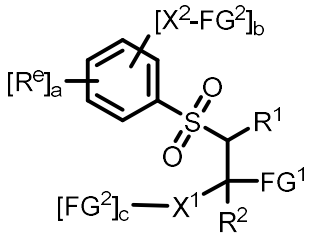
~~PROPOSED CLAIM AMENDMENTS~~Claims

1. A releasable linker having a structure according to formula (I):



(I)

or stereoisomer, tautomer or mixture thereof, or isotopic variant thereof;

wherein:

X^1 is a first spacer moiety;

X^2 is a second spacer moiety;

R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^e is an electron altering group selected from nitro, cyano, halogen, amide, substituted amide, sulfone, substituted sulfone, sulfonamide, substituted sulfonamide, alkoxy, substituted alkoxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

a is an integer from 0 to 4;

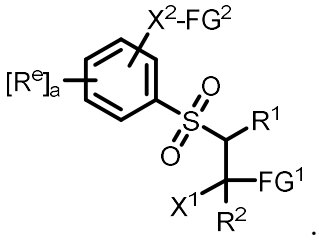
b is an integer from 1 to 3;

c is an integer from 0 to 1;

FG^1 is a functional group capable of reacting with an amino group of an active agent to form a releasable linkage; and

FG^2 is a functional group capable of reacting through click chemistry.

2. The releasable linker of claim 1, wherein the releasable linker has a structure according to formula (I-B):



(I-B)

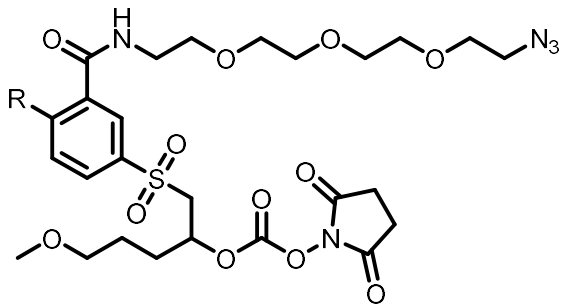
3. The releasable linker of claim 1 or 2, wherein

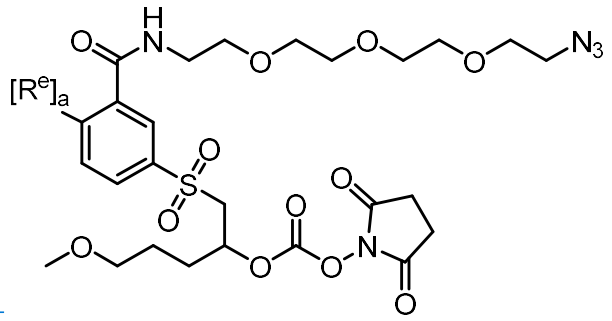
a is an integer from 0 to 2;

R^1 and R^2 are each independently hydrogen, Me, or Et; and

R^e is nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.

4. ~~The~~ A releasable linker ~~of claim 3, wherein the compound has~~having the ~~following~~ structure:

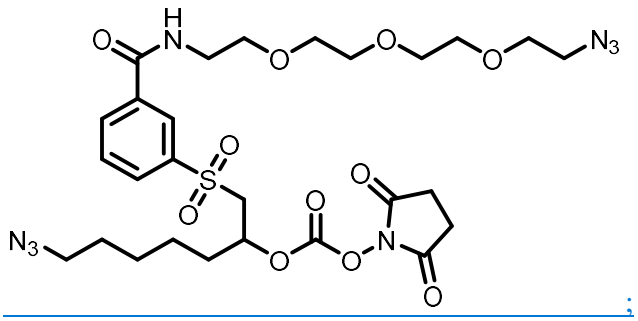




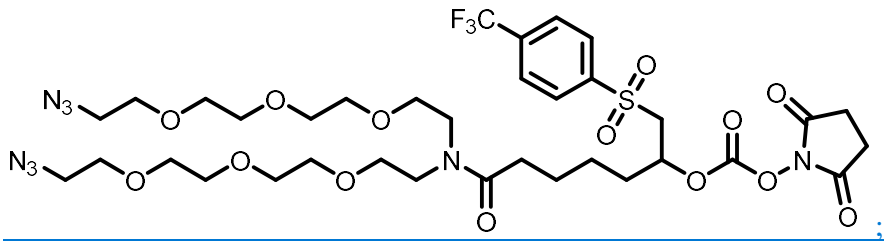
wherein:

a is 0 or 1; and

R^e is H, CF_3 or Cl;



;



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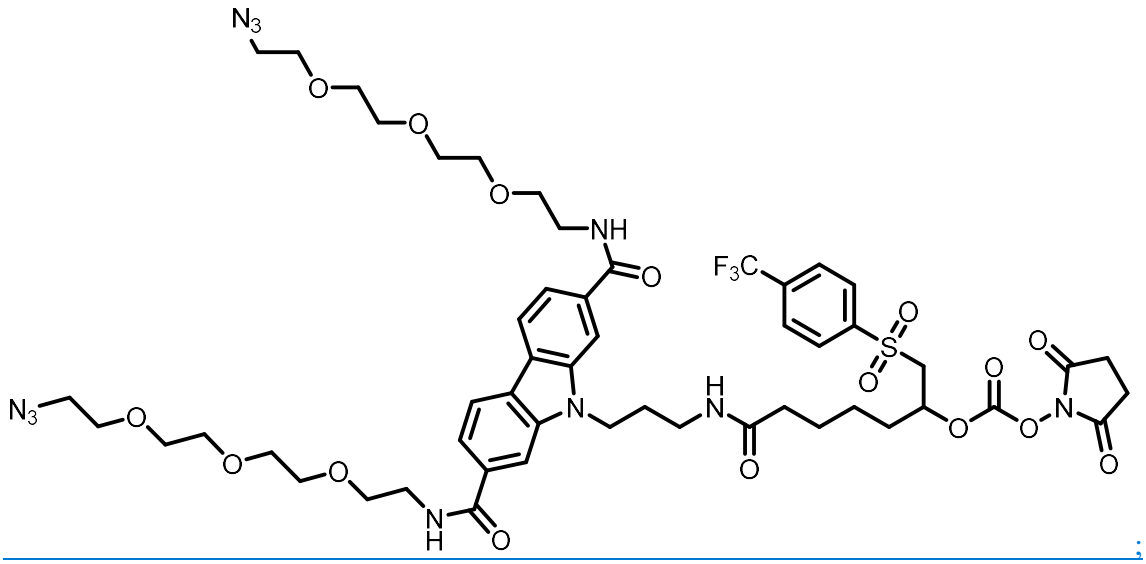

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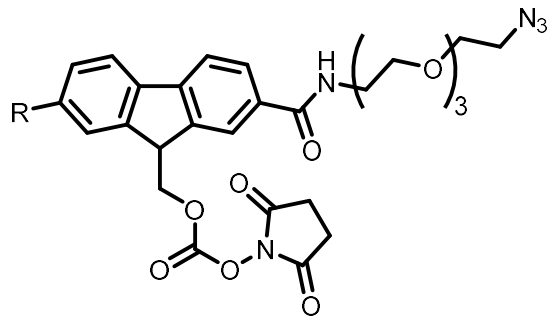
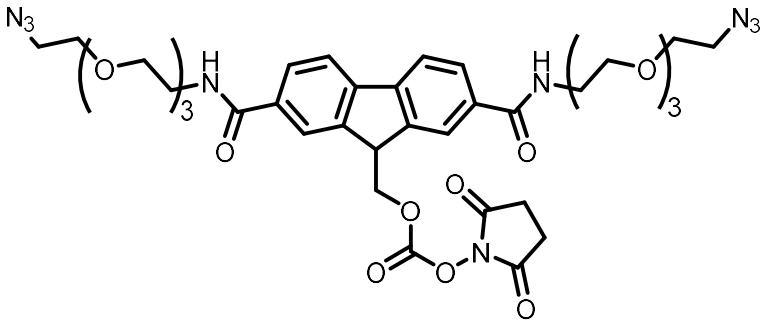
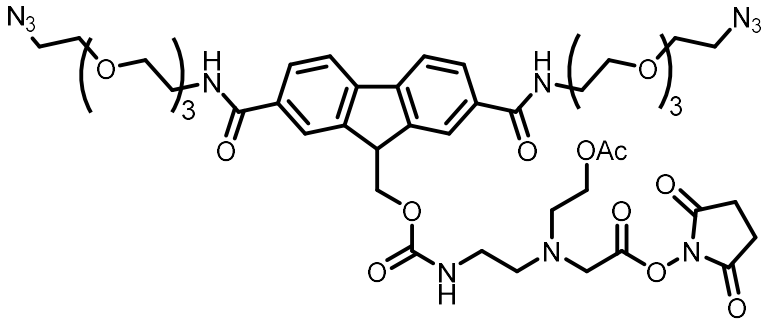


R = H, F ;



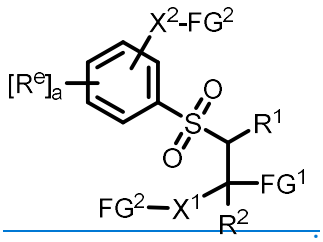
(II-B); or



(III-A),

or stereoisomer, tautomer or mixture thereof, or isotopic variant thereof.

~~5. The releasable linker of claim 1, wherein the releasable linker has a structure according to formula (I-C):~~



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(I-C)

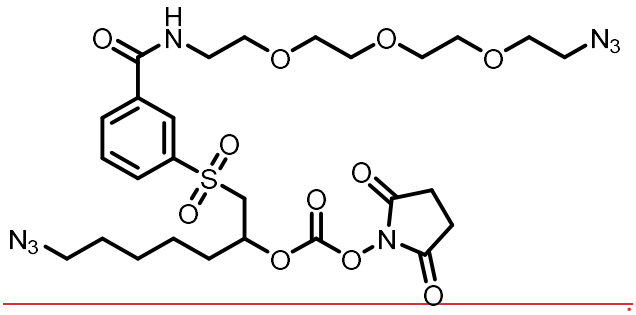
6. The releasable linker of claim 5, wherein

a is an integer from 0 to 2;

R^1 and R^2 are each independently hydrogen, Me, or Et; and

R^e is nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.

7. The releasable linker of claim 6, wherein the compound has following structure:



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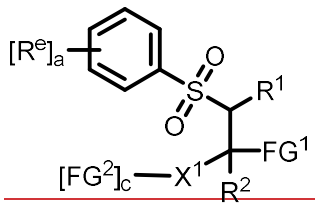
8. A releasable linker having a structure according to formula (XVIII):



(XVIII)

or stereoisomer, tautomer or mixture thereof, or isotopic variant thereof ;

wherein:

X^1 is a spacer moiety;

R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^e is an electron altering group selected from nitro, cyano, halogen, amide, substituted amide, sulfone, substituted sulfone, sulfonamide, substituted sulfonamide, alkoxy, substituted alkoxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

a is an integer from 0 to 4;

c is 2;

FG^1 is a functional group capable of reacting with an amino group of an active agent to form a releasable linkage; and

FG^2 is a functional group capable of reacting through click chemistry.

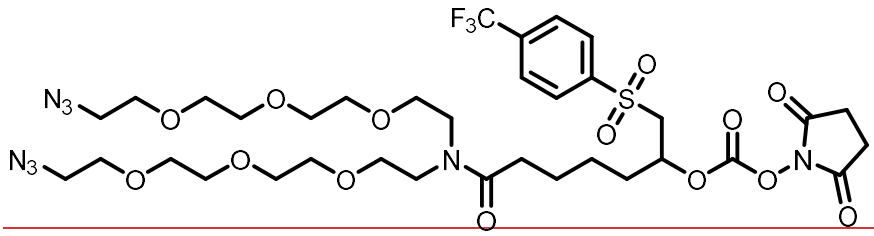
9. The releasable linker of claim 8, wherein

a is an integer from 0 to 2;

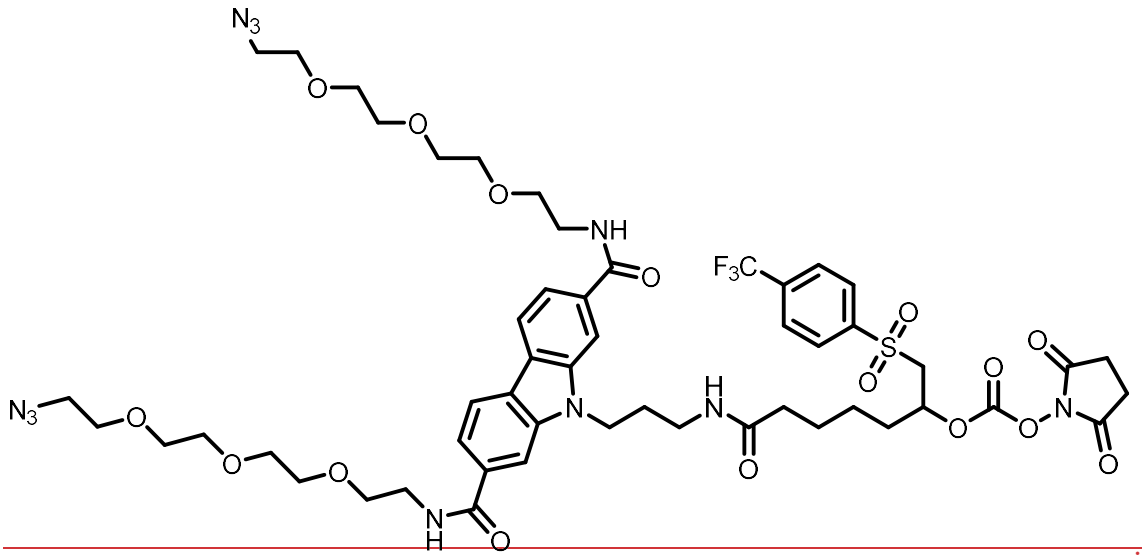
R^1 and R^2 are each independently hydrogen, Me, or Et; and

R^e is nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.

10. The releasable linker of claim 9, wherein the compound has following structure:



; or



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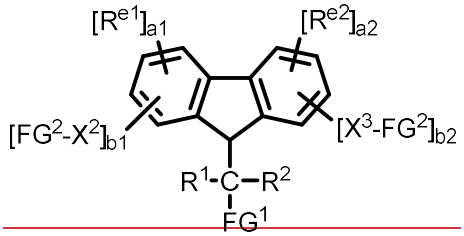
11. A releasable linker having a structure according to formula (II):



(II)

or stereoisomer, tautomer or mixture thereof, or isotopic variant thereof ;

wherein:

R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

a1 and a2 are each independently an integer from 0 to 4;

b1 is 1;

b2 is an integer from 0 to 1;

R^{el}, when present, is a first electron altering group;

R^{e2}, when present, is a second electron altering group;

X^2, when present, is a spacer moiety;

X^3, when present, is a spacer moiety;

FG^1 is a functional group capable of reacting with an amino group of an active agent to form a releasable linkage; and

FG^2 is a functional group capable of reacting through click chemistry.

