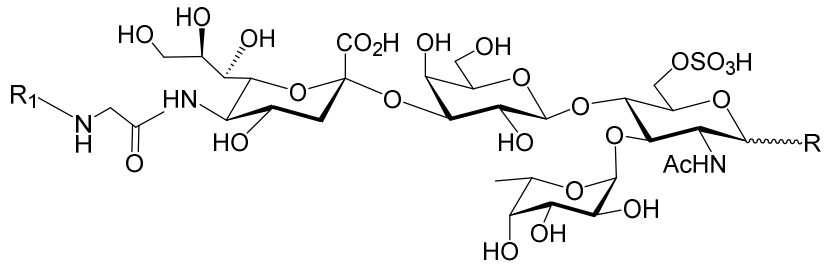
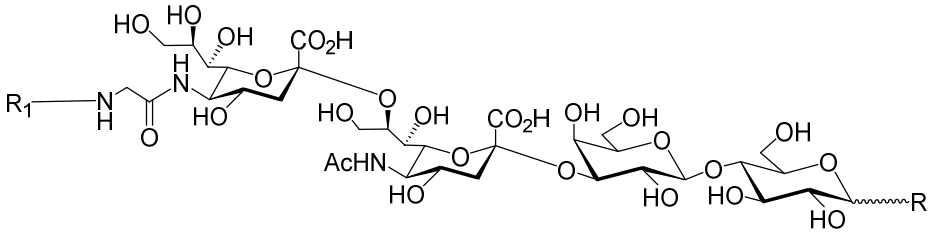
CLAIMS

1. A compound represented by any one of the following structural formulas:



(S-1), or



(D-1),

or a pharmaceutically acceptable salt thereof,

wherein:

R_1, for each occurrence independently, is -C(O)-A, wherein A is a C_1-C_6 alkyl, a C_6-C_{18} aryl, a (C_6-C_{18})aryl(C_1-C_3)alkyl, a 5-18-member heteroaryl, a (5-18-member)heteroaryl(C_1-C_3)alkyl, a C_3-C_8 cycloalkyl, a (C_3-C_8)cycloalkyl(C_1-C_3)alkyl, a 5-8-member heterocycloalkyl, or a (5-8-member)heterocycloalkyl(C_1-C_3)alkyl;

wherein one or two carbon atoms within the alkyl portion of A is optionally, each independently, replaced with a heteroatom selected from N, O, or S;

and wherein A is optionally substituted with 1 to 3 R^{11} groups, each said R^{11} group independently selected from a C_1-C_6 alkyl, a C_1-C_6 haloalkyl, a C_1-C_6 alkoxy, a halogen, a C_6-C_{12} aryl, a 5-12-member heteroaryl and cyano, or two groups R^{11}, taken together with the atoms to which they are attached, form a 5-7-member heterocyclyl having 1 to 3 heteroatoms selected from N, O, or S;

wherein R^{11}, each independently, is optionally substituted with 1 to 3 substituents selected from a halogen, a C_1-C_6 alkyl, a C_1-C_6 haloalkyl, a C_1-C_6 alkoxy, or cyano; and and further wherein:

R, for each occurrence independently, is -R^L-R^F, and wherein:

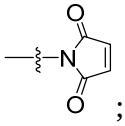
R^L is, for each occurrence independently:

-O-(C_1-C_{12}) alkylenyl-, -O-, -S-, -NR^{100}-, -S-(C_1-C_{12}) alkylenyl-, -NR^{101}-(C_1-C_{12}) alkylenyl-, -NR^{101a}-O-(C_1-C_{12})alkylenyl-; -O-$(CH_2CH_2O)_m$-, -O-$(CH_2CH_2O)_k$-(CH_2CH_2)-, -NR^{102}-X^{100}-(C_1-C_{12}) alkylenyl-, -NR^{102a}-NR^{102b}-C(O)-(C_1-C_{12})alkylenyl, wherein R^{100}, R^{101}, R^{101a}, R^{102}, R^{102a}, and R^{102b}, each independently is H or a C_1-C_3 alkyl, and X^{100} is -O- or -NH-, and wherein m and k, each independently, is an integer from 1 to 12;

R^F, for each occurrence independently, is:

H, a C_1-C_3 alkyl, -NH_2, -NH-Fmoc, -NH-Boc, -NH-CBz, -NH-Troc, -NH-TFA, a mono(C_1-C_3)alkylamino, a di(C_1-C_3 alkyl)amino;

