AMINOBENZAZEPINE COMPOUNDS, IMMUNOCONJUGATES, AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This non-provisional application claims the benefit of priority to U.S. Provisional Application No. 62/963,884, filed 21 January 2020, and U.S. Provisional Application No. 62/861,139, filed 13 June 2019, each of which are incorporated by reference in their 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 June 2, 2020, is named 17019_002WO1_SL.txt and is 299,523 bytes in size

FIELD OF THE INVENTION

The invention relates generally to an immunoconjugate comprising an antibody conjugated to one or more 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 ~~OF THE INVENTION~~

The ~~invention~~ disclosure is generally directed to immunoconjugates comprising an antibody linked by conjugation to one or more aminobenzazepine derivatives. The ~~invention~~ disclosure is further directed to 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 to one or more aminobenzazepine derivatives, through a linker or linking moiety. The ~~invention~~ disclosure is further directed to use of such an immunoconjugates in the treatment of an illness, in particular cancer.

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

Another example~~aspect~~ of the ~~invention~~disclosure is an aminobenzazepine-linker compound.

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

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

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

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

$$Ab–[L–Bza]_p \qquad I$$

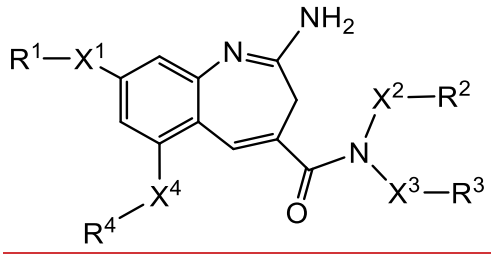
or a pharmaceutically acceptable salt thereof,

wherein:

Ab is the antibody;

p is an integer from 1 to 8;

Bza is the aminobenzazepine moiety having the formula:



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_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} aryl)–*;

–(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)–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)–NR^5–C(=NR^{5a})NR^5–*;

–(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(=O)–*;

–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)–*;

–$N(R^5)C(=O)R^5$;

–$N(R^5)C(=O)$–*;

–$N(R^5)C(=O)N(R^5)_2$;

–$N(R^5)C(=O)N(R^5)$–*;

–$N(R^5)CO_2R^5$;

–$NR^5C(=NR^{5a})N(R^5)_2$;

–$NR^5C(=NR^{5a})N(R^5)$–*;

–$NR^5C(=NR^{5a})R^5$;

–$N(R^5)$–(C_2-C_5 heteroaryl);

–O–(C_1-C_{12} alkyl);

–O–(C_1-C_{12} alkyldiyl)–$N(R^5)_2$;

–O–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–$S(=O)_2$–(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 $S(O)_2N(R^5)$;

R^5 is selected from the group consisting of H, C_6-C_{20} aryl, 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)–;

–C(=O)–(PEG)–O–;

–C(=O)–(PEG)–C(=O)–(PEP)–;

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

–C(=O)–(PEG)–$C(=O)N(R^5)$–(C_1-C_{12} alkyldiyl)–$N(R^5)C(=O)$–(C_2-C_5 monoheterocyclyldiyl)–;

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

–C(=O)–(PEG)–C(=O)–(MCgluc)–;

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

–C(=O)–(PEG)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

–C(=O)–(PEG)–N(R^5)–;

–C(=O)–(PEG)–N(R^5)–(PEG)–C(=O)–(PEP)–;

–C(=O)–(PEG)–N^+(R^5)$_2$–(PEG)–C(=O)–(PEP)–;

–C(=O)–(PEG)–C(=O)–N(R^5)CH(AA_1)C(=O)–(PEG)–C(=O)–(PEP)–;

–C(=O)–(PEG)–C(=O)–N(R^5)CH(AA_1)C(=O)–N(R^5)–(C_1-C_{12} alkyldiyl)–;

–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^5)–(C_1-C_{12} alkyldiyl)–;

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

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

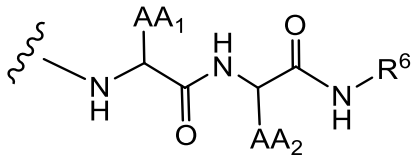
–C(=O)–$CH_2CH_2OCH_2CH_2$–(C_1-C_{20} heteroaryldiyl)–CH_2O–(PEG)–C(=O)–(MCgluc)–;

–C(=O)–$CH_2CH_2OCH_2CH_2$–(C_1-C_{20} heteroaryldiyl)–CH_2O–(PEG)–C(=O)–(MCgluc)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–; and

–(succinimidyl)–(CH_2)$_m$–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

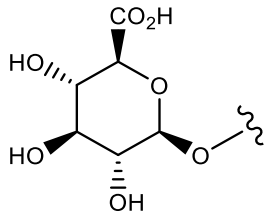
PEG has the formula: –(CH_2CH_2O)$_n$–(CH_2)$_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

PEP has the formula:



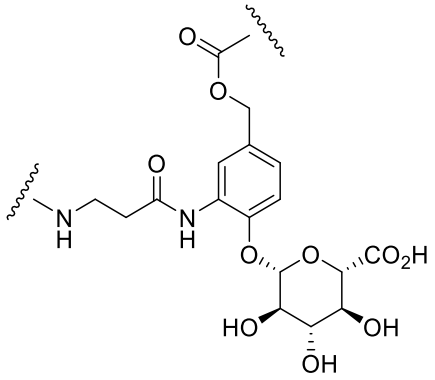
where AA_1 and AA_2 are independently selected from an amino acid side chain, or AA_1 or AA_2 and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment;

R^6 is selected from the group consisting of C_6-C_{20} aryldiyl and C_1-C_{20} heteroaryldiyl, substituted with –CH_2O–C(=O)– and optionally with:



; and

MCgluc is selected from the groups:



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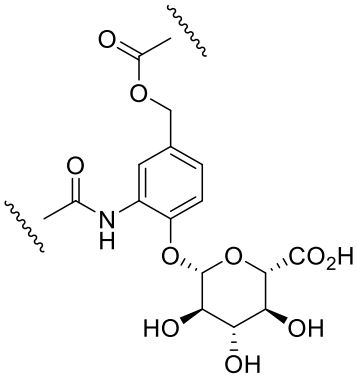
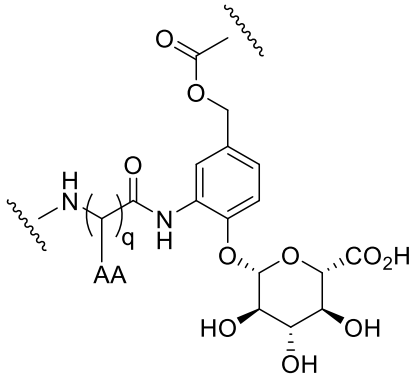


; and

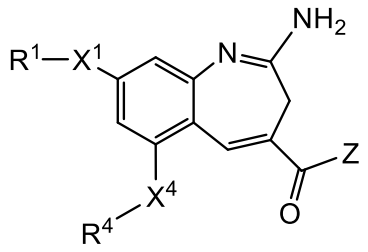


where q is 1 to 8, and AA is an amino acid side chain; and

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

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

In another aspect, there is provided an aminobenzazepine-linker compound of Formula II:



II

wherein

Z is selected from H, $-O(C_1\text{-}C_8$ alkyl), and $N(X^2R^2)(X^3R^3)$;

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

$-(C_1\text{-}C_{12}$ alkyldiyl$)-N(R^5)-*$;

$-(C_1\text{-}C_{12}$ alkyldiyl$)-N(R^5)_2$;

$-(C_3\text{-}C_{12}$ carbocyclyl$)$;

$-(C_3\text{-}C_{12}$ carbocyclyl$)-*$;

