BIS-BENZIMIDAZOLE STING AGONIST IMMUNOCONJUGATES, AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This non-provisional application claims the benefit of priority to U.S. Provisional Application No. 63/215,100, filed 25 June 2021, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

The invention relates generally to an immunoconjugate comprising an antibody conjugated to one or more bis-benzimidazole molecules.

BACKGROUND OF THE INVENTION

STING (Stimulator of Interferon Genes), also known as transmembrane protein 173 (TMEM173) and MPYS/MITA/ERIS, is a protein encoded in humans by the STING1 gene. STING is broadly expressed, particularly in immune cells, lung, and ovary. STING plays a role in innate immunity by inducing type I interferon production when cells are infected with intracellular pathogens, such as viruses, mycobacteria, and intracellular parasites. Type I interferon, mediated by STING, protects infected cells and nearby cells from local infection by binding to the same cell that secretes it by autocrine signaling and nearby cells by paracrine signaling. STING works as both a direct cytosolic DNA sensor (CDS) and an adaptor protein in Type I interferon signaling through different molecular mechanisms. STING has been shown to activate downstream transcription factors STAT6 and IRF3 through TBK1, which are responsible for antiviral response and innate immune response against intracellular pathogens.. Compounds that bind to STING and act as an agonist have been shown to induce secretion of proinflammatory cytokines including type 1 interferons on incubation with human PBMCs (WO 2017/175147). STING modulators may be useful in the treatment of various disorders, for example, allergic diseases, neurodegenerative diseases, pre-cancerous syndromes, and cancer, and may also be useful in immunogenic compositions or vaccine adjuvants.

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.

SUMMARY

The disclosure is generally directed to immunoconjugates comprising an antibody covalently attached to one or more STING agonist moieties by a linker, and having Formula I:

$$Ab–[L–D]_p \qquad I$$

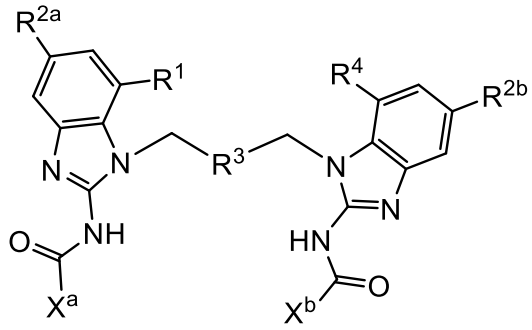
or a pharmaceutically acceptable salt thereof,

wherein:

Ab is the antibody;

p is an integer from 1 to 8;

D is the STING agonist moiety having the formula:



where the substituents are defined herein.

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

Another example of the disclosure is a bis-benzimidazole-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 bis-benzimidazole moieties.

Another example of the disclosure is a use of an immunoconjugate comprising an antibody linked by conjugation to one or more bis-benzimidazole moieties for treating cancer.

Another example of the disclosure is a method of preparing an immunoconjugate by conjugation of one or more bis-benzimidazole moieties with an antibody.

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

$$Ab–[L–D]_p \qquad I$$

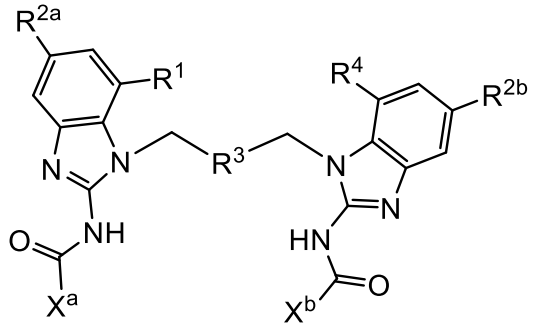
or a pharmaceutically acceptable salt thereof,

wherein:

Ab is the antibody;

p is an integer from 1 to 8;

D is the STING agonist moiety having the formula:



X^a and X^b are independently selected from a five-membered heteroaryl, optionally substituted with R^5;

R^1 and R^4 are independently selected from the group consisting of H, F, Cl, Br, I, –CN, –OH, –O–(C_1-C_6 alkyl), and R^5;

R^{2a} and R^{2b} are independently selected from H, –C(=O)N(R^6)$_2$, and R^5;

where one of X^a, X^b, R^1, R^4, R^{2a} and R^{2b} is substituted with R^5;

R^3 is selected from C_1-C_6 alkyldiyl, –(C_1-C_3 alkyldiyl)–O–(C_1-C_3 alkyldiyl)–, C_2-C_6 alkenyldiyl and C_2-C_6 alkynyldiyl, optionally substituted with one or more groups selected from F, Cl, –OH, –OCH_3, –OCH_2CH_3, –$OCH_2CH_2OCH_3$, –OCH_2CH_2OH, –$OCH_2CH_2N(CH_3)_2$;

R^5 is selected from the group consisting of:

–(C_1-C_{12} alkyldiyl)–*;

–(C_1-C_{12} alkyldiyl)–N(R^6)–*;

–(C_1-C_{12} alkyldiyl)–O–*;

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

–O–(C_1-C_{12} alkyldiyl)–*;

–O–(C_1-C_{12} alkyldiyl)–N(R^6)–*;

–O–(C_1-C_{12} alkyldiyl)–O–*;

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

–O–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–N(R^6)–*;

–OC(=O)N(R^6)–*;

–OC(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)–*;

–N(R^6)–*;

–N(R^6)–(C_1-C_{12} alkyldiyl)–*;

–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)–*;

–N(R^6)–(C_1-C_{12} alkyldiyl)–O–*;

–N(R^6)–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–*;

–C(=O)N(R^6)–*;

–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–*;

–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)–*;

–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–O–*;

–(C_2-C_{20} heterocyclyldiyl)–*;

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

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^6)–*;

where the asterisk * indicates the attachment site of L;

