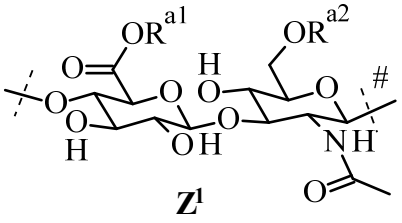
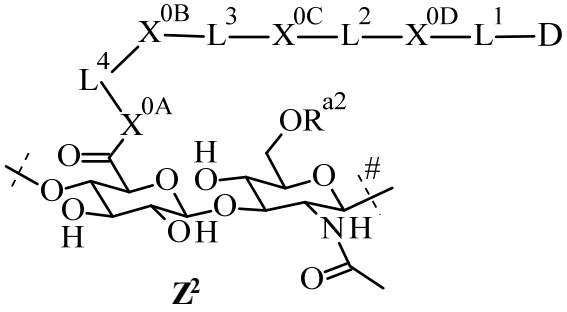
Claims

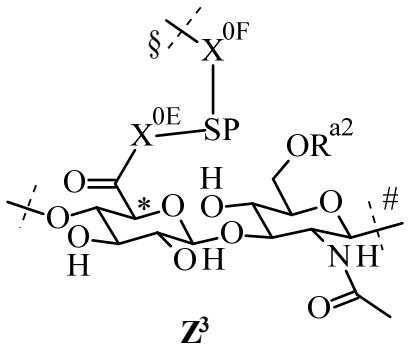
1. A conjugate comprising crosslinked hyaluronic acid strands to which a plurality of drug moieties are covalently and reversibly conjugated, wherein the conjugate comprises a plurality of connected units selected from the group consisting of



Z¹,



Z²,



Z³

and ,

wherein

an unmarked dashed line indicates a point of attachment to an adjacent unit at a dashed line marked with # or to a hydrogen;

a dashed line marked with # indicates a point of attachment to an adjacent unit at an unmarked dashed line or to a hydroxyl;

a dashed line marked with § indicates a point of connection between at least two units Z^3 via a moiety -CL-;

each -D is independently a drug moiety;

each $-L^1-$ is independently a linker moiety to which -D is covalently and reversibly conjugated;

each $-L^2-$, $-L^3-$ and $-L^4-$ is independently either absent or a spacer moiety;

each -CL- is independently a moiety connecting at least two units Z^3 and wherein there is at least one degradable bond in the direct connection between any two carbon atoms marked with the * connected by a moiety -CL-;

each -SP- is independently absent or a spacer moiety;

each -R^{a1} is independently selected from the group consisting of -H, C_{1-4} alkyl, an ammonium ion, a tetrabutylammonium ion, a cetyl methylammonium ion, an alkali metal ion and an alkaline earth metal ion;

each -R^{a2} is independently selected from the group consisting of -H and C_{1-10} alkyl;

each -X^{0A}-, -X^{0B}-, -X^{0C}-, -X^{0D}-, -X^{0E}- and -X^{0F}- is independently either absent or a linkage;

optionally -X^{0A}- and/or -X^{0B}- form together with -L^4- or parts of -L^4- one or more ring structure selected from the group consisting of 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl and adamantyl;

optionally -X^{0B}- and/or -X^{0C}- form together with -L^3- or parts of -L^3- one or more ring structure selected from the group consisting of 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl and adamantyl;

optionally, -X^{0C}- and/or -X^{0D}- form together with -L^2- or parts of -L^2- one or more ring structure selected from the group consisting of 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl and adamantyl;

optionally -X^{0E}- and/or -X^{0F}- form together with -SP- or parts of -SP- one or more ring structure selected from the group consisting of 4- to 7-membered heterocyclyl, 8- to 11-membered heterobicyclyl and adamantyl;

wherein

all units Z^1 present in the conjugate may be the same or different;

all units Z^2 present in the conjugate may be the same or different;