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

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

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

$-(C_6\text{-}C_{20}$ aryl$)$;

$-(C_6\text{-}C_{20}$ aryl$)-*$;

$-(C_6\text{-}C_{20}$ aryldiyl$)-N(R^5)-*$;

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

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

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

$-(C_2\text{-}C_{20}$ heterocyclyl$)$;

$-(C_2\text{-}C_{20}$ heterocyclyl$)-*$;

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

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

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

–(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(=O)–*;

–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_2R^5;

–NR^5C(=NR^{5a})N(R^5)$_2$;

–NR^5C(=NR^{5a})N(R^5)–*;

–NR^5C(=NR^{5a})R^5;

–N(R^5)–(C_2-C_5 heteroaryl);

–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)–*;

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

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

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

L is the linker selected from the group consisting of:

Q–C(=O)–(PEG)–;

Q–C(=O)–(PEG)–C(=O)–;

Q–C(=O)–(PEG)–O–;

Q–C(=O)–(PEG)–C(=O)–(PEP)–;

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

Q–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

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

Q–C(=O)–(PEG)–C(=O)–(MCgluc)–;

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

Q–C(=O)–(PEG)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

Q–C(=O)–(PEG)–N(R^5)–;

Q–C(=O)–(PEG)–N(R^5)–(PEG)–C(=O)–(PEP)–;

Q–C(=O)–(PEG)–N$^+$(R^5)$_2$–(PEG)–C(=O)–(PEP)–;

Q–C(=O)–(PEG)–C(=O)–N(R^5)CH(AA_1)C(=O)–(PEG)–C(=O)–(PEP)–;

Q–C(=O)–(PEG)–C(=O)–N(R^5)CH(AA_1)C(=O)–N(R^5)–(C_1-C_{12} alkyldiyl)–;

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

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

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

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

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

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

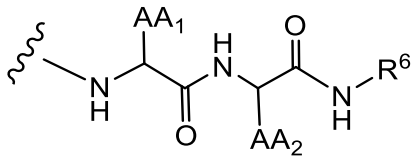
Q–C(=O)–$CH_2CH_2OCH_2CH_2$–(C_1-C_{20} heteroaryldiyl)–CH_2O–(PEG)–C(=O)–(MCgluc)–;

Q–C(=O)–$CH_2CH_2OCH_2CH_2$–(C_1-C_{20} heteroaryldiyl)–CH_2O–(PEG)–C(=O)–(MCgluc)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–; and

Q–$(CH_2)_m$–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

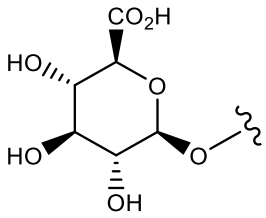
where PEG has the formula:–$(CH_2CH_2O)_n$–$(CH_2)_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

PEP has the formula:



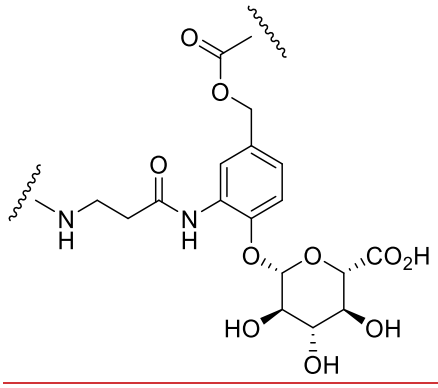
where AA_1 and AA_2 are independently selected from an amino acid side chain, or AA_1 or AA_2 and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment and;

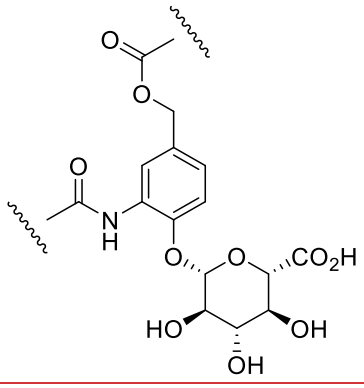
R^6 is selected from the group consisting of C_6-C_{20} aryldiyl and C_1-C_{20} heteroaryldiyl, substituted with –CH_2O–C(=O)– and optionally with:



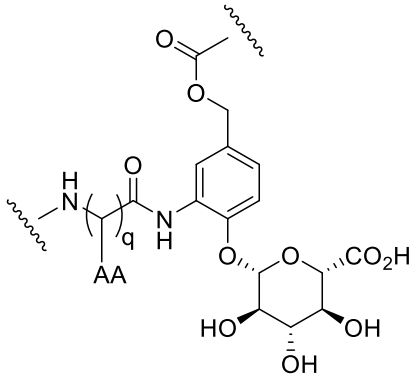
; and

MCgluc is selected from the groups:



; 

; and



where q is 1 to 8, and AA is an amino acid side chain; and

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

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

$(CH_2)_mCO_2H$, $-O(CH_2CH_2O)_nH$, $-OP(O)(OH)_2$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-S(O)_2CH_3$, and $-S(O)_3H$.

In another aspect, there is provided an immunoconjugate prepared by conjugation of an antibody with an 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 for treating cancer, wherein the cancer is selected from 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 an aminobenzazepine-linker compound of Formula II as defined above is conjugated with the 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.

Figures 8A-B show heavy chain variable region (VH) of PD-L1 Type B binding agents 1-21.

Figures 8C-D show light chain variable region (VL) of PD-L1 Type B binding agents 1-21.

DETAILED DESCRIPTION OF THE INVENTION

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is

CLAIMS:

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

$$Ab–[L–Bza]_p \qquad I$$

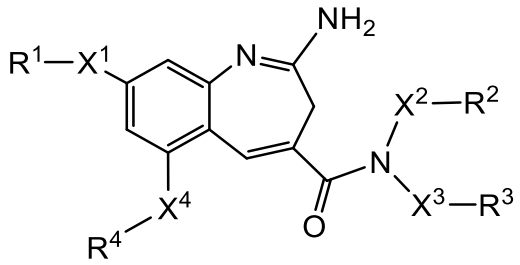
or a pharmaceutically acceptable salt thereof,

wherein:

Ab is the antibody;

p is an integer from 1 to 8;

Bza is the aminobenzazepine moiety having the formula:



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_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} aryl)–*;

–(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)–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)–NR^5–$C(=NR^{5a})NR^5$–*;

–(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(=O)–*;

–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–*;

–$N(R^5)_2$;

–$N(R^5)$–*;

–$N(R^5)C(=O)R^5$;

–$N(R^5)C(=O)$–*;

–$N(R^5)C(=O)N(R^5)_2$;

–$N(R^5)C(=O)N(R^5)$–*;

–$N(R^5)CO_2R^5$;

–$NR^5C(=NR^{5a})N(R^5)_2$;

–$NR^5C(=NR^{5a})N(R^5)$–*;

–$NR^5C(=NR^{5a})R^5$;

–$N(R^5)$–(C_2-C_5 heteroaryl);

–O–(C_1-C_{12} alkyl);

–O–(C_1-C_{12} alkyldiyl)–$N(R^5)_2$;

–O–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

–$S(=O)_2$–(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 $S(O)_2N(R^5)$;

R^5 is selected from the group consisting of H, C_6-C_{20} aryl, 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)–;

–C(=O)–(PEG)–O–;

–C(=O)–(PEG)–C(=O)–(PEP)–;

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

–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

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

–C(=O)–(PEG)–C(=O)–(MCgluc)–;

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

–C(=O)–(PEG)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

–C(=O)–(PEG)–N(R^5)–;

–C(=O)–(PEG)–N(R^5)–(PEG)–C(=O)–(PEP)–;