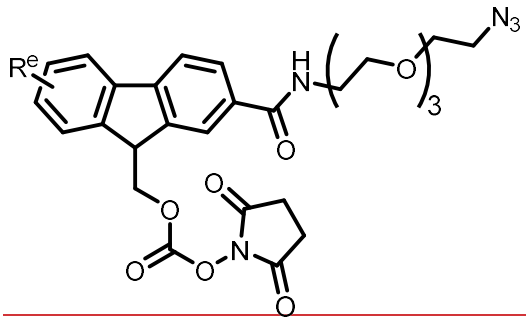
12. The releasable linker of claim 11, wherein

a1 and a2 are each independently an integer from 0 to 2;

R^1 and R^2 are each independently hydrogen, Me, or Et; and

R^{e1} and R^{e2} are each independently nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.

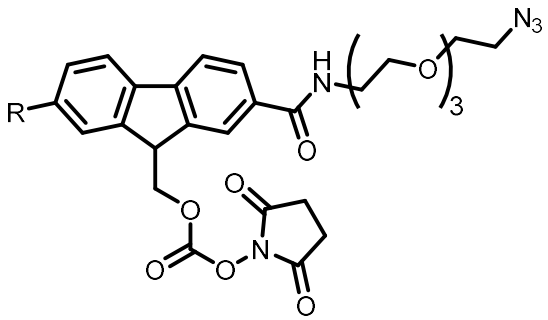
13. The releasable linker of claim 11, wherein the releasable linker has a structure according to formula (II-A):



(II-A)

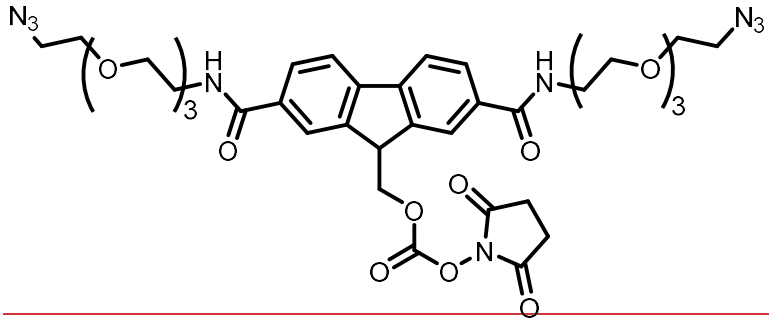
wherein R^e is hydrogen or an electron altering group selected from nitro, cyano, halogen, amide, substituted amide, sulfone, substituted sulfone, sulfonamide, substituted sulfonamide, alkoxy, substituted alkoxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

14. The releasable linker of claim 13, wherein the compound has following structure:



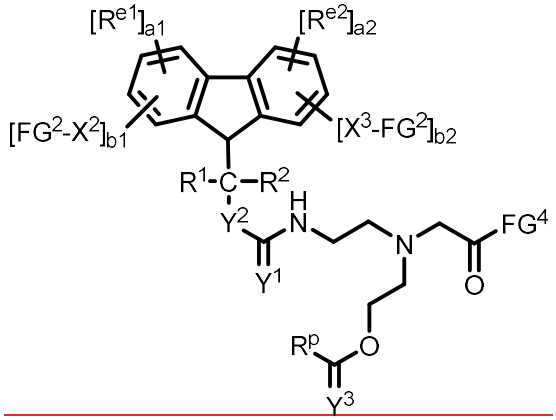
R = H, F

~~15. The releasable linker of claim 12, wherein the releasable linker has a structure according to formula (II-B):~~



~~(II-B)~~

~~16. A releasable linker having a structure according to formula (III):~~



~~(III)~~

~~or stereoisomer, tautomer or mixture thereof, or isotopic variant thereof ;~~

~~wherein:~~

~~R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~a1 and a2 are each independently an integer from 0 to 4;~~

~~b1 is 1;~~

~~b2 is an integer from 0 to 1;~~

~~R^{e1}, when present, is a first electron altering group;~~

~~R^{e2}, when present, is a second electron altering group;~~

~~R^p is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~X^2, when present, is a spacer moiety;~~

~~X^3, when present, is a spacer moiety;~~

~~Y^1 is O or S;~~

~~Y^2 is O or S;~~

~~Y^3 is O or S;~~

~~FG^4 is a functional group capable of reacting with an amino group of an active agent to form an amide linkage; and~~

~~FG^2 is a functional group capable of reacting through click chemistry.~~

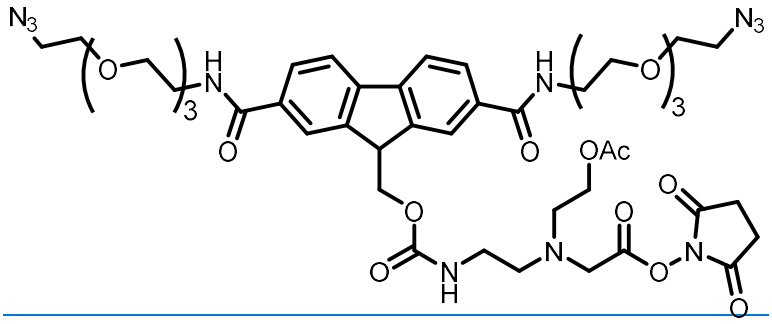
~~17. The releasable linker of claim 16, wherein~~

~~a1 and a2 are each independently an integer from 0 to 2;~~

~~R^1 and R^2 are each independently hydrogen, Me, or Et; and~~

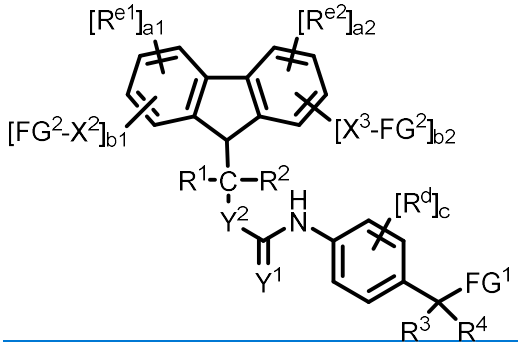
~~R^{e1} and R^{e2} are each independently nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.~~

~~18. The releasable linker of claim 17, wherein the releasable linker has a structure according to formula (III-A):~~



~~(III-A)~~

~~19. A releasable linker having a structure according to formula (IV):~~



~~(IV)~~

~~or stereoisomer, tautomer or mixture thereof, or isotopic variant thereof;~~

~~wherein:~~

~~R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~R^3 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~R^4 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~a1 and a2 are each independently an integer from 0 to 4;~~

~~b1 is 1;~~

~~b2 is an integer from 0 to 1;~~

~~c is an integer from 0 to 4;~~

~~R^{e1}, when present, is a first electron altering group;~~

~~R^{e2}, when present, is a second electron altering group;~~

~~R^d is nitro, cyano, halogen, amide, substituted amide, sulfone, substituted sulfone, sulfonamide, substituted sulfonamide, alkoxy, substituted alkoxy, alkyl or cycloalkyl, substituted alkyl or cycloalkyl, aryl or heteroaryl, substituted aryl or heteroaryl;~~

~~X^2, when present, is a spacer moiety;~~

~~X^3, when present, is a spacer moiety;~~

~~Y^1 is O or S;~~

~~Y^2 is O or S;~~

~~FG^1 is a functional group capable of reacting with an amino group of an active agent to form a releasable linkage; and~~

~~FG^2 is a functional group capable of reacting through click chemistry.~~

~~20. The releasable linker of any one of claims 1-19, wherein FG^1 is a functional group capable of reacting with an amino group of an active agent to form a carbamate linkage.~~

~~21. The releasable linker of any one of claims 1-20, wherein FG^2 is an azide, an alkynyl, or a cycloalkynyl group.~~

~~22. The releasable liner of any one of claims 1-21, wherein the cycloalkynyl group is dibenzocyclooctyne (DBCO).~~

~~23~~35. A conjugate comprising a protein covalently attached to at least one linker; wherein the conjugate comprises a structure according to formula (XIX):

Protein-$(L)_z$

(XIX)

or a stereoisomer, regioisomer, tautomer or mixture thereof, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;

wherein:

z is an integer from 1 to 25;

L is a linker, wherein at least one linker is a releasable linker; or a releasable linker or a non-releasable linker that contains a functional group capable of reacting through click chemistry selected from the group consisting of azide, alkynyl, and cycloalkynyl groups; and

~~protein~~ Protein is a chemokine, a chemokine antagonist, a cytokine, a cytokine antagonist, an antibody, or a therapeutic peptide.

~~24. The conjugate of claim 23, wherein at least one linker is a releasable linker.~~

~~25. The conjugate of claim 24, wherein the releasable linker is the releasable linker of claims 1-22.~~

~~26. The conjugate of claim 24 or 25, wherein the linker is covalently attached to an amine group of a residue within the protein.~~

~~27. The conjugate of claim 26, wherein the residue is lysine.~~

~~28. The conjugate of any one of claims 23-27, wherein one or more linkers are attached to the protein.~~

~~29~~6. A composition comprising a mixture of ~~the~~ two or more different conjugates of ~~any one of~~ claim~~s~~ ~~23~~5 ~~-28~~.

~~30. A conjugate comprising a protein, at least one linker, and at least one water-soluble polymer, wherein the protein is covalently attached to each water-soluble polymer via a linker, wherein the water-soluble polymer is straight or branched.~~

~~31. The conjugate of claim 30, comprising two or more linkers.~~

~~32. The conjugate of claim 31, wherein the two or more linkers comprise at least one non-releasable linker.~~

~~33. The conjugate of claim 31 or 32, wherein the two or more linkers comprise at least one releasable linker.~~

~~34. The conjugate of any one of claims 31-33, wherein the two or more linkers comprise at least one releasable linker and at least one non-releasable linker.~~

~~35. The conjugate of any one of claims 31-34, wherein the two or more linkers comprise from 1 to 8 releasable linkers and one to two non-releasable linkers.~~

~~36. The conjugate of claim 30, wherein the at least one linker is a releasable linker.~~

~~37. The conjugate of claim 30 or 36, wherein each of the linkers is a releasable linker.~~

~~38. The conjugate of claim 36 or 37, wherein the releasable linker is the releasable linker of any one of claims 1-22.~~

~~39. The conjugate of claim 30, wherein the at least one linker includes a non-releasable linker.~~

~~40. The conjugate of any one of claims 30-39, wherein the water-soluble polymer is a polymer of poly(ethylene glycol).~~

~~41. The conjugate of claim 40, wherein the poly(ethylene glycol) is terminally capped with an end-capping moiety selected from the group consisting of hydroxy, alkoxy, substituted alkoxy, alkenoxy, substituted alkenoxy, alkynoxy, substituted alkynoxy, aryloxy and substituted aryloxy.~~

~~42. The conjugate of any one of claims 30-41, wherein the water-soluble polymer has a weight-average molecular weight in a range of from about 500 Daltons to about 100,000 Daltons.~~

~~43. The conjugate of claim 42, wherein the water-soluble polymer has a weight-average molecular weight in a range of from about 500 Daltons to less than 20,000 Daltons.~~

~~44. The conjugate of claim 42, wherein the water-soluble polymer has a weight-average molecular weight in a range of from about 20,000 Daltons to less than 85,000 Daltons.~~

~~45. The conjugate of claim 42, wherein the water-soluble polymer has a weight-average molecular weight in a range of from about 85,000 Daltons to about 100,000 Daltons.~~

~~46. The conjugate of any one of claims 30-45, wherein the conjugate is covalently attached at an amine group of a residue within the protein via the linker.~~

~~47. The conjugate of claim 46, wherein the residue is lysine.~~

~~48. The conjugate of any one of claims 30-47, wherein one or more water-soluble polymers are attached to the protein via one or more linkers.~~

~~49. The conjugate of any one of claims 30-48, wherein eight or more water-soluble polymers are attached to the protein via eight or more linkers.~~

~~50~~7. ~~The~~ A conjugate ~~of any one of claims 30-49, wherein the conjugate comprises~~comprising a structure according to formula (XX):

$$\text{Protein-(L-Macromolecule)}_z$$

(XX)

or a stereoisomer, regioisomer, tautomer or mixtures thereof, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;

wherein:

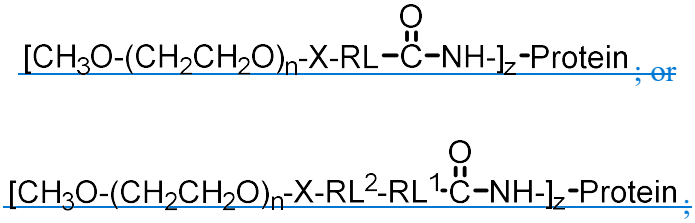
z is an integer from 1 to 25;

L is a linker comprising functional groups resulting from click chemistry;

~~protein~~ Protein is a chemokine, a chemokine antagonist, a cytokine, a cytokine antagonist, an antibody, or a therapeutic peptide; and

~~macromolecule~~ Macromolecule is a water-soluble polymer, a lipid, a protein or a polypeptide.

~~51. The conjugate of any one of claims 30-50, wherein the conjugate comprises a structure according to the following formula:~~



~~wherein:~~

~~n is an integer having a value of from 2 to 4000;~~

~~X is a spacer moiety;~~

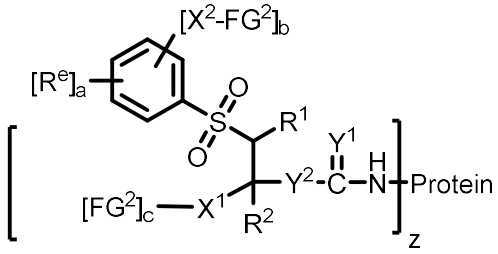
~~RL, RL[1], and RL[2] are independently a releasable linker;~~

~~z is an integer from 1 to 25; and~~

~~NH is an amine group of a residue within the protein.~~

~~52~~8. A composition comprising a mixture of ~~the~~ two or more different conjugates of ~~any one of~~ claim~~s 30-51~~7.

~~53~~9. The conjugate of ~~any one of~~ claim~~s 23~~5~~-28~~, wherein the conjugate comprises a structure according to formula (VII):



(VII)

wherein:

X^1 is a first spacer moiety;

X^2, when present, is a second spacer moiety;

R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^e is an electron altering group selected from nitro, cyano, halogen, amide, substituted amide, sulfone, substituted sulfone, sulfonamide, substituted sulfonamide, alkoxy, substituted alkoxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

a is an integer from 0 to 5;

b is an integer from 0 to 3;

c is an integer from 0 to 2;

z is an integer from 1 to 25;

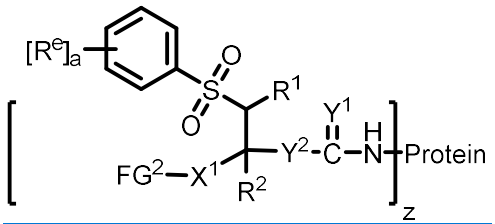
Y^1 is O or S;

Y^2 is O or S;

FG^2 is a functional group capable of reacting through click chemistry selected from the group consisting of azide, alkynyl, and cycloalkynyl groups; and

-NH- is an amine group of a residue within the protein.

