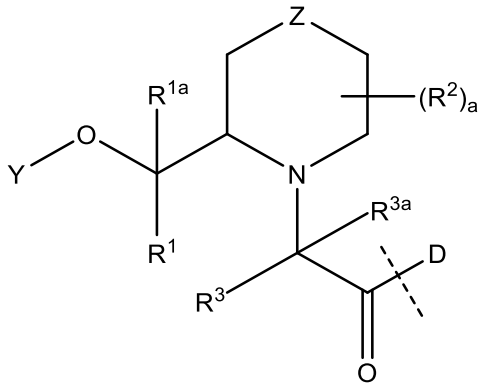
CLAIMS

1. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (I), where D is an ANGPTL3 polypeptide comprising at least one primary amine; and

R has the formula:



(I),

where the dashed line indicates attachment to the primary amine of D;

R^1 is hydrogen or C_1-C_4alkyl;

R^{1a} is hydrogen or C_1-C_4alkyl, or CR^1R^{1a}, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

R^2 is independently selected at each occurrence from C_1-C_4alkyl or oxo, or two R^2 groups taken in combination with the carbon atom(s) to which they are attached form a fused C_3-C_6 cycloalkyl or spiro C_3-C_6cycloalk-1,1-diyl group;

a is 0, 1, 2, 3 or 4;

R^3 is hydrogen or C_1-C_4alkyl;

R^{3a} is hydrogen, C_1-C_4alkyl, or CR^3R^{3a}, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

Y is $C(O)R^4$, $C(O)OR^4$, $C(O)NHR^4$, $C(O)NR^5R^6$, $SiR^5R^6R^7$, or $CR^{12}R^{12a}OR^{13}$;

R^{12} is hydrogen or C_1-C_4alkyl;

R^{12a} is hydrogen or C_1-C_4alkyl, or $CR^{12}R^{12a}$, taken in combination form a C_3-C_6cycloalk-1,1-diyl;

R^{13} is C_1-C_4alkyl; or

R^{12} and R^{13}, taken in combination with $C(R^{12a})$ and O form a 5, 6, or 7-member cyclic ether;

R^4 is C_1-C_8alkyl or C_3-C_7cycloalkyl, wherein cycloalkyl is optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups and wherein alkyl is optionally substituted by C_1-C_4alkoxy;

R^5 and R^6 are each independently selected from C_1-C_4alkyl and C_3-C_6cycloalkyl;

R^7 is C_1-C_8alkyl, C_3-C_7cycloalkyl, C_1-C_8alkoxy, C_3-C_7cycloalkyloxy, heterocycloalkyloxy, or -$(OCHR^3CH_2)_bO$-C_1-C_4alkyl, wherein the heterocycloalkyloxy is a 4 to 7 member saturated heterocyclic ring having one ring heteroatom selected from N, O, and S and optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups;

b is an integer of from 1 to 10;

Z is, N-L-A, [[or]] N-A, or NR^9;

L is an optionally substituted bivalent linker Q-[Sp-Q]h-Q;

Q is independently selected at each occurrence from a bond, O, C(O), N(H), N(C_1-C_4alkyl), C(O)NH, C(O)N(C_1-C_4alkyl), N(H)C(O), N(C_1-C_4alkyl)C(O), N(H)C(O)O, N(C_1-C_4alkyl)C(O)O, OC(O)N(H), OC(O)N(C1-C_4alkyl), N(H)C(O)N(H), N(C_1-C_4alkyl)C(O)N(H), N(H)C(O)N(C_1-C_4alkyl), N(C_1-C4alkyl)C(O)N(C_1-C_4alkyl), C(O)O, OC(O), OC(O)O, S, $S(O)_2$, N(H)$S(O)_2$, N(C_1-C_4alkyl)$S(O)_2$, $S(O)_2$N(H), $S(O)_2$N(C_1-C_4alkyl), C_1-C_2alkyl-C(O)N(H), N(H)C(O)C_1-C_2alkyl, C_1-C_2alkyl-C(O)O, OC(O)C_1-C_2alkyl, 1,2,3-triazole, $OP(O)_2$, $P(O)_2O$, C_1-C_4alkyl-$P(O)_2$-O, or O-$P(O)_2$-C_1-$_4$alkyl;

