WHAT IS CLAIMED IS:

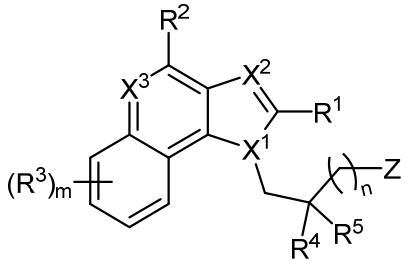
1. Use of a chimeric antigen receptor (CAR) T-cell-rejuvenating conjugate in the manufacture of a medicament for rejuvenating exhausted CAR T-cells in a subject with a cancer being treated with:

(a) (i) a vector comprising a promoter operably linked to a nucleic acid sequence encoding a CAR or (ii) T-cells expressing the CAR, wherein the CAR binds a first targeting moiety, a second targeting moiety, or the first targeting moiety and the second targeting moiety, and

(b) a cancer-binding conjugate comprising a ligand that binds a cancer cell with specificity and conjugated with a third targeting moiety, wherein the ligand that binds a cancer and the third targeting moiety are optionally conjugated via a first linker, and wherein the first targeting moiety of (a) or the third targeting moiety of (b) comprises the same type of targeting moiety;

wherein the T-cell rejuvenating conjugate further comprises an agonist of toll-like receptor 7, toll-like receptor 8, or toll-like receptor 7 and toll-like receptor 8 (agonist of TLR7/8) conjugated with either the first targeting moiety or the second targeting moiety, wherein the agonist and either of the first targeting moiety or the second targeting moiety are conjugated via a second linker,

wherein the CAR T-cell-rejuvenating conjugate has the structure:



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is an acyclic or cyclic alkyl, which is optionally substituted with one or more substituents independently selected from an alkyl, halo, heteroalkyl, alkoxy, and cycloalkyl;

R^2 is $-NR^{2x}R^{2y}$, hydrogen (H), $-OR^z$, $-SO_2N(R^z)_2$, or N_3, wherein:

R^{2x} and R^{2y} are each independently H, -$N(R^z)_2$, -$CON(R^z)_2$, -$C(R^z)_2$-$N(R^z)_2$, -CS-$N(R^z)_2$, or an alkyl that is optionally substituted with one or more substituents independently selected from oxo, halo, alkyl, heteroalkyl, alkoxy, and cycloalkyl;

each R^z is independently H or alkyl, which is optionally substituted; or

R^{2x} and R^{2y} are taken together to form a 3-10 membered mono- or bicyclic heterocycloalkyl, which is optionally substituted;

each R^3 is independently H, halo, -N_3, -CN, -NO_2, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkoxy, aryl, heteroaryl, heterocycloalkyl, amino, hydroxy, carbonyl, or thiol, wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, or alkoxy that is optionally substituted;

R^4 and R^5 are each independently alkyl, alkoxy, halo, or cycloalkyl, wherein the alkyl, alkoxy, or cycloalkyl that is optionally substituted;

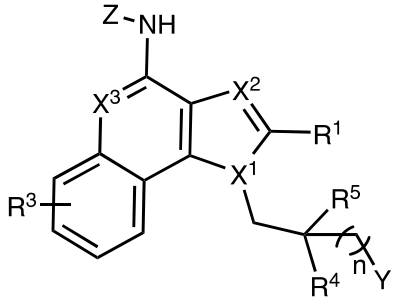
X^1, X^2, and X^3 are independently N or CR^q, wherein each R^q is independently H, halo, or an optionally substituted alkyl;

Z is G-L-, wherein L is the second linker and G is the first targeting moiety or the second targeting moiety;

n in Formula (I) is 1-6; and

m in Formula (I) is 0-4; or

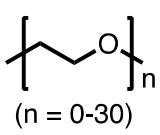
wherein the CAR T-cell-rejuvenating conjugate has the structure:

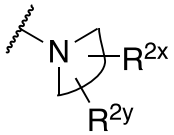


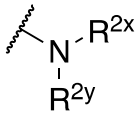
Formula (II)

or is a pharmaceutically acceptable salt thereof, wherein:

R^1, R^3, R^4, and R^5 are each independently H, alkyl, alkoxyl, alkenyl, alkynyl, alicyclic, aryl, biaryl, halo, heteroaryl, -COR^{2x},



, 

, or 

, wherein each of R^{2x} and R^{2y} is independently selected from the group consisting of H, -OH, $-CH_2$-OH, $-NH_2$, $-CH_2$-NH_2, -COOMe, -COOH, $-CONH_2$, $-COCH_3$, alkyl, alkenyl, alkynyl, alicyclic, aryl, biaryl, and heteroaryl;

Z is G-L-, wherein L is the second linker and G is the first targeting moiety or the second targeting moiety;

X^1, X^2, and X^3 are independently CR^q or N, wherein each R^q is independently H, halo, or optionally substituted alkyl;

Y is H, $-OR^z$, $-NR^{2x}R^{2y}$, $-SR^z$, $-SOR^z$, $-SO_3R^z$, $-N_3$, $-COR^z$, $-COOR^z$, $-CON(R^z)_2$, $-COSR^z$, $-SO_2N(R^z)_2$, or $-CON(R^z)_2$, wherein:

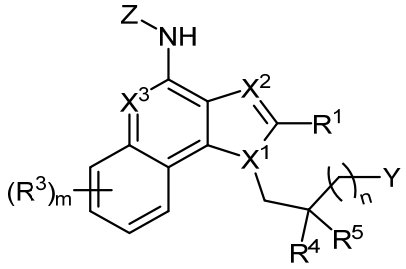
R^{2x} and R^{2y} are each independently H, $-N(R^z)_2$, $-CON(R^z)_2$, $-C(R^z)_2$-$N(R^z)_2$, -CS-$N(R^z)_2$, or optionally substituted alkyl;

each R^z is independently H or optionally substituted alkyl; or

R^{2x} and R^{2y} are taken together to form an optionally substituted heterocycloalkyl; and

n in Formula (II) is 0-30; or

wherein the CAR T-cell-rejuvenating conjugate has the structure:



Formula (III)

or is a pharmaceutically acceptable salt thereof, wherein:

R^1 is an acyclic or cyclic alkyl, which is optionally substituted with one or more substituents independently selected from halo, alkyl, heteroalkyl, alkoxy, and cycloalkyl;

Y is H, $-OR^z$, $-NR^{2x}R^{2y}$, $-SR^z$, $-SOR^z$, $-SO_3R^z$, $-N_3$, $-COR^z$, $-COOR^z$, $-CONR^z_2$, $-COSR^z$, $-SO_2N(R^z)_2$, or $-CON(R^z)_2$, wherein: R^{2x} and R^{2y} are each independently H, $-N(R^z)_2$, $-CON(R^z)_2$, $-C(R^z)_2$-$N(R^z)_2$, -CS-$N(R^z)_2$, or an alkyl that is optionally substituted

with one or more substituents independently selected from oxo, halo, alkyl, heteroalkyl, alkoxy, and cycloalkyl;

each R^z is independently H or an optionally substituted alkyl; or

R^{2x} and R^{2y} are taken together to form a 3-10 membered mono- or bicyclic heterocycloalkyl, which is optionally substituted;

each R^3 is independently halo, $-N_3$, -CN, $-NO_2$, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkoxy, aryl, heteroaryl, heterocycloalkyl, amino, hydroxy, carbonyl, or thiol, wherein the alkyl, alkoxy, heteroalkyl, cycloalkyl, or heterocycloalkyl that is optionally substituted;

R^4 and R^5 are each independently alkyl, alkoxy, halogen, or cycloalkyl, wherein the alkyl, alkoxy, or cycloalkyl and is optionally substituted;

X^1, X^2, and X^3 are independently CR^q or N, wherein each R^q is independently H, halogen, or optionally substituted alkyl;

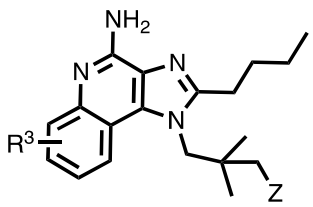
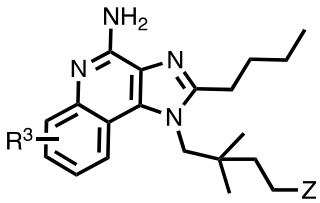
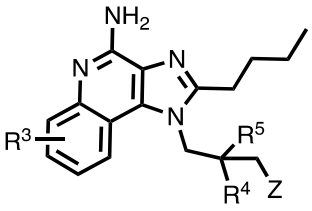
Z is L-G, wherein L is the second linker and G is the first targeting moiety or the second targeting moiety;

n in Formula (III) is 0-30; and

m in Formula (III) is 0-4.

