AMIDE-LINKED, AMINOBENZAZEPINE IMMUNOCONJUGATES, AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This non-provisional application claims the benefit of priority to U.S. Provisional Application No. 62/908,253, filed 30 September 2019, 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 September 21, 2020, is named 17019_004WO1_SL.txt and is 54,747 bytes in size.

FIELD OF THE INVENTION

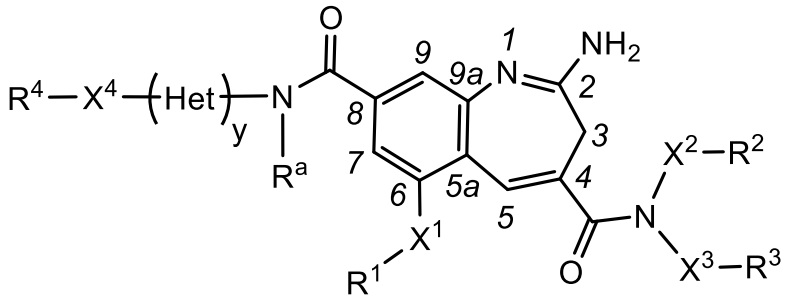
The invention relates generally to an immunoconjugate comprising an antibody conjugated to one or more 8-amido-2-aminobenzazepine molecules.

BACKGROUND OF THE INVENTION

New compositions and methods for the delivery of antibodies and dendritic cell/myeloid cell 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 8-amido-2-aminobenzazepine derivatives. The ~~invention~~ disclosure is further directed to 8-amido-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 the 8-position of an 8-amido-2-aminobenzazepine moiety having the formula:



where one of R^1, R^2, R^3 and R^4 is attached to L, y is 0 or 1, and Het is a 5- or 6-membered monocyclic heterocyclyldiyl or a 5- or 6-membered monocyclic heteroaryldiyl. The positions of the 3H-benzo[b]azepine structure are numbered according to IUPAC conventions. The R^a, X^{1-4} and R^{1-4} substituents are defined herein.

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 8-amido-2-aminobenzazepine moieties.

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

$$Ab–[L–8AmBza]_p \qquad I$$

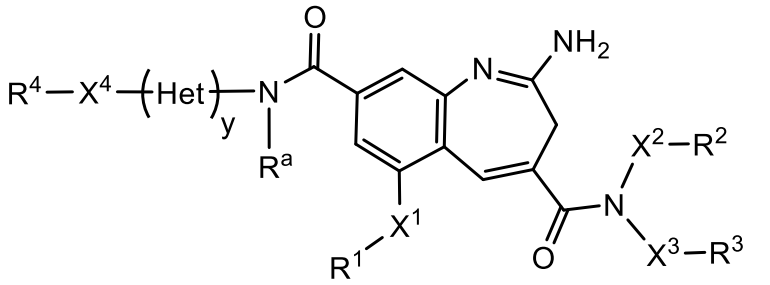
or a pharmaceutically acceptable salt thereof,

wherein:

Ab is the antibody;

p is an integer from 1 to 8;

8AmBza is the 8-amido-2-aminobenzazepine moiety having the formula:



y is 0 or 1;

Het is selected from the group consisting of heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl;

R^a is H or forms Het with the nitrogen atom it is bound to;

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} 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)–(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)–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_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_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:

–C(=O)–(PEG)–C(=O)–(PEP)–;

–C(=O)–(PEG)–NR^5–;

–C(=O)–(PEG)–NR^5–(PEG)–C(=O)–(PEP)–;

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

–C(=O)–(PEG)–C(=O)–;

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

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

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

–C(=O)–(PEG)–;

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

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

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

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

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

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

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

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

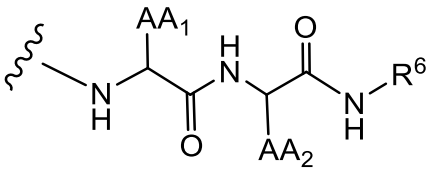
–C(=O)–(PEG)–C(=O)–(PEP)–NR^5(C$_1$-C$_{12}$ alkyldiyl)–;

–C(=O)–(PEG)–C(=O)–(PEP)–NR^5(C$_1$-C$_{12}$ alkyldiyl)NR^{5}C(=O)–(C$_2$-C$_5$ monoheterocyclyldiyl)–; and

–(succinimidyl)–(CH$_2$)$_m$–C(=O)–(PEP)–NR^5(C$_1$-C$_{12}$ alkyldiyl)NR^{5}C(=O)–(C$_2$-C$_5$ monoheterocyclyldiyl)–;

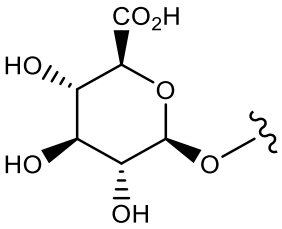
PEG has the formula: –(CH$_2$CH$_2$O)$_n$–(CH$_2$)$_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

PEP has the formula:



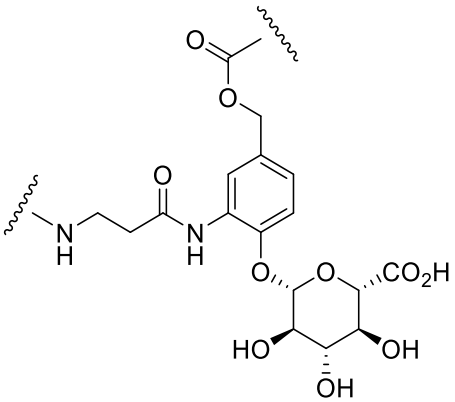
where AA$_1$ and AA$_2$ are independently selected from an amino acid side chain, or AA$_1$ or AA$_2$ and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment and;

R^6 is selected from the group consisting of C$_6$-C$_{20}$ aryldiyl and C$_1$-C$_{20}$ heteroaryldiyl, substituted with –CH$_2$O–C(=O)– and optionally with:

