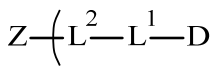
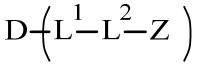
Claims

1. An IL-2 conjugate or a pharmaceutically acceptable salt thereof of formula (Ia) or (Ib)



(Ia)



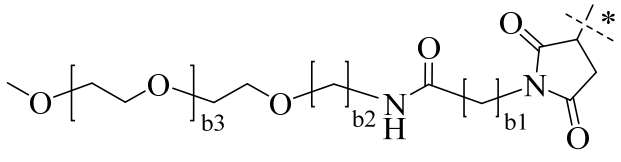
(Ib),

wherein

-D is a biased IL-2 moiety, which biased IL-2 moiety comprises an IL-2 moiety and for which biased IL-2 moiety the ratio of the K_D of said biased IL-2 to IL-2Rαβ to the K_D of said biased IL-2 to IL-2Rβ is larger than the ratio of the K_D of aldesleukin to IL-2Rαβ to the K_D of aldesleukin to IL-2Rβ; wherein -D comprises at least one stable attachment of a modifying moiety M_{mod}, wherein the IL-2 moiety comprises at least one amino acid mutation at a position selected from the group consisting of K34, R37, M38, T40, F41, K42, F43, Y44, E61, and L71 based on SEQ ID NO:2, wherein the naturally occurring amino acid is replaced by a cysteine resulting in mutations K34C, R37C, M38C, T40C, F41C, K42C, F43C, Y44C, E61C, and L71C, and wherein the at least one moiety M_{mod} is conjugated to the sulfur of such cysteine;

wherein

M_{mod} is of formula (A-1a)



(A-1a),

wherein

the dashed line marked with the asterisk indicates attachment to the sulfur of a side chain of an amino acid residue of the IL-2 moiety;

b1 is 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 and 20;

b2 is 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 and 20; and

b3 is an integer ranging from 69 to 4540;

-L^1- is a linker moiety covalently and reversibly attached to -D;

-L^2- is a chemical bond or is a spacer moiety;

-Z is a PEG-based polymeric moiety;

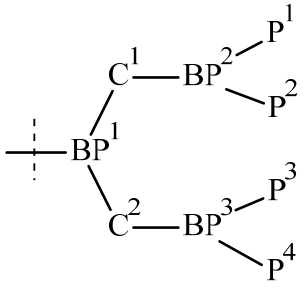
x is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16; and

y is an integer selected from the group consisting of 2, 3, 4 and 5.

2. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of claim 1, wherein the IL-2 moiety comprises the R37C mutation and wherein a moiety M_{mod} is conjugated to the sulfur of the cysteine that replaced the arginine at position 37.

3. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of claim 1 or 2, wherein the IL-2 conjugate is of formula (Ia) with x being 1.

4. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of any one of claims 1 to 3, wherein -Z comprises a moiety of formula (A)



(A),

wherein

$-BP^1<$, $-BP^2<$, $-BP^3<$ are independently of each other selected from the group consisting of $-N<$ and $-C(R^8)<$;

R^8 is selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

$-P^1$, $-P^2$, $-P^3$, $-P^4$ are independently of each other a PEG-based chain comprising at least 40% PEG and having a molecular weight ranging from 3 to 40 kDa;

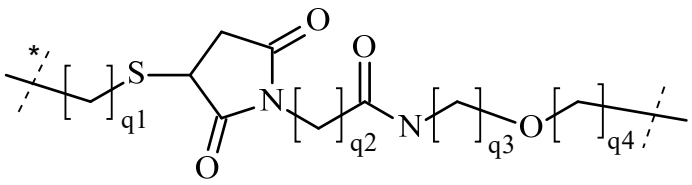
$-C^1-$, $-C^2-$ are independently of each other selected from the group consisting of C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl; wherein C_{1-50} alkyl, C_{2-50} alkenyl, and C_{2-50} alkynyl are optionally substituted with one or more R^9, which are the same or different and wherein C_{1-50} 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)-, $-C(O)N(R^{10})-$, $-S(O)_2N(R^{10})-$, $-S(O)N(R^{10})-$, $-S(O)_2-$, -S(O)-, $-N(R^{10})S(O)_2N(R^{10a})-$, -S-, $-N(R^{10})-$, $-OC(OR^{10})(R^{10a})-$, $-N(R^{10})C(O)N(R^{10a})-$, and $-OC(O)N(R^{10})-$;

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^9, which are the same or different;

each R^9 is independently selected from the group consisting of halogen, -CN, oxo (=O), $-COOR^{11}$, $-OR^{11}$, $-C(O)R^{11}$, $-C(O)N(R^{11}R^{11a})$, $-S(O)_2N(R^{11}R^{11a})$, $-S(O)N(R^{11}R^{11a})$, $-S(O)_2R^{11}$, $-S(O)R^{11}$, $-N(R^{11})S(O)_2N(R^{11a}R^{11b})$, $-SR^{11}$, $-N(R^{11}R^{11a})$, $-NO_2$, $-OC(O)R^{11}$, $-N(R^{11})C(O)R^{11a}$, $-N(R^{11})S(O)_2R^{11a}$, $-N(R^{11})S(O)R^{11a}$, $-N(R^{11})C(O)OR^{11a}$, $-N(R^{11})C(O)N(R^{11a}R^{11b})$, $-OC(O)N(R^{11}R^{11a})$, 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^{10}, R^{10a}, R^{11}, R^{11a} and R^{11b} 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.

5. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of claim 4, wherein C^1 and C^2 of formula (A) are of formula (A-a)



(A-a),

wherein

the dashed line marked with the asterisk indicates attachment to BP^1;

the unmarked dashed line indicates attachment to BP^2 or BP^3, respectively;

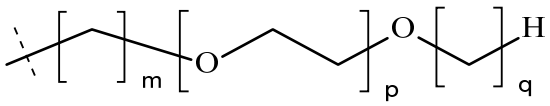
q1 is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7 and 8;

q2 is selected from the group consisting of 1, 2, 3, 4, and 5;

q3 is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7 and 8; and

q4 is selected from the group consisting of 1, 2 and 3.

6. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of claim 4 or 5, wherein P^1, P^2, P^3 and P^4 of formula (A) are independently of each other of formula (A-b)



(A-b),

wherein

the dashed line indicates attachment to the remainder of -Z;

m is 0 or 1;

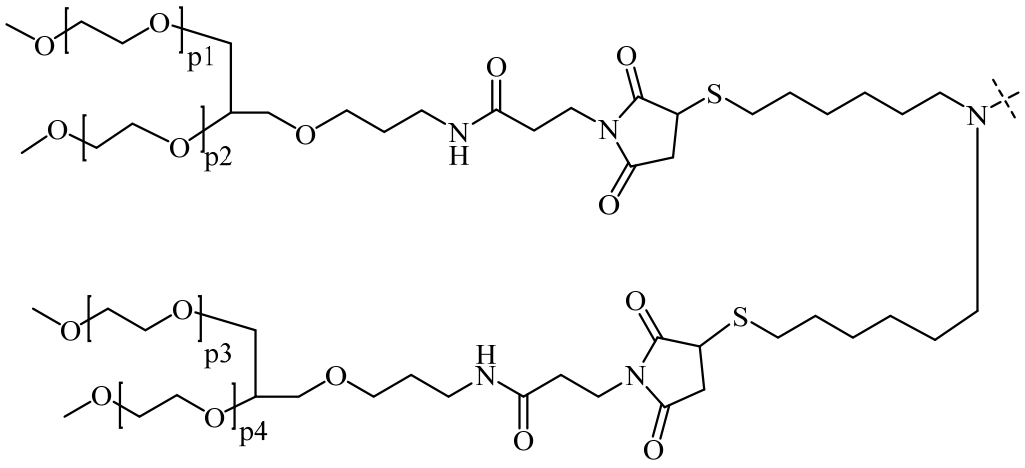
p is an integer ranging from 70 to 900; and

q is selected from the group consisting of 1, 2, 3, 4, 5, and 6.

7. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of any one of claims 4 to 6, wherein BP^1 of formula (A) is –N<.

8. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of any one of claims 4 to 7, wherein BP^2 and BP^3 of formula (A) are both –CH<.

9. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of any one of claims 1 to 8, wherein -Z comprises a moiety of formula (A-c):



(A-c),

wherein

p1, p2, p3, p4 are independently of each other an integer ranging from 70 to 900.

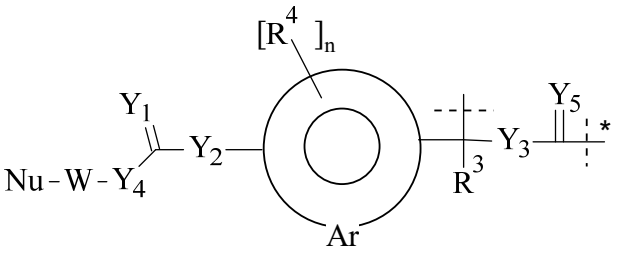
10. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of any one of claims 1 to 9, wherein -L^1- is attached to an amino acid residue of the IL-2 moiety.

11. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of any one of claims 1 to 10, wherein -L^1- is attached to an amino acid residue of the IL-2 moiety selected

from the group consisting of cysteine, methionine, histidine, lysine, tryptophan, serine, threonine, tyrosine, aspartic acid, glutamic acid, glutamine and arginine.

12. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of any one of claims 1 to 11, wherein L^1- is attached to a lysine residue selected from the group consisting of K7, K8, K31, K34, K42, K47, K48, K53, K63, K75 and K96, based on SEQ ID NO:2.

13. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of any one of claims 1 to 12, wherein -L^1- is of formula (IX-a):



(IX-a),

wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of -D and the unmarked dashed line indicates attachment to -L^2-Z;

n is 0, 1, 2, 3, or 4;

=Y_1 is selected from the group consisting of =O and =S;

-Y_2- is selected from the group consisting of -O- and -S-;

-Y_3- is selected from the group consisting of -O- and -S-;

-Y_4- is selected from the group consisting of -O-, -NR^5- and -$C(R^6R^{6a})$-;

=Y_5 is selected from the group consisting of =O and =S;

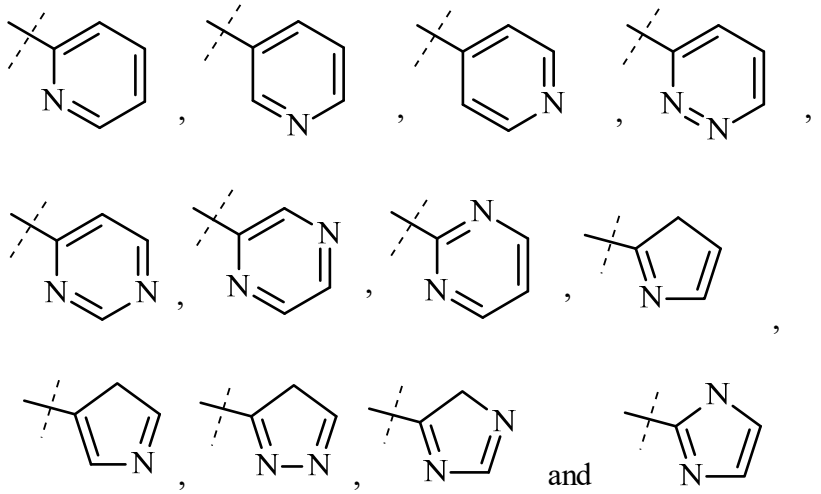
-R^3, -R^5, -R^6, -R^{6a} are independently of each other selected from the group consisting of -H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

-R^4 is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylpropyl;

-W- is selected from the group consisting of C_{1-20} alkyl optionally interrupted by one or more groups selected from the group consisting of C_{3-10} cycloalkyl, 8- to 30-

membered carbopolycyclyl, 3- to 10-membered heterocyclyl, -C(O)-, -C(O)N(R^7)-, -O-, -S- and -N(R^7)-;

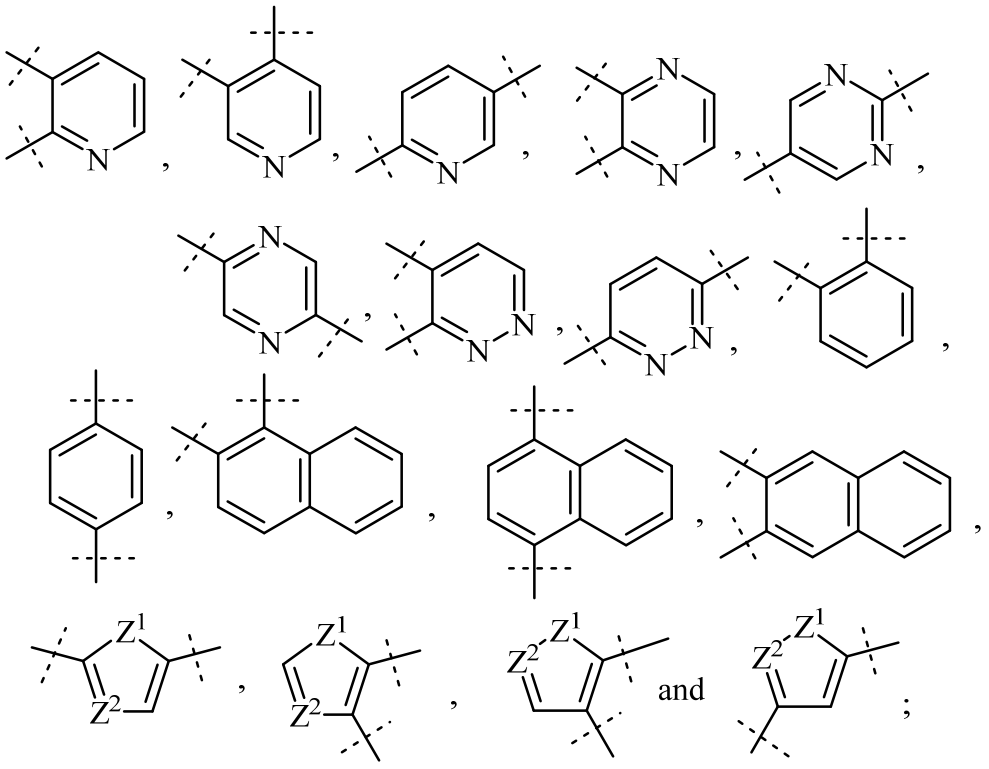
-Nu is a nucleophile selected from the group consisting of -N(R^7R^{7a}), -N(R^7OH), -N(R^7)-N($R^{7a}R^{7b}$), -S(R^7),-COOH,



and

;

-Ar- is selected from the group consisting of



wherein

dashed lines indicate attachment to the remainder of -L^1-,

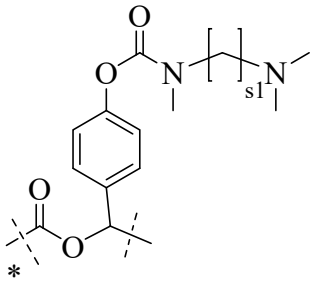
-Z^1- is selected from the group consisting of -O-, -S- and -N(R^7)-, and

-Z^2- is -N(R^7)-; and

-R^7, -R^{7a}, -R^{7b} are independently of each other selected from the group consisting of -H, C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl;

wherein -L^1- is optionally further substituted.

14. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of any of claims 1 to 13, wherein -L^1- is of formula (IX-c)



(IX-c),

wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of -D;

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

s1 is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10.

15. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of any one of claims 1 to 14, wherein -L^2- is 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})-;

-R^{y1} and -R^{y1a} are independently of each other 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-,

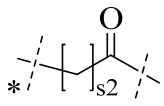
-C(O)O-, -O-, -C(O)-, -C(O)N(R^{y4})-, -S(O)$_2$N(R^{y4})-, -S(O)N(R^{y4})-, -S(O)$_2$-, -S(O)-, -N(R^{y4})S(O)$_2$N(R^{y4a})-, -S-, -N(R^{y4})-, -OC(OR^{y4})(R^{y4a})-, -N(R^{y4})C(O)N(R^{y4a})-, and -OC(O)N(R^{y4})-;

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.

16. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of any one of claims 1 to 15, wherein -L^2- is of formula (IX-e)



(IX-e),

wherein

the dashed line marked with the asterisk indicates attachment to -L^1-;

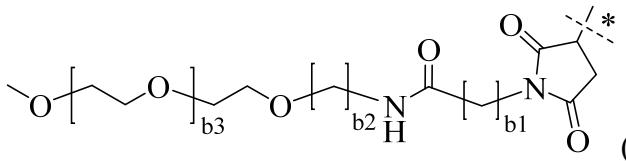
the unmarked dashed line indicates attachment to -Z; and

s2 is an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20.

17. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of any one of claims 1 to 16, wherein the IL-2 conjugate is of formula (Ia) with x being 1;

wherein

the IL-2 moiety comprises the R37C mutation based on SEQ ID NO:2; wherein a moiety M_{mod} is conjugated to the sulfur of the cysteine that replaced the arginine at position 37; wherein M_{mod} is of formula (A-1a)



(A-1a),

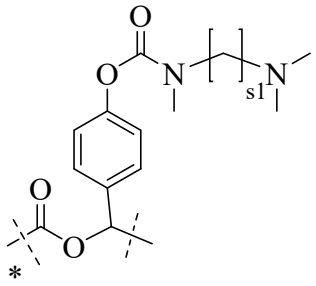
wherein

b1 is an integer ranging from 1 to 4;

b2 is an integer ranging from 1 to 4; and

b3 is an integer such that the molecular weight of M_{mod} is 5 ± 25% kDa;

$-L^1-$ is of formula (IX-c)



(IX-c),

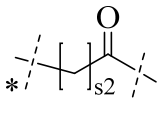
wherein

the dashed line marked with the asterisk indicates attachment to a nitrogen of -D;

the unmarked dashed line indicates attachment to $-L^2-Z$; and

s1 is an integer selected from the group consisting of 1, 2, 3, 4 and 5;

$-L^2-$ is of formula (IX-e)



(IX-e),

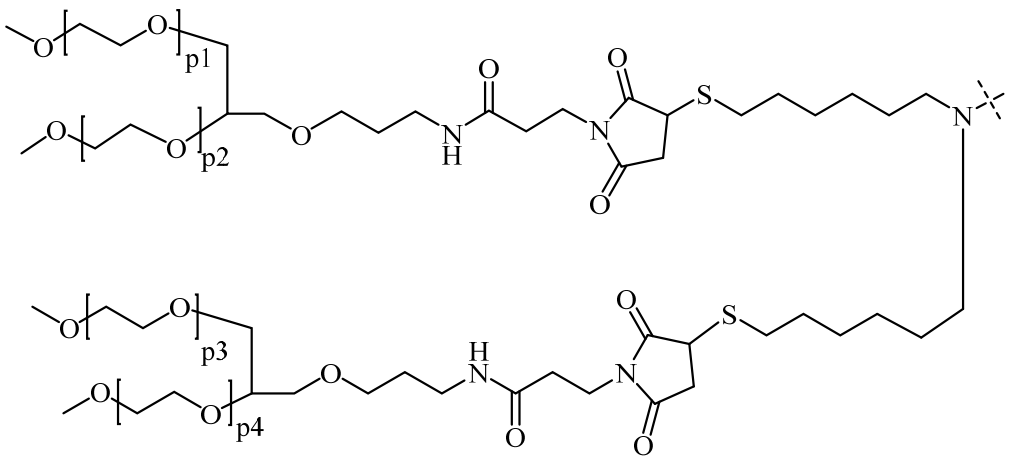
wherein

the dashed line marked with the asterisk indicates attachment to $-L^1-$;

the unmarked dashed line indicates attachment to -Z; and

s2 is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7 and 8; and

-Z comprises a moiety of formula (A-c):



(A-c),

wherein

p1, p2, p3, p4 are independently of each other an integer ranging from 185 to 450.

18. The IL-2 conjugate or the pharmaceutically acceptable salt thereof of claim 17, wherein b1 is 2; b2 is 2; b3 is about 112; s1 is 3; s2 is 3; and p1, p2, p3, p4 are independently of each other an integer ranging from 220 to 240.

19. A pharmaceutical composition comprising at least one IL-2 conjugate or the pharmaceutically acceptable salt thereof of any one of claims 1 to 18 and at least one excipient.

20. The IL-2 conjugate or a pharmaceutically acceptable salt thereof of any one of claims 1 to 18 or the pharmaceutical composition of claim 19 for use as a medicament.

21. Use of the IL-2 conjugate or a pharmaceutically acceptable salt thereof of any one of claims 1 to 18 or the pharmaceutical composition of claim 19 in the manufacture of a medicament for the treatment of cancer.

22. The use of claim 21, wherein the cancer is selected from the group consisting of sarcoma, chordoma, colon cancer, rectal cancer, colorectal cancer, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell cancer, basal cell cancer, adenocarcinoma, sweat gland cancer, sebaceous gland cancer, papillary cancer, papillary adenocarcinomas, cystadenocarcinoma, medullary cancer, bronchogenic cancer, renal cell cancer, hepatoma, bile duct cancer, choriocarcinoma, seminoma, embryonal cancer, Wilms' tumor, cervical cancer, testicular cancer, gastric cancer, non-small cell lung cancer, small cell lung cancer, bladder cancer, renal cell carcinoma,

urothelial cancer, epithelial cancer, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, acute myeloid leukemia and leukemias.