~~54. The conjugate of claim 53, wherein the conjugate comprises a structure according to formula (VII-A):~~



~~(VII-A)~~

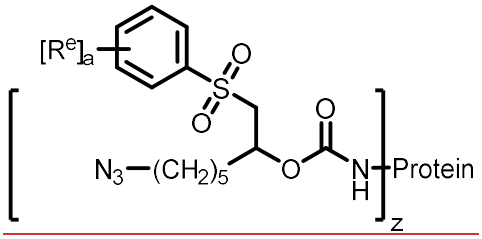
~~55. The conjugate of claim 54, wherein~~

~~a is an integer from 0 to 2;~~

~~R^1 and R^2 are each independently hydrogen, Me, or Et; and~~

~~R^e is nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.~~

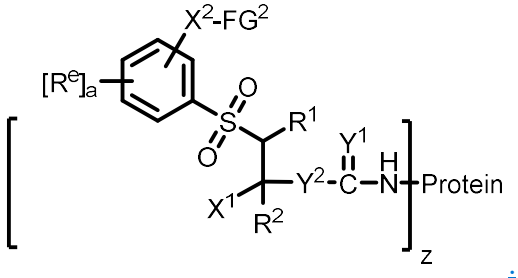
~~56. The conjugate of claim 55, wherein the conjugate comprises a structure according to formula (VII-A1):~~



~~(VII-A1)~~

~~wherein a is an integer from 1 to 2; and R^e is 4-F, 4-Cl, 4-CF_3, 2,4-difluoro, or 2-CF_3-4-F substitution.~~

~~57~~10. The conjugate of claim 5 or ~~53~~9, wherein the conjugate comprises a structure according to formula (VII-B):



(VII-B)

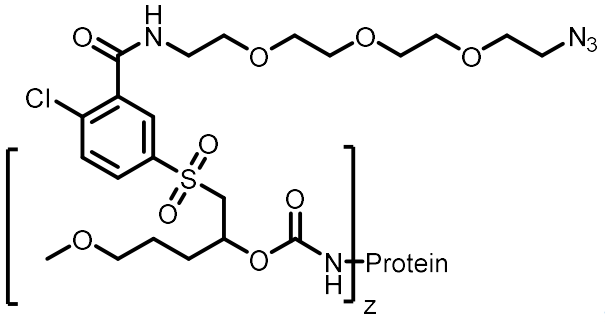
~~58~~11. The conjugate of claim ~~57~~9 or 10, wherein

a is an integer from 0 to 2;

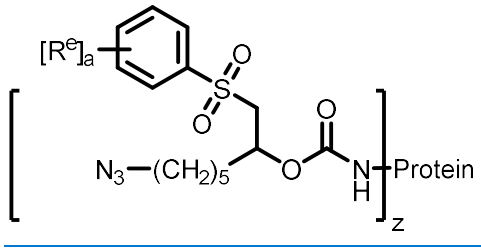
R^1 and R^2 are each independently hydrogen, Me, or Et; and

R^e is nitro, cyano, halogen, -CF_3, -CONHMe, -SO_2NHMe, -OMe, -NHMe, -NHAc, -$NHSO_2Me$, or -OCF_3.

~~59~~12. The conjugate of any one of claims ~~58~~5, 9, 10 or 11 wherein the conjugate has following structure:

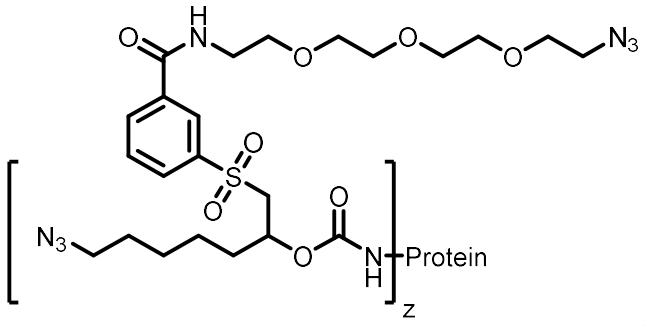


;

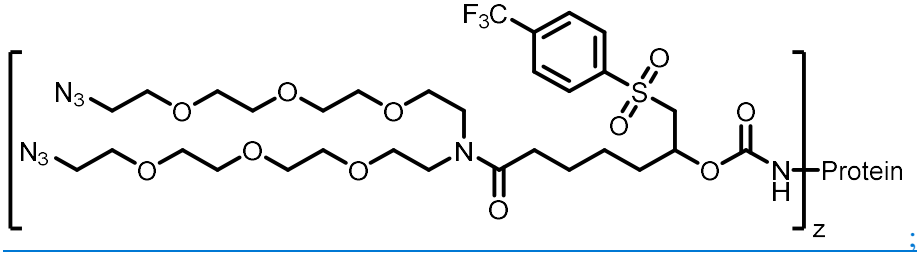


(VII-A1),

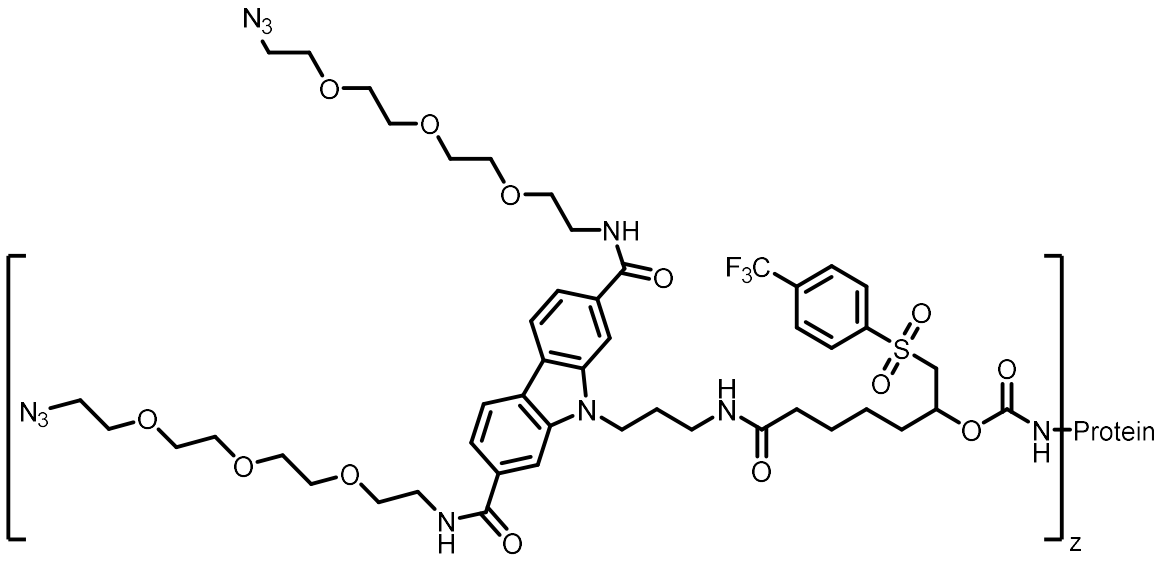
wherein a is an integer from 1 to 2; and R^e is 4-F, 4-Cl, 4-CF_3, 2,4-difluoro, or 2-CF_3-4-F;



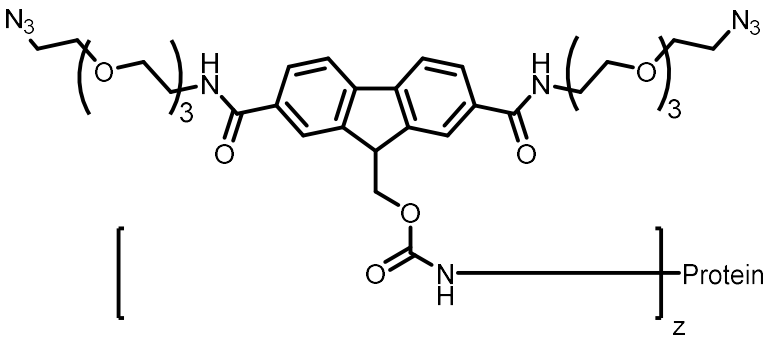
;



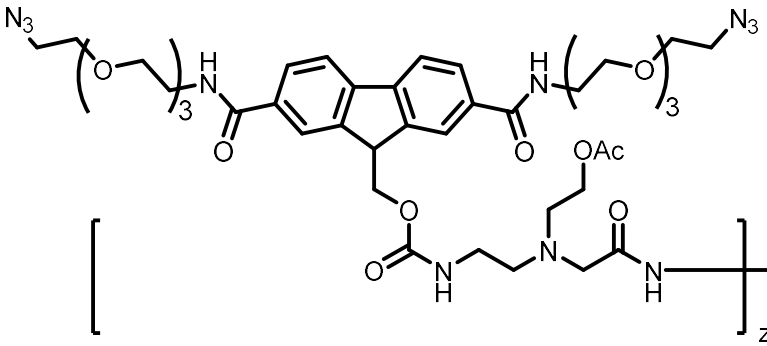
;



;



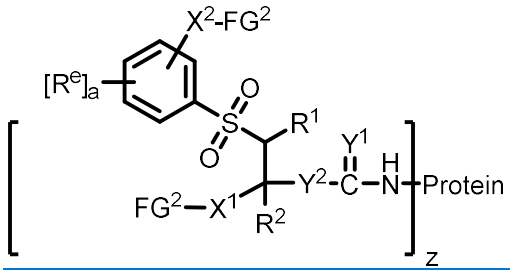
(VIII-A); or



(IX-A).

.

~~60. The conjugate of claim 53, wherein the conjugate comprises a structure according to formula (VII-C):~~



(VII-C)

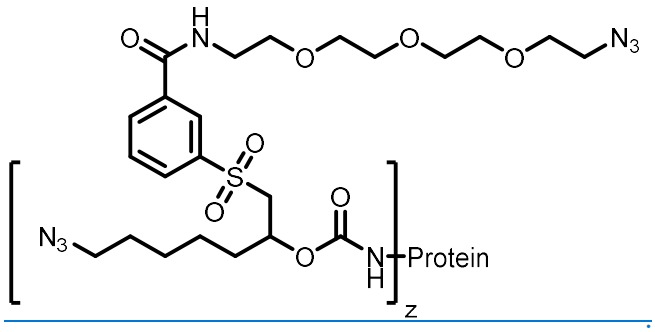
61. The conjugate of claim 60, wherein

a is an integer from 0 to 2;

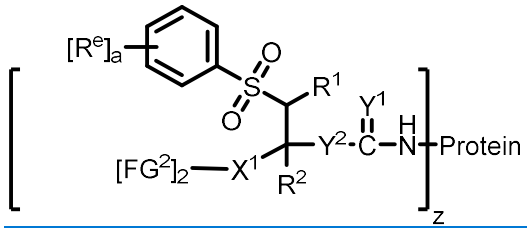
R^1 and R^2 are each independently hydrogen, Me, or Et; and

R^e is nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.

62. The conjugate of claim 61, wherein the conjugate has following structure:



63. The conjugate of 53, wherein the conjugate comprises a structure according to formula (VII-D):



~~(VII-D)~~

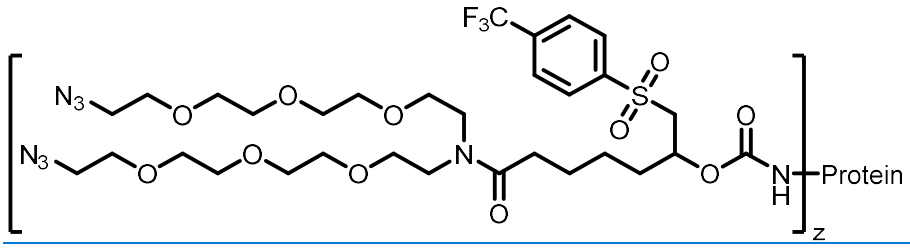
~~64. The conjugate of claim 63, wherein~~

~~a is an integer from 0 to 2;~~

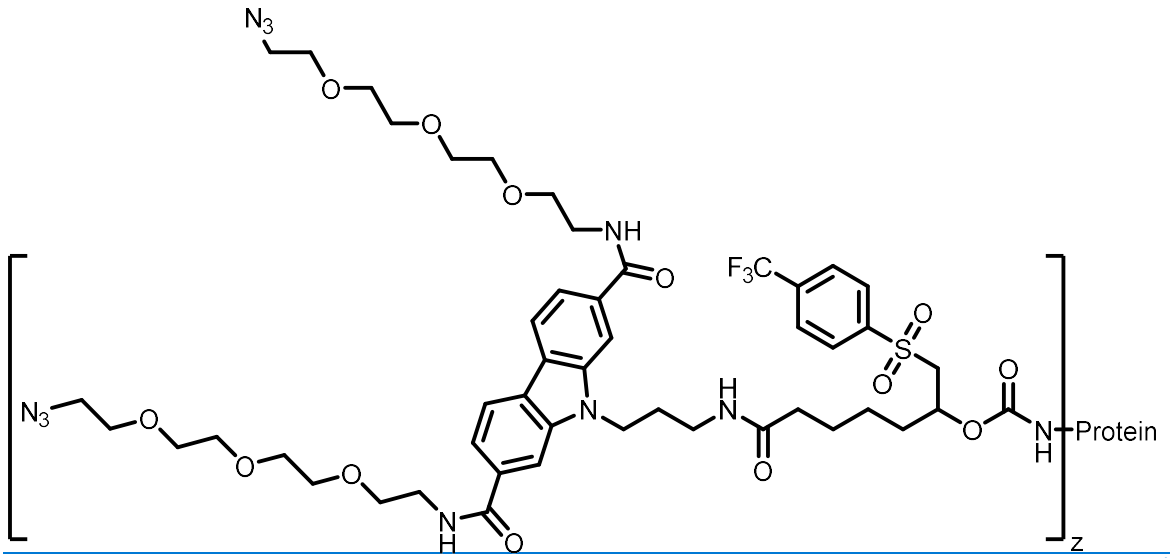
~~R^1 and R^2 are each independently hydrogen, Me, or Et; and~~

~~R^e is nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.~~

~~65. The conjugate of claim 64, wherein the conjugate has following structure:~~

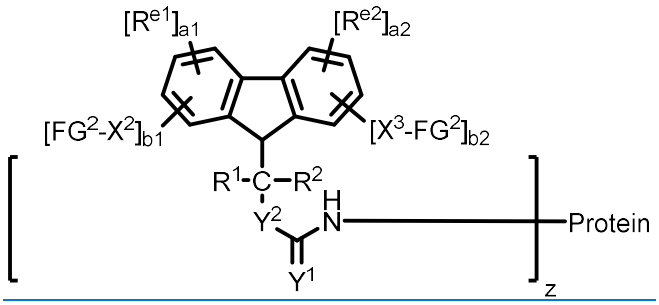


~~; or~~



~~.~~

~~66. The conjugate of any one of claims 23-28, wherein the conjugate comprises a structure according to formula (VIII):~~



(VIII)

wherein:

R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

a1 and a2 are each independently an integer from 0 to 4;

b1 is 1;

b2 is an integer from 0 to 1;

z is an integer from 1 to 25;

R^{e1}, when present, is a first electron altering group;

R^{e2}, when present, is a second electron altering group;

X^2, when present, is a spacer moiety;

X^3, when present, is a spacer moiety;

Y^1 is O or S;

Y^2 is O or S;

FG^2 is a functional group capable of reacting through click chemistry selected from the group consisting of azide, alkynyl, and cycloalkynyl groups; and

-NH- is an amine group of a residue within the protein.