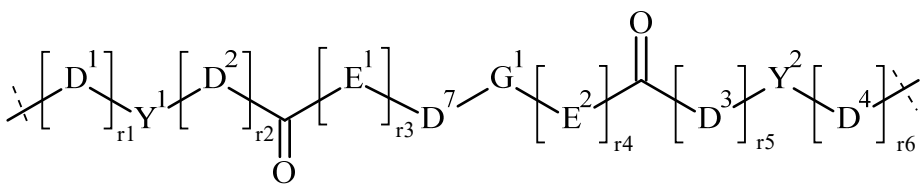
all units Z^3 present in the conjugate may be the same or different;

at least one unit Z^3 is present per hyaluronic acid strand which is connected to at least one unit Z^3 on a different hyaluronic acid strand; and

the conjugate comprises at least one moiety -L^1-D

wherein

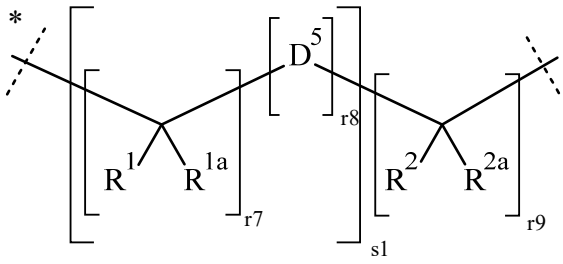
-CL- is a moiety of formula (A)



(A),

wherein

-Y^1- is of formula

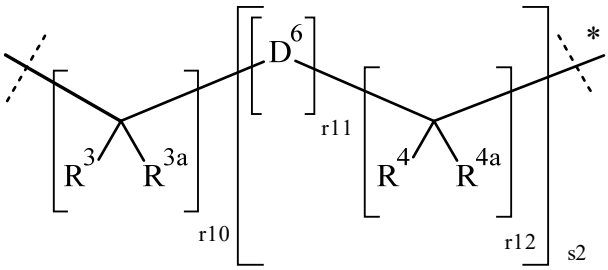


,

wherein

the dashed line marked with the asterisk indicates attachment to -D^1- and the unmarked dashed line indicates attachment to -D^2-;

-Y^2- is of formula

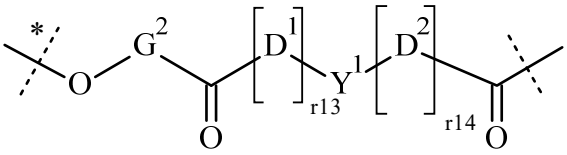


,

wherein

the dashed line marked with the asterisk indicates attachment to -D^4- and the unmarked dashed line indicates attachment to -D^3-;

-E^1- is of formula

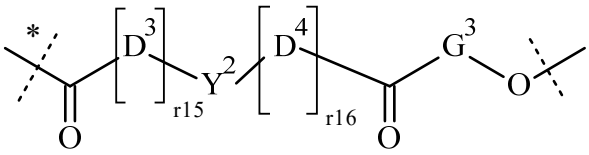


,

wherein

the dashed line marked with the asterisk indicates attachment to -(C=O)- and the unmarked dashed line indicates attachment to -O-;

-E^2- is of formula

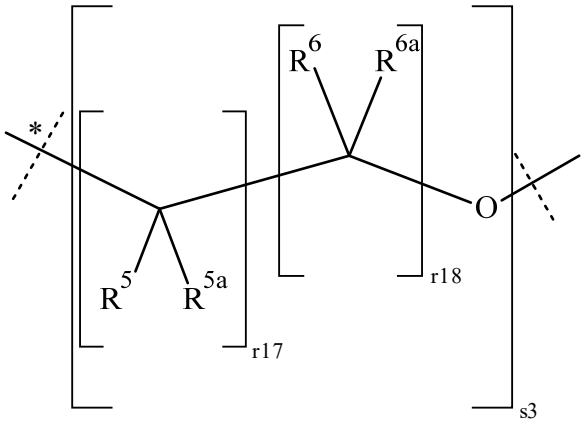


,

wherein

the dashed line marked with the asterisk indicates attachment to -G^1- and the unmarked dashed line indicates attachment to -(C=O)-;