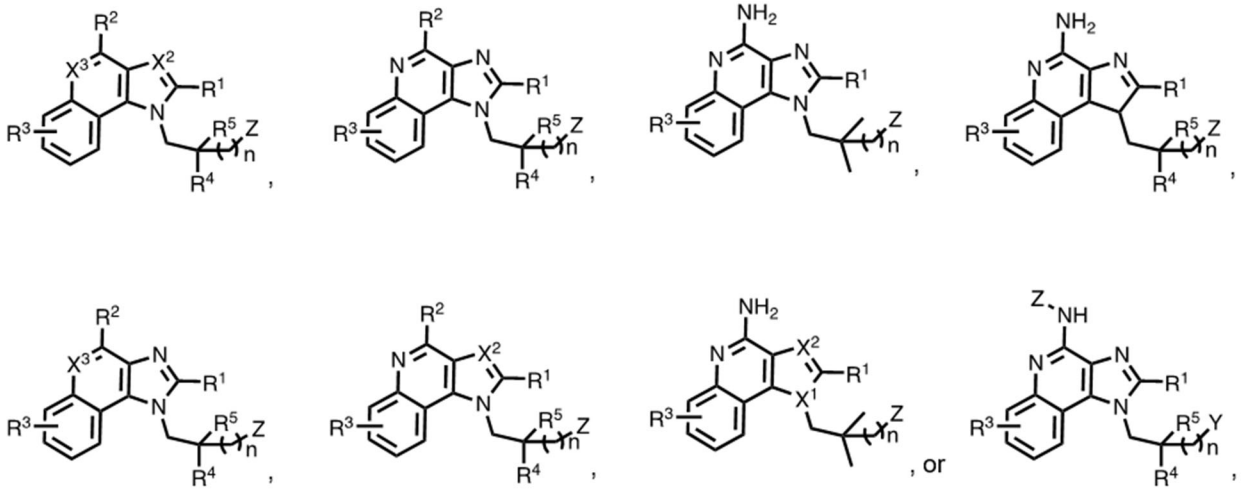
2. The use of claim 1, wherein each of X^1, X^2, and X^3 of Formula (I), Formula (II), or Formula (III) is N.

3. The use of claim 2, wherein the CAR T-cell-rejuvenating conjugate has the structure:

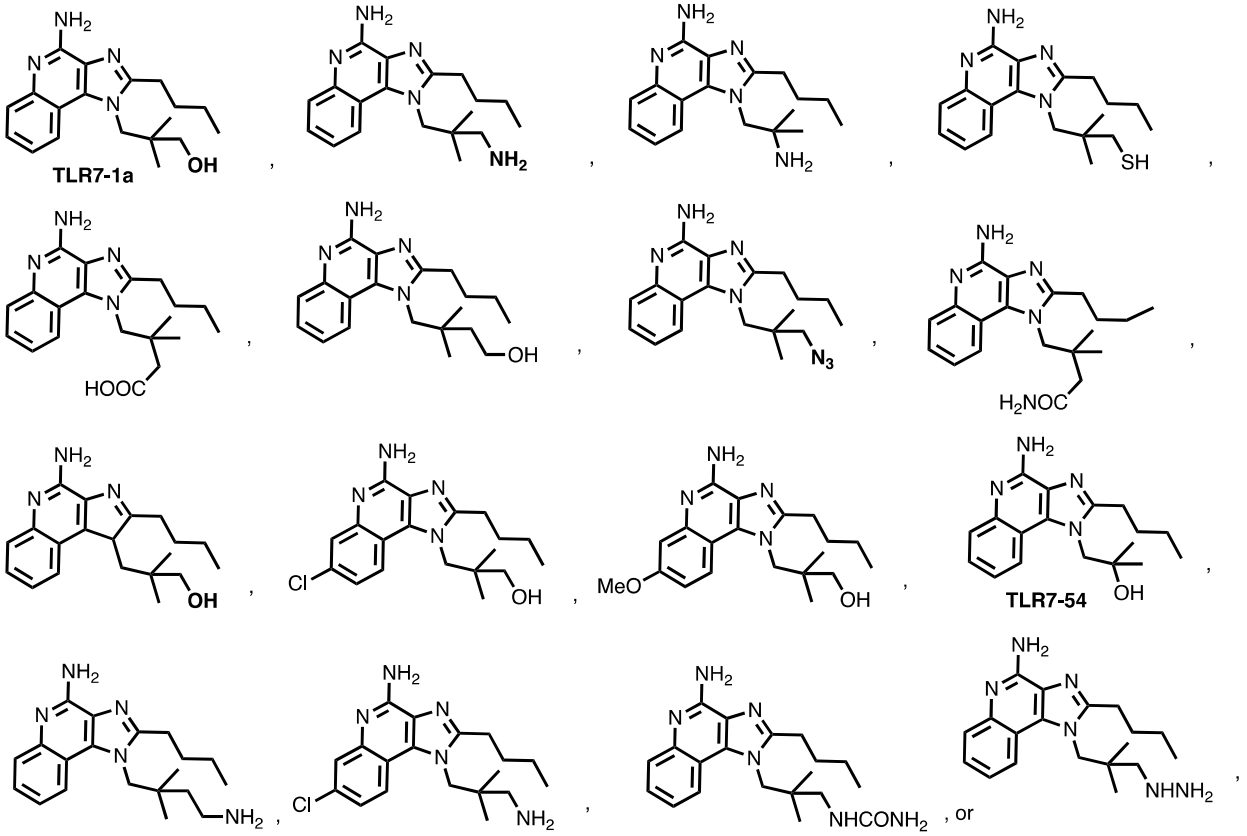
or is a pharmaceutically acceptable salt of any of the foregoing structures.

4. The use of claim 1, wherein the CAR T-cell-rejuvenating conjugate has the structure:



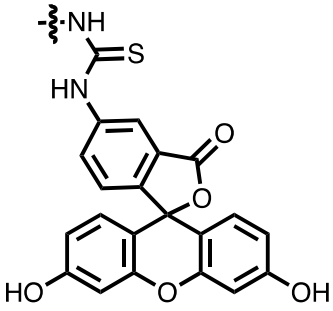
or is a pharmaceutically acceptable salt of any of the foregoing structures.

5. The use of claim 1, wherein the CAR T-cell-rejuvenating conjugate comprises an agonist of TLR7/8 and has the structure:

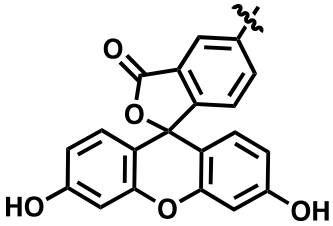


or is a pharmaceutically acceptable salt of any of the foregoing structures.