-C(O)-R^{103}, wherein R^{103} is -H, -OH, or a (C_1-C_3) alkyl;

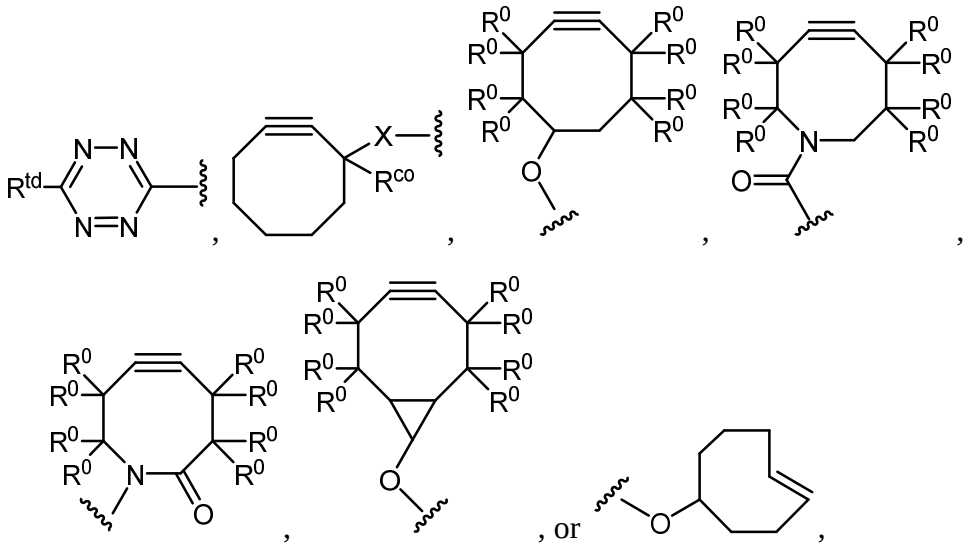


-SH, a moiety represented by the following structural formula ;

or a click chemistry reagent.

2. The compound of Claim 1, wherein the click chemistry reagent comprises an azide, a C_2-C_3 alkyne, a tetrazine, a trans-cyclooctene, or a cyclooctyne.

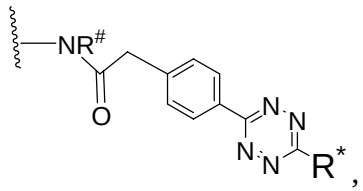
3. The compound of Claim 2, wherein the click chemistry reagent is an azide, a C_2-C_3 alkyne, or a moiety represented by any one of the following structural formulas:



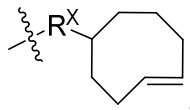
, , , , , , , or ,

wherein: R^{co} is hydrogen or halogen; X is null or O; and R^0 is in each case independently selected from hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkoxy, a C_6-C_{12} aryl, 5-8 member heteroaryl, C_{3-8}cycloalkyl, or 3-8-member heterocyclyl; wherein any two or more R^0 groups together with the atoms to which they are attached optionally form an unsaturated, saturated, or aromatic 5-8-member ring; and R^{td} is hydrogen, C_{1-8}alkyl, C_{1-8}alkoxy, a C_6-C_{12} aryl, a 5-8-member heteroaryl, C_{3-8}cycloalkyl, or a 3-8 member heterocyclyl.

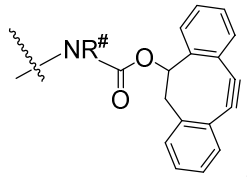
4. The compound of Claim 2, wherein the click reagent is an azide, a C_2-C_3 alkyne, or any one of the moieties represented by the following structural formulas:



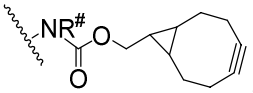
,



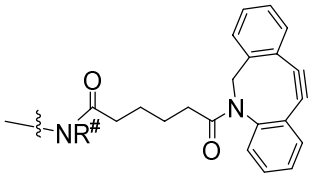
, or



,



,



,

wherein R* is H or methyl, $R^{\#}$, for each occurrence independently, is H or a C_1-C_3 alkyl, and R^X is -NH-C(O)O-.

5. The compound of Claim 1, wherein R, for each occurrence independently, is -O-$(CH_2)_x$-NH_2 or -O-$(CH_2)_x$-NH-Fmoc, wherein x, for each occurrence independently, is an integer from 1 to 10.

