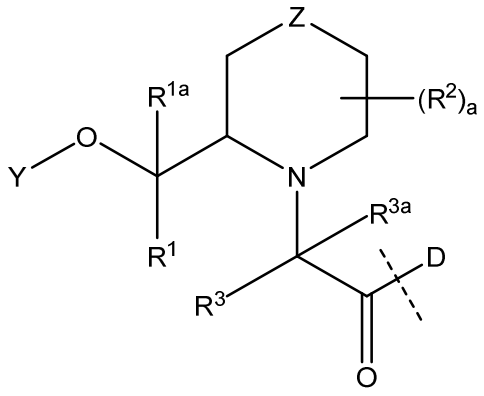
CLAIMS

1. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (I), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and
R is a linker suitable for release of biologically active moiety D:



(I),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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 CH-L-A, CH-A, N-L-A, or N-A;

L is an optionally substituted bivalent linker;

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}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.

2. The drug delivery system or pharmaceutically acceptable salt of claim 1, wherein D comprises a protein, peptide, polypeptide, nucleic acid, oligo- or poly-nucleotide, carbohydrate, oligo- or poly-saccharide, or small molecule each of which comprises at least one primary amine, secondary amine, or a ring nitrogen atom of an azaheteroaryl ring and the small molecule has a molecular weight of between 100 g/mol and about 2000 g/mol.

3. The drug delivery system or pharmaceutically acceptable salt of claim 1 or 2, wherein D comprises a protein, peptide, nucleic acid, Fab, scFv, monoclonal antibody, or small molecule.

4. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 3, wherein D comprises brolucizumab (SEQ ID NO:4), D2 (SEQ ID NO:5), D3 (SEQ ID NO:6), D4 (SEQ ID NO:7), abciximab, adalimumab, aflibercept, alemtuzumab, basiliximab, belimumab, bevacizumab, brentuximab, canakinumab, certolizumab, cetuximab, daclizumab, daratumumab, denosumab, eculizumab, efalizumab, golimumab, ibritumomab, infliximab, ipilimumab, lampalizumab, muromonab-CD3, natalizumab, nivolumab, ofatumumab, omalizumab, palivizumab, panitumumab, pegpleranib pembrolizumab, ranibizumab, rituximab, tocilizumab, tositumomab, trastuzumab, ustekinumab, or vedolizumab, or combinations thereof.

5. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 3, wherein D comprises one or more biologically active peptides including, but not limited to C-type natriuretic peptide (CNP), atrial natriuretic peptide (ANP), exendin-4, insulin, adrenocorticotropic hormone, adrenomedullin, adropin, ω-agatoxin, agouti-related protein, angiotensin(s), apelin 12, apelin 13, apelin 36, or derivatives thereof, bradykinin, calcitonin, cocaine- and amphetamine-regulated transcript (CART), corticotropin releasing factor (CRF), α-defensins, β-defensins, delta sleep-inducing peptide (DSIP), elastase-specific inhibitor (Elafin), endokinins, endomorphins, endorphins, endothelins, exendin, fibronectin active fragment, galanin, galanin-like peptide, big gastrin, gastrin I, gastrin related peptide, gastric inhibitory polypeptide, gastrin releasing peptide, ghrelin, des-acyl ghrelin, glucagon, glucagon-like peptide, growth hormone releasing factor, *Grammostola spatulata* GsMTx-4, guangxitoxin-1E, guanylin, hepcidin 1, hepcidin / LEAP-1, histatin 5, human growth hormone, humanin, huwentoxin, iberiotoxin, imperatoxin A, insulin like growth factors, intermedin, IRL 1620, joining peptide, kaliotoxin, kisspeptins, kurtoxin, lipotropin, lipotropin, liver-cell growth factor, liver-expressed antimicrobial peptide 2, luteinizing hormone releasing hormone, lysenin, LL-37, margatoxin, mastoparan, mast cell degranulating peptide, melanin-concentrating hormone, melanocyte stimulating hormone, MSH-release inhibiting factor, midkine, molluscan cardioexcitatory neuropeptide, morphine tolerance peptide, motilin, muscarinic toxins, neuroendocrine regulatory peptide-2, neurokinin A, neurokinin B, neuromedins, neuronostatin-13, neuropeptides, neurotensin, neurotoxin NSTX-3,

nocistatin, nociceptin, obestatin, opioid peptides (enkephalins, endorphins, BAM-12P, casomorphin, dynorphins, endomorphins, neo-endorphins, nociceptin), orexin-A/-B, orphanin, osteocalci, oxytocin, pancreastatin, parathyroid hormone, parathyroid hormone related protein, peptide 234, peptide histidine-methionine, peptide T, peptide YY, Physalaemin, pituitary adenylate cyclase activating polypeptides, platelet factor-4, plectasin, pleiotrophin, proadrenomedullin, prolactin-releasing peptide, psalmotoxin 1, purotoxin-1, pyroglutamylated RFamide peptide, renin, RFamide-related peptide-1, RFamide-related peptide-3, salusin-α/β, sarafotoxins, schizophrenia related peptide, scyllatoxin, secretin, serelaxin, serum thymic factor, sodium potassium ATPase inhibitor-1, somatostatin, stichodactyla toxin, substance K, stresscopin, stresscopin-related peptide, substance P, tachykinins, tarantula SNX-482, tarantula ProTx-I, tarantula ProTx-II, tertiapin, tityustoxin Ka, thyrotropin releasing hormone, tuftsin, uroguanylin, uroguanylin isomer A or B, urocortin, urocortin II, urotensin II, urotensin II-related peptide, vasoactive intestinal peptide, vasopressin, vasotocin, virus replication inhibiting peptide, xenin, or combinations thereof.

6. The compound of any one of claims 1 to 3, wherein D is a small molecule having a molecular weight of between about 100 g/mol to about 2000 g/mol or less, that is connected to R through a primary amine, secondary amine, or a ring nitrogen atom of an azaheteroaryl ring.

7. The drug delivery system or pharmaceutically acceptable salt of claim 6, wherein the small molecule comprises 5-(5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidin-4-yloxy)-indole-1-carboxylic acid [5-(1-methyl-cyclopropyl)-2*H*-pyrazol-3-yl]-amide; 5-(6,7-dihydro-5*H*-pyrrolo[3,4 *d*]pyrimidin-4-yloxy)-indole-1-carboxylic acid [5-(1-methyl-cyclopropyl)-2*H*-pyrazol-3-yl]-amide; N-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-5-((6-((methylamino)methyl)pyrimidin-4-yl)oxy)-1*H*-indole-1-carboxamide; (*S*)-5-(6-methyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yloxy)-N-(5-(1-methylcyclopropyl)-1*H*-pyrazol-3-yl)-1*H*-indole-1-carboxamide, or combinations thereof.

8. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 7 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.

9. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 8, wherein the variable a is 0.

10. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 9, wherein R^3 and R^{3a} are each hydrogen.

11. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 10, 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.

12. The drug delivery system or pharmaceutically acceptable salt of claim 11, wherein R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl.

13. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 10, wherein Y is $SiR^5R^6R^7$;

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.

14. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 13, wherein Z is CH-L-A, CH-A, N-L-A, or N-A;

L is an optionally substituted bivalent linker Q-$[Sp\text{-}Q]_h$-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;

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)OC_1-C_8alkyl, C(O)N(H)C_1-C_8alkyl, R^{10}, or R^{11} wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.

15. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 13, wherein Z is CHR^8 or 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}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.

16. The drug delivery system or pharmaceutically acceptable salt of claim 15, wherein Z is NR^9;
R^9 is $C(O)-(CH_2)_n-Q-A$ or $-C(O)(CH_2)_q[O-W]_g(NHC(O))_m(CH_2)_q[O-W]_p-Q-A$;
n is an integer of 1 to 8; and
A is R^{10} or R^{11}.

17. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16, wherein R^{10} is azidyl, alkynyl, substituted or unsubstituted C_7-C_{12} cycloalkynyl, substituted or unsubstituted C_7-C_{12} heterocycloalkynyl, substituted or unsubstituted C_7-C_{12} cycloalkenyl, norbornyl, substituted or unsubstituted vinyl carboxyl, substituted or unsubstituted vinyl sulfonyl, substituted or unsubstituted C_2-C_8 alkenyl, amino, thiol, substituted or unsubstituted C_1-C_8 carboxyl, substituted or unsubstituted C_1-C_8 carbonyl, -O-NH_2, hydrazidyl, maleimide, alpha-halo carbonyl, furan, substituted or unsubstituted tetrazinyl, lysine, glutamine, cyclodextrin, or adamantanyl.

18. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 17, wherein R^{10} comprises a reactive functional group suitable for coupling the drug delivery system or pharmaceutically acceptable salt of Formula (I) to a carrier.

19. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16, wherein R^{11} is biodegradable.

20. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16 or 19, wherein R^{11} comprises a polymer or cross-linked polymer.

21. The drug delivery system or pharmaceutically acceptable salt of claim 19 or 20, wherein R^{11} comprises a hydrogel comprising one or more cross-linked polymers.

22. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16 and 19 to 21, 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.

23. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16 and 19 to 22, wherein R^{11} comprises hyaluronic acid, polyethylene glycol, a cross-linked hydrogel of hyaluronic acid, a cross-linked hydrogel of polyethylene glycol, or combinations thereof.

24. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16 and 19 to 23, wherein R^{11} comprises hyaluronic acid or polyethylene glycol.

25. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16 and 19 to 23, wherein R^{11} comprises a hydrogel comprising cross-linked hyaluronic acid or cross-linked polyethylene glycol.

26. The drug delivery system or pharmaceutically acceptable salt of claim 24 or 25, wherein the hyaluronic acid or polyethylene glycol are functionalized with at least one 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, adamantanyl, or combinations thereof.

27. The drug delivery system or pharmaceutically acceptable salt of any one of claims 1 to 16 and 19 to 26, 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.

28. The drug delivery system or pharmaceutically acceptable salt of claim 27, wherein V is azide.

29. A process for making a cross-linked carrier formulation, the process comprising:

(a) functionalizing a carrier molecule, R^{11};

(b) preparing a reactive cross-linker; and

(c) reacting the functionalized carrier molecule with the reactive cross-linker to form a cross-linked carrier by incubation for about 0.5 hours to about 48 hours at a temperature of about 4 °C to about 60 °C.

30. The process of claim 29, wherein the carrier molecule comprises hyaluronic acid or polyethylene glycol.

31. The process of claim 30, wherein the carrier molecule is functionalized with azide, sulfhydryl, amine, aminoxy (O-NH_2) or aldehyde moieties to provide reactive functional groups for cross-linking.

32. The process of any one of claims 29 to 31, wherein the preparation of the reactive crosslinker comprises reacting a polyethylene glycol with 1-((tert-butoxycarbonyl)amino)cyclopropane-1-carboxylic acid, 3-((tert-butoxycarbonyl)amino)propanoic acid, 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid, 2-(1-(((tert-butoxycarbonyl)amino)methyl)cyclopropyl)acetic acid, 2-methyl-3-((tert-butoxycarbonyl)amino)propanoic acid, or 7-((tert-butoxycarbonyl)amino)heptanoic acid and deprotecting the functionalized polyethylene glycol ester.

33. The process of claim 32, wherein the preparation of the reactive crosslinker further comprises introduction at least two bicyclo[6.1.0]non-4-yn-9-yl)methyl groups after deprotection of the functionalzed polyethylene glycol ester.

34. A cross-linked hydrogel obtainable using the methods of any one of claims 29 to 33.

35. The cross-linked hydrogel of claim 34, wherein the carrier molecule is functionalized with azide.

36. A process for preparing a drug adduct, comprising a traceless linker, R, coupled to a biologically-active agent, D, the process comprising:
    (a) providing a biologically active agent, D, comprising a primary amine, secondary amine, or a ring nitrogen atom of an azaheteroaryl ring;
    (b) reacting the biologically active agent with a traceless linker, R, that has an activated carbonyl functional group; and
    (c) purifying the drug adduct from the reagents.