6. The use of any of claims 1-5, wherein the first targeting moiety, the second targeting moiety, or the first targeting moiety and the second targeting moiety is/are a group or comprise(s) a group with the structure:

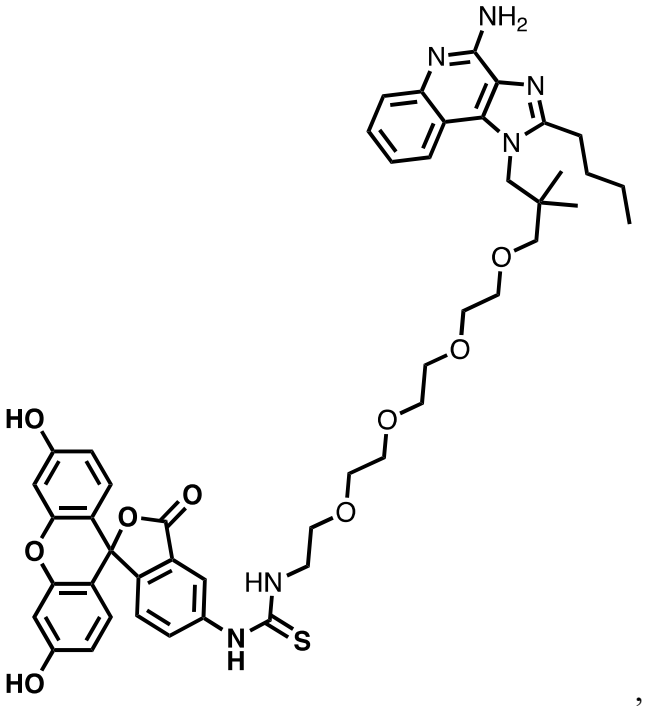


Formula (V), or

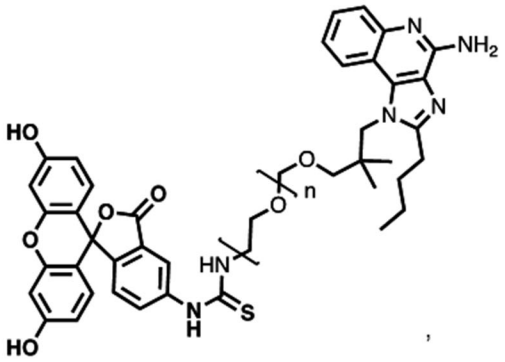


Formula (IV).

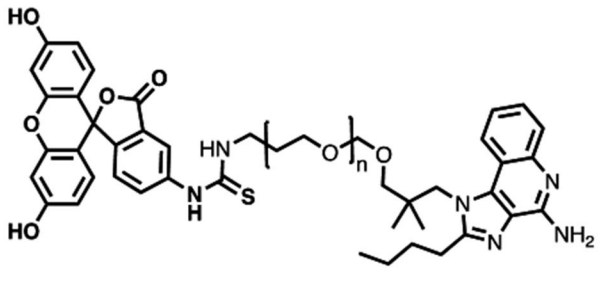
7. The use of claim 1, wherein the CAR T-cell-rejuvenating conjugate has the structure:



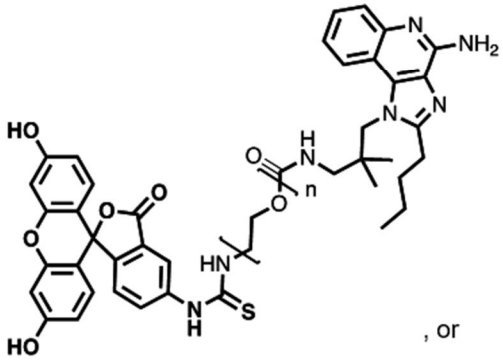
,



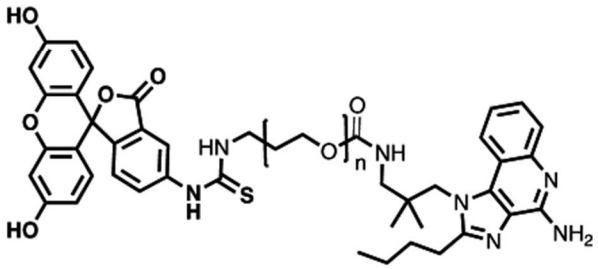
,



,



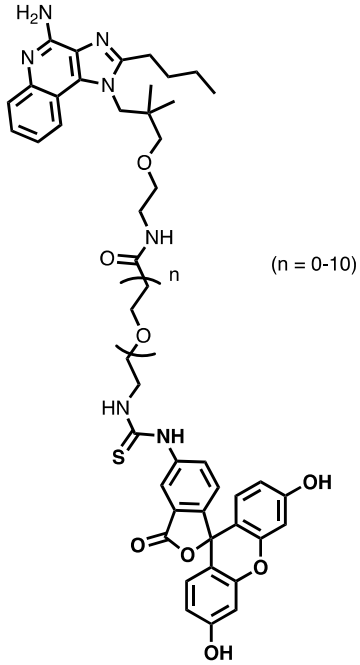
, or



,

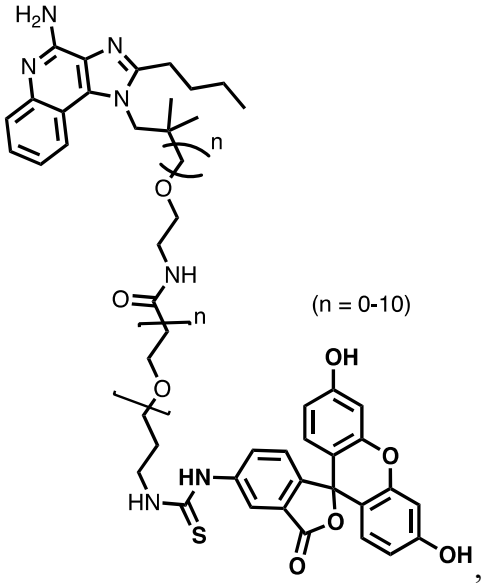
wherein n = 0-200, or is a pharmaceutically acceptable salt of any of the foregoing structures.

8. The use of claim 1, wherein the CAR T-cell-rejuvenating conjugate has the structure:



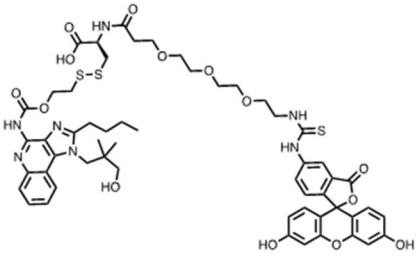
(n = 0-10)

,

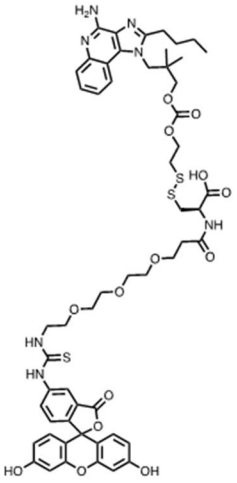


(n = 0-10)

