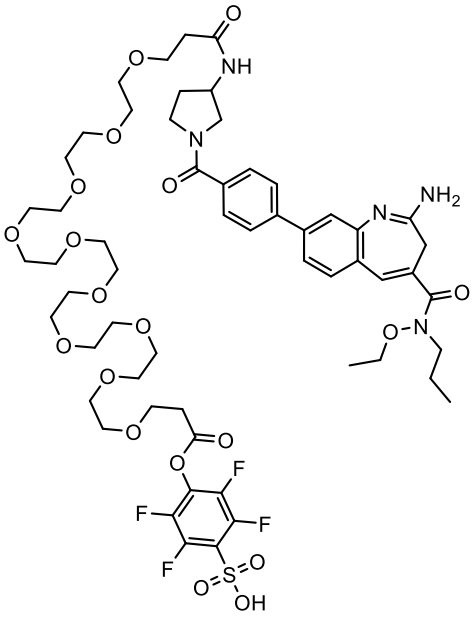

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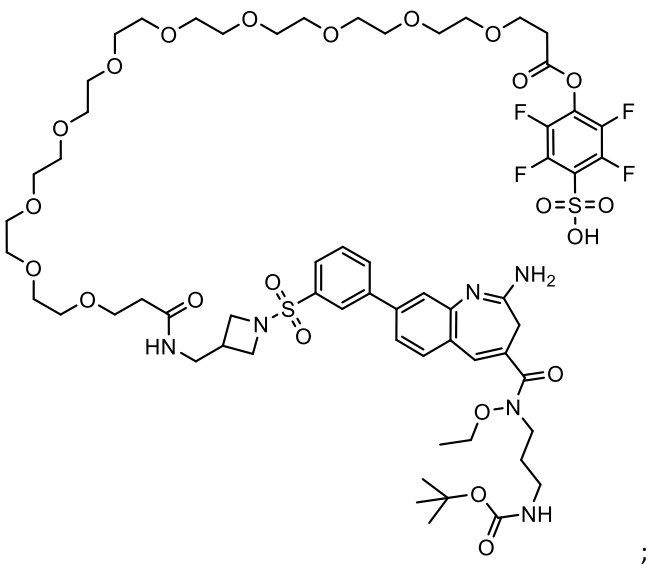
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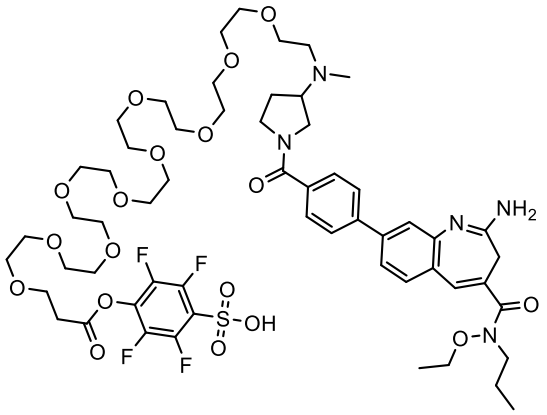
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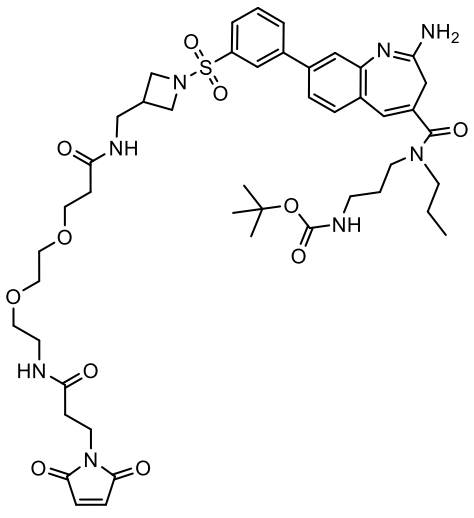
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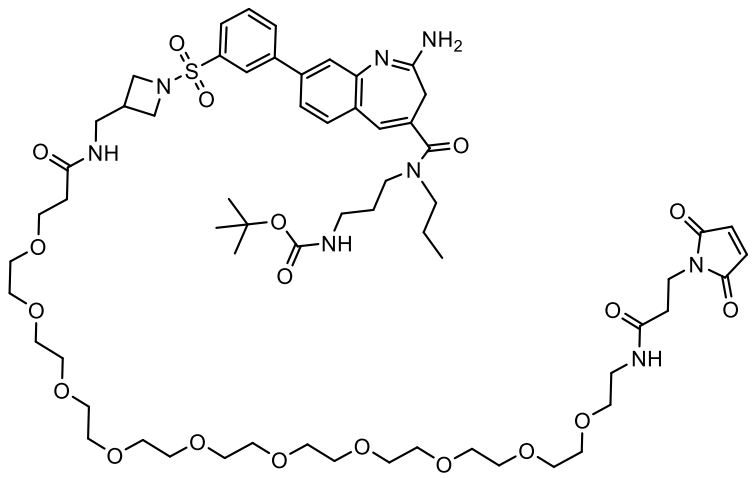
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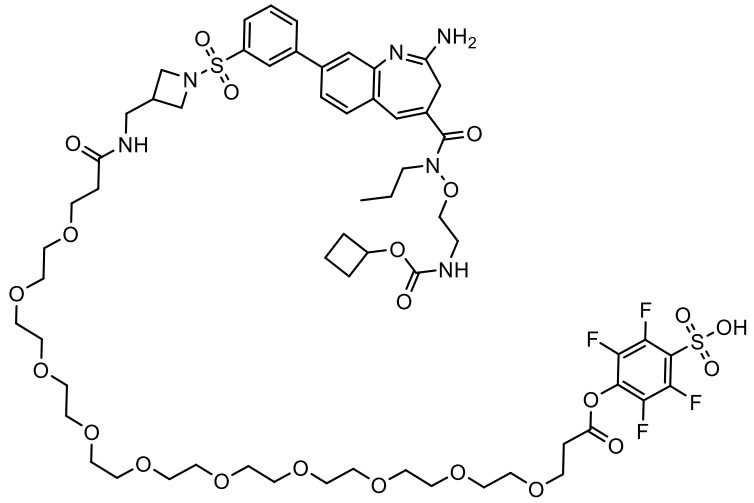
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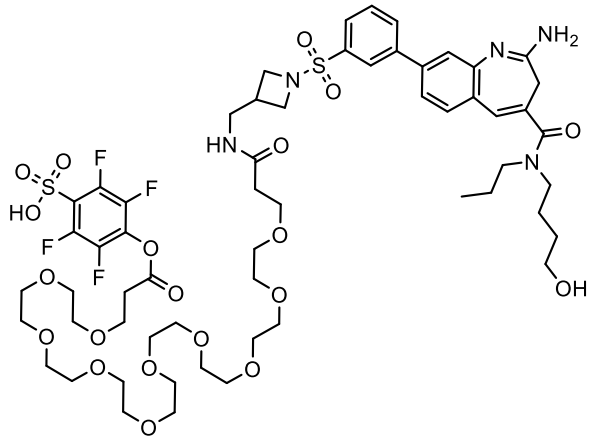
