2-AMINO-4-CARBOXAMIDE-BENZAZEPINE IMMUNOCONJUGATES, AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This non-provisional application claims the benefit of priority to U.S. Provisional Application No. 63/166,716, filed 26 March 2021, 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 March 25, 2022, is named 17019_016WO1_SL.txt and is 85,369 bytes in size.

FIELD OF THE INVENTION

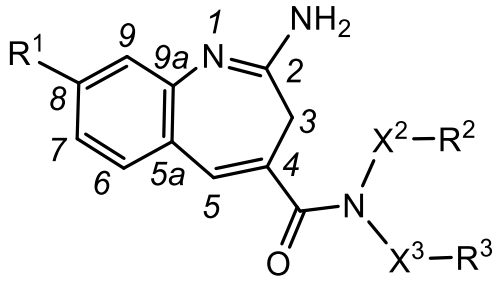
The invention relates generally to an immunoconjugate comprising an antibody conjugated to one or more 2-amino-4-carboxamide-benzazepine molecules.

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

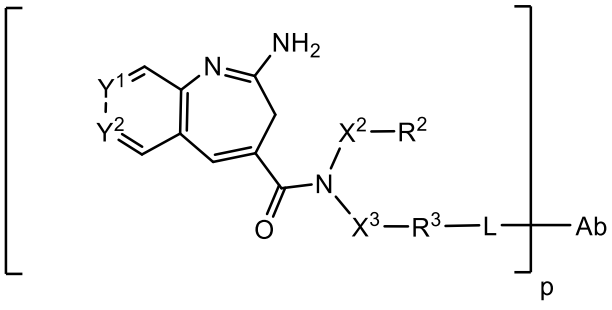
The disclosure is generally directed to immunoconjugates comprising an antibody linked by conjugation to one or more 2-amino-4-carboxamide-benzazepine derivatives. The disclosure is further directed to 2-amino-4-carboxamide-benzazepine derivative intermediate compositions comprising a reactive functional group. Such intermediate compositions are suitable substrates for formation of immunoconjugates wherein an antibody may be covalently bound by a linker L to the 4-position of an 2-amino-4-carboxamide-benzazepine moiety having the formula:



where R^3 is attached to the linker L. The positions of the 3H-benzo[b]azepine structure are numbered according to IUPAC conventions. The X^{2-3} and R^{1-3} substituents are defined herein. Additionally, the carbon atoms at the 7- and 8-positions may independently be replaced by nitrogen to form the pyridyl and pyrazine analogs of 3H-benzo[b]azepines.

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

In one aspect, the present disclosure refers to an immunoconjugate comprising an antibody covalently attached to one or more 2-amino-4-carboxamide-benzazepine moieties by a linker, and having Formula I:



I

or a pharmaceutically acceptable salt thereof,

wherein:

Ab is the antibody which is an antibody construct or antigen binding domain that binds to a target selected from the group consisting of PD-L1, HER2, TROP2, and CEA;

p is an integer from 1 to 8;

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

Y^1 is CR^1 or N;

Y^2 is CH or N;

R^1 is selected from the group consisting of H, C_3-C_{12} carbocyclyl, C_6-C_{20} aryl, C_2-C_9 heterocyclyl, and C_1-C_{20} heteroaryl;

R^2 is 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;

R^3 is selected from the group consisting of:

–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

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

–(C_1-C_{12} alkyldiyl)–N(R^5)–C(=O)O–(C_3-C_{12} carbocyclyldiyl)–*;

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

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

–(C_1-C_{12} alkyldiyl)–N(R^5)–S(O_2)–*;

–(C_1-C_{12} alkyldiyl)–OC(=O)–(C_2-C_9 heterocyclyldiyl)–*;

–(C_1-C_{12} alkyldiyl)–O–*;

–(C_1-C_{12} alkyldiyl)–(C_3-C_{12} carbocyclyldiyl)–*;

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

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

–(C_1-C_{12} alkyldiyl)–(C_2-C_9 heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

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

–(C_1-C_{12} alkyldiyl)–(C_1-C_{20} heteroaryldiyl)–*;

–(C_1-C_{12} alkyldiyl)–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–*;

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

–(C_3-C_{12} carbocyclyldiyl)–*;