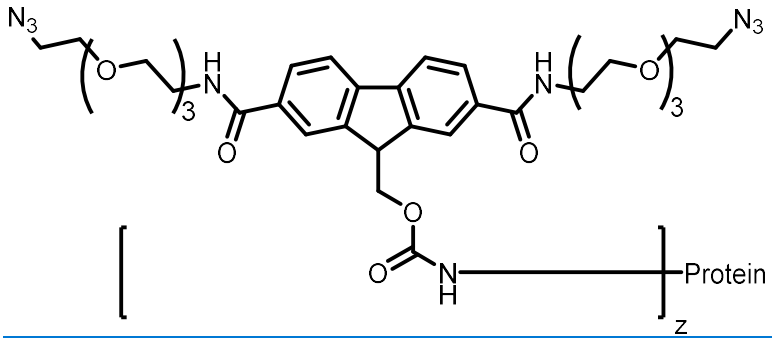
67. The conjugate of claim 66, wherein

~~a1 and a2 are each independently an integer from 0 to 2;~~

~~R^1 and R^2 are each independently hydrogen, Me, or Et; and~~

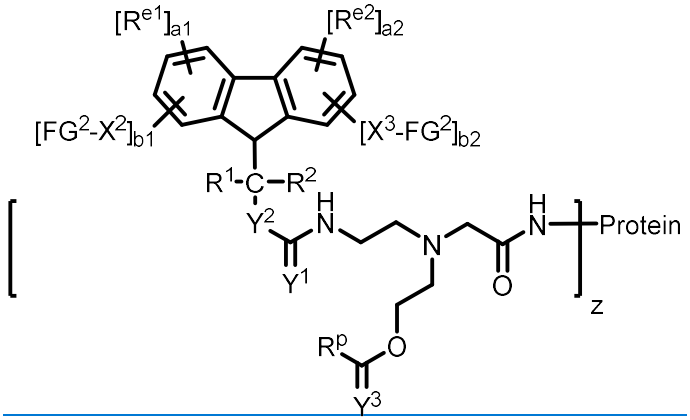
~~R^{e1} and R^{e2} are each independently nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.~~

~~68. The conjugate of claim 67, wherein the conjugate comprises a structure according to formula (VIII-A):~~



~~(VIII-A).~~

~~69. The conjugate of any one of claims 23-28, wherein the conjugate comprises a structure according to formula (IX):~~



~~(IX)~~

~~wherein:~~

~~R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~a1 and a2 are each independently an integer from 0 to 4;~~

~~b1 is 1;~~

~~b2 is an integer from 0 to 1;~~

~~z is an integer from 1 to 25;~~

~~R^{e1}, when present, is a first electron altering group;~~

~~R^{e2}, when present, is a second electron altering group;~~

~~R^p is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~X^2, when present, is a spacer moiety;~~

~~X^3, when present, is a spacer moiety;~~

~~Y^1 is O or S;~~

~~Y^2 is O or S;~~

~~Y^3 is O or S;~~

~~FG^2 is a functional group capable of reacting through click chemistry selected from the group consisting of azide, alkynyl, and cycloalkynyl groups; and~~

~~-NH- is an amine group of a residue within the protein.~~

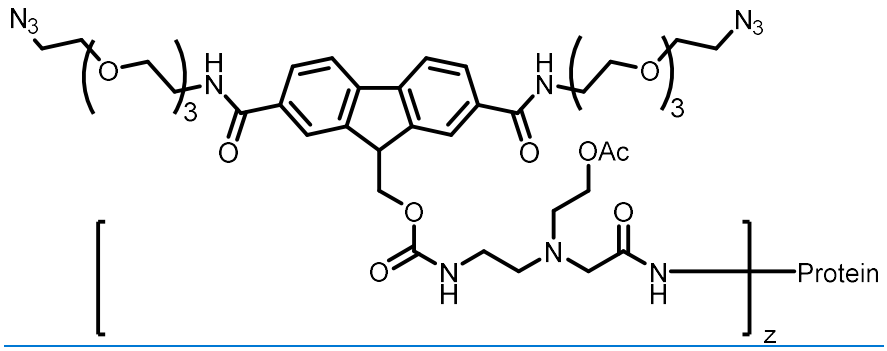
~~70. The conjugate of claim 69, wherein~~

~~a1 and a2 are each independently an integer from 0 to 2;~~

~~R^1 and R^2 are each independently hydrogen, Me, or Et; and~~

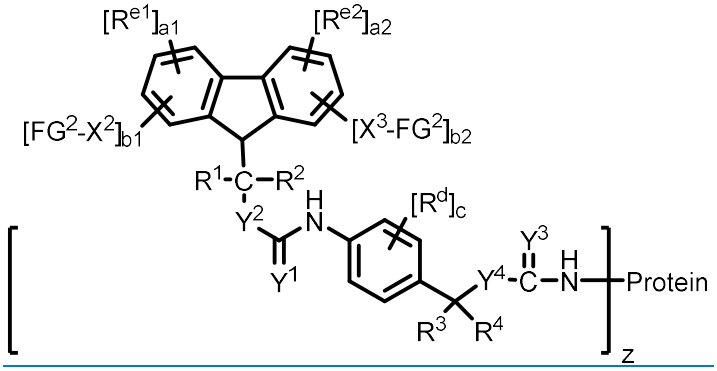
~~R^{e1} and R^{e2} are each independently nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.~~

~~71. The conjugate of claim 70, wherein the conjugate comprises a structure according to formula (IX-A):~~



~~(IX-A)~~

~~72. The conjugate of any one of claims 23-28, wherein the conjugate comprises a structure according to formula (X):~~



~~(X)~~

~~wherein:~~

~~R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~R^3 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~R^4 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~a1 and a2 are each independently an integer from 0 to 4;~~

~~b1 is 1;~~

~~b2 is an integer from 0 to 1;~~

~~c is an integer from 0 to 4;~~

~~z is an integer from 1 to 25;~~

~~R^{e1}, when present, is a first electron altering group;~~

~~R^{e2}, when present, is a second electron altering group;~~

~~R^d is nitro, cyano, halogen, amide, substituted amide, sulfone, substituted sulfone, sulfonamide, substituted sulfonamide, alkoxy, substituted alkoxy, alkyl or cycloalkyl, substituted alkyl or cycloalkyl, aryl or heteroaryl, substituted aryl or heteroaryl;~~

~~X^2, when present, is a spacer moiety;~~

~~X^3, when present, is a spacer moiety;~~

~~Y^1 is O or S;~~

~~Y^2 is O or S;~~

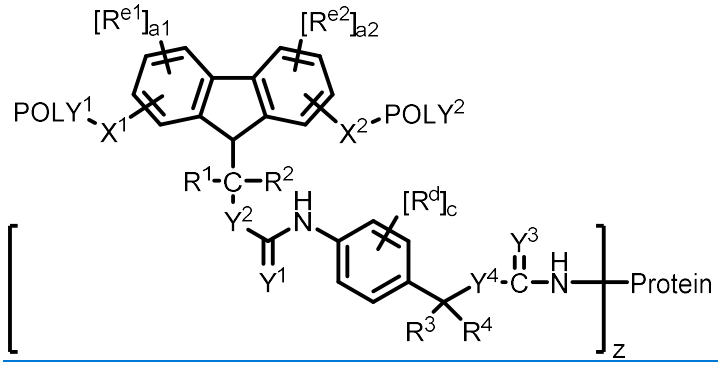
~~Y^3 is O or S;~~

~~Y^4 is O or S;~~

~~FG^2 is a functional group capable of reacting through click chemistry selected from the group consisting of azide, alkynyl, and cycloalkynyl groups; and~~

~~-NH- is an amine group of a residue within the protein.~~

~~73. The conjugate of any one of claims 30-51, wherein the conjugate comprises a structure according to formula (XI):~~



~~(XI)~~

~~wherein:~~

~~$POLY^1$ is a first water-soluble polymer;~~

~~$POLY^2$ is a second water-soluble polymer;~~

~~X^1 is a first spacer moiety;~~

~~X^2 is a second spacer moiety;~~

~~Y^1 is O or S;~~

~~Y^2 is O or S;~~

~~Y^3 is O or S;~~

~~Y^4 is O or S;~~

~~R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~R^3 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~R^4 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~a1 is an integer from 0 to 3;~~

~~a2 is an integer from 0 to 3;~~

~~c is an integer from 0 to 4;~~

~~z is an integer from 1 to 25;~~

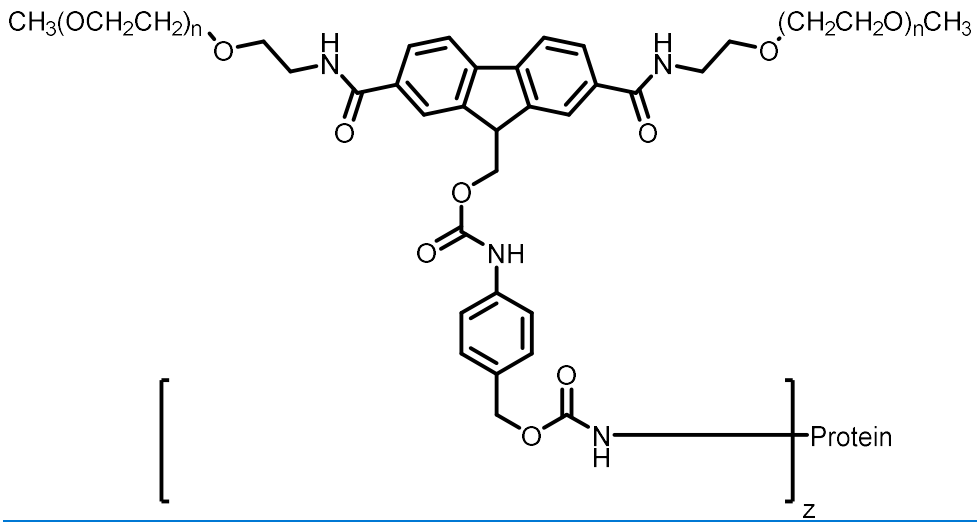
~~R^{e1}, when present, is a first electron altering group;~~

~~R^{e2}, when present, is a second electron altering group;~~

~~R^{d} is nitro, cyano, halogen, amide, substituted amide, sulfone, substituted sulfone, sulfonamide, substituted sulfonamide, alkoxy, substituted alkoxy, alkyl or cycloalkyl, substituted alkyl or cycloalkyl, aryl or heteroaryl, substituted aryl or heteroaryl; and~~

~~-NH- is an amine group of a residue within the protein.~~

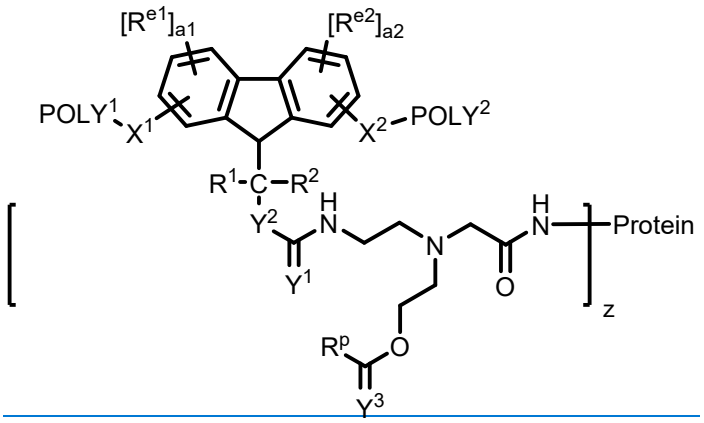
~~74. The conjugate of claim 73, wherein the conjugate comprises a structure according to formula (XI-A):~~



~~(XI-A)~~

~~wherein n is independently an integer from 4 to 1500.~~

~~75. The conjugate of any one of claims 30-51, wherein the conjugate comprises a structure according to formula (XII):~~



(XII)

wherein:

$POLY^1$ is a first water-soluble polymer;

$POLY^2$ is a second water-soluble polymer;

X^1 is a first spacer moiety;

X^2 is a second spacer moiety;

Y^1 is O or S;

Y^2 is O or S;

Y^3 is O or S;

R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

a1 is an integer from 0-3;

a2 is an integer from 0-3;

z is an integer from 1 to 25;

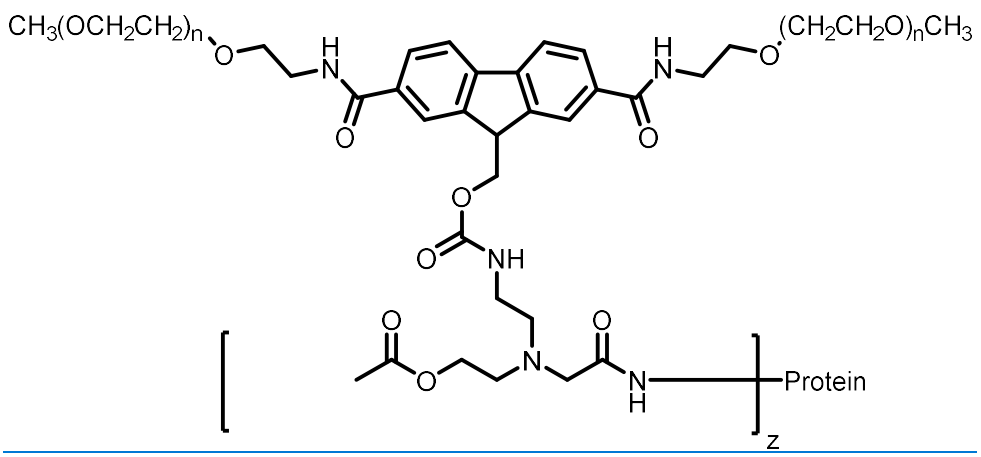
R^{e1}, when present, is a first electron altering group;

R^{e2}, when present, is a second electron altering group;