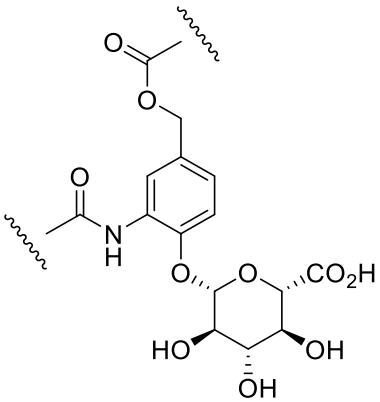


; and

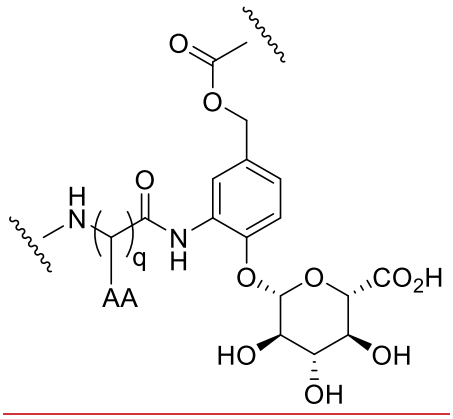
MCgluc is selected from the groups:



;



; and

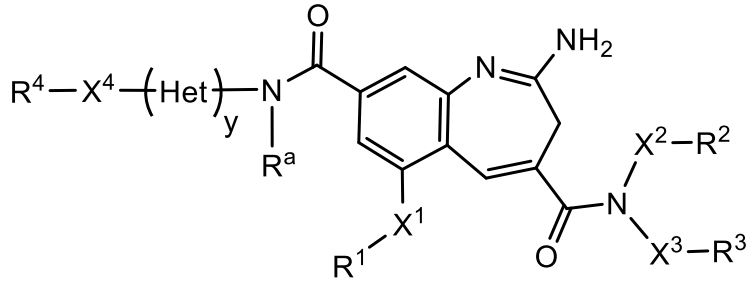


where q is 1 to 8, and AA is an amino acid side chain;

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, –$NHCH_3$, –$N(CH_3)_2$, –$NHCOCH_3$, –$N(CH_3)COCH_3$, –$NHS(O)_2CH_3$, –$N(CH_3)C(CH_3)_2CONH_2$, –$N(CH_3)CH_2CH_2S(O)_2CH_3$, –$NO_2$, =O, –OH, –$OCH_3$, –$OCH_2CH_3$, –$OCH_2CH_2OCH_3$, –$OCH_2CH_2OH$, –$OCH_2CH_2N(CH_3)_2$, –$O(CH_2CH_2O)_n$–$(CH_2)_mCO_2H$, –$O(CH_2CH_2O)_nH$, –$OP(O)(OH)_2$, –$S(O)_2N(CH_3)_2$, –$SCH_3$, –$S(O)_2CH_3$, and –$S(O)_3H$.

Another ~~aspect~~ example of the ~~invention~~ disclosure is an 8-amido-2-aminobenzazepine-linker compound.

In another aspect of the disclosure, there is provided an 8-amido-2-aminobenzazepine-linker compound of Formula II:



II

wherein

y is 0 or 1;

Het is selected from the group consisting of heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl;

R^a is H or forms Het with the nitrogen atom it is bound to;

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} 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)–(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)–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_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_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)–C(=O)–(PEP)–;

Q–C(=O)–(PEG)–NR^5–;

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

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

Q–C(=O)–(PEG)–C(=O)–;

Q–C(=O)–(PEG)–NR^{5}CH(AA_1)C(=O)–(PEG)–C(=O)–(PEP)–;

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)–(PEG)–;

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

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

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

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

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

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

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

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

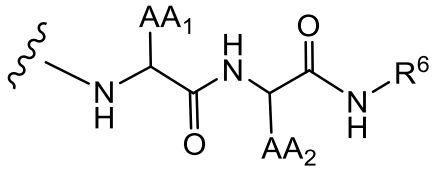
Q–C(=O)–(PEG)–C(=O)–(PEP)–NR^5(C_1-C_{12} alkyldiyl)–;

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

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

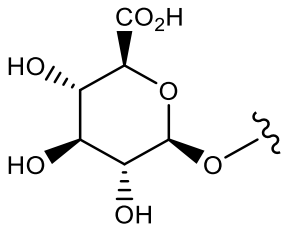
where PEG has the formula: –$(CH_2CH_2O)_n$–$(CH_2)_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

PEP has the formula:



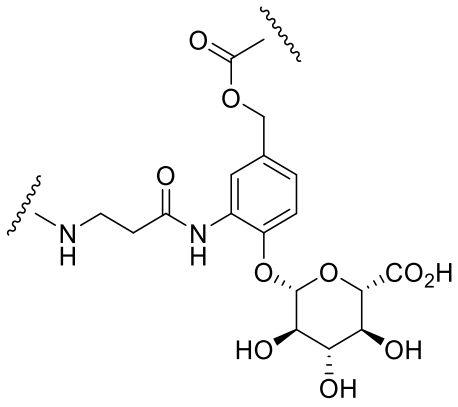
where AA_1 and AA_2 are independently selected from an amino acid side chain, or AA_1 or AA_2 and an adjacent nitrogen atom form a 5-membered ring proline amino acid,, and the wavy line indicates a point of attachment and;

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:

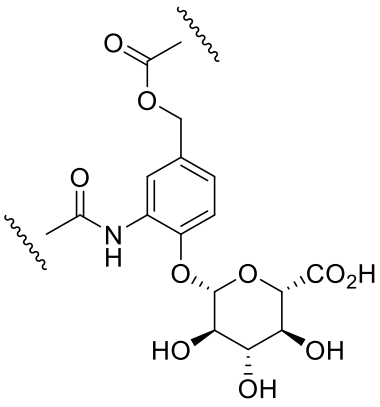


; and

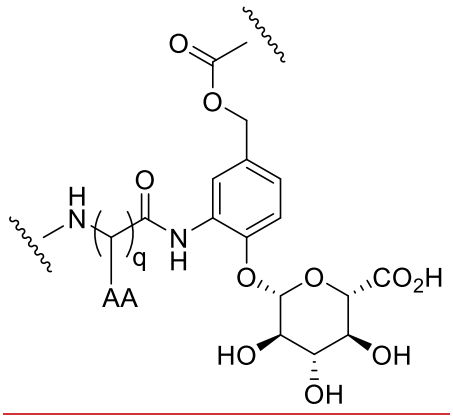
MCgluc is selected from the groups:



;



; 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, $-CN$, $-CH_3$, $-CH_2CH_3$, $-CH=CH_2$, $-C\equiv CH$, $-C\equiv CCH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CH_2OP(O)(OH)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CN$, $-C(CH_3)_2CN$, $-CH_2CN$, $-CH_2NH_2$, $-CH_2NHSO_2CH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CO_2H$, $-COCH_3$, $-CO_2CH_3$, $-CO_2C(CH_3)_3$, $-COCH(OH)CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $-NO_2$, $=O$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH_2N(CH_3)_2$, $-O(CH_2CH_2O)_n-(CH_2)_mCO_2H$, $-O(CH_2CH_2O)_nH$, $-OP(O)(OH)_2$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-S(O)_2CH_3$, and $-S(O)_3H$.