37. A drug adduct obtainable using the process of claim 36.

38. A process for making a drug delivery system, the process comprising:
    (a) preparing a carrier molecule, R^{11}, wherein R^{11} is a cross-linked hydrogel; optionally, step (a) may further comprise purifying the cross-linked hydrogel carrier molecule R^{11};

(b) separately conjugating the traceless linker, R, to a biologically active agent, D, comprising a primary amine, secondary amine, or a ring nitrogen atom of an azaheteroaryl ring, thereby forming the traceless linker-D adduct; step (b) may optionally further comprise purification of the traceless linker-D adduct,

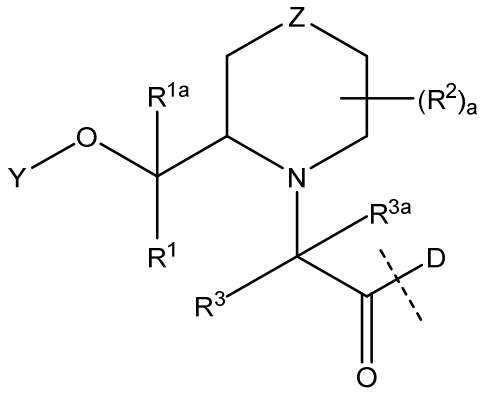
(c) conjugating the carrier molecule, R^{11}, with the traceless linker-D adduct; and

(d) purifying the drug delivery system from the reagents.

39. A drug delivery system made using the method of claim 38.

40. A drug delivery system or pharmaceutically acceptable salt thereof for use in treating macular degeneration in a subject in need thereof, comprising a conjugate D–R, that is represented by Formula (I), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring, comprising brolucizumab (SEQ ID NO:4), aflibercept, pegpleranib, ranibizumab, 5-(5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidin-4-yloxy)-indole-1-carboxylic acid [5-(1-methyl-cyclopropyl)-2*H*-pyrazol-3-yl]-amide; 5-(6,7-dihydro-5*H*-pyrrolo[3,4 *d*]pyrimidin-4-yloxy)-indole-1-carboxylic acid [5-(1-methyl-cyclopropyl)-2*H*-pyrazol-3-yl]-amide;N-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-5-((6-((methylamino) methyl)pyrimidin-4-yl)oxy)-1*H*-indole-1-carboxamide;(*S*)-5-(6-methyl-5,6,7,8-tetrahydro pyrido[3,4-*d*]pyrimidin-4-yloxy)-N-(5-(1-methylcyclopropyl)-1*H*-pyrazol-3-yl)-1*H*-indole-1-carboxamide, or combinations thereof;

R is a linker suitable for release of biologically active moiety D:



(I),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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 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

$CHR^{12}OR^{13}$, taken in combination 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 hydroxy, amino, C_1-C_4alkoxy or mono- and di- C_1-C_4alkylamino;

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 CHR^8 or NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, $C(O)C_1$-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 the 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);

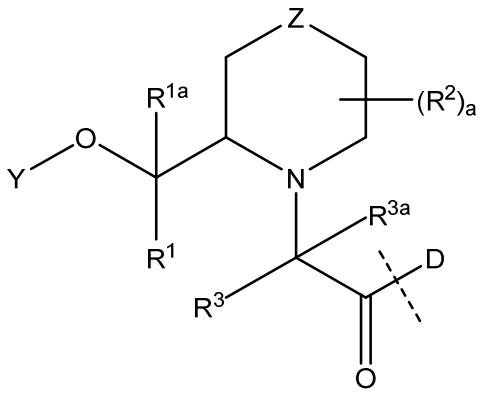
A is hydrogen, C_1-C_8alkyl, C(O)C_1-C_8alkyl, C(O)N(H)C_1-C_8alkyl, C(O)OC_1-C_8alkyl, R^{10}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.

41. A drug delivery system or pharmaceutically acceptable salt thereof for use in treating musculoskeletal disorders in a subject in need thereof, comprising a conjugate D–R, that is represented by Formula (I), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring comprising D2 (SEQ ID NO:4), D3 (SEQ ID NO:5), other insulin like growth factors, or a combination thereof;

R is a linker suitable for release of biologically active moiety D:



(I),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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 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

$CHR^{12}OR^{13}$, taken in combination 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 hydroxy, amino, C_1-C_4alkoxy or mono- and di- C_1-C_4alkylamino;

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 CHR^8 or NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, $C(O)C_1$-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 the 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);

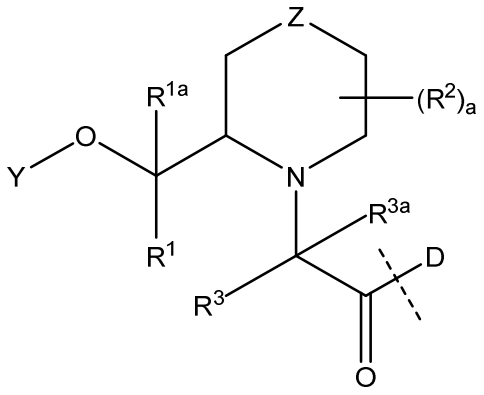
A is hydrogen, C_1-C_8alkyl, C(O)C_1-C_8alkyl, C(O)N(H)C_1-C_8alkyl, C(O)OC_1-C_8alkyl, R^{10}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.

42. A drug delivery system or pharmaceutically acceptable salt thereof for use in treating cardiac disorders in a subject in need thereof, comprising a conjugate D–R, that is represented by Formula (I), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring comprising serelaxin or SEQ ID NO:7;

R is a linker suitable for release of biologically active moiety D:



(I),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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 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

$CHR^{12}OR^{13}$, taken in combination 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 hydroxy, amino, C_1-C_4alkoxy or mono- and di- C_1-C_4alkylamino;

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 CHR^8 or NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, $C(O)C_1$-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;

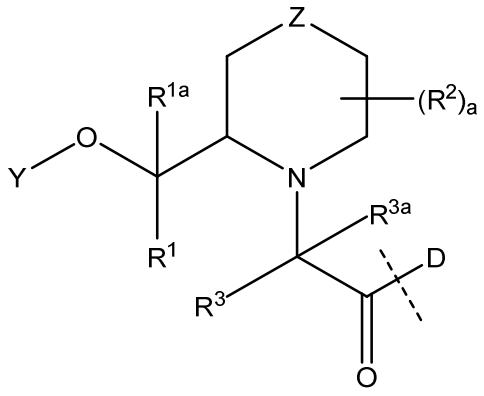
W is C_2-C_4alkyl-1,2-diyl in which the hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;

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}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and
R^{11} is a carrier.

43. A drug delivery system or pharmaceutically acceptable salt thereof for use in treating a disease or disorder in a subject in need thereof, comprising a conjugate D–R, that is represented by Formula (I), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; R is a linker suitable for release of biologically active moiety D:



(I),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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 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

$CHR^{12}OR^{13}$, taken in combination 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 hydroxy, amino, C_1-C_4alkoxy or mono- and di- C_1-C_4alkylamino;

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 CHR^8 or NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, $C(O)C_1$-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 the 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);

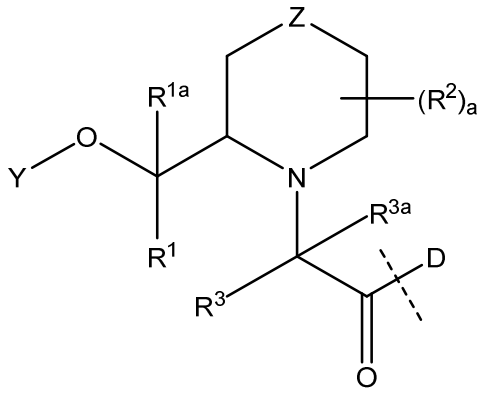
A is hydrogen, C_1-C_8alkyl, $C(O)C_1$-C_8alkyl, $C(O)N(H)C_1$-C_8alkyl, $C(O)OC_1$-C_8alkyl, R^{10}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.

44. A means for extending half-life of a biologically active moiety, D, comprising at least one primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring, the

means comprising attaching D to R, that is represented by Formula (I), where R is a linker suitable for release of biologically active moiety D:



(I),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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 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

$CHR^{12}OR^{13}$, taken in combination 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 hydroxy, amino, C_1-C_4alkoxy or mono- and di- C_1-C_4alkylamino;

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 CHR^8 or NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, $C(O)C_1$-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 the hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;

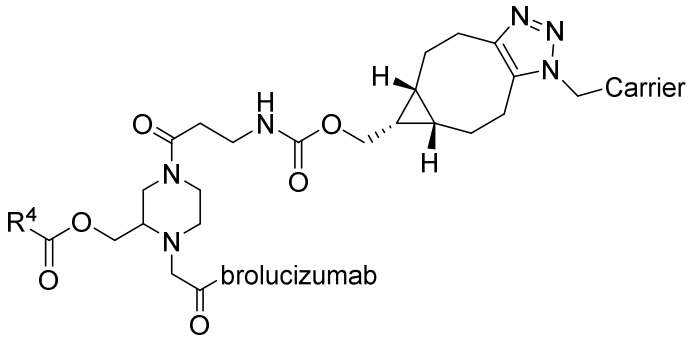
Q is a bond, O, N(H) or N(C_1-C_4alkyl);

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}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.

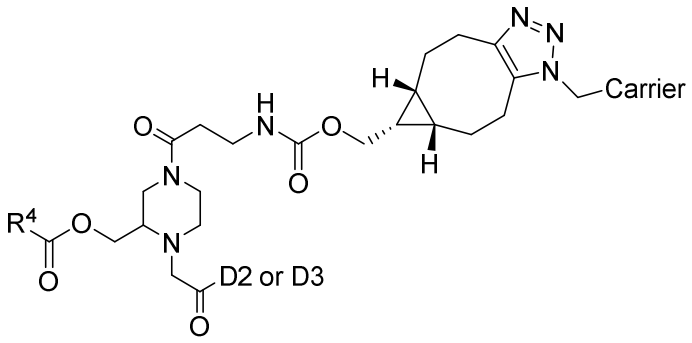
45. A drug delivery system comprising Formula (III):



(III),

wherein brolucizumab comprises SEQ ID NO:4; R^4 is CH_3-, CH_3-O-CH_2-, CH_3CH_2-, or $(CH_3)_2CH$-; and carrier comprises hyaluronic acid, polyethylene glycol, a hydrogel thereof, a cross-linked hydrogel thereof, or combinations thereof.