R^6 is independently H or C_1-C_6 alkyl;

L is the linker selected from the group consisting of:

–C(=O)–PEG–;

–C(=O)–PEG-C(=O)N(R^6)-(C_1-C_{12} alkyldiyl)-C(=O)–Gluc–;

–C(=O)–PEG–O–;

–C(=O)–PEG–O–C(=O)–;

–C(=O)–PEG–C(=O)–;

–C(=O)–PEG–C(=O)–PEP–;

–C(=O)–PEG–N(R^6)–;

–C(=O)–PEG–N(R^6)–C(=O)–;

–C(=O)–PEG–N(R^6)–PEG–C(=O)–PEP–;

–C(=O)–PEG–N^+(R^6)$_2$–PEG–C(=O)–PEP–;

–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

-C(=O)-PEG-C(=O)N(R^6)-(C_1-C_{12} alkyldiyl)-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)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–;

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^5)–C(=O);

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–;

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

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–O–;

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–O–C(=O)–;

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–C(=O)–;

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–N(R^5)–;

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–N(R^5)–C(=O)–;

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–C(=O)–PEP–;

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

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

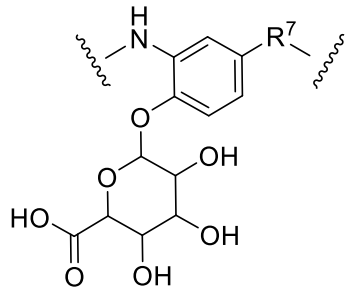
-succinimidyl-$(CH_2)_m$-C(=O)N(R^6)-PEG-C(=O)N(R^6)-(C_1-C_{12} alkyldiyl)-C(=O)-PEP-;

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

–succinimidyl–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

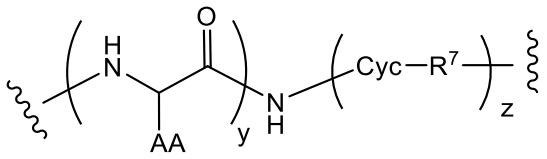
PEG has the formula: $–(CH_2CH_2O)_n–(CH_2)_m–$; m is an integer from 1 to 5, and n is an integer from 2 to 50;

Gluc has the formula:



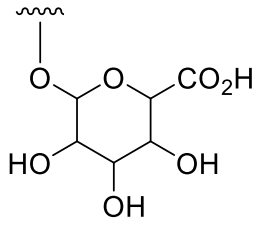
;

PEP has the formula:



where AA is independently selected from a natural or unnatural amino acid side chain, or one or more of AA, and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment;

Cyc is selected from C_6-C_{20} aryldiyl and C_1-C_{20} heteroaryldiyl, optionally substituted with one or more groups selected from F, Cl, NO_2, –OH, $–OCH_3$, and a glucuronic acid having the structure:



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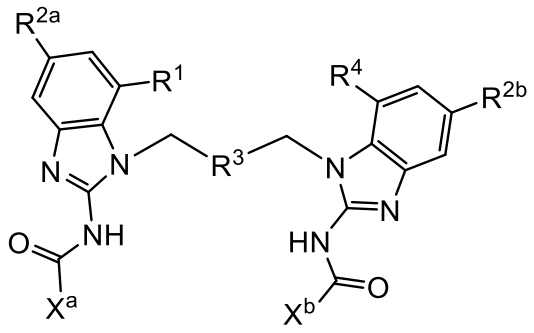
R^7 is selected from the group consisting of $–CH(R^8)O–$, $–CH_2–$, $–CH_2N(R^8)–$, and $–CH(R^8)O–C(=O)–$, where R^8 is selected from H, C_1-C_6 alkyl, $C(=O)–C_1$-C_6 alkyl, and $–C(=O)N(R^9)_2$, where R^9 is independently selected from the group consisting of H, C_1-C_{12} alkyl, and $–(CH_2CH_2O)_n–(CH_2)_m–OH$, where m is an integer from 1 to 5, and n is an integer from 2 to 50, or two R^9 groups together form a 5- or 6-membered heterocyclyl ring;

y is an integer from 2 to 12;

z is 0 or 1; and

alkyl, alkyldiyl, alkenyl, alkenyldiyl, alkynyl, alkynyldiyl, aryl, aryldiyl, carbocyclyl, carbocyclyldiyl, heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl are independently and optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, $–CH_3$, $–CH_2CH_3$, $–CH=CH_2$, $–C≡CH$, $–C≡CCH_3$, $–CH_2CH_2CH_3$, $–CH(CH_3)_2$, $–CH_2CH(CH_3)_2$, $–CH_2OH$, $–CH_2OCH_3$, $–CH_2CH_2OH$, $–C(CH_3)_2OH$, $–CH(OH)CH(CH_3)_2$, $–C(CH_3)_2CH_2OH$, $–CH_2CH_2SO_2CH_3$, $–CH_2OP(O)(OH)_2$, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CF_3$, $–CH_2CHF_2$, $–CH(CH_3)CN$, $–C(CH_3)_2CN$, $–CH_2CN$, $–CH_2NH_2$, $–CH_2NHSO_2CH_3$, $–CH_2NHCH_3$, $–CH_2N(CH_3)_2$, $–CO_2H$, $–COCH_3$, $–CO_2CH_3$, $–CO_2C(CH_3)_3$, $–COCH(OH)CH_3$, $–CONH_2$, $–CONHCH_3$, $–CON(CH_3)_2$, $–C(CH_3)_2CONH_2$, $–NH_2$, $–NHCH_3$, $–N(CH_3)_2$, $–NHCOCH_3$, $–N(CH_3)COCH_3$, $–NHS(O)_2CH_3$, $–N(CH_3)C(CH_3)_2CONH_2$, $–N(CH_3)CH_2CH_2S(O)_2CH_3$, –NHC(=NH)H, $–NHC(=NH)CH_3$, $–NHC(=NH)NH_2$, $–NHC(=O)NH_2$, $–NO_2$, =O, –OH, $–OCH_3$, $–OCH_2CH_3$, $–OCH_2CH_2OCH_3$, $–OCH_2CH_2OH$, $–OCH_2CH_2N(CH_3)_2$, $–O(CH_2CH_2O)_n–(CH_2)_mCO_2H$, $–O(CH_2CH_2O)_nH$, $–OCH_2F$, $–OCHF_2$, $–OCF_3$, $–OP(O)(OH)_2$, $–S(O)_2N(CH_3)_2$, $–SCH_3$, $–S(O)_2CH_3$, and $–S(O)_3H$.