-G^1- is of formula

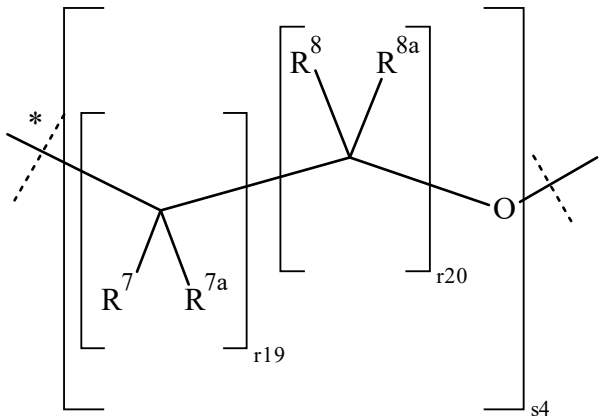


,

wherein

the dashed line marked with the asterisk indicates attachment to -O- and the unmarked dashed line indicates attachment to -E^2-;

-G^2- is of formula

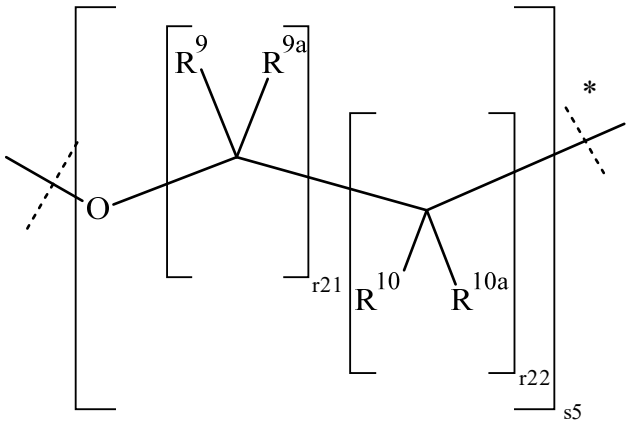


,

wherein

the dashed line marked with the asterisk indicates attachment to -O- and the unmarked dashed line indicates attachment to -(C=O)-,

-G^3- is of formula



,

wherein

the dashed line marked with the asterisk indicates attachment to -O- and the unmarked dashed line indicates attachment to -(C=O)-;

-D^1-, -D^2-, -D^3-, -D^4-, -D^5-, -D^6- and -D^7- are identical or different and each is independently of the others selected from the group comprising -O-, -NR^{11}-, -$N^+R^{12}R^{12a}$-, -S-, -(S=O), -$(S(O)_2)$, -C(O), -P(O), R^{13} and -$CR^{14}R^{14a}$-;

-R^1, -R^{1a}, -R^2, -R^{2a}, -R^3, -R^{3a}, -R^4, -R^{4a}, -R^5, -R^{5a}, -R^6, -R^{6a}, -R^7, -R^{7a}, -R^{8a}, -R^9, -R^{9a}, -R^{10}, -R^{10a}, -R^{11}, -R^{12}, -R^{12a}, -R^{13}, -R^{14} and -R^{14a} are identical or different and each is independently of the others selected from the group comprising -H and C_{1-6} alkyl;

optionally, one or more of the pairs R^1/ R^{1a}, R^2/ R^{2a}, R^3/ R^{3a}, R^4/ R^{4a}, R^1/ R^2, R^3/ R^4, R^{1a}/ R^{2a}, R^{3a}/ R^{4a}, R^{12}/ R^{12a}, and R^{14}/ R^{14a} , form a chemical bond or are joined together with the atom to which they are attached to form a C_{3-8} cycloalkyl or to form a ring A or are joined together with the atom to which they are attached to form a 4- to 7-membered heterocyclyl or 8- to 11-membered heterobicyclyl or adamantyl;