–(C_3-C_{12} carbocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_3-C_{12} carbocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_3-C_{12} carbocyclyldiyl)–NR^5–C(=NR^{5a})–N(R^5)–*;

–(C_6-C_{20} aryldiyl)–*;

–(C_6-C_{20} aryldiyl)–N(R^5)–*;

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

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

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

–(C_2-C_{20} heterocyclyldiyl)–*;

–(C_2-C_9 heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

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

–(C_1-C_{20} heteroaryldiyl)–*;

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

–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–O–*; and

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

where the asterisk * indicates the attachment site of the linker L;

R^5 is selected from the group consisting of H, C_6-C_{20} aryl and C_1-C_{12} alkyl, 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;

L is selected from the group consisting of:

–C(=O)–PEG–C(=O)–;

–C(=O)–PEG–C(=O)–PEP–;

–C(=O)–PEG–N(R^5)–;

–C(=O)–PEG–N(R^5)–C(=O)–;

–C(=O)–PEG–NR^5–PEG–C(=O)–PEP–;

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

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

–C(=O)–PEG–O–;

–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)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)–;

–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)–;

–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)–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)–;

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

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

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

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

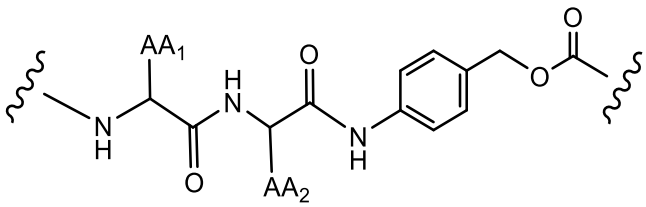
–succinimidyl–$(CH_2)_m$–C(=O)–PEP–N(R^5)–(C_1-C_{12} alkyldiyl)–;

–succinimidyl–$(CH_2)_m$–C(=O)–PEP–N(R^5)–(C_1-C_{12} alkyldiyl)N(R^5)C(=O)–; 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: $–(CH_2CH_2O)_n–(CH_2)_m–$ where 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

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 $–S(O)_3H$.

In another aspect, the present disclosure refers to a 2-amino-4-carboxamide-benzazepine-linker compound selected from Tables 2a and 2b.

In another aspect, the present disclosure refers to an immunoconjugate prepared by conjugation of an antibody with a 2-amino-4-carboxamide-benzazepine-linker compound selected from Tables 2a and 2b.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising a therapeutically effective amount of an immunoconjugate as defined above, and one or more pharmaceutically acceptable diluent, vehicle, carrier or excipient.

In another aspect, there is provided the use of an immunoconjugate as defined above in the manufacture of a medicament for the treatment of 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, the present disclosure refers to a method of preparing an immunoconjugate of Formula I as defined above wherein the 2-amino-4-carboxamide-benzazepine-linker as defined above is conjugated with the antibody.

In another aspect, the present disclosure refers to an immunoconjugate as defined above for use in therapy.

An example of the disclosure is an immunoconjugate comprising an antibody covalently attached to a linker which is covalently attached to one or more 2-amino-4-carboxamide-benzazepine moieties.

Another example of the disclosure is a 2-amino-4-carboxamide-benzazepine-linker compound.

Another example of the disclosure is a method for treating cancer comprising administering a therapeutically effective amount of an immunoconjugate comprising an antibody linked by conjugation to one or more 2-amino-4-carboxamide-benzazepine moieties.

Another example of the disclosure is a use of an immunoconjugate comprising an antibody linked by conjugation to one or more 2-amino-4-carboxamide-benzazepine moieties for treating cancer.

Another example of the disclosure is a method of preparing an immunoconjugate by conjugation of one or more 2-amino-4-carboxamide-benzazepine moieties with an antibody.

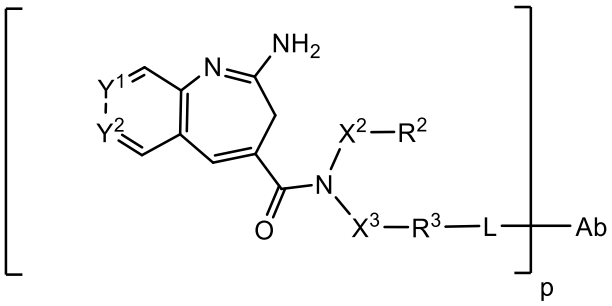
DETAILED DESCRIPTION OF THE INVENTION

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

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The invention is in no way limited to the methods and materials described.