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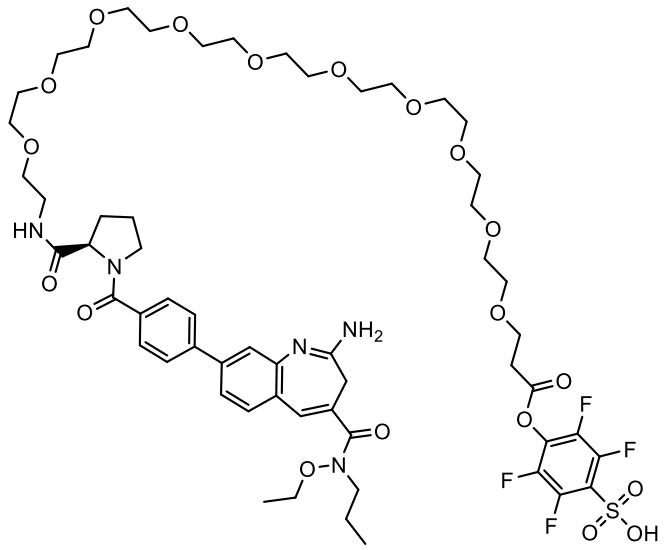
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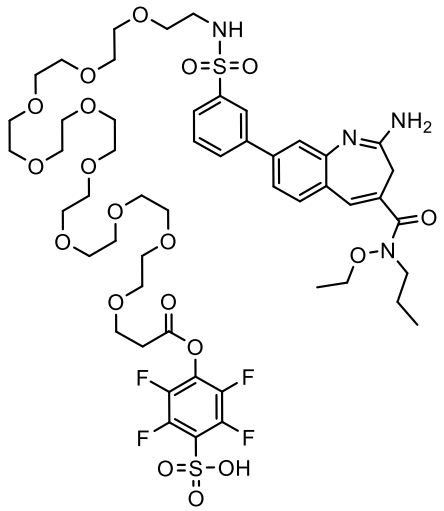
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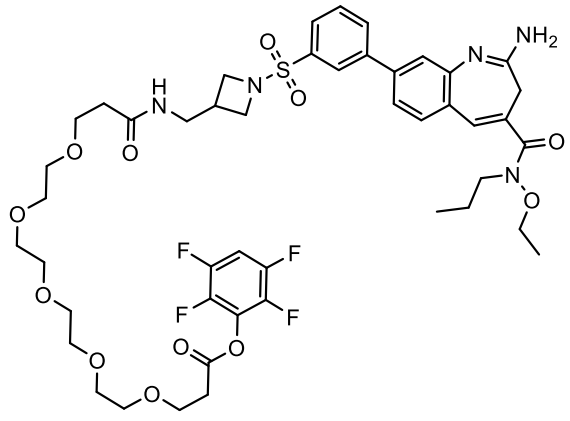
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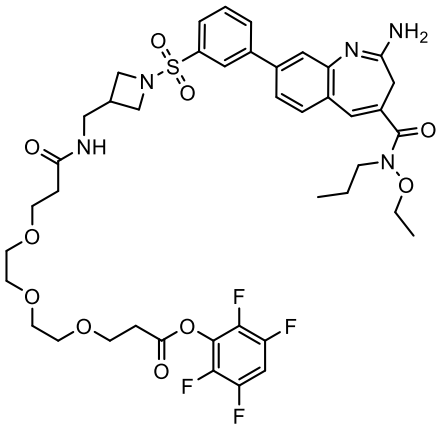
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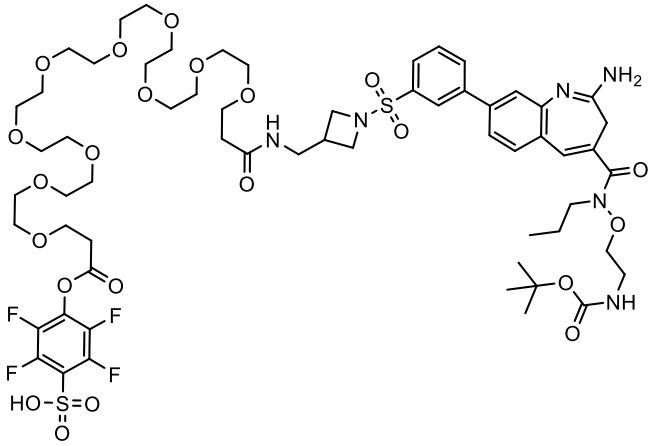
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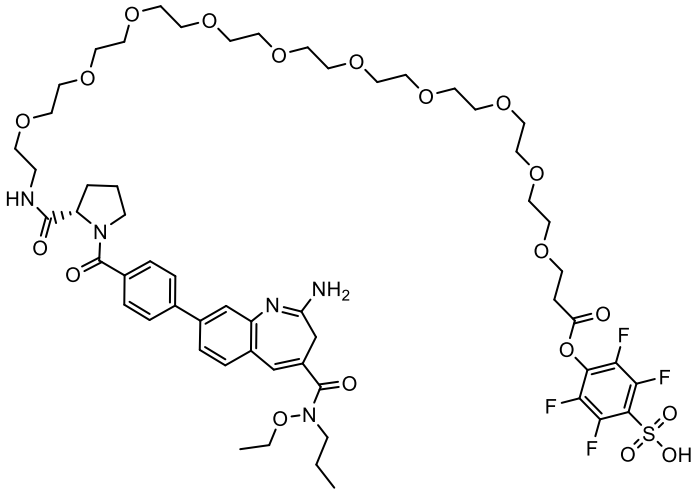
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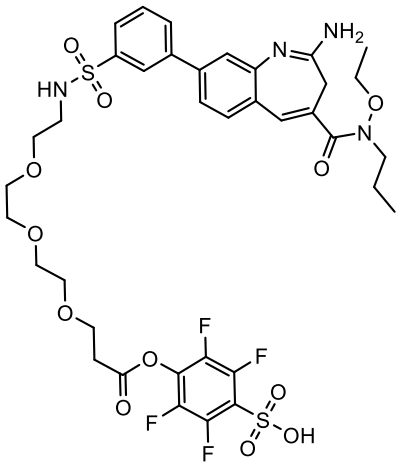