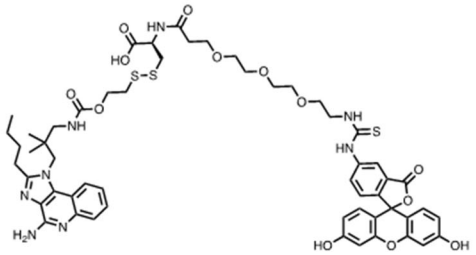
,



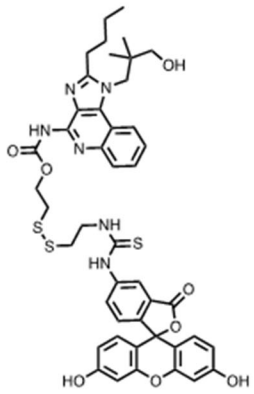
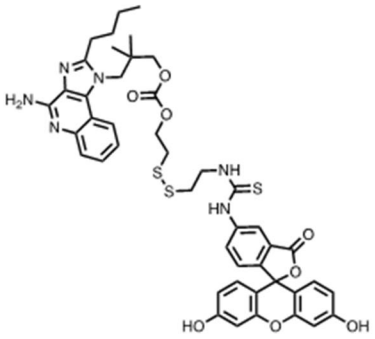
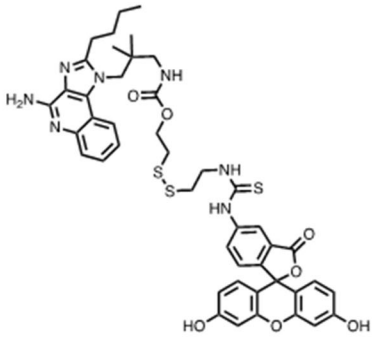
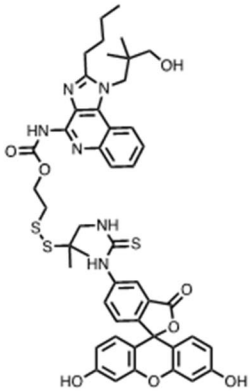
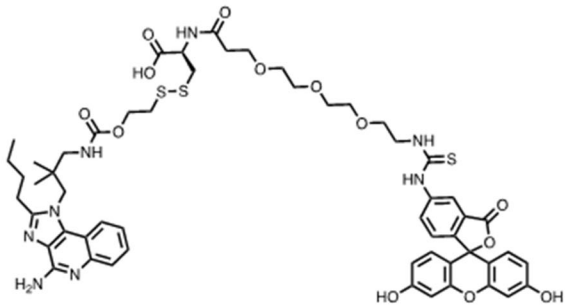
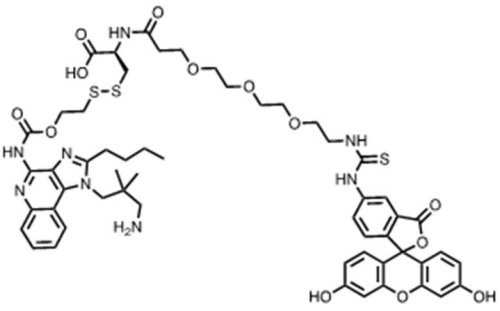
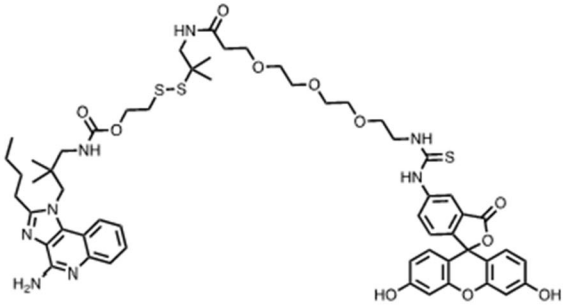
,

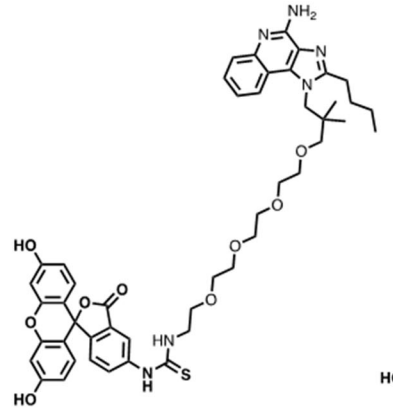
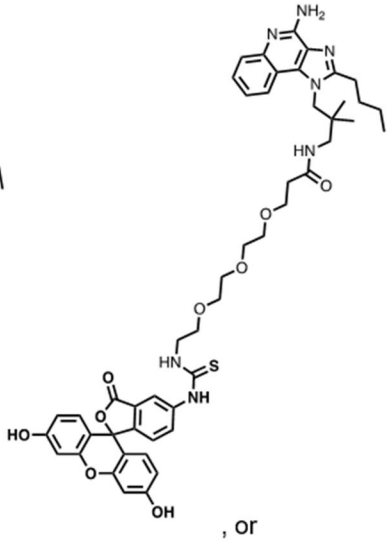
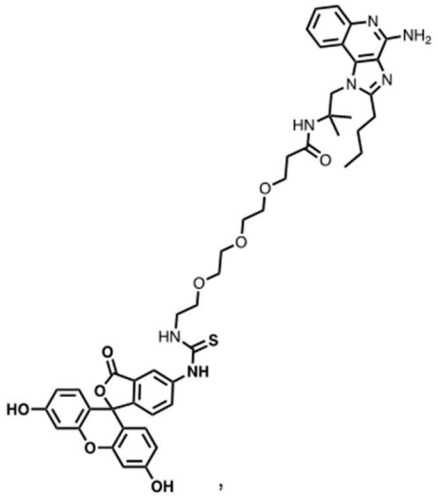
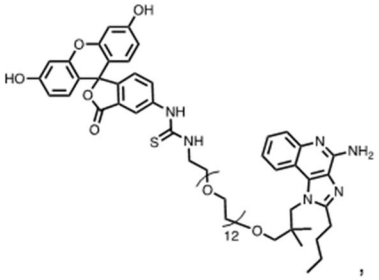
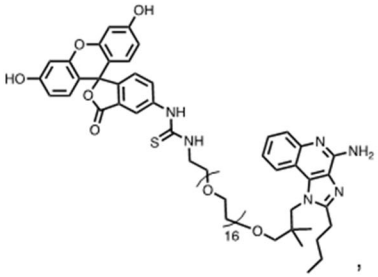
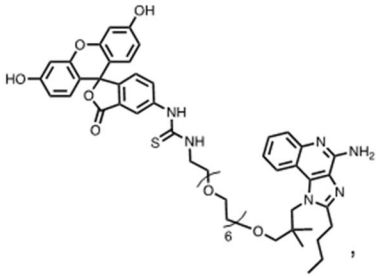
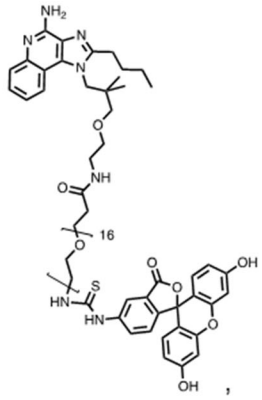
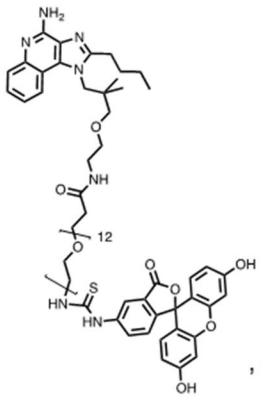
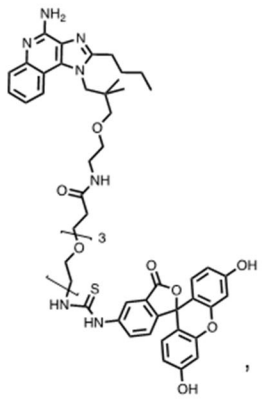


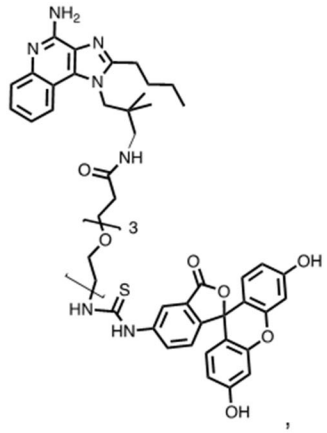
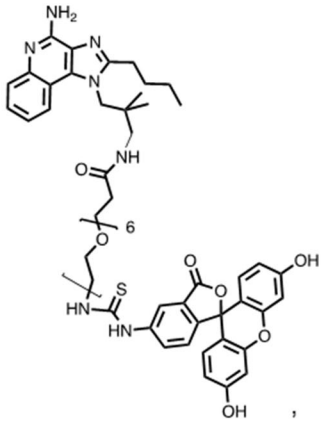
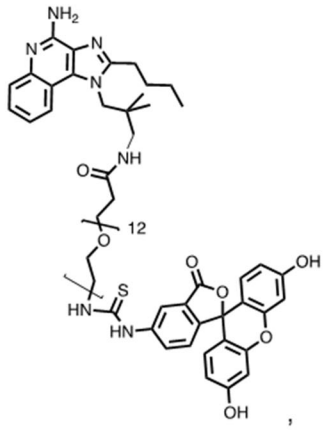
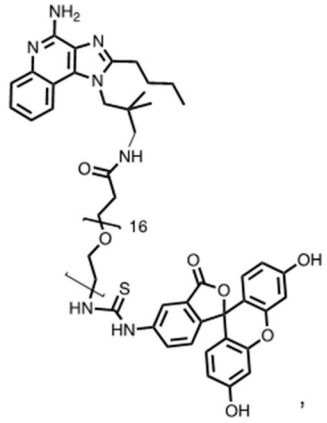
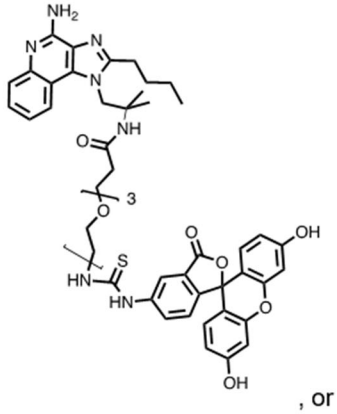
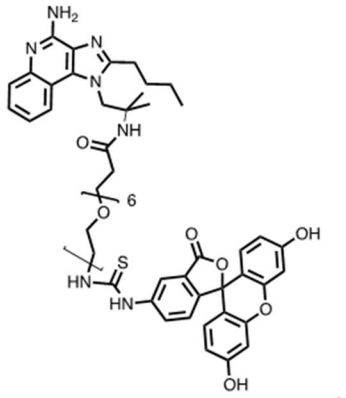
,