Sp is independently selected at each occurrence from an optionally substituted C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, $[W\text{-}O]_g$, C_1-C_8alkyl-$[O\text{-}W]_g$, $[O\text{-}W]_g$-O-C_1-C_8alkyl, C_1-C_8Calkyl-$[O\text{-}W]_g$-O-C_1-C_8alkyl, or oligopeptide;

h is an integer of between 1 and 20;

g is a weighted average number of between about 2 and about 50;

<u>R^9 is selected from hydrogen, C_1-C_8 alkyl, C(O)-$(CH_2)_n$-Q-A, C(O)C_1-C_8 alkyl, or –C(O)$(CH_2)_q[O–W]_g(NHC(O))_m(CH_2)_q[O–W]_p$-Q-A, wherein the alkyl group is optionally substituted with 0 or 1 Q-A;</u>

W is C_2-C_4alkyl-1,2-diyl in which a hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;

A is hydrogen, C_1-C_8alkyl, C(O)C_1-C_8alkyl, C(O)N(H)C_1-C_8alkyl, C(O)OC_1-C_8alkyl, [[R^{10}]], or R^{11},; and

R^{11} is a carrier.

2. The drug delivery system or pharmaceutically acceptable salt of claim 1, wherein D comprises an ANGPTL3 polypeptide having at least 95% identity to any one of SEQ ID NOS: 1 or 3–45.

3. The drug delivery system or pharmaceutically acceptable salt of claim 1, wherein D comprises an ANGPTL3 polypeptide comprising amino acid residues 201–460; 207–460; 225–455; 225–455; 225–460; 225–460; 226–455; 226–455; 226–460; 226–460; 228–455; 228–455; 228–460; 228–460; 233–455; 233–455; 233–460; 233–460; 241–455; 241–455; 241–460; 241–460; 242–455; 242–455; 242–460; or 242–460, each in reference to SEQ ID NO:1.

4. The drug delivery system or pharmaceutically acceptable salt of claim1, wherein D comprises an ANGPTL3 polypeptide comprising at least 95% identity to amino acid residues 242–460 in reference to SEQ ID NO:1 and a K423Q substitution.

5. The drug delivery system or pharmaceutically acceptable salt of claim 1 wherein R^1 is hydrogen or methyl, R^{1a} is hydrogen or methyl, or CR^1R^{1a}, taken in combination form a cyclopropan-1,1-diyl group.

6. The drug delivery system or pharmaceutically acceptable salt of claim 1, wherein the variable a is 0.

7. The drug delivery system or pharmaceutically acceptable salt of claim 1, wherein R^3 and R^{3a} are each hydrogen.

8. The drug delivery system or pharmaceutically acceptable salt of claim 1, wherein
Y is $C(O)R^4$ and R^4 is C_1-C_6alkyl, C_3-C_6cycloalkyl or C_1-C_2alkoxyC_1-C_2alkyl, or
Y is $SiR^5R^6R^7$;
wherein
R^5 and R^6 are each methyl, ethyl, propyl or isopropyl; and
R^7 is C_1-C_4 alkyl, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, 2-ethoxyethoxy, 2-isopropoxy-ethoxy, tetrahydropyranyloxy, or $-(OCHR^3CH_2)_bO$-C_1-C_4alkyl where b is 2, 3, or 4.

9. The drug delivery system or pharmaceutically acceptable salt of claim 8, wherein Y is $C(O)R^4$ and R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl.

10. The drug delivery system or pharmaceutically acceptable salt of claim 1, wherein Z is NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, C(O)-$(CH_2)_n$-Q-A, C(O)C_1-C_8 alkyl, or –C(O)$(CH_2)_q$[O–W]$_g$(NHC(O))$_m$$(CH_2)_q$[O–W]$_p$-Q-A, wherein the alkyl group is optionally substituted with 0 or 1 Q-A;

q is independently at each occurrence 1, 2, or 3;

g and p each independently have a weighted average length of between about 2 and about 50;

m is 1 or 0;

W is C_2-C_4alkyl-1,2-diyl in which a hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;

Q is a bond, O, N(H) or N(C_1-C_4alkyl);

A is hydrogen, C_1-C_8alkyl, C(O)C_1-C_8alkyl, C(O)N(H)C_1-C_8alkyl, C(O)OC_1-C_8alkyl, R^{10}; and

R^{11} is a carrier.