In another aspect, there is provided a STING agonist-linker intermediate compound having Formula II:



II

wherein

X^a and X^b are independently selected from a five-membered heteroaryl, optionally substituted with R^5;

R^1 and R^4 are independently selected from the group consisting of F, Cl, Br, I, –CN, –OH, –O–(C_1-C_6 alkyl), and R^5;

R^{2a} and R^{2b} are independently selected from –C(=O)N(R^6)$_2$ and R^5;

where one of X^a, X^b, R^1, R^4, R^{2a} and R^{2b} is substituted with R^5;

R^3 is selected from C_1-C_6 alkyldiyl, –(C_1-C_3 alkyldiyl)–O–(C_1-C_3 alkyldiyl)–, C_2-C_6 alkenyldiyl and C_2-C_6 alkynyldiyl, optionally substituted with one or more groups selected from F, Cl, –OH, –OCH_3, –OCH_2CH_3, –$OCH_2CH_2OCH_3$, –OCH_2CH_2OH, –$OCH_2CH_2N(CH_3)_2$;

R^5 is selected from the group consisting of:

–(C_1-C_{12} alkyldiyl)–L;

–(C_1-C_{12} alkyldiyl)–N(R^6)–L;

–(C_1-C_{12} alkyldiyl)–O–L;

–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–L;

–O–(C_1-C_{12} alkyldiyl)–L;

–O–(C_1-C_{12} alkyldiyl)–N(R^6)–L;

–O–(C_1-C_{12} alkyldiyl)–O–L;

–O–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–L;

–O–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–N(R^6)–L;

–OC(=O)N(R^6)–L;

–OC(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)–L;

–N(R^6)–L;

–N(R^6)–(C_1-C_{12} alkyldiyl)–L;

–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)–L;

–N(R^6)–(C_1-C_{12} alkyldiyl)–O–L;

–N(R^6)–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–L;

–C(=O)N(R^6)–L;

–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–L;

–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)–L;

–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–O–L;

–(C_2-C_{20} heterocyclyldiyl)–L;

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–L; and

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^6)–L;

R^6 is independently H or C_1-C_6 alkyl;

L is a linker selected from the group consisting of:

Q–C(=O)–PEG–;

Q–C(=O)–PEG-C(=O)N(R^6)-(C_1-C_{12} alkyldiyl)-C(=O)–Gluc–;

Q–C(=O)–PEG–O–;

Q–C(=O)–PEG–O–C(=O)–;

Q–C(=O)–PEG–C(=O)–;

Q–C(=O)–PEG–C(=O)–PEP–;

Q–C(=O)–PEG–N(R^6)–;

Q–C(=O)–PEG–N(R^6)–C(=O)–;

Q–C(=O)–PEG–N(R^6)–PEG–C(=O)–PEP–;

Q–C(=O)–PEG–N^+(R^6)$_2$–PEG–C(=O)–PEP–;

Q–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

Q-C(=O)-PEG-C(=O)N(R^6)-(C_1-C_{12} alkyldiyl)-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)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–;

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^5)–C(=O);

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

Q–(CH_2)$_m$–C(=O)N(R^6)–PEG–;

Q–(CH_2)$_m$–C(=O)N(R^6)–PEG-C(=O)N(R^6)-(C_1-C_{12} alkyldiyl)-C(=O)–Gluc–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–O–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–O–C(=O)–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–C(=O)–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–N(R^5)–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–N(R^5)–C(=O)–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–C(=O)–PEP–;

Q–$(CH_2)_m$–C(=O)N(R^6)–PEG–SS–(C_1-C_{12} alkyldiyl)–OC(=O)–;

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

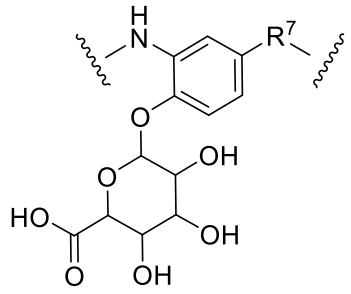
Q-$(CH_2)_m$-C(=O)N(R^6)-PEG-C(=O)N(R^6)-(C_1-C_{12} alkyldiyl)-C(=O)-PEP-;

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

Q–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

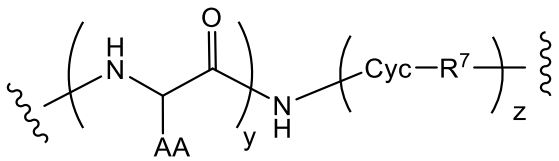
PEG has the formula: –$(CH_2CH_2O)_n$–$(CH_2)_m$–; m is an integer from 1 to 5, and n is an integer from 2 to 50;

Gluc has the formula:



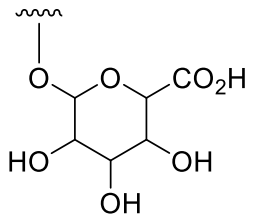
;

PEP has the formula:



where AA is independently selected from a natural or unnatural amino acid side chain, or one or more of AA, and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment;