A is selected from the group consisting of phenyl, naphthyl, indenyl, indanyl and tetralinyl;

r1, r2, r5, r6, r13, r14, r15 and r16 are independently 0 or 1;

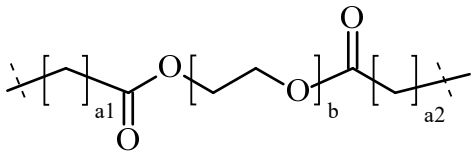
r3, r4, r7, r8, r9, r10, r11, r12 are independently 0, 1, 2, 3, or 4;

r17, r18, r19, r20, r21 and r22 are independently 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

s1, s2, s4, s5 are independently 1, 2, 3, 4, 5 or 6; and

s3 ranges from 1 to 200, preferably from 1 to 100 and more preferably from 1 to 50.

2. The conjugate of claim 1, wherein CL is of formula (B):



(B),

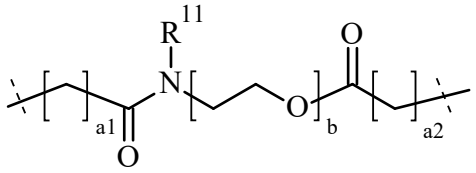
wherein

the dashed lines indicate attachment to a moiety -X^{0F}-;

a1 and a2 are independently selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14; and

b is an integer ranging from 1 to 50.

3. The conjugate of claim 1, wherein CL is of formula (C):



(C),

wherein

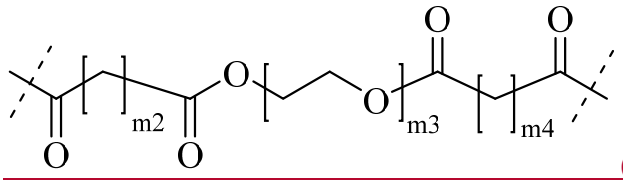
the dashed lines indicate attachment to a moiety -X^{0F}-;

a1 and a2 are independently selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14;

b is an integer ranging from 1 to 50; and

-R^{11} is selected from the group comprising -H and C_{1-6} alkyl.

4. The conjugate of claim 1, wherein CL is of formula (D):



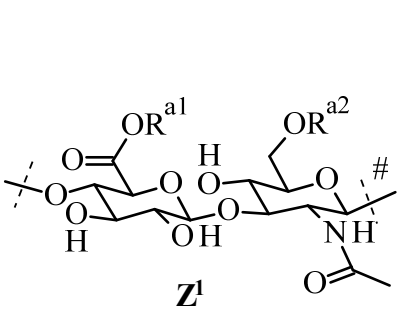
(D),

wherein

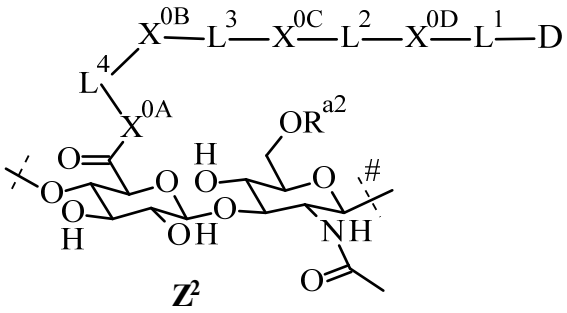
the dashed lines indicate attachment to a moiety -X^{0F}-; and

m2, m3 and m4 are independently an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25.

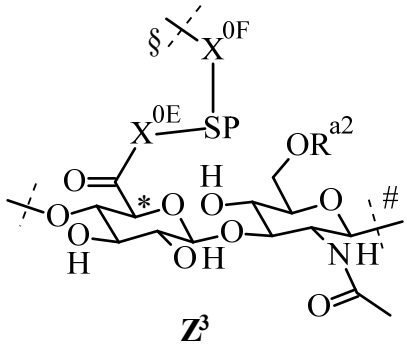
~~2~~5. The conjugate of any one of claim 1 to 4, wherein the conjugate comprises crosslinked hyaluronic acid strands to which a plurality of drug moieties are covalently and reversibly conjugated, wherein the conjugate comprises a plurality of connected units selected from the group consisting of