–C(=O)–(PEG)–$N^+(R^5)_2$–(PEG)–C(=O)–(PEP)–;

–C(=O)–(PEG)–C(=O)–N(R^5)CH(AA_1)C(=O)–(PEG)–C(=O)–(PEP)–;

–C(=O)–(PEG)–C(=O)–N(R^5)CH(AA_1)C(=O)–N(R^5)–(C_1-C_{12} alkyldiyl)–;

–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^5)–(C_1-C_{12} alkyldiyl)–;

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

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

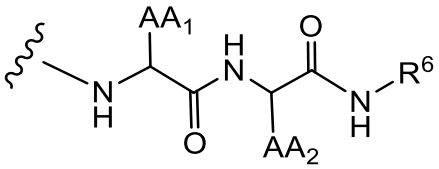
–C(=O)–$CH_2CH_2OCH_2CH_2$–(C_1-C_{20} heteroaryldiyl)–CH_2O–(PEG)–C(=O)–(MCgluc)–;

–C(=O)–$CH_2CH_2OCH_2CH_2$–(C_1-C_{20} heteroaryldiyl)–CH_2O–(PEG)–C(=O)–(MCgluc)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–; and

–(succinimidyl)–$(CH_2)_m$–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

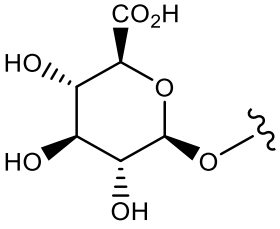
PEG has the formula: –$(CH_2CH_2O)_n$–$(CH_2)_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

PEP has the formula:



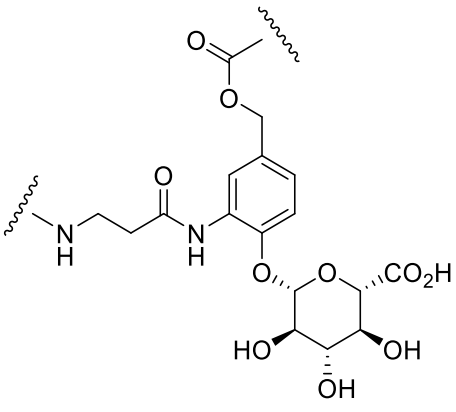
where AA_1 and AA_2 are independently selected from an amino acid side chain, or AA_1 or AA_2 and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment;

R^6 is selected from the group consisting of C_6-C_{20} aryldiyl and C_1-C_{20} heteroaryldiyl, substituted with –CH_2O–C(=O)– and optionally with:



; and

MCgluc is selected from the groups: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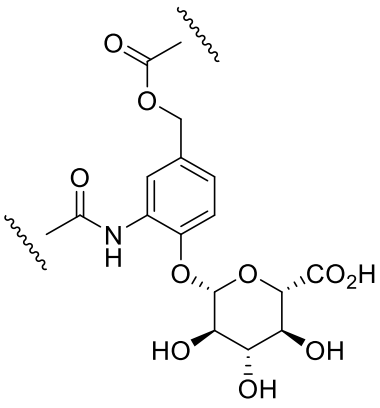
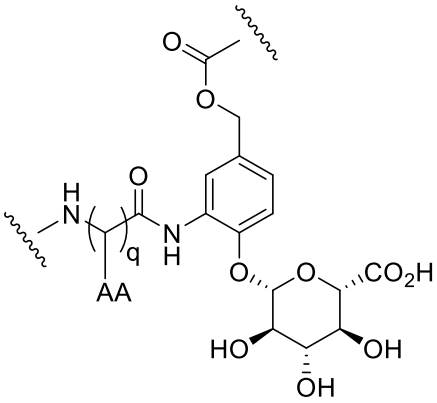

; and


where q is 1 to 8, and AA is an amino acid side chain; and

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

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

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

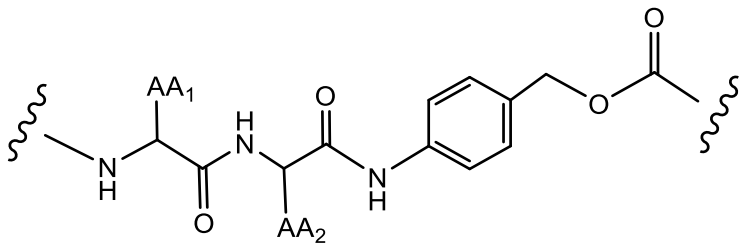
~~4. The immunoconjugate of claim 1 wherein the antibody is an antibody construct that has an antigen binding domain that binds HER2.~~

~~5. The immunoconjugate of claim 4 wherein the antibody is selected from the group consisting of trastuzumab and pertuzumab, or a biosimilar or a biobetter thereof.~~

~~6. The immunoconjugate of claim 1 wherein the antibody is an antibody construct that has an antigen binding domain that binds CEA.~~

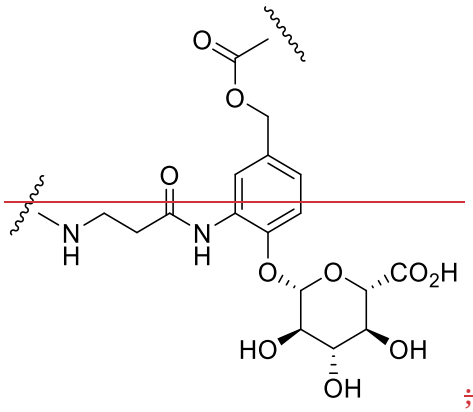
~~7. The immunoconjugate of claim 6 wherein the antibody is labetuzumab, or a biosimilar or a biobetter thereof.~~

~~8~~4. The immunoconjugate of any one of claims 1 to ~~7~~ 3 wherein PEP has the formula:

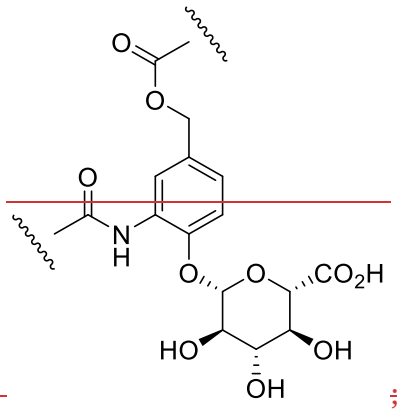


wherein AA_1 and AA_2 are independently selected from a side chain of a naturally-occurring amino acid.

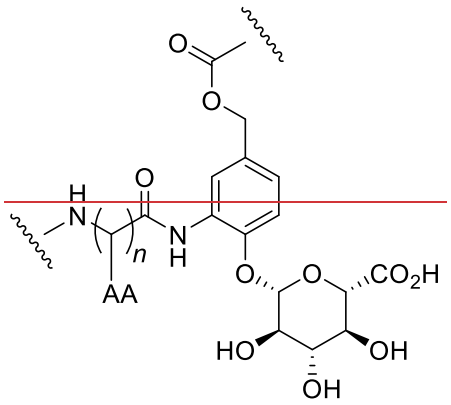
~~9. The immunoconjugate of any one of claims 1 to 7 wherein PEP is selected from the groups:~~



~~;~~



~~; and~~



~~where n is 1 or more, and AA is an amino acid side chain.~~

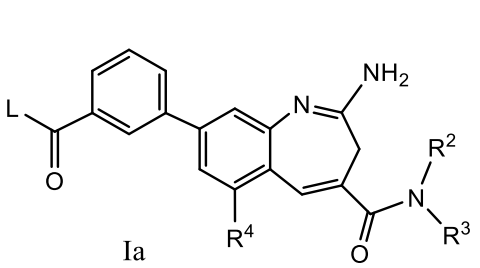
~~10. The immunoconjugate of any one of claims 1 to 9 wherein AA_1 and AA_2 are independently selected from a side chain of a naturally-occurring amino acid.~~

~~11~~5. The immunoconjugate of any one of claims 1 to ~~9~~4 wherein AA_1 and AA_2 are independently selected from H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2(C_6H_5)$, $-CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, $-CH_2CH(CH_3)_2$, $-CH_2SO_3H$, and $-CH_2CH_2CH_2NHC(O)NH_2$.