11. The drug delivery system or pharmaceutically acceptable salt of claim 1, wherein R^{11} comprises a hydrogel comprising one or more cross-linked polymers.

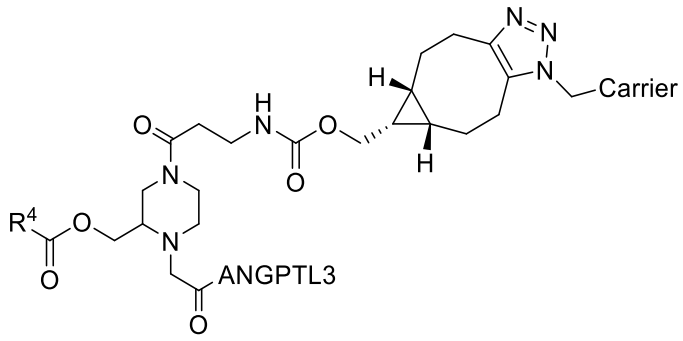
12. The drug delivery system or pharmaceutically acceptable salt of claim 1, wherein R^{11} comprises a polymer, cross-linked polymer, or hydrogel comprising one or more of hyaluronic acid, polyethylene glycol, polypropylene glycol, polyethylene oxide, polypropylene oxide, polyglutamate, polylysine, polysialic acid, polyvinyl alcohol, polyacrylate, polymethacrylate, polyacrylamide, polymethacrylamide, polyvinyl pyrrolidone, polyoxazoline, polyiminocarbonate, polyamino acid, hydrophilic polyester, polyamide, polyurethane, polyurea, dextran, agarose, xylan, mannan, carrageenan, alginate, gelatin, collagen, albumin, cellulose, methylcellulose, ethylcellulose, hydroxypropylmethylcellulose, hydroxyethyl starch, chitosan, nucleic acids, derivatives thereof, co-polymers thereof, or combinations thereof.

13. The drug delivery system or pharmaceutically acceptable salt of claim 12, wherein R^{11} comprises a hydrogel comprising cross-linked hyaluronic acid, wherein the hyaluronic acid comprises at least one side chain selected from -NH(W1) (O(W1))$_d$-V, wherein W1 is C_2-C_4alkyl-1,2-diyl in which a hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;

d is a number average of 0 to 500; and

V is a suitable functional group comprising azidyl, alkynyl, substituted or unsubstituted C_7-C_{12} cycloalkynyl, substituted or unsubstituted C_7-C_{12} heterocycloalkynyl, C_7-C_{12} cycloalkenyl, norbornyl, vinyl carboxyl, vinyl sulfonyl, C_2-C_8 alkenyl, amino, thiol, C_1-C_8 carboxyl, C_1-C_8 carbonyl, -O-NH2, carbohydrazide, maleimide, alpha-halo carbonyl, furan, substituted or unsubstituted tetrazinyl, lysine, glutamine, cyclodextrin, or adamantanyl.