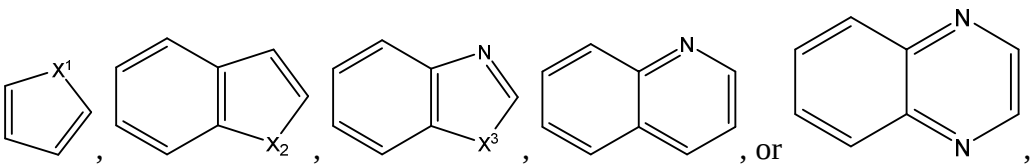
6. The compound of any one of Claims 1-5, wherein:

the cycloalkyl portion of moiety A is selected from a C_6-C_7 cycloalkyl;

the heterocycloalkyl portion of moiety A is selected from a 5-6-member heterocycloalkyl having 1 or 2 heteroatoms selected from N, O, or S;

the aryl portion of moiety A is selected from a phenyl or a naphthalenyl; and

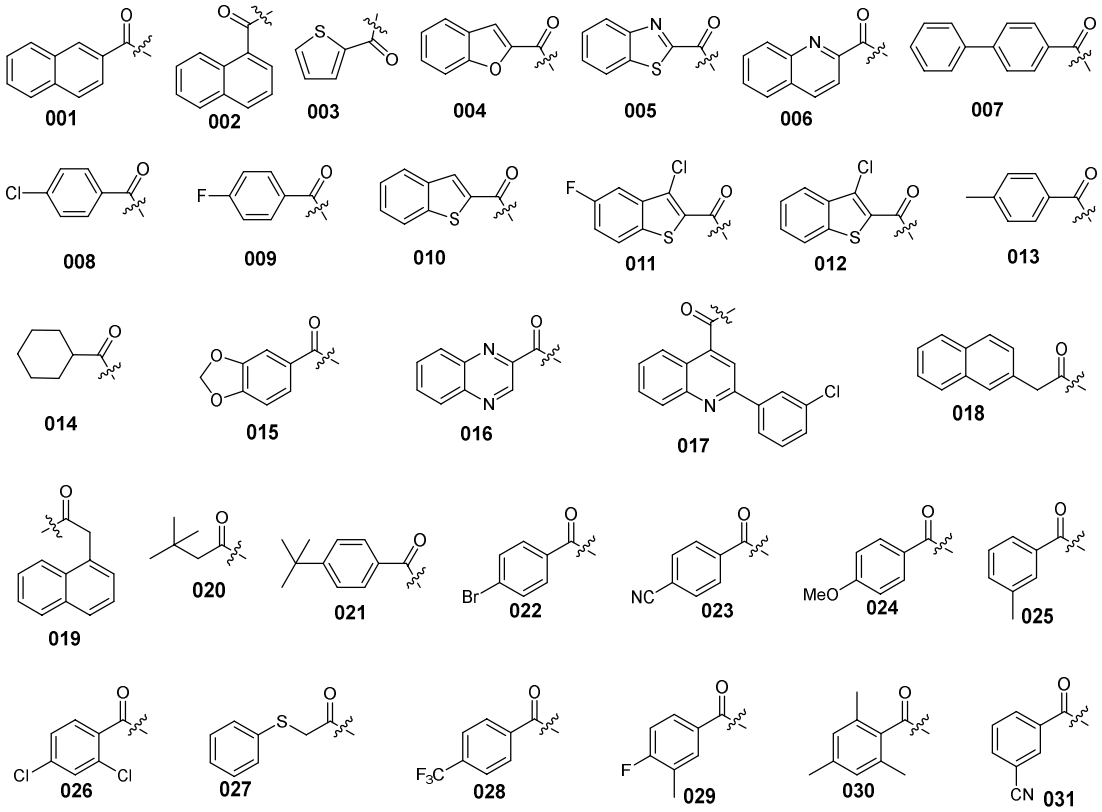
the heteroaryl portion of moiety A is selected from a moiety represented by any of the following structural formulas:



wherein X^1, X^2 and X^3, each independently, is selected from NR^H, O, or S, wherein R^H is H or a C_1-C_3 alkyl; and further

wherein if present each R^{11} is independently selected from cyano, a halogen, a phenyl, a halophenyl, a C_1-C_6 alkyl, a C_1-C_6 haloalkyl, a C_1-C_3 alkoxy, or two groups R^{11}, taken together with the atoms to which they are attached, form a [1,3]dioxolo group, optionally substituted with one or two methyl or ethyl groups.