~~R^p is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl; and~~

~~-NH- is an amine group of a residue within the protein.~~

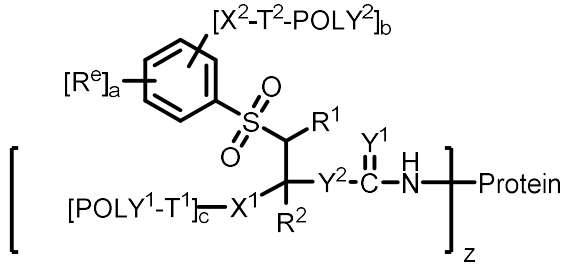
~~76. The conjugate of claim 75, wherein the conjugate comprises a structure according to formula (XII-A):~~



~~(XII-A)~~

~~wherein n is independently an integer from 4 to 1500.~~

~~77~~13. The conjugate of ~~any one of~~ claim~~s 30-51~~7, wherein the conjugate comprises a structure according to formula (XIII):



(XIII)

wherein:

$POLY^1$ is a first straight or branched water-soluble polymer;

$POLY^2$ is a second straight or branched water-soluble polymer;

X^1 is a first spacer moiety; or -X-FG^2;

X^2, when present, is a second spacer moiety;

T^1 is a first triazole functional group;

T^2 is a second triazole functional group;

R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^e is an electron altering group selected from nitro, cyano, halogen, amide, substituted amide, sulfone, substituted sulfone, sulfonamide, substituted sulfonamide, alkoxy, substituted alkoxy, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and -X-FG^2;

wherein:

X is a spacer moiety; and

FG^2 is a functional group capable of reacting through click chemistry selecting from the group consisting of azide, alkynyl, and cycloalkynyl groups.

a is an integer from 0 to 5;

b is an integer from 0 to 3;

c is an integer from 0 to 2;

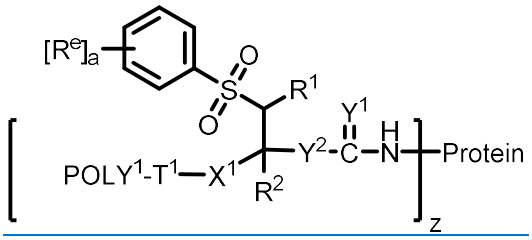
z is an integer from 1 to 25;

Y^1 is O or S;

Y^2 is O or S; and

-NH- is an amine group of a residue within the protein.

~~78. The conjugate of claim 77, wherein the conjugate comprises a structure according to (XIII-A):~~



(XIII-A)

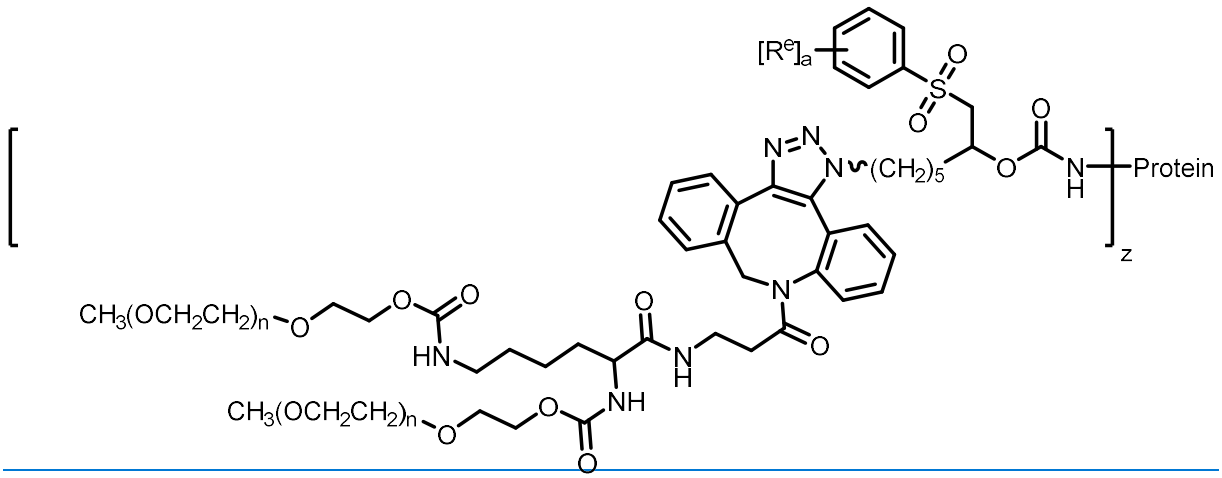
79. The conjugate of claim 78, wherein

a is an integer from 0 to 2;

R^1 and R^2 are each independently hydrogen, Me, or Et; and

R^e is nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.

80. The conjugate of claim 79, wherein the conjugate comprises a structure according to formula (XIII-A1):



(XIII-A1)

wherein:

~~a is an integer from 1 to 2;~~

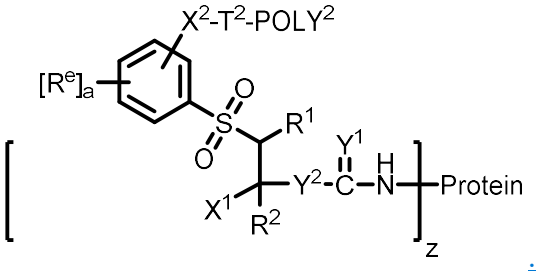
~~R^e is 4-F, 4-Cl, 4-CF_3, 2,4-difluoro, or 2-CF_3-4-F substitution;~~

~~n is independently an integer from 4 to 1500;~~

~~z is an integer from 1 to 25; and~~

~~-NH- is an amine group of a residue within the protein.~~

~~81~~14. The conjugate of claim ~~50~~7 or ~~77~~13, wherein the conjugate comprises a structure according to formula (XIII-B):



(XIII-B)

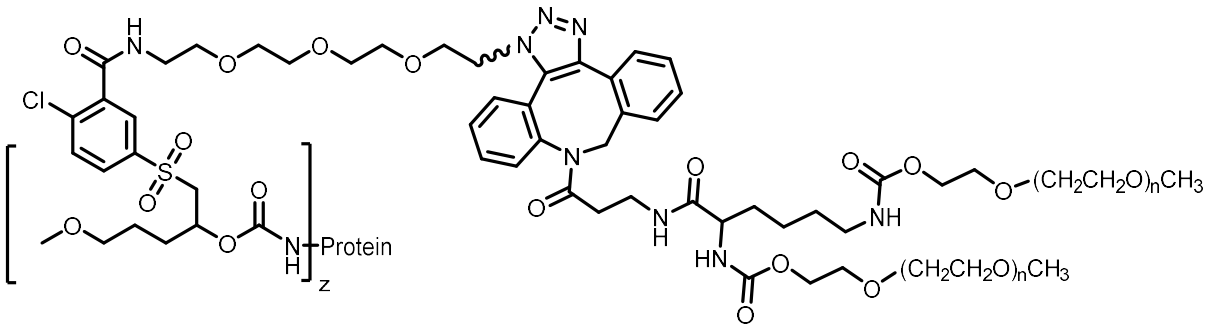
~~82~~15. The conjugate of claim 13 or ~~81~~14, wherein

a is an integer from 0 to 2;

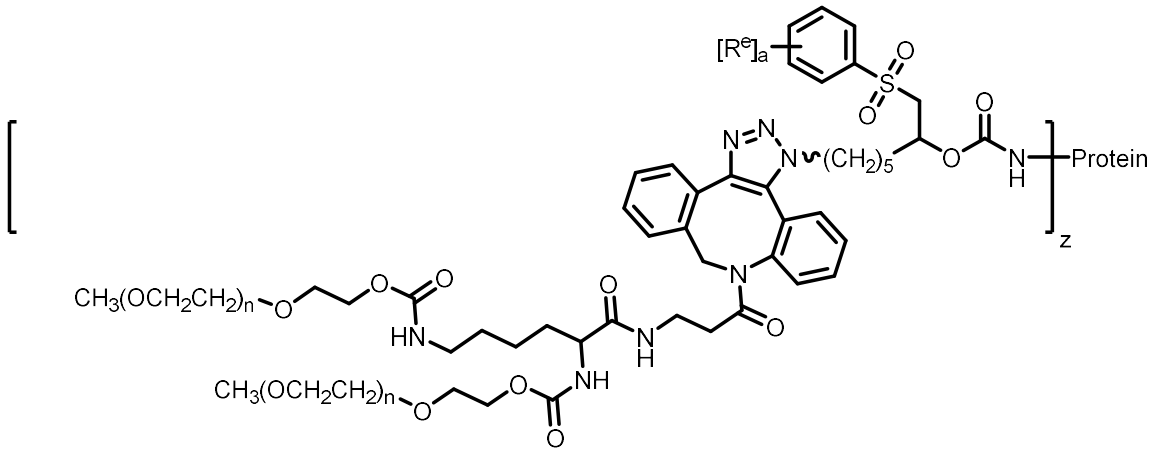
R^1 and R^2 are each independently hydrogen, Me, or Et; and

R^e is nitro, cyano, halogen, -CF_3, -CONHMe, -SO_2NHMe, -OMe, -NHMe, -NHAc, -$NHSO_2$Me, or -OCF_3.

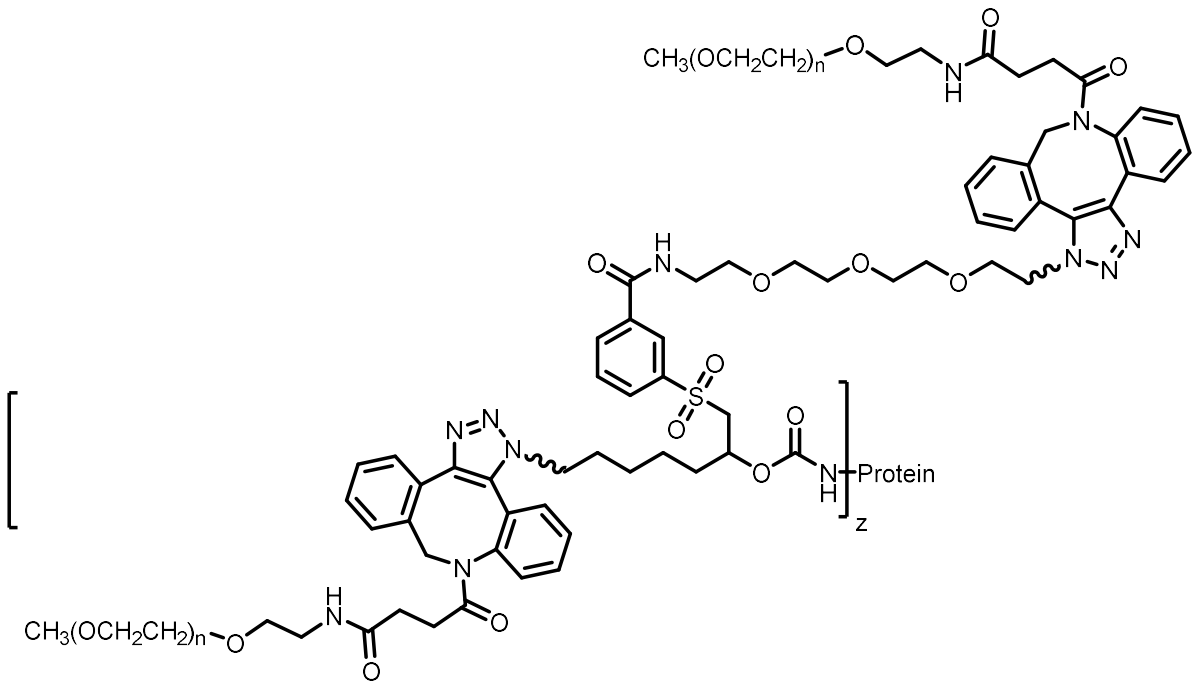
~~83~~16. The conjugate of any one of claims ~~82~~7, 13, 14 and 15, wherein the conjugate comprises ~~a structure according to formula (XIII-B1)~~the structure:



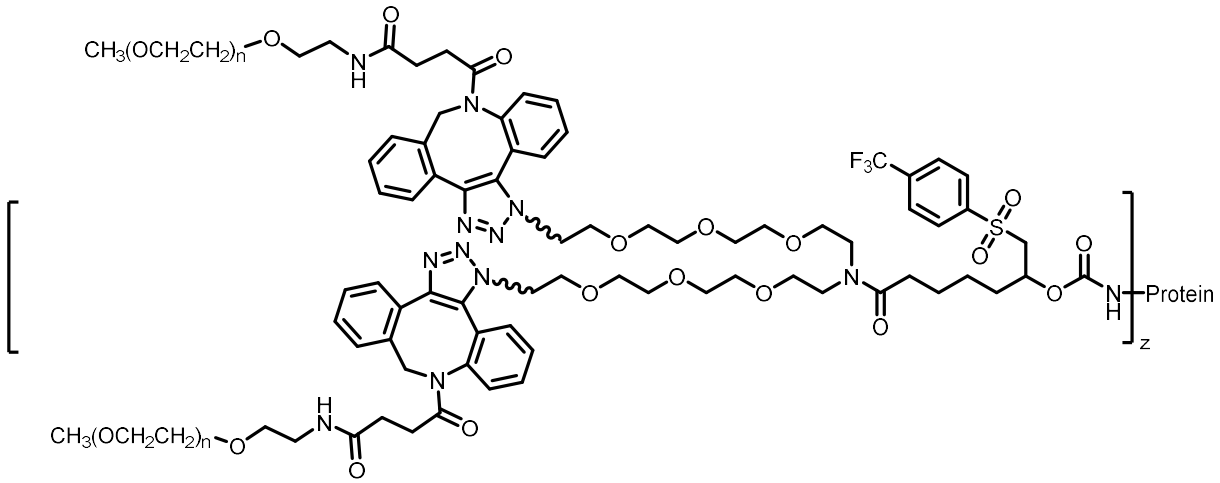
(XIII-B1);



