Claims

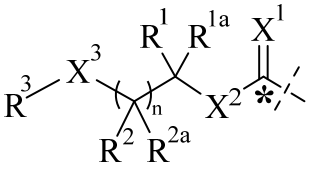
1. A conjugate or a pharmaceutically acceptable salt thereof comprising at least one moiety -D conjugated via at least one moiety -L^1-L^2- to at least one moiety Z, wherein a moiety -L^1- is conjugated to a π-electron-pair-donating heteroaromatic N of a moiety -D and wherein the linkage between -D and -L^1- is reversible and wherein a moiety -L^2- is conjugated to Z, wherein

each -D is independently a π-electron-pair-donating heteroaromatic N-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~~hydrogel;

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



(I),

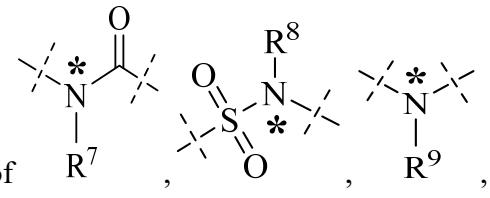
wherein

the dashed line indicates the attachment to the π-electron-pair-donating heteroaromatic N of -D;

n is an integer selected from the group consisting of 0, 1, 2, 3 and 4;

=X^1 is selected from the group consisting of =O, =S and =N(R^4);

-X^2- is selected from the group consisting of -O-, -S-, -N(R^5)- and -C(R^6)(R^{6a})-;

-X^3- is selected from the group consisting of , -$C(R^{10})(R^{10a})$-, -$C(R^{11})(R^{11a})$-$C(R^{12})(R^{12a})$-, -O- and -C(O)-;

-R^1, -R^{1a}, -R^6, -R^{6a}, -R^{10}, -R^{10a}, -R^{11}, -R^{11a}, -R^{12}, -R^{12a} and each of -R^2 and -R^{2a} are independently selected from the group consisting of -H, -C(O)OH, halogen, -CN, -OH, 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)$_2$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^3, -R^4, -R^5, -R^7, -R^8 and -R^9 are independently selected from the group consisting of -H, -T, -CN, 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)$_2$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})-;

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;

wherein -R^{13} is selected from the group consisting of -H, -NO_2, -OCH_3, -CN, -N(R^{14})(R^{14a}), -OH, -C(O)OH 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} and -R^{14a} 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;

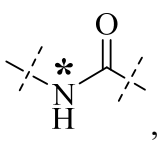
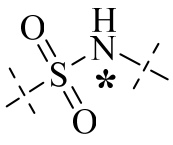
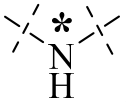
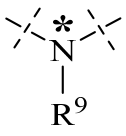
optionally, one or more of the pairs -R^1/-R^{1a}, -R^2/-R^{2a}, two adjacent -R^2, -R^6/-R^{6a}, -R^{10}/-R^{10a}, -R^{11}/-R^{11a}, -R^{12}/-R^{12a} and -R^3/-R^9 are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl or an 8- to 11-membered heterobicyclyl;

optionally, one or more of the pairs -R^1/-R^2, -R^1/-R^5, -R^1/-R^6, -R^1/-R^9, -R^1/-R^{10}, -R^2/-R^5, -R^3/-R^{6a}, -R^4/-R^5, -R^4/-R^6, -R^5/-R^{10}, -R^6/-R^{10} and -R^{11}/-R^{12} 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, -R^1 and an adjacent -R^2 form a carbon-carbon double bond provided that n is selected from the group consisting of 1, 2, 3 and 4;

optionally, two adjacent -R^2 form a carbon-carbon double bond provided that n is selected from the group consisting of 2, 3 and 4;

provided that ~~if~~ -X^2- is -N(R^5)-, -X^3- is selected from the group consisting of , ,  and , and the distance between the nitrogen atom marked with an asterisk and the carbon atom marked with an asterisk

in formula (I) is 5, 6 or 7 atoms and if present the carbon-carbon double bond formed between -R^1 and -R^2 or two adjacent -R^2 is in a cis configuration; and

each -L^1- is substituted with -L^2- and optionally further substituted.

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

3. The conjugate or pharmaceutically acceptable salt thereof of claim 1 or 2, wherein -D is a small molecule drug moiety.