46. A drug delivery system comprising Formula (IV):



(IV),

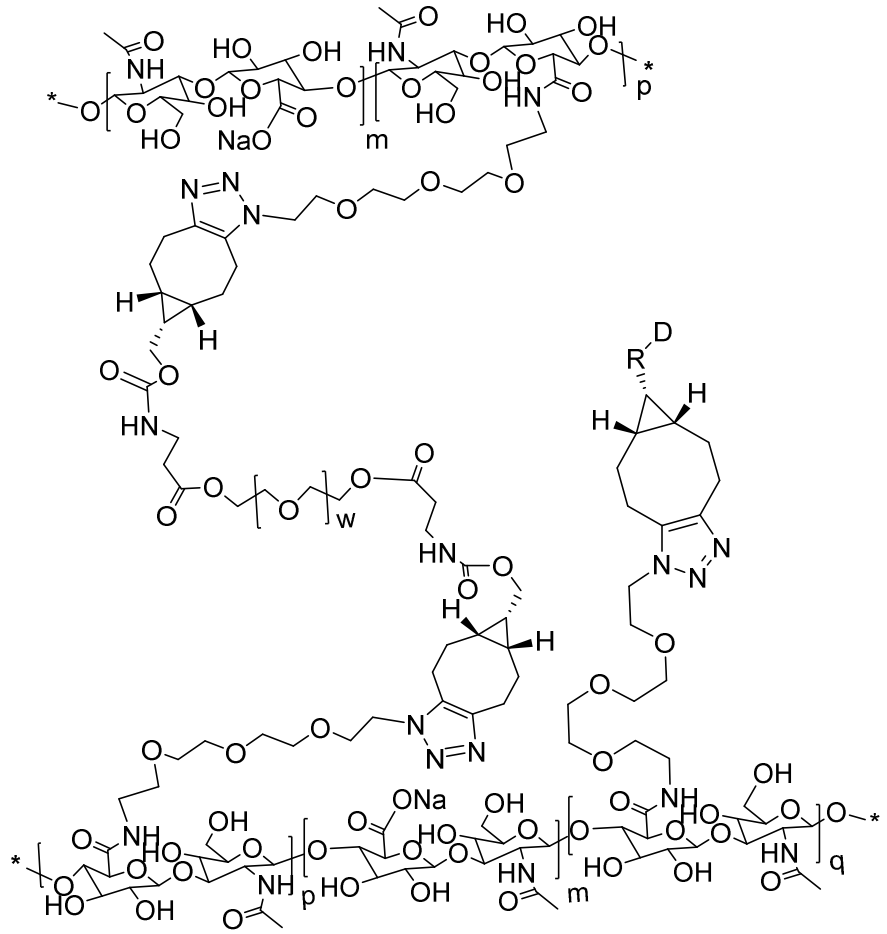
wherein D2 comprises SEQ ID NO:5, D3 comprises SEQ ID NO:6; R^4 is CH_3-, CH_3-O-CH_2-, CH_3CH_2-, or $(CH_3)_2CH$-; and carrier comprises hyaluronic acid, polyethylene glycol, a hydrogel thereof, a cross-linked hydrogel thereof, or combinations thereof.

47. A drug delivery system comprising D–R–R^{11}, wherein R comprises a traceless linker, coupled to a biologically-active agent, D; D comprises a biologically active moiety comprising at least one primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring; and R^{11} comprises a plurality of hyaluronic acid polymers each of which comprises a random series of unfunctionalized D-glucuronic acid monomers, one or more D-glucuronic acid monomers functionalized with a cross-linker, or one or more D-glucuronic acid monomers functionalized with a drug adduct, D–R.

48. The means of claim 44, wherein D comprises brolucizumab, D1 (SEQ ID NO:4), D2 (SEQ ID NO:5), D3 (SEQ ID NO:6), D4 (SEQ ID NO:7), serelaxin, aflibercept, pegpleranib, ranibizumab, 5-(5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidin-4-yloxy)-indole-1-carboxylic acid [5-(1-methyl-cyclopropyl)-2*H*-pyrazol-3-yl]-amide; 5-(6,7-dihydro-5*H*-pyrrolo[3,4 *d*]pyrimidin-4-yloxy)-indole-1-carboxylic acid [5-(1-methyl-cyclopropyl)-2*H*-pyrazol-3-yl]-amide; N-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-5-((6-

((methylamino)methyl)pyrimidin-4-yl)oxy)-1*H*-indole-1-carboxamide; (*S*)-5-(6-methyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yloxy)-N-(5-(1-methylcyclopropyl)-1*H*-pyrazol-3-yl)-1*H*-indole-1-carboxamide, or combinations thereof.

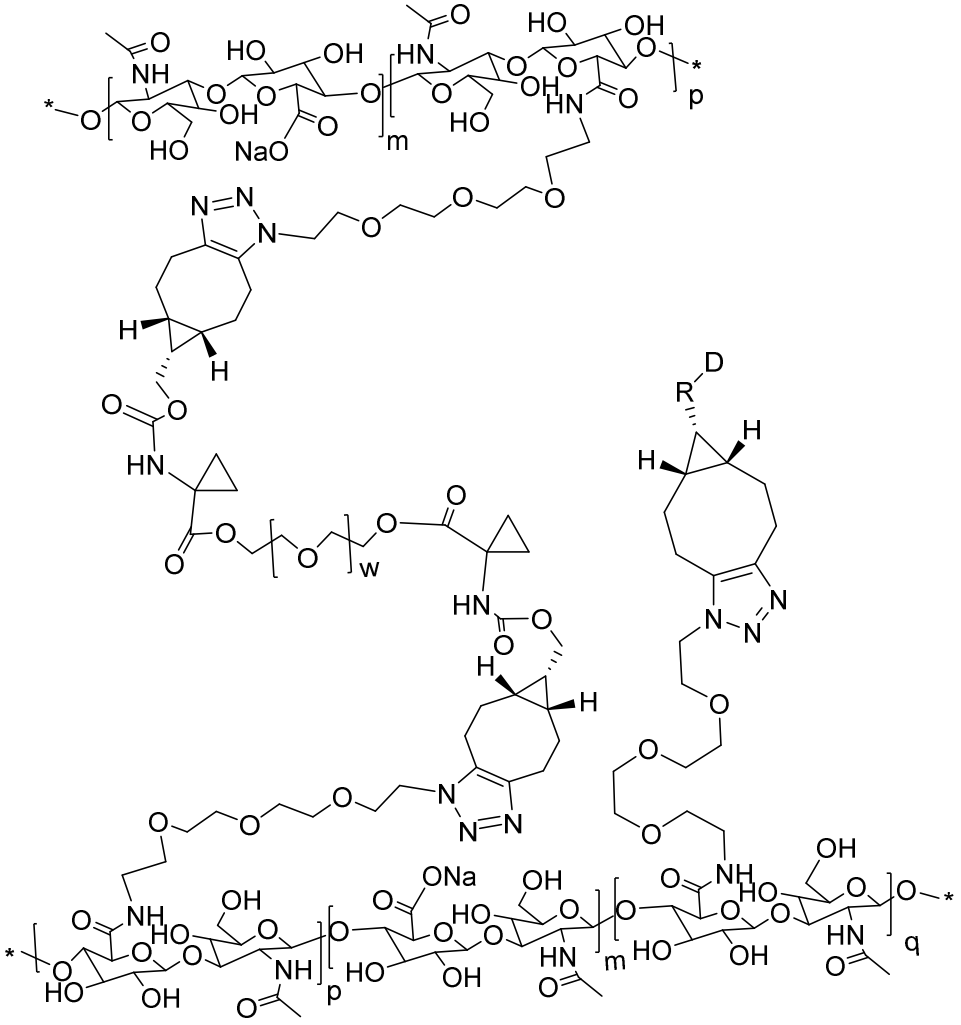
49. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (XXIV), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and R is a linker suitable for release of biologically active moiety D:



(XXIV).

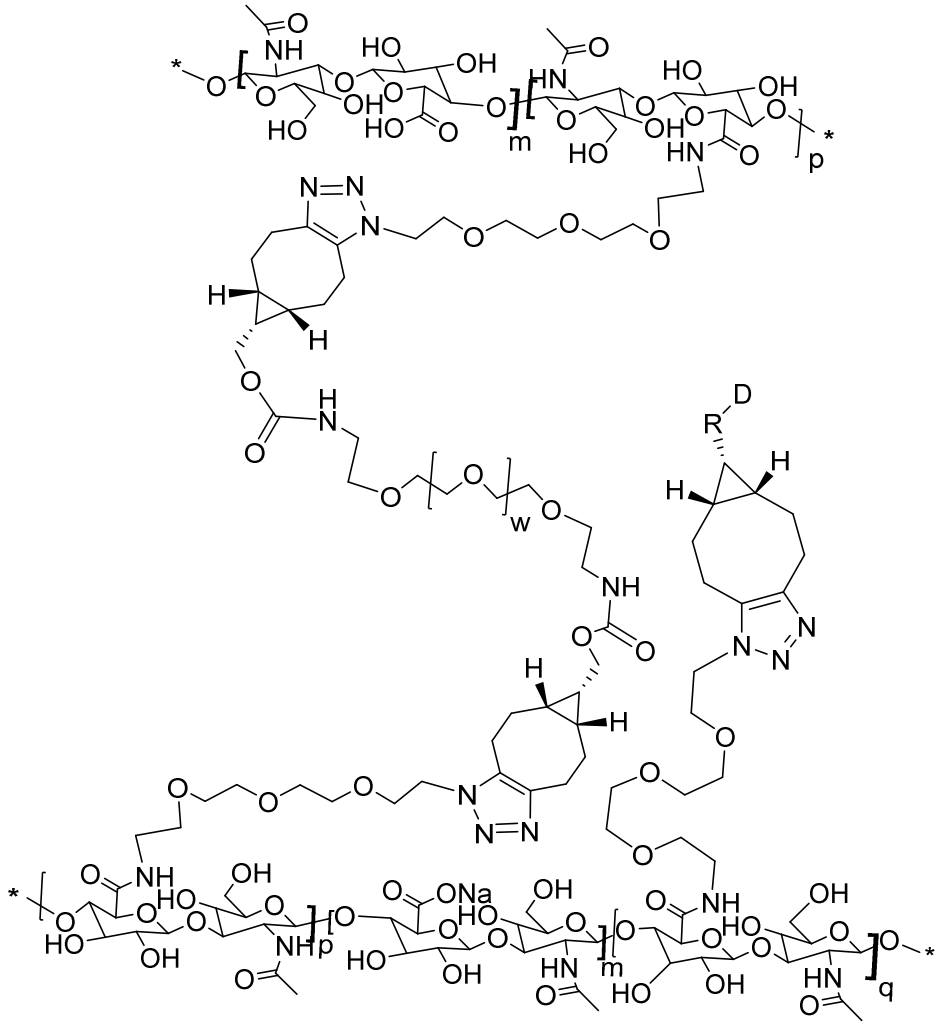
50. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (XXV), where D is a biologically active moiety comprising at

least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and R is a linker suitable for release of biologically active moiety D:



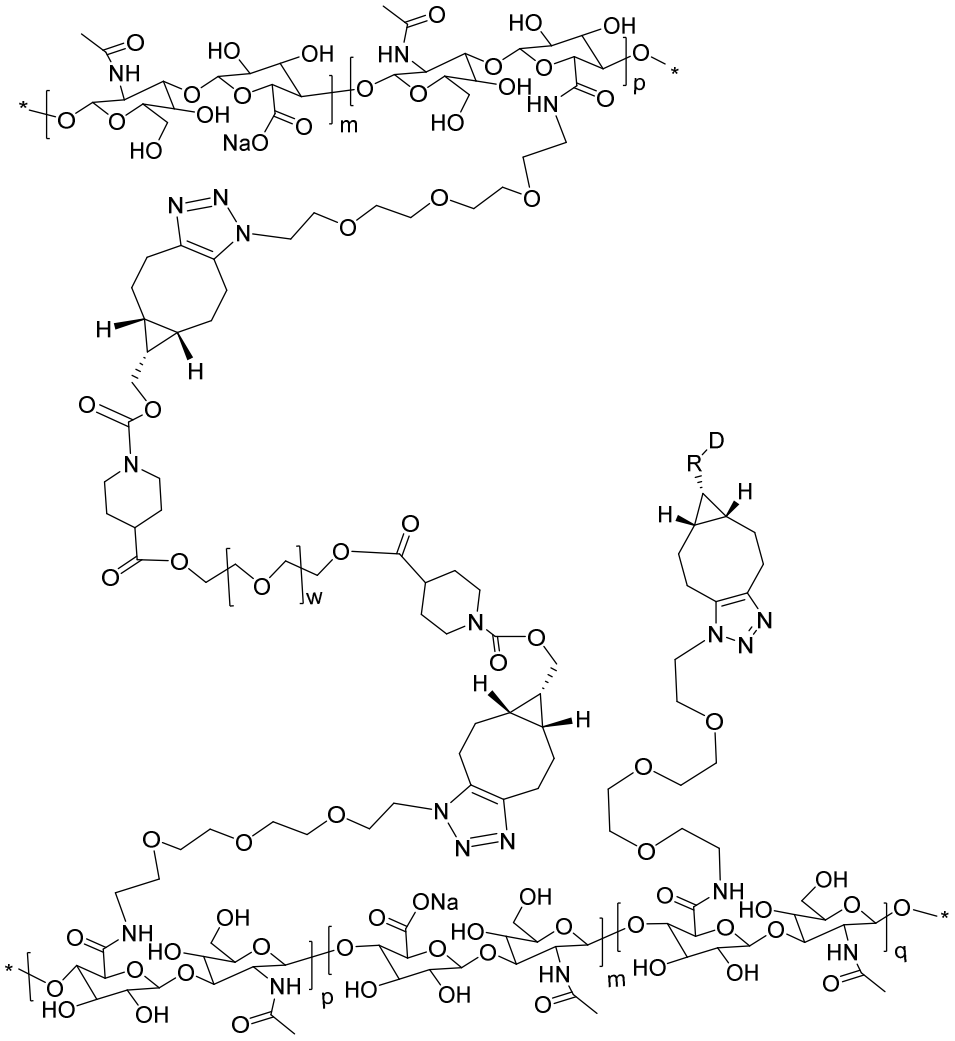
(XXV).

51. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (XXVI), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and R is a linker suitable for release of biologically active moiety D:



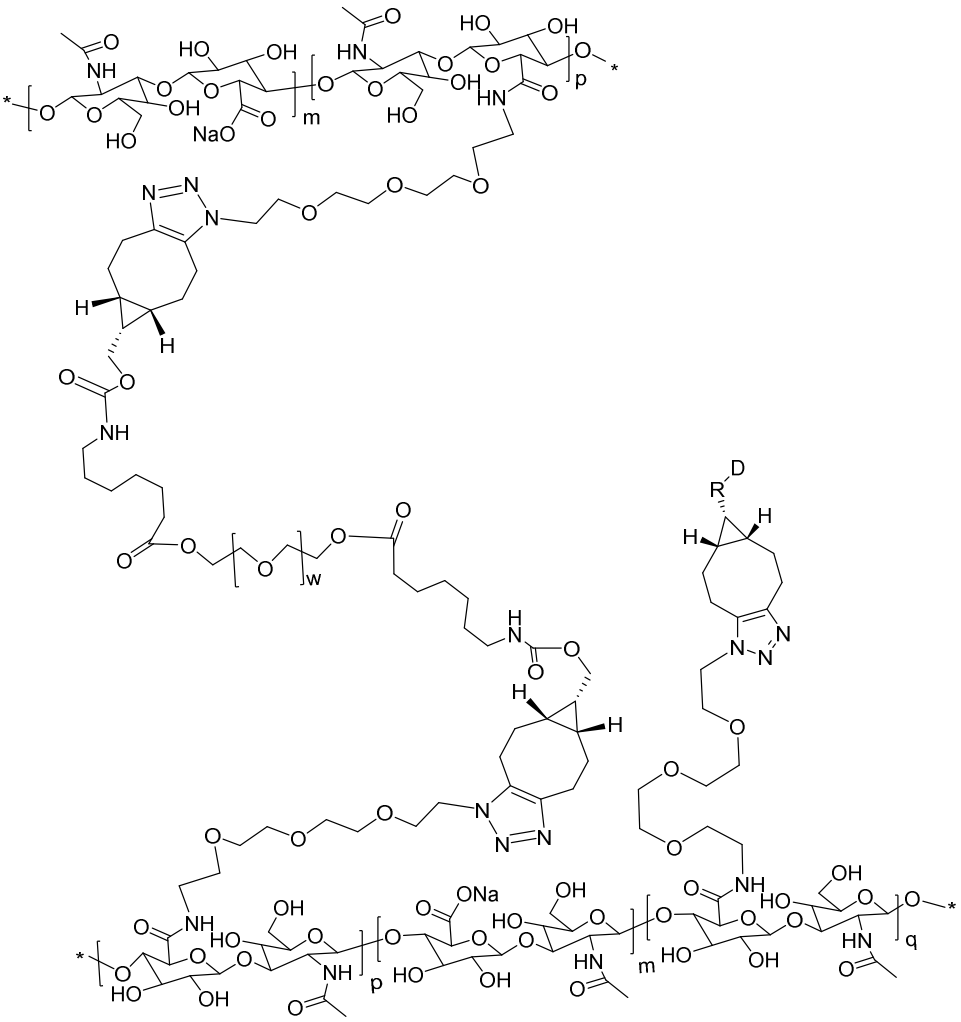
(XXVI).

52. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (XXVII), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and R is a linker suitable for release of biologically active moiety D:



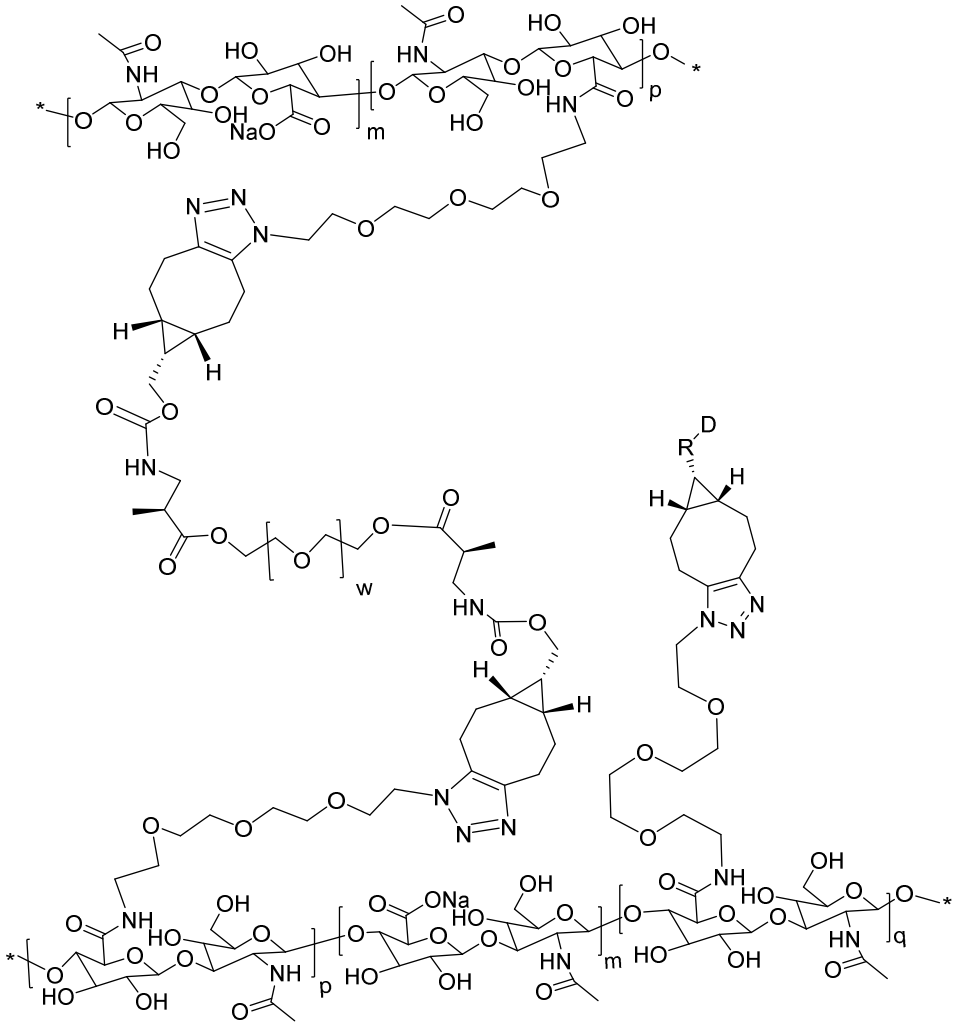
(XXVII).

53. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (XXVIII), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and R is a linker suitable for release of biologically active moiety D:



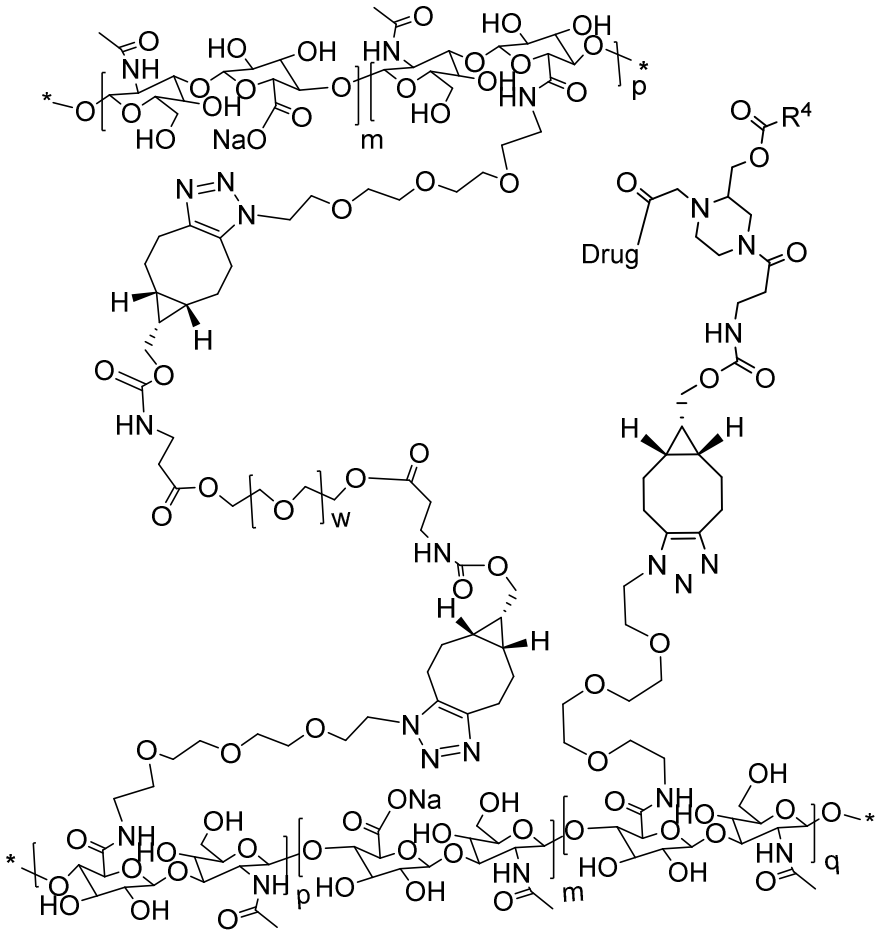
(XXVIII).

54. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (XXIX), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and R is a linker suitable for release of biologically active moiety D:



(XXIX).

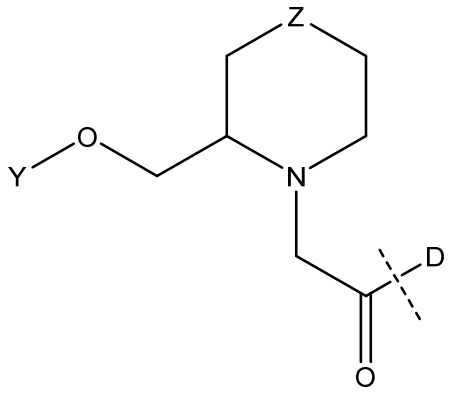
55. A drug delivery system or pharmaceutically acceptable salt thereof that is represented by Formula (XXX), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl:



(XXX).

56. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (XXXI), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and

R is a linker suitable for release of biologically active moiety D:



(XXXI),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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;

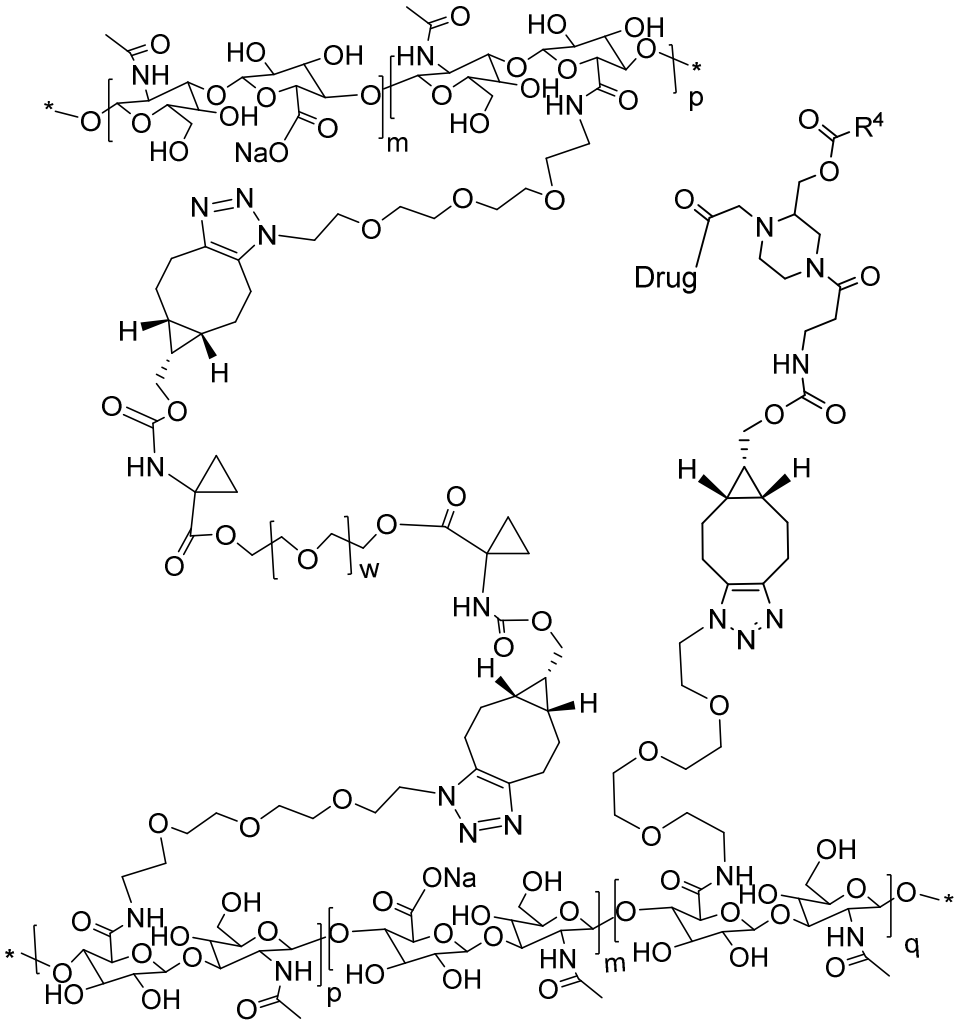
Z is N-L-A;

L is $C(O)CH_2CH_2NH$;

A is R^{11};

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 $N(H)(CH_2CH_2O)_3CH_2CH_2N_3$, and wherein the cross-linker used to form the hydrogel comprises PEG(2000)-bis-[3-(((((1R,8S,9s)-bicyclo[6.1.0]non-4-yn-9-yl)methoxy)carbonyl)amino)propanoate].

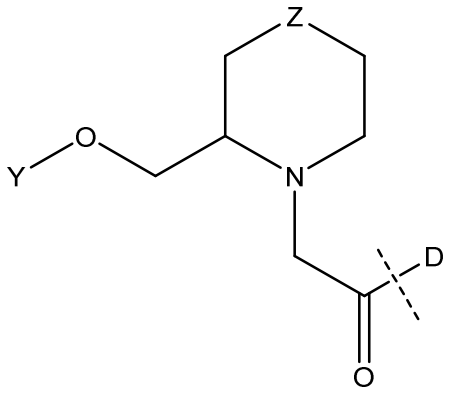
57. A drug delivery system or pharmaceutically acceptable salt thereof that is represented by Formula (XXXII), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl:



(XXXII).

58. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula XXXIII, where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and

R is a linker suitable for release of biologically active moiety D:



(XXXIII),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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;

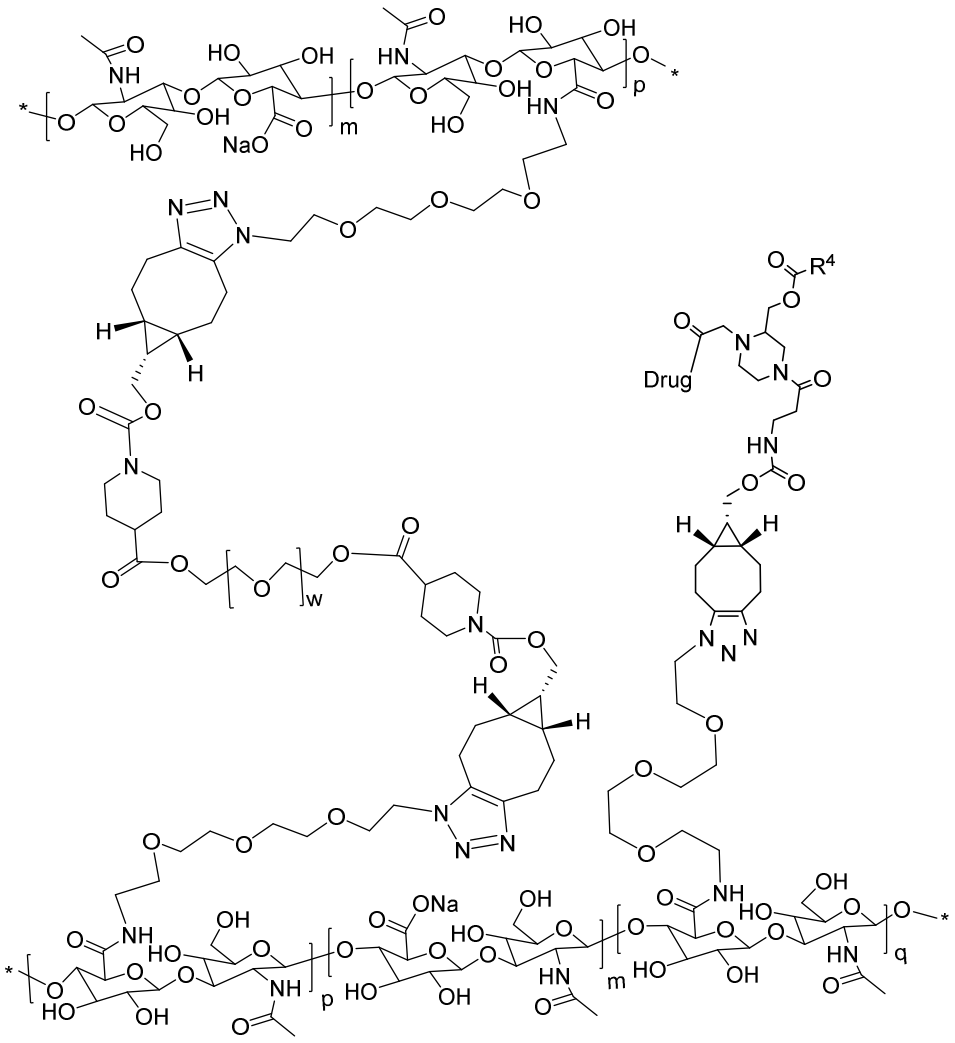
Z is N-L-A;

L is $C(O)CH_2CH_2NH$;

A is R^{11};

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 $N(H)(CH_2CH_2O)_3CH_2CH_2N_3$, 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].

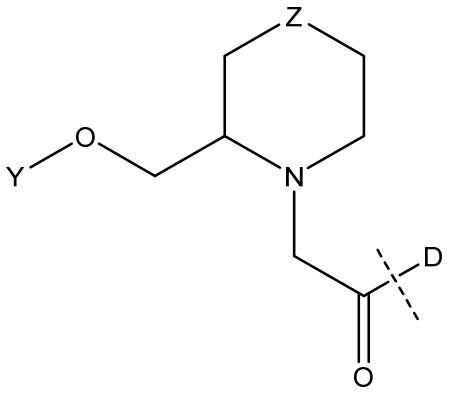
59. A drug delivery system or pharmaceutically acceptable salt thereof that is represented by Formula (XXXIV), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl:



(XXXIV).

60. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula XXXV, where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and

R is a linker suitable for release of biologically active moiety D:



(XXXV),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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;

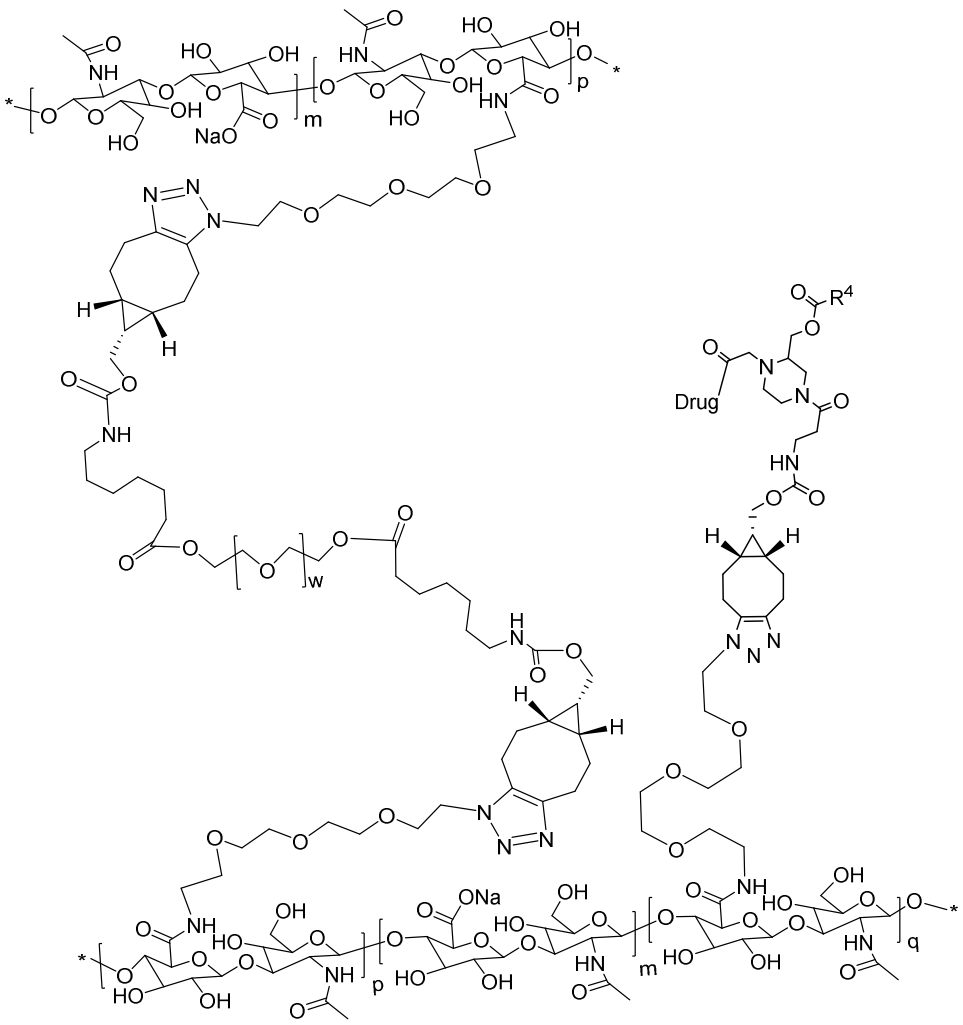
Z is N-L-A;

L is $C(O)CH_2CH_2NH$;

A is R^{11};

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 $N(H)(CH_2CH_2O)_3CH_2CH_2N_3$, 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].