Another ~~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 8-amido-2-aminobenzazepine moieties.

In another aspect of the disclosure, there is provided an immunoconjugate as defined herein for use as a medicament.

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

In another aspect of the disclosure, there is provided a use of an immunoconjugate as defined herein in the manufacture of a medicament for the treatment of cancer.

Another ~~aspect~~ example of the ~~invention~~ disclosure is a method of preparing an immunoconjugate by conjugation of one or more 8-amido-2-aminobenzazepine moieties with an antibody.

In another aspect of the disclosure, there is provided a method of preparing an immunoconjugate of Formula I as defined herein wherein an 8-amido-2-aminobenzazepine-linker compound of Formula II as defined herein is conjugated with the antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A shows *in vitro* TLR8 potency of BZA-1 and BZA-2, agonists in Human HEK293 reporter cells. BZA-1: 2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-N,N-dipropyl-3H-benzo[b]azepine-4-carboxamide. BZA-2: tert-butyl (3-(2-amino-8-(3-((3-(hydroxymethyl)azetidin-1-yl)sulfonyl)phenyl)-N-propyl-3H-benzo[b]azepine-4-carboxamido)propyl)carbamate.

Figure 1B shows *in vitro* TLR7 potency of BZA-1 and BZA-2, agonists in Human HEK293 reporter cells.

Figure 1C shows *in vitro* TLR8 potency of BZA-3 and BZA-4, agonists in Human HEK293 reporter cells. BZA-3: 2-amino-8-benzamido-N,N-dipropyl-3H-benzo[b]azepine-4-

CLAIMS:

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

$$Ab–[L–8AmBza]_p \qquad I$$

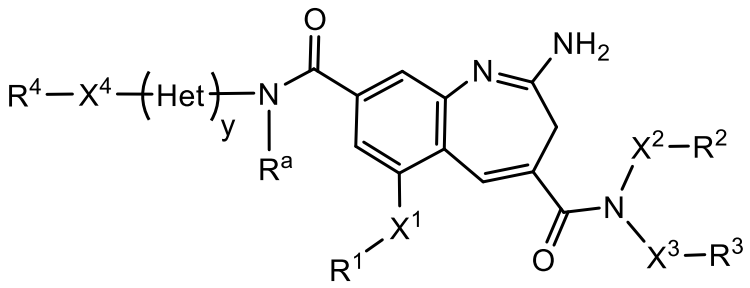
or a pharmaceutically acceptable salt thereof,

wherein:

Ab is the antibody;

p is an integer from 1 to 8;

8AmBza is the 8-amido-2-aminobenzazepine moiety having the formula:



y is 0 or 1;

Het is selected from the group consisting of heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl;

R^a is H or forms Het with the nitrogen atom it is bound to;

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} 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)–(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)–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_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_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:

–C(=O)–(PEG)–C(=O)–(PEP)–;

–C(=O)–(PEG)–NR^5–;

–C(=O)–(PEG)–NR^5–(PEG)–C(=O)–(PEP)–;

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

–C(=O)–(PEG)–C(=O)–;

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

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

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

–C(=O)–(PEG)–;

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

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

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

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

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

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

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

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

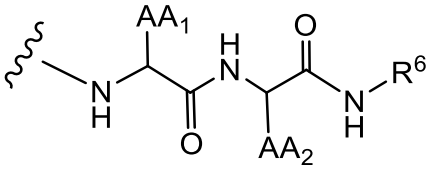
–C(=O)–(PEG)–C(=O)–(PEP)–NR^5(C_1-C_{12} alkyldiyl)–;

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

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

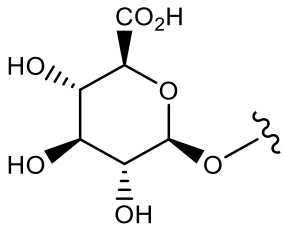
PEG has the formula: –$(CH_2CH_2O)_n$–$(CH_2)_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

PEP has the formula:



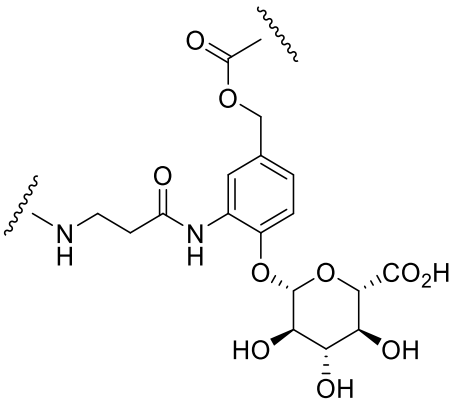
where AA_1 and AA_2 are independently selected from an amino acid side chain, or AA_1 or AA_2 and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment and;

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:

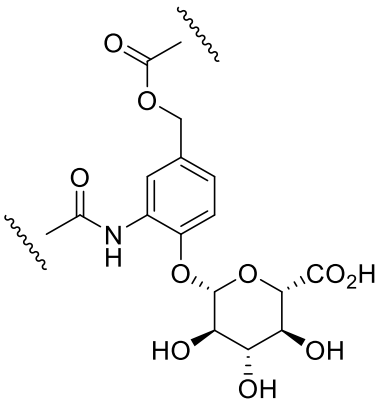


; and

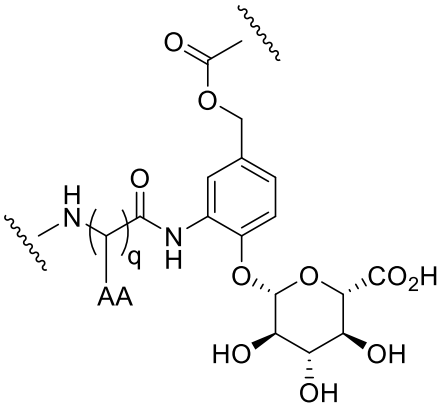
MCgluc is selected from the groups:



;



; and



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

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, –$NHCH_3$, –$N(CH_3)_2$, –$NHCOCH_3$, –

$N(CH_3)COCH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $-NO_2$, =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 PD-L1.

