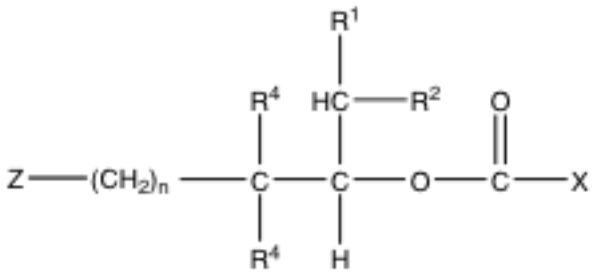
CLAIMS

1. A linker of formula (I),



(I),

wherein:

n is an integer from 0 to 6;

R^1 and R^2 are independently an electron-withdrawing group, alkyl, or H, and wherein at least one of R^1 and R^2 is an electron-withdrawing group;

each R^4 is independently C_1-C_3 alkyl or the two R^4 are taken together with the carbon atom to which they attach to form a 3-6 member ring;

X is a leaving group; and

Z is a functional group for connecting the linker to a macromolecular carrier.

2. The linker of claim 1, wherein X is halogen, active ester, optionally substituted heteroaryl, or -N(R^6)CH_2Cl wherein R^6 is optionally substituted C_1-C_6 alkyl, optionally substituted aryl, or optionally substituted heteroaryl.

3. The linker of claim 1 or 2, wherein X is halogen, N-succinimidyloxy, nitrophenoxy, pentahalophenoxy, imidazolyl, triazolyl, tetrazolyl, or -N(R^6)CH_2Cl.

4. The linker of any one of claims 1-3, wherein Z is selected from the group consisting of amine, aminooxy, ketone, aldehyde, maleimidyl, thiol, alcohol, azide, 1,2,4,6-tetrazinyl, trans-cyclooctenyl, bicyclononynyl, cyclooctynyl, and protected variants thereof.

5. The linker of any one of claims 1-4, wherein the electron-withdrawing group of R^1 and R^2 is

-CN;

-NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

$-COR^3$, $-SOR^3$, or $-SO_2R^3$,

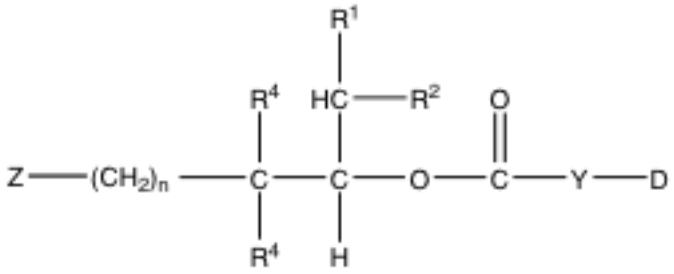
wherein R^3 is H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$ or $-NR^8_2$, wherein each R^8 is independently H or optionally substituted alkyl, or both R^8 groups are taken together with the nitrogen to which they are attached to form a heterocyclic ring; or

SR^9, wherein R^9 is optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl.

6. The linker of any one of claims 1-5, wherein at least one of R^1 and R^2 is –CN or $-SO_2R^3$.

7. The linker of any one of claims 1-6, wherein each R^4 is independently C_1-C_3 alkyl.

8. A linker-drug of formula (II),



(II),

wherein:

n is an integer from 0 to 6;

R^1 and R^2 are independently an electron-withdrawing group, alkyl, or H, and wherein at least one of R^1 and R^2 is an electron-withdrawing group;

each R^4 is independently C_1-C_3 alkyl or the two R^4 are taken together with the carbon atom to which they attach to form a 3-6 member ring;

Z is a functional group for connecting the linker-drug to a macromolecular carrier;

D is a drug; and

Y is absent when D is a drug connected through an amine, or Y is -N(R^6)CH_2- when D is a drug connected through a phenol, alcohol, thiol, thiophenol, imidazole, or non-basic amine wherein R^6 is optionally substituted C_1-C_6 alkyl or optionally substituted aryl or heteroaryl.

9. The linker-drug of claim 8, wherein Z is selected from the group consisting of amine, aminooxy, ketone, aldehyde, maleimidyl, thiol, alcohol, azide, 1,2,4,6-tetrazinyl, trans-cyclooctenyl, bicyclononynyl, cyclooctynyl, and protected variants thereof.

10. The linker-drug of claim 8 or 9, wherein D is a peptide selected from the group consisting of octreotide (SEQ ID No: 5), [N28Q]exenatide (SEQ ID NO:1), insulin lispro (A chain: SEQ ID NO:2; B chain: SEQ ID NO:3; disulfide bridges: A6-A11, A7-B7, A20-B19), and Teduglutide ([Gly^2]GLP-2) (SEQ ID NO:4).