,


,

,

,

,

,

, or

,


,

, or

,

,

,

,

,

, or

,


,

,

,

,

, or

,

or is a pharmaceutically acceptable salt of any of the foregoing structures.

9. The use of any one of claims 1-5, wherein the ligand that binds a cancer cell with specificity is selected from the group consisting of a folate, a 5-methyltetrahydrofolate, a 2-[3-(1,3-dicarboxypropyl)ureido]pentanedioic acid (DUPA) ligand, a neurokinin 1 receptor (NK-1R) ligand, a carbonic anhydrase IX (CAIX) ligand, a ligand of gamma glutamyl transpeptidase, a ligand of luteinizing hormone releasing hormone (LHRHR), a ligand of CD73, a ligand of heat shock protein (HSP), a ligand of glucose transporter 1 (glut-1), a ligand of fibroblast activation protein, a ligand of a natural killer group 2D receptor (NKG2D) ligand, and a cholecystokinin B receptor (CCKBR or CCK2) ligand.

10. The use of any one of claims 1-5, wherein the first targeting moiety and the second targeting moiety are independently selected from the group consisting of 2,4-dinitrophenyl

(DNP), L-rhamnose, tacrolimus (FK506), 2,4,6-trinitrophenol (TNP), biotin, rapamycin, digoxigenin, folate, 5-methyl tetrahydrofolate, fluorescein, fluorescein isothiocyanate (FITC), NHS-fluorescein, pentafluorophenyl ester, tetrafluorophenyl ester, knottin, centyrin, and DARPin.

11. The use of any one of claims 1-5, wherein:

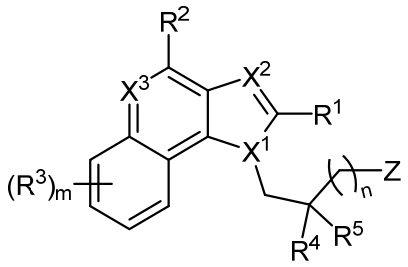
the first targeting moiety and the second targeting moiety are independently selected from the group consisting of DNP, FK506, TNP, biotin, rapamycin, digoxigenin, folate, 5-methyl tetrahydrofolate, fluorescein, FITC, NHS-fluorescein, pentafluorophenyl ester, tetrafluorophenyl ester, knottin, centyrin, and DARPin; and

the ligand that binds a cancer cell with specificity is selected from the group consisting of a folate, a DUPA ligand, a NK-1R ligand, a CAIX ligand, a ligand of gamma glutamyl transpeptidase, a ligand of LHRHR, a ligand of CD73, a ligand of HSP, a ligand of glut-1, a ligand of fibroblast activation protein, a ligand of a NKG2D ligand, and a CCKBR or CCK2 ligand.

12. The use of any one of claims 1-5, wherein the first linker and the second linker are independently releasable or non-releasable, and/or the first linker, the second linker, or both the first linker and the second linker comprise PEG.

13. The use of any one of claims 1-5, wherein the first linker and the second linker independently comprise C_1-C_{20} alkyl, alkylene, heteroalkylene, -O-alkynylene, alkenylene, acyl, aryl, heteroaryl, amide, oxime, ether, ester, triazole, -S-S, -CO-O-$(CH_2)_n$-S-S- (where n = 2-6), -O-CO-O-$(CH_2)_n$-S-S- (where n = 2-6), -S-CO-O-$(CH_2)_n$-S-S- (where n = 2-6), -NH-CO-O-$(CH_2)_n$-S-S- (where n = 2-6), carboxylate, carbonate, carbamate, urea, thiourea, polyethylene glycol (PEG), polyproline, oligo-(4-piperidine) carboxylic acid, oligo piperidine, amino acid, peptide, saccharo-peptide, sugar, peptidoglycan, a polyvinylpyrrolidone, pluronic F-127, or any combination of two or more of the foregoing.

14. A chimeric antigen receptor (CAR) T-cell-rejuvenating conjugate comprising an agonist of toll-like receptor 7, toll-like receptor 8, or toll-like receptor 7 and toll-like receptor 8 conjugated via a linker with a targeting moiety that binds a CAR of a CAR T-cell with specificity, wherein the CAR T-cell-rejuvenating conjugate has the structure:



Formula (I)

or is a pharmaceutically acceptable salt thereof, wherein:

R^1 is an acyclic or cyclic alkyl, which is optionally substituted with one or more substituents independently selected from an alkyl, halo, heteroalkyl, alkoxy, and cycloalkyl;

R^2 is $-NR^{2x}R^{2y}$, H, $-OR^z$, $-SO_2N(R^z)_2$, or N_3, wherein:

R^{2x} and R^{2y} are each independently hydrogen (H), $-N(R^z)_2$, $-CON(R^z)_2$, $-C(R^z)_2-N(R^z)_2$, $-CS-N(R^z)_2$, or an alkyl, which is optionally substituted with one or more substituents independently selected from oxo, halo, alkyl, heteroalkyl, alkoxy, and cycloalkyl;

each R^z is independently H or alkyl that is optionally substituted; or

R^{2x} and R^{2y} are taken together to form a 3-10 membered mono- or bicyclic heterocycloalkyl, which is optionally substituted;

each R^3 is independently H, halo, $-N_3$, -CN, $-NO_2$, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkoxy, aryl, heteroaryl, heterocycloalkyl, amino, hydroxy, carbonyl, or thiol, wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, or alkoxy that is optionally substituted;

R^4 and R^5 are each independently alkyl, alkoxy, halo, or cycloalkyl, wherein the alkyl, alkoxy, or cycloalkyl that is optionally substituted;

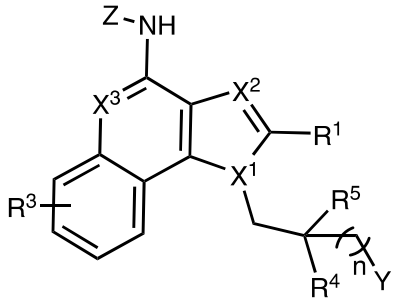
X^1, X^2, and X^3 are independently N or CR^q, wherein each R^q is independently H, halo, or optionally substituted alkyl;

Z is G-L-, wherein L is the linker and G is the targeting moiety;

n in Formula (I) is 1-6; and

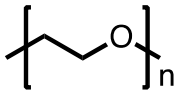
m in Formula (I) is 0-4; or

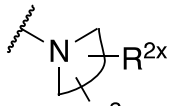
wherein the CAR T-cell-rejuvenating conjugate has the structure:

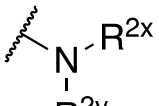


Formula (II)

or is a pharmaceutically acceptable salt thereof, wherein:

R^1, R^3, R^4, and R^5 are each independently H, alkyl, alkoxyl, alkenyl, alkynyl, alicyclic, aryl, biaryl, halo, heteroaryl, $-COR^{2x}$, 

, 

, or 

, wherein each of R^{2x} and R^{2y} is independently selected from the group consisting of H, -OH, $-CH_2$-OH, $-NH_2$, $-CH_2$-NH_2, -COOMe, -COOH, $-CONH_2$, $-COCH_3$, alkyl, alkenyl, alkynyl, alicyclic, aryl, biaryl, and heteroaryl;

Z is G-L-, wherein L is the linker and G is the targeting moiety;

X^1, X^2, and X^3 are independently CR^q or N, wherein each R^q is independently H, halo, or optionally substituted alkyl;

Y is H, $-OR^z$, $-NR^{2x}R^{2y}$, $-SR^z$, $-SOR^z$, $-SO_3R^z$, $-N_3$, $-COR^z$, $-COOR^z$, $-CON(R^z)_2$, $-COSR^z$, $-SO_2N(R^z)_2$, or $-CON(R^z)_2$, wherein:

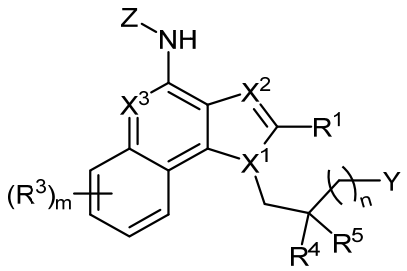
R^{2x} and R^{2y} are each independently hydrogen, $-N(R^z)_2$, $-CON(R^z)_2$, $-C(R^z)_2$-$N(R^z)_2$, -CS-$N(R^z)_2$, or optionally substituted alkyl;

each R^z is independently H or optionally substituted alkyl; or

R^{2x} and R^{2y} are taken together to form an optionally substituted heterocycloalkyl; and

n in Formula (II) is 0-30; or

wherein the CAR T-cell-rejuvenating conjugate has the structure:



Formula (III)

or is a pharmaceutically acceptable salt thereof, wherein:

R^1 is an acyclic or cyclic alkyl, which is optionally substituted with one or more substituents independently selected from halo, alkyl, heteroalkyl, alkoxy, and cycloalkyl;

Y is H, $-OR^z$, $-NR^{2x}R^{2y}$, $-SR^z$, $-SOR^z$, $-SO_3R^z$, $-N_3$, $-COR^z$, $-COOR^z$, $-CONR^z_2$, $-COSR^z$, $-SO_2N(R^z)_2$, or $-CON(R^z)_2$, wherein:

each R^z is independently H or optionally substituted alkyl;

R^{2x} and R^{2y} are each independently H, $-N(R^z)_2$, $-CON(R^z)_2$, $-C(R^z)_2$-$N(R^z)_2$, $-CS$-$N(R^z)_2$, or alkyl that is optionally substituted with one or more substituents independently selected from oxo, halo, alkyl, heteroalkyl, alkoxy, and cycloalkyl; or

R^{2x} and R^{2y} are taken together to form a 3-10 membered mono- or bicyclic heterocycloalkyl, which is optionally substituted;

each R^3 is independently halo, $-N_3$, -CN, $-NO_2$, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkoxy, aryl, heteroaryl, heterocycloalkyl, amino, hydroxy, carbonyl, or thiol, wherein the alkyl, alkoxy, heteroalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted;

R^4 and R^5 are each independently alkyl, alkoxy, halogen, or cycloalkyl, wherein the alkyl, alkoxy, or cycloalkyl is optionally substituted;

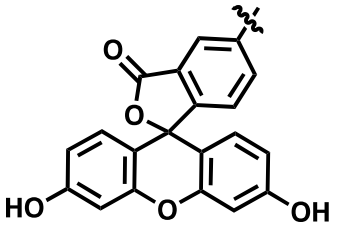
X^1, X^2, and X^3 are independently CR^q or N, wherein each R^q is independently hydrogen, halogen, or optionally substituted alkyl;

Z is L-G, wherein L is the linker and G is the targeting moiety;

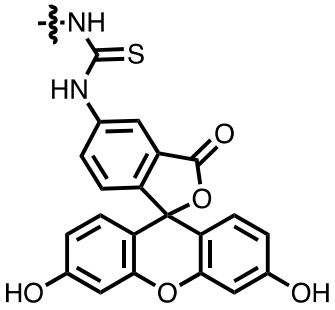
n in Formula (III) is 0-30; and

m in Formula (III) is 0-4; and

wherein G in Formula (I), Formula (II) or Formula (III) is a group or comprises a group with the structure:



or

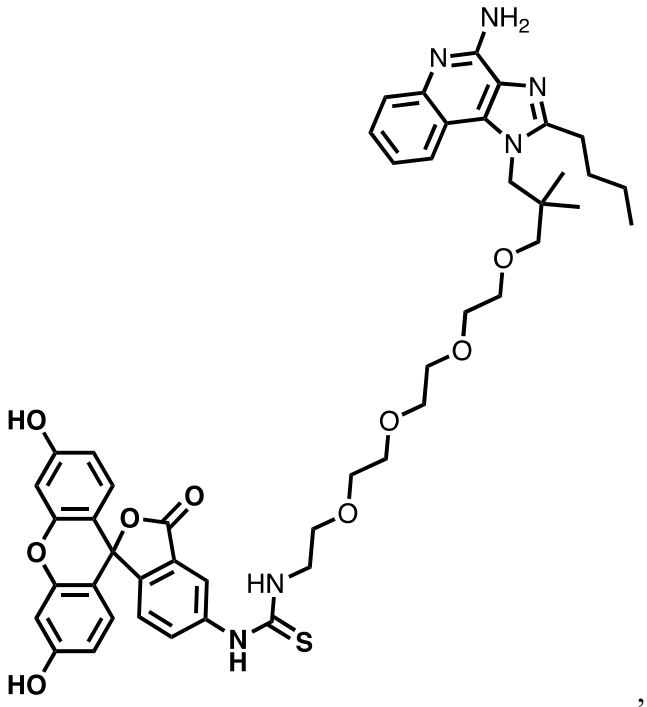


Formula (IV) Formula (V)

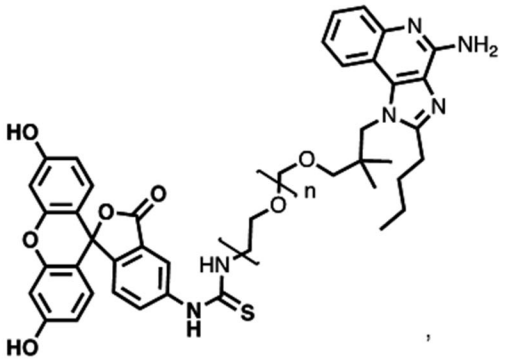
or is a pharmaceutically acceptable salt thereof.

15. The CAR T-cell-rejuvenating conjugate of claim 14, wherein each of X^1, X^2, and X^3 of Formula (I), Formula (II), and Formula (III) is N.