Z^1,



Z^2,



Z^3

and ,

wherein

an unmarked dashed line indicates a point of attachment to an adjacent unit at a dashed line marked with # or to a hydrogen;

a dashed line marked with # indicates a point of attachment to an adjacent unit at an unmarked dashed line or to a hydroxyl;

a dashed line marked with § indicates a point of connection between at least two units Z^3 via a moiety -CL-;

-D, -L^1-, -L^2-, -L^3-, -L^4-, -SP-, -CL-, -X^{0A}-, -X^{0B}-, -X^{0C}-, -X^{0D}-, -X^{0E}-, -X^{0F}-, -R^{a1} and -R^{a2} are used as in claim 1;

wherein

all units Z^1 present in the conjugate may be the same or different;

all units Z^2 present in the conjugate may be the same or different;

all units Z^3 present in the conjugate may be the same or different;

the number of Z^1 units ranges from 1% to 98% of the total number of units present in the conjugate;

the number of Z^2 units ranges from 1% to 98% of the total number of units present in the conjugate, provided at least one unit Z^2 is present in the conjugate;

the number of Z^3 units ranges from 1% to 97% of the total number of units present in the conjugate, provided that at least one unit Z^3 is present per strand; and

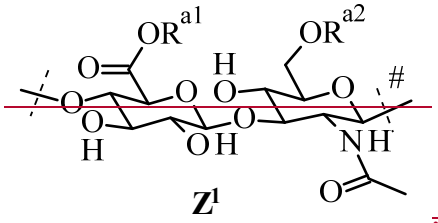
wherein at least 70% of all hyaluronic acid strands comprise at least one moiety Z^2 and at least one moiety Z^3.

~~3~~6. The conjugate of claim ~~2~~5, wherein the number of units Z^2 ranges from 1% to 70% of all units present in the conjugate.

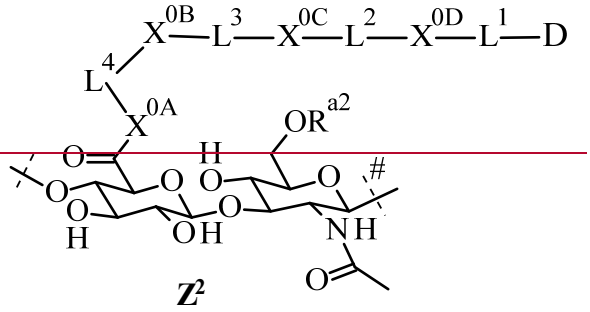
~~4~~7. The conjugate of claim ~~2 -~~5 or ~~3~~6, wherein the number of units Z^3 ranges from 1% to 30%.

~~5~~8. The conjugate of any one of claims ~~2 -~~5 to ~~4~~7, wherein the number of units Z^1 ranges from 10% to 97%.

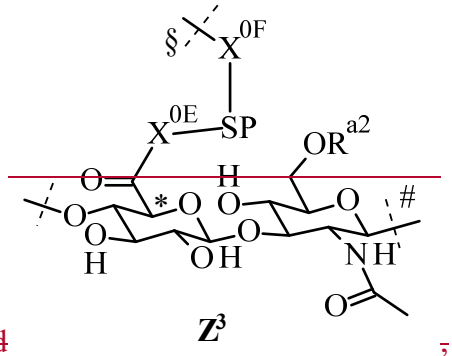
~~6. The conjugate of claim 1, wherein the conjugate comprises crosslinked hyaluronic acid strands to which a plurality of drug moieties are covalently and reversibly conjugated, wherein the conjugate comprises a plurality of connected units selected from the group consisting of~~



Z¹



Z²



Z³

and

wherein

an unmarked dashed line indicates a point of attachment to an adjacent unit at a dashed line marked with # or to a hydrogen;