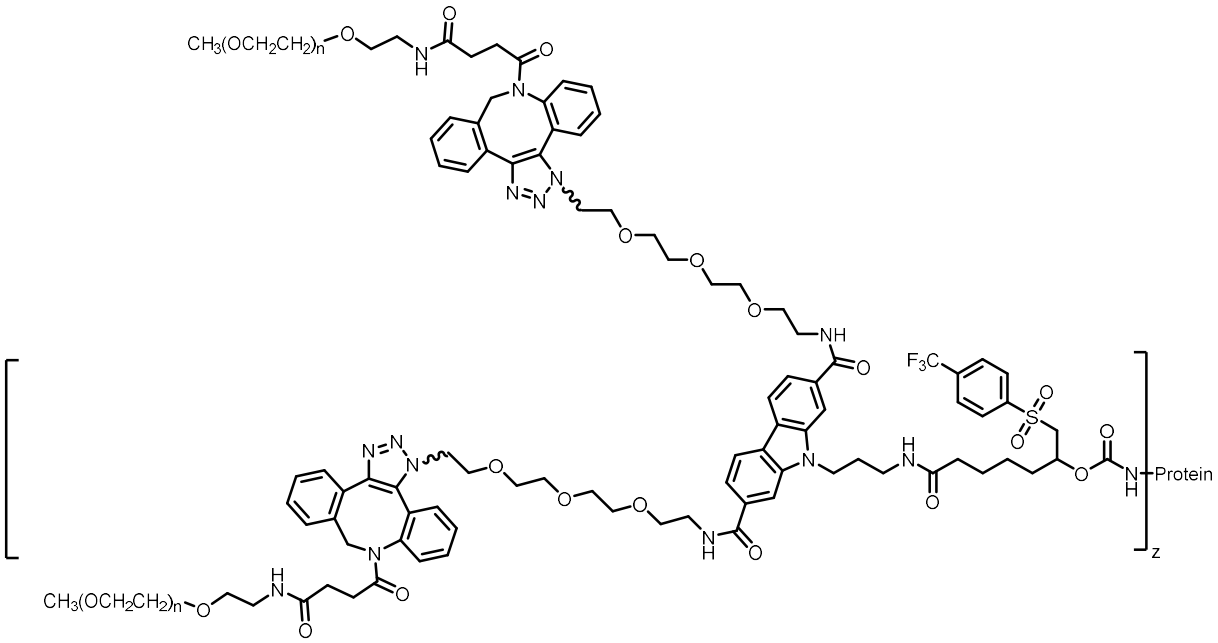
(XIII-A1);



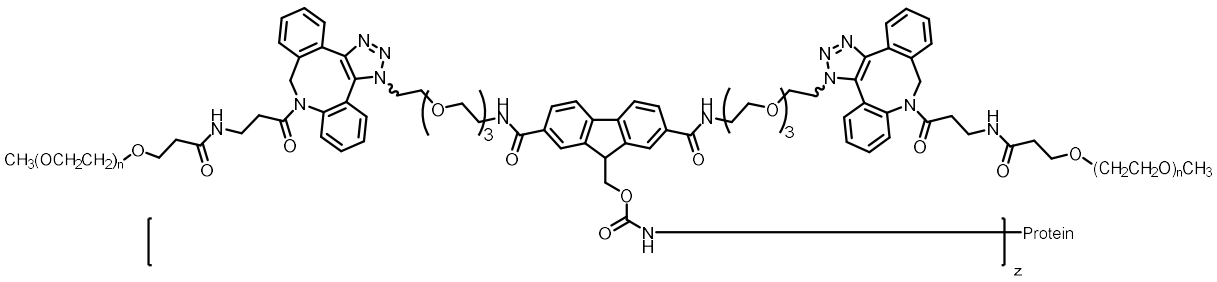
(XIII-C1);



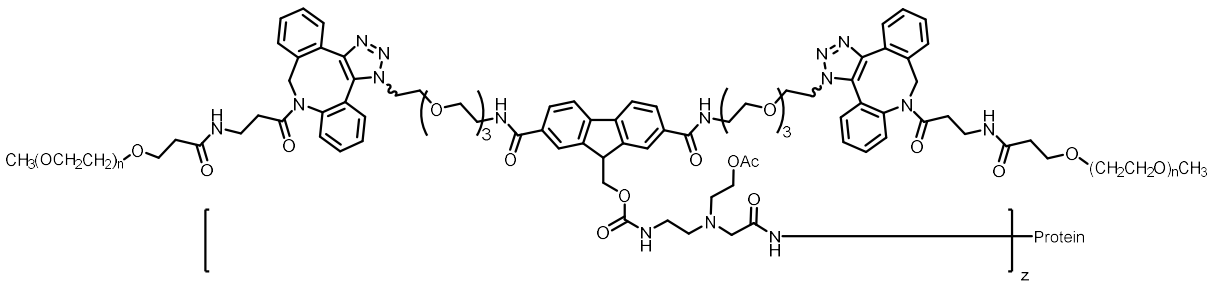
(XIII-D1);



(XIII-D2);



(XIV-A); or



(XV-A);

wherein:

a is 1 or 2;

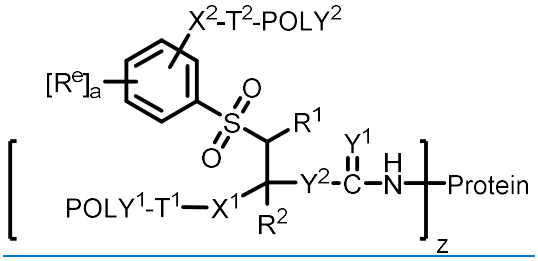
R^e is 4-F, 4-Cl, 4-CF_3, 2,4-difluoro, or 2-CF_3-4-F;

n is independently an integer from 4 to 1500;

z is an integer from 1 to 25; and

-NH- is an amine group of a residue within the protein.

~~84. The conjugate of claim 77, wherein the conjugate comprises a structure according to formula (XIII-C):~~



~~(XIII-C)~~

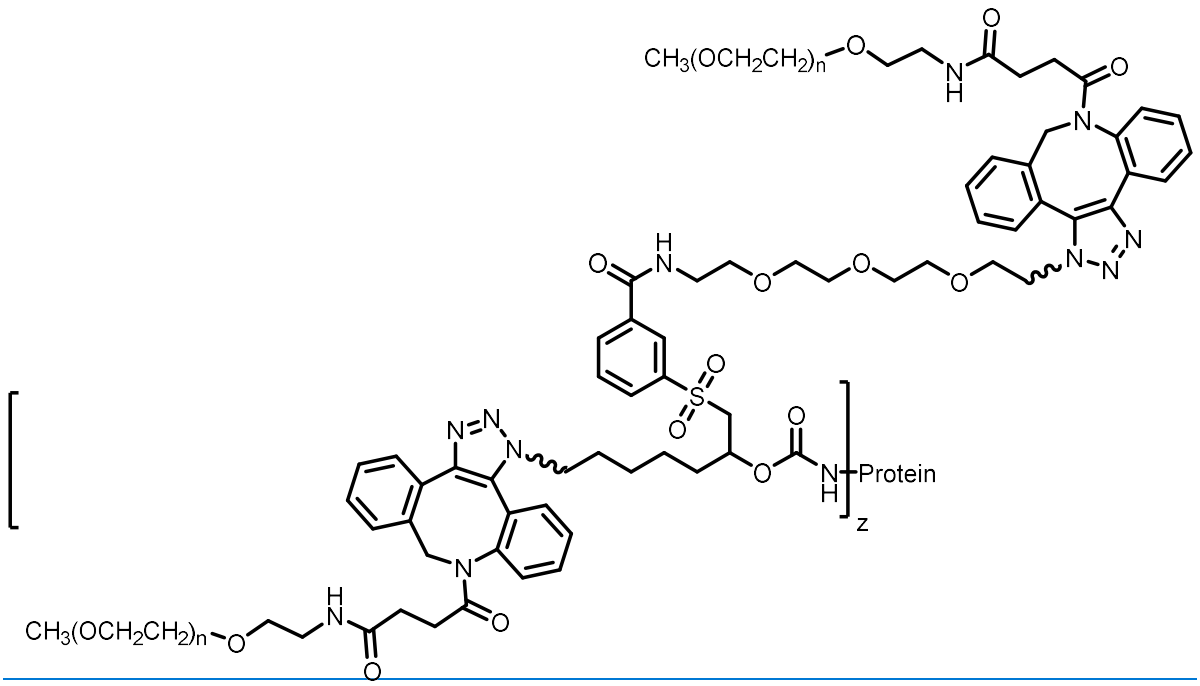
~~85. The conjugate of claim 84, wherein~~

~~a is an integer from 0 to 2;~~

~~R^1 and R^2 are each independently hydrogen, Me, or Et; and~~

~~R^e is nitro, cyano, halogen, -CF_3, -CONHMe, -SO_2NHMe, -OMe, -NHMe, -NHAc, -NHSO_2Me, or -OCF_3.~~

~~86. The conjugate of claim 85, wherein the conjugate comprises a structure according to formula (XIII-C1):~~



(XIII-C1)

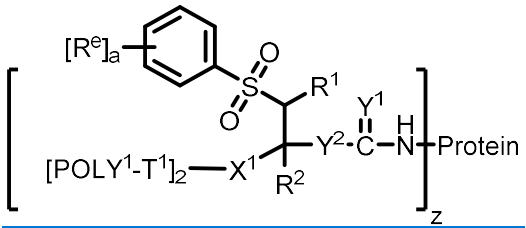
wherein:

n is independently an integer from 4 to 1500;

z is an integer from 1 to 25; and

-NH- is an amine group of a residue within the protein.

87. The conjugate of 77, wherein the conjugate comprises a structure according to formula (XIII-D):



(XIII-D)

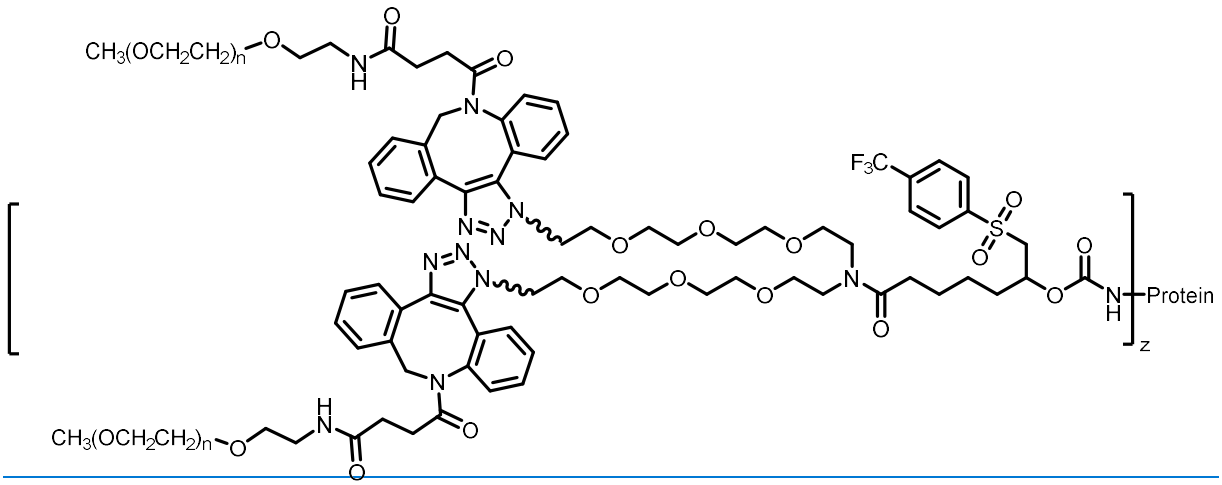
88. The conjugate of claim 87, wherein

a is an integer from 0 to 2;

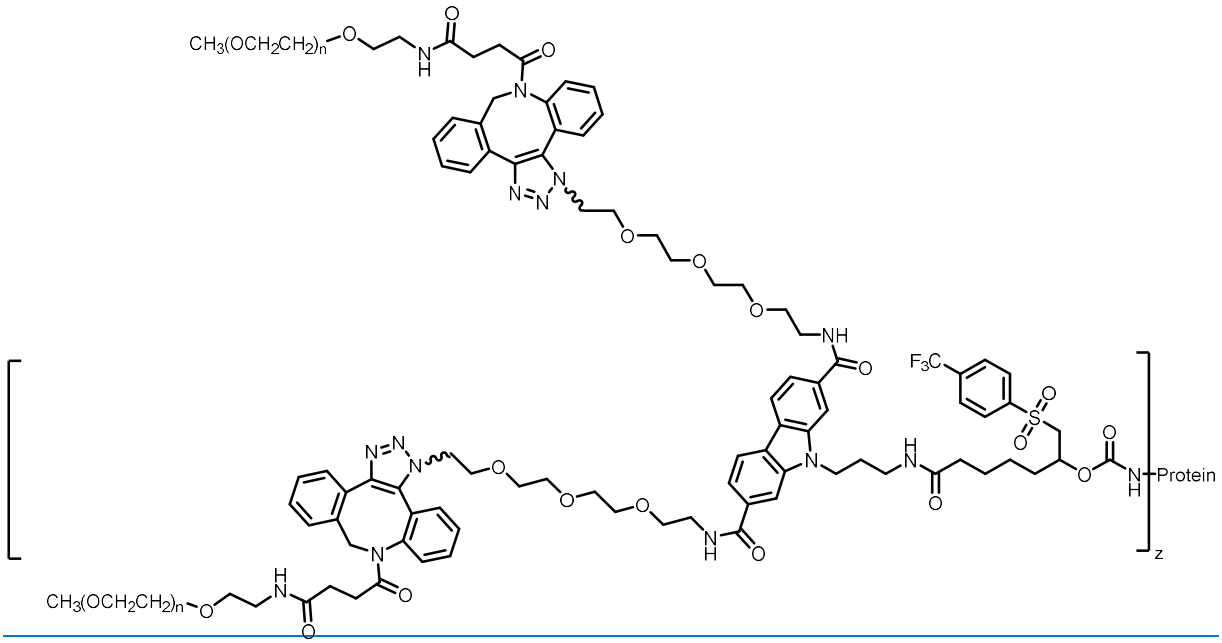
~~R^1 and R^2 are each independently hydrogen, Me, or Et; and~~

~~R^e is nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.~~

~~89. The conjugate of claim 88, wherein the conjugate comprises a structure according to formula (XIII-D1), or (XIII-D2):~~



~~(XIII-D1); or~~



~~(XIII-D2)~~

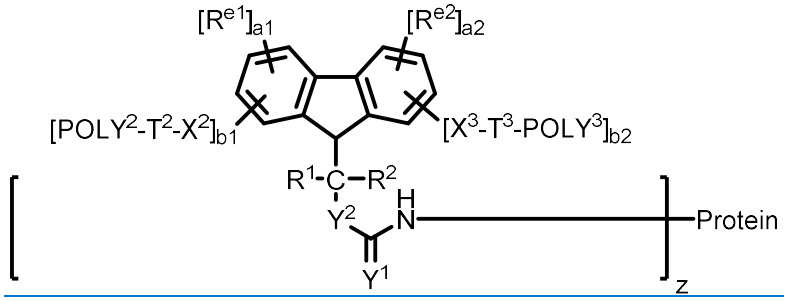
wherein:

n is independently an integer from 4 to 1500;

z is an integer from 1 to 25; and

-NH- is an amine group of a residue within the protein.

90. The conjugate of any one of claims 30-51, wherein the conjugate comprises a structure according to formula (XIV):



(XIV)

wherein:

$POLY^2$ is a straight or branched water-soluble polymer;

$POLY^3$ is a straight or branched water-soluble polymer;

R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

a1 and a2 are each independently an integer from 0 to 4;

b1 is 1;

b2 is an integer from 0 to 1;

z is an integer from 1 to 25;

R^{e1}, when present, is a first electron altering group;

R^{e2}, when present, is a second electron altering group; or -X-FG^2;

wherein

X is a spacer moiety; and

FG^2 is a functional group capable of reacting through click chemistry selected from the group consisting of azide, alkynyl, and cycloalkynyl groups.

