

Claims

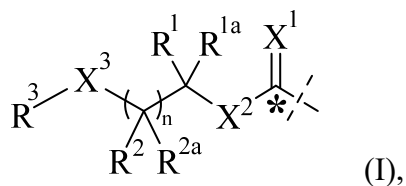
1. A conjugate or a pharmaceutically acceptable salt thereof comprising at least one moiety -D conjugated via at least one moiety -L¹-L²- to at least one moiety Z, wherein a moiety -L¹- is conjugated to a π -electron-pair-donating heteroaromatic N of a moiety -D and wherein the linkage between -D and -L¹- is reversible and wherein a moiety -L²- is conjugated to Z, wherein

each -D is independently a π -electron-pair-donating heteroaromatic N-comprising moiety of a drug D-H;

each -L²- is independently a single bond or a spacer moiety;

each Z is independently a hydrogel;

each -L¹- is independently a linker moiety of formula (I):



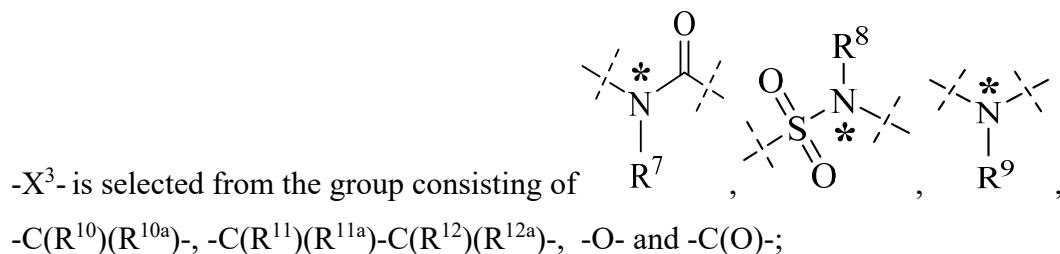
wherein

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;

=X¹ is selected from the group consisting of =O, =S and =N(R⁴);

-X²- is selected from the group consisting of -O-, -S-, -N(R⁵)- and -C(R⁶)(R^{6a})-;



-R¹, -R^{1a}, -R⁶, -R^{6a}, -R¹⁰, -R^{10a}, -R¹¹, -R^{11a}, -R¹², -R^{12a} and each of -R² and -R^{2a} are independently selected from the group consisting of -H, -C(O)OH, halogen, -CN, -OH, C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl; wherein C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are optionally substituted with one or more -R¹³, which are the same or different; and wherein C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ 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(R¹⁴)-, -S(O)₂N(R¹⁴)-, -S(O)N(R¹⁴)-, -S(O)₂-, -S(O)-, -N(R¹⁴)S(O)₂N(R^{14a})-, -S-, -N(R¹⁴), -OC(OR¹⁴)(R^{14a})-, -N(R¹⁴)C(O)N(R^{14a})- and -OC(O)N(R¹⁴)-;

-R³ is -H which is replaced by -L²-;

-R⁴, -R⁵, -R⁷, -R⁸ and -R⁹ are independently selected from the group consisting of -H, -T, -CN, C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl; wherein C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ alkynyl are optionally substituted with one or more -R¹³, which are the same or different; and wherein C₁₋₆ alkyl, C₂₋₆ alkenyl and C₂₋₆ 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(R¹⁴)-, -S(O)₂N(R¹⁴)-, -S(O)N(R¹⁴)-, -S(O)₂-, -S(O)-, -N(R¹⁴)S(O)₂N(R^{14a})-, -S-, -N(R¹⁴), -OC(OR¹⁴)(R^{14a})-, -N(R¹⁴)C(O)N(R^{14a})- and -OC(O)N(R¹⁴)-;

each T is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl and 8- to 11-membered heterobicycyl; wherein each T is independently optionally substituted with one or more -R¹³, 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;

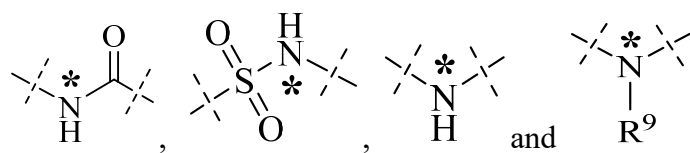
optionally, one or more of the pairs $-R^1/-R^2$, $-R^1/-R^5$, $-R^1/-R^6$, $-R^1/-R^9$, $-R^1/-R^{10}$, $-R^2/-R^5$, $-R^3/-R^{6a}$, $-R^4/-R^5$, $-R^4/-R^6$, $-R^5/-R^{10}$, $-R^6/-R^{10}$ and $-R^{11}/-R^{12}$ are joined together with the atoms to which they are attached to form a ring $-A-$;

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

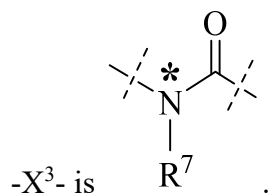


, and the distance between the nitrogen atom marked with an asterisk and the carbon atom marked with an asterisk in formula (I) is 5, 6 or 7 atoms and if present the carbon-carbon double bond formed between $-R^1$ and $-R^2$ or two adjacent $-R^2$ is in a cis configuration; and

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



10. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 9, wherein -L²- is a spacer moiety.
11. The conjugate or pharmaceutically acceptable salt thereof of any one of claims 1 to 10, wherein -L²- 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 -L²- is a spacer moiety selected from the group consisting of -T'-, -C(O)O-, -O-, -C(O)-, -C(O)N(R^{y1})-, -S(O)₂N(R^{y1})-, -S(O)N(R^{y1})-, -S(O)₂-, -S(O)-, -N(R^{y1})S(O)₂N(R^{y1a})-, -S-, -N(R^{y1})-, -OC(OR^{y1})(R^{y1a})-, -N(R^{y1})C(O)N(R^{y1a})-, -OC(O)N(R^{y1})-, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl; wherein -T'-, C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl and C₂₋₅₀ alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different and wherein C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ 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)₂N(R^{y3})-, -S(O)N(R^{y3})-, -S(O)₂-, -S(O)-, -N(R^{y3})S(O)₂N(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', C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl and C₂₋₅₀ alkynyl; wherein -T', C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl, and C₂₋₅₀ alkynyl are optionally substituted with one or more -R^{y2}, which are the same or different, and wherein C₁₋₅₀ alkyl, C₂₋₅₀ alkenyl and C₂₋₅₀ 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)₂N(R^{y4})-, -S(O)N(R^{y4})-, -S(O)₂-,

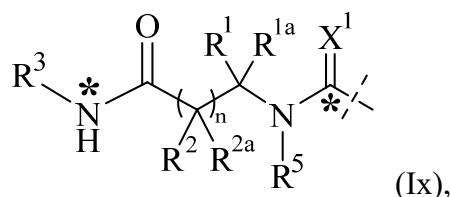
-S(O)-, -N(R^{y4})S(O)₂N(R^{y4a})-, -S-, -N(R^{y4})-, -OC(OR^{y4})(R^{y4a})-, -N(R^{y4})C(O)N(R^{y4a})-, and -OC(O)N(R^{y4})-;

each T' is independently selected from the group consisting of phenyl, naphthyl, indenyl, indanyl, tetralinyl, C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, 8- to 11-membered heterobicycyl, 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}), -NO₂, -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 C₁₋₆ alkyl; wherein C₁₋₆ 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 C₁₋₆ alkyl; wherein C₁₋₆ 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 -L¹- is of formula (Ix):



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

=X¹, -R¹, -R^{1a}, -R², -R^{2a}, -R³, -R⁵ 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.