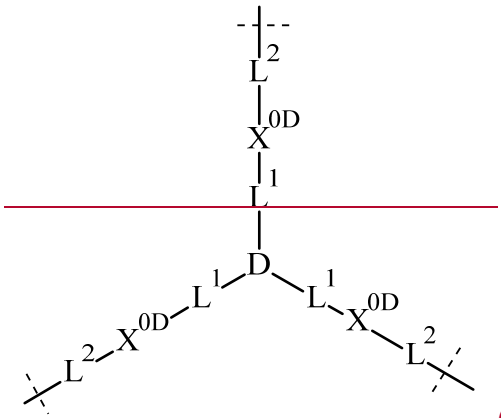
a dashed line marked with # indicates a point of attachment to an adjacent unit at an unmarked dashed line or to a hydroxyl;

a dashed line marked with § indicates a point of connection between at least two units Z^3 via a moiety -CL-;

each -CL- comprises at least one degradable bond between the two carbon atoms marked with the * connected by a moiety -CL- and each -CL- is independently selected from the group consisting of formula (C-i) and (C-ii)



(C-i),



(C-ii),

wherein

dashed lines indicate attachment to a moiety -X^{0F}- of a unit Z^3;

-D, -L^1-, -L^2-, -L^3-, -L^4-, -SP-, -X^{0A}-, -X^{0B}-, -X^{0C}-, -X^{0D}-, -X^{0E}-, -X^{0F}-, -R^{a1}- and -R^{a2}- are used as in claim 1;

wherein

all units Z^1 present in the conjugate may be the same or different;

all units Z^2 present in the conjugate may be the same or different;

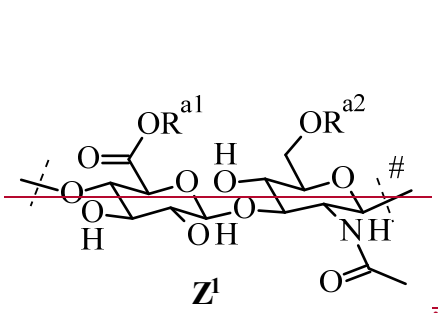
all units Z^3 present in the conjugate may be the same or different;

the number of Z^1 units ranges from 1% to 98% of the total number of units present in the conjugate;

the number of Z^2 units ranges from 0% to 98% of the total number of units present in the conjugate;

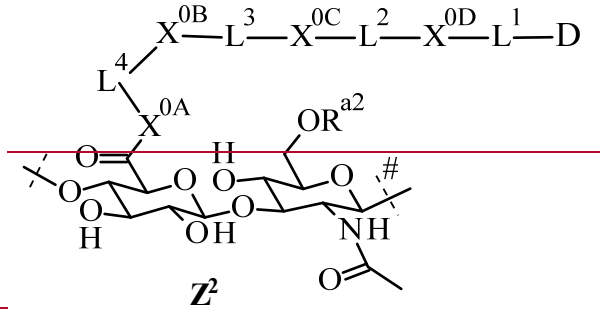
the number of Z^3 units ranges from 1% to 97% of the total number of units present in the conjugate, provided that at least one unit Z^3 is present per strand which is connected to at least one unit Z^3 on a different hyaluronic acid strand.

7. The conjugate of claim 1, wherein the conjugate comprises crosslinked hyaluronic acid strands to which a plurality of drug moieties are covalently and reversibly conjugated, wherein the conjugate comprises a plurality of connected units selected from the group consisting of