3. The immunoconjugate of claim 2 wherein the antibody is selected from the group consisting of atezolizumab, durvalumab, and avelumab, 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.

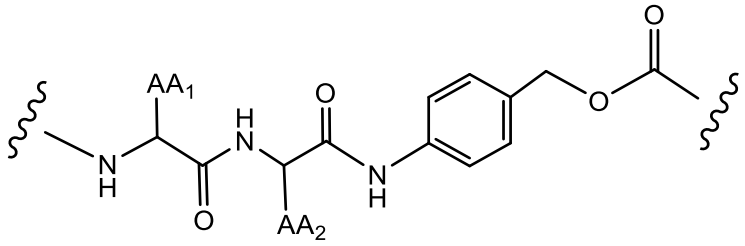
6. The immunoconjugate of claim 1 wherein the antibody is an antibody construct that has an antigen binding domain that binds CEA.

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

8. The immunoconjugate of any one of claims 1 to 7 wherein y is 0.

9. The immunoconjugate of any one of claims 1 to 7 wherein y is 1.

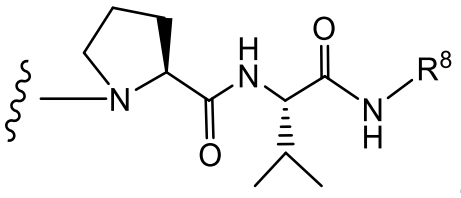
10. The immunoconjugate of any one of claims 1 to 7 wherein PEP has the formula:



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

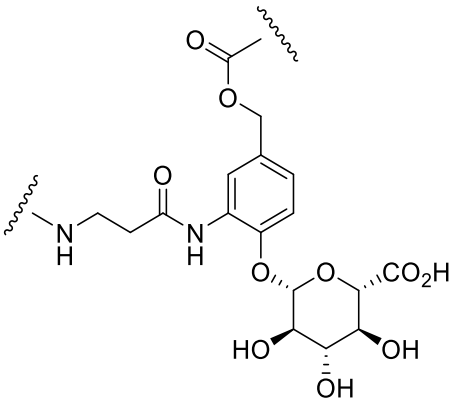
11. The immunoconjugate of claim 10 wherein AA_1 or AA_2 with an adjacent nitrogen atom form a 5-membered ring proline amino acid.

12. The immunoconjugate of claim 11 wherein PEP has the formula:



.

13. The immunoconjugate of any one of claims 1 to 7 wherein MCgluc has the formula:



.

14. The immunoconjugate of claim 10 wherein AA_1 and AA_2 are independently selected from H, $–CH_3$, $–CH(CH_3)_2$, $–CH_2(C_6H_5)$, $–CH_2CH_2CH_2CH_2NH_2$, $–CH_2CH_2CH_2NHC(NH)NH_2$, $–CHCH(CH_3)CH_3$, $–CH_2SO_3H$, and $–CH_2CH_2CH_2NHC(O)NH_2$.

15. The immunoconjugate of claim 10 wherein AA_1 is $–CH(CH_3)_2$, and AA_2 is $–CH_2CH_2CH_2NHC(O)NH_2$.

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

17. 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.

18. 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)$–N(R^5)CO_2R^5$, and $–O–(C_1$-C_{12} alkyl)$–N(R^5)CO_2R^5$.

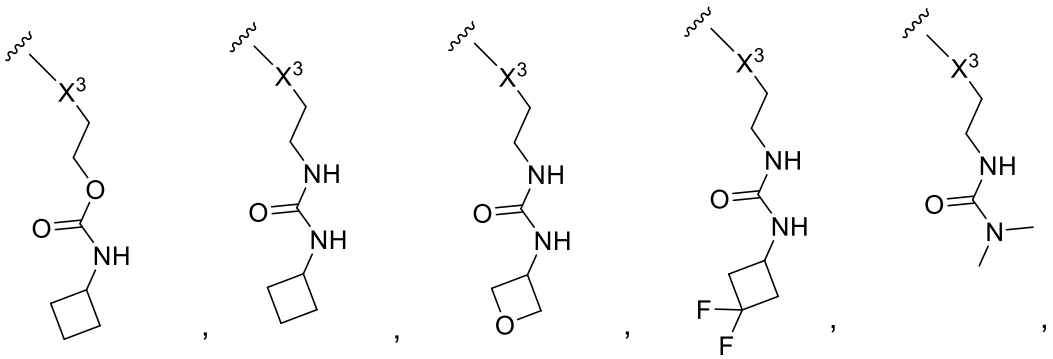
19. The immunoconjugate of claim 18 wherein R^2 and R^3 are each independently selected from $–CH_2CH_2CH_3$, $–OCH_2CH_3$, $–CH_2CH_2CF_3$, and $–CH_2CH_2CH_2OH$.

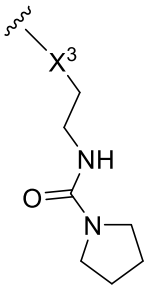
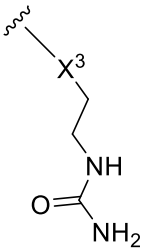
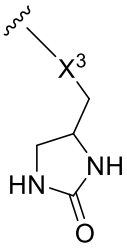
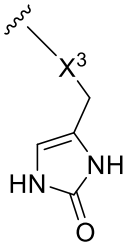
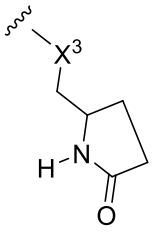
20. The immunoconjugate of claim 18 wherein R^2 is C_1-C_8 alkyl and R^3 is $–(C_1$-C_8 alkyldiyl)$–N(R^5)CO_2R^4$.