7. The compound of any of Claims 1-6, wherein R_1, for each occurrence independently, is selected from the moiety represented by the following structural formulas, wherein the wavy line represents the point of attachment of R_1 to the nitrogen atom:



8. The compound of any one of Claims 1-7, wherein the compound is any one of the compounds S-101 through S-131, or D-101 through D-131, wherein the moiety R is -O-$(CH_2)_5$-NH-Fmoc.

9. A particle, comprising a compound represented by the following structural formula:

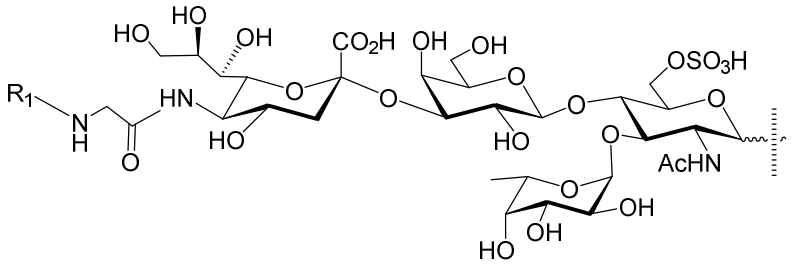
G——L——P,

wherein:

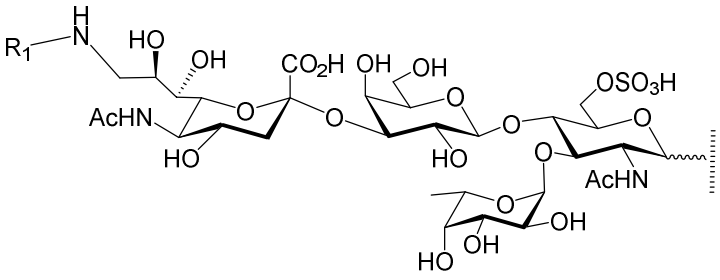
P is a biocompatible polymer;

L is a covalent linker; and

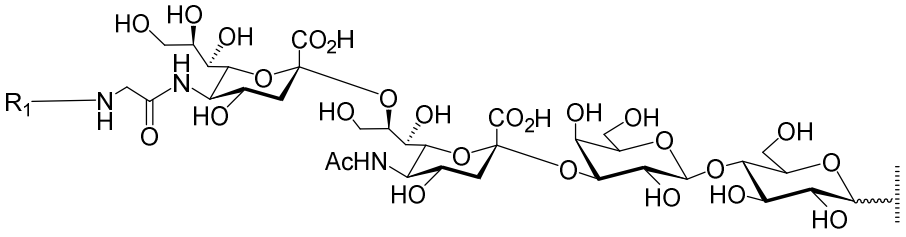
G is any one of the moieties represented by the following structural formulas:



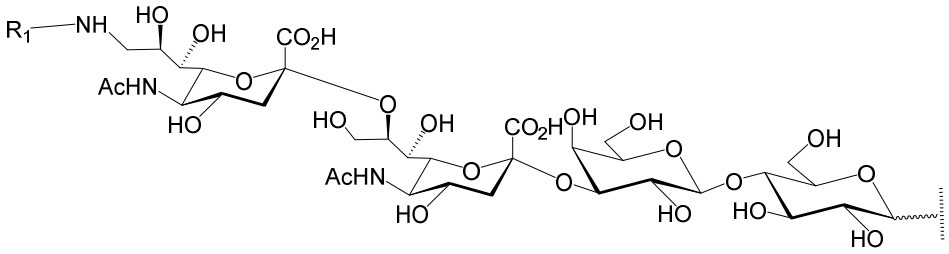
(S-1A),



(S-2A),



(D-1A), or



(D-2A),

or a pharmaceutically acceptable salt thereof,

wherein:

the symbol ..... represents the point of attachment to L;

R_1, for each occurrence independently, is -C(O)-A, wherein A is a C_1-C_6 alkyl, a C_6-C_{18} aryl, a (C_6-C_{18})aryl(C_1-C_3)alkyl, a 5-18-member heteroaryl, a (5-18-member)heteroaryl(C_1-C_3)alkyl, a C_3-C_8 cycloalkyl, a (C_3-C_8)cycloalkyl(C_1-C_3)alkyl, a 5-8-member heterocycloalkyl, or a (5-8-member)heterocycloalkyl(C_1-C_3)alkyl;