X^2, when present, is a spacer moiety;

X^3, when present, is a spacer moiety;

T^2 is a triazole functional group;

T^3 is a triazole functional group;

Y^1 is O or S;

Y^2 is O or S; and

-NH- is an amine group of a residue within the protein.

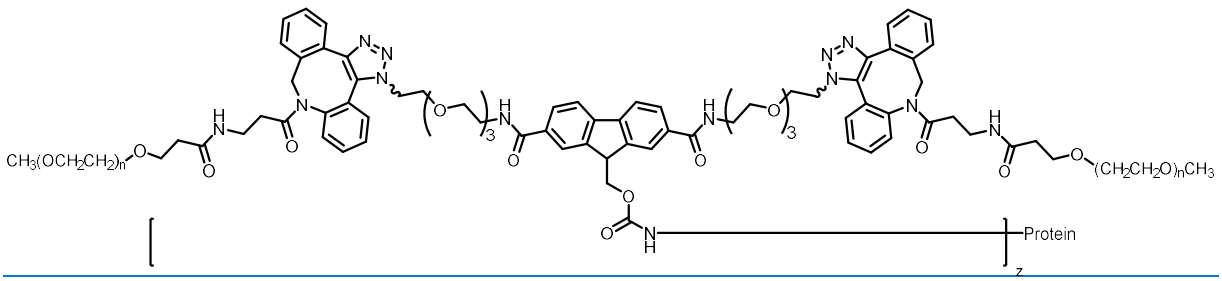
91. The conjugate of claim 90, wherein

a1 and a2 are each independently an integer from 0 to 2;

R^1 and R^2 are each independently hydrogen, Me, or Et; and

R^{e1} and R^{e2} are each independently nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.

92. The conjugate of claim 91, wherein the conjugate comprises a structure according to formula (XIV-A):



(XIV-A)

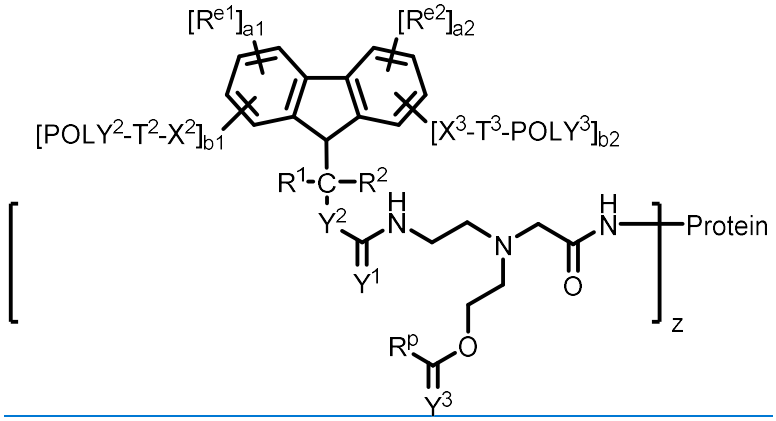
wherein:

~~n is independently an integer from 4 to 1500;~~

~~z is an integer from 1 to 25; and~~

~~-NH- is an amine group of a residue within the protein.~~

~~93. The conjugate of any one of claims 30-51, wherein the conjugate comprises a structure according to formula (XV):~~



~~(XV)~~

~~wherein:~~

~~$POLY^2$ is a straight or branched water-soluble polymer;~~

~~$POLY^3$ is a straight or branched water-soluble polymer;~~

~~R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~a1 and a2 are each independently an integer from 0 to 4;~~

~~b1 is 1;~~

~~b2 is an integer from 0 to 1;~~

~~z is an integer from 1 to 25;~~

R^{e1}, when present, is a first electron altering group;

R^{e2}, when present, is a second electron altering group; or -X-FG^2;

wherein

X is a spacer moiety; and

FG^2 is a functional group capable of reacting through click chemistry selected from the group consisting of azide, alkynyl, and cycloalkynyl groups;

R^p is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

X^2, when present, is a spacer moiety;

X^3, when present, is a spacer moiety;

T^2 is a triazole functional group;

T^3 is a triazole functional group;

Y^1 is O or S;

Y^2 is O or S;

Y^3 is O or S; and

-NH- is an amine group of a residue within the protein.

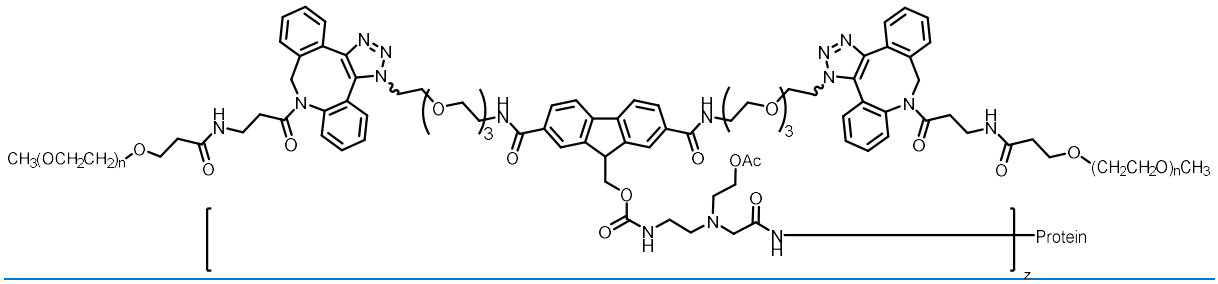
94. The conjugate of claim 93, wherein

a1 and a2 are each independently an integer from 0 to 2;

R^1 and R^2 are each independently hydrogen, Me, or Et; and

R^{e1} and R^{e2} are each independently nitro, cyano, halogen, $-CF_3$, -CONHMe, $-SO_2NHMe$, -OMe, -NHMe, -NHAc, $-NHSO_2Me$, or $-OCF_3$.

95. The conjugate of claim 94, wherein the conjugate comprises a structure according to formula (XV-A):



(XV-A)

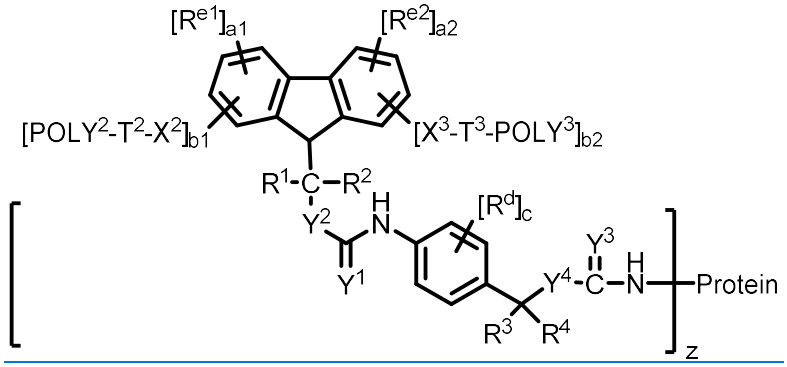
wherein:

n is independently an integer from 4 to 1500;

z is an integer from 1 to 25; and

-NH- is an amine group of a residue within the protein.

96. The conjugate of any one of claims 30-51, wherein the conjugate comprises a structure according to formula (XVI):



(XVI)

wherein:

$POLY^2$ is a straight or branched water-soluble polymer;

$POLY^3$ is a straight or branched water-soluble polymer;

R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^3 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^4 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

a1 and a2 are each independently an integer from 0 to 4;

b1 is 1;

b2 is an integer from 0 to 1;

c is an integer from 0 to 4;

z is an integer from 1 to 25;

R^{e1}, when present, is a first electron altering group;

R^{e2}, when present, is a second electron altering group; or -X-FG^2;

wherein

X is a spacer moiety; and

FG^2 is a functional group capable of reacting through click chemistry selected from the group consisting of azide, alkynyl, and cycloalkynyl groups;

R^d is nitro, cyano, halogen, amide, substituted amide, sulfone, substituted sulfone, sulfonamide, substituted sulfonamide, alkoxy, substituted alkoxy, alkyl or cycloalkyl, substituted alkyl or cycloalkyl, aryl or heteroaryl, substituted aryl or heteroaryl;

X^2, when present, is a spacer moiety;

X^3, when present, is a spacer moiety;

T^2 is a triazole functional group;

T^3 is a triazole functional group;

Y^1 is O or S;

Y^2 is O or S;

~~Y^3 is O or S;~~

~~Y^4 is O or S; and~~

~~-NH- is an amine group of a residue within the protein.~~

~~97. The conjugate of any one of claims 53-96, wherein the cycloalkynyl is dibenzocyclooctyne (DBCO).~~

~~98~~17. The conjugate of any one of claims ~~23-28, 30-51, and 53-97~~5, 7 and 9-16, wherein the protein is ~~a chemokine, a chemokine antagonist, a cytokine, a cytokine antagonist, an antibody, or a therapeutic peptide~~IL-2.

~~99. The conjugate of claim 98, wherein the cytokine is GM-CSF, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IFN-α, IFN-β, IFN-γ, MIP-1α, MIP-1β, TGF-β, TNF-α, or TNF-β.~~

~~100. The conjugate of claim 98 or 99, wherein the cytokine is IL-2.~~

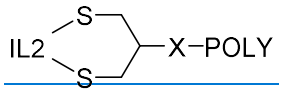
~~101. The conjugate of claim 100, where the IL-2 comprises about 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:1.~~

~~102. The conjugate of claim 98, wherein the chemokine is MCP-1, MCP-2, MCP-3, MCP-24, MCP-5, CXCL76, I-309 (CCL1), BCA1 (CXCL13), MIG, SDF-1/PBSF, IP-10, I-TAC, MIP-1α, MIP-1β, RANTES, eotaxin-1, eotaxin-2, GCP-2, Gro-α, Gro-β, Gro-γ, LARC (CCL20), ELC (CCL19), SLC (CCL21), ENA-78, PBP, TECK(CCL25), CTACK (CCL27), MEC, XCL1, XCL2, HCC-1, HCC-2, HCC-3, or HCC-4.~~

~~103. The conjugate of claim 98, wherein the antibody targets one or more of angiopoietin 2, AXL, ACVR2B, angiopoietin 3, activin receptor-like kinase 1, amyloid A protein, β- amyloid, AOC3, BAFF, BAFF-R, B7-H3, BCMAC, A-125 (imitation), C5, CA-125, CCL11 (eotaxin-1), CEA, CSF1R, CD2, CD3, CD4, CD6, CD15, CD19, CD20, CD22, CD23, CD25, CD28, CD30, CD33, CD37, CD38, CD40, CD41, CD44, CD51, CD52, CD54, CD56, CD70, CD74, CD97B, CD125, D134, CD147, CD152, CD154, CD279, CD221, C242 antigen, CD276, CD278, CD319, clostridium difficile, claudin 18 isoform 2, CSF1R, CEACAM5, CSF2, carbonic anhydrase 9, CLDN18.2, cardiac myosin, CCR4, CGRP, coagulation factor III, c-Met,~~

~~CTLA-4, DPP4, DR5, DLL3, DLL4, dabigatran, EpCAM, ebolavirus glycoprotein, endoglin, episialin, EPHA3, c-Met, FGFR2, fibrin II beta chain, FGF-23, folate receptor-1, GMCSF, GD2 ganglioside, GDF-8, GCGR, gelatinase B, glypican-3, GPNMB, GMCSF receptor α-chain, kallikrein, KIR2D, ICAM-1, ICOS, IGF1, IGF2, IGF-1 receptor, IL-1α, IL-1β, IL-2, IL-4Rα, IL-5, IL-6, IL-6 R, IL-9, IL-12, IL-13, IL17A, IL17F, IL-20, IL-22, IL-23, IL-31, IFN-α, IFN-β, IFN-γ, integrin α4β7, interferon α/β receptor, Influenza A hemagglutinin, ILGF2, HER1, HER2, HER3, HHGFR, HGF, HLA-DR, hepatitis B surface antigen, HNGF, Hsp90, HGFR, L-selectin, Lewis-Y antigen, LYPD3, LOXL2, LIV-1, MUC1, MCP-1, MSLN, mesothelin, MIF, MCAM, NCA-90, NCA-90Notch-1, nectin-4, PCDP1, PD-L1, PD-1, PCSK9, PTK7, PCDC1, phosphatidylserine, RANKL, RTN4, Rhesus factor, ROR1, SLAMF7, *Staphylococcus aureus* alpha toxin, *Staphylococcus aureus* bi-component leucocidin, SOST, selectin P, SLITRK6, SDC1, TFPI, TRAIL-R2, tumor antigen CTAA16.88, TNF-α, TWEAK receptor, TNFRSF8, TYRP1, tau protein, TAG-72, TSLP, TRAIL-R1, TRAIL-R2, TGF-β, TAG-72, TRAP, TIGIT, tenascin C, OX-40, VEGF-A, VWF, VEGFR1, or VEGFR2.~~

~~104. The conjugate of any one of claims 30-51, wherein the conjugate comprises a structure according to formula (XVII):~~



~~(XVII)~~

~~or a stereoisomer, tautomer or mixture thereof, regioisomer or mixture thereof, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;~~

~~wherein~~

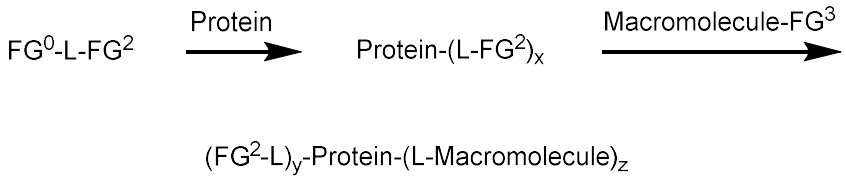
~~X is a spacer moiety;~~

~~POLY is a straight or branched water-soluble polymer; and~~

~~"-S-" is a sulfur group of a residue within the IL-2 moiety.~~

~~105. The conjugate of claim 104, wherein the water-soluble polymer is a polymer poly(ethylene glycol).~~

~~106~~18. A method for preparing Protein-Macromolecule conjugates according to scheme (I):



(Scheme I)

wherein x is an integer from 1 to 25;

y is an integer from 0 to 24;

z is an integer from 1 to 25, wherein x = y + z;

L is a linker;

FG^0 is a functional group capable of reacting with a nucleophilic group of an active protein agent to form a linkage, including a carbamate linkage, a thiol bridge and the like;

FG^2 is a functional group capable of reacting with FG^3 through click chemistry selected from the group consisting of azide, alkynyl, and cycloalkynyl groups;