~~4. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 3, wherein Z is a polymeric moiety.~~

~~5. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 4, wherein Z is a water-insoluble polymeric moiety.~~

~~6. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 5, 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.~~

~~7. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 6, wherein Z is a hydrogel.~~

~~8~~4. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to ~~7~~3, wherein Z is a PEG-based or hyaluronic-acid based hydrogel.

~~9~~5. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to ~~8~~4, wherein Z is a PEG-based hydrogel.

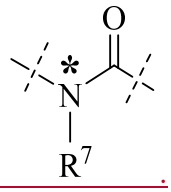
~~10~~6. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to ~~8~~4, wherein Z is a hyaluronic-acid based hydrogel.

~~11. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 4, wherein Z is a water-soluble polymeric moiety.~~

~~12~~7. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to ~~11~~6, wherein $=X^1$ is =O and $-X^2-$ is -O-.

~~13~~8. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to ~~11~~6, wherein $=X^1$ is =O and $-X^2-$ is $-N(R^5)-$.

9. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 8, wherein



-X^3- is .

~~14~~10. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to ~~13~~9, wherein -L^2- is a spacer moiety.

~~15~~11. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to ~~14~~10, wherein -L^2- has a molecular weight in the range of ~~from~~ 14 g/mol to 750 g/mol.

~~16~~12. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to ~~15~~11, 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;

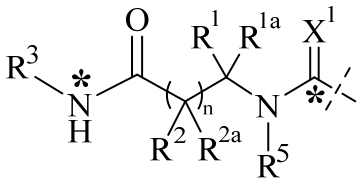
each -R^{y2} is independently selected from the group consisting of halogen, -CN, oxo (=O), -COOR^{y5}, -OR^{y5}, -C(O)R^{y5}, -C(O)N($R^{y5}R^{y5a}$), -S(O)$_2$N($R^{y5}R^{y5a}$), -S(O)N($R^{y5}R^{y5a}$), -S(O)$_2R^{y5}$, -S(O)R^{y5}, -N(R^{y5})S(O)$_2$N($R^{y5a}R^{y5b}$), -SR^{y5}, -N($R^{y5}R^{y5a}$), -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.

~~17~~13. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to ~~16~~12, wherein one hydrogen given by -R^3 is replaced by -L^2-.

~~18~~14. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to ~~17~~13, wherein the linkage between Z and -L^2- is stable.

~~19~~15. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to ~~11~~6 and ~~13~~8 to ~~18~~14, wherein -L^1- is of formula (Ix):



(Ix),

wherein the dashed line indicates the attachment to the π-electron-pair-donating heteroaromatic N of -D;

$=X^1$, $-R^1$, $-R^{1a}$, $-R^2$, $-R^{2a}$, $-R^3$, $-R^5$ and n are used as defined in claim 1;

optionally, one or more of the pairs $-R^1/-R^{1a}$, $-R^2/-R^{2a}$, two adjacent $-R^2$ 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 $-R^1/-R^2$, $-R^1/-R^5$, $-R^2/-R^5$ and $-R^4/-R^5$ 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, $-R^1$ and an adjacent $-R^2$ form a carbon-carbon double bond provided that n is selected from the group consisting of 1, 2, 3 and 4;

optionally, two adjacent $-R^2$ form a carbon-carbon double bond provided that n is selected from the group consisting of 2, 3 and 4;

and wherein the distance between the nitrogen atom marked with an asterisk and the carbon atom marked with an asterisk in formula (Ix) is 5, 6 or 7 atoms and if present the carbon-carbon double bond formed between $-R^1$ and $-R^2$ or two adjacent $-R^2$ is in a cis configuration.

~~20~~16. The conjugate or pharmaceutically acceptable salt thereof of claim ~~19~~15, wherein -R^5 of formula (Ix) is methyl.

~~21~~17. The conjugate or pharmaceutically acceptable salt thereof of claim ~~19~~15 or ~~20~~16, wherein -R^1 and -R^{1a} of formula (Ix) are both -H.

~~22~~18. A pharmaceutical composition comprising the conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to ~~21~~17.

~~23~~19. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to ~~21~~17 or the pharmaceutical composition of claim ~~22~~18 for use as a medicament.

~~24. Use of the conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 21 or the pharmaceutical composition of claim 22 in the manufacture of a medicament for the treatment of a disease that can be treated with D-H.~~