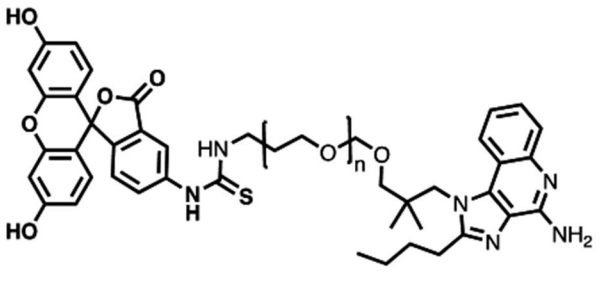
16. A CAR T-cell-rejuvenating conjugate, which has the structure:



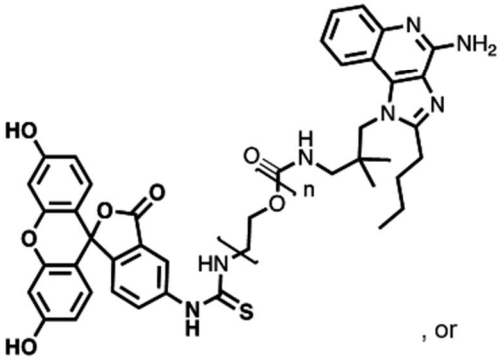
,



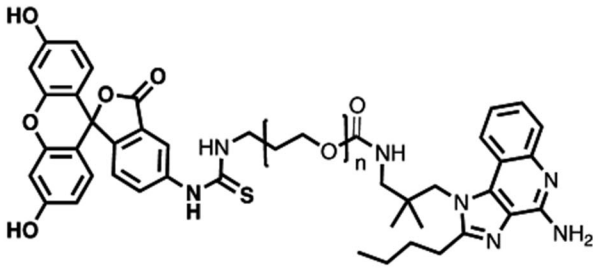
,



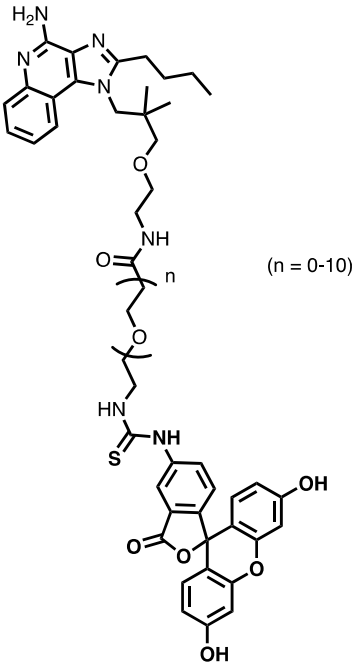
,



, or

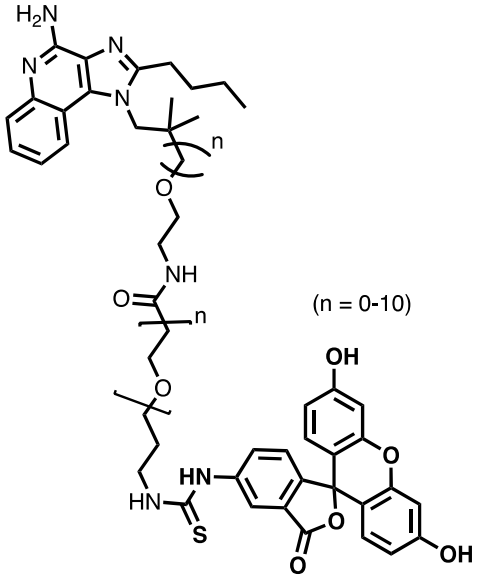


,

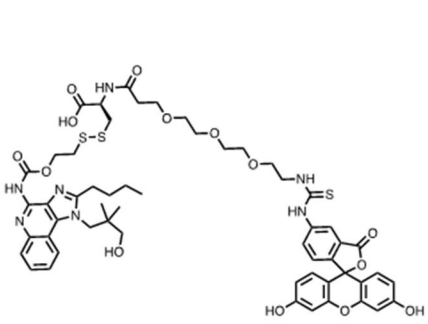
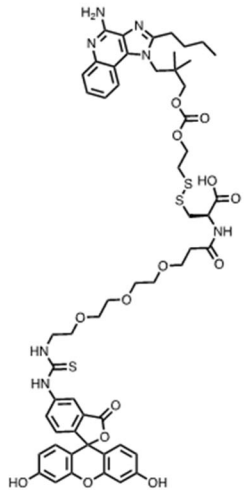
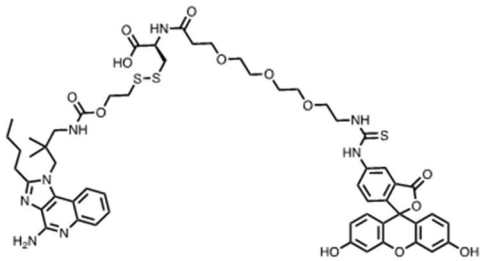


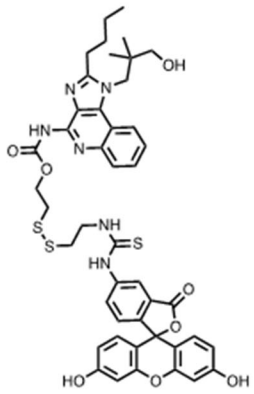
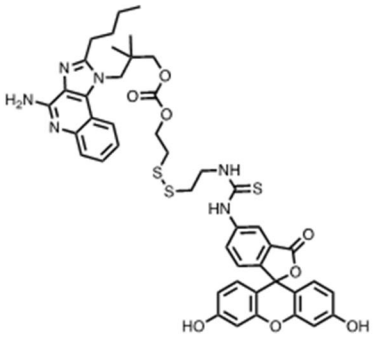
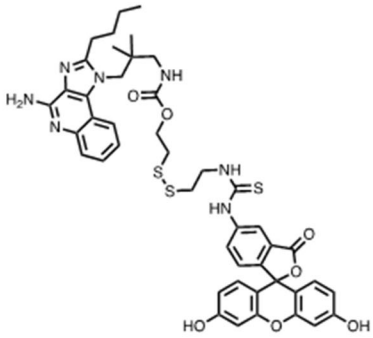
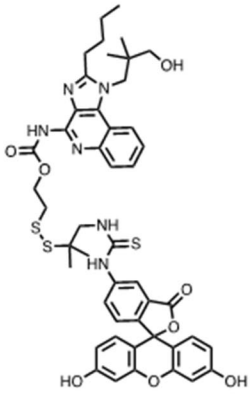
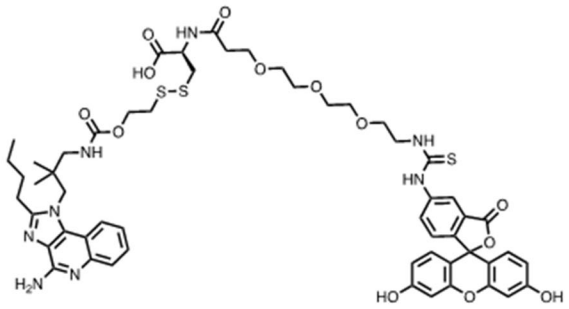
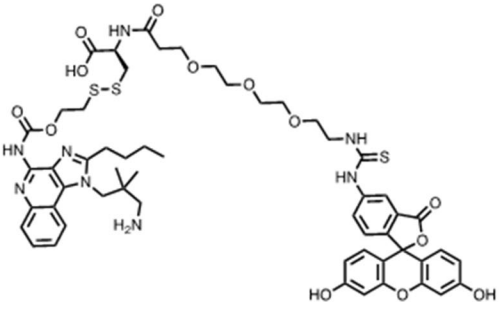
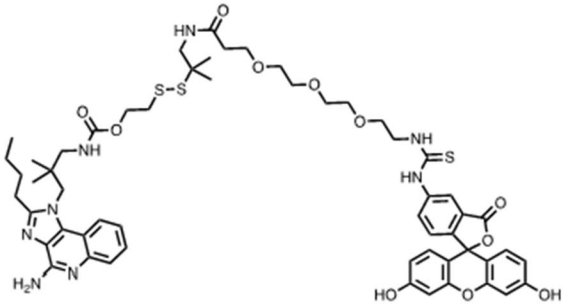
(n = 0-10)