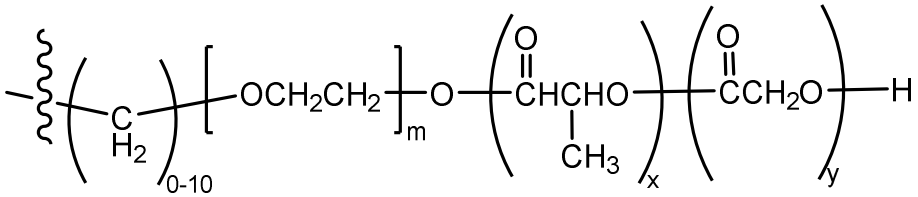
wherein one or two carbon atoms within the alkyl portion of A is optionally, each independently, replaced with a heteroatom selected from N, O, or S;

and wherein A is optionally substituted with 1 to 3 R^{11} groups, each said R^{11} group independently selected from a C_1-C_6 alkyl, a C_1-C_6 haloalkyl, a C_1-C_6 alkoxy, a halogen, a C_6-C_{12} aryl, a 5-12-member heteroaryl and cyano, or two groups R^{11}, taken together with the atoms to which they are attached, form a 5-7-member heterocyclyl having 1 to 3 heteroatoms selected from N, O, or S;

wherein R^{11}, each independently, is optionally substituted with 1 to 3 substituents selected from a halogen, a C_1-C_6 alkyl, a C_1-C_6 haloalkyl, a C_1-C_6 alkoxy, or cyano.

10. The particle of Claim 9, wherein the biocompatible polymer comprises a copolymer PLGA-PEG.

11. The particle of Claim 9, wherein P is represented by the following structural formula:



,

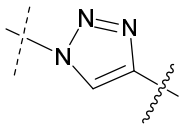
wherein the symbol ~~~ represents the point of attachment of the polymer to the linker L, and further wherein:

y is an integer from 0 to 1000, x is an integer from 0 to 1000, and m is an integer from 0 to 450, provided that x and y are not simultaneously 0.

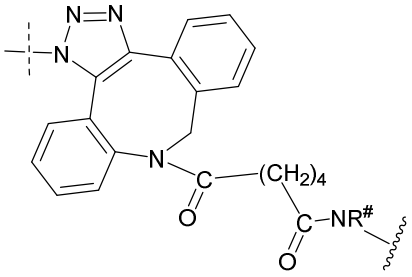
12. The particle of Claim 11, wherein y is an integer from 0 to 500, x is an integer from 0 to 500, and m is an integer from 0 to 250.

13. The particle of any one of Claims 9-12, wherein the linker L includes a portion that is a product of a click chemistry reaction.

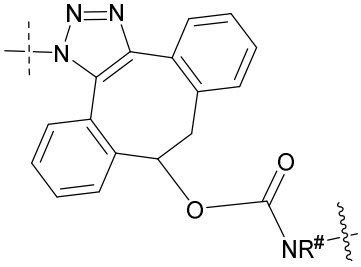
14. The particle of any one of Claims 9-13, wherein the linker L comprises a portion represented by any one of the following structural formulas, wherein the symbols ------ and ∿∿∿ , each independently, represents the point of attachment to additional portions of the linker L, to P, or to G:



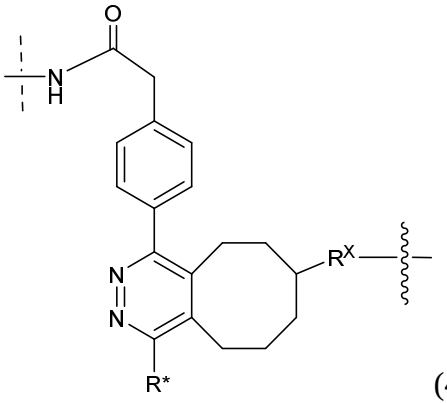
(1),

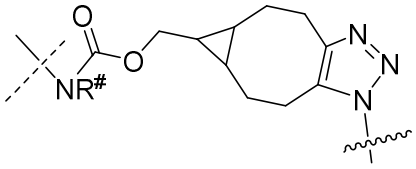


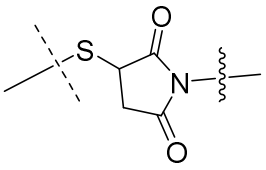
(2),

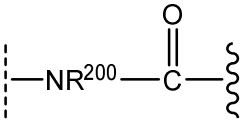


(3),


(4),


(5),


(6),


(7),

wherein R* is H or methyl, $R^{\#}$, for each occurrence independently, is H or a C_1-C_3 alkyl, and R^X is -NH-C(O)O-, and R^{200} is an –H or a C_1-C_3 alkyl.