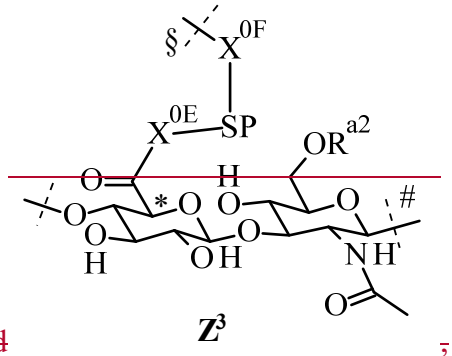
Z^1

,



Z^2

,



Z^3

and

,

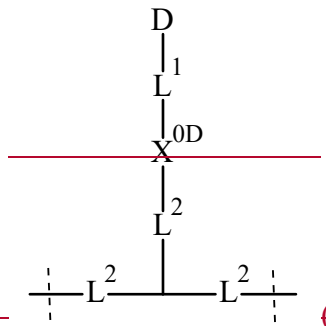
wherein

an unmarked dashed line indicates a point of attachment to an adjacent unit at a dashed line marked with # or to a hydrogen;

a dashed line marked with # indicates a point of attachment to an adjacent unit at an unmarked dashed line or to a hydroxyl;

a dashed line marked with § indicates a point of connection between two units Z^3 via a moiety -CL-;

each -CL- comprises at least one degradable bond between the two carbon atoms marked with the * connected by a moiety -CL- and each -CL- is independently of formula (D-i)



(D-i),

wherein

dashed lines indicate attachment to a moiety $-X^{0F}-$ of a unit Z^3;

-D, $-L^1-$, $-L^2-$, $-L^3-$, $-L^4-$, -SP-, $-X^{0A}-$, $-X^{0B}-$, $-X^{0C}-$, $-X^{0D}-$, $-X^{0E}-$, $-X^{0F}-$, $-R^{a1}-$ and $-R^{a2}-$ are used as defined in claim 1;

wherein

all units Z^1 present in the conjugate may be the same or different;

all units Z^2 present in the conjugate may be the same or different;

all units Z^3 present in the conjugate may be the same or different;

the number of units Z^1 ranges from 1% to 99% of the total number of units present in the conjugate;

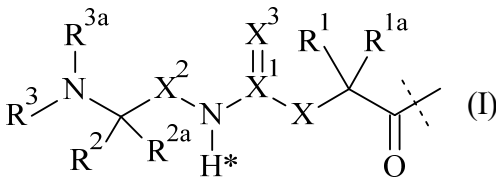
the number of units Z^2 ranges from 0% to 98% of the total number of units present in the conjugate; and

the number of units Z^3 ranges from 1% to 97% of the total number of units present in the conjugate, provided that at least one unit Z^3 is present per strand.

~~8~~9. The conjugate of any one of claims 1 to ~~7~~8, wherein -D is an antibiotic moiety.

~~9~~10. The conjugate of any one of claims 1 to ~~7~~8, wherein -D is an anti VEGF antibody moiety or fragment thereof.

~~10~~11. The conjugate of any one of claims 1 to ~~9~~10, wherein -L^1- is of formula (I):


(I)

,

wherein the dashed line indicates the attachment to a nitrogen, hydroxyl or thiol of -D;

-X- is selected from the group consisting of -$C(R^4R^{4a})$-, -$N(R^4)$-, -O-, -$C(R^4R^{4a})$-$C(R^5R^{5a})$-, -$C(R^5R^{5a})$-$C(R^4R^{4a})$-, -$C(R^4R^{4a})$-$N(R^6)$-, -$N(R^6)$-$C(R^4R^{4a})$-, -$C(R^4R^{4a})$-O-, -O-$C(R^4R^{4a})$-, and -$C(R^7R^{7a})$-,

X^1 is selected from the group consisting of C and S(O);

-X^2- is selected from the group consisting of -$C(R^8R^{8a})$- and -$C(R^8R^{8a})$-$C(R^9R^{9a})$-;

$=X^3$ is selected from the group consisting of =O, =S, and =N-CN;

-R^1, -R^{1a}, -R^2, -R^{2a}, -R^4, -R^{4a}, -R^5, -R^{5a}, -R^6, -R^8, -R^{8a}, -R^9 and -R^{9a} are independently selected from the group consisting of -H and C_{1-6} alkyl;

-R^3 and -R^{3a} are independently selected from the group consisting of -H and C_{1-6} alkyl, provided that in case one of -R^3 and -R^{3a} or both are other than -H they are connected to N to which they are attached through an sp^3-hybridized carbon atom;