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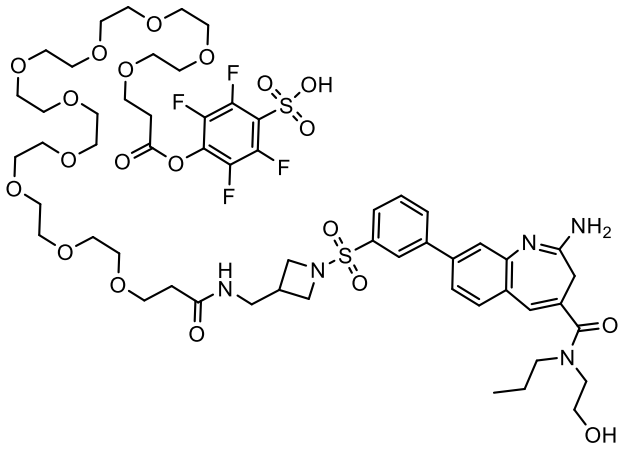
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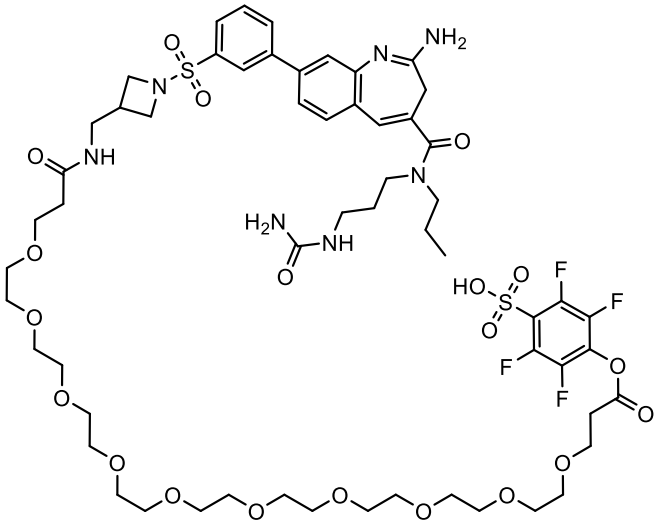
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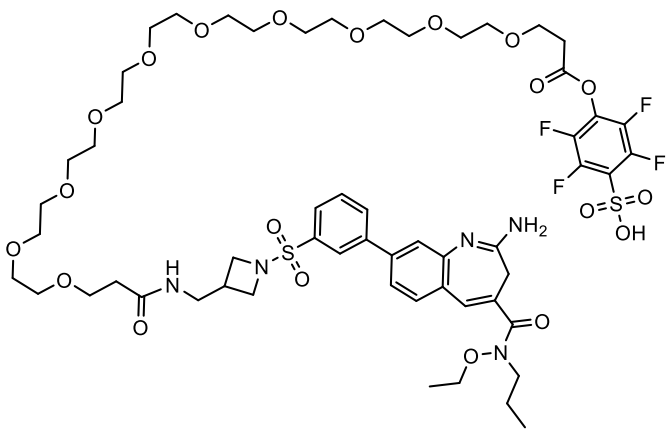
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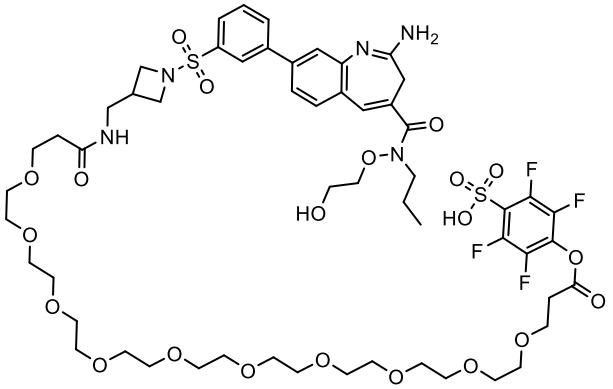
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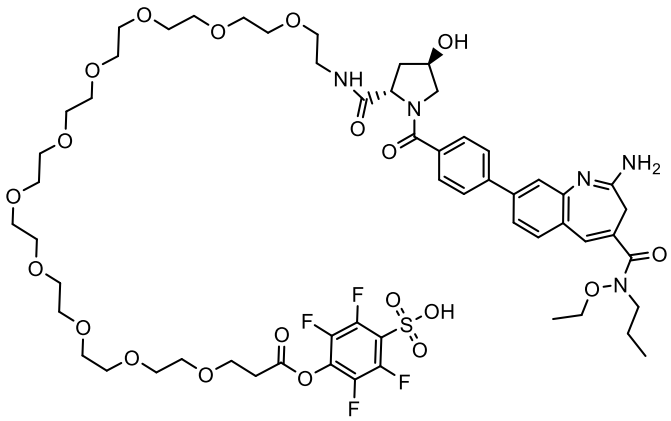
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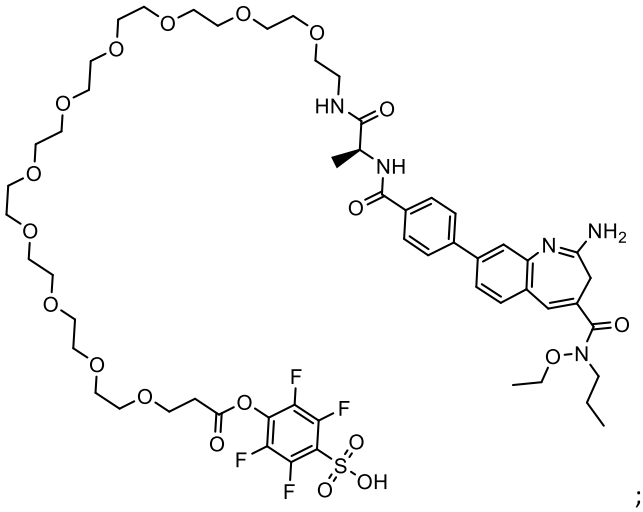
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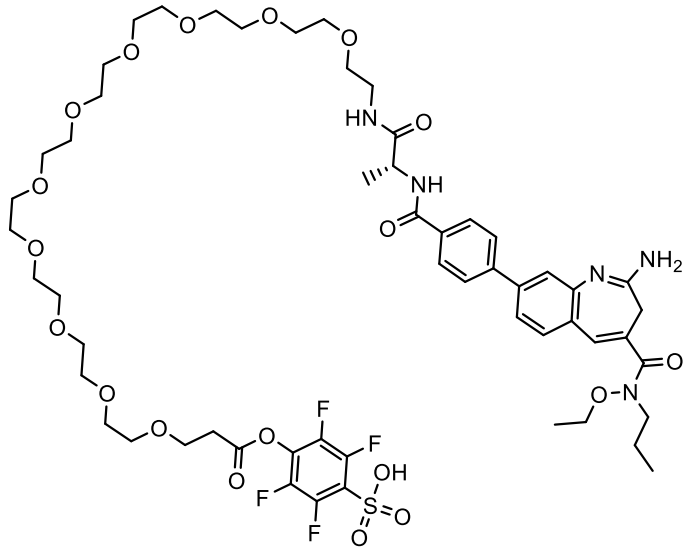