15. The particles of any one of Claims 9-14, wherein the P is a PLGA(10k)-PEG(5k).

16. The particle of any one of Claims 9-15, wherein the weight of G per unit weight of P (ligand density) is from 10 to 75 μg/mg.

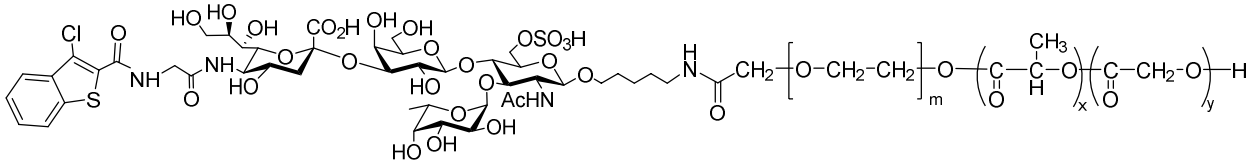
17. Use of a compound of any one of Claims 1, 5-8, 21 or 22, or particles of any one of Claims 9-16, 23-26, 27, 28, 29, and 30 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder, wherein the disorder is selected from a cancer, an ophthalmic disease, a fibrotic disease, a parasitic inflammation, a fungal inflammation, a viral inflammation, an autoimmune inflammation, a neurological inflammation, a neurological degeneration, a dermatologic inflammation, a renal

inflammation, a cardiovascular disease, a gastrointestinal inflammation, or a rheumatic disease.

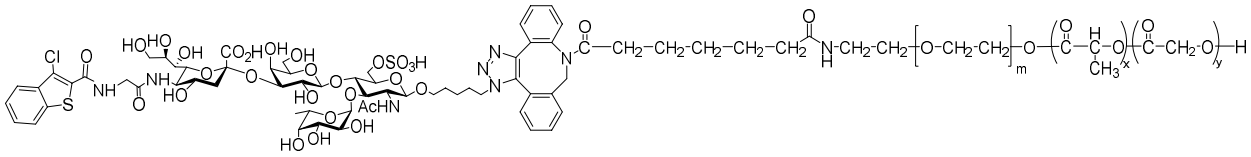
18. A pharmaceutical composition, comprising a compound of any one of Claims 1 or 5-8 or a particle of any one of Claims 9-16, or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier.

19. Any of the compounds represented by the structural formulas listed in Table 4 or a pharmaceutically acceptable salt thereof, wherein the variable R is -O-$(CH_2)_5$-NH_2 , -O-$(CH_2)_5$-NH-Fmoc, –O-$(CH_2)_5$-N_3, or –O-$(CH_2)_5$-biotin.

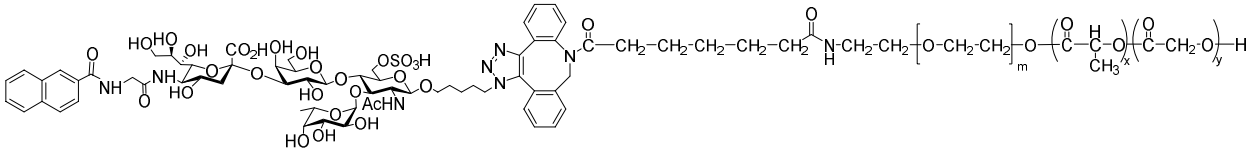
20. A compound represented by any of the following structural formulas of a pharmaceutically acceptable salts thereof:



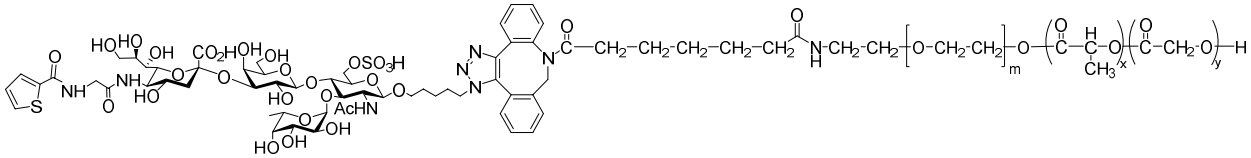
(S112-NP01);