14. A drug delivery system comprising Formula (III):

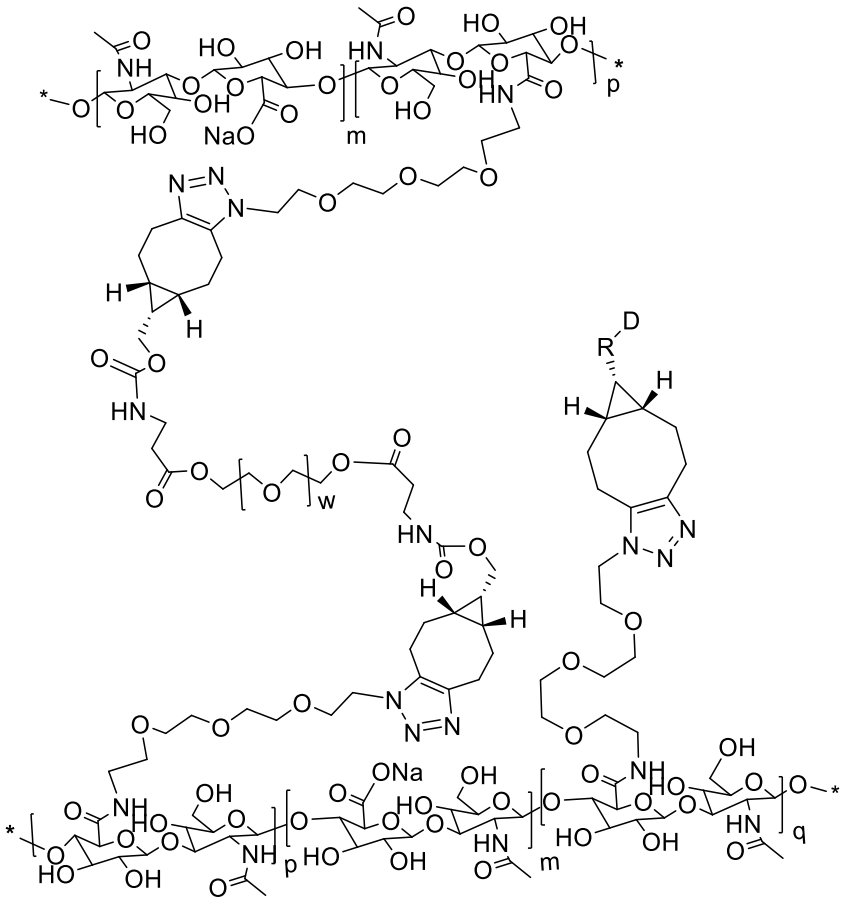


(III),

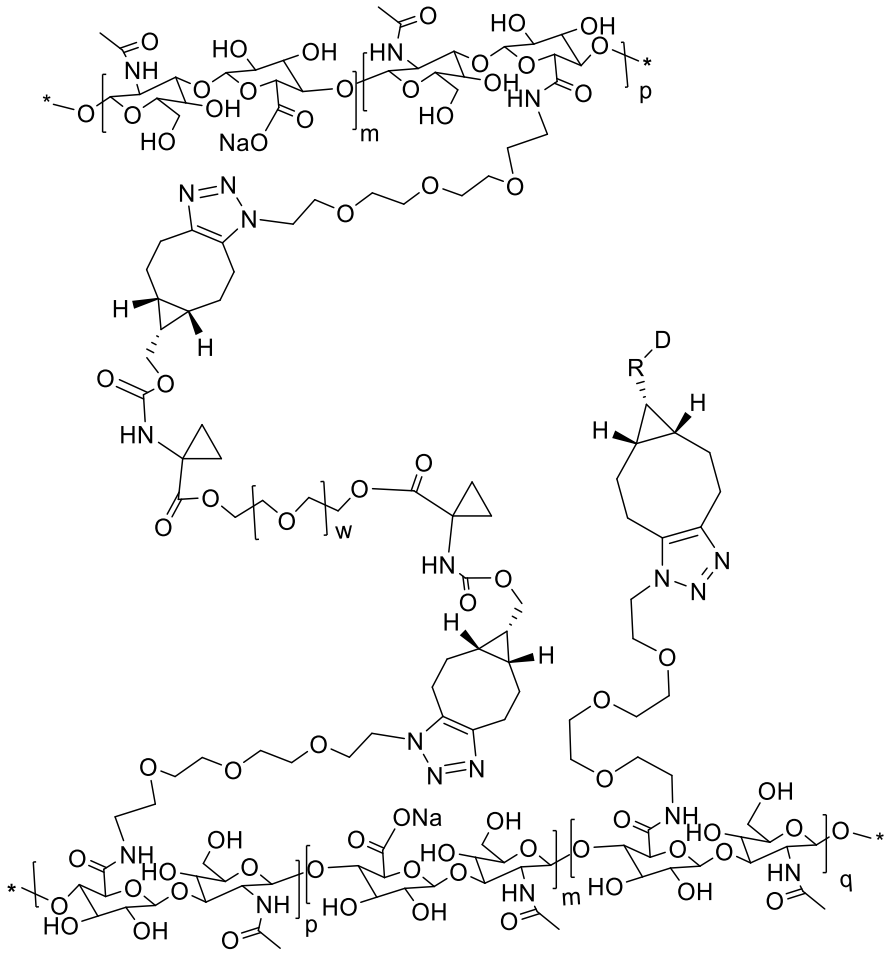
wherein ANGPTL3 comprises an ANGPTL3 polypeptide having at least 95% identity to any one of SEQ ID NO: 1 or 3–45, or combinations thereof.