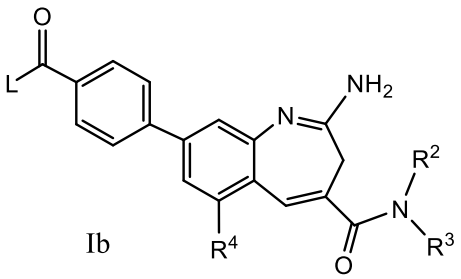
6~~12~~. The immunoconjugate of claim ~~11~~5 wherein AA_1 is $-CH(CH_3)_2$, and AA_2 is $-CH_2CH_2CH_2NHC(O)NH_2$.

~~13~~7. The immunoconjugate of any one of claims 1 to ~~7~~3 wherein AA_1 and AA_2 are independently selected from GlcNAc aspartic acid, $-CH_2SO_3H$, and $-CH_2OPO_3H$.

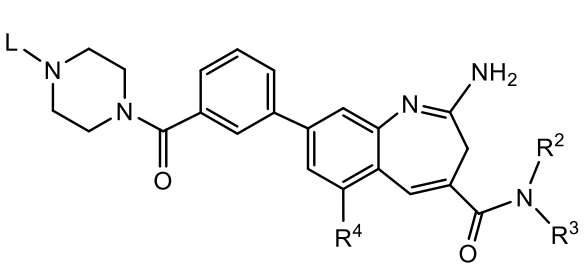
~~14~~8. The immunoconjugate of any one of claims 1 to 7~~13~~ wherein Bza is selected from Formulas Ia-~~d~~h:



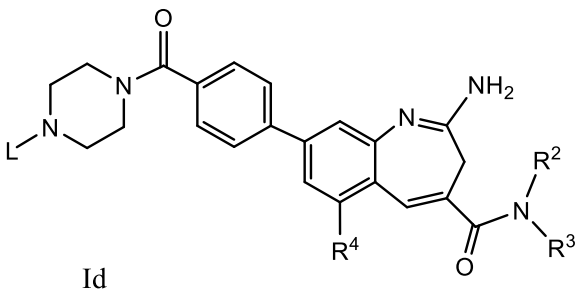
Ia



Ib

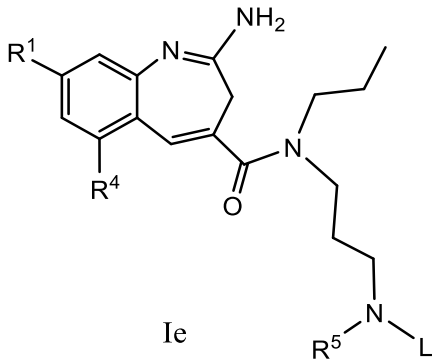


Ic

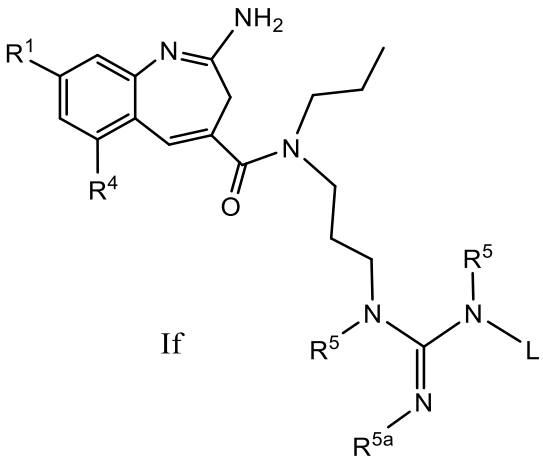


Id

~~15. The immunoconjugate of any one of claims 1 to 13 wherein Bza is selected from Formulas Ie and If:~~



Ie

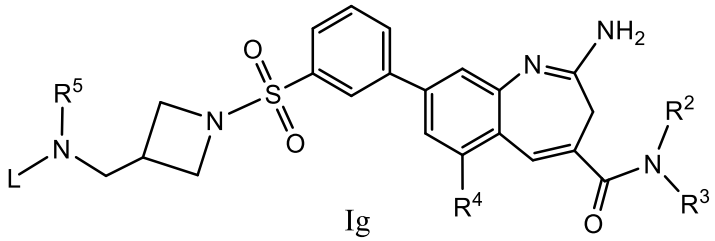


If

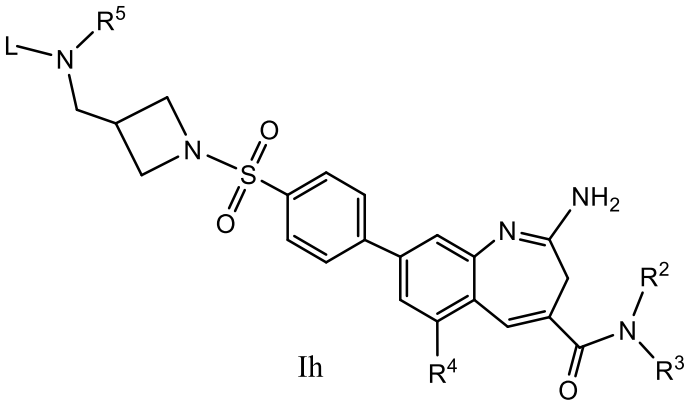
where R^{5a} of Formula If is selected from the group consisting of phenyl and pyridyl, optionally substituted with one or more groups selected from F, Cl, Br, I, –CN, $–NO_2$ and $–OCH_3$~~.~~;

~~16. The immunoconjugate of claim 15 wherein L is –C(=O)–(PEG)–.~~

~~17. The immunoconjugate of any one of claims 1 to 13 wherein Bza is selected from Formulas Ig and Ih:~~



Ig



Ih

.

~~18~~9. The immunoconjugate of claim ~~17~~ 8 wherein L is –C(=O)–(PEG)– or –C(=O)–(PEG)–C(=O)–.

~~19~~10. The immunoconjugate of claim ~~18~~ 9 wherein R^2 and R^3 are each C_1-C_8 alkyl.

~~20~~11. The immunoconjugate of claim ~~19~~10 wherein R^2 and R^3 are each $–CH_2CH_2CH_3$.

~~21~~12. The immunoconjugate of claim 1 wherein X^2 and X^3 are each a bond, and R^2 or R^3 is –O–(C_1-C_{12} alkyl).

~~22~~13. The immunoconjugate of claim ~~21~~12 wherein R^2 or R^3 is $-OCH_2CH_3$.