FG^3 is a functional group capable of reacting with FG^2 through click chemistry selected from the group consisting of azide, alkynyl, and cycloalkynyl groups;

protein is a chemokine, a chemokine antagonist, a cytokine, a cytokine antagonist, an antibody, or a therapeutic peptide;

macromolecule is a water-soluble polymer, a lipid, a protein or a polypeptide. It can include any of the following: a fatty acid comprises from about 6 to about 26 carbon atoms, one of the polymers selected from the group consisting of 2-methacryloyl-oxyethyl phosphoyl cholins, poly(acrylic acids), poly(acrylates), poly(acrylamides), poly(N-acryloylmorpholine), poly(alkyloxy) polymers, poly(amides), poly(amidoamines), poly(amino acids), poly(anhydrides), poly(aspartamides), poly(butyric acids), poly(glycolic acids), polybutylene terephthalates, poly(caprolactones), poly(carbonates), poly(cyanoacrylates), poly(dimethylacrylamides), poly(esters), poly(ethylenes), poly(ethylene glycols), poly(ethylene oxides), poly(ethyl phosphates), poly(ethyloxazolines), poly(glycolic acids), poly(α-hydroxy

acid), poly(hydroxyethyl acrylates), poly(hydroxyethyloxazolines), poly(hydroxymethacrylates), poly(hydroxyalkylmethacrylamides), poly(hydroxyalkylmethacrylates), poly(hydroxypropyloxazolines), poly(iminocarbonates), poly(lactic acids), poly(lactic-co-glycolic acids), poly(methacrylamides), poly(methacrylates), poly(methyloxazolines), poly(organophosphazenes), poly(ortho esters), poly(oxazolines), poly(oxyethylated polyol), poly(olefinic alcohol), polyphosphazene, poly(propylene glycols), poly(saccharide), poly(siloxanes), poly(urethanes), poly(vinyl alcohols), poly(vinyl amines), poly(vinylmethylethers), poly(vinylpyrrolidones), silicones, amylose, celluloses, carbomethyl celluloses, hydroxypropyl methylcelluloses, chitins, chitosans, dextrans, dextrins, gelatins, hyaluronic acids (HA) and derivatives, functionalized hyaluronic acids, mannans, pectins, heparin, heparan sulfate (HS), rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches (HES), polysialic acid (PSA) and other carbohydrate-based polymers, xylans, and copolymers, of albumin, transferrin, transthyretin, immunoglobulin, a XTEN peptide, a glycine-rich homoamino acid polymer (HAP), a PAS polypeptide, an elastin-like polypeptide (ELP), a CTP peptide, or a gelatin-like protein (GLK) polymer.

~~107. The method of claim 106, wherein x or z is an integer from 2 to 25.~~

~~108. The method of claim 106, wherein x or z is an integer from 3 to 25.~~

~~109. The method of claim 106, wherein x or z is an integer from 4 to 25.~~

~~110. The method of claim 106, wherein x or z is an integer from 5 to 25.~~

~~111. The method of claim 106, wherein x or z is an integer from 6 to 25.~~

~~112. The method of any one of claims 106-111, wherein L is a releasable linker.~~

~~113. The method of claim 112, wherein the releasable linker is the releasable linker of any one of claims 1-22.~~

~~114. The method of any one of claims 106-113, wherein the protein is a chemokine, a chemokine antagonist, a cytokine, a cytokine antagonist, an antibody, or a therapeutic peptide.~~

~~115. The method of claim 114, wherein the cytokine is GM-CSF, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IFN-α, IFN-β, IFN-γ, MIP-1α, MIP-1β, TGF-β, TNF-α, or TNF-β.~~

~~116. The method of claim 114 or 115, wherein the cytokine is IL-2.~~

~~117. The method of claim 116, where the IL-2 comprises about 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:1.~~

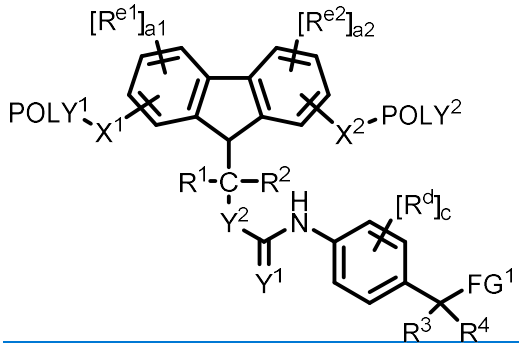
~~118. The method of claim 114, wherein the chemokine is MCP-1, MCP-2, MCP-3, MCP-24, MCP-5, CXCL76, I-309 (CCL1), BCA1 (CXCL13), MIG, SDF-1/PBSF, IP-10, I-TAC, MIP-1α, MIP-1β, RANTES, eotaxin-1, eotaxin-2, GCP-2, Gro-α, Gro-β, Gro-γ, LARC (CCL20), ELC (CCL19), SLC (CCL21), ENA-78, PBP, TECK(CCL25), CTACK (CCL27), MEC, XCL1, XCL2, HCC-1, HCC-2, HCC-3, or HCC-4.~~

~~119. The method of claim 114, wherein the antibody targets one or more of angiopoietin 2, AXL, ACVR2B, angiopoietin 3, activin receptor-like kinase 1, amyloid A protein, β-amyloid, AOC3, BAFF, BAFF-R, B7-H3, BCMAC, A-125 (imitation), C5, CA-125, CCL11 (eotaxin-1), CEA, CSF1R, CD2, CD3, CD4, CD6, CD15, CD19, CD20, CD22, CD23, CD25, CD28, CD30, CD33, CD37, CD38, CD40, CD41, CD44, CD51, CD52, CD54, CD56, CD70, CD74, CD97B, CD125, D134, CD147, CD152, CD154, CD279, CD221, C242 antigen, CD276, CD278, CD319, clostridium difficile, claudin 18 isoform 2, CSF1R, CEACAM5, CSF2, carbonic anhydrase 9, CLDN18.2, cardiac myosin, CCR4, CGRP, coagulation factor III, c-Met, CTLA-4, DPP4, DR5, DLL3, DLL4, dabigatran, EpCAM, ebolavirus glycoprotein, endoglin, episialin, EPHA3, c-Met, FGFR2, fibrin II beta chain, FGF-23, folate receptor 1, GMCSF, GD2 ganglioside, GDF-8, GCGR, gelatinase B, glypican-3, GPNMB, GMCSF receptor α-chain, kallikrein, KIR2D, ICAM-1, ICOS, IGF1, IGF2, IGF-1 receptor, IL-1α, IL-1β, IL-2, IL-4Rα, IL-5, IL-6, IL-6 R, IL-9, IL-12, IL-13, IL17A, IL17F, IL-20, IL-22, IL-23, IL-31, IFN-α, IFN-β, IFN-γ, integrin α4β7, interferon α/β receptor, Influenza A hemagglutinin, ILGF2, HER1, HER2, HER3, HHGFR, HGF, HLA-DR, hepatitis B surface antigen, HNGF, Hsp90, HGFR, L-selectin, Lewis-Y antigen, LYPD3, LOXL2, LIV-1, MUC1, MCP-1, MSLN, mesothelin, MIF, MCAM, NCA-90, NCA-90Notch-1, nectin-4, PCDP1, PD-L1, PD-1, PCSK9, PTK7, PCDC1, phosphatidylserine, RANKL, RTN4, Rhesus factor, ROR1, SLAMF7, *Staphylococcus aureus*~~

alpha toxin, *Staphylococcus aureus* bi-component leucocidin, SOST, selectin P, SLITRK6, SDC1, TFPI, TRAIL-R2, tumor antigen CTAA16.88, TNF-α, TWEAK receptor, TNFRSF8, TYRP1, tau protein, TAG-72, TSLP, TRAIL-R1, TRAIL-R2, TGF-β, TAG-72, TRAP, TIGIT, tenascin C, OX-40, VEGF-A, VWF, VEGFR1, or VEGFR2.

120. The method of any one of claims 106-119, wherein the cycloalkynyl is dibenzocyclooctyne (DBCO).

121. A polymeric reagent, wherein the polymeric reagent has a structure according to formula (V):



(V)

or a stereoisomer, tautomer or mixture thereof, or an isotopic variant thereof;

wherein:

$POLY^1$ is a first water-soluble polymer;

$POLY^2$ is a second water-soluble polymer;

X^1 is a first spacer moiety;

X^2 is a second spacer moiety;

Y^1 is O or S;

Y^2 is O or S;

R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^3 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

R^4 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;

a1 is an integer from 0 to 3;

a2 is an integer from 0 to 3;

c is an integer from 0 to 4;

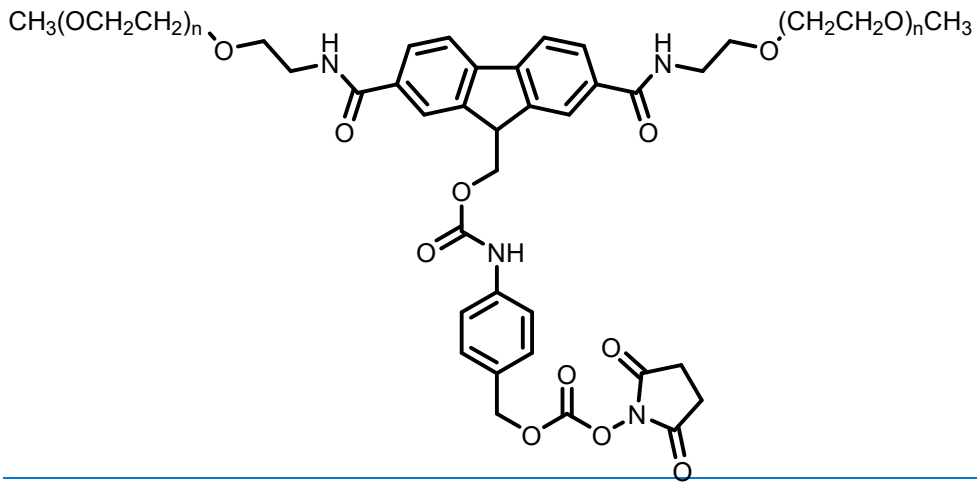
R^{e1}, when present, is a first electron altering group;

R^{e2}, when present, is a second electron altering group;

R^d is nitro, cyano, halogen, amide, substituted amide, sulfone, substituted sulfone, sulfonamide, substituted sulfonamide, alkoxy, substituted alkoxy, alkyl or cycloalkyl, substituted alkyl or cycloalkyl, aryl or heteroaryl, substituted aryl or heteroaryl; and

FG^1 is a functional group capable of reacting with an amino group of an active agent to form a releasable linkage, such as a carbamate linkage.

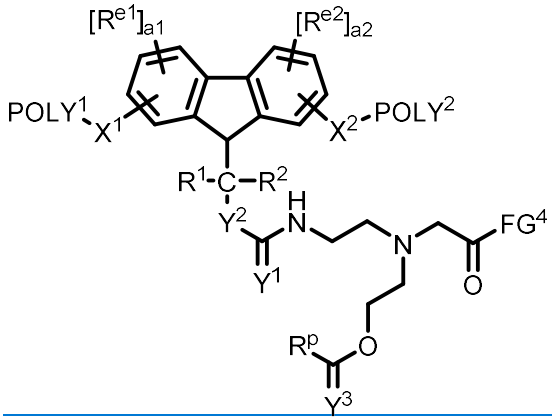
122. The polymeric reagent of claim 121, wherein the polymeric reagent has a structure according to formula (V-A):



(V-A)

wherein n is independently an integer from 4 to 1500.

123. A polymeric reagent, wherein the polymeric reagent has a structure according to formula (VI):



(VI)

or a stereoisomer, tautomer or mixture thereof, or an isotopic variant thereof;

wherein:

$POLY^1$ is a first water-soluble polymer;

$POLY^2$ is a second water-soluble polymer;

~~X^1 is a first spacer moiety;~~

~~X^2 is a second spacer moiety;~~

~~Y^1 is O or S;~~

~~Y^2 is O or S;~~

~~Y^3 is O or S;~~

~~R^1 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~R^2 is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl;~~

~~a1 is an integer from 0-3;~~

~~a2 is an integer from 0-3;~~

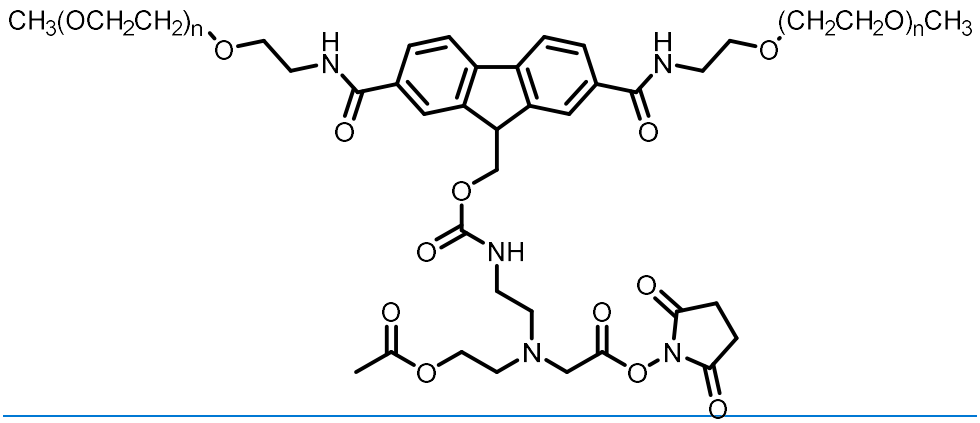
~~R^{e1}, when present, is a first electron altering group;~~

~~R^{e2}, when present, is a second electron altering group;~~

~~R^p is a hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or substituted aryl; and~~

~~FG^4 is a functional group capable of reacting with an amino group of an active agent to form a releasable linkage, such as an amide linkage.~~

~~124. The polymeric reagent of claim 123, wherein the polymeric reagent has a structure according to formula (VI-A):~~



~~(VI-A)~~

~~wherein n is independently an integer from 4 to 1500.~~

~~125~~19. A pharmaceutical composition comprising the conjugate of any one of claims ~~23-28, 30-51, and 53-105~~7 and 13-16 and one or more pharmaceutically acceptable excipients.

~~126~~20. ~~A method of treatment comprising administering to a subject in need thereof, a~~Use of the pharmaceutical composition of claim ~~125~~ 19 in the manufacture of a medicament for treating cancer, an infection, or an autoimmune disease in a subject.

~~127. The method of claim 126, wherein the pharmaceutical composition is administered for the treatment of cancer, an infection, or an autoimmune disease.~~

~~128. A method of treatment comprising administering to a subject in need thereof, the pharmaceutical composition of claim 125 in combination with other suitable therapeutic agents.~~

~~129. The method of claim 128, wherein the therapeutic agent is an antibody.~~

~~130. The method of claim 129, wherein the antibody is an anti-tumor antigen antibody.~~

~~131. The method of claim 130, wherein the anti-tumor antigen antibody has its activity through ADCC functions.~~