Cyc is selected from C_6-C_{20} aryldiyl and C_1-C_{20} heteroaryldiyl, optionally substituted with one or more groups selected from F, Cl, NO_2, –OH, $–OCH_3$, and a glucuronic acid having the structure:



;

R^7 is selected from the group consisting of $–CH(R^8)O–$, $–CH_2–$, $–CH_2N(R^8)–$, and $–CH(R^8)O–C(=O)–$, where R^8 is selected from H, C_1-C_6 alkyl, $C(=O)–C_1$-C_6 alkyl, and $–C(=O)N(R^9)_2$, where R^9 is independently selected from the group consisting of H, C_1-C_{12} alkyl, and $–(CH_2CH_2O)_n–(CH_2)_m–OH$, where m is an integer from 1 to 5, and n is an integer from 2 to 50, or two R^9 groups together form a 5- or 6-membered heterocyclyl ring;

y is an integer from 2 to 12;

z is 0 or 1;

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

In another aspect, there is provided a STING agonist-linker intermediate compound selected from Table 1.

In another aspect, there is provided an immunoconjugate prepared by conjugation of an antibody with a STING agonist-linker intermediate compound as defined above.

In another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of an immunoconjugate as defined above, and one or more pharmaceutically acceptable diluent, vehicle, carrier or excipient.

In another aspect, there is provided the use of an immunoconjugate as defined above, in the manufacture of a medicament for treating cancer, wherein the cancer is selected from bladder cancer, salivary gland cancer, endometrial 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 a STING agonist-linker intermediate compound as defined above is conjugated with the 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.

CLAIMS:

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

$$Ab–[L–D]_p \qquad I$$

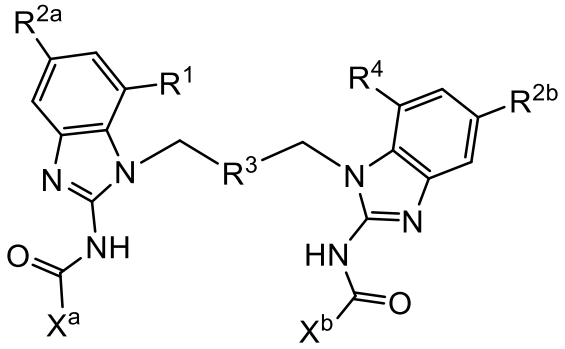
or a pharmaceutically acceptable salt thereof,

wherein:

Ab is the antibody;

p is an integer from 1 to 8;

D is the STING agonist moiety having the formula:



X^a and X^b are independently selected from a five-membered heteroaryl, optionally substituted with R^5;

R^1 and R^4 are independently selected from the group consisting of H, F, Cl, Br, I, –CN, –OH, –O–(C_1-C_6 alkyl), and R^5;

R^{2a} and R^{2b} are independently selected from H, –C(=O)N(R^6)$_2$, and R^5;

where one of X^a, X^b, R^1, R^4, R^{2a} and R^{2b} is substituted with R^5;

R^3 is selected from C_1-C_6 alkyldiyl, –(C_1-C_3 alkyldiyl)–O–(C_1-C_3 alkyldiyl)–, C_2-C_6 alkenyldiyl and C_2-C_6 alkynyldiyl, optionally substituted with one or more groups selected from F, Cl, –OH, –OCH_3, –OCH_2CH_3, –$OCH_2CH_2OCH_3$, –OCH_2CH_2OH, –$OCH_2CH_2N(CH_3)_2$;

R^5 is selected from the group consisting of:

–(C_1-C_{12} alkyldiyl)–*;

–(C_1-C_{12} alkyldiyl)–N(R^6)–*;

–(C_1-C_{12} alkyldiyl)–O–*;

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

–O–(C_1-C_{12} alkyldiyl)–*;

–O–(C_1-C_{12} alkyldiyl)–N(R^6)–*;

–O–(C_1-C_{12} alkyldiyl)–O–*;

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

–O–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–N(R^6)–*;

–OC(=O)N(R^6)–*;

–OC(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)–*;

–N(R^6)–*;

–N(R^6)–(C_1-C_{12} alkyldiyl)–*;

–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)–*;

–N(R^6)–(C_1-C_{12} alkyldiyl)–O–*;

–N(R^6)–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–*;

–C(=O)N(R^6)–*;

–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–*;

–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)–*;

–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–O–*;

–(C_2-C_{20} heterocyclyldiyl)–*;

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

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^6)–*;

where the asterisk * indicates the attachment site of L;

R^6 is independently H or C_1-C_6 alkyl;

L is the linker selected from the group consisting of:

–C(=O)–PEG–;

–C(=O)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–C(=O)–Gluc–;

–C(=O)–PEG–O–;

–C(=O)–PEG–O–C(=O)–;

–C(=O)–PEG–C(=O)–;

–C(=O)–PEG–C(=O)–PEP–;

–C(=O)–PEG–N(R^6)–;

–C(=O)–PEG–N(R^6)–C(=O)–;

–C(=O)–PEG–N(R^6)–PEG–C(=O)–PEP–;

–C(=O)–PEG–N^+(R^6)$_2$–PEG–C(=O)–PEP–;

–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

–C(=O)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–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)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–;

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^5)–C(=O);

–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–;

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

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–O–;

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–O–C(=O)–;

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–C(=O)–;

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–N(R^5)–;

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–N(R^5)–C(=O)–;

–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–C(=O)–PEP–;

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

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

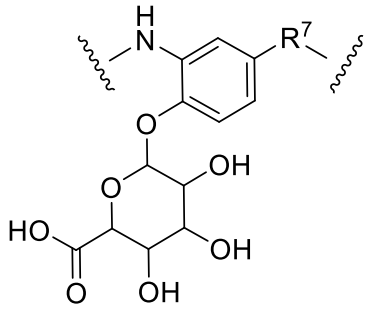
–succinimidyl–$(CH_2)_m$–C(=O)N(R^6)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–;