15. The drug delivery system according to claim 14, wherein ANGPTL3 is a polypeptide comprising amino acid residues 242–460 in reference to SEQ ID NO:1 and a K423Q substitution.

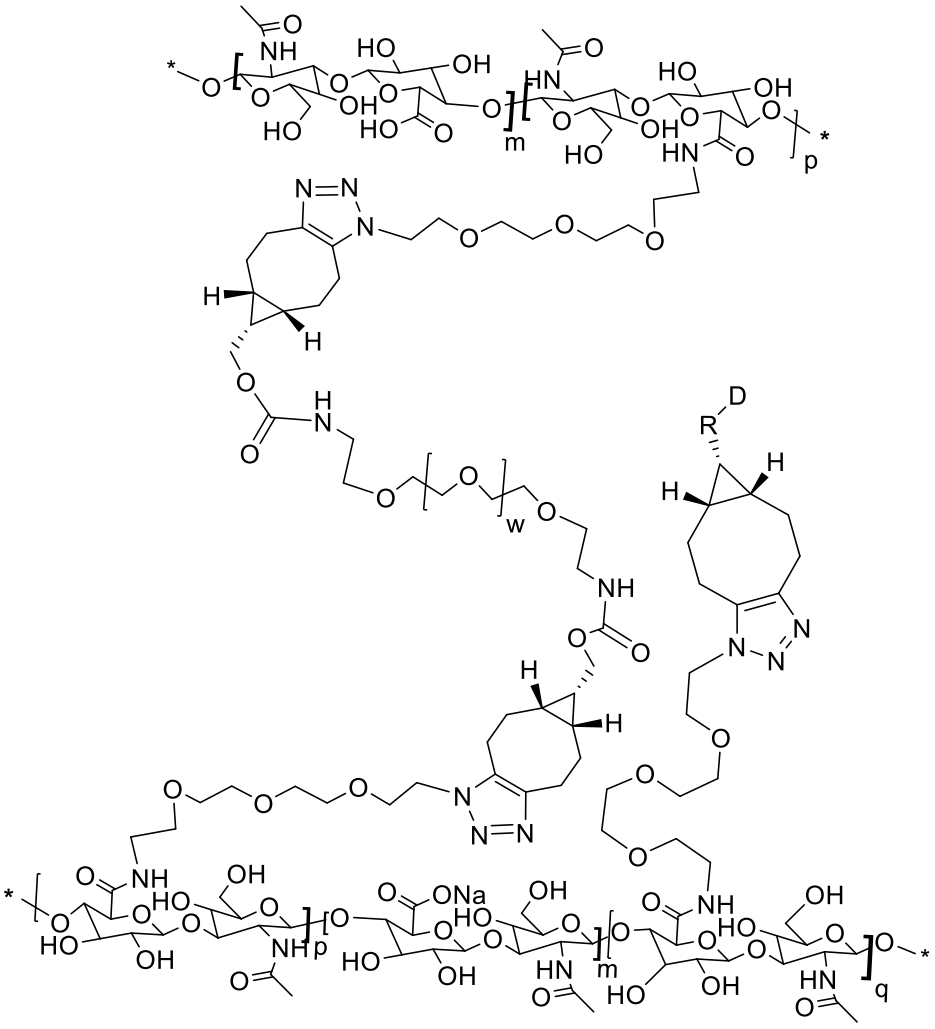
16. The drug delivery system or pharmaceutically acceptable salt thereof according to claim 1, having one of the following formulae:



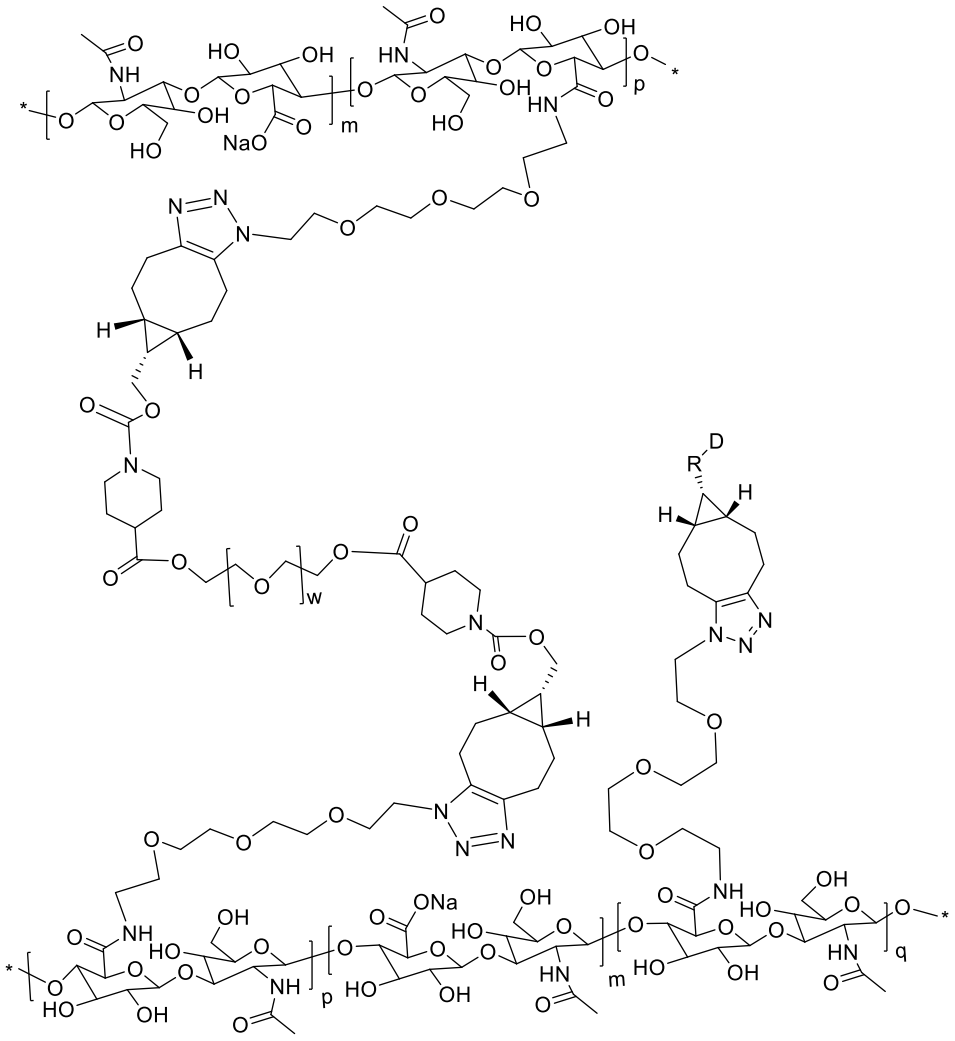
(XXIV),



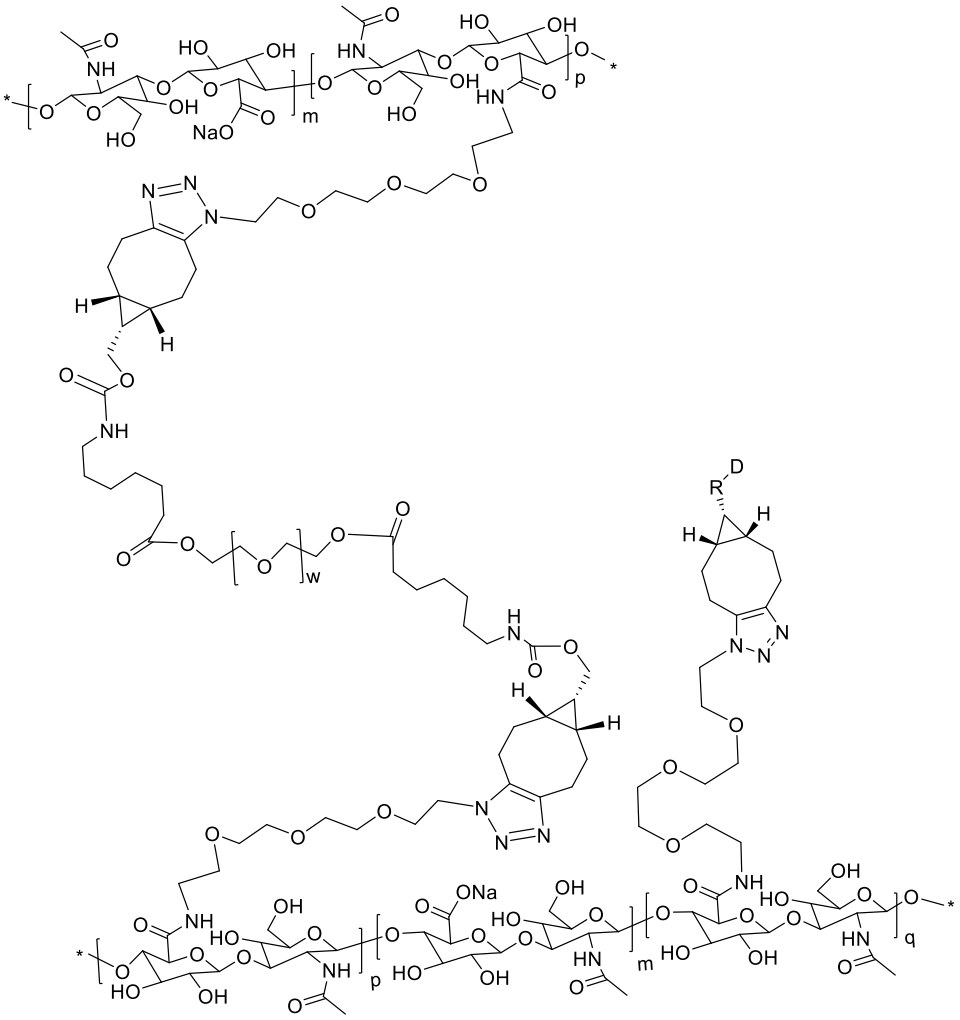
(XXV),



(XXVI),

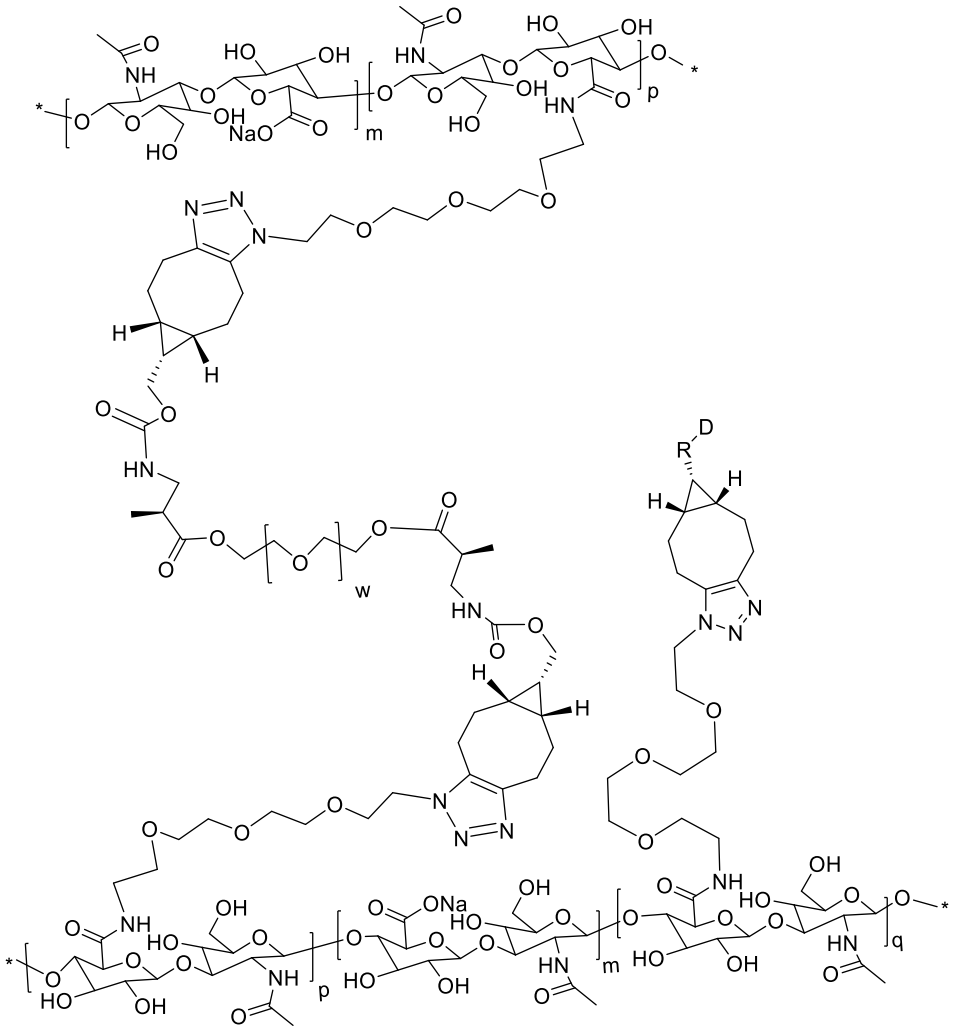


(XXVII),



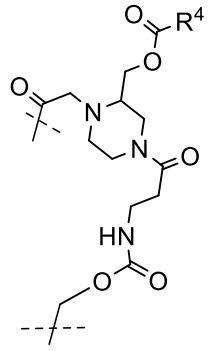
(XXVIII),

or



(XXIX).

17. The drug delivery system or pharmaceutically acceptable salt thereof according to claim 16, wherein each R has the following formula:



wherein the dashed lines indicate attachment to D and the bicyclo[6.1.0]non-4-yn-9-yl moiety, and

R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl.

18. The drug delivery system or pharmaceutically acceptable salt thereof of claim 1, wherein Y is $C(O)R^4$;

R^4 is C_1-C_8alkyl or C_3-C_7cycloalkyl, wherein cycloalkyl is optionally substituted with 0, 1, or 2 independently selected C_1-C_4alkyl groups and wherein alkyl is optionally substituted by C_1-C_4alkoxy;

Z is N-L-A;

L is $C(O)CH_2CH_2NH$;

A is R^{11}; and