-R^7 is selected from the group consisting of -$N(R^{10}R^{10a})$ and -NR^{10}-(C=O)-R^{11};

-R^{7a}, -R^{10}, -R^{10a} and -R^{11} are independently selected from the group consisting of -H and C_{1-6} alkyl;

alternatively, one or more of the pairs -R^{1a}/-R^{4a}, -R^{1a}/-R^{5a}, -R^{1a}/-R^{7a}, -R^{4a}/-R^{5a} and -R^{8a}/-R^{9a} form a chemical bond;

alternatively, one or more of the pairs -R^1/-R^{1a}, -R^2/-R^{2a}, -R^4/-R^{4a}, -R^5/-R^{5a}, -R^8/-R^{8a} and -R^9/-R^{9a} are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl or 3- to 10-membered heterocyclyl;

alternatively, one or more of the pairs -R^1/-R^4, -R^1/-R^5, -R^1/-R^6, -R^1/-R^{7a}, -R^4/-R^5, -R^4/-R^6, -R^8/-R^9 and -R^2/-R^3 are joined together with the atoms to which they are attached to form a ring A;

alternatively, -R^3/-R^{3a} are joined together with the nitrogen atom to which they are attached to form a 3- to 10-membered heterocycle;

A is selected from the group consisting of phenyl; naphthyl; indenyl; indanyl; tetralinyl; C_{3-10} cycloalkyl; 3- to 10-membered heterocyclyl; and 8- to 11-membered heterobicyclyl; and

wherein $-L^1-$ is substituted with $-X^{0D}-L^2-$ and wherein $-L^1-$ is optionally further substituted, provided that the hydrogen marked with the asterisk in formula (I) is not replaced by $-X^{0D}-L^2-$ or a substituent.

~~11. The conjugate of any one of claims 1 to 10, wherein -CL- is C_{1-50} alkyl, which is optionally interrupted by one or more atoms or groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{e1})-, -$S(O)_2$-, -S(O)-, -S-, -N(R^{e1})-, -OC(OR^{e1})(R^{e1a})- and -OC(O)N(R^{e1})-;~~

~~wherein -T- is selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, and 8- to 11-membered heterobicyclyl; and~~

~~$-R^{e1}$ and $-R^{e1a}$ are selected from the group consisting of -H and C_{1-6} alkyl.~~

12. A pharmaceutical composition comprising at least one conjugate of any one of claims 1 to 11 and at least one excipient.

13. The conjugate of any one of claims 1 to 11 or the pharmaceutical composition of claim 12 for use in therapy.

14. Use of the conjugate of any one of claims 1 to 11 or the pharmaceutical composition of claim 12 in the preparation of a medicament for treating a disease that can be treated with D-H or D-OH.

15. A method of preparing a pharmaceutical formulation comprising a conjugate of any one of claims 1 to 11, wherein the method comprises the steps of

(a) providing said conjugate;

(b) subjecting the conjugate of step (a) to a solution comprising a buffering agent, a surfactant and a salt comprising multivalent ions to which a swelling agent is added after addition of said solution;

(c) homogenizing the admixture of step (b);

(d) deswelling the conjugate of step (c) in a deswelling solution comprising at least a deswelling agent;

(e) isolating the conjugate from the admixture of step (d);

(f) subjecting the conjugate of step (e) to a solution comprising a buffering agent, a surfactant, a salt comprising bivalent ions, a hydrophilic polymer of a molecular weight higher than 10 kDa, a density-modifying agent and a polarity-modifying agent, to which a swelling agent is added after addition of said solution;

(g) homogenizing the admixture of step (f);

(h) deswelling the conjugate of step (g) in a deswelling solution comprising at least a deswelling agent;

(i) isolating the conjugate from the admixture of step (h); and

wherein, there may be optional washing steps between steps (c) and (d), (f) and (g), and (g) and (h).