~~23. The immunoconjugate of any one of claims 1 to 7 wherein one of R^1 and R^4 is selected from:~~

~~–(C_1-C_{12} alkyldiyl)–N(R^5)–*;~~

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

~~–(C_6-C_{20} aryldiyl)–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–*;~~

~~–(C_6-C_{20} aryldiyl)–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;~~

~~–(C_6-C_{20} aryldiyl)–C(=O)–*;~~

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

~~–(C_6-C_{20} aryldiyl)–C(=O)–(C_2-C_{20} heterocyclyldiyl)–*;~~

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

~~–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–*.~~

~~X^1 and X^4 are a bond, and where the asterisk * indicates the attachment site of L.~~

~~24. The immunoconjugate of any one of claims 1 to 7 wherein one of R^2 and R^3 is selected from:~~

~~–(C_1-C_{12} alkyldiyl)–N(R^5)–*;~~

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

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

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

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

~~–(C_2-C_6 alkynyldiyl)–N(R^5)–*; and~~

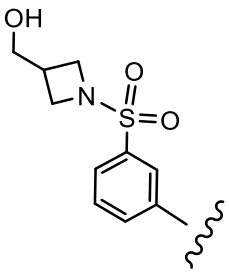
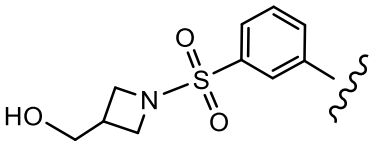
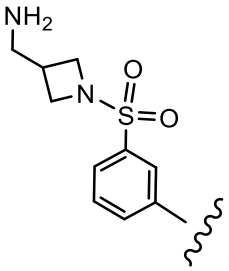
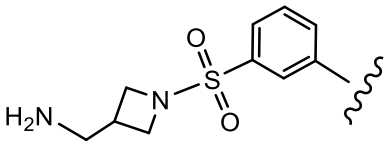
~~–(C_2-C_6 alkynyldiyl)–N(R^5)C(=NR^5)N(R^5)–*;~~

~~X^2 and X^3 are a bond, and where the asterisk * indicates the attachment site of L.~~

~~25. The immunoconjugate of any one of claims 1 to 7 wherein one of R^1 and R^4 is selected from –(C_6-C_{20} aryldiyl)–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)$_2$ and –(C_6-C_{20} aryldiyl)–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–OH.~~

~~26. The immunoconjugate of claim 25 wherein C_6-C_{20} aryldiyl is phenyldiyl and C_2-C_{20} heterocyclyldiyl is azetidindiyl.~~

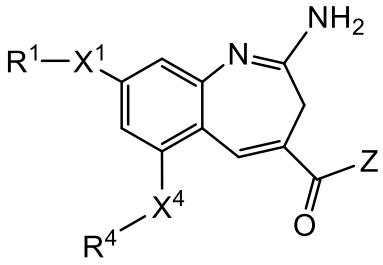
~~27. The immunoconjugate of claim 26 wherein one of R^1 and R^4 is selected from the formulas:~~

28. The immunoconjugate of any one of claims 1 to 7 wherein one of R^1 and R^4 is $-C(=O)NR^5-(C_1-C_{20}$ heteroaryldiyl$)-(C_2-C_{20}$ heterocyclyldiyl$)-C(=O)NR^5-(C_1-C_{12}$ alkyldiyl$)-NR^5-L$.

29. The immunoconjugate of claim 28 wherein C_1-C_{20} heteroaryldiyl is pyridindiyl and C_2-C_{20} heterocyclyldiyl is piperidiyl.

3014. An aminobenzazepine-linker compound of Formula II:



II

wherein

Z is selected from H, $-O(C_1-C_8$ alkyl), and $N(X^2R^2)(X^3R^3)$;

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$)-N(R^5)_2$;

$-(C_3-C_{12}$ 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} aryl)–*;

–(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)–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)–NR^5–C(=NR^{5a})NR^5–*;

–(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(=O)–*;

–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_2R^5;

–NR^5C(=NR^{5a})N(R^5)$_2$;

–NR^5C(=NR^{5a})N(R^5)–*;

–NR^5C(=NR^{5a})R^5;

–N(R^5)–(C_2-C_5 heteroaryl);

–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)–*;

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

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

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

L is the linker selected from the group consisting of:

Q–C(=O)–(PEG)–;

Q–C(=O)–(PEG)–C(=O)–;

Q–C(=O)–(PEG)–O–;

Q–C(=O)–(PEG)–C(=O)–(PEP)–;

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

Q–C(=O)–(PEG)–C(=O)N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

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

Q–C(=O)–(PEG)–C(=O)–(MCgluc)–;

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

Q–C(=O)–(PEG)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

Q–C(=O)–(PEG)–N(R^5)–;

Q–C(=O)–(PEG)–N(R^5)–(PEG)–C(=O)–(PEP)–;

Q–C(=O)–(PEG)–N^+(R^5)$_2$–(PEG)–C(=O)–(PEP)–;

Q–C(=O)–(PEG)–C(=O)–N(R^5)CH(AA_1)C(=O)–(PEG)–C(=O)–(PEP)–;

Q–C(=O)–(PEG)–C(=O)–N(R^5)CH(AA_1)C(=O)–N(R^5)–(C_1-C_{12} alkyldiyl)–;

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

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

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

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

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

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

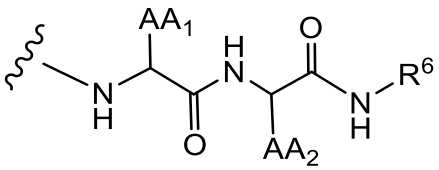
Q–C(=O)–$CH_2CH_2OCH_2CH_2$–(C_1-C_{20} heteroaryldiyl)–CH_2O–(PEG)–C(=O)–(MCgluc)–;

Q–C(=O)–$CH_2CH_2OCH_2CH_2$–(C_1-C_{20} heteroaryldiyl)–CH_2O–(PEG)–C(=O)–(MCgluc)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–; and

Q–(CH_2)$_m$–C(=O)–(PEP)–N(R^5)–(C_1-C_{12} alkyldiyl)–N(R^5)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

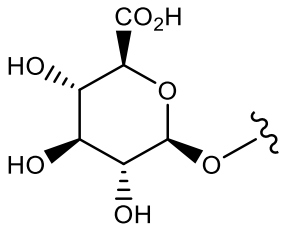
where PEG has the formula:–(CH_2CH_2O)$_n$–(CH_2)$_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

PEP has the formula:



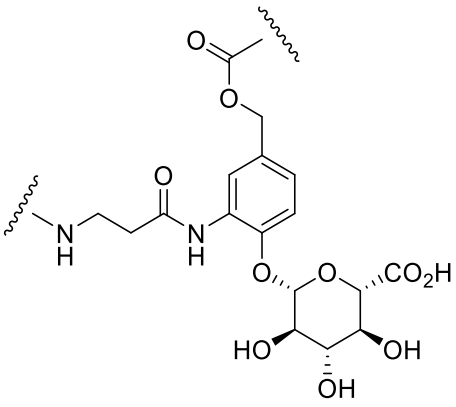
where AA_1 and AA_2 are independently selected from an amino acid side chain, or AA_1 or AA_2 and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment and;

R^6 is selected from the group consisting of C_6-C_{20} aryldiyl and C_1-C_{20} heteroaryldiyl, substituted with $–CH_2O–C(=O)–$ and optionally with:

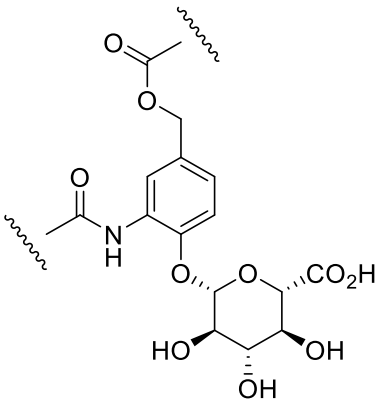


; and

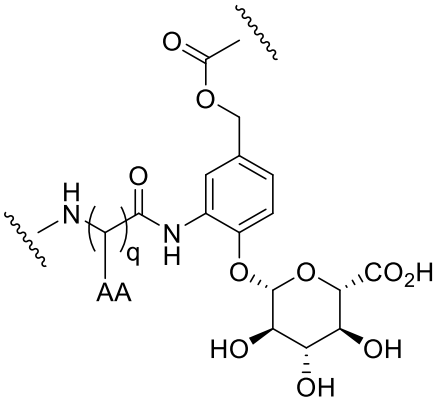
MCgluc is selected from the groups:



;



; and



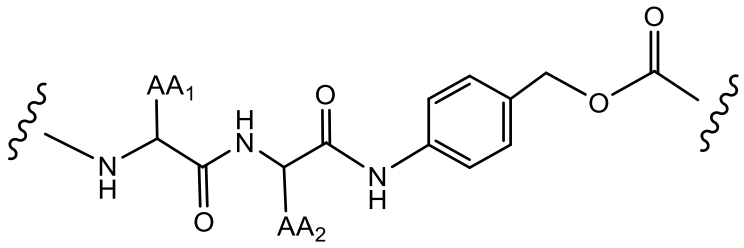
where q is 1 to 8, and AA is an amino acid side chain; and

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

where alkyl, alkyldiyl, alkenyl, alkenyldiyl, alkynyl, alkynyldiyl, aryl, aryldiyl carbocyclyl, carbocyclyldiyl, heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, $–CH_3$, $–CH_2CH_3$, $–CH=CH_2$, $–C≡CH$, $–C≡CCH_3$, $–CH_2CH_2CH_3$, $–CH(CH_3)_2$, $–CH_2CH(CH_3)_2$, $–CH_2OH$, $–CH_2OCH_3$, $–CH_2CH_2OH$, $–C(CH_3)_2OH$, $–CH(OH)CH(CH_3)_2$, $–C(CH_3)_2CH_2OH$, $–CH_2CH_2SO_2CH_3$, $–CH_2OP(O)(OH)_2$, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CF_3$, $–CH_2CHF_2$, –

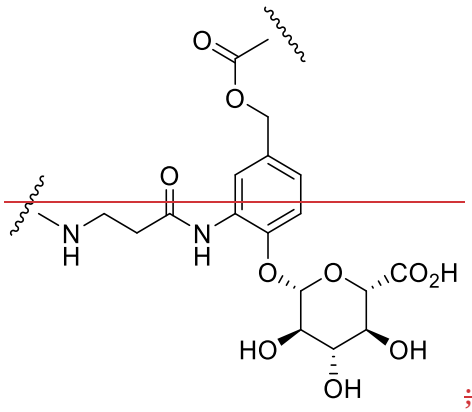
$CH(CH_3)CN$, $-C(CH_3)_2CN$, $-CH_2CN$, $-CH_2NH_2$, $-CH_2NHSO_2CH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-COCH_3$, $-CO_2CH_3$, $-CO_2C(CH_3)_3$, $-COCH(OH)CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $-NHC(=NH)H$, $-NHC(=NH)CH_3$, $-NHC(=NH)NH_2$, $-NHC(=O)NH_2$, $-NO_2$, =O, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH_2N(CH_3)_2$, $-O(CH_2CH_2O)_n-(CH_2)_mCO_2H$, $-O(CH_2CH_2O)_nH$, $-OP(O)(OH)_2$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-S(O)_2CH_3$, and $-S(O)_3H$.

~~31~~15. The aminobenzazepine-linker compound of claim ~~30~~14 wherein PEP has the formula:

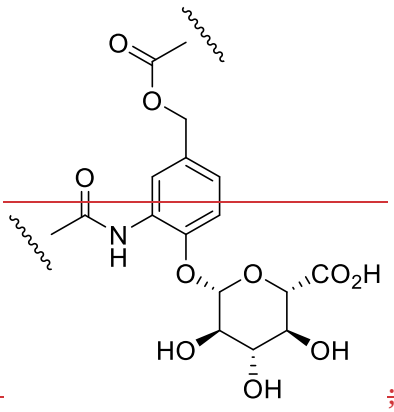


wherein AA_1 and AA_2 are independently selected from a side chain of a naturally-occurring amino acid.

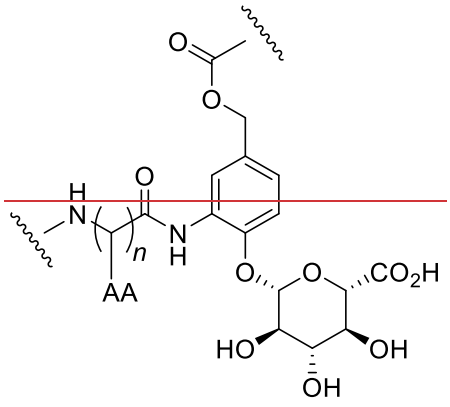
~~32. The aminobenzazepine-linker compound of claim 30 wherein PEP is selected from the groups:~~



~~;~~



~~; and~~



~~where n is 1 or more, and AA is an amino acid side chain.~~

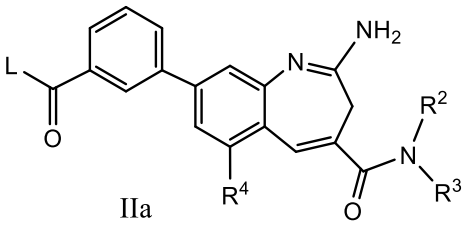
~~33. The aminobenzazepine-linker compound of any one of claims 30 to 32 wherein AA_1 and AA_2 are independently selected from a side chain of a naturally-occurring amino acid.~~

~~34~~16. The aminobenzazepine-linker compound of ~~any one of~~ claim~~s 30~~ 14 ~~to~~or ~~32~~ 15 wherein AA_1 and AA_2 are independently selected from H, $–CH_3$, $–CH(CH_3)_2$, $–CH_2(C_6H_5)$, $–CH_2CH_2CH_2CH_2NH_2$, $–CH_2CH_2CH_2NHC(NH)NH_2$, $–CH_2CH(CH_3)_2$, $–CH_2SO_3H$, and $–CH_2CH_2CH_2NHC(O)NH_2$.

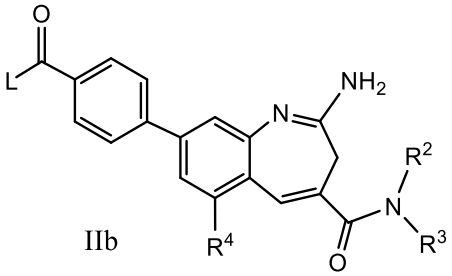
~~35~~17. The aminobenzazepine-linker compound of claim ~~34~~ 16 wherein AA_1 is $–CH(CH_3)_2$, and AA_2 is $–CH_2CH_2CH_2NHC(O)NH_2$.

~~36~~18. The aminobenzazepine-linker compound ~~of any one~~ of claim~~s 30~~ 14 ~~to~~or ~~32~~ 15 wherein AA_1 and AA_2 are independently selected from GlcNAc aspartic acid, $–CH_2SO_3H$, and $–CH_2OPO_3H$.