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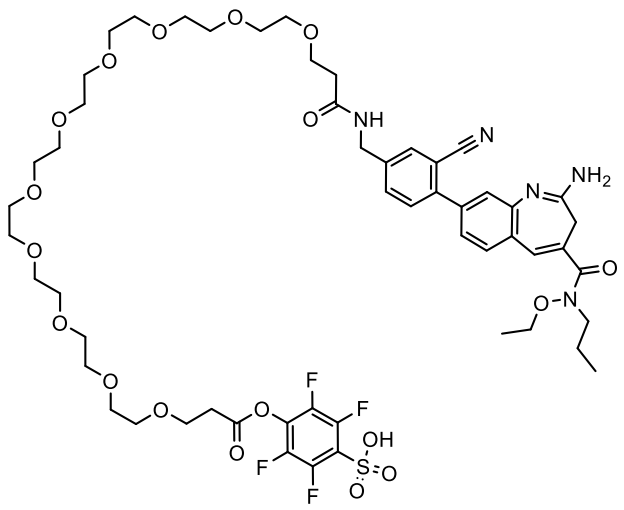
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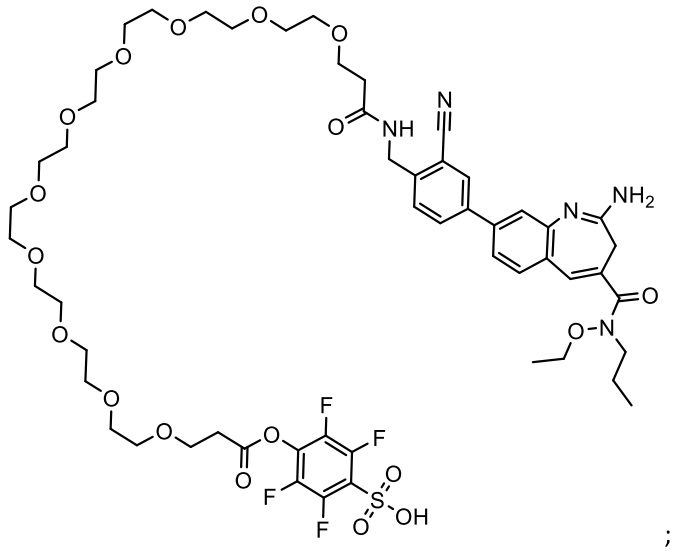
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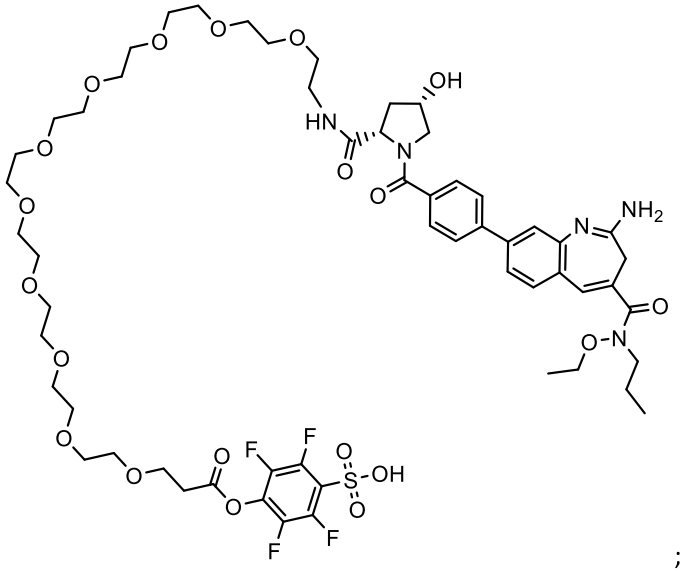
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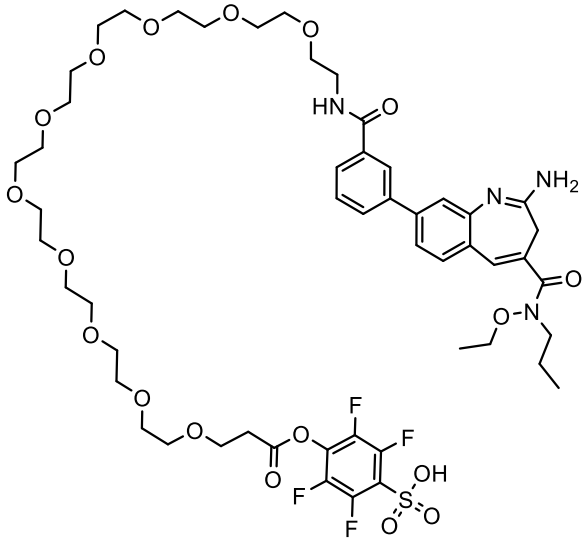
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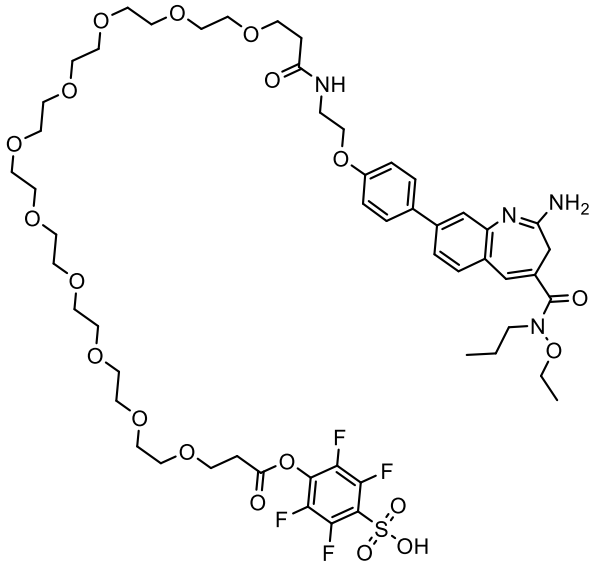
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In another aspect, there is provided an immunoconjugate prepared by conjugation of an anti PD-L1 antibody with a 8-Cyc-2-aminobenzazepine-linker compound as defined above.