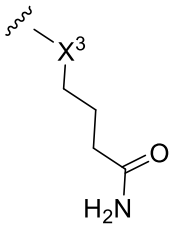
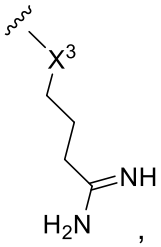
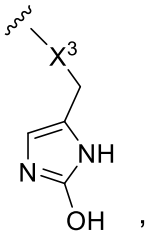
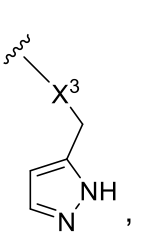
21. The immunoconjugate of claim 20 wherein R^2 is $–CH_2CH_2CH_3$ and R^3 is $–CH_2CH_2CH_2NHCO_2(t\text{-Bu})$.

22. The immunoconjugate of claim 23 wherein R^2 and R^3 are each $–CH_2CH_2CH_3$.

23. The immunoconjugate of claim 17 wherein X^3-R^3 is selected from the group consisting of:


,
,
,
,
,


, 
, 
, 
, 
,


, 
, 
, 
,

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

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

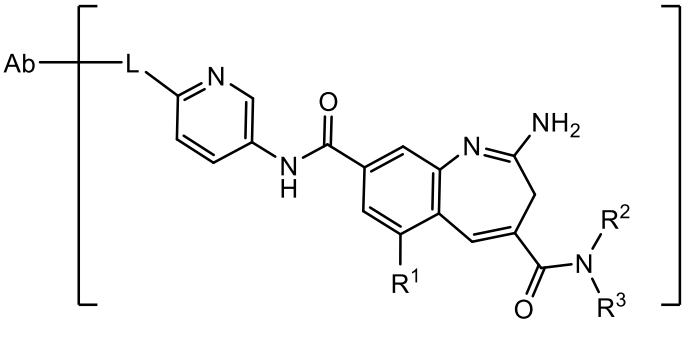
–C(=O)–(PEG)–C(=O)–NR^5(C_1-C_{12} alkyldiyl)NR^5C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

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

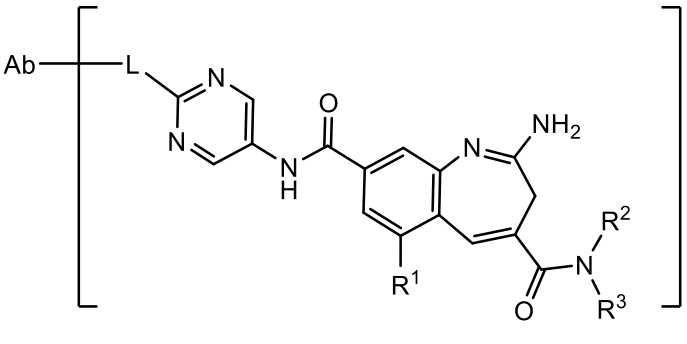
–C(=O)–(PEG)–C(=O)–(PEP)–NR^5(C_1-C_{12} alkyldiyl)NR^5C(=O)–(C_2-C_5 monoheterocyclyldiyl)–; and

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

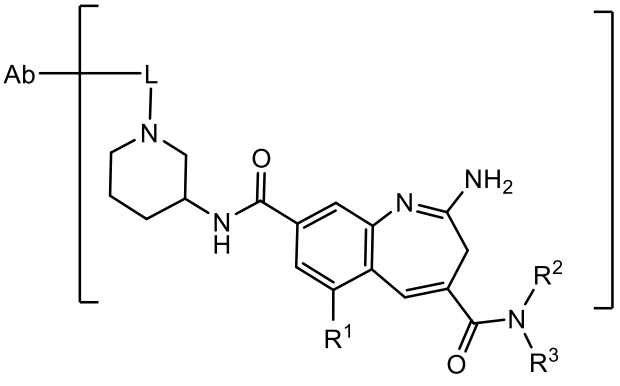
28. The immunoconjugate of any one of claims 1 to 7 selected from Formulae Ia-d:



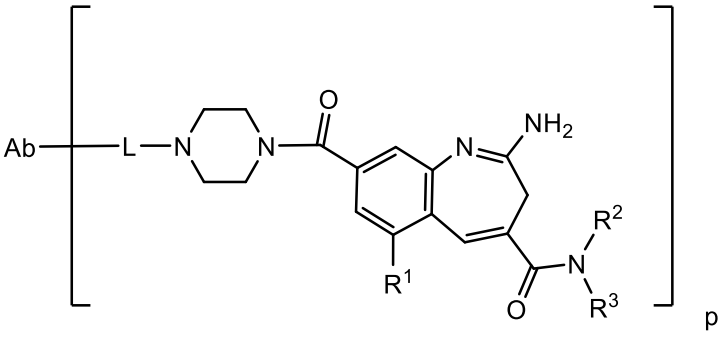
Ia;



Ib;

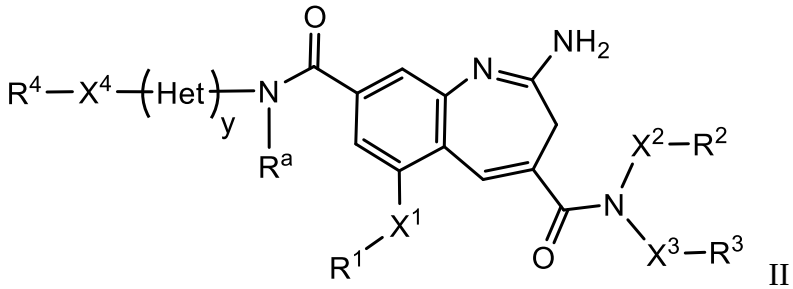


Ic; and



Id.