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

–succinimidyl–$(CH_2)_m$–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

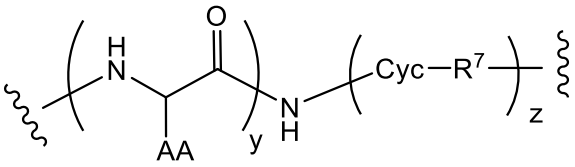
PEG has the formula: $–(CH_2CH_2O)_n–(CH_2)_m–$; m is an integer from 1 to 5, and n is an integer from 2 to 50;

Gluc has the formula:



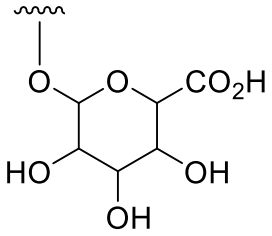
;

PEP has the formula:



where AA is independently selected from a natural or unnatural amino acid side chain, or one or more of AA, and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment;

Cyc is selected from C_6-C_{20} aryldiyl and C_1-C_{20} heteroaryldiyl, optionally substituted with one or more groups selected from F, Cl, NO_2, –OH, $–OCH_3$, and a glucuronic acid having the structure:



;

R^7 is selected from the group consisting of $–CH(R^8)O–$, $–CH_2–$, $–CH_2N(R^8)–$, and $–CH(R^8)O–C(=O)–$, where R^8 is selected from H, C_1-C_6 alkyl, $C(=O)–C_1$-C_6 alkyl, and $–C(=O)N(R^9)_2$, where R^9 is independently selected from the group consisting of H, C_1-C_{12} alkyl, and $–(CH_2CH_2O)_n–(CH_2)_m–OH$, where m is an integer from 1 to 5, and n is an integer from 2 to 50, or two R^9 groups together form a 5- or 6-membered heterocyclyl ring;

y is an integer from 2 to 12;

z is 0 or 1; and

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

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

2. The immunoconjugate of claim 1 wherein the antibody is an antibody construct that has an antigen binding domain that binds a target selected from PD-L1, HER2, CEA and Trop2.

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

4. The immunoconjugate of any one of claims 1 to 3 wherein X^a and X^b are independently selected from the group consisting of imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, oxadiazolyl, and thiadiazolyl.

5. The immunoconjugate of claim 4 wherein X^a and X^b are each pyrazolyl, substituted with one or more groups selected from $-CH_3$, $-CH_2CH_3$, $-CH=CH_2$, $-C\equiv CH$, $-C\equiv CCH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, and $-CH_2CH(CH_3)_2$.

6. The immunoconjugate of any one of claims 1 to 3 wherein one of X^a and X^b is substituted with R^5.

7. The immunoconjugate of any one of claims 1 to 3 wherein R^1 is selected from the group consisting of $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OCH_3$, $-OCH_2CH_2OH$, and $-OCH_2CH_2N(CH_3)_2$.

8. The immunoconjugate of claim 7 wherein R^1 is $-OCH_3$ or F.

9. The immunoconjugate of any one of claims 1 to 3 wherein R^{2a} and R^{2b} are each $-C(=O)NH_2$.

10. The immunoconjugate of any one of claims 1 to 3 wherein one of R^{2a} and R^{2b} is substituted with R^5.

11. The immunoconjugate of any one of claims 1 to 3 wherein R^3 is selected from –CH_2CH_2–, –CH=CH–, and –C≡C–.

12. The immunoconjugate of any one of claims 1 to 3 wherein R^3 is C_2-C_4 alkenyldiyl, substituted with one or more groups selected from F, –OH, and –OCH_3.

13. The immunoconjugate of any one of claims 1 to 3 wherein R^4 is –O–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–*.

14. The immunoconjugate of claim 13 wherein C_1-C_{12} alkyldiyl is propyldiyl and C_2-C_{20} heterocyclyldiyl is piperidiyl.

15. The immunoconjugate of any one of claims 1 to 3 wherein one of R^1 and R^4 is substituted with R^5.

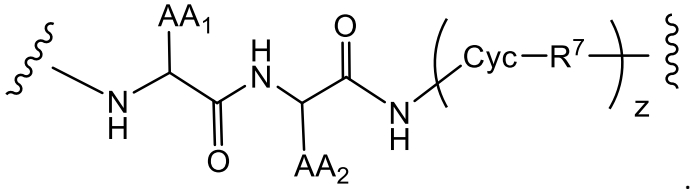
16. The immunoconjugate of any one of claims 1 to 3 wherein L is –C(=O)–PEG– or –C(=O)–PEG–C(=O)–.

17. The immunoconjugate of any one of claims 1 to 3 wherein L is attached to a cysteine thiol of the antibody.

18. The immunoconjugate of any one of claims 1 to 3 wherein for the PEG, m is 1 or 2, and n is an integer from 2 to 10.

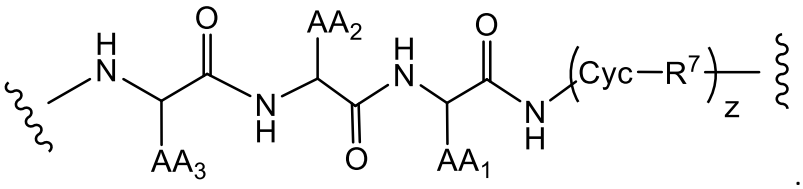
19. The immunoconjugate of claim 18 wherein n is 10.