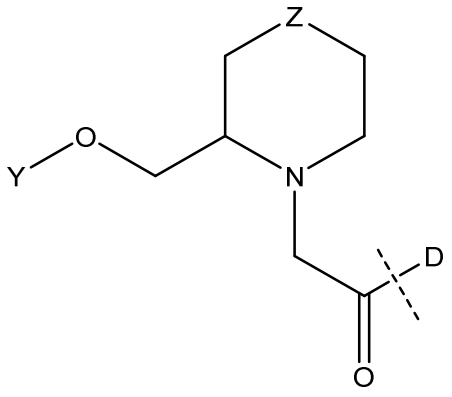
61. A drug delivery system or pharmaceutically acceptable salt thereof that is represented by Formula (XXXVI), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl:



(XXXVI).

62. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula XXXVII, where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and

R is a linker suitable for release of biologically active moiety D:



(XXXVII),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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;

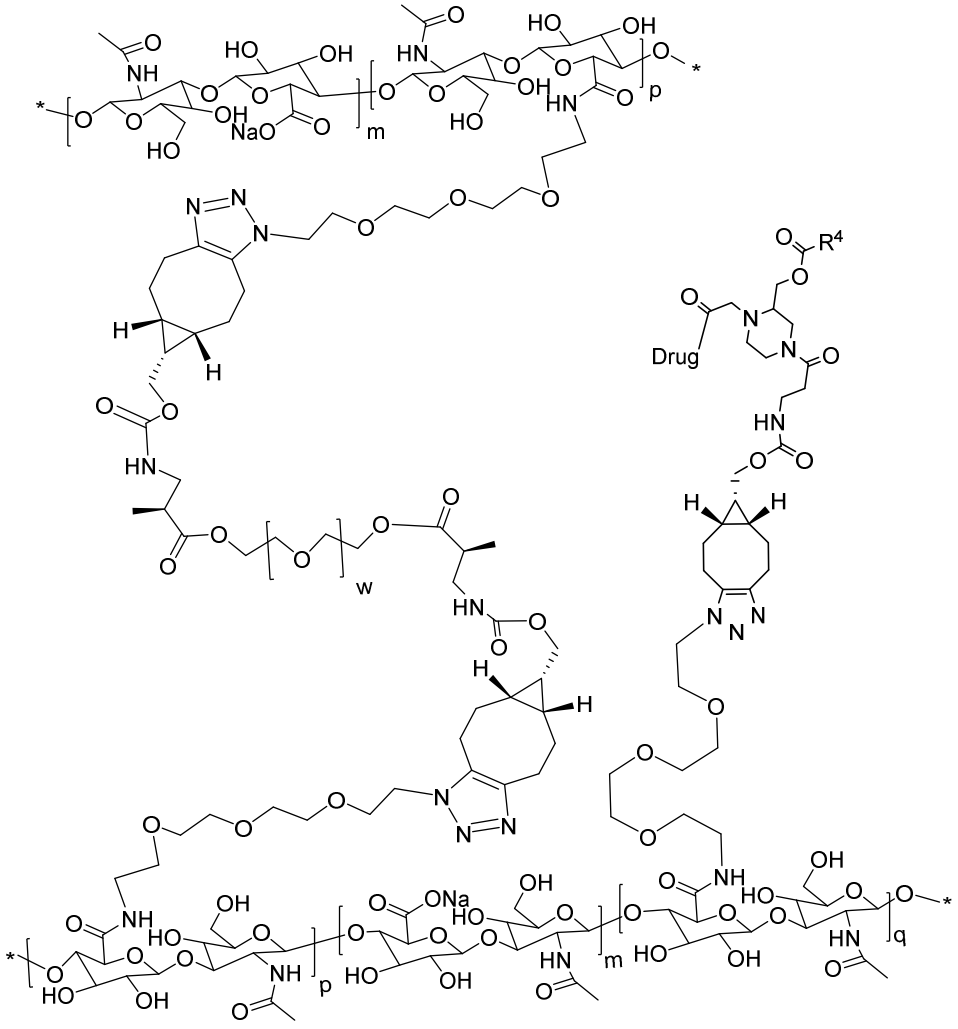
Z is N-L-A;

L is $C(O)CH_2CH_2NH$;

A is R^{11};

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 $N(H)(CH_2CH_2O)_3CH_2CH_2N_3$, 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].

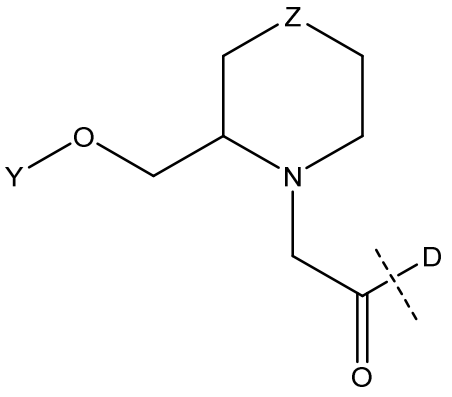
63. A drug delivery system or pharmaceutically acceptable salt thereof that is represented by Formula (XXXVIII), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and R^4 is methyl, ethyl, propyl, isopropyl, 1-methyl-cyclopropyl, or methoxymethyl:



(XXXVIII).

64. A drug delivery system or pharmaceutically acceptable salt thereof comprising D–R, that is represented by Formula (XXXIX), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; and

R is a linker suitable for release of biologically active moiety D:



(XXXIX),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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 $C(O)CH_2CH_2NH$;

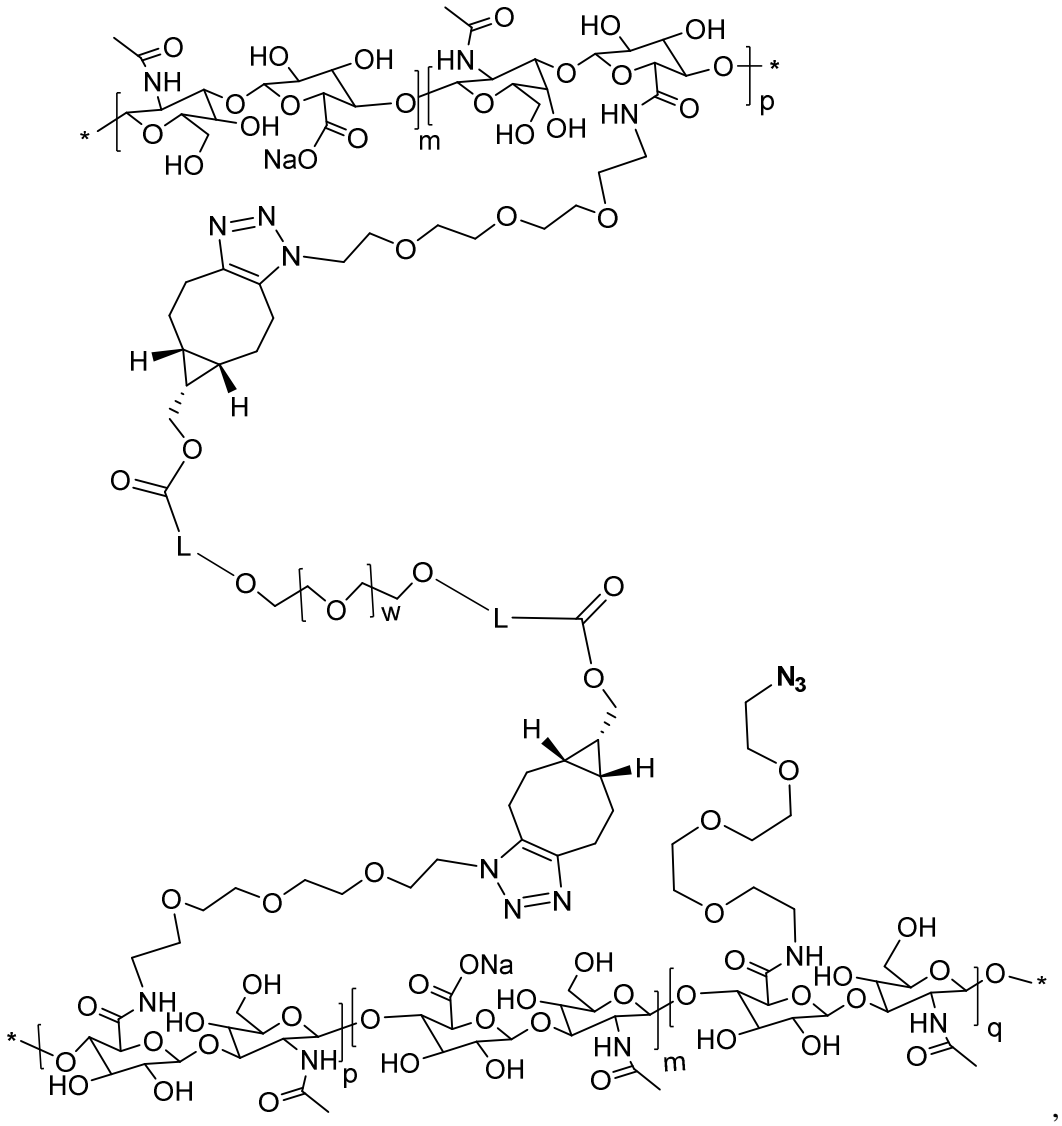
A is R^{11};

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 $N(H)(CH_2CH_2O)_3CH_2CH_2N_3$, 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].

65. The drug delivery systems of any one of claims 55 to 64, wherein D is brolucizumab and R^4 is CH_2CH_3.

66. The drug delivery systems of any one of claims 55 to 64, wherein D is brolucizumab and R^4 is $CH(CH_3)CH_3$.

67. A carrier composition or pharmaceutically acceptable salt thereof, represented by formula:



wherein

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)$_2$O, 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;

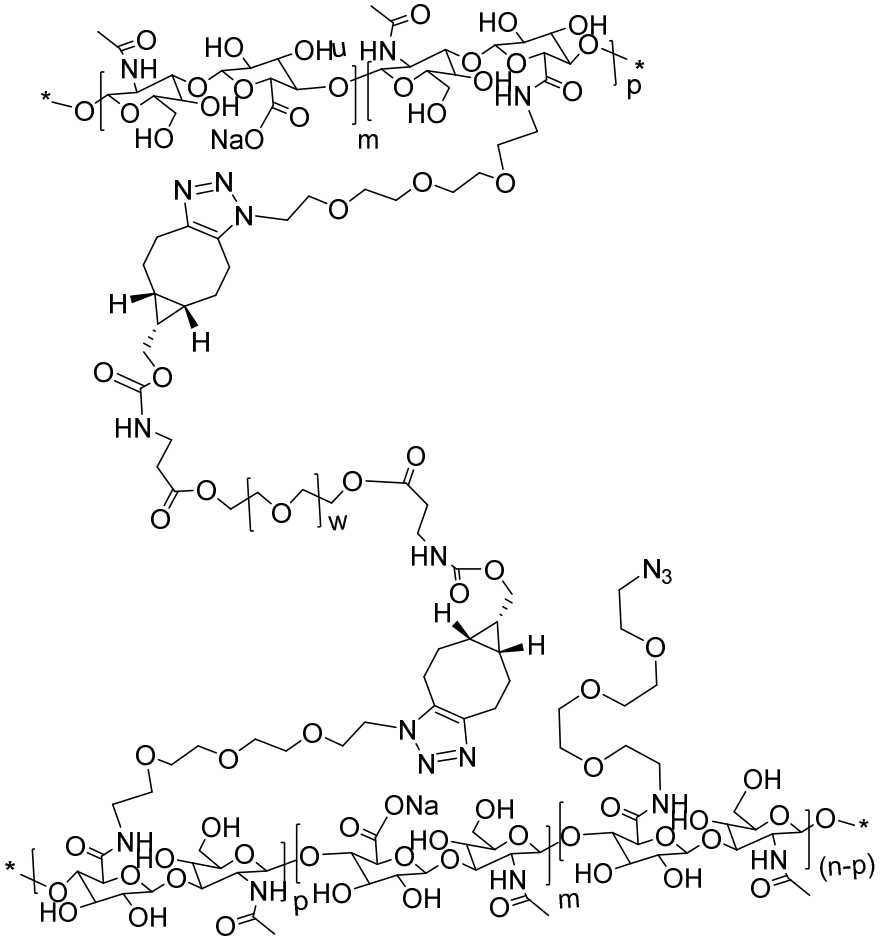
h is an integer of between 1 and 20;

