Claims

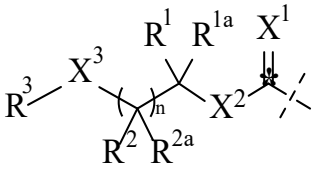
1. A conjugate or a pharmaceutically acceptable salt thereof comprising at least one moiety -D conjugated via at least one moiety -L^1-L^2- to at least one moiety Z, wherein a moiety -L^1- is conjugated to a π-electron-pair-donating heteroaromatic N of a moiety -D and wherein the linkage between -D and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

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



(I),

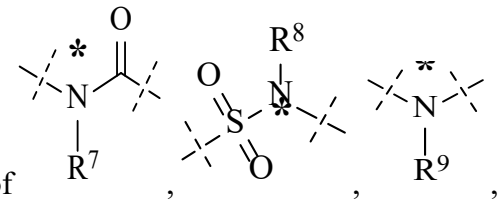
wherein

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)-, -$C(O)N(R^{14})$-, -$S(O)_2N(R^{14})$-, -$S(O)N(R^{14})$-, -$S(O)_2$-, -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^3 is -H which is replaced by -L^2-;

-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)-, -$C(O)N(R^{14})$-, -$S(O)_2N(R^{14})$-, -$S(O)N(R^{14})$-, -$S(O)_2$-, -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 -$OC(O)N(R^{14})$-;

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;

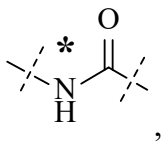
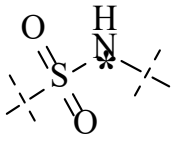
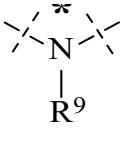
optionally, one or more of the pairs -R^1/-R^{1a}, -R^2/-R^{2a}, two adjacent -R^2, -R^6/-R^{6a}, -R^{10}/-R^{10a}, -R^{11}/-R^{11a}, -R^{12}/-R^{12a} and -R^3/-R^9 are joined together with the atom to which they are attached to form a C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl or an 8- to 11-membered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

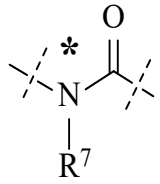
5. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 4, wherein Z is a PEG-based hydrogel.

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

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

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

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

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

12. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 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)$_2$-,

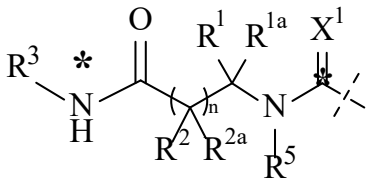
-S(O)-, -N(R^{y4})S(O)$_2$N(R^{y4a})-, -S-, -N(R^{y4})-, -OC(OR^{y4})(R^{y4a})-, -N(R^{y4})C(O)N(R^{y4a})-, and -OC(O)N(R^{y4})-;

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.

13. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 6 and 8 to 12, 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.

14. The conjugate or pharmaceutically acceptable salt thereof of claim 13, wherein -R^5 of formula (Ix) is methyl.

15. The conjugate or pharmaceutically acceptable salt thereof of claim 13 or 14, wherein -R^1 and -R^{1a} of formula (Ix) are both -H.

16. A pharmaceutical composition comprising the conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 15.

17. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 15 or the pharmaceutical composition of claim 16 for use as a medicament.