29. An 8-amido-2-aminobenzazepine-linker compound of Formula II:



II

wherein

y is 0 or 1;

Het is selected from the group consisting of heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl;

R^a is H or forms Het with the nitrogen atom it is bound to;

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} 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)–(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)–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_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;

–$N(R^5)C(=O)$–*;

–$N(R^5)C(=O)N(R^5)_2$;

–$N(R^5)C(=O)N(R^5)$–*;

–$N(R^5)CO_2R^5$;

–$NR^5C(=NR^{5a})N(R^5)_2$;

–$NR^5C(=NR^{5a})N(R^5)$–*;

–$NR^5C(=NR^{5a})R^5$;

–$N(R^5)$–(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:

Q–C(=O)–(PEG)–C(=O)–(PEP)–;

Q–C(=O)–(PEG)–NR^5–;

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

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

Q–C(=O)–(PEG)–C(=O)–;

Q–C(=O)–(PEG)–$NR^5CH(AA_1)$C(=O)–(PEG)–C(=O)–(PEP)–;

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)–(PEG)–;

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

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

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

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

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

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

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

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

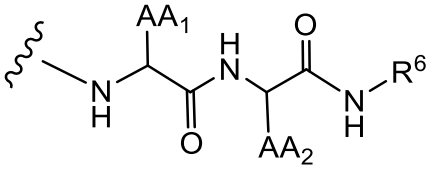
Q–C(=O)–(PEG)–C(=O)–(PEP)–NR^5(C_1-C_{12} alkyldiyl)–;

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

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

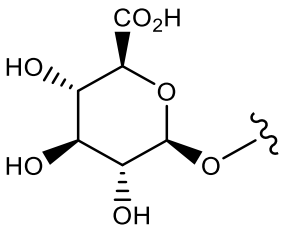
where PEG has the formula: –$(CH_2CH_2O)_n$–$(CH_2)_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

PEP has the formula:



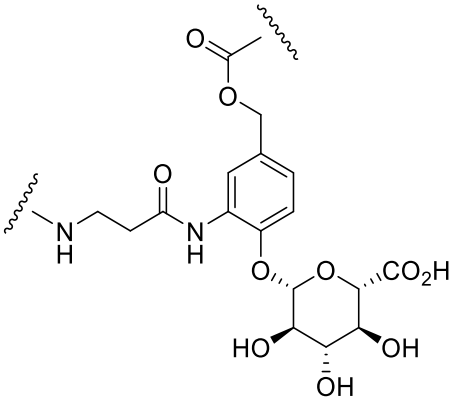
where AA_1 and AA_2 are independently selected from an amino acid side chain, or AA_1 or AA_2 and an adjacent nitrogen atom form a 5-membered ring proline amino acid,, and the wavy line indicates a point of attachment and;

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:

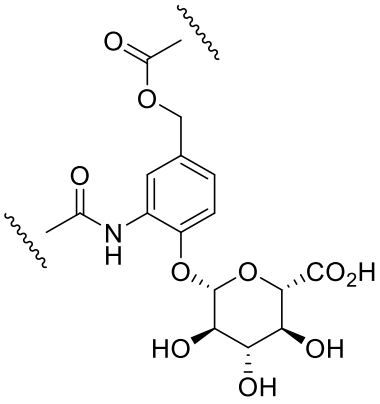


; and

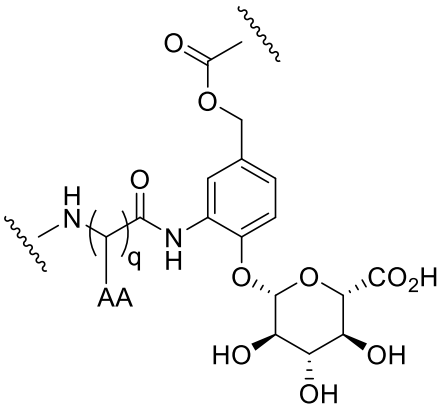
MCgluc is selected from the groups:



;



; 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^-;

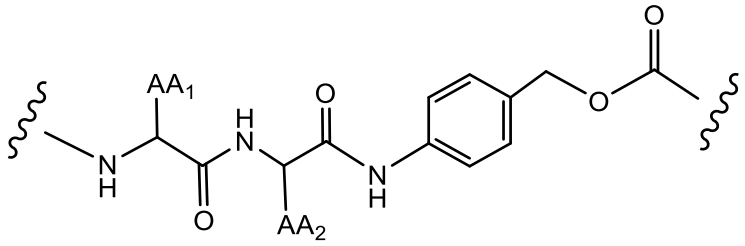
where alkyl, alkyldiyl, alkenyl, alkenyldiyl, alkynyl, alkynyldiyl, aryl, aryldiyl carbocyclyl, carbocyclyldiyl, heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, –CH_3, –CH_2CH_3, –$CH{=}CH_2$, –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, –$CO_2C(CH_3)_3$, –$COCH(OH)CH_3$, –$CONH_2$, –

$CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCOCH_3$, $-N(CH_3)COCH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $-NO_2$, =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 $-S(O)_3H$.

30. The 8-amido-2-aminobenzazepine-linker compound of claim 29 wherein y is 0.

31. The 8-amido-2-aminobenzazepine-linker compound of claim 29 wherein y is 1.

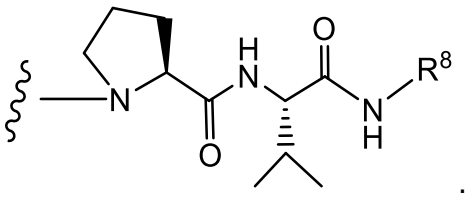
32. The 8-amido-2-aminobenzazepine-linker compound of claim 29 wherein PEP has the formula:



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

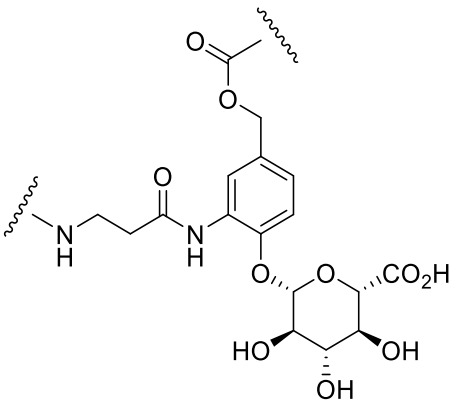
33. The 8-amido-2-aminobenzazepine-linker compound of claim 32 wherein AA_1 or AA_2 with an adjacent nitrogen atom form a 5-membered ring to form a proline amino acid.

34. The 8-amido-2-aminobenzazepine-linker compound of claim 33 wherein PEP has the formula:



.

35. The 8-amido-2-aminobenzazepine-linker compound of claim 29 wherein MCgluc has the formula:



.

36. The 8-amido-2-aminobenzazepine-linker compound of claim 32 wherein AA_1 and AA_2 are independently selected from H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2(C_6H_5)$, $-CH_2CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2NHC(NH)NH_2$, $-CHCH(CH_3)CH_3$, $-CH_2SO_3H$, and $-CH_2CH_2CH_2NHC(O)NH_2$.