CLAIMS:

1. An immunoconjugate comprising an antibody covalently attached to one or more 2-amino-4-carboxamide-benzazepine moieties by a linker, and having Formula I:



I

or a pharmaceutically acceptable salt thereof,

wherein:

Ab is the antibody which is an antibody construct or antigen binding domain that binds to a target selected from the group consisting of PD-L1, HER2, TROP2, and CEA;

p is an integer from 1 to 8;

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

Y^1 is CR^1 or N;

Y^2 is CH or N;

R^1 is selected from the group consisting of H, C_3-C_{12} carbocyclyl, C_6-C_{20} aryl, C_2-C_9 heterocyclyl, and C_1-C_{20} heteroaryl;

R^2 is 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;

R^3 is selected from the group consisting of:

–(C_1-C_{12} alkyldiyl)–$N(R^5)$–*;

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

–(C_1-C_{12} alkyldiyl)–$N(R^5)$–C(=O)O–(C_3-C_{12} carbocyclyldiyl)–*;

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

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

–(C_1-C_{12} alkyldiyl)–$N(R^5)$–$S(O_2)$–*;

–(C_1-C_{12} alkyldiyl)–OC(=O)–(C_2-C_9 heterocyclyldiyl)–*;

–(C_1-C_{12} alkyldiyl)–O–*;

–(C_1-C_{12} alkyldiyl)–(C_3-C_{12} carbocyclyldiyl)–*;

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

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

–(C_1-C_{12} alkyldiyl)–(C_2-C_9 heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

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

–(C_1-C_{12} alkyldiyl)–(C_1-C_{20} heteroaryldiyl)–*;

–(C_1-C_{12} alkyldiyl)–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–*;

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

–(C_3-C_{12} carbocyclyldiyl)–*;

–(C_3-C_{12} carbocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_3-C_{12} carbocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

–(C_3-C_{12} carbocyclyldiyl)–NR^5–C(=NR^{5a})–N(R^5)–*;

–(C_6-C_{20} aryldiyl)–*;

–(C_6-C_{20} aryldiyl)–N(R^5)–*;

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

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

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

–(C_2-C_{20} heterocyclyldiyl)–*;

–(C_2-C_9 heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^5)–*;

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

–(C_1-C_{20} heteroaryldiyl)–*;

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

–(C_1-C_{20} heteroaryldiyl)–(C_1-C_{12} alkyldiyl)–O–*; and

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

where the asterisk * indicates the attachment site of the linker L;

R^5 is selected from the group consisting of H, C_6-C_{20} aryl and C_1-C_{12} alkyl, 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;

L is selected from the group consisting of:

–C(=O)–PEG–C(=O)–;

–C(=O)–PEG–C(=O)–PEP–;

–C(=O)–PEG–N(R^5)–;

–C(=O)–PEG–N(R^5)–C(=O)–;

–C(=O)–PEG–NR^5–PEG–C(=O)–PEP–;

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

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

–C(=O)–PEG–O–;

–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)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)–;

–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)–;

–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)–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)–;

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

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

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

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

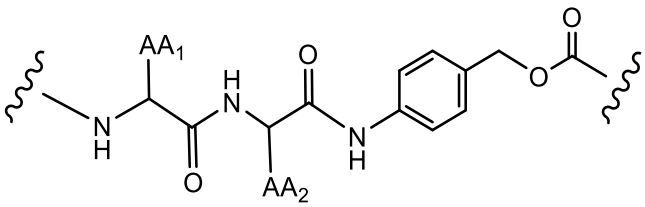
–succinimidyl–$(CH_2)_m$–C(=O)–PEP–N(R^5)–(C_1-C_{12} alkyldiyl)–;

–succinimidyl–$(CH_2)_m$–C(=O)–PEP–N(R^5)–(C_1-C_{12} alkyldiyl)N(R^5)C(=O)–; 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: $–(CH_2CH_2O)_n–(CH_2)_m–$ where 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

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 claim 1 wherein the antibody is an antibody construct that has an antigen binding domain that binds TROP2.

