Claims

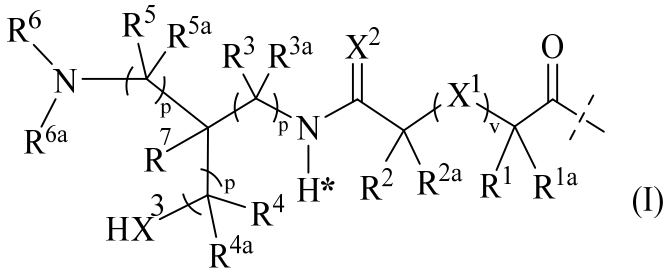
1. A conjugate or a pharmaceutically acceptable salt thereof comprising at least one moiety -D conjugated via at least one moiety -L^1-L^2- to at least one moiety Z, wherein a moiety -L^1- is conjugated to the nitrogen of a primary or secondary amine of a moiety -D and wherein the linkage between -D and -L^1- is reversible and wherein a moiety -L^2- is conjugated to Z, wherein

each -D is independently a primary or secondary amine-comprising moiety of a drug D-H;

each -L^2- is independently a single bond or a spacer moiety;

each Z is independently a polymeric moiety or a C_{8-24} alkyl;

each -L^1- is independently a linker moiety of formula (I):



(I)

wherein

the dashed line indicates the attachment to the nitrogen of the primary or secondary amine of -D;

v is selected from the group consisting of 0 or 1;

-X^1- is selected from the group consisting of -$C(R^8)(R^{8a})$-, -$N(R^9)$- and -O-;

$=X^2$ is selected from the group consisting of =O and $=N(R^{10})$;

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

each p is independently selected from the group consisting of 0 or 1, provided that at most one p is 0;

$-R^6$, $-R^{6a}$, $-R^{10}$ are independently selected from the group consisting of -H, $-C(R^{11})(R^{11a})(R^{11b})$ and -T;

$-R^9$ is selected from the group consisting of $-C(R^{11})(R^{11a})(R^{11b})$ and -T;

$-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^3$, $-R^{3a}$, $-R^4$, $-R^{4a}$, $-R^5$, $-R^{5a}$, $-R^7$, $-R^8$ $-R^{8a}$, $-R^{11}$, $-R^{11a}$ and $-R^{11b}$ are independently selected from the group consisting of -H, halogen, -CN, $-C(O)OR^{12}$, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)N(R^{12})(R^{12a})$, $-S(O)_2N(R^{12})(R^{12a})$, $-S(O)N(R^{12})(R^{12a})$, $-S(O)_2R^{12}$, $-S(O)R^{12}$, $-N(R^{12})S(O)_2N(R^{12a})(R^{12b})$, $-SR^{12}$, $-NO_2$, $-N(R^{12})C(O)OR^{12a}$, $-N(R^{12})C(O)N(R^{12a})(R^{12b})$, $-OC(O)N(R^{12})(R^{12a})$, -T, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl; wherein C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl are optionally substituted with one or more $-R^{13}$, which are the same or different; and wherein C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{14})-$, $-S(O)_2N(R^{14})-$, $-S(O)N(R^{14})-$, $-S(O)_2-$, -S(O)-, $-N(R^{14})S(O)_2N(R^{14a})-$, -S-, $-N(R^{14})-$, $-OC(OR^{14})(R^{14a})-$, $-N(R^{14})C(O)N(R^{14a})-$ and $-OC(O)N(R^{14})-$;

$-R^{12}$, $-R^{12a}$, $-R^{12b}$ are independently selected from the group consisting of -H, -T, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl; wherein -T, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl are optionally substituted with one or more $-R^{13}$, which are the same or different and wherein C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, $-C(O)N(R^{14})-$, $-S(O)_2N(R^{14})-$,

-S(O)N(R^{14})-, -S(O)$_2$-, -S(O)-, -N(R^{14})S(O)$_2$N(R^{14a})-, -S-, -N(R^{14})-, -OC(OR^{14})(R^{14a})-, -N(R^{14})C(O)N(R^{14a})- and -OC(O)N(R^{14})-;

wherein each T is independently 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; wherein each T is independently optionally substituted with one or more -R^{13}, which are the same or different;