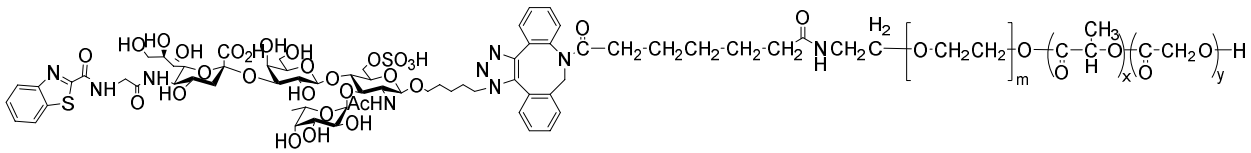
(S112-NP02);



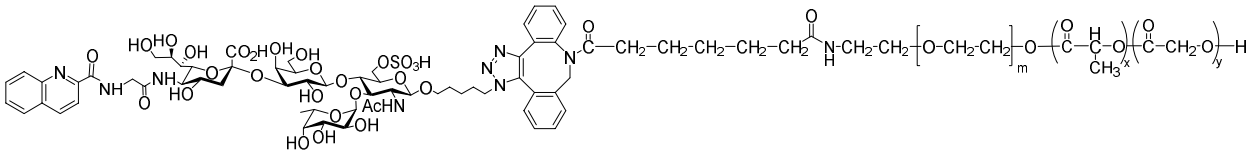
(S101-NP01);



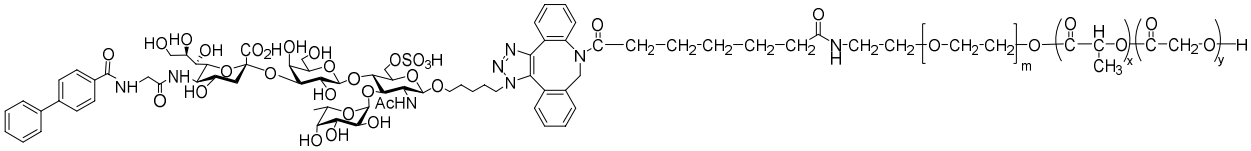
(S103-NP01);



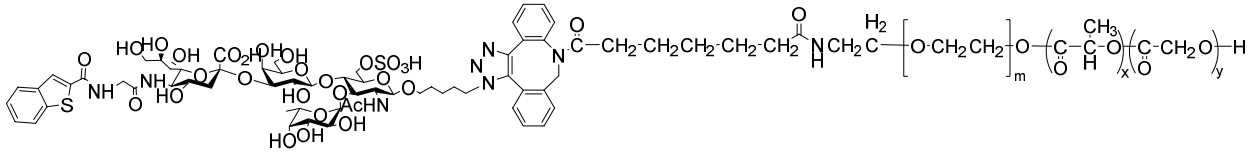
(S105-NP01);



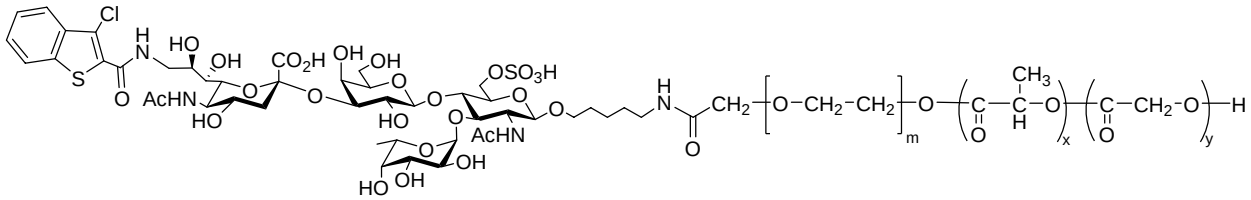
(S106-NP01);



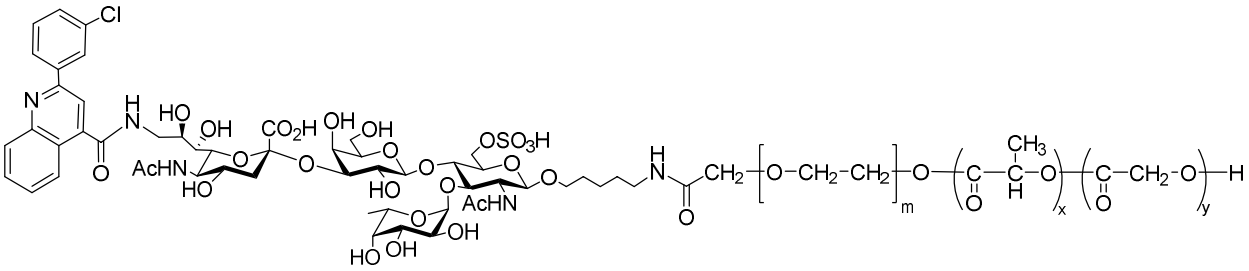
(S107-NP01);



(S110-NP01);



(S212-NP01);



(S217-NP01),

wherein, for each occurrence independently,

x is an integer from 90 to 140;

y is an integer from 10 to 75; and

m is an integer from 90 to 140.