20. The immunoconjugate of any one of claims 1 to 3 wherein L comprises PEP and PEP is a dipeptide and has the formula:



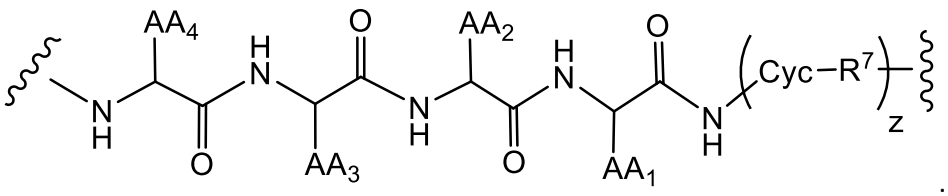
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21. The immunoconjugate of any one of claims 1 to 3 wherein L comprises PEP and PEP is a tripeptide and has the formula:

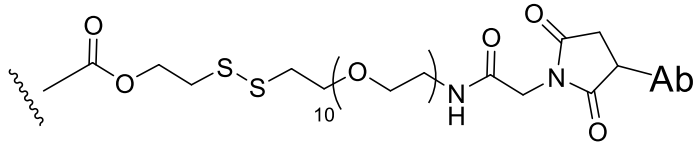


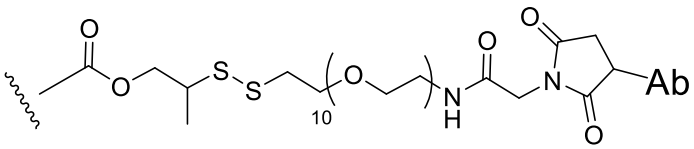
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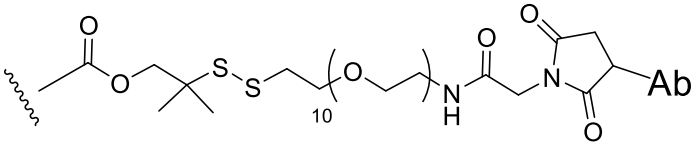
22. The immunoconjugate of any one of claims 1 to 3 wherein L comprises PEP and PEP is a tetrapeptide and has the formula:

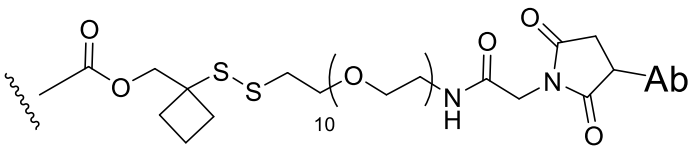


23. The immunoconjugate of any one of claims 1 to 3 wherein L is selected from the structures:



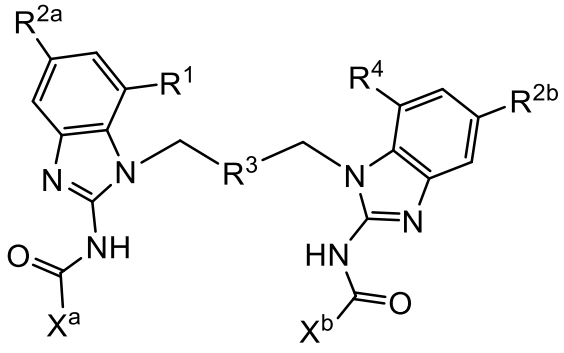






where the wavy line indicates the attachment to R^5.

24. A STING agonist-linker intermediate compound having Formula II:



II

wherein

X^a and X^b are independently selected from a five-membered heteroaryl, optionally substituted with R^5;

R^1 and R^4 are independently selected from the group consisting of F, Cl, Br, I, –CN, –OH, –O–(C_1-C_6 alkyl), and R^5;

R^{2a} and R^{2b} are independently selected from –C(=O)N(R^6)$_2$ and R^5;

where one of X^a, X^b, R^1, R^4, R^{2a} and R^{2b} is substituted with R^5;

R^3 is selected from C_1-C_6 alkyldiyl, –(C_1-C_3 alkyldiyl)–O–(C_1-C_3 alkyldiyl)–, C_2-C_6 alkenyldiyl and C_2-C_6 alkynyldiyl, optionally substituted with one or more groups selected from F, Cl, –OH, –OCH_3, –OCH_2CH_3, –$OCH_2CH_2OCH_3$, –OCH_2CH_2OH, –$OCH_2CH_2N(CH_3)_2$;

R^5 is selected from the group consisting of:

–(C_1-C_{12} alkyldiyl)–L;

–(C_1-C_{12} alkyldiyl)–N(R^6)–L;

–(C_1-C_{12} alkyldiyl)–O–L;

–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–L;

–O–(C_1-C_{12} alkyldiyl)–L;

–O–(C_1-C_{12} alkyldiyl)–N(R^6)–L;

–O–(C_1-C_{12} alkyldiyl)–O–L;

–O–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–L;

–O–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–N(R^6)–L;

–OC(=O)N(R^6)–L;

–OC(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)–L;

–N(R^6)–L;

–N(R^6)–(C_1-C_{12} alkyldiyl)–L;

–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)–L;

–N(R^6)–(C_1-C_{12} alkyldiyl)–O–L;

–N(R^6)–(C_1-C_{12} alkyldiyl)–(C_2-C_{20} heterocyclyldiyl)–L;

–C(=O)N(R^6)–L;

–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–L;

–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)–L;

–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–O–L;

–(C_2-C_{20} heterocyclyldiyl)–L;

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–L; and

–S(=O)$_2$–(C_2-C_{20} heterocyclyldiyl)–(C_1-C_{12} alkyldiyl)–N(R^6)–L;

R^6 is independently H or C_1-C_6 alkyl;

L is a linker selected from the group consisting of:

Q–C(=O)–PEG–;

Q–C(=O)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–C(=O)–Gluc–;

Q–C(=O)–PEG–O–;

Q–C(=O)–PEG–O–C(=O)–;