-R^{13} is selected from the group consisting of halogen, -CN, oxo, -C(O)OR^{15}, -OR^{15}, -C(O)R^{15}, -C(O)N(R^{15})(R^{15a}), -S(O)$_2$N(R^{15})(R^{15a}), -S(O)N(R^{15})(R^{15a}), -S(O)$_2$$R^{15}$, -S(O)$R^{15}$, -N($R^{15}$)S(O)$_2$N($R^{15a}$)($R^{15b}$), -S$R^{15}$, -N($R^{15}$)($R^{15a}$), -NO$_2$, -OC(O)$R^{15}$, -N($R^{15}$)C(O)$R^{15a}$, -N($R^{15}$)S(O)$_2$$R^{15a}$, -N($R^{15}$)S(O)$R^{15a}$, -N($R^{15}$)C(O)O$R^{15a}$, -N($R^{15}$)C(O)N($R^{15a}$)($R^{15b}$), -OC(O)N($R^{15}$)($R^{15a}$) and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

wherein -R^{14}, -R^{14a}, -R^{15}, -R^{15a} and -R^{15b} are independently selected from the group consisting of -H and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

optionally, one or more of the pairs -R^1/-R^{1a}, -R^2/-R^{2a}, -R^3/-R^{3a}, -R^4/-R^{4a}, -R^5/-R^{5a} or -R^8/-R^{8a} are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl or an 8- to 11-membered heterobicyclyl;

optionally, one or more of the pairs -R^1/-R^2, -R^1/-R^8, -R^1/-R^9, -R^2/-R^9 or -R^2/-R^{10} are joined together with the atoms to which they are attached to form a ring -A-;

wherein -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;

optionally, one or more of the pairs -R^3/-R^6, -R^4/-R^6, -R^5/-R^6, -R^6/-R^{6a} or -R^6/-R^7 can form together with the atoms to which they are attached a ring -A´-;

wherein -A´- is selected from the group consisting of 3- to 10-membered heterocyclyl and 8- to 11-membered heterobicyclyl; and

each -L^1- is substituted with at least one -L^2- and optionally further substituted provided that the hydrogen marked with the asterisk in formula (I) is not replaced by a substituent.

2. The conjugate or pharmaceutically acceptable salt thereof of claim 1, wherein -D is selected from the group consisting of small molecule, medium size molecule, oligonucleotide, peptide nucleic acid, peptide and protein drug moieties.

3. The conjugate or pharmaceutically acceptable salt thereof of claim 1 or 2, wherein -D is selected from the group consisting of small molecule, medium size, peptide and protein drug moieties.

4. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 3, wherein -D is a protein drug moiety.

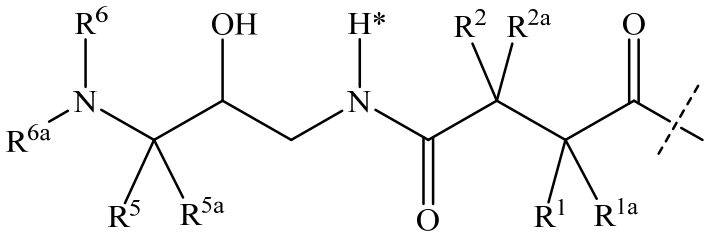
5. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 4, wherein v is 0.

6. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 5, wherein =X^2 is =O.

7. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 6, wherein $-X^3-$ is -O-.

8. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 7, wherein both $-R^3$ and $-R^{3a}$ are -H.

9. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 8, wherein $-L^1-$ is of formula (I-a):



(I-a),

wherein

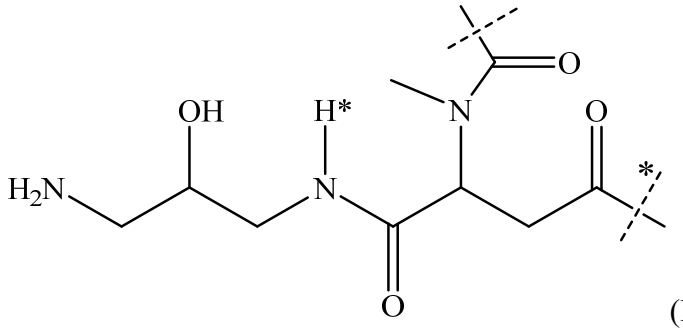
the dashed line indicates the attachment to the nitrogen of the primary or secondary amine of -D of claim 1; and

$-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^5$, $-R^{5a}$, $-R^6$, $-R^{6a}$, $-L^2-$ and Z are used as defined in claim 1.

10. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 9, wherein both $-R^6$ and $-R^{6a}$ are -H.

11. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 10, wherein both $-R^1$ and $-R^{1a}$ are -H.

12. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 11, wherein $-L^1-$ is of formula (I-d):



(I-d),

wherein

the dashed line marked with the asterisk indicates the attachment to the nitrogen of the primary or secondary amine of -D of claim 1 and the unmarked dashed line indicates attachment to -L^2-; and wherein -L^2- and Z are used as defined in claim 1-.

13. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 12, wherein Z is a polymeric moiety.

14. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 13, wherein Z is a water-insoluble polymeric moiety.

15. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 14, wherein Z is a water-insoluble polymeric moiety comprising a polymer selected from the group consisting of 2-methacryloyl-oxyethyl phosphoyl cholins, poly(acrylic acids), poly(acrylates), poly(acrylamides), poly(alkyloxy) polymers, poly(amides), poly(amidoamines), poly(amino acids), poly(anhydrides), poly(aspartamides), poly(butyric acids), poly(glycolic acids), polybutylene terephthalates, poly(caprolactones), poly(carbonates), poly(cyanoacrylates), poly(dimethylacrylamides), poly(esters), poly(ethylenes), poly(ethyleneglycols), poly(ethylene oxides), poly(ethyl phosphates), poly(ethyloxazolines), poly(glycolic acids), poly(hydroxyethyl acrylates), poly(hydroxyethyl-oxazolines), poly(hydroxymethacrylates), poly(hydroxypropylmethacrylamides), poly(hydroxypropyl methacrylates), poly(hydroxypropyloxazolines), poly(iminocarbonates), poly(lactic acids), poly(lactic-co-glycolic acids), poly(methacrylamides), poly(methacrylates), poly(methyloxazolines), poly(organophosphazenes), poly(ortho esters), poly(oxazolines), poly(propylene glycols), poly(siloxanes), poly(urethanes), poly(vinyl alcohols), poly(vinyl amines), poly(vinylmethylethers), poly(vinylpyrrolidones), silicones, celluloses, carbomethyl celluloses, hydroxypropyl methylcelluloses, chitins, chitosans, dextrans, dextrins, gelatins, hyaluronic acids and derivatives, functionalized hyaluronic acids, mannans, pectins, rhamnogalacturonans, starches, hydroxyalkyl starches, hydroxyethyl starches and other carbohydrate-based polymers, xylans, and copolymers thereof.

16. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 13, wherein Z is a water-soluble polymeric moiety.

17. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 16, wherein -L^2- is a spacer moiety selected from the group consisting of -T′-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y1})-, -S(O)$_2$N(R^{y1})-, -S(O)N(R^{y1})-, -S(O)$_2$-, -S(O)-, -N(R^{y1})S(O)$_2$N(R^{y1a})-, -S-, -N(R^{y1})-, -OC(OR^{y1})(R^{y1a})-, -N(R^{y1})C(O)N(R^{y1a})-, -OC(O)N(R^{y1})-, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein -T′-, C_{1-50} alkyl, C_{2-50} alkenyl and C_{2-50} alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different and wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T′-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y3})-, -S(O)$_2$N(R^{y3})-, -S(O)N(R^{y3})-, -S(O)$_2$-, -S(O)-, -N(R^{y3})S(O)$_2$N(R^{y3a})-, -S-, -N(R^{y3})-, -OC(OR^{y3})(R^{y3a})-, -N(R^{y3})C(O)N(R^{y3a})- and -OC(O)N(R^{y3})-;

wherein -R^{y1} and -R^{y1a} are independently selected from the group consisting of -H, -T′, C_{1-50} alkyl, C_{2-50} alkenyl and C_{2-50} alkynyl; wherein -T′, C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different, and wherein C_{1-50} alkyl, C_{2-50} alkenyl and C_{2-50} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T′-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y4})-, -S(O)$_2$N(R^{y4})-, -S(O)N(R^{y4})-, -S(O)$_2$-, -S(O)-, -N(R^{y4})S(O)$_2$N(R^{y4a})-, -S-, -N(R^{y4})-, -OC(OR^{y4})(R^{y4a})-, -N(R^{y4})C(O)N(R^{y4a})-, and -OC(O)N(R^{y4})-;

each T′ is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, 8- to 30-membered carbopolycyclyl and 8- to 30-membered heteropolycyclyl; wherein each T′ is independently optionally substituted with one or more -R^{y2}, which are the same or different;