21. The compound of Claim 1, wherein R, for each occurrence independently, is -O-$(CH_2)_x$-N_3, wherein x, for each occurrence independently, is an integer from 1 to 10.

22. The compound of any one of Claims 1-7, wherein the compound is any one of the compounds S-101 through S-131, or D-101 through D-131, wherein the moiety R is -O-$(CH_2)_5$-NH_2 or -O-$(CH_2)_5$-N_3.

23. The particle of Claim 14, wherein the additional portion of the linker is a -O-(C_1-C_{12}) alkylenyl-.

24. The particle of Claim 9, wherein the biocompatible polymer comprises at least one of polyglycolic acid, poly(lactic acid), poly(lactic-co-glycolic acid), polycaprolactone, poly(3-hydroxybutyric acid), polyethylene oxide, polyoxyethylene-polyoxypropylene block copolymer, poly(hydroxymethylmethacrylate), polyvinyl alcohol, poly(vinylpyrrolidone), hyaluronic acid, heparin, heparin sulfate, polysialic acid and chitosan.

25. The particle of Claim 9, wherein the biocompatible polymer comprises poly(L-lactic acid), poly(D-lactic acid), poly(D/L-lactic acid), a copolymer thereof, or a combination thereof.

26. The particle of Claim 9, wherein the biocompatible polymer comprises polyethylene oxide, polyoxyethylene-polyoxypropylene block copolymer, a copolymer thereof, or a combination thereof.

27. The particle of Claim 11, wherein:

x is an integer from 90 to 140;

y is an integer from 10 to 75; and

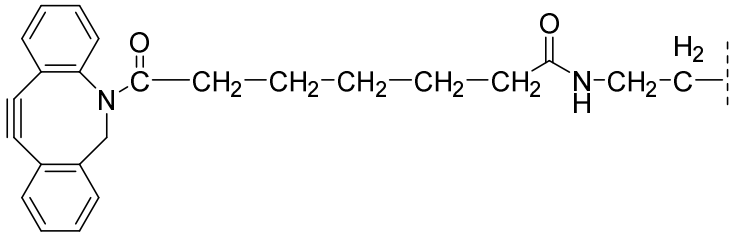
m is an integer from 90 to 140.

28. The particle of Claims 9, wherein the particle further comprises one or more of:

an acid-terminated PLGA (PLGA-COOH);

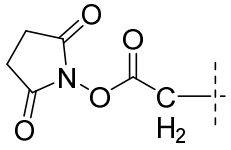
an acid-terminated PLGA-PEG copolymer, wherein the acid moiety terminates the PEG block (PLGA-PEG-COOH);

an PLGA-PEG copolymer, wherein the PEG block is terminated with the moiety represented by the following structural formula:



(PLGA-PEG-DBCO); or

an PLGA-PEG copolymer, wherein the PEG block is terminated by the the moiety represented by the following structural formula:



(PLGA-PEG-NHS),

wherein the dash line denotes the point of attachment of the terminating moiety to PEG block.

29. The particle of Claim 28, wherein the particle comprises at least one of:

a blend of 75% by weight of PLGA-COOH and 25% by weight of PLGA-PEG-DBCO;

a blend of 75% by weight of PLGA-COOH and 25% by weight of PLGA-PEG-NHS;

a blend of 90% by weight of PLGA-PEG-COOH and 10% by weight of PLGA-PEG-DBCO; and

PLGA-PEG-NHS.

30. The particle of any one of Claims 9-15, 23-26, 27, 28 or 29, wherein the amount of G per unit weight of the particle is from 1μg/mg to 1000 μg/mg.

31. A compound of any one of Claims 1, 5-8, 21 or 22, or particles of any one of Claims 9-16, 23-26, 27, 28, 29, and 30 or a pharmaceutically acceptable salt thereof, for use in therapy.