9. The immunoconjugate of claim 8 wherein the TROP2 antibody is a monoclonal antibody.

10. The immunoconjugate of any one of claims 1 to 9 wherein R^1 is optionally substituted C_1-C_{20} heteroaryl.

11. The immunoconjugate of any one of claims 1 to 9 wherein R^1 is pyrimidinyl or pyridinyl.

12. The immunoconjugate of any one of claims 1 to 9 wherein X^2 and X^3 are each a bond, and R^2 and R^3 are independently selected from C_1-C_8 alkyl, –O–(C_1-C_{12} alkyl), –(C_1-C_{12} alkyldiyl)–OR^5, –(C_1-C_8 alkyldiyl)–$N(R^5)CO_2R^5$, –(C_1-C_{12} alkyl)–$OC(O)N(R^5)_2$, –O–(C_1-C_{12} alkyl)–$N(R^5)CO_2R^5$, and –O–(C_1-C_{12} alkyl)–$OC(O)N(R^5)_2$.

13. The immunoconjugate of any one of claims 1 to 9 wherein X^2 is a bond, and R^2 is C_1-C_{12} alkyl.

14. The immunoconjugate of any one of claims 1 to 9 wherein X^3 is O and R^3 is –(C_1-C_{12} alkyldiyl)–$N(R^5)$–*.

15. The immunoconjugate of claim 14 wherein R^3 is $–CH_2CH_2CH_2NH–$.

16. The immunoconjugate of claim 14 wherein L is –C(=O)–PEG–C(=O)–.

17. The immunoconjugate of any one of claims 1 to 9 wherein L comprises PEG.

18. The immunoconjugate of claim 17 wherein n is 10 and m is 1.

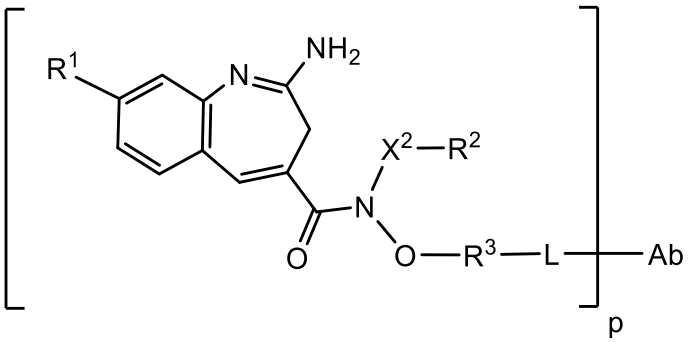
19. The immunoconjugate of any one of claims 1 to 9 wherein AA_1 and AA_2 are independently selected from a side chain of a naturally-occurring amino acid.

20. The immunoconjugate of claim 19 wherein AA_1 or AA_2 with an adjacent nitrogen atom form a 5-membered ring proline amino acid.

21. The immunoconjugate of claim 19 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 $–CH_2CH_2CH_2NHC(O)NH_2$.

22. The immunoconjugate of claim 21 wherein AA_1 is $–CH(CH_3)_2$, and AA_2 is $–CH_2CH_2CH_2NHC(O)NH_2$.

23. The immunoconjugate of any one of claims 1 to 9 having Formula Ia:



Ia.

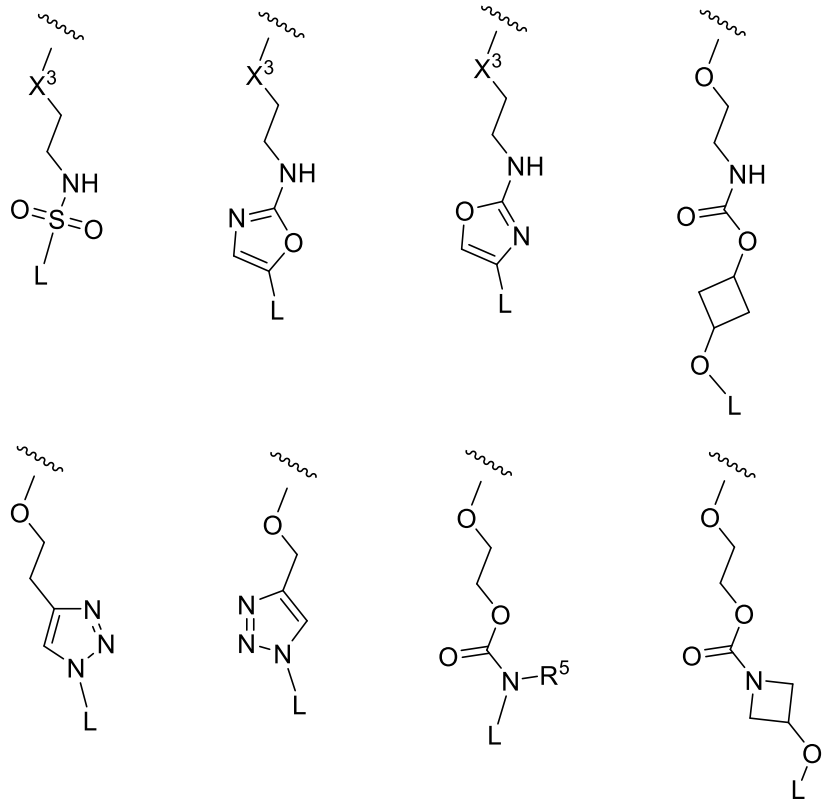
24. The immunoconjugate of claim 23 wherein R^1 is optionally substituted C_1-C_{20} heteroaryl.