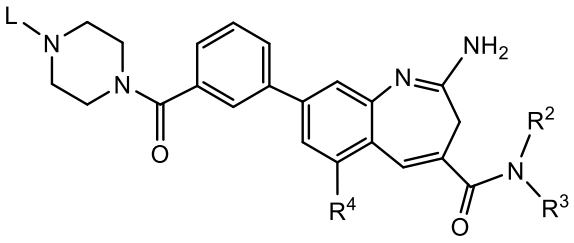
~~37~~19. The aminobenzazepine-linker compound ~~of any one~~ of claim~~s 30~~ 14 ~~to~~or ~~32~~15 selected from Formulas IIa-~~d~~h:



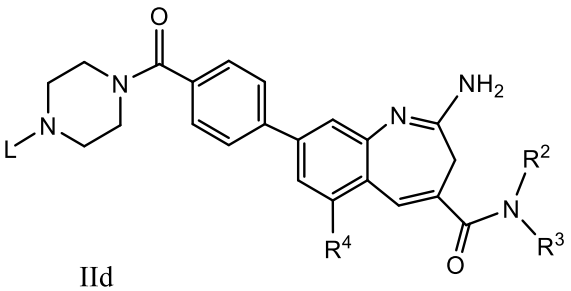
IIa



IIb



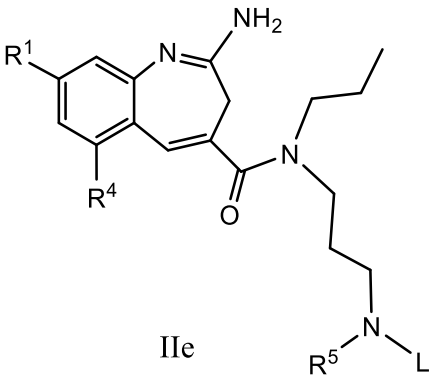
IIc



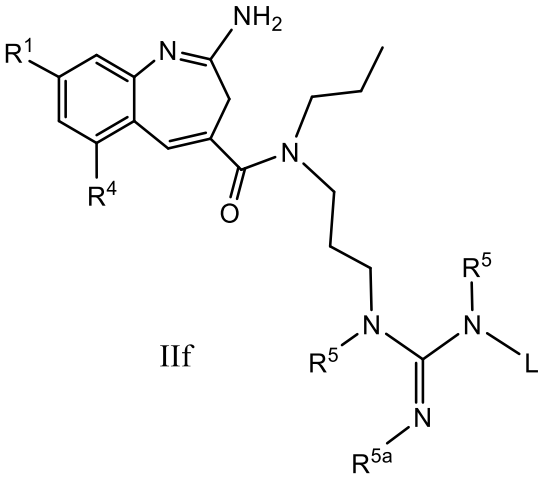
IId

~~.~~

~~38. The aminobenzazepine-linker compound of any one of claims 30 to 32 selected from Formulas IIe and IIf:~~



IIe

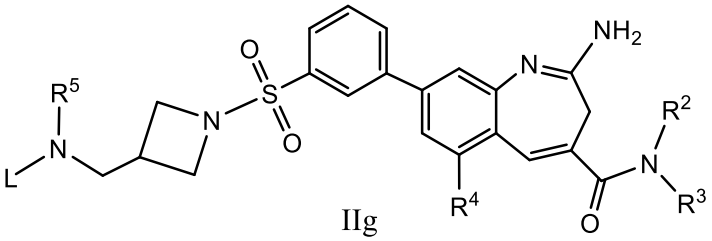


IIf

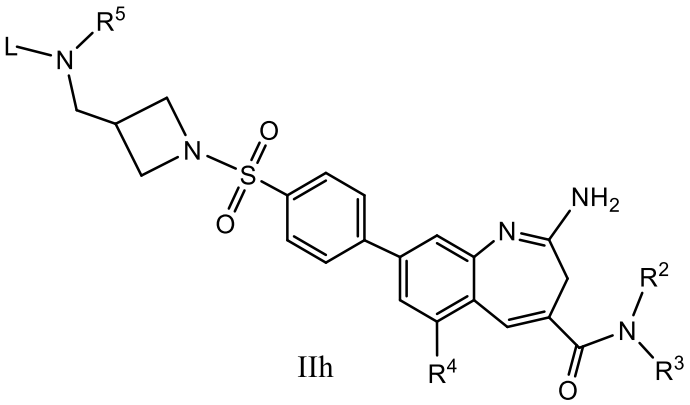
where R^{5a} of Formula If is selected from the group consisting of phenyl and pyridyl, optionally substituted with one or more groups selected from F, Cl, Br, I, –CN, $–NO_2$ and $–OCH_3$~~.~~;

~~39. The aminobenzazepine-linker compound of claim 38 wherein L is Q–C(=O)–(PEG)– or Q–C(=O)–(PEG)–C(=O)–.~~

~~40. The aminobenzazepine-linker compound of any one of claims 30 to 32 selected from Formulas IIg and IIh:~~



IIg



IIh

.

~~41~~20. The aminobenzazepine-linker compound of claim ~~40~~ 19 wherein L is –C(=O)–(PEG)–C(=O)–(PEP)–.

~~42~~21. The aminobenzazepine-linker compound of any one of claims ~~30~~14 to ~~41~~20 wherein R^2 and R^3 are each C_1-C_8 alkyl.

~~43~~22. The aminobenzazepine-linker compound of claim ~~42~~21 wherein R^2 and R^3 are each $-CH_2CH_2CH_3$.

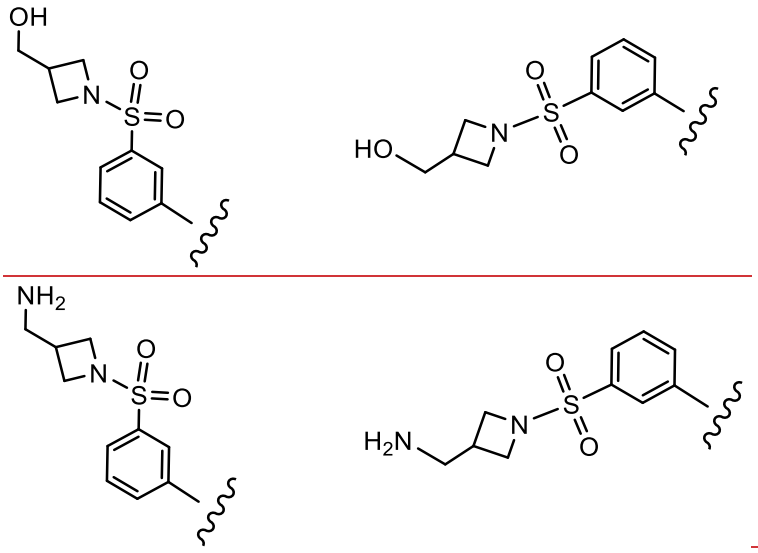
~~44~~23. The aminobenzazepine-linker compound of claim ~~43~~22 wherein X^2 and X^3 are each a bond, and R^2 or R^3 is $-O-(C_1\text{-}C_{12}$ alkyl).

~~45~~24. The aminobenzazepine-linker compound of claim ~~44~~23 wherein R^2 or R^3 is $-OCH_2CH_3$.

~~46. The aminobenzazepine-linker compound of any one of claims 30 to 32 wherein one of R^1 and R^4 is selected from $-(C_6\text{-}C_{20}$ aryldiyl$)\text{-}S(=O)_2\text{-}(C_2\text{-}C_{20}$ heterocyclyldiyl$)\text{-}(C_1\text{-}C_{12}$ alkyldiyl$)\text{-}N(R^5)_2$ and $-(C_6\text{-}C_{20}$ aryldiyl$)\text{-}S(=O)_2\text{-}(C_2\text{-}C_{20}$ heterocyclyldiyl$)\text{-}(C_1\text{-}C_{12}$ alkyldiyl$)\text{-}OH$.~~

~~47. The aminobenzazepine-linker compound of claim 46 wherein $C_6\text{-}C_{20}$ aryldiyl is phenyldiyl and $C_2\text{-}C_{20}$ heterocyclyldiyl is azetidindiyl.~~

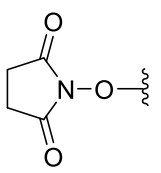
~~48. The aminobenzazepine-linker compound of any one of claims 30 to 32 wherein one of R^1 and R^4 is selected from the formulas:~~