11. The linker-drug of any one of claims 8-10, wherein the electron-withdrawing group of R^1 and R^2 is

-CN;

-NO_2;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

-COR^3, -SOR^3, or -SO_2R^3,

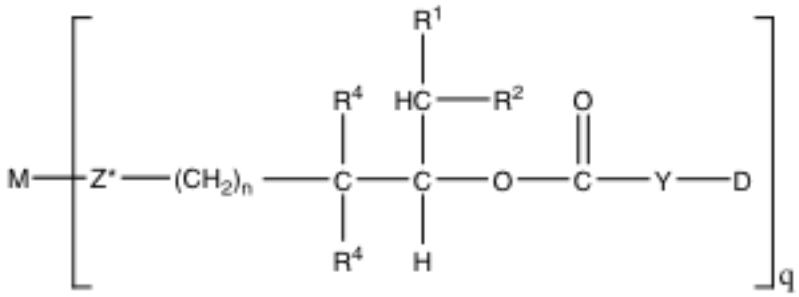
wherein R^3 is H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -OR^8 or -$NR^8{}_2$, wherein each R^8 is independently H or optionally substituted alkyl, or both R^8 groups are taken together with the nitrogen to which they are attached to form a heterocyclic ring; or

SR^9, wherein R^9 is optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl.

12. The linker-drug of any one of claims 8-11, wherein at least one of R^1 and R^2 is –CN or $-SO_2R^3$.

13. The linker-drug of any one of claims 8-12, wherein each R^4 is independently C_1-C_3 alkyl.

14. A conjugate of formula (III),



(III),

wherein:

n is an integer from 0 to 6;

R^1 and R^2 are independently an electron-withdrawing group, alkyl, or H, and wherein at least one of R^1 and R^2 is an electron-withdrawing group;

each R^4 is independently C_1-C_3 alkyl or the two R^4 are taken together with the carbon atom to which they attach to form a 3-6 member ring;

D is a drug; and

Y is absent when D is a drug connected through an amine, or Y is $-N(R^6)CH_2-$ when D is a drug connected through a phenol, alcohol, thiol, thiophenol, imidazole, or non-basic amine wherein R^6 is optionally substituted C_1-C_6 alkyl or optionally substituted aryl or heteroaryl;

M is a macromolecular carrier;

q is an integer from 1 to 10 when M is a soluble macromolecule, or q is a multiplicity when M is an insoluble matrix; and

Z* indicates coupling to M.

15. The conjugate of claim 14, wherein M is a soluble macromolecule and q is an integer from 1 to 10.

16. The conjugate of claim 14, wherein M is an insoluble matrix and q is a multiplicity.

17. The conjugate of any one of claims 14-16, wherein Z* comprises a carboxylic amide, oxime, 1,2,3-triazole, thioether, thiosuccinimide, or ether.

18. The conjugate of any one of claims 14-17, wherein the electron-withdrawing group of R^1 and R^2 is

-CN;

$-NO_2$;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

$-COR^3$, $-SOR^3$, or $-SO_2R^3$,

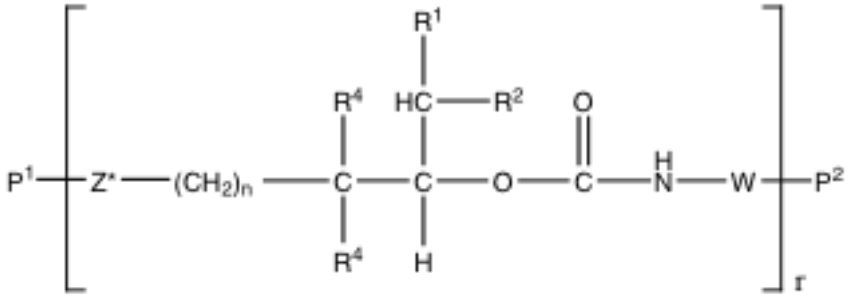
wherein R^3 is H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$ or $-NR^8_2$, wherein each R^8 is independently H or optionally substituted alkyl, or both R^8 groups are taken together with the nitrogen to which they are attached to form a heterocyclic ring; or

SR^9, wherein R^9 is optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl.