Q–C(=O)–PEG–C(=O)–;

Q–C(=O)–PEG–C(=O)–PEP–;

Q–C(=O)–PEG–N(R^6)–;

Q–C(=O)–PEG–N(R^6)–C(=O)–;

Q–C(=O)–PEG–N(R^6)–PEG–C(=O)–PEP–;

Q–C(=O)–PEG–N^+(R^6)$_2$–PEG–C(=O)–PEP–;

Q–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–PEG–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

Q–C(=O)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–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)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–;

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–;

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^5)–C(=O);

Q–C(=O)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–N(R^6)–(C_1-C_{12} alkyldiyl)–N(R^6)C(=O)–(C_2-C_5 monoheterocyclyldiyl)–;

Q–(CH_2)$_m$–C(=O)N(R^6)–PEG–;

Q–(CH_2)$_m$–C(=O)N(R^6)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–C(=O)–Gluc–;

Q–(CH_2)$_m$–C(=O)N(R^6)–PEG–O–;

Q–(CH_2)$_m$–C(=O)N(R^6)–PEG–O–C(=O)–;

Q–(CH_2)$_m$–C(=O)N(R^6)–PEG–C(=O)–;

Q–(CH_2)$_m$–C(=O)N(R^6)–PEG–N(R^5)–;

Q–(CH_2)$_m$–C(=O)N(R^6)–PEG–N(R^5)–C(=O)–;

Q–(CH_2)$_m$–C(=O)N(R^6)–PEG–C(=O)–PEP–;

Q–(CH_2)$_m$–C(=O)N(R^6)–PEG–SS–(C_1-C_{12} alkyldiyl)–OC(=O)–;

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

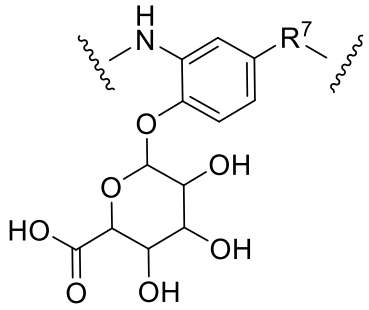
Q–(CH_2)$_m$–C(=O)N(R^6)–PEG–C(=O)N(R^6)–(C_1-C_{12} alkyldiyl)–C(=O)–PEP–;

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

$Q–(CH_2)_m–C(=O)–PEP–N(R^6)–(C_1\text{-}C_{12}$ alkyldiyl)$N(R^6)C(=O)–(C_2\text{-}C_5$ monoheterocyclyldiyl)–;

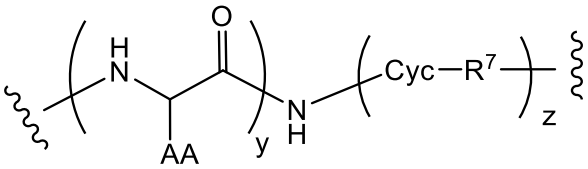
PEG has the formula: $–(CH_2CH_2O)_n–(CH_2)_m–$; m is an integer from 1 to 5, and n is an integer from 2 to 50;

Gluc has the formula:



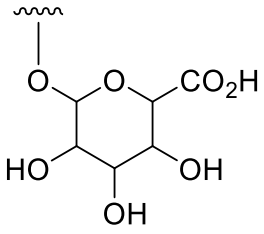
;

PEP has the formula:



where AA is independently selected from a natural or unnatural amino acid side chain, or one or more of AA, and an adjacent nitrogen atom form a 5-membered ring proline amino acid, and the wavy line indicates a point of attachment;

Cyc is selected from $C_6\text{-}C_{20}$ aryldiyl and $C_1\text{-}C_{20}$ heteroaryldiyl, optionally substituted with one or more groups selected from F, Cl, NO_2, –OH, $–OCH_3$, and a glucuronic acid having the structure:



;

R^7 is selected from the group consisting of $–CH(R^8)O–$, $–CH_2–$, $–CH_2N(R^8)–$, and $–CH(R^8)O–C(=O)–$, where R^8 is selected from H, $C_1\text{-}C_6$ alkyl, $C(=O)–C_1\text{-}C_6$ alkyl, and $–C(=O)N(R^9)_2$, where R^9 is independently selected from the group consisting of H, $C_1\text{-}C_{12}$ alkyl, and $–(CH_2CH_2O)_n–(CH_2)_m–OH$, where m is an integer from 1 to 5, and n is an integer from 2 to 50, or two R^9 groups together form a 5- or 6-membered heterocyclyl ring;

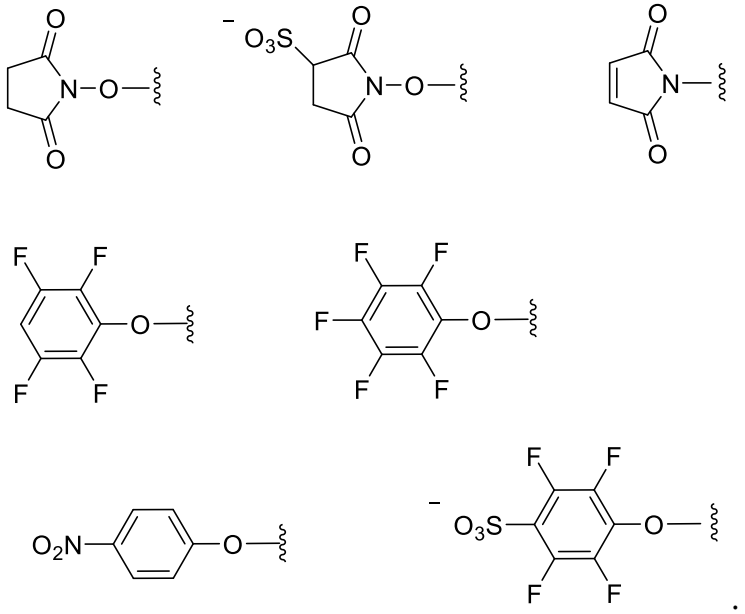
y is an integer from 2 to 12;

z is 0 or 1;