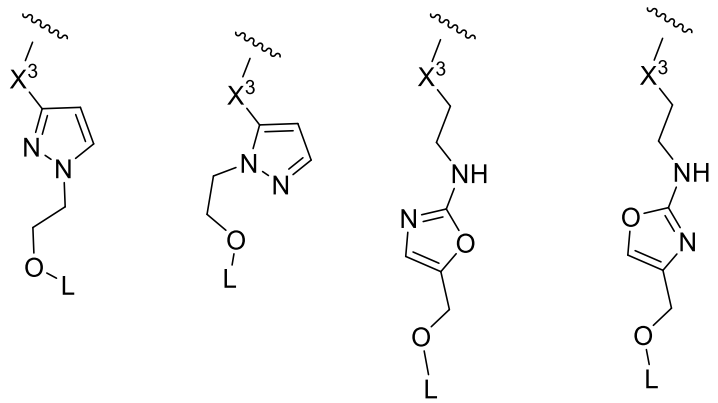
25. The immunoconjugate of claim 24 wherein R^1 is pyrimidinyl or pyridyl.

26. The immunoconjugate of claim 23 wherein X^2 is a bond, and R^2 is C_1-C_{12} alkyl.

27. The immunoconjugate of claim 23 wherein R^3 is –(C_1-C_{12} alkyldiyl)–N(R^5)–*.

28. The immunoconjugate of any one of claims 1 to 9 wherein X^3–R^3–L is selected from the group consisting of:





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

29. The immunoconjugate of claim 28 wherein L comprises PEG.

30. The immunoconjugate of claim 29 wherein n is 10 and m is 1.

31. The immunoconjugate of any one of claims 1 to 9 wherein Y^1 is CR^1 and Y^2 is CH.

32. The immunoconjugate of any one of claims 1 to 9 wherein Y^1 is N and Y^2 is CH.

33. The immunoconjugate of any one of claims 1 to 9 wherein Y^1 is N and Y^2 is N.

34. A 2-amino-4-carboxamide-benzazepine-linker compound selected from Tables 2a and 2b.

35. An immunoconjugate prepared by conjugation of an antibody with a 2-amino-4-carboxamide-benzazepine-linker compound selected from Tables 2a and 2b.

36. A pharmaceutical composition comprising a therapeutically effective amount of an immunoconjugate according to any one of claims 1 to 9, and one or more pharmaceutically acceptable diluent, vehicle, carrier or excipient.

37. Use of an immunoconjugate according to any one of claims 1 to 9 in the manufacture of a medicament for the treatment of 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.

38. The use of claim 37, wherein the cancer is susceptible to a pro-inflammatory response induced by TLR7 and/or TLR8 agonism.

39. The use of claim 37, wherein the breast cancer is triple-negative breast cancer.

40. The use of claim 37, wherein the Merkel cell carcinoma cancer is metastatic Merkel cell carcinoma.

41. The use of claim 39, wherein the cancer is gastroesophageal junction adenocarcinoma.

42. A method of preparing an immunoconjugate of Formula I of any one of claims 1 to 9 wherein the 2-amino-4-carboxamide-benzazepine-linker of claim 34 is conjugated with the antibody.

43. An immunoconjugate according to any one of claims 1 to 9 for use in therapy.