19. The conjugate of any one of claims 14-18, wherein at least one of R^1 and R^2 is –CN or $-SO_2R^3$.

20. The conjugate of any one of claims 14-19, wherein each R^4 is independently C_1-C_3 alkyl.

21. A hydrogel of formula (IV),



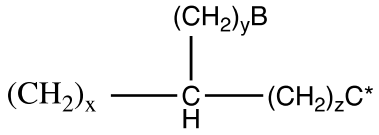
(IV),

wherein:

n is an integer from 0 to 6;

R^1 and R^2 are independently an electron-withdrawing group, alkyl, or H, and wherein at least one of R^1 and R^2 is an electron-withdrawing group;

each R^4 is independently C_1-C_3 alkyl or the two R^4 are taken together with the carbon atom to which they attach to form a 3-6 member ring;

W is absent or is ,

wherein each of x, y, and z is independently an integer from 0 to 6, B is $-NH_2$, $-ONH_2$, ketone, aldehyde, -SH, -OH, $-CO_2H$, carboxamide group, or a group comprising a cyclooctyne or bicyclononyne, and C* is carboxamide, thioether, thiosuccinimidyl, triazole, or oxime; and

P^1 and P^2 are independently r-armed polymers wherein r is an integer from 2 to 8.

22. The hydrogel of claim 21, wherein P^1 and P^2 are both 4-armed polymers.

23. The hydrogel of claim 21 or 22, wherein the electron-withdrawing group of R^1 and R^2 is

-CN;

$-NO_2$;

optionally substituted aryl;

optionally substituted heteroaryl;

optionally substituted alkenyl;

optionally substituted alkynyl;

$-COR^3$, $-SOR^3$, or $-SO_2R^3$,

wherein R^3 is H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$ or $-NR^8{}_2$, wherein each R^8 is independently H or optionally substituted alkyl, or both R^8 groups are taken together with the nitrogen to which they are attached to form a heterocyclic ring; or

SR^9, wherein R^9 is optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl.

24. The hydrogel of any one of claims 21-23, wherein at least one of R^1 and R^2 is –CN or $-SO_2R^3$.

25. The hydrogel of any one of claims 21-24, wherein each R^4 is independently C_1-C_3 alkyl.

26. The hydrogel of any one of claims 21-25, further comprising a drug attached to the hydrogel via the linker-drug of any one of claims 8-13.

27. The hydrogel of claim 26, wherein the drug is a peptide selected from the group consisting of octreotide (SEQ ID No: 5), [N28Q]exenatide (SEQ ID NO:1), insulin lispro (A chain: SEQ ID NO:2; B chain: SEQ ID NO:3; disulfide bridges: A6-A11, A7-B7, A20-B19), and Teduglutide ([Gly^2]GLP-2) (SEQ ID NO:4).

28. A method of preparing the linker-drug of any one of claims 8-13, comprising the steps of:

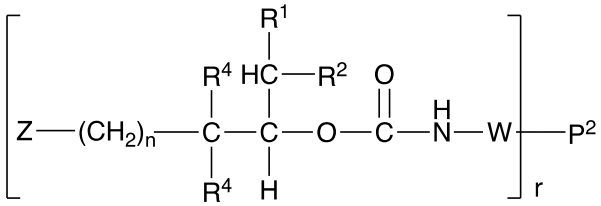
contacting the drug with the linker of any one of claims 1-7 under conditions wherein the linker-drug is formed, and

optionally isolating the linker-drug.

29. A method of preparing the conjugate of any one of claim 14-20, comprising reacting the linker-drug of any one of claims 8-13 with a macromolecular carrier comprising cognate reactive groups Z' under conditions whereby groups Z and Z' react to form a residual connecting functional group Z*.

30. A method of preparing the hydrogel of any one of claims 21-25, comprising the steps of:

(a) providing a first prepolymer of formula (V) comprising a multi-arm polymer wherein each arm is terminated by the linker of any one of claims 1-7 comprising a reactive functional group Z,



(V);

(b) providing a second prepolymer comprising a multi-arm polymer wherein each arm is terminated by a cognate reactive functional group Z' that reacts with Z;

(c) mixing the two polymers under conditions wherein Z and Z' react to form a residual connecting functional group Z*; and optionally

(d) isolating the resulting hydrogel.

31. A method of preparing a drug-releasing degradable hydrogel conjugate comprising reacting the hydrogel of any one of claims 21-25 with the linker-drug of any one of claims 8-13, wherein functional group B on the hydrogel reacts with group Z on the linker-drug to form the conjugate.

32. The method of claim 30, wherein step (a) further comprises:

reacting the first prepolymer of formula (V) with the linker-drug of any one of claims 8-13, under conditions whereby the Z group of the linker-drug is attached to the first prepolymer through reaction with group B.