each -R^{y2} is independently selected from the group consisting of halogen, -CN, oxo (=O), -$COOR^{y5}$, -OR^{y5}, -$C(O)R^{y5}$, -$C(O)N(R^{y5}R^{y5a})$, -$S(O)_2N(R^{y5}R^{y5a})$, -$S(O)N(R^{y5}R^{y5a})$, -$S(O)_2R^{y5}$, -$S(O)R^{y5}$, -$N(R^{y5})S(O)_2N(R^{y5a}R^{y5b})$, -$SR^{y5}$, -$N(R^{y5}R^{y5a})$, -$NO_2$, -$OC(O)R^{y5}$, -$N(R^{y5})C(O)R^{y5a}$, -$N(R^{y5})S(O)_2R^{y5a}$, -$N(R^{y5})S(O)R^{y5a}$, -$N(R^{y5})C(O)OR^{y5a}$, -$N(R^{y5})C(O)N(R^{y5a}R^{y5b})$, -$OC(O)N(R^{y5}R^{y5a})$, and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different; and

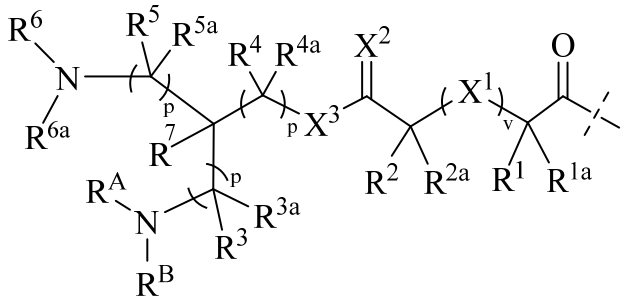
each -R^{y3}, -R^{y3a}, -R^{y4}, -R^{y4a}, -R^{y5}, -R^{y5a} and -R^{y5b} is independently selected from the group consisting of -H and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different.

18. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 17, wherein -L^2- has a molecular weight ranging from 14 g/mol to 750 g/mol.

19. A reagent comprising a moiety -L*-, wherein the moiety -L*- is conjugated to -Q, wherein

-Q is -OH or -LG, wherein -LG is a leaving group moiety;

-L*- is a linker moiety of formula (II):



(II)

wherein

the dashed line indicates the attachment to -Q;

v is selected from the group consisting of 0 or 1;

-X^1- is selected from the group consisting of -$C(R^8)(R^{8a})$-, -$N(R^9)$- and -O-;

=X^2 is selected from the group consisting of =O and =$N(R^{10})$;

-X^3- is selected from the group consisting of -O-, -S- and -Se-;

each p is independently selected from the group consisting of 0 or 1, provided that at most one p is 0;

-R^6 is -PG and -R^{6a} is selected from the group consisting of -H, -$C(R^{11})(R^{11a})(R^{11b})$, -T and -PG; or -$R^6$ and -R^{6a} are independently selected from the group consisting of -$C(R^{11})(R^{11a})(R^{11b})$ and -T;

-R^A and -R^B are independently selected from the group consisting of -H and -PG provided that not more than one of -R^A or -R^B can be -H;

-PG is an amine protecting group moiety;

-R^9 is selected from the group consisting of -$C(R^{11})(R^{11a})(R^{11b})$ and -T;

-R^{10} is selected from the group consisting of H, -$C(R^{11})(R^{11a})(R^{11b})$ and -T;

-R^1, -R^{1a}, -R^2, -R^{2a}, -R^3, -R^{3a}, -R^4, -R^{4a}, -R^5, -R^{5a}, -R^7, -R^8 -R^{8a}, -R^{11}, -R^{11a} and -R^{11b} are independently selected from the group consisting of -H, halogen, -CN, -$C(O)OR^{12}$, -OR^{12}, -$C(O)R^{12}$, -$C(O)N(R^{12})(R^{12a})$, -$S(O)_2N(R^{12})(R^{12a})$, -$S(O)N(R^{12})(R^{12a})$, -$S(O)_2R^{12}$, -$S(O)R^{12}$, -$N(R^{12})S(O)_2N(R^{12a})(R^{12b})$, -$SR^{12}$, -$NO_2$, -$N(R^{12})C(O)OR^{12a}$, -$N(R^{12})C(O)N(R^{12a})(R^{12b})$, -$OC(O)N(R^{12})(R^{12a})$, -T, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl and $C_{2\text{-}6}$ alkynyl; wherein

C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl are optionally substituted with one or more -R^{13}, which are the same or different; and wherein C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{14})-, -S(O)$_2$N(R^{14})-, -S(O)N(R^{14})-, -S(O)$_2$-, -S(O)-, -N(R^{14})S(O)$_2$N(R^{14a})-, -S-, -N(R^{14})-, -OC(OR^{14})(R^{14a})-, -N(R^{14})C(O)N(R^{14a})- and -OC(O)N(R^{14})-;

-R^{12}, -R^{12a}, -R^{12b} are independently selected from the group consisting of -H, -T, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein -T, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more -R^{13}, which are the same or different and wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally interrupted by one or more groups selected from the group consisting of -T-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{14})-, -S(O)$_2$N(R^{14})-, -S(O)N(R^{14})-, -S(O)$_2$-, -S(O)-, -N(R^{14})S(O)$_2$N(R^{14a})-, -S-, -N(R^{14})-, -OC(OR^{14})(R^{14a})-, -N(R^{14})C(O)N(R^{14a})- and -OC(O)N(R^{14})-;

wherein each T is independently 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; wherein each T is independently optionally substituted with one or more -R^{13}, which are the same or different;

-R^{13} is selected from the group consisting of halogen, -CN, oxo, -C(O)OR^{15}, -OR^{15}, -C(O)R^{15}, -C(O)N(R^{15})(R^{15a}), -S(O)$_2$N(R^{15})(R^{15a}), -S(O)N(R^{15})(R^{15a}), -S(O)$_2$$R^{15}$, -S(O)$R^{15}$, -N($R^{15}$)S(O)$_2$N($R^{15a}$)($R^{15b}$), -S$R^{15}$, -N($R^{15}$)($R^{15a}$), -NO$_2$, -OC(O)$R^{15}$, -N($R^{15}$)C(O)$R^{15a}$, -N($R^{15}$)S(O)$_2$$R^{15a}$, -N($R^{15}$)S(O)$R^{15a}$, -N($R^{15}$)C(O)O$R^{15a}$, -N($R^{15}$)C(O)N($R^{15a}$)($R^{15b}$), -OC(O)N($R^{15}$)($R^{15a}$) and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

wherein -R^{14}, -R^{14a}, -R^{15}, -R^{15a} and -R^{15b} are independently selected from the group consisting of -H and C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

optionally, one or more of the pairs -R^6/-R^{6a}, -R^A/-R^B or -R^6/-R^A can form a moiety -PG;

optionally, one or more of the pairs -R^1/-R^{1a}, -R^2/-R^{2a}, -R^3/-R^{3a}, -R^4/-R^{4a}, -R^5/-R^{5a} or -R^8/-R^{8a} are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl or an 8- to 11-membered heterobicyclyl;

optionally, one or more of the pairs -R^1/-R^2, -R^1/-R^8, -R^1/-R^9, -R^2/-R^9 or -R^2/-R^{10} are joined together with the atoms to which they are attached to form a ring -A-;

wherein -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;

optionally, one or more of the pairs -R^3/-R^6, -R^4/-R^6, -R^5/-R^6, -R^6/-R^{6a} or -R^6/-R^7 can form together with the atoms to which they are attached a ring -A´-;

wherein -A´- is selected from the group consisting of 3- to 10-membered heterocyclyl and 8- to 11-membered heterobicyclyl;

wherein -L*- is optionally substituted with at least one moiety -L^2-Z or at least one moiety -L^2-Y and optionally is further substituted;

wherein -L^2- is a single bond or a spacer moiety;

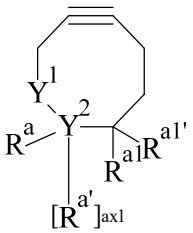
Z is independently a polymeric moiety or a C_{8-24} alkyl;

and wherein -Y is a functional group which may optionally be present in its protected form.

20. The reagent of claim 19, wherein -L*- of formula (II) is substituted with at least one moiety $-L^2-Y$ or at least one moiety $-L^2-Z$ and optionally is further substituted.

21. The reagent of claim 19 or 20, wherein -L*- of formula (II) is substituted with one moiety $-L^2-Y$.

22. The reagent of any one of claims 19 to 21, wherein -Y is selected from the group consisting of thiol, maleimide, amine, hydroxyl, carboxylic acid and derivatives, carbonate and derivatives, carbamate and derivatives, isothiocyanate, disulfide, pyridyl disulfide, methylthiosulfonyl, vinylsulfone, aldehyde, ketone, haloacetyl, selenide, azide, $-NH-NH_2$, $-O-NH_2$, a terminal alkyne, a compound of formula (z'i)



(z'i),

wherein

Y^1, Y^2 are independently C or N,

R^a, $R^{a'}$, R^{a1}, $R^{a1'}$ are independently -H or C_{1-6} alkyl,

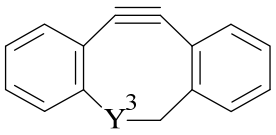
ax1 is 0, if Y^2 is N; ax1 is 1, if Y^2 is C,

optionally, the pair R^a/R^{a1} forms a chemical bond, if Y^2 is C,

optionally, the pair $R^{a'}/R^{a1'}$ are joined together with the atom to which they are attached to form a ring A', if Y^2 is C, and

A' is cyclopropyl or phenyl;

a compound of formula (z'ii)

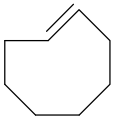


(z'ii),

wherein

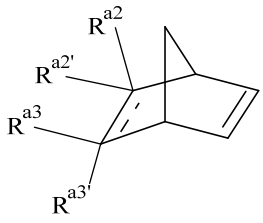
Y^3 is C or N;

a compound of formula (z'iii)



(z'iii),

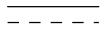
a compound of formula (z'iv),



(z'iv)

wherein

R^{a2}, $R^{a2'}$, R^{a3}, $R^{a3'}$ are -H,

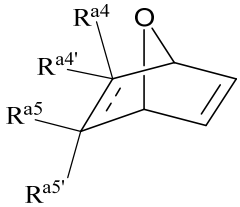


indicates a single or double bond,

optionally, the pair $R^{a2'}/R^{a3'}$ are joined together with the atoms to which they are attached to form a ring $A^{1'}$; and

$A^{1'}$ is 5-membered heterocyclyl;

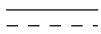
a compound of formula (z'v)



(z'v),

wherein

R^{a4}, $R^{a4'}$, R^{a5}, $R^{a5'}$ are -H,



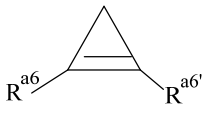
indicates a single or double bond,

optionally, the pair R^{a4}/R^{a5} forms a chemical bond,

optionally, the pair $R^{a4'}/R^{a5'}$ are joined together with the atoms to which they are attached to form a ring $A^{2'}$, and

$A^{2'}$ is 5-membered heterocyclyl;

a compound of formula (z'vi)



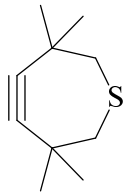
(z'vi),

wherein

R^{a6}, $R^{a6'}$ are either both C_{1-6} alkyl or one of R^{a6}, $R^{a6'}$ is -H and the other one is selected from C_{1-6} alkyl, $-COOR^{a7}$, $-CONHR^{a7'}$, and $CH_2OR^{a7''}$, and

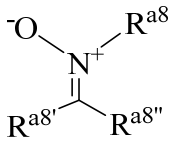
R^{a7}, $R^{a7'}$, $R^{a7''}$ are independently -H or C_{1-4} alkyl;

a compound of formula (z'vii)



(z'vii);

a compound of formula (z'viii)



(z'viii),

wherein

R^{a8}, $R^{a8'}$, $R^{a8''}$ are independently selected from the group consisting of -H and C_{1-4} alkyl;

a compound of formula (z'ix)

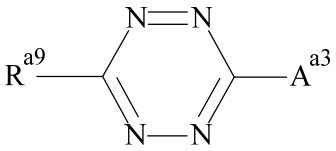


(z'ix),

wherein

R^{a9} is -H or C_{1-4} alkyl;

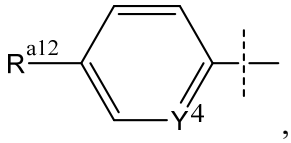
a compound of formula (z'x)



(z'x),

wherein

R^{a9} is selected from $-COOR^{a11}$, $-CONHR^{a11}$, and



,

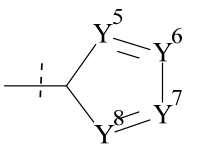
wherein

Y^4 is C or N,

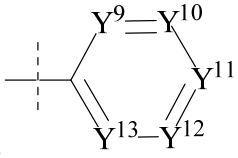
R^{a12} is selected from the group consisting of -H, $-COOR^{a13}$, $-CONR^{a13}R^{a13'}$, $-CH_2NR^{a13}R^{a13'}$, and $-NR^{a13}COR^{a13'}$, and

R^{a13}, $R^{a13'}$ are independently selected from the group consisting of -H and C_{1-4} alkyl,

A^{a3} is selected from the group consisting of -H, methyl, tert-butyl, $-CF_3$, -COR,



and

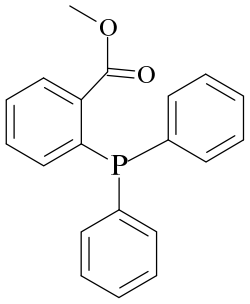


, wherein

each Y^5, Y^6, Y^7, Y^8 is independently C or N, provided that no more than 3 of Y^5, Y^6, Y^7, Y^8 are N,

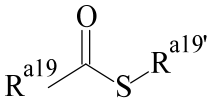
each of Y^9, Y^{10}, Y^{11}, Y^{12}, Y^{13} is either C, N, S or O, provided that no more than 4 of Y^9, Y^{10}, Y^{11}, Y^{12}, Y^{13} are N, S, or O;

a compound of formula (z'xi)



(z'xi);

a compound of formula (z'xii)

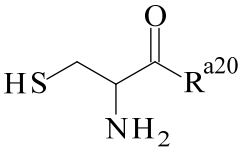


(z'xii),

wherein

R^{a19}, $R^{a19'}$ are independently selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl;

a compound of formula (z'xiii)

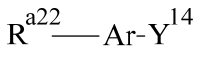


(z'xiii),

wherein

R^{a20} is selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl;

a compound of formula (z'xiv)



(z'xiv),

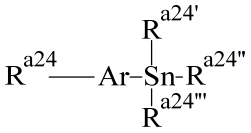
wherein

Ar is selected from phenyl, naphthyl, indenyl, indanyl, and tetralinyl,

Y^{14} is halogen,

R^{a22}, R^{a23}, $R^{a23'}$ are independently selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl;

a compound of formula (z'xv)

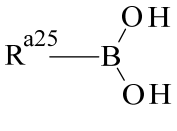


(z'xv),

Ar is selected from phenyl, naphthyl, indenyl, indanyl, and tetralinyl,

R^{a24}, $R^{a24'}$, $R^{a24''}$, $R^{a24'''}$ are independently selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl;

a compound of formula (z'xvi)

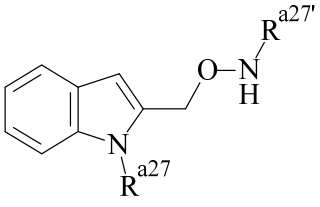


(z'xvi),

wherein

R^{a25} is selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicyclyl, phenyl, naphthyl, indenyl, indanyl, and tetralinyl;

a compound of formula (z'xvii)

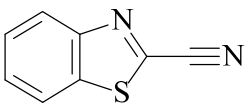


(z'xvii),

wherein

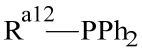
R^{a27}, $R^{a27'}$ are independently -H or C_{1-6} alkyl;

a compound of formula (z'xviii)



(z'xviii);

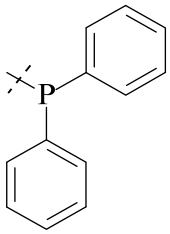
a compound of formula (z'xix)



(z'xix),

wherein

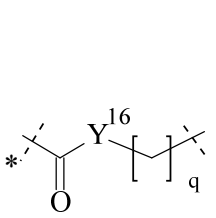
-PPh_2 represents a group having the following formula



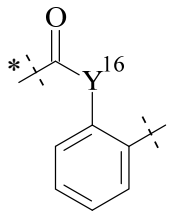
,

wherein the dashed line indicates attachment to the rest of the moiety of formula (z'xix),

R^{a12} is selected from the group consisting of



, and



,

wherein

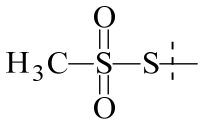
the unmarked dashed line indicates attachment to the rest of the moiety of formula (z'xix),

the dashed line with the asterisk indicates attachment to -L^2-,

q is 1 or 2, and

Y^{16} is O or S;

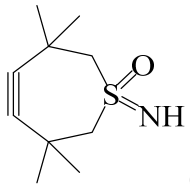
a compound of formula (z'xx)



(z'xx),

wherein the dashed line indicates attachment to -L^2-; and

a compound of formula (z'xxi)



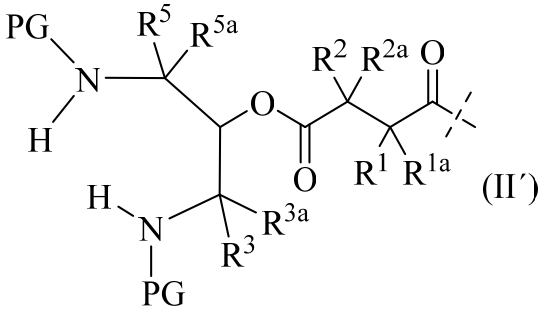
(z'xxi); wherein the moieties of formula (z'i), (z'ii), (z'iii), (z'iv), (z'v), (z'vi), (z'vii), (z'viii), (z'ix), (z'x), (z'xi), (z'xii), (z'xiii), (z'xiv), (z'xv), (z'xvi), (z'xvii), (z'xviii) and (z'xxi) are substituted with a moiety -L^2- and are optionally further substituted.

23. The reagent of any one of claims 19 to 22, wherein -Q is -LG.

24. The reagent of any one of claims 19 to 23, wherein -R^6 is -PG and -R^{6a} is -H.

25. The reagent of any one of claims 19 to 24, wherein -X^3- is -O-.

26. The reagent of any one of claims 19 to 25, wherein -L*- is of formula (II′):



(II′)

wherein the dashed line indicates attachment to -Q;

-R^1, -R^{1a}, -R^2, -R^{2a}, -R^3, -R^{3a}, -R^5, -R^{5a} and -PG are used as defined in claim 1~~9~~2;

-L*- is substituted with at least one moiety -L^2-Z or at least one moiety -L^2-Y and optionally is further substituted; and

wherein -L^2-, -Y and Z are used as defined in claim 19.

27. The reagent of any one of claims 19 to 26, wherein -R^1, -R^{1a}, -R^2, -R^{2a}, -R^3, -R^{3a}, -R^5 and -R^{5a} are -H.

28. An intermediate (A) comprising a moiety -L*- of formula (II) of any one of claims 19 to 27, wherein -L*- is conjugated to at least one moiety -D, wherein

each -D is independently a primary or secondary amine-comprising moiety of a drug D-H;

the dashed line in formula (II) indicates the attachment to the nitrogen of the primary or secondary amine of -D;

-L*- of formula (II) is optionally substituted with at least one moiety -L^2-Z or at least one moiety -L^2-Y and optionally is further substituted;

-L^2- is independently a single bond or a spacer moiety;

Z is independently a polymeric moiety or a C_{8-24} alkyl;

and wherein -Y is a functional group which may optionally be present in its protected form.

29. The intermediate of claim 28, wherein -L*- of formula (II) is substituted with at least one moiety -L^2-Y or at least one moiety -L^2-Z and optionally is further substituted~~;~~ .

~~30. A method for synthesizing a conjugate of any one of claims 1 to 18, wherein the method comprises the steps of:~~

~~(a) providing a reagent comprising a linker -L*- of formula (II) of any one of claims 19 to 27;~~

~~(b) conjugating the reagent of step (a) with a primary or secondary amine-comprising drug to obtain an intermediate (A);~~

~~(c) subjecting the intermediate (A) of step (b) to deprotection conditions to obtain an intermediate (C′) or conjugate comprising a linker -L^1- of formula (I) or an intermediate (B);~~

~~(d) optionally, subjecting the intermediate (B) or (C′) obtained from step (c) to shift conditions;~~

~~(e) optionally, deprotecting the intermediate (B) or (C′) of step (d); and~~

~~(f) isolating the conjugate resulting from steps (c), (d) or (e);~~

~~wherein optionally at least one Z moiety is attached to at least one intermediate (A) (B) or (C′) in between steps (b) and (c), (c) and (d), (d) and (e) or (e) and (f).~~

~~31.~~30. A pharmaceutical composition comprising the conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 18.

~~32.~~31. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 18 or the pharmaceutical composition of claim 30~~1~~ for use as a medicament.

~~33. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 18 or the pharmaceutical composition of claim 31 for use in a method of treating a disease that can be treated with D-H.~~

~~34. A method of preventing a disease or treating a patient suffering from a disease that can be prevented or treated with D-H, comprising administering an effective amount of the conjugate or the pharmaceutically acceptable salt thereof of any one of claims 1 to 18 or the pharmaceutical composition of claim 31 to the patient.~~