~~49. The aminobenzazepine-linker compound of any one of claims 30 to 32 wherein one of R^1 and R^4 is $-C(=O)NR^5\text{-}(C_1\text{-}C_{20}$ heteroaryldiyl$)\text{-}(C_2\text{-}C_{20}$ heterocyclyldiyl$)\text{-}C(=O)NR^5\text{-}(C_1\text{-}C_{12}$ alkyldiyl$)\text{-}NR^5\text{-}L$.~~

~~50. The aminobenzazepine-linker compound of claim 49 wherein $C_1\text{-}C_{20}$ heteroaryldiyl is pyridindiyl and $C_2\text{-}C_{20}$ heterocyclyldiyl is piperidiyl.~~

~~51~~25. The aminobenzazepine-linker compound of ~~any one of~~ claim~~s~~ ~~30~~14 ~~to~~or ~~32~~15 wherein Q is selected from: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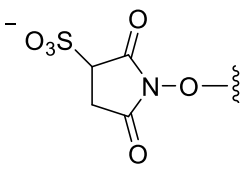
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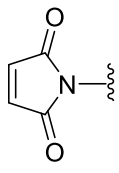
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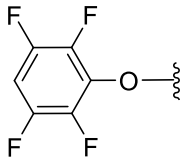
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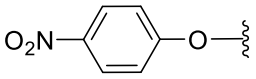
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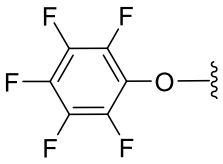
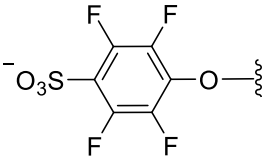

, and

.

~~52~~26. The aminobenzazepine-linker compound of claim ~~30~~14 selected from Table 2a, Table 2b, and Table 2c.

~~53. The aminobenzazepine-linker compound of claim 30 selected from Table 2b.~~

~~54. The aminobenzazepine-linker compound of claim 30 selected from Table 2c.~~

~~55~~27. An immunoconjugate prepared by conjugation of an antibody with an aminobenzazepine-linker compound of ~~any one of~~ claim~~s~~ 26~~52 to 54~~.

~~56~~28. A pharmaceutical composition comprising a therapeutically effective amount of an immunoconjugate according to any one of claims 1-~~29~~13 and one or more pharmaceutically acceptable diluent, vehicle, carrier or excipient.

~~57. A method for treating cancer comprising administering a therapeutically effective amount of the pharmaceutical composition according to claim 56 to a patient in need thereof.~~

~~58. The method of claim 57, wherein the cancer is susceptible to a pro-inflammatory response induced by TLR7 and/or TLR8 agonism.~~

~~59. The method of claim 57, wherein the cancer is a PD-L1-expressing cancer.~~

~~60. The method of claim 57, wherein the cancer is a HER2-expressing cancer.~~

~~61. The method of claim 57, wherein the cancer is a CEA-expressing cancer.~~

~~62. The method of any one of claims 57-61, wherein the cancer is selected from 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.~~

~~63. The method of claim 62, wherein the breast cancer is triple-negative breast cancer.~~

~~64. The method of claim 62, wherein the Merkel cell carcinoma cancer is metastatic Merkel cell carcinoma.~~

~~65. The method of claim 62, wherein the gastric cancer is HER2 overexpressing gastric cancer.~~

~~66. The method of claim 62, wherein the cancer is gastroesophageal junction adenocarcinoma.~~

~~67~~29. Use of an immunoconjugate according to any one of claims 1-~~29~~ 13 for treating cancer, wherein the cancer is selected from 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.

~~68~~30. A method of preparing an immunoconjugate of Formula I of claim 1 wherein an aminobenzazepine-linker compound of Formula II of claim ~~30~~ 14 is conjugated with the antibody.

~~69. The immunoconjugate of claim 2 wherein the antibody construct is a Type A PD-L1 antibody and comprises an immunoglobulin heavy chain variable region polypeptide and an immunoglobulin light chain variable region polypeptide, wherein:~~

~~the immunoglobulin heavy chain variable region polypeptide comprises a complementarity determining region 1 (HCDR1) comprising any one of Type A SEQ ID NOs: 1-23, a complementarity determining region 2 (HCDR2) comprising any one of SEQ ID NOs: 24-57, and a complementarity determining region 3 (HCDR3) comprising any one of SEQ ID NOs: 58-95; or~~

~~the immunoglobulin light chain variable region polypeptide comprises a complementarity determining region 1 (LCDR1) comprising any one of SEQ ID NOs: 96-128, a complementarity determining region 2 (LCDR2) comprising any one of SEQ ID NOs: 129-151, and a complementarity determining region 3 (LCDR3) comprising any one of SEQ ID NOs: 152-155;~~

~~wherein the sequences are from Figures 1-4.~~

~~70. The immunoconjugate of claim 2 wherein the antibody construct is a Type A PD-L1 antibody and comprises an immunoglobulin heavy chain variable region of any one of SEQ ID NOs: 223-264 or at least the CDRs thereof; and an immunoglobulin light chain variable region of any one of SEQ ID NOs: 265-306 or at least the CDRs thereof;~~

~~wherein the sequences are from Figures 1-4.~~

~~71. The immunoconjugate of claim 2 wherein the antibody construct is a Type A PD-L1 antibody and comprises an immunoglobulin heavy chain variable region polypeptide with an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 223-264, and an~~

~~immunoglobulin light chain variable region polypeptide with an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 265-306;~~

~~wherein the sequences are from Figures 1-4.~~

~~72. The immunoconjugate of claim 2 wherein the antibody construct is a Type A PD-L1 antibody and comprises the heavy and light chain immunoglobulin polypeptides, or at least the CDRs thereof, of a PD-L1 binding agent of Figures 1A-D.~~

~~73. The immunoconjugate of claim 2 wherein the antibody construct is a Type B PD-L1 antibody and comprises an immunoglobulin heavy chain variable region polypeptide and an immunoglobulin light chain variable region polypeptide, wherein:~~

~~the immunoglobulin heavy chain variable region polypeptide comprises a complementarity determining region 1 (HCDR1) comprising any one of SEQ ID NOs: 308-321, a complementarity determining region 2 (HCDR2) comprising any one of SEQ ID NOs: 322-338, and a complementarity determining region 3 (HCDR3) comprising any one of SEQ ID NOs: 339-359; or~~

~~the immunoglobulin light chain variable region polypeptide comprises a complementarity determining region 1 (LCDR1) comprising any one of SEQ ID NOs: 360-374, a complementarity determining region 2 (LCDR2) comprising any one of SEQ ID NOs: 131 and 375-386, and a complementarity determining region 3 (LCDR3) comprising any one of SEQ ID NOs: 387-398;~~

~~wherein the sequences are from Figures 5-8.~~

~~74. The immunoconjugate of claim 2 wherein the antibody construct is a Type B PD-L1 antibody and comprises an immunoglobulin heavy chain variable region of any one of SEQ ID NOs: 430-450 or at least the CDRs thereof; and an immunoglobulin light chain variable region of any one of SEQ ID NOs: 451-471 or at least the CDRs thereof;~~

~~wherein the sequences are from Figures 5-8.~~

~~75. The immunoconjugate of claim 2 wherein the antibody construct is a Type B PD-L1 antibody and comprises an immunoglobulin heavy chain variable region polypeptide with an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 430-450, and an immunoglobulin light chain variable region polypeptide with an amino acid sequence that is at least 90% identical to any one of SEQ ID NOs: 451-471;~~

~~wherein the sequences are from Figures 5-8.~~

~~76. The immunoconjugate of claim 2 wherein the antibody construct is a Type B PD-L1 antibody and comprises the heavy and light chain immunoglobulin polypeptides, or at least the CDRs thereof, of a PD-L1 binding agent of Figures 5A-B.~~