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-Cyc-2-amino-thienoazepine-linker compound as defined above is conjugated with the anti PD-L1 antibody.

An example of the disclosure is an immunoconjugate comprising an anti PD-L1 antibody covalently attached to a linker which is covalently attached to one or more 8-Cyc-2-aminobenzazepine moieties.

Another example of the disclosure is a 8-cyclyl-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 PD-L1 antibody linked by conjugation to one or more 8-Cyc-2-aminobenzazepine moieties.

Another example of the disclosure is a use of an immunoconjugate comprising an anti PD-L1 ntibody linked by conjugation to one or more 8-Cyc-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-Cyc-2-aminobenzazepine moieties with an anti PD-L1 antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-D show heavy chain and light chain CDRs of PD-L1 Type A binding agents 1-42.

Figures 2A-D show first (HFW1), second (HFW2), third (HFW3), and fourth (HFW4) heavy chain framework region polypeptides of PD-L1 Type A binding agents 1-42.

Figures 3A-D show first (LFW1), second (LFW2), third (LFW3), and fourth (LFW4) light chain framework region polypeptides of PD-L1 Type A binding agents 1-42.

Figures 4 A-D show heavy chain variable region (VH) of PD-L1 Type A binding agents 1-42.

Figures 4 E-G show light chain variable region (VL) of PD-L1 Type A binding agents 1-42.

Figures 5A-B show heavy chain and light chain CDRs of PD-L1 Type B binding agents 1-21.

Figures 6A-B show first (HFW1), second (HFW2), third (HFW3), and fourth (HFW4) heavy chain framework region polypeptides of PD-L1 Type B binding agents 1-21.

Figures 7A-B show first (LFW1), second (LFW2), third (LFW3), and fourth (LFW4) light chain framework region polypeptides of PD-L1 Type B binding agents 1-21.