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^-; and

alkyl, alkyldiyl, alkenyl, alkenyldiyl, alkynyl, alkynyldiyl, aryl, aryldiyl, carbocyclyl, carbocyclyldiyl, heterocyclyl, heterocyclyldiyl, heteroaryl, and heteroaryldiyl are independently and optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, $–CH_3$, $–CH_2CH_3$, $–CH{=}CH_2$, $–C{\equiv}CH$, $–C{\equiv}CCH_3$, $–CH_2CH_2CH_3$, $–CH(CH_3)_2$, $–CH_2CH(CH_3)_2$, $–CH_2OH$, $–CH_2OCH_3$, $–CH_2CH_2OH$, $–C(CH_3)_2OH$, $–CH(OH)CH(CH_3)_2$, $–C(CH_3)_2CH_2OH$, $–CH_2CH_2SO_2CH_3$, $–CH_2OP(O)(OH)_2$, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CF_3$, $–CH_2CHF_2$, $–CH(CH_3)CN$, $–C(CH_3)_2CN$, $–CH_2CN$, $–CH_2NH_2$, $–CH_2NHSO_2CH_3$, $–CH_2NHCH_3$, $–CH_2N(CH_3)_2$, $–CO_2H$, $–COCH_3$, $–CO_2CH_3$, $–CO_2C(CH_3)_3$, $–COCH(OH)CH_3$, $–CONH_2$, $–CONHCH_3$, $–CON(CH_3)_2$, $–C(CH_3)_2CONH_2$, $–NH_2$, $–NHCH_3$, $–N(CH_3)_2$, $–NHCOCH_3$, $–N(CH_3)COCH_3$, $–NHS(O)_2CH_3$, $–N(CH_3)C(CH_3)_2CONH_2$, $–N(CH_3)CH_2CH_2S(O)_2CH_3$, $–NHC(=NH)H$, $–NHC(=NH)CH_3$, $–NHC(=NH)NH_2$, $–NHC(=O)NH_2$, $–NO_2$, =O, –OH, $–OCH_3$, $–OCH_2CH_3$, $–OCH_2CH_2OCH_3$, $–OCH_2CH_2OH$, $–OCH_2CH_2N(CH_3)_2$, $–O(CH_2CH_2O)_n–(CH_2)_mCO_2H$, $–O(CH_2CH_2O)_nH$, $–OCH_2F$, $–OCHF_2$, $–OCF_3$, $–OP(O)(OH)_2$, $–S(O)_2N(CH_3)_2$, $–SCH_3$, $–S(O)_2CH_3$, and $–S(O)_3H$.

25. The STING agonist-linker intermediate compound of claim 24 wherein Q is selected from:



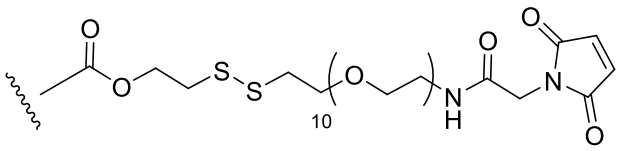
.

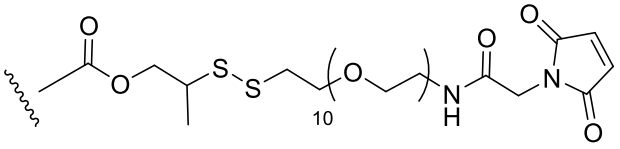
26. The STING agonist-linker intermediate compound of claim 24 wherein Q is phenoxy substituted with one or more groups independently selected from F, Cl, NO_2, and SO_3^-.

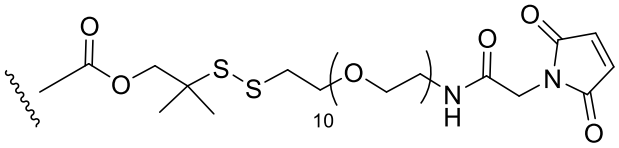
27. The STING agonist-linker intermediate compound of claim 24 wherein Q is 2,3,5,6-tetrafluorophenoxy, or 2,3,5,6-tetrafluoro-4-sulfonato-phenoxy.

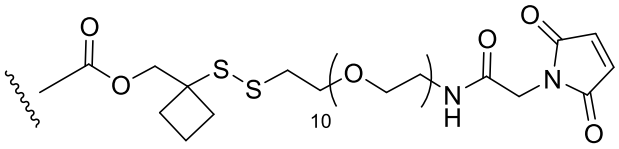
28. The STING agonist-linker intermediate compound of claim 24 wherein Q is maleimide.

29. The STING agonist-linker intermediate compound of claim 24 wherein L is selected from the structures:









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

30. A STING agonist-linker intermediate compound selected from Table 1.

31. An immunoconjugate prepared by conjugation of an antibody with a STING agonist-linker intermediate compound of any one of claims 24 to 30.

32. A pharmaceutical composition comprising a therapeutically effective amount of an immunoconjugate of any one of claims 1 to 3, and one or more pharmaceutically acceptable diluent, vehicle, carrier or excipient.

33. Use of an immunoconjugate according to any one of claims 1 to 3, in the manufacture of a medicament for treating cancer, wherein the cancer is selected from bladder cancer, salivary gland cancer, endometrial 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 .

34. The use of claim 33, wherein the cancer is susceptible to a pro-inflammatory response induced by STING agonism.

35. A method of preparing an immunoconjugate of Formula I of claim 1 wherein a STING agonist-linker intermediate compound of claim 24 is conjugated with the antibody.