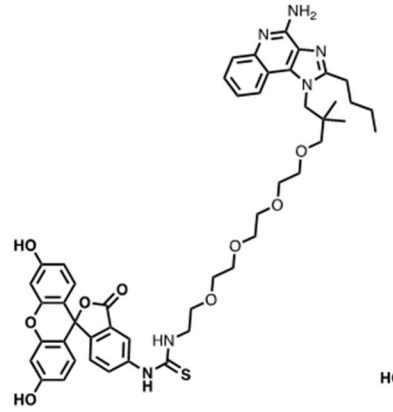
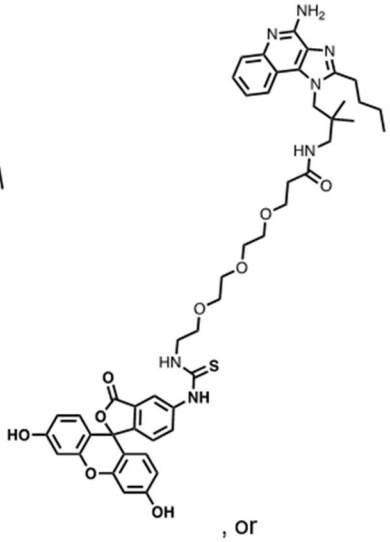
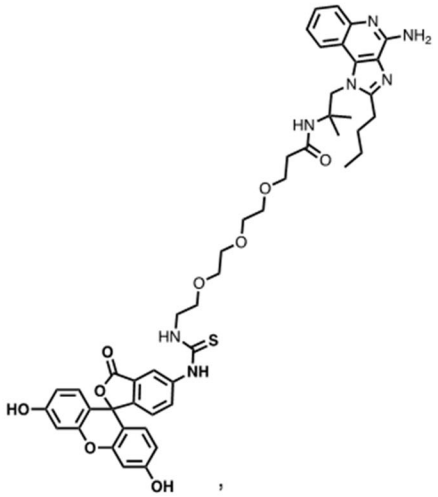
or

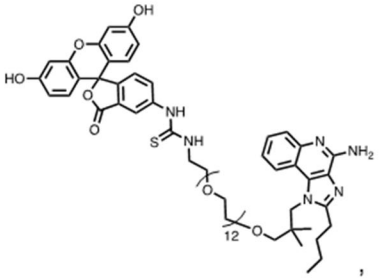
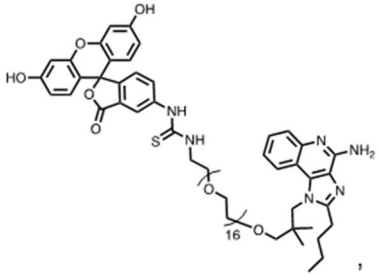
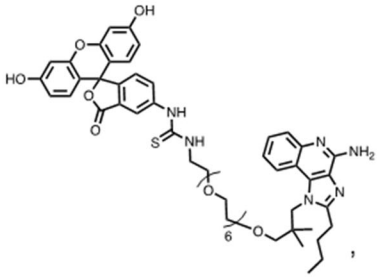


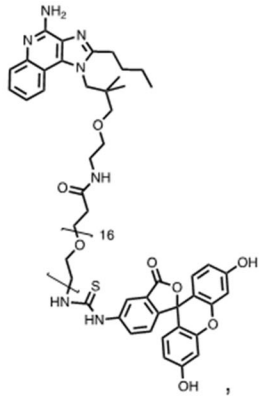
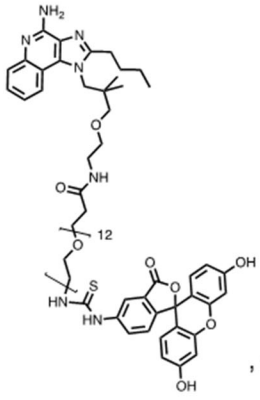
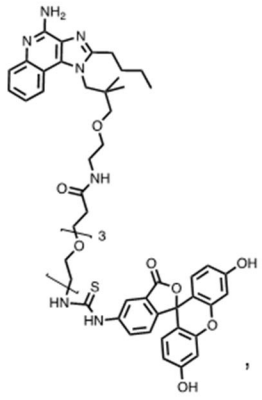
(n = 0-10)

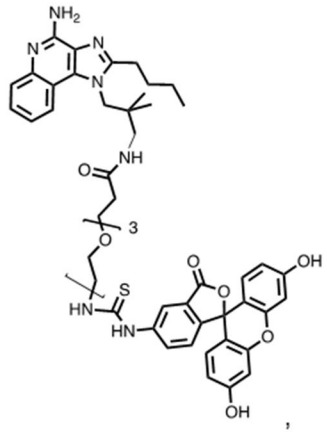
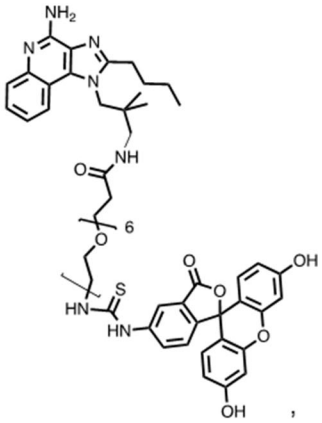
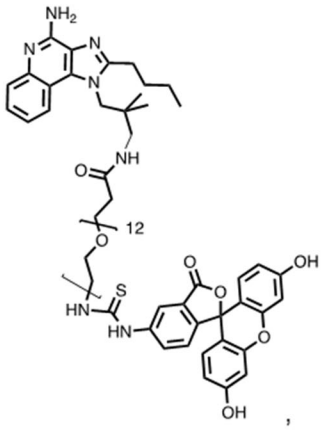
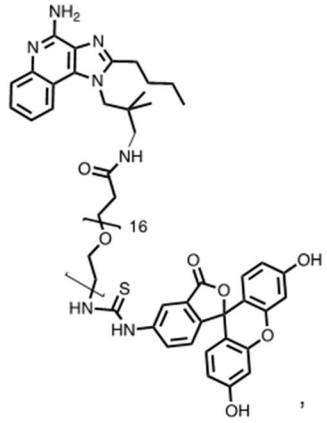
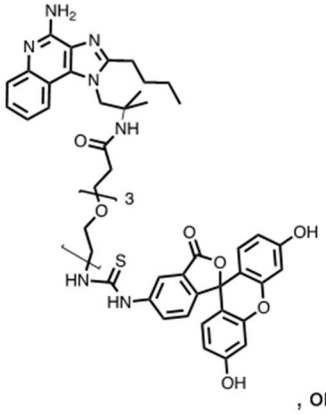
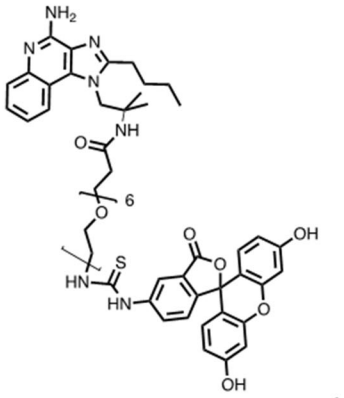

,

,

,


,

,

,

,

,

, or

,


,

, or

,


,

,

,


,

, or

,


,

,

,

,

, or

,

or is a pharmaceutically acceptable salt of any of the foregoing structures.

17. The CAR T-cell-rejuvenating conjugate of claim 14, wherein the linker is releasable or non-releasable.

18. The CAR T-cell-rejuvenating conjugate of claim 14 or 17, wherein the linker comprises C_1-C_{20} alkyl, alkylene, heteroalkylene, -O-alkynylene, alkenylene, acyl, aryl, heteroaryl, amide, oxime, ether, ester, triazole, carboxylate, carbonate, carbamate, urea, thiourea, -S-S-, -CO-O-$(CH_2)_n$-S-S- (where n = 2-6), -O-CO-O-$(CH_2)_n$-S-S- (where n = 2-6), -S-CO-O-$(CH_2)_n$-S-S- (where n = 2-6), -NH-CO-O-$(CH_2)_n$-S-S- (where n = 2-6), PEG, polyproline, oligo-(4-piperidine) carboxylic acid, oligo piperidine, amino acid (e.g., hydrophilic amino acid),

peptide, saccharo-peptide, sugar, peptidoglycan, a polyvinylpyrrolidone, pluronic F-127, or any combination of two or more of the foregoing.

19. The CAR T-cell-rejuvenating conjugate of claim 14 or 17, wherein the linker comprises PEG.

20. A pharmaceutical composition comprising the CAR T-cell-rejuvenating conjugate of any one of claims 14-19 and a pharmaceutically acceptable carrier.