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

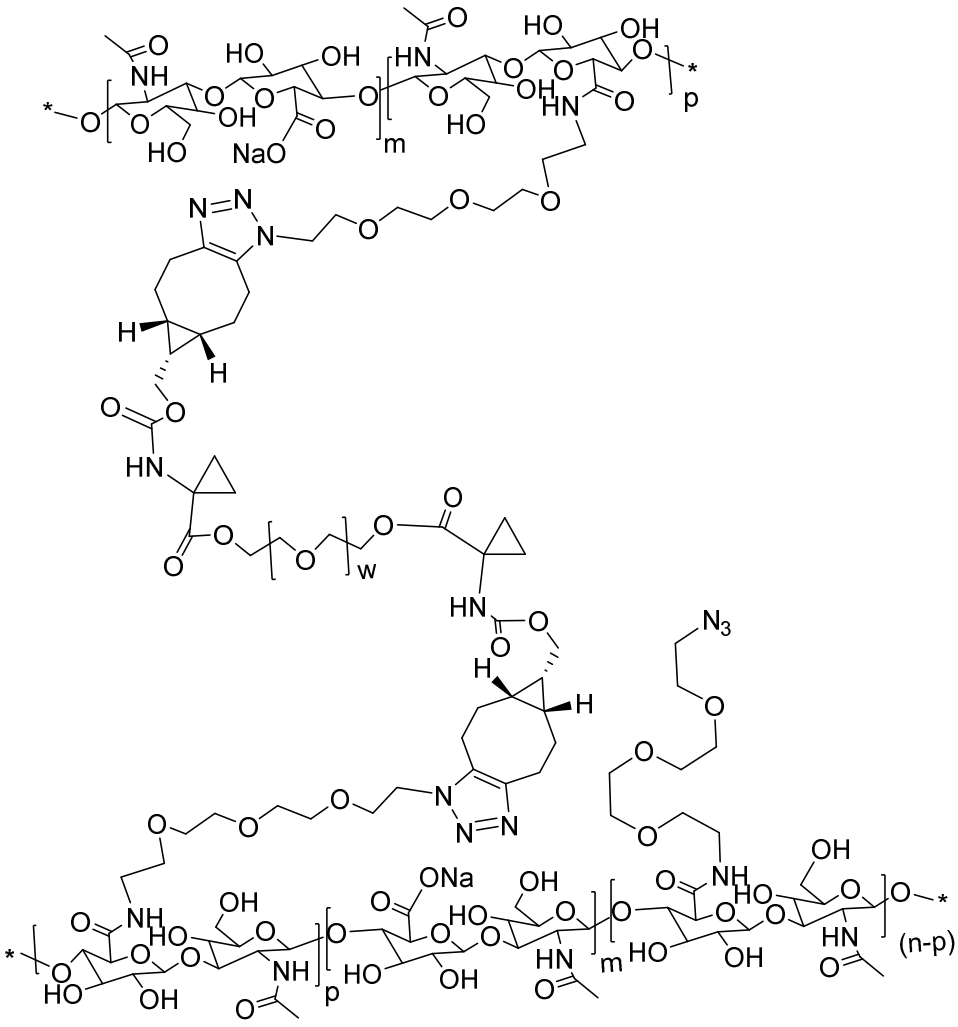
W is C_2-C_4alkyl-1,2-diyl in which a hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom; and

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.

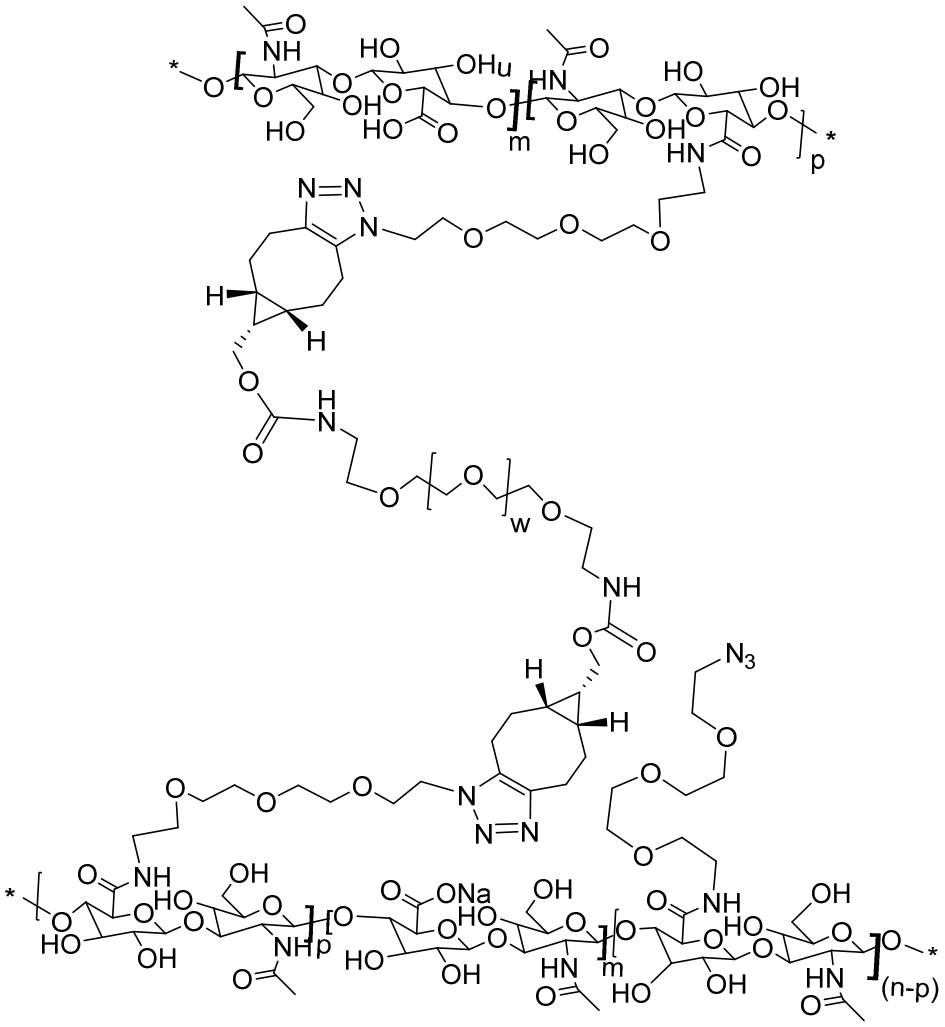
68. The carrier composition of claim 67, having one of the following formulae:



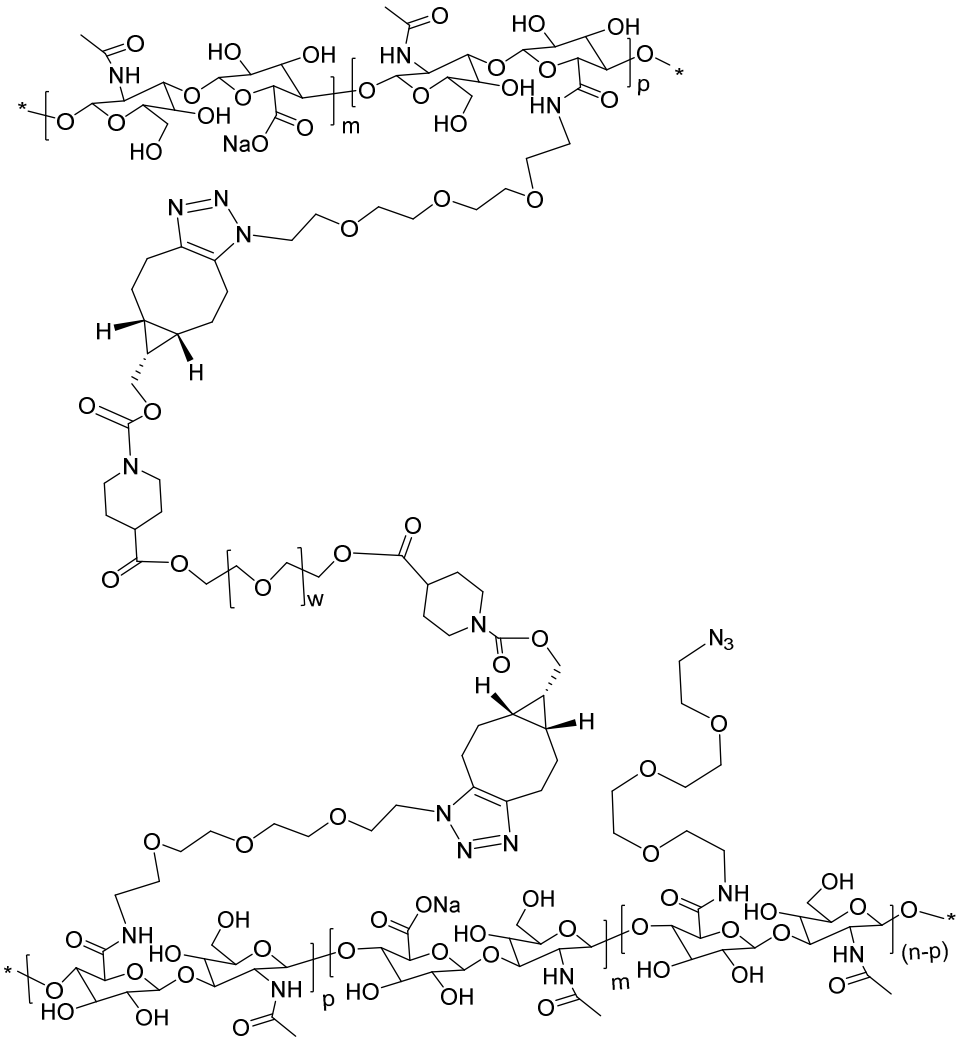
(X),



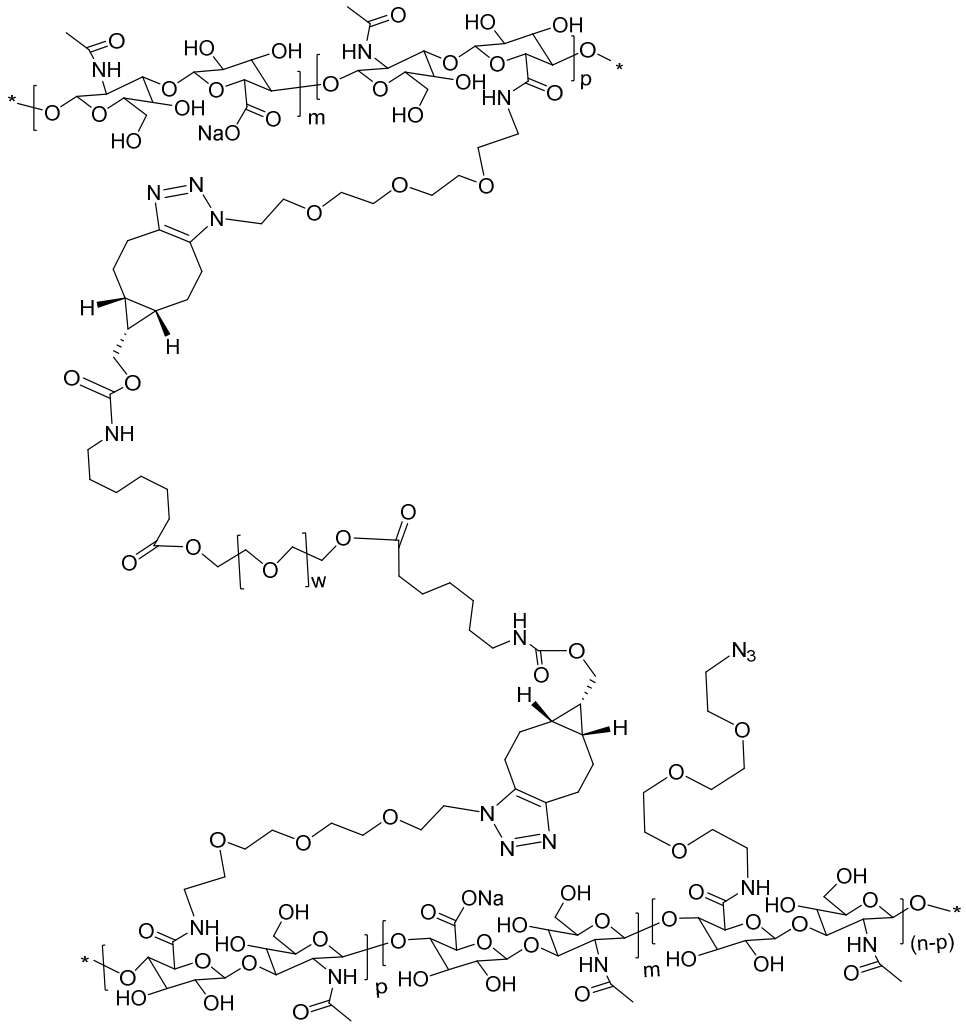
(XI),



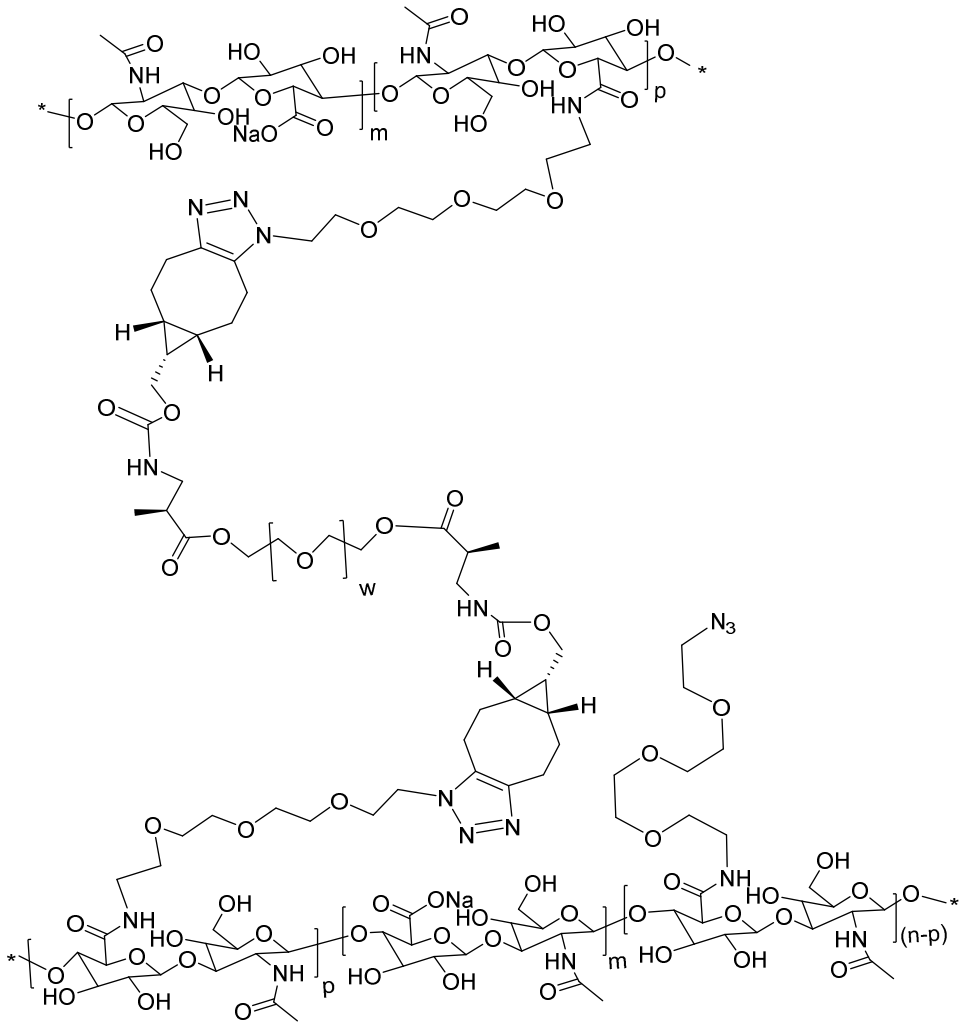
(XII),



(XIIa),



(XIIb), or

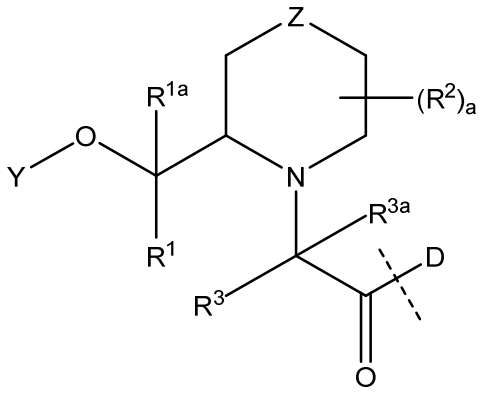


(XIIc).

69. Use of a drug delivery system or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treamtnet of macular degeneration in a subject in need thereof, comprising a conjugate D–R, that is represented by Formula (I), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring, comprising brolucizumab (SEQ ID NO:4), aflibercept, pegpleranib, ranibizumab, 5-(5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidin-4-yloxy)-indole-1-carboxylic acid [5-(1-methyl-cyclopropyl)-2*H*-pyrazol-3-yl]-amide; 5-(6,7-dihydro-5*H*-pyrrolo[3,4 *d*]pyrimidin-4-yloxy)-indole-1-carboxylic acid [5-(1-methyl-cyclopropyl)-2*H*-pyrazol-3-yl]-amide;N-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl)-5-((6-((methylamino) methyl)pyrimidin-4-yl)oxy)-1*H*-indole-1-

carboxamide;(*S*)-5-(6-methyl-5,6,7,8-tetrahydro pyrido[3,4-*d*]pyrimidin-4-yloxy)-N-(5-(1-methylcyclopropyl)-1*H*-pyrazol-3-yl)-1*H*-indole-1-carboxamide, or combinations thereof;

R is a linker suitable for release of biologically active moiety D:



(I),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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 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

$CHR^{12}OR^{13}$, taken in combination 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 hydroxy, amino, C_1-C_4alkoxy or mono- and di- C_1-C_4alkylamino;

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 CHR^8 or NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, $C(O)C_1$-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 the 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}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

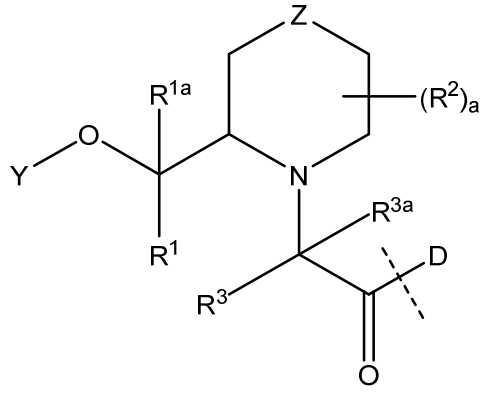
R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.

70. Use of a drug delivery system or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of musculoskeletal disorders in a subject in need thereof, comprising a conjugate D–R, that is represented by Formula (I), where D is a biologically active moiety comprising at least one primary or secondary amine or a

ring nitrogen atom of an azaheteroaryl ring comprising D2 (SEQ ID NO:4), D3 (SEQ ID NO:5), other insulin like growth factors, or a combination thereof;

R is a linker suitable for release of biologically active moiety D:



(I),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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 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

$CHR^{12}OR^{13}$, taken in combination 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 hydroxy, amino, C_1-C_4alkoxy or mono- and di- C_1-C_4alkylamino;

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 CHR^8 or NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, $C(O)C_1$-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 the 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);

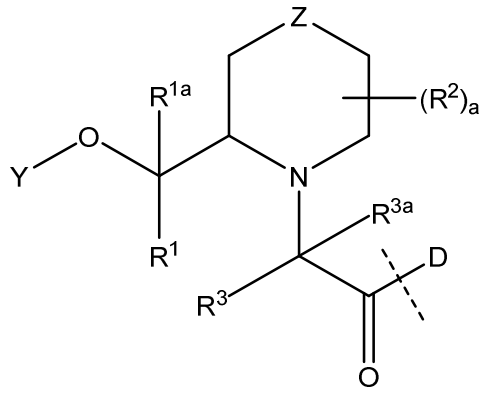
A is hydrogen, C_1-C_8alkyl, $C(O)C_1$-C_8alkyl, $C(O)N(H)C_1$-C_8alkyl, $C(O)OC_1$-C_8alkyl, R^{10}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.

71. Use of a drug delivery system or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cardiac disorders in a subject in need thereof, comprising a conjugate D–R, that is represented by Formula (I), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring comprising serelaxin or SEQ ID NO:7;

R is a linker suitable for release of biologically active moiety D:



(I),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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 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

$CHR^{12}OR^{13}$, taken in combination 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 hydroxy, amino, C_1-C_4alkoxy or mono- and di- C_1-C_4alkylamino;

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 CHR^8 or NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, $C(O)C_1$-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 the hydrogen, methyl, or ethyl side chain may be present on either backbone carbon atom;

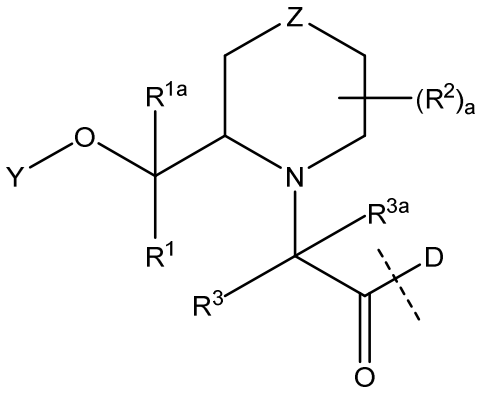
Q is a bond, O, N(H) or N(C_1-C_4alkyl);

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}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.

72. Use of a drug delivery system or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease or disorder in a subject in need thereof, comprising a conjugate D–R, that is represented by Formula (I), where D is a biologically active moiety comprising at least one primary or secondary amine or a ring nitrogen atom of an azaheteroaryl ring; R is a linker suitable for release of biologically active moiety D:



(I),

where the dashed line indicates attachment to the primary amine, secondary amine, or ring nitrogen atom of an azaheteroaryl ring;

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 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

$CHR^{12}OR^{13}$, taken in combination 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 hydroxy, amino, C_1-C_4alkoxy or mono- and di- C_1-C_4alkylamino;

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 CHR^8 or NR^9;

R^8 and R^9 are each independently selected from hydrogen, C_1-C_8 alkyl, $C(O)C_1$-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 the 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}, or R^{11}, wherein the alkyl group is optionally substituted with 0 or 1 R^{10};

R^{10} is a reactive functional group suitable for coupling Formula (I) to a carrier; and

R^{11} is a carrier.