R^{11} is a hydrogel derived from a cross-linked hyaluronic acid, wherein the hyaluronic acid comprises at least one amide-linked side chain of $N(H)(CH_2CH_2O)_3$ $CH_2CH_2N_3$, and wherein the cross-linker used to form the hydrogel comprises PEG(2000)-bis-[3-(((((1*R*,8*S*,9s)-bicyclo[6.1.0]non-4-yn-9-yl)methoxy)carbonyl)amino)propanoate], or

R^{11} is a hydrogel derived from a cross-linked hyaluronic acid, wherein the hyaluronic acid comprises at least one amide-linked side chain of $N(H)(CH_2CH_2O)_3$ $CH_2CH_2N_3$, and wherein the cross-linker used to form the hydrogel comprises PEG(2000)-bis-[1-((((1′*R*,8′*S*,9′s)-bicyclo[6.1.0]non-4′-yn-9′-yl)methoxy)carbonyl)amino-cyclopropane-1-carboxylic acid ester], or

R^{11} is a hydrogel derived from a cross-linked hyaluronic acid, wherein the hyaluronic acid comprises at least one amide-linked side chain of $N(H)(CH_2CH_2O)_3$ $CH_2CH_2N_3$, and wherein the cross-linker used to form the hydrogel comprises PEG(2000)-bis-[1-((((1′*R*,8′*S*,9′s)-bicyclo[6.1.0]non-4′-yn-9′-yl)methoxy)carbonyl)piperidine-4-carboxylic acid ester], or

R^{11} is a hydrogel derived from a cross-linked hyaluronic acid, wherein the hyaluronic acid comprises at least one amide-linked side chain of $N(H)(CH_2CH_2O)_3$ $CH_2CH_2N_3$, and wherein the cross-linker used to form the hydrogel comprises PEG(2000)-bis-[7-(((((1′*R*,8′*S*,9′s)-bicyclo[6.1.0]non-4′-yn-9′-yl)methoxy)carbonyl)amino)heptanoate], or

R^{11} is a hydrogel derived from a cross-linked hyaluronic acid, wherein the hyaluronic acid comprises at least one amide-linked side chain of $N(H)(CH_2CH_2O)_3$ $CH_2CH_2N_3$, and wherein the cross-linker used to form the hydrogel comprises PEG(2000)-bis-

[2-methyl-3-(((((1′*R*,8′*S*,9′s)-bicyclo[6.1.0]non-4′-yn-9′-yl)methoxy)carbonyl)amino)propanoate].