37. The 8-amido-2-aminobenzazepine-linker compound of claim 32 wherein AA_1 is $-CH(CH_3)_2$, and AA_2 is $-CH_2CH_2CH_2NHC(O)NH_2$.

38. The 8-amido-2-aminobenzazepine-linker compound of claim 29 wherein X^1 is a bond, and R^1 is H.

39. The 8-amido-2-aminobenzazepine-linker compound of claim 29 wherein X^2 is a bond, and R^2 is C_1-C_8 alkyl.

40. The 8-amido-2-aminobenzazepine-linker compound of claim 29 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$)-N(R^5)CO_2R^5$.

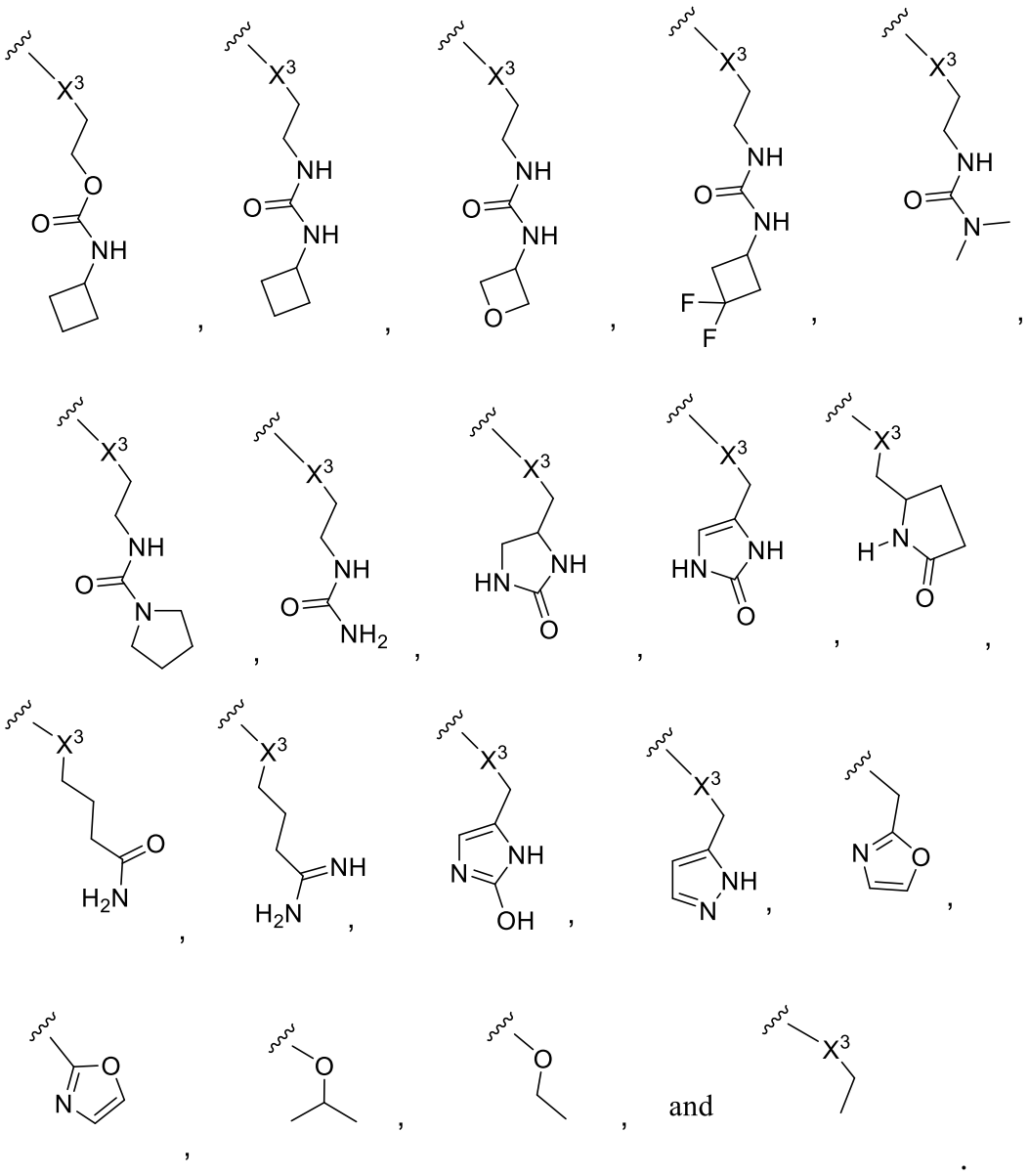
41. The 8-amido-2-aminobenzazepine-linker compound of claim 40 wherein R^2 and R^3 are each independently selected from $-CH_2CH_2CH_3$, $-OCH_2CH_3$, $-CH_2CH_2CF_3$, and $-CH_2CH_2CH_2OH$.

42. The 8-amido-2-aminobenzazepine-linker compound of claim 40 wherein R^2 is C_1-C_8 alkyl and R^3 is $-(C_1$-C_8 alkyldiyl$)-N(R^5)CO_2R^4$.

43. The 8-amido-2-aminobenzazepine-linker compound of claim 42 wherein R^2 is $-CH_2CH_2CH_3$ and R^3 is $-CH_2CH_2CH_2NHCO_2(t\text{-Bu})$.

44. The 8-amido-2-aminobenzazepine-linker compound of claim 40 wherein R^2 and R^3 are each $-CH_2CH_2CH_3$.

45. The 8-amido-2-aminobenzazepine-linker ~~5-amino-pyrazoloazepine-linker~~ compound of claim 39 wherein X^3-R^3 is selected from the group consisting of:



46. The 8-amido-2-aminobenzazepine-linker compound of claim 29 wherein Het is a 5- or 6-membered monocyclic heteroaryldiyl selected from the group consisting of pyridyldiyl, imidazolyldiyl, pyrimidinyldiyl, pyrazolyldiyl, triazolyldiyl, pyrazinyldiyl, tetrazolyldiyl, furyldiyl, thienyldiyl, isoxazolyldiyldiyl, thiazolyldiyl, oxadiazolyldiyl, oxazolyldiyl, isothiazolyldiyl, and pyrrolyldiyl.

47. The 8-amido-2-aminobenzazepine-linker compound of claim 29 wherein Het is a 5- or 6-membered monocyclic heterocyclyldiyl selected from the group consisting of morpholinyldiyl, piperidinyldiyl, piperazinyldiyl, pyrrolidinyldiyl, dioxanyldiyl,thiomorpholinyldiyl, and S-dioxothiomorpholinyldiyl.

48. The 8-amido-2-aminobenzazepine-linker compound of claim 29 wherein Het is 1,6-naphthyridyl or 1,6-naphthyridiyl.

49. The 8-amido-2-aminobenzazepine-linker compound of claim 29 wherein L is selected from the group consisting of:

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

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

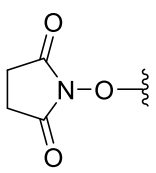
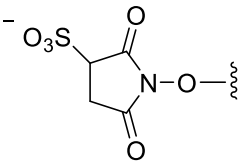
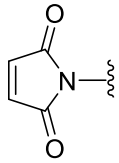
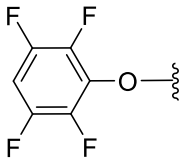
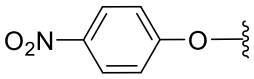
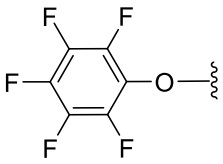
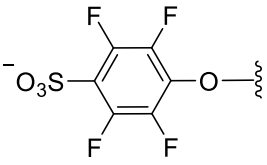
Q–C(=O)–(PEG)–C(=O)–NR^5(C_1-C_{12} alkyldiyl)NR^5C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

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

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

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

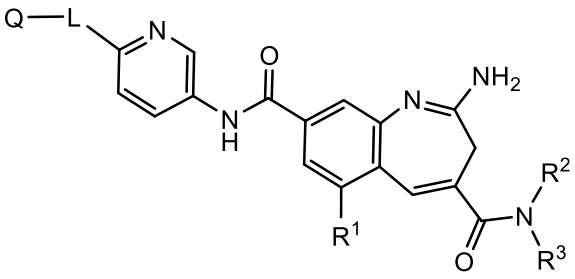
50. The 8-amido-2-aminobenzazepine-linker compound of claim 29 wherein Q is selected from:

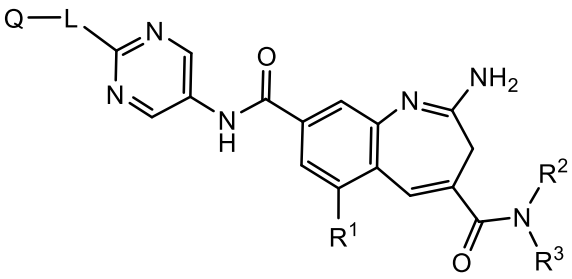

,

,

,

,

,

, and

.

51. The 8-amido-2-aminobenzazepine-linker ~~aminoquinoline-linker~~ compound of claim 29 wherein Q is phenoxy substituted with one or more F.

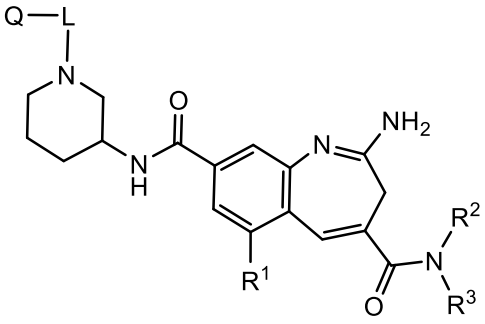
52. The 8-amido-2-aminobenzazepine-linker ~~aminoquinoline-linker~~ compound of claim 51 wherein Q is 2,3,5,6-tetrafluorophenoxy.

53. The 8-amido-2-aminobenzazepine-linker compound of claim 29 selected from Formulae IIa-d:

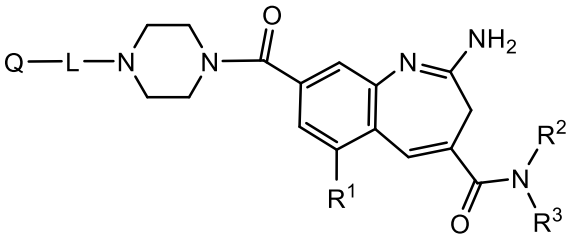

IIa;



IIb;



IIc; and



IId.

54. The 8-amido-2-aminobenzazepine-linker compound of claim 29 selected from Table 2a.

55. The 8-amido-2-aminobenzazepine-linker compound of claim 29 selected from Table 2b.

56. An immunoconjugate according to any one of claims 1 to 7 for use as a medicament.

5756. ~~A method for treating cancer comprising administering a therapeutically effective amount of an~~Use of an immunoconjugate according to any one of claims 1 to 7 in the manufacture of a medicament for the treatment of cancer~~, to a patient in need thereof~~.

5857. The use of claim 57~~method of claim 56~~, wherein the cancer is susceptible to a pro-inflammatory response induced by TLR7 and/or TLR8 agonism.

5958. The use of claim 57~~method of claim 56~~, wherein the cancer is a PD-L1-expressing cancer.

6059. The use of claim 57~~method of claim 56~~, wherein the cancer is a HER2-expressing cancer.

6160. The use of claim 57method of claim 56 wherein the cancer is a CEA-expressing cancer.

6261. The use of claim 57method of claim 56 wherein the cancer is a Caprin-1-expressing cancer.

6362. The use of any one of claims 57 to 62method of any one of claims 56-61, 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.

6463. The use of claim 63method of claim 62, wherein the breast cancer is triple-negative breast cancer.

6564. The use of claim 63method of claim 62, wherein the Merkel cell carcinoma cancer is metastatic Merkel cell carcinoma.

6665. The use of claim 63method of claim 62, wherein the gastric cancer is HER2 overexpressing gastric cancer.

6766. The use of claim 63method of claim 62, wherein the cancer is gastroesophageal junction adenocarcinoma.

~~67. Use of an immunoconjugate according to any one of claims 1 to 7 for treating cancer.~~

68. A method of preparing an immunoconjugate of Formula I of claim 1 wherein an 8-amido-2-aminobenzazepine-linker compound of Formula II of claim 29 is conjugated with the antibody.

69. The method of claim 68 wherein the 8-amido-2-aminobenzazepine-linker compound